Scientists Learn How Adjuvant Makes Vaccines Effective

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DENVER, CO — Eighty years after adjuvants were first used to boost the effectiveness of vaccines, researchers at National Jewish Medical and Research Center have finally begun to understand how they work. They report in the June 18 issue of *Science* that the most common adjuvant, alum, provokes a previously unrecognized group of immune-system cells to secrete the protein interleukin-4, which primes B cells for a better response to the vaccine.

"Adjuvants have been included in vaccines given to hundreds of millions of people for decades," said Michael Jordan, MD, co-lead author and researcher at National Jewish. "These findings give us new insight into how they boost the immune response to a vaccine."

Live vaccines, containing weakened forms of an infectious organism, generally work fine by themselves. But vaccines containing dead organisms (inactivated vaccines) or pieces of the infectious organisms or their toxins (acellular or recombinant vaccines) generally need adjuvants to boost their effectiveness. Aluminum salts, known as alum, are the only adjuvant approved for use in the United States for routine preventive vaccines.

The discovery of alum as a vaccine booster actually began with tapioca, a starchy substance used in pudding and as a thickener in cooking. In the early 1920s a scientist named Ramone reported that, for unknown reasons, he had mixed tapioca with inactivated tetanus toxin and found that it served as a more effective vaccine than did the toxin itself. Several years later, a researcher named A.T. Glenny read Ramone's account and decided to mix aluminum salts, or alum, with inactivated tetanus toxin in a test vaccine he tried on rabbits. Again the vaccine with the adjuvant was more effective than a vaccine containing the toxin alone.

The adjuvant alum was first widely used in humans in the 1950s as part of the Salk poliomyelitis vaccine. Since then, adjuvants have been widely used in many vaccines, including the Diptheria/Tetanus/Pertussis (DtaP), Hepatitis, Haemophilus influenzae (Hib), typhoid and some flu vaccines.
No one fully understands why adjuvants boost the effectiveness of nonliving vaccines. Several theories have been proposed but none have been widely accepted.

The National Jewish team was investigating a phenomenon known as MHC class II signaling, which occurs during interactions between B cells and T cells. When properly stimulated, B cells mature into plasma cells, which release antibodies, one of the immune system's major disease-fighting tools.

However, researchers had noticed that B cells must be prepared, or primed, if they are to be stimulated through this signaling pathway. If not primed, they will do nothing or even self-destruct. Priming, however, had been mainly observed in cell cultures. The National Jewish team wanted to determine whether priming occurs in animals, learn how it occurs, and how it might affect the overall antibody response.

They discovered that the injection of the adjuvant alum alone could prime B cells in mice. Then they discovered that cells bearing a marker known as Gr1 appeared in the spleen shortly after the injection of alum into mice. Gr1 is a marker found on a variety of immune-system cells, including granulocytes.

This group of Gr1 cells in the spleen had not been previously recognized, and researchers have not yet completely characterized them. But they did show that the Gr1 cells secrete interleukin-4 and that both the Gr1 cells and the interleukin-4 are necessary for the priming of the B cells. When they inactivated the Gr1 cells, mice responded to a vaccine containing the adjuvant with fewer B cells and fewer antibodies.

"Our research shows that alum injection triggers the accumulation of Gr1 cells in the spleen, which prime B cells and facilitate their response to vaccines," said senior author John Cambier, PhD, Chairman of the Integrated Department of Immunology at National Jewish and the University of Colorado Denver. "We suspect that alum may influence the

immune system in other ways as well. Our findings, however, have begun to unravel the mystery of adjuvants and will lead us in the future to better understand how they have helped prevent disease in millions of people. By understanding how they work we may be able to design new and more effective adjuvants".

National Jewish Health is the leading respiratory hospital in the nation. Founded 123 years ago as a nonprofit hospital, National Jewish Health today is the only facility in the world dedicated exclusively to groundbreaking medical research and treatment of patients with respiratory, cardiac, immune and related disorders. Patients and families come to National Jewish Health from around the world to receive cutting-edge, comprehensive, coordinated care. To learn more, visit the media resources page.

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