

## Researchers Learn How Beryllium Causes Deadly Lung Disease

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DENVER, CO — Using exquisitely detailed maps of molecular shapes and the electrical charges surrounding them, researchers at National Jewish Health have discovered how the metal beryllium triggers a deadly immune response in the lungs. In the July 3, 2014 issue of the journal *Cell*, [John Kappler, PhD](#), and his colleagues show how a genetic susceptibility to the disease creates a molecular pocket in an immune system protein, which captures beryllium ions and triggers an inflammatory response in the lungs. The findings describe for the first time an immune response that lies somewhere between classic forms of allergic hypersensitivity and autoimmunity.

“The immune system does not actually ‘see’ beryllium,” said Dr. Kappler. “The beryllium changes the shape of otherwise innocuous self-peptides so that T cells recognize them as foreign and dangerous.”

Beryllium is a relatively rare metal whose unique combination of strength and lightness makes it invaluable for various industrial uses, ranging from triggers for nuclear bombs to satellite components, computers and cell phones. It can cause disease when people who work with the metal inhale particles that become lodged in the lungs. People who develop chronic beryllium disease can have varied courses of disease, from stable with medications to progressive lung damage and death.

Not everyone who works with the metal becomes ill. About 85 percent of people who develop chronic beryllium disease have an immune system protein known as HLA-DP2. Cells throughout the body use this molecule to tell the immune system what is going on inside of them. HLA-DP2 sits on the cell surface holding small protein fragments taken from the cell’s interior. Immune system sentinels known as T cells bump against HLA-DP2 and its displayed protein fragment. If the protein fragment is derived from the body’s own proteins, the T cell ignores it; if it is a foreign peptide, say from a bacterium, virus or other pathogen, the T cell sounds the alarm and triggers an immune response.

HLA-DP2 differs from most other peptide-presenting proteins by a single amino acid. Dr. Kappler and his colleagues performed a series of highly detailed genetic, X-ray diffraction, molecular binding and electrostatic studies to show how this single amino acid can combine with other amino acids from HLA-DP2 and some of its bound self-peptides to create a unique molecular pocket that captures a single beryllium ion along with a sodium ion.

The peptides that bind to HLA-DP2 come from the body’s own tissues and normally elicit no immune response. With the beryllium and sodium firmly lodged in the molecular pocket, however, those peptides have a very slightly altered shape and electrical charge, which roving T cells recognize as foreign and dangerous. They initiate an immune response that causes inflammation and scarring in the lungs.

“This response resembles allergic hypersensitivity in that a metal ion causes an allergic reaction,” said Dr. Kappler. “But it also resembles autoimmunity in that the immune system is mounting an attack against a self-peptide. It is a new form of immune response, and may lead to new therapeutic strategies to treat and prevent the disease.”

Dr. Kappler also noted that these findings and many previous ones results from a long-term collaboration with his laboratory and those of Shaodong Dai, PhD, at National Jewish Health and Andrew Fontenot, MD, at the University of Colorado School of Medicine.

**National Jewish Health** is the leading respiratory hospital in the nation. Founded 122 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

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