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Lupus Research Institute

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LRI Distinguished Innovator's Discovery Could Result in Drugs to Reverse Autoimmune Attack

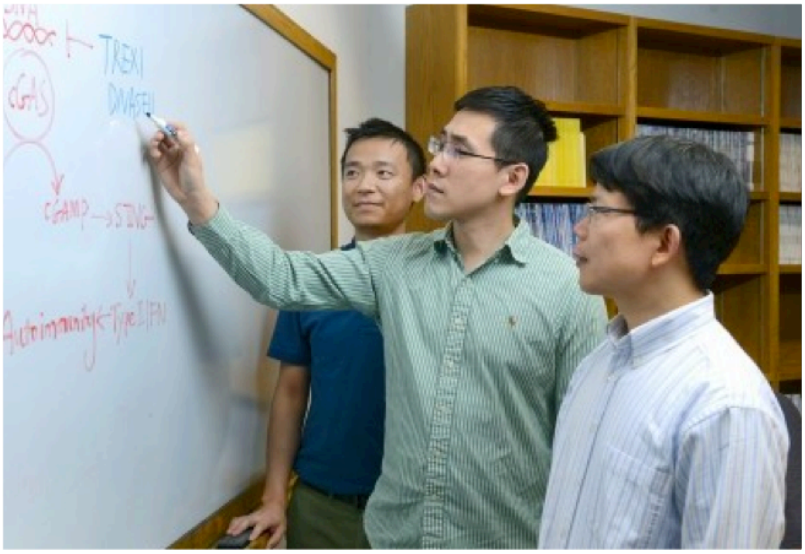
University of Texas Southwestern has just reported a major discovery by Dr. Zhijian "James" Chen, Professor of Molecular Biology and a recent recipient of the Lupus Research Institute's (LRI) Distinguished Innovator (DI) Award.

With his Award from the LRI and other funding, Dr. Chen has identified a specific enzyme, cGAS, that when activated in mice "sounds the alarm" for the autoimmune system to attack --and then, when inhibited "rescues them" from the disease. According to Dr. Chen, this breakthrough should facilitate development of new drugs that would inhibit the cGAS enzyme and stop the autoimmune response.

The LRI's Distinguished Innovator Award provides grants of up to $1 million to exceptional researchers worldwide like Dr. Chen who match scientific rigor with innovative vision. His work exemplifies the goal of the DI Award -- to find and fund the highly novel large-scale projects that can get to the root of lupus and advance treatments that could arrest or reverse disease.

UT Southwestern's news release below describes these new findings from Dr. Chen and his team, and the potential to transform treatment for lupus and other autoimmune diseases:

Researchers identify an enzyme as a major culprit of autoimmune diseases



DALLAS – Activating an enzyme that sounds an alarm for the body's innate immune system causes two lethal autoimmune diseases in mice, while inhibiting the same enzyme rescues them, UT Southwestern Medical Center researchers report.

The findings, published in the Oct. 20 issue of the Proceedings of the National Academy of Sciences (PNAS), could someday lead to new therapies for autoimmune diseases.

Photo: UT Southwestern researchers (l-r) Dr. Tuo Li, Daxing Gao, and Dr. Zhijian "James" Chen.

"These results suggest that inhibition of the enzyme cGAS may be an effective therapy for autoimmune diseases such as Aicardi-Goutieres Syndrome (AGS) and systemic lupus erythematosus (SLE), which are linked to the same inflammatory pathway," said senior author Dr. Zhijian "James" Chen, Professor of Molecular Biology and a Howard Hughes Medical Institute (HHMI) investigator at UT Southwestern.

In autoimmune diseases, the immune system turns against the body instead of protecting it. AGS is a

rare genetic disorder that mainly affects the brain, while SLE can affect the skin, joints, kidneys, brain, and other organs. Neither disease has a cure, only treatments to control symptoms.

Dr. Chen said cGAS is likely amenable to inhibition by small-molecule drugs and that the recent determination of the high-resolution structures of cGAS should facilitate development of such inhibitors.

The work builds on two back-to-back studies the Chen lab published in Science in late 2012 that identified cGAS as a sensor of innate immunity – the body's first line of defense against invaders. A commentary in the same issue of PNAS refers to the Chen lab's identification of that long-sought sensor of DNA in the cytoplasm, the cell's gel-like interior, as a "groundbreaking discovery."

The Science studies described a novel cell signaling pathway that starts when cGAS detects foreign DNA, such as viral DNA, and sounds the alarm. That alarm sets off an inflammatory cascade that induces antiviral molecules, including a family of secreted proteins called interferons. The same elegant system can trigger autoimmune disease when self-DNA is inappropriately present in the cytoplasm, Dr. Chen explained.

The current study in PNAS examined TREX1, a protein that digests DNA in the cell's interior. Loss-of-function mutations in the gene that codes for the TREX1 protein are linked to AGS and SLE in humans. Like humans, mice lacking TREX1 exhibit autoimmunity, inflammation, and elevated levels of interferons, the researchers report. When the researchers genetically inhibited cGAS in those mice, their symptoms disappeared.

"Even deletion of just one of the two genes for cGAS largely rescued the mice from the autoimmune disease," said Dr. Chen, who also is an investigator in the Center for the Genetics of Host Defense and holder of the George L. MacGregor Distinguished Chair in Biomedical Science.

The researchers also studied mice genetically engineered to lack a DNA-digesting enzyme called DNase-II. While the resulting inability to degrade lysosomal DNA led to lethal autoimmunity, once again cGAS inhibition rescued the mice, the researchers report.

Graduate student Daxing Gao and postdoctoral researcher Dr. Tuo Li were the study's lead authors. Other UT Southwestern researchers involved in the study were Dr. Xiao-Dong Li, a former Instructor in Molecular Biology who is now Assistant Professor at UT Health Science Center at San Antonio; Dr. Xiang Chen, a research scientist in Molecular Biology and a research specialist with the HHMI; Dr. Quan-Zhen Li, Associate Professor of Immunology and Internal Medicine; and Dr. Mary Wight-Carter, Assistant Director of the Animal Resources Center.

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