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Treatment doctor tested on himself can put others into remission

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David C. Fajgenbaum, MD, MBA, MSc. Credit: Penn Medicine

Five years ago, David C. Fajgenbaum, MD, MBA, MSc, both a Penn Medicine researcher and patient, tried an experimental treatment on himself based on his laboratory research findings in the hopes of saving

his own life. He has been in remission ever since. Now his research is shedding new light on why it worked, paving the way for further testing of a new treatment approach in Castleman disease, a rare and deadly condition with limited options for patients. The work is led by Fajgenbaum, who is both the director of the Center for Study & Treatment of Castleman's & Inflammatory Lymphadenopathies (CSTL) in the Perelman School of Medicine at the University of Pennsylvania as well as Patient 1 in the study. The findings show patients who do not respond to the only drug currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of the disease may have another option that targets a specific pathway called PI3K/Akt/mTOR. The research is published in the *Journal of Clinical Investigation* today.

Castleman disease isn't actually a single disease. The term describes a group of inflammatory disorders that share a common appearance under the microscope. It's diagnosed in about 5,000 people of all ages each year in the United States, which makes it roughly as common as Lou Gehrig's disease, also called ALS. Patients experience a range of symptoms—from a single abnormal lymph node with mild flu-like symptoms to abnormal lymph nodes located throughout their entire body, abnormal blood cell counts, and life-threatening failure of multiple organ systems, such as the kidneys, liver, heart, and lungs.

The most severe subtype, idiopathic multicentric Castleman disease (iMCD), has similarities to both autoimmune conditions as well as cancer. About 35 percent of patients with iMCD will die within five years of diagnosis. In 2014, the FDA approved the drug siltuximab to treat iMCD, and studies have shown it can send between one-third and one-half of patients into a remission that generally lasts for years.

"Patients who don't respond to siltuximab have limited options. They typically receive chemotherapy but often relapse," said Fajgenbaum, who is also an assistant professor of Medicine in the division of

Translational Medicine & Human Genetics at Penn and executive director of the Castleman Disease Collaborative Network. The study's senior authors are Thomas S. Uldrick, MD, MS, the deputy head of Global Oncology at Fred Hutchinson Cancer Research Center who was also Fajgenbaum's treating physician while practicing at the National Institutes of Health, and Frits van Rhee, MD, Ph.D., the clinical director of the Myeloma Center at the University of Arkansas for Medical Sciences.

A med student, a former Division I quarterback, and a state-champion weight lifter, Fajgenbaum suddenly became sick in July 2010. In 2012, after failing to respond to other therapies and having relapsed multiple times after chemo, Fajgenbaum's research on his own condition suggested that an inhibitor drug called sirolimus that blocked the PI3K/Akt/mTOR pathway could be effective. This drug is already available for the treatment of other conditions, particularly to prevent organ rejection after kidney transplantation. Fajgenbaum's decision to test it on himself, which was based on his own research and made in consultation with Uldrick, his treating physician, has kept him in remission ever since. This study also examines two additional patients treated with the same approach who also achieved a sustained remission. Research showed all three patients saw an increase in two aspects of the immune system—increased numbers of activated T cells and elevated levels of a protein called VEGF-A that causes blood vessel growth—before a flare up, then a return to normal levels once remission began.

"Our findings are the first to link T cells, VEGF-A, and the PI3K/Akt/mTOR pathway to iMCD," Fajgenbaum said. "Most importantly, these patients improved when we inhibited mTOR. This is crucial because it gives us a therapeutic target for patients who don't respond to siltuximab."

Fajgenbaum and his team will test the treatment in a clinical trial (NCT03933904) set to open in the coming weeks at the University of Pennsylvania, with Sunita Nasta, MD, FACP, an associate professor of Hematology-Oncology, and Adam Cohen, MD, an assistant professor of Hematology-Oncology, enrolling and treating patients. The University of Arkansas for Medical Sciences will also serve as a trial site under the direction of van Rhee.

Fajgenbaum also points out the larger implications this research has for the rare disease community.

"This highlights the potential for the approximately 1,500 drugs already approved for one condition to also be treatments or cures for the 7,000 diseases with no or insufficient treatment options like ALS and many pediatric cancers," Fajgenbaum said.

Provided by Perelman School of Medicine at the University of Pennsylvania

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