SOUTHWESTERN NEWS

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NEW FORM OF GENE THERAPY HOLDS PROMISE FOR THE FUTURE

DALLAS – October 23, 1997 – Scientists at UT Southwestern Medical Center at Dallas are one step closer to producing a "drug" that is internally regulated and activated only when needed.

They have developed a system in mice in which the level of a genetically engineered protein responds to inflammatory signals produced by the mice themselves. This method of gene therapy, described in the October issue of *Nature Biotechnology*, may have great potential for treating chronic relapsing and remitting inflammatory diseases, such as rheumatoid arthritis, and organ transplant rejection.

"Our long-range goal is to give patients the right amount of an anti-inflammatory protein, at the right time and in the right place, to control damaging inflammation by introducing the gene for the protein and allowing the body's own signals to control its production," said Dr. Robert Munford, professor of internal medicine and microbiology and holder of the Jan and Henri Bromberg Chair in Internal Medicine.

According to Munford, who worked with Dr. Alan Varley, a research fellow in internal medicine, and research technician Steven Geiszler, "There are lots of hurdles to overcome, but Varley and Geiszler seem to have jumped the first one, showing that recombinant genes can actually be regulated in animals in response to inflammation."

The investigators used a "reporter" gene – a gene that encodes an easily measured protein – to test the ability of a mouse's immune response to turn on that gene. The reporter gene they used was firefly luciferase, an enzyme that causes light emission and can be measured easily with a luminometer. In the laboratory, they inserted the luciferase gene into a genetically altered virus that could not reproduce. To stimulate

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and control the production of luciferase, the researchers inserted specific short pieces of deoxyribonucleic acid (DNA) in front of the luciferase gene. These short DNA elements respond to internal signals by turning genes on and off.

The trick was to find the right combination of DNA elements to dramatically enhance production of luciferase in response to an inflammatory reaction.

The successful combination consisted of three elements – one from the mouse and two from a virus – that worked in concert and greatly amplified the production of luciferase when the proper signals (in this case, an inflammatory reaction) were received.

The luciferase gene preceded by the three short pieces of DNA was genetically inserted into the viral molecule and injected into mice. Researchers then induced two different types of inflammatory responses. They determined how successful their combination of elements was by measuring the amount of luciferase produced in the mouse's liver, spleen, lung, heart and kidney.

If a gene for an anti-inflammatory protein is used in place of the luciferase gene, this type of gene therapy, in theory, would activate that protein in response to the body's own inflammatory signals.

"The production level of the anti-inflammatory protein should reflect the intensity and duration of the inflammatory condition," said Munford. "If the gene can be delivered to a specific site, such as an inflamed joint or an organ about to be transplanted into a recipient, it may be possible to provide effective anti-inflammatory treatment while avoiding systemic immunosuppression with its risk of infection."

Dr. Richard Gaynor, professor of internal medicine and microbiology, and holder of the Andrea L. Simmons Distinguished Chair in Cancer Virology, also collaborated in the studies.

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