SOUTHWESTERN NEWS

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SCIENTISTS DESIGN NOVEL PROTEINS THAT BLOCK INFLAMMATION REGULATOR ASSOCIATED WITH RHEUMATOID ARTHRITIS

DALLAS – Sept. 26, 2003 – Researchers at UT Southwestern Medical Center at Dallas have tested and validated novel proteins, created by California-based Xencor, that block activity of a major molecule involved in the onset of inflammation, an innovation that may translate into new therapeutic options for people with rheumatoid arthritis.

Researchers at both institutions report in today's issue of *Science* that blocking the activation of a regulator of inflammation called tumor necrosis factor (TNF) decreased swelling by 25 percent in a rodent model of the human disease rheumatoid arthritis. Elevated TNF levels are associated with the onset of rheumatoid arthritis.

The uniqueness of the new inhibitors, the scientific team reports, lies in their design and mode of action. Unlike the drugs that are currently available, the structure and sequence of these newly designed molecules are similar to naturally produced proteins, making it less likely that the body will elicit an immune response to fight off foreign agents.

"What we've engineered are variant proteins that are very similar to the protein that the body expresses on its own, which makes it less likely that the body will see it as foreign," said Dr. Malú Tansey, a lead author of the study and assistant professor of physiology at UT Southwestern, where some of the in vivo testing and validation was completed and where work will continue on these TNF inhibitors.

"The inhibitors are actually modified versions of the TNF protein that is naturally found in the body, but with a few mutations that prevent them from binding to receptors but still allow the proteins to bind TNF. The end result is sequestration of active TNF away from the receptors that mediate inflammatory responses implicated in rheumatoid arthritis and several other autoimmune diseases," said Dr. Tansey, former member of the Xencor team.

These findings provide a "promising new avenue" for physicians who treat the 2.1 million Americans with rheumatoid arthritis, said Dr. David Karp, chief of rheumatic

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diseases and associate director of the Harold C. Simmons Arthritis Research Center.

"This is a very novel approach; one that has not been looked at by other investigators," he said. "This family of proteins is not only implicated in the painful inflammation of rheumatoid arthritis, but also the joint destruction that accompanies the disease. These proteins also may be critical for other autoimmune diseases like multiple sclerosis and systemic lupus erythematosis."

Rheumatoid arthritis is an autoimmune disease in which the body's immune system attacks its own tissues, mistaking them for foreign substances like bacteria or viruses. This disease is characterized by redness, swelling, loss of joint function and deterioration of cartilage and bone in the joints.

There is no cure for the disease, but there are currently three drugs that specifically target TNF inhibition. Although these drugs have been shown to be effective in decreasing the pain associated with the disease and in some cases joint destruction, some patients develop antibodies against the drugs, which may require the administration of higher doses.

"This side effect may lower the effectiveness of these drugs," Dr. Tansey said. "Our prediction is that because these TNF variants are virtually identical to native TNF, the body will not form antibodies against them, but this will have to be tested."

The TNF variants are currently in preclinical development at Xencor.

Anti-TNF therapy may also be useful in blocking inflammation in neurodegenerative diseases like Alzheimer's and Parkinson's disease, Dr. Tansey said.

Dr. Tansey recently received a $200,000 grant from the Michael J. Fox Foundation to examine the role that elevated levels of TNF play in the loss of dopamine-producing neurons, which lead to Parkinson's disease.

Other researchers who contributed to this study include Sabrina Martinez, a research technician II in physiology at UT Southwestern.

The study was funded by Xencor, a private biotechnology company founded in 1997.

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