TB breakthrough could lead to stronger vaccine

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A breakthrough strategy to improve the effectiveness of the only tuberculosis vaccine approved for humans provided superior protection against the deadly disease in a pre-clinical test, report scientists at The University of Texas Health Science Center at Houston in *Nature Medicine*'s Advance Online Publication March 1. Their findings resulted from more than 6 years of research funded by the National Institutes of Health (NIH).

Bacille Calmette-Guérin (BCG) provides only partial protection against tuberculosis (TB) in children and is ineffective in adults. As a result, tuberculosis still kills almost 2 million people a year world wide. "An improved vaccine is widely seen as the best potential method of controlling the disease and is an urgent public health priority," said Chinnaswamy Jagannath, Ph.D., lead author and associate professor at The University of Texas Medical School at Houston.

BCG is a live but weakened form of a bacterium, M. bovis, which causes tuberculosis in cattle. It is sufficiently related to the human pathogen to stimulate production of specialized immune cells that fight off TB infection when it is injected into a person as a vaccine.

Many attempts have been made to improve the vaccine by incorporating antigens (molecular components of the bacteria) to induce a stronger immune response. However, tuberculosis and BCG have evasive mechanisms that prevent the development of stronger immune responses. Investigators at the UT Health Science Center at Houston

investigated mechanisms by which BCG evades immune stimulating mechanisms and devised two means to neutralize them. The scientists used genetically-modified organisms and a drug used for organ transplantation to block BCG's evasive mechanisms, causing it to induce stronger immune responses. Research collaborator on the genetically-modified organisms project was Subramanian Dhandayuthapani, Ph.D., an assistant professor at The University of Texas Health Science Center at San Antonio's Medical Research Division in Edinburg, Texas.

This dual approach to the BCG vaccine was associated with a tenfold increase in the number of TB organisms killed and a threefold increase in the duration of protection in tests with an NIH-approved mouse model, Jagannath said.

"The breakthrough is that Dr. Jagannath has countered the ability of TB organisms to subvert immunization," said Robert L. Hunter Jr., M.D., Ph.D., one of the study's two senior authors and chair of the Department of Pathology and Laboratory Medicine at the UT Medical School at Houston.

Tuberculosis hides in cells so the antigens are not recognized by the immune system. The BCG vaccine also does the same thing, as previously reported in The Journal of Immunology in 2006 by Jagannath and Christopher Singh, a doctoral student at The University of Texas Graduate School of Biomedical Sciences at Houston.

"Dr. Jagannath hypothesized that a drug, rapamycin, which modulates the movement of particles in cells, would cause BCG antigens to enter pathways leading to improved immunization," Hunter said. "In addition, Dr. Jagannath had previously demonstrated that genetic deletion of the fpbA gene has similar effects."

Rapamycin is a drug used to fight cancer and inflammation. In 1992, the

Organ Transplantation Center at the UT Medical School was first to conduct rapamycin clinical trials. The UT group led by Barry D. Kahan, M.D., Ph.D., now professor emeritus, showed that rapamycin significantly reduces the frequency of acute kidney transplant rejection.

"Our findings break new ground in vaccine research in general and make improvements for antituberculosis vaccines in particular, because they provide a simple and powerful strategy to enhance vaccine efficiency," the researchers wrote in the paper. They now plan to add additional antigens to the BCG vaccine to further improve its effectiveness before clinical trials.

The study is titled "Autophagy enhances the efficacy of BCG vaccine by increasing peptide presentation in mouse dendritic cells."

Source: University of Texas Health Science Center at Houston