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New Pneumococcal Vaccine Approach Successful in Early Tests; Vaccine Inhibits Bacteria by Mimicking Naturally-Acquired Immunity

Pneumococcus (Streptococcus pneumoniae) accounts for as much as 11 percent of mortality in young children worldwide. While successful vaccines like Prevnar® exist, they are expensive and only work against specific pneumococcal strains, with the risk of becoming less effective as new strains emerge. Through a novel discovery approach, researchers at Children's Hospital Boston and Genocea Biosciences, Inc., in collaboration with the international nonprofit organization PATH, developed a new vaccine candidate that is potentially cheaper and able to protect against any pneumococcal strain.

Tested in mice, the protein-based vaccine successfully inhibited *S. pneumoniae* from establishing a foothold in the body, the researchers report in the February 17 issue of Cell Host & Microbe.

The current multivalent conjugate pneumococcal vaccines work by inducing people to make antibodies against the sugars on the bacterium's outer capsule. The antibodies then help fight off development of disease after the bacteria have colonized the body. But these vaccines are complex to manufacture, requiring separate individual components for sugars produced by multiple pneumococcal strains. Since pneumococci can make more than 90 different types of sugars, the vaccines may become less effective over time.

The new protein-based vaccine takes a different approach. Based on close to a decade of research at Children's Hospital Boston and utilizing Genocea's novel vaccine discovery technology developed at Harvard Medical School, it stimulates a group of cells in the body known as TH17 cells. These cells provide natural immunity to pneumococcal infection by clearing the bacteria from the surfaces of the upper respiratory tract where infection starts.

Six years ago, Children's Richard Malley, MD, and colleagues showed in mice that while antibodies against surface proteins can protect against pneumococcal disease, there is another mechanism of protection that doesn't require antibodies: the body has natural defenses that act as security guards, preventing the bacteria from becoming squatters in the upper respiratory tract. More recently, they showed that this protection is centered in TH17 cells and production of the chemical messenger IL-17A.

The current study, led by Malley and Kristin Moffit, MD of Children's and Todd Gierahn, PhD, and Jessica Flechtner, PhD, of Genocea Biosciences, began by evaluating a comprehensive library of *S. pneumoniae* proteins, seeking those that stimulated TH17 cells in mice. They identified specific pneumococcal proteins that activated TH17 cells and used them to make a new vaccine formulation.

When live mice were immunized with these antigens, they showed near-complete protection from *S. pneumoniae* upper respiratory tract colonization. These same antigenic proteins also potently stimulated human TH17 cells from healthy adult volunteers, causing them to secrete IL-17A.

"The next steps, already in motion, are to optimize the formulation of this vaccine, confirm its efficacy and safety in animals, and then proceed to human trials," says Malley.

In further collaboration with PATH, the researchers will refine and test the most promising formulation in preclinical studies. If the vaccine proves to be effective and safe, the group will prepare an Investigational New Drug (IND) application to the FDA to begin clinical trials.

Unlike existing conjugate vaccine components, the new pneumococcal protein-based vaccine antigens are common to all strains of *S. pneumoniae*. The researchers hope that a combination of 3 to 5 antigens will protect against pneumococcal colonization and disease from all strains, thereby providing comprehensive immunity with a universal vaccine that would be significantly less complex and expensive to manufacture.

Malley believes that an approach focusing on stimulating TH17 cells or IL-17A secretion may also be effective in providing protection against other pathogens such as *Staphylococcus aureus, Mycobacterium tuberculosis*, or *Listeria monocytogenes*.

"By combining advances in molecular biology, immunology and bioinformatics, the strategy we use at Genocea allows comprehensive, rapid, and unbiased screens of every protein produced by an infectious agent to identify the most effective T cell- stimulating antigens," says Flechtner. "We look forward to our continued collaboration and the development of an improved pneumococcal vaccine."

Source: Kristin L. Moffitt, Todd M. Gierahn, Ying-jie Lu, Paulo Gouveia, Mark Alderson, Jessica Baker Flechtner, Darren E. Higgins, Richard Malley. TH17-Based Vaccine Design for Prevention of Streptococcus pneumoniae Colonization. Cell Host & Microbe, 2011; 9 (2): 158-165 DOI: 10.1016/j.chom.2011.01.007