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Office of Medical Information
The University of Texas Southwestern Medical Center at Dallas
5323 Harry Hines Boulevard Dallas, Texas 75235-9060 214/688-3404

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Contact: David Doremus
Office: 214/688-3404
Home: 817/496-8571

****UT Southwestern researchers announce arthritis breakthrough

DALLAS --Researchers at The University of Texas Southwestern Medical Center and The Howard Hughes Medical Institute in Dallas say experiments with genetically altered rats confirm the long-suspected link between the genetic element HLA-B27, involved in the regulation of the human immune system, and a family of rheumatic diseases affecting 200,000 Americans.

Even more significant, perhaps, are the genetically altered rats themselves. They represent an animal model so startling in its authenticity that it may provide the most powerful tool yet for investigating certain kinds of arthritis and other inflammatory disorders. The rats are the subject of a patent application. The patent would be shared by the sponsors of the research.

The twin breakthroughs are the result of the ongoing collaboration between Dr. Joel D. Taurog of UT Southwestern's Harold C. Simmons Arthritis Research Center and Dr. Robert E. Hammer of Howard Hughes Medical Institute. Hammer and Taurog published their findings in the Nov. 30, 1990, issue of *Cell* under the title, "Spontaneous Inflammatory Disease in Transgenic Rats Expressing HLA-B27 and Human Beta-2 Microglobulin: An Animal Model of HLA-B27-Associated Human Disorders."

HLA-B27 is the name of a genetically determined protein common to spondyloarthropathies--a group of arthritic disorders that often involve inflammation of the spine. HLA-B27 is a member of the Human Lymphocyte Antigen family of molecules, which play a major role in regulating the white blood cells that make up the body's immune system.

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Transgenic refers to the process by which one or more foreign genes--in this case, the two genes that encode the B27 molecule--are inserted into a fertilized egg, becoming part of the developing individual's own genetic material. It has become common for mice to be genetically altered in this way, but it had never been accomplished in rats before.

"For me, the B27 transgenic rats are the result of a 10-year quest for an animal model of the B27-associated diseases," says Taurog.

In an attempt to develop such a model, Hammer and Taurog, as well as several groups of researchers elsewhere, produced transgenic mice expressing HLA-B27. For reasons still not fully understood, the mice did not show any of the features of B27-associated human disease. But when B27 genes were introduced into rat embryos, the descendants of two of the transgenic rats spontaneously developed inflammatory disease involving not only the joints, but also the gastrointestinal tract, the male genital tract, skin, nails and heart. This pattern of organ involvement bears a striking resemblance to the spectrum of B27-associated disorders in humans.

"This work underscores the important differences that can be found even between apparently similar species such as rats and mice," notes Hammer. "Clearly, in developing transgenic animal models of human diseases, it will become increasingly necessary to determine the most appropriate species for each particular disease."

The association between B27 and the spondyloarthropathies was first noted in 1973, when two groups of researchers--one in Los Angeles and one in London--reported simultaneously that B27 was present in 90 percent of patients affected by a chronic form of spondyloarthropathy, ankylosing spondylitis, but in only 7 percent of the normal population. Ankylosing spondylitis is characterized by inflammation of the joints that link the vertebrae. In severe cases, the patient can lose all flexibility and end up with a "poker" spine.

An important association also exists between HLA-B27 and reactive arthritis, in which certain bacterial infections trigger inflammation in joints and other tissues.

The B27-associated diseases are classified as rheumatic disorders because the most common complaints associated with them are joint

inflammation and pain. All, however, can involve more than one organ system, particularly the gastrointestinal and genitourinary tracts, as well as the skin, eyes and heart.

Hammer and Taurog's results establish that B27 plays a central role in causing spondyloarthropathies such as reactive arthritis and ankylosing spondylitis. Thanks to the remarkably authentic model provided by the transgenic rat, researchers now may be able to gain new insights into the disease process and to test a variety of new treatments.

"This project exemplifies the abundant possibilities that can result from the successful collaboration between an M.D.-trained physician-investigator such as myself and a Ph.D.-trained basic scientist such as Dr. Hammer," says Taurog.

"There are no guarantees in this business, and we're usually quite happy when we make slow progress. But this is a quantum leap," says Dr. Peter E. Lipsky, director of the Simmons Arthritis Research Center. Established in 1982 with funds from Dallas businessman Harold Simmons, the center is dedicated to the search for the causes of the spondyloarthropathies.

The Howard Hughes Medical Institute, founded in 1953 by the late aviator-industrialist Howard R. Hughes, currently employs about 200 biomedical researchers at academic medical centers, hospitals, universities and other research institutions throughout the United States--including UT Southwestern.

Additional support for the study of B27-associated diseases in transgenic rats was provided by the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the North Texas Chapter of the Arthritis Foundation.

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Note: The University of Texas Southwestern Medical Center at Dallas comprises Southwestern Medical School, Southwestern Graduate School of Biomedical Sciences and Southwestern Allied Health Sciences School.