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Experimental compound dramatically reduces joint inflammation

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An experimental compound synthesized and developed by scientists from the Florida campus of The Scripps Research Institute (TSRI) has the capacity to significantly reduce joint inflammation in animal models of rheumatoid arthritis, an autoimmune disease that affects more than two million Americans.

The study was published recently online ahead of print by the journal *Arthritis & Rheumatism*.

The study showed the compound, known as SR2211, blocked development of virtually all symptoms of rheumatoid arthritis in mice within the first eight to ten days of treatment. The mice also showed significantly reduced bone and cartilage erosion compared to animals that did not receive treatment.

The experimental compound targets the nuclear receptor RORγ, a key regulator of TH17 cells, one of a family of white blood cells that play a role in the immune system. Identified only a decade ago, TH17 cells have been implicated in numerous autoimmune diseases, including multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease and lupus.

"This compound, and its precursors, showed the ability to block the release of specific inflammatory mediators from Th17 cells in culture, so we were confident that SR2211 would demonstrate good efficacy in rodent models of autoimmune disease," said biochemist Patrick R.

Griffin, chair of the TSRI Department of Molecular Therapeutics. "Our newest study strongly supports the idea that by targeting the RORγ receptor, we can therapeutically repress inflammation and joint destruction associated with rheumatoid arthritis."

While several treatments are currently available for rheumatoid arthritis, Griffin noted their use is associated with the increased risk of infections and pneumonia. Since they have to be taken by injection, they are optimized for long, sustained immunosuppressive action, which is a disadvantage in managing opportunistic infections. An oral medication could be taken daily and stopped immediately to allow the drug to leave the body in the case of a potentially life-threatening infection.

"This study with SR2211 shows that repressing the activity of the RORγ receptor alone works to reduce joint erosion and inflammation," Griffin said. "It's an alternative mechanism of action that can provide doctors with additional treatment options for patients who do not respond well or cannot tolerate current therapies."

"We wanted to develop a compound with the potential to help treat patients suffering from a range of autoimmune diseases, including rheumatoid arthritis," said Staff Scientist Mi Ra Chang, the first author of the study and a member of the Griffin lab. "Compounds such as SR2211 work directly and specifically on at least two immune cell types directly involved in the pathogenesis of autoimmune disease."

More information: "Pharmacological Repression of RORγ Is Therapeutic in the Collagen-induced Arthritis Experimental Model" DOI: 10.1002/art.38272

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