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India-specific infant diarrhoea vaccine soon

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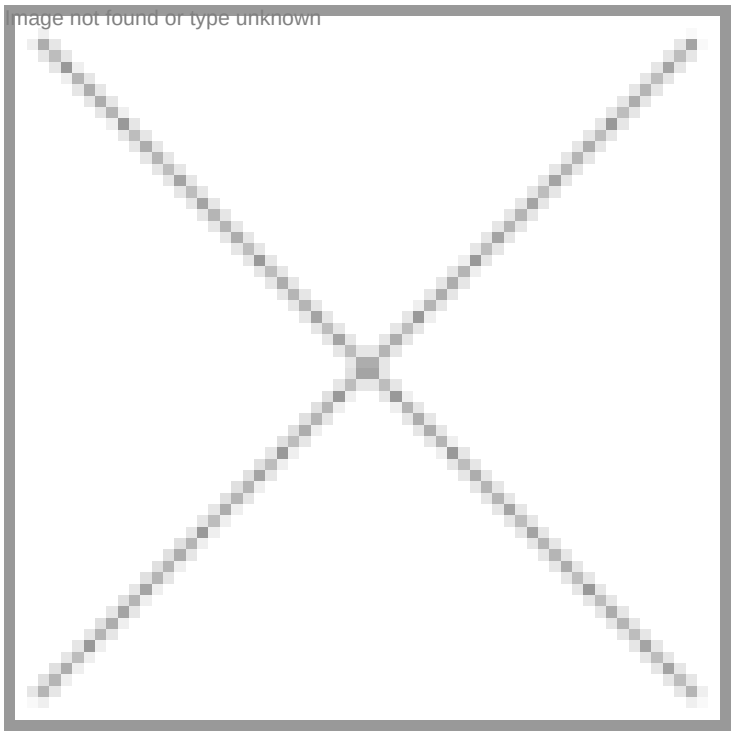

India-specific infant diarrhoea vaccine soon

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The first rotaviral diarrhoea vaccine specific to India completes phase-1 human clinical trial in India.

The loss of fluids can be deadly unless it is treated. Most of the estimated half-million deaths each year are in poor countries.

Rotavirus is the most common cause of severe dehydrating diarrhoea in in- fants and children. Among children under five years of age, it has been estimated to be responsible for an estimated two million hospitalizations, 5 lakh deaths and more than 25 million clinic visits worldwide each year. The disease contributes to about 40 percent of the total dehydrating diarrhoea disease in children. In India it causes about 1,50,000 deaths per year. There are several different serotypes of rotavirus and the prevalence of these serotypes varies by geographic region.

Under the Indo-US Vaccine Action Program, two candidate vaccines 116E and I321 were developed. Candidate vaccine 116E was developed by the collaborative efforts of Dr MK Bhan, Dr Pratima Ray of the All India Institute of Medical Sciences, New Delhi, Dr Nita Bhandari of the Society for Applied Sciences, New Delhi and Dr Roger I Glass, Centre for Disease Control and Prevention, Atlanta, USA, while I321 was jointly developed by Dr C Durga Rao of the Indian Institute of Science, Bangalore and Dr Harry Greenberg of Stanford University, 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 the 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. 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. Dr NK Ganguly, director general, Indian Council of Medical Research, said, "The Rotavirus vaccine developed by Dr MK Bhan has entered phase-II trials in India. Rotavirus causes severe diarrhoea and this has the largest morbidity rate and hence development and use of this vaccine in India is extremely important".

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.

Meanwhile US-based multinational Merck and PATH, an international, non-profit organization that creates sustainable solutions to break cycles of poor health, are collaborating to conduct clinical studies of Merck's investigational rotavirus vaccine Rotateq in Asia and Africa. The clinical trial sites will be identified in Africa and Asia over the next six months, with a goal of starting at least one trial by the end of 2006. The efficacy studies of Rotateq will be conducted in regions of the world where it has not been studied before and where factors including poor nutrition and the presence of intestinal bacteria or viruses might play a role in the response to the vaccine. The studies also will assess how this vaccine fits into the range of childhood vaccine schedules used in different countries.

According to Adel AF Mahmoud, chief medical advisor, vaccines and infectious diseases, Merck & Co., although rotavirus infection is as common in developed countries as it is in developing nations, most of the children who die from the effects of rotavirus, live in countries where emergency medical care such as intravenous rehydration is often less readily available. "Merck is as committed to identifying innovative ways to bring our vaccines to children in the developing world as we are to developing the innovative vaccines themselves," he said.

Rotateq is Merck's investigational vaccine to protect against rotavirus gastroenteritis. It is an oral, liquid vaccine that contains five rotavirus strains â€“ G1, G2, G3, G4 and P1. These serotypes cause most rotavirus disease worldwide. Merck has submitted an application for licensure of its vaccine in more than 50 countries worldwide, including the US and the European Union.

John Wecker, director of PATH's Rotavirus Vaccine Program, said, "It is our hope that demonstrating the impact of rotavirus vaccines in developing countries will ultimately reduce the potentially serious effects of this disease on children. By pooling our collective strengths, we seek to address one of the most serious public health problems affecting infants and young children worldwide".

With funding from the Global Alliance for Vaccines and Immunizations (GAVI) and the Vaccine Fund, PATH established the Rotavirus Vaccine Program (RVP) in 2003. Along with its strategic partners, the World Health Organization (WHO) and the US Centers for Disease Control and Prevention (CDC), RVP is testing and developing a new model for accelerated vaccine introduction. By demonstrating to governments the impact of the disease and the promise of a vaccine, RVP will help countries make informed decisions about the use of rotavirus vaccines.

At the same time RVP is working with Merck and other manufacturers to establish a consistent supply of rotavirus vaccine to meet the demand for these vaccines. Life-saving intravenous treatments to rehydrate children with severe rotavirus diarrhoea are often unavailable to many of the developing world's 575 million children under age five. Consequently, both the WHO and the Pan American Health Organization (PAHO) believe that availability of a rotavirus vaccine will be a major contribution to children across the world.

Another company working actively in the Rotavirus vaccine arena is GlaxoSmithKline Biologicals (GSK Bio), one of the world's leading vaccine manufacturers. Its vaccine against rotavirus infection, Rotarix has received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP), the scientific committee, which evaluates the quality, safety and efficacy of medicinal products in the European Union.

A European Marketing Authorization from the European Commission could be expected from late February 2006 onwards which will make Rotarix, the first rotavirus vaccine available to children in Europe. GSK Bio submitted a registration file for Rotarix in December 2004 and intends to introduce this vaccine throughout Europe immediately after the marketing authorization has been granted. The rotavirus market potential by 2010 is estimated between £1.0-1.3 billion. Europe accounts for 20 percent of the total market.

Approximately 4.5 million cases of rotavirus gastroenteritis occur every year among children under 5 years of age in the EU, which makes rotavirus the most frequent vaccine preventable illness among children in the EU.

Rotarix has been developed by GSK Biologicals since 1997 when it was in-licensed from Avant Immunotherapeutics. It is probably the first human rotavirus vaccine available in the market. The vaccine which is given orally confers significant protection against rotavirus diarrhea. Clinical trials have shown high efficacy against the most prevalent rotavirus strains. Since Rotarix launch in Mexico in 2004, an additional 24 licenses have been granted worldwide (12 Latin American countries including Brazil; Philippines and Singapore being the first Asian countries). Furthermore, Rotarix has been filed in 75 countries. There are plans to file in the US where discussions are going on with the FDA. Recently, Brazil and Panama included for the first time the rotavirus vaccine in their national official vaccination calendars.

Rolly Dureha

Scientists grow new stem cell lines in animal cell-free culture

Scientists at the WiCell Re search Institute, a private laboratory affiliated to the University of Wisconsin-Madison, have developed a precisely defined stem cell culture system free of animal cells and used it to derived two new human embryonic stem cell lines.

This work reported in the journal Nature Biotechnology, helps move stem cells a small step closer to clinical reality by completely ridding the culture medium in which they are grown of animal products that could harbor viruses or other deleterious agents.

Successfully growing living cells outside the body generally requires providing the cells in a lab dish with the right mix of nutrients, hormones, growth factors and blood serum. But those methods have often depended on animal cells, such as those obtained from mouse embryos in the case of embryonic stem cells, and other animal products to keep the cells alive and thriving in culture. Some scientists worry that animal viruses and other problematic agents might be taken up in the human cells and infect human patients, should those cells be used for therapy.

The two new Wisconsin stem cell lines have survived for more than seven months in the new culture medium. James Thomson, senior author of the new study and a UW-Madison professor of anatomy, said that one of the new lines had an abnormal chromosome at four months while the second line initially was normal but developed an abnormality by seven months.

In addition to testing the new stem cell culture medium on new lines, Thomson's group successfully cultured four existing stem cell lines in the new culture mix for extended periods, and their chromosomes remained normal.

In early 2005, WiCell scientists reported that they were able to culture stem cells in the absence of mouse feeder cells, the most prominent animal product in stem cell culture systems. The new work effectively removes remaining animal products such as bovine serum and replaces them with products of human origin in a recipe that is completely defined.

WiCell Research Institute is a private non-profit organization with a mission to provide human embryonic stem cells for research purposes to academic scientists all over the world. The NIH selected WiCell from a field of applicants in the United States to create the nation's first and only National Stem Cell Bank (NSCB).

Plasmodium falciparum's immune evasion methods revealed

The world's deadliest malaria parasite, Plasmodium falciparum, sneaks past the human immune system with the help of a wardrobe of invisibility cloaks. If a person's immune cells learn to recognize one of the parasite's many camouflage proteins, the surviving invaders can swap disguises and slip away again to cause more damage. Malaria kills an estimated 2.7 million people annually worldwide of which 75 percent of them are children in Africa. Howard Hughes Medical Institute (HHMI) international research scholars in Australia have determined how P. falciparum can turn on one cloaking gene and keep dozens of others silent until each is needed in turn. Their findings, published in Nature, reveal the mechanism of action of the genetic machinery thought to be the key to the parasite's survival.

A DNA sequence near the start of a cloaking gene, known as the gene's promoter, not only turns up production of its protein, but also keeps all other cloaking genes under wraps, according to Alan Cowman and Brendan Crabb, HHMI international research scholars at the Walter and Eliza Hall Institute of Medical Research in Melbourne, Australia, and their co-authors.

Malaria parasites enter human blood from infected mosquitoes. The organisms invade and promptly remodel red blood cells. They decorate the surface of the cells they occupy with a protein called PfEMP1, made by the var gene family. The diverse

genetic sequences of the 60 var cloaking genes all code for remarkably similar protein structures, the malaria researcher added. The scientists are continuing to disassemble the var gene machinery, piece by piece and eventually they think their work may lead to new types of therapies that interfere with the parasite's immune evasion strategies.

BioGrid project to help companies integrate data

T he European Union has started a BioGrid project, which aims at
gleaming useful information from the loads of data accumulated by biotechnology companies. As of now it is becoming more and more difficult to find lucid information about interactions between genes and proteins for example. The researchers involved in it have delivered a better search engine for PubMed, which includes over 16 million citations from Medline and other life science journals for biomedical articles by analyzing over-expressing genes and predicting the protein interactions that are likely occurring. The project has developed a suite of tools that will enable researchers to mine through vast quantities of data and many of the tools developed by BioGrid are available for public use.

The BioGrid project brought together six partners from the UK, Germany, Cyprus and The Netherlands to address the information overload, one of the key problems facing the life sciences today. BioGrid's protein interaction software includes a database of the 20,000 known protein structures and uses that database to identify which ones could potentially interact, among the thousands of proteins created by the over-expressing genes. The researchers have developed a Gene Ontology (GO) as a vocabulary to describe all the different genetic processes and then used this vocabulary to mine through the 15,000,000 entries of PubMed.

A novel way to switch therapeutic genes 'on' and 'off'

Agene therapy research team at Cedars-Sinai Medical Center, California has developed a new method of signaling therapeutic genes to turn "off" or "on," a mechanism that could enable scientists to fine-tune genetic and stem cell-based therapies so that they are safer, more controllable and more effective.

Although other similar signaling systems have been developed, the Cedars-Sinai research is the first to give physicians the flexibility to arbitrarily turn the gene expression on or off even in the presence of an immune response to adenovirus, as would be present in most patients undergoing clinical trials. This has been a major obstacle in bringing the testing of genetic therapies to humans in a clinical setting.

In this study, researchers created a genetic switch system that is turned on in the presence of the antibiotic tetracycline. Therefore, if this method is tested eventually in humans, patients would need to be given this antibiotic before they begin gene therapy treatment. The switch system also produces a protein called silencer, which completely shuts down gene expression in the "off" state, thereby preventing leakage of the therapeutic gene when it is no longer needed. The next step in the development of this new signaling system is to activate the newly developed genetic switch to actively express compounds that are known to be effective at reversing the symptoms and rescuing the damaged neurons in Parkinson's disease patients. Researchers hope to begin a Phase 1 clinical trial in humans in the near future.

"India could build a world-class position in understanding how genomes work"

Richard J Feldmann, *scientist and president of Global Determinants Inc.*

Richard J Feldmann, scientist and president of Global Determinants Inc., was recently in India to visit his grandchildren and to give scientific talks at the University of Madras in Chennai, and at the Institute for Bioinformatics and Applied Biotechnology (IBAB) and Indian Institute of Science (IISc) in Bangalore. Feldmann, who spent his first career developing graphical techniques for modeling proteins and nucleic acids at the US National Institutes of Heal (NIH) in Bethesda, Maryland, shared his thoughts on the results of his studies of how Connectrons control the expression of genes in mouse cells.

Twenty five years ago, on his first trip to India, Feldmann spent several weeks installing software for searching crystallographic structures that he had developed on the computer at the Tata Institute of Fundamental Research (TIFR) in Mumbai. At that time, the TIFR computer was one of the few American computers in India used for doing science. Seventeen

years ago in 1988, Feldmann toured India giving a scientific talk on the molecular graphic and modeling work that he had been doing. At that time he also tried to convince young Indian scientific workers to write programs for PCs that were just becoming popular. These PCs were instances of American chips in Indian computers made by Hindustan Computers Ltd (HCL). Many of the young scientific workers have now risen to prominence in Indian academia.

On this trip, Feldmann said that he has brought to India a revolutionary idea about how cells function. Six years ago, he had a fundamental insight about how RNA and DNA interact to regulate the expression of genes. He has discovered four-sequence relationships that he calls Connectrons. Connectrons occur in good numbers and in important places in the genomes of many creatures. In collaboration with workers in the Genome Science Center of RIKEN in Japan, he has taken data for the transcriptome of the mouse genome and shown how DNA that does not code for proteins - the so-called Junk DNA - plays an important role in controlling how gene expression is controlled and therefore how proteins are produced.

In the scientific talks that he gave, Feldmann hopes to build relationships with Indian scientists and bioinformaticians that will result in developing and proving the work that he has done. In addition, Feldmann hopes to focus entrepreneurial interest in developing applications that will eventually affect human health and food production.

Feldmann was awash with stories about Connectrons and how his idea could be applied to solving problems of human health. Having been exposed to malaria for the first time on his other trips, Feldmann said that he would love to understand how the genome of the malarial parasite interacts with the human genome. The difference between his earlier trips and this trip is that now the DNA sequencing of both the malarial parasite genome and the human genome have been completed. Now with a modest amount of computing, he should be able to determine how the malarial parasite imbeds itself in the human body causing so much disease and economic loss.

India's potential

Feldmann argues that India is poised on the edge of the Information Age. That India is in the process of discovering how information, which travels at the speed of light, can transform the state of human health. He argues that the different layers of cellular information - first the genome, then the transcriptome and now the Connectrome - are the most powerful types of information to emerge in the last few years. With entrepreneurial help, Feldmann argues that India could build a world-class position in understanding how genomes work, in understanding how to cure many different diseases and in producing more food.

Future of Connectrons

"The Connectron idea of expression control seems to be very powerful. In the six years since the idea first emerged, I have performed computations on many genomes ranging from the simplest prokaryotes, symbiots and the Archea through the single-celled eukaryotes to the intermediate - and large-genome higher eukaryotes such as worm, fly, human, rat and mouse.

For decades the central paradigm has been that of doing physical experiments. With the sequencing of complete genomes, it becomes possible to conduct wide-ranging computational experiments such as Connectron determination. The balance between physical and computational experimentation is shifting. My sense is that in the decades to come, scientists will first do computations that are then followed by simple physical array measurements as verification of hypotheses. Right now, patenting is hung-up on doing sample physical experiments to show the existence and utility of Connectrons. We are trying to formulate physical experiments to that end."

Control of gene expression by means of Connectrons

"The Connectrome of the transcriptome of a genome is the statement of how each transcript affects the expression of other transcripts. As such, the Connectrome is the logical vehicle for doing simulation of transcript dynamics. In order to accelerate progress in Connectromics, it seems that the time is right for establishing a database of all Connectromes on the Internet. Such a database would act as the support for doing simulations of generalized expression control in all genomes," he added.