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Newly refined antibody therapy may be potent treatment for autoimmune diseases

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An old, fickle therapy for a variety of autoimmune diseases is getting a makeover, thanks to a decade-long investigation by Rockefeller University researchers. The original treatment, called intravenous immunoglobulin or IVIG, is an amalgam of specific antibodies made from the pooled blood plasma of thousands of healthy donors.

Physicians have used it both on-label and off in patients with lupus, arthritis, asthma and other immune disorders, to varying degrees of success. But new research shows that understanding how the therapy works at a molecular level can help researchers create a version in the lab that's many times more potent.

Jeffrey Ravetch, Theresa and Eugene M. Lang Professor and head of the Leonard Wagner Laboratory of Molecular Genetics and Immunology, has been interested in IVIG ever since he became aware of its inherent paradox: IgG antibodies, the very class of antibodies that triggers autoimmune diseases, give IVIG its anti-inflammatory properties when pooled from healthy donors.

In 2006, Ravetch and his colleagues discovered that this apparent contradiction could be attributed to a single sugar molecule called sialic acid, located at the very tip of some IgG antibodies. When present, the molecule confers anti-inflammatory properties. When absent, the IgG molecules lose their protective abilities and can actually cause inflammation.

Once the scientists had pinned down the molecular mechanism at the source of the contradiction and proved that they could map out a strategy for building a drug with the therapeutic properties of IVIG, they set about creating it. Ravetch, together with his collaborators at the University of New Hampshire and The Scripps Research Institute, produced an engineered, sialylated IgG molecule that — when given to arthritic mice — was about 30 times more effective than IVIG alone.

“This paper provides a clear route for developing an alternative for IVIG, which could be of great benefit to patients with autoimmune diseases,” Ravetch says. The results, reported in the latest issue of Science, also describe the precise structural requirements needed to create IgG with protective properties.

Rockefeller has licensed the technology to the biotechnology company Centaurus Pharmaceuticals, which is working to create a product that can be used in clinical trials. Ravetch believes that the resulting drug will have the potential to provide relief to people with a wide range of ailments, including those for whom IVIG just barely scratches the surface. In lupus, for instance, the current preparation has such low activity that the amount required to effect a noticeable difference exceeds the amount that can be realistically derived from the blood supply. “But with the recombinant form,” Ravetch says, “you can make an unlimited, potent supply.”

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