Discovery shows medications can treat inflammation without increasing risk for infection

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In a discovery that can fundamentally change how drugs for arthritis, and potentially many other diseases, are made, University of Utah medical researchers have identified a way to treat inflammation while potentially minimizing a serious side effect of current medications: the increased risk for infection.

These findings provide a new roadmap for making powerful anti-inflammatory medicines that will be safer not only for arthritis patients but also for millions of others with inflammation-associated diseases, such as diabetes, traumatic brain injury, and inflammatory bowel disease , according to cardiologist Dean Y. Li, M.D., Ph.D., the U School of Medicine vice dean for research and HA and Edna Benning endowed professor of medicine who led the study. "This can change the way medication is made," he says. "If we can find a way to replace our most powerful drugs for arthritis, we might be able to develop another way to treat inflammation in other diseases that we've been unable to touch because of the danger of suppressing people's immune systems."

The research, funded by the National Institutes of Health (NIH) and published Sunday, Nov. 11, 2012, *Nature* online, provides the University the opportunity to explore commercializing the technology either through collaboration outside of the state with pharmaceutical companies or within the state via initiatives such as USTAR. The Utah Legislature established USTAR (Utah Science Technology and

Research) initiative in 2006 to promote economic growth and high paying jobs through research at the U of U and Utah State University.

"This is just one example of many scientific opportunities for the University and USTAR to work together to benefit not only millions of patients but build medical innovations in Utah," says Li, who's also director of the U of U Molecular Medicine program.

Two Cellular Pathways

When the body undergoes trauma or gets an infection, it responds by releasing cytokines—proteins that enter cells and unleash a three-pronged attack to kill invading bugs, hype up the immune system, and cause inflammation. While inflammation fights infection, it also produces an undesired side effect by weakening blood vessels, which can lead to swelling in the joints, brain or other areas. Scientists long have believed that cytokines use one cellular pathway in their response to infection, meaning that drugs made to block cytokines from causing inflammation also block the immune system and the ability to kill invading bugs.

In a study with mice, Li and his research colleagues upended the one-pathway belief by showing that cytokines use not one but two cellular pathways to battle infection: one to turn on the immune system and kill intruders and a separate one that destroys the architecture of tissues and organs. Identifying the separate pathway for inflammation has vast potential for developing drugs. "We can selectively block inflammation without making the patient immunosuppressed," Li says. "This rewrites the strategy for today's medicines. We focused the work on arthritis given this is a proven market for drugs that reduce damage from inflammation and fibrosis, but we suspect that many other diseases ranging from fibrosis following heart attacks to inflammatory bowel disease may benefit from such an approach."

Li's discovery has dramatic implications for the field of rheumatology, according to Tracy M. Frech, M.D., U of U assistant professor of internal medicine who specializes in rheumatology. "This may lead to more effective treatments for conditions such as lupus, systemic sclerosis, and the spectrum of inflammatory arthritis, without putting patients at risk for infections," she says. "This phenomenal work is a credit to the strong molecular medicine program here at the University of Utah."

Before a new generation of anti-inflammation drugs can be made, researchers must screen for molecules of chemical compounds that can be turned in pharmaceutical-grade drugs, something the University can and should do, according to Li. This can be accomplished either through collaboration with pharmaceutical companies outside of the state or with sources inside Utah, such as the USTAR initiative.

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