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# India unlocks TB germ secrets

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In a landmark study that could provide new pathways for Tuberculosis (TB) therapy, Indian scientists have unlocked the secret formula that the TB bacterium uses to survive inside the human body. The results could be used to create a novel TB therapy, one that isn't antibiotics-based and could be a valuable tool in the fight against antibiotic-resistant TB.

The study, led by researchers at the International Centre for Genetic Engineering and Biotechnology (ICGEB) in New Delhi, is the largest of its kind to be done in India.

"It's rare that, in India, we're the first to do something. This time, we were," says Kanury Rao, 51, who leads the immunology group at ICGEB. Together with colleague Dhiraj Kumar, Rao led the 20-member team that did the lab research. ICGEB also partnered with scientists at the All India Institute of Medical Sciences in New Delhi.

Rao and Kumar isolated the 74 human proteins critical for TB's survival inside the human body. If scientists create a therapy that suppresses the production of these proteins, Rao says, public health officials could combine it with existing treatments to "hit TB from two sides at once."

Once considered a dead disease, like smallpox or bubonic plague, TB has re-emerged as one of the major public health challenges of the century.

Many of the new strains of TB are immune to existing antibiotics, creating a massive challenge for public health officials. The existing therapy, a 9-month antibiotic course known as DOTS, isn't effective against drug-resistant cases. At least 8000 Indians will require treatment for multi-drug resistant TB in 2010, according to the World Health Organization.

With this in mind, Rao and Kumar decided to approach TB from another angle, looking at how the TB bacteria interacts with its human host.

"We asked, what are the factors within human cells that help the bacteria to survive," says Kumar.

Exposed patients usually inhale the bacteria that cause TB, Mycobacterium tuberculosis, in the form of very tiny droplets. The bacteria lodge in the lungs, where they enter white blood cells and latch onto proteins inside these cells. By manipulating these proteins, the bacteria can live like parasites in the cell, leaching off cell nutrients and replicating themselves.

Rao and Kumar set out to discover exactly which proteins within the host cell were being targeted by the TB bacteria.

The human body contains 18,174 proteins. These proteins are the essential building blocks that regulate all human functions. To analyze them all is a mammoth task. Scientists refer to it as a genome-wide screen.

Rao and Kumar purchased access to a library of interfering RNA's, a class of chemicals that can block the production of individual proteins. They set up a temporary lab on ICGEB's sprawling South Delhi campus. The cost came to about Rs. 2 crore, footed by the Department of Biotechnology.

Rao and Kumar hired 18 MSc students from all over India. The students injected the interfering RNA's one by one into white blood cells that had been infected with TB bacteria. Three weeks later, the students checked the cells again. They tested 2000 proteins a week. Working 12 hours a day for six months, they analyzed every protein coded for by the human genome.

"It was long hours, but we got exposure to highly technical work," said Mukul Midha, 23, an MSc student at Jaipur National University when the project took place. Because they were working with hazardous diseases, where a single mistake could lead to a deadly infection, the students had to wear special protective gear, including head-to-toe biosafety suits. "Yes, those were strange," said Midha. "But after a while we started to enjoy it."

It's the first time such an experiment has been done by MSc students.

"I think one of the best things about Rao's project is that he showed you can do this kind of cutting-edge, high-throughput work in India, with students," said Satyajit Mayor, a scientist who works with genome screen technology at the National Centre for Biological Sciences in Bangalore. "Abroad, most people use highly skilled postdoc and PhD students."

"These young students are the strength of this country when it comes to research," says Rao. His colleague, Kumar, was once his student. Rao describes Kumar as "one of the few guys who didn't want to be exported abroad." Rao was such an expert. He returned from the United States in 1988 to work with ICGEB.

A year after the experiment began, the scientists had a list of 74 proteins that are critical to the TB bacterium's survival in a cell. Almost every strain of TB, including a set of drug resistant strains that the researchers got from AIIMS, relied on these proteins to survive.

"The actual behavior of bacteria within the host cell is an area where we don't have enough research," said Rajesh

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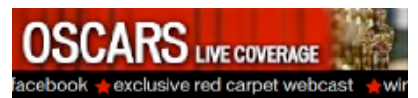
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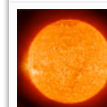


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"That's why this work is interesting."

The findings appear Friday in the journal Cell.

Rao says pharmaceutical companies are already interested in developing therapies based on the findings.

Such a therapy wouldn't mean the end of drug resistance, since bacteria, like humans, are constantly evolving. But it would provide a new avenue for treatment, especially for those infected with drug-resistant strains.

With the global re-emergence of TB, many companies are interested, says Rao.

"It depends on how it's taken forward, either inside India or abroad, but it definitely has promise," says Mayor.

"TB used to be a neglected disease, but it isn't anymore," says Rao.



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**Pawan** 3 days ago

The PubMed search ("Cell"[Journal]) AND India[Affiliation] throws up 8 hits involving several labs across the country. I do not agree that credit should go to only two labs. I also do not agree with PK that "targeting anyone of them should be fine to effect the Mycobacterium survival in the host cell." This is a GROSS UNDERSTATEMENT of cellular dynamics that Kanury himself wouldn't probably make. Please read a bit about Systems Biology and you would know why tweaking one key parameter wouldn't ensure success, given that a cell represents a non-linear situation. Identifying a team of 44 players that we are up against is a very important finding. It is a lot of work, lot of ingenuity and lot of intellectual input. However, merely by knowing the opposite team, let us not claim that we know their "strategy". Imagine if each one of them scores 200 not out :) In my opinion, the press statement could have waited for some more time...

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**amit** 3 days ago

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**PK** 3 days ago

This is an excellent discovery by Renowned Scientist published in the top journal (Cell). There are only two labs in India that have able published research article in this journal so far in Indian history, For those who did not understand clearly, He has identified 44 proteins that are critical for Mycobacterium survival in the host cell. These all genes are essential. Therefore, targeting anyone of them should be fine to effect the Mycobacterium survival in the host cell. He used the complex method to identify these genes that is first of its kind in india, although common is US lab.. I think it should get more attention by Indian NEWS media...

good job keep it up. mr Rao!!!

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**Ravi** 3 days ago

I agree with the comments made about tabloid reporters giving out information on matters of scientific interest. What is the relevance of 44 proteins, did he bother to explain that? The possibilities of identifying one protein out of 44 possible responsible are mind-boggling. This scientist is a nut job & misleading the non-scientific community for cheap publicity. This is like claiming "I figured I lost a stone pebble on one of the 100 beaches I visited, I have now found the beach, but now I just need to figure out where I dropped it on the beach & if I do find it then I have to figure out if that particular pebble is the one that I lost on this beach". What a joke!

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**Observer** 3 days ago in reply to Ravi

By reading your comments it is evident that you are not qualified to make these statements. Please refrain.

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