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SCIENTISTS DISCOVER HOW ASPIRIN REDUCES INFLAMMATION

DALLAS — November 5, 1998 — Everyone knows that aspirin helps reduce inflammation, but for years no one knew how. Researchers at UT Southwestern Medical Center at Dallas now have an answer, which could lead to the design of more effective anti-inflammatory drugs.

Dr. Richard Gaynor, interim director of the Harold C. Simmons Comprehensive Cancer Center and professor of internal medicine, and colleagues describe the molecular action of aspirin and salicylate (from which aspirin is derived) in the Nov. 5 issue of the journal *Nature*.

Inflammation occurs due to a complex series of responses, many of which have been known for the last decade. Some of the initial steps take place within the nucleus of the cell where "gene regulators" switch on the production of specific genes, which in turn act on other genes causing a cascade of events leading to inflammation.

One of the initiators in this inflammatory cascade, a cellular protein called NF-κB, is inactive until it gets into the nucleus where it turns on genes involved in the inflammatory response. The gatekeeper or inhibitor of NF-κB is another protein, IκB, which if destroyed frees up NF-κB to enter the nucleus and start the inflammatory process.

"This work suggests that one of the critical cellular proteins that aspirin targets to inhibit inflammation is a kinase that activates the NF-κB pathway. Since NF-κB is a critical inducer of cellular genes involved in the inflammatory process, aspirin inhibition of this kinase prevents NF-κB activation and suppresses inflammation," Gaynor said. "This kinase is an excellent target for the development of novel anti-inflammatory agents."

In this paper Gaynor and colleagues clearly define a molecular step where aspirin and salicylate act to block the inflammatory cascade -- they inhibit one of the proteins involved in the destruction of IκB. The result is that NF-κB remains sequestered outside the cell's nucleus thereby

preventing the NF-κB-induced inflammatory response. This process, in addition to the inhibition of inflammatory mediators known as prostaglandins, likely explains many of aspirin's inflammation-reducing effects.

Other UT Southwestern co-authors were internal medicine research fellow Min-Jean Yin and research assistant Yumi Yamamoto. Gaynor, who holds the Andrea L. Simmons Distinguished Chair in Cancer Virology, is chief of hematology-oncology at UT Southwestern.