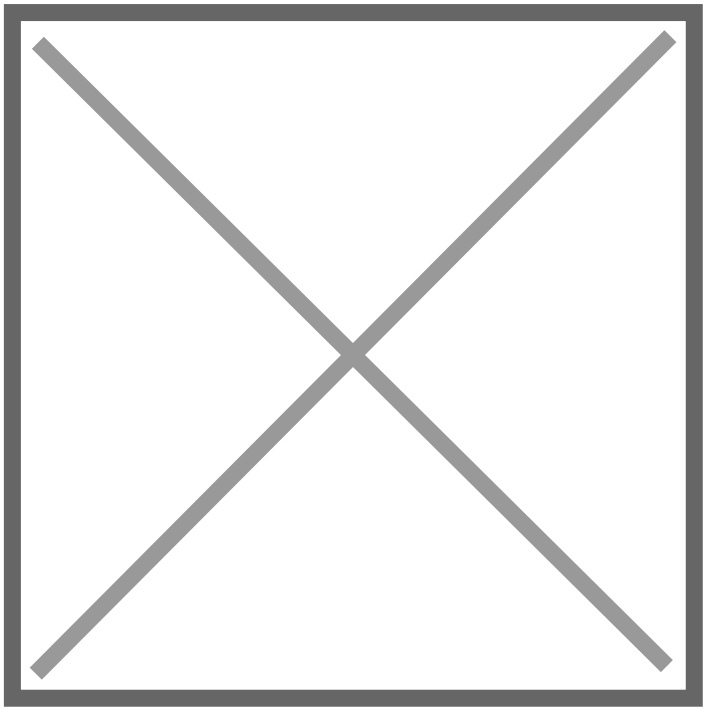
BioSpect
the business of Bi
24 years of leveraging the business of Bio
www.biospectrumindia.co

Indian scientists identify new pathway to combat TB

15 March 2006 | News



Indian scientists identify new pathway to combat TB

A team of Indian scientists led by Rajesh S Gokhale, an HHMI (Howard Hughes Medical Institute) international research scholar at the National Institute of Immunology in New Delhi, has identified five key genes that enable Mycobacterium tuberculosis to acquire the iron it needs to sustain growth and promote infection.

"Targeting genes within this cluster represents a good strategy for preventing tuberculosis and other mycobacterial infections," said Gokhale, the lead investigator on the study. "Because some of these genes are conserved across a number of related bacterial families, they are promising targets for drugs to treat TB and other bacterial diseases."

The tuberculosis bacterium, which infects more than one third of the world's inhabitants, is a leading cause of death and disease worldwide. Gokhale and his colleagues have reported their findings in early online publication January 30, 2006, in the Proceedings of the National Academy of Sciences.

When M tuberculosis infects humans, it takes up residence in immune cells called macrophages. To survive in this harsh environment, mycobacteria, like many other types of bacteria, need iron to carry out life-sustaining functions, such as creating proteins and synthesizing nucleotides to form DNA. However, free iron is not easily found in an intracellular environment. To obtain this rare element, most bacteria manufacture and secrete chemical compounds called siderophores that scavenge iron from the environment.

Researchers discovered siderophores-chemical compounds used by bacteria to scavenge iron from their cellular environment-well over 50 years ago, but the genes involved in adding the long-chain lipid anchor that enables M. tuberculosis to do so more efficiently, remained a mystery until now.

Mycobacteria have evolved siderophores with lipid-chain tails that enable them to exploit the macrophage's lipid-trafficking system to capture iron more efficiently. Instead of using siderophores that diffuse freely, mycobacteria anchor their siderophores to lipid membranes by means of a long fatty acid tail. After these siderophores bind to iron within the macrophage, the lipid tail makes the iron "sticky" enough to permit delivery to the very compartment in macrophages where the mycobacteria are lurking.

Using microarray data, the available literature, and intuition, Gokhale's group identified the location of the four genes that produce the lipid tail after observing that the expression of the genes significantly increased in response to low iron concentrations. The gene required for the synthesis of the siderophore core, called mbt-1, functions the same way, so Gokhale's team named the new locus mbt-2 and the new genes mbtK, mbtL, mbtM, and mbtN. His team has already determined that some of genes from the mbt-2 cluster are conserved across several other bacterial species that cause

various pulmonary, skin, and organ diseases. Since the mbt-1 genes are also conserved across many bacterial families, the mbt genes appear to be ideal antibacterial targets for treating tuberculosis and other bacterial infections, he said.

Biodegradable implant to increase success rate for glaucoma surgery

A Taiwan-based company has developed a collagen matrix which significantly increased the success rate for glaucoma and other selective ophthalmic surgeries. The product has been approved by four university hospitals in both Taiwan and China. The first IRB approval was done last June. The clinical trial has been conducted in these hospitals and the results have been very encouraging.

This collagen matrix was developed by the Taiwan based Pro Top & Mediking company. Last year in December OculusGen Biomedical Inc. acquired Pro Top & Mediking completely and the product was christened as OculusGen Collagen Matrix Implant.

OculusGen is probably the only product of its type worldwide and its research team consists of several eminent ophthalmologists and biologists. It is primarily designed to increase the success rate of glaucoma filtration surgery. The collagen matix is implanted on the top of the sclera flap under conjunctiva before the suturing. It is biodegraded within 90 days and it normalizes the bleb function by offering both physical and physiological effects. Good results were observed in the animal and preliminary clinical trial without any anti-metabolite.

In addition, OculusGen can be used in other selected ophthalmic surgeries, such as pterygium excision, eye plastic surgery, strabismus correction surgery, conjunctiva scar removal surgery, and nasolacrimal duct surgery, etc to prevent scar formation and speed up wound healing.

The product follows a strict quality management system and is a biocompatible collagen implant. The company is now processing an application for the CE Mark and expects to attain the mark in April 2006. The US FDA IDE submission will be made in a month or two.

Scientists develop avian flu vaccine

University of Pittsburgh researchers have announced that they have genetically engineered an avian flu vaccine from the critical components of the deadly H5N1 virus that completely protected mice and chickens from infection. Avian flu has devastated bird populations in Southeast Asia and Europe and so far has killed more than 80 people.

Because this vaccine contains a live virus, it may be more immune-activating than avian flu vaccines prepared by traditional methods, said the researchers. Furthermore, because it is grown in cells, it can be produced much more quickly than traditional vaccines, making it an extremely attractive candidate for preventing the spread of the virus in domestic livestock populations and potentially in humans, according to the study, published in the February 15 issue of the Journal of Virology and made available early online.

"The results of this animal trial are very promising, not only because our vaccine completely protected animals that otherwise would have died, but also because we found that one form of the vaccine stimulates several lines of immunity against H5N1," said Andrea Gambotto, assistant professor in the departments of surgery and molecular genetics and biochemistry, University of Pittsburgh School of Medicine, and lead author of the study.

Dr Gambotto and his colleagues constructed the vaccine by genetically engineering a common cold virus, called adenovirus, to express either all or parts of an avian influenza protein called hemagglutinin (HA) on its surface. Found on the surface of all influenza viruses, HA allows the virus to attach to the cell that is being infected and is, therefore, critical to the influenza virus' ability to cause illness and death.

Since the late 1990s, a number of outbreaks of the avian influenza H5N1 in poultry have occurred in Cambodia, China, Indonesia, Japan, Laos, South Korea, Thailand and Vietnam. Outbreaks recently have been reported in Turkey and Romania. To date, H5N1 has caused the most large-scale and widespread bird deaths in known history - an estimated 150 to 200 million birds have either died in the outbreaks or been killed as part of infection control actions in the last eight years.

Based on the published sequence of the Vietnam strain of the H5N1 avian influenza virus, members of the University of Pittsburgh Vector Core Facility, led by Wentao Gao, PhD, research instructor in the School of Medicine's department of surgery, constructed several adenovirus "vectors" - viruses that have been modified to serve as a vector, or delivery vehicle, for foreign genes or DNA - containing either the full genetic sequence of the HA protein or sequences for only parts, or subunits, of HA. They also constructed a vector containing sequences for a portion of the HA protein from the H5N1 Hong Kong strain.

Collaborating with investigators of the Influenza Branch of the Centers for Disease Control and Prevention, Dr Gambotto's team tested the ability of their slightly different vaccines to protect mice from infection by wild-type H5N1 by comparing its performance to an adenovirus vector containing no H5N1 genes, or an "empty vector." The investigators then observed the H5NI-exposed mice for any signs of illness, including weight loss and death, and also checked their blood for anti-viral antibodies and other markers of H5N1-specific immunity.

All of the mice immunized with the empty vector vaccine experienced substantial weight loss beginning about three days after exposure to wild-type H5N1, and all were dead within six to nine days of avian flu exposure. In sharp contrast, most of the mice immunized with the adenovirus containing either the whole or part of the HA protein showed only mild and short-lived weight loss and survived H5N1 infection.

Dr Gambotto and his colleagues suggest that rather than replacing traditional inactivated influenza vaccines, their adenovirus-based vaccine could be a critically important complement to them. Because it appears to be so successful in immunizing chickens against H5N1, widespread inoculation of susceptible poultry populations could provide a significant barrier to the spread of the virus via that route in this country and other countries that have so far been spared from avian flu. Also, if there were a disruption in the traditional vaccine production pipeline, a recombinant vaccine could be an attractive alternative for human immunization as well, they said.

The recombinant vaccine approach grows the vaccine in cell cultures, which are unlimited in supply. Another major advantage of this approach is its speed.

"It takes a little over a month for us to develop a recombinant vector vaccine compared to a minimum of several months via traditional methods," he explained. "This capacity will be particularly invaluable if the virus begins to mutate rapidly, a phenomenon that often limits the ability of traditional vaccines to contain outbreaks of mutant strains." Dr Gambotto added that his group is planning a small clinical trial of the vaccine in humans in the very near future.

Adult stem cell trial may bring hope to heart patients

A world-first human clinical trial being conducted at John Hunter Hospital, Australia may bring new hope to patients with severe coronary artery disease.

Medical investigators have safely implanted adult stem cells into the heart of two patients via cardiac catheter under local anaesthesia as part of a trial which aims to evaluate the safety and standard operating procedures of Mesoblast's adult stem cell technology.

Mesoblast Limited is an Australian biotechnology company committed to the development of novel treatments for orthopaedic conditions, including the commercialization of a unique adult stem cell technology aimed at the regeneration and repair of bone and cartilage.

Interventional Cardiologist and Hunter Medical Research Institute (HMRI) researcher, Dr Suku Thambar, who is chief investigator for the trial, said that both procedures went well and the patients have been discharged from hospital. HMRI is one of Australia's most innovative health and medical research institutes.

"We hope that Mesoblast's specialist stem cell technology will provide greater hope and better outcomes for patients with severe coronary artery disease who otherwise have very few options for significant improvement or quality of life," said Dr Thambar.

"Each patient's stem cells were extracted from bone marrow in December 2005 and then grown in a laboratory using Mesoblast's proprietary technology, which can cultivate millions of cells from a single donor within a six to eight week period. In each procedure about 100 million of the patient's own stem cells were injected into damaged areas of the heart muscle, which we hope will begin to repair damaged tissue. "Improvement will be assessed in terms of patient symptoms and objective evidence of improved blood supply to the target areas," Dr Thambar added.

Mesoblast chief scientific advisor, Prof. Silviu Itescu, said that Mesoblast aims to develop a safe and effective treatment for a broad range of degenerative diseases.

"Millions of people worldwide are affected by congestive heart failure and coronary artery disease. There are very few options available to treat these conditions. Current methods of treatment including pharmaceuticals, surgery, cardiac replacement and mechanical assistance do not result in cardiac regeneration and are generally extremely expensive and highly invasive," Prof. Itescu said.

The trial has been approved by the Hunter Area Research Ethics Committee.

Dow AgroSciences achieves world's first registration for plant-made vaccine

U S-based Dow AgroSciences LLC, a wholly owned subsidiary of The Dow Chemical Company, has received the world's first regulatory approval for a plant-made vaccine from the United States Department of Agriculture (USDA) Center for Veterinary Biologics. This approval represents an innovative milestone for the company and the industry.

"With this achievement, Dow AgroSciences is revolutionizing the field of preventative medicine with plant-cell-produced vaccines," said Butch Mercer, Dow AgroSciences' global business leader for Animal Health.

The Dow AgroSciences Concert Plant-Cell-Produced System represents a new category of plant-made vaccines. This leading edge technology utilizes plant cells instead of whole plants in a secure, bio-contained environment to produce vaccines. Because of this bio-contained production system, concerns and challenges associated with making vaccines in whole plants or food crops are eliminated.

The Concert Plant-Cell-Produced System uses only the necessary parts of the disease causing agent to stimulate immunity in a manufacturing process that is totally free of animal components. According to John Cuffe, Dow AgroSciences' R&D leader for Animal Health, "This approval is a perfect example of how biotechnology is advancing science by creating a new category of vaccines that is both safe and effective."

By achieving this regulatory milestone, the company has demonstrated that this new technology fits within the existing USDA Center for Veterinary Biologics regulatory approval process. It can now focus its efforts on developing new, innovative vaccines with an emphasis on animal health. Possible target animals include: horses, companion animals (such as dogs and cats), poultry, swine, and cattle. Furthermore, utilizing this revolutionary technology for human diseases is a real possibility.

This milestone achievement by Dow AgroSciences was the result of effective collaborations with prominent organizations and institutions including Washington University, Boyce Thompson Institute for Plant Research, Benchmark Biolabs, Inc., and The Biodesign Institute at Arizona State University. In less than five years Dow AgroSciences moved the science forward, established a production facility, and received this regulatory approval.

Study unearths mutant gene behind heart drug inaction

New research from China indicates that about 30 to 50 percent of East Asians might carry a genetic trait that blocks the body's ability to process the heart drug, nitroglycerin, rendering it useless.

In the normal run, the human body converts nitroglycerin to nitric oxide, which relaxes and expands the smooth muscles of blood vessels. This improves blood flow and means the heart has to pump less forcefully to keep blood circulating. Nitroglycerin has since been used in pill form and in a pump spray to provide quick relief, and as a patch worn for continuous improvement to blood flow.

However, the exact mechanism of action of nitroglycerin was not known till the year 2002. It was only then that the researchers discovered that the enzyme ALDH-2 helps the body convert nitroglycerin into its helpful form of nitric oxide.

Significantly the gene which produces this enzyme, has an unusual expression in Asians, especially the East Asians. In fact, earlier studies have estimated that 30 to 50 percent of Asians have a mutated and inactive form of this gene where as other populations have a very low frequency of this phenomenon.

Dr Li Jin, a population geneticist and lead scientist of the project along with his colleagues conducted their study with 111 Han Chinese patients who all had coronary heart disease and dosed themselves with a nitroglycerin tablet under the tongue during acute angina attacks. While 80 people in the study reported relief within 10 minutes of taking nitroglycerin, the other 31 people said they experienced no pain relief at all.

Testing showed most of these "non-responders" carried the mutant gene. However, the researchers note other genes and environmental factors might also be in play since this one genetic trait could not explain the lack of response in all the patients who felt no relief.

Nevertheless these observations are so striking that scientists at Fudan University in Shanghai suggest doctors reconsider prescribing nitroglycerin to East Asians. This report will appear soon in the Journal of Clinical Investigation.

The linkage of the drug "inaction" to the mutant gene comes under the field of pharmacogenomics, where the drugs could be tailored to a person's gene type to maximize benefits and minimize side effects. Presently the tests to detect the genetic trait

are not widely available and thus personalized medication is still far off.

Since designing drugs for the individual remains a distant goal, research into the genetic traits common in particular groups and ethnic populations has become a proxy in the interim. Critics warn, however, that it could be dangerous to apply these findings in the clinic since nearly all mutations can be found in people of various ethnic backgrounds, albeit at lower frequencies.

However, enthused by these results, the Fudan researchers now have a much larger investigation under way. As scientists have rightly pointed out that the present study sample was a small one for a genetics study.

New protein discovery could improve ability to fight viruses

Scientists have discovered how a single protein could dramatically improve the body's ability to fight viruses such as the flu. A study, published in the January edition of Nature Immunology, identified a protein found naturally in the body may be the secret weapon scientists have been looking for in the fight against infectious diseases such as the flu and hepatitis.

Australia-based Monash Institute of Medical Research (MIMR) led the collaborative study that discovered how the protein, SOCS1, is involved in the body's defence system, and could be manipulated to become a powerful antiviral drug.

"SOCS1 acts like a switch that tells the body when to inhibit interferon; a protein produced as part of the body's normal immune response," said MIMR Post-Doctoral scientist and lead author, Dr Jennifer Fenner.

"Our discovery means we can now manipulate the relationship between SOCS1 and interferon, and eventually target specific diseases," she said. "This could improve resistance to infections, reduce complications of inflammatory diseases and improve vaccinations."

Prof. Paul Hertzog, director of MIMR's Centre for functional Genomics and Disease, said the discovery could have implications for a wide range of diseases for which there are no cures. "Although it will be about 10 years before any drugs are available, we're already working with biotechnology company Zenyth (formally Amrad) to develop potential therapies, including vaccines, based on our research," he said. "As SOCS1 is produced by most cells in the body it has the potential to become a generic treatment for a range of infectious and inflammatory diseases and possibly even cancer."