Compound effectively halts progression of multiple sclerosis

Scientists from the Florida campus of The Scripps Research Institute have developed the first of a new class of highly selective compounds that effectively suppresses the severity of multiple sclerosis in animal models. The discovery also holds promise for other autoimmune disorders.

The new compound could provide new and potentially more effective therapeutic approaches to multiple sclerosis and other autoimmune diseases that affect patients worldwide.

The study appeared 17 April 2011, in an advance online edition of the journal *Nature*.

Current treatments for autoimmunity suppress the patient's entire immune system, leaving patients vulnerable to a range of adverse side effects. Because the new compound, known as SR1001, only blocks the actions of a specific cell type playing a significant role in autoimmunity, it appears to avoid many of the widespread side effects of current therapies.

A 'novel' drug

"This is a novel drug that works effectively in animal models with few side effects," said Tom Burris, Ph.D., a professor in the Department of Molecular Therapeutics at Scripps Florida who led the study, which was a multidisciplinary collaboration with scientists including Patrick Griffin, William Roush, and Ted Kamenecka of Scripps Research, and Paul Drew of the University of Arkansas for Medical Sciences. "We have been involved in several discussions with both pharmaceutical and biotechnology firms who are very interested in developing it further."

A lengthy process of drug development and review is required to ensure a new drug's safety and efficacy before it can be brought to market.

"This impressive multidisciplinary team has used a combined structural and functional approach to describe a class of molecules that could lead to new medicines for treating autoimmune diseases," said Charles Edmonds, Ph.D., who oversees structural biology grants at the National Institutes of Health. "Breakthroughs such as this highlight the value of scientists with diverse expertise joining forces to solve important biological problems that have the potential to benefit human health."

Targeting specific receptors

For the past several years, Burris and his colleagues have been investigating small-molecule compounds that affect

particular disease-related receptors (structures that bind other molecules, triggering some effect on the cell). In particular, the scientists have been interested in a pair of "orphan nuclear receptors" (receptors with no known natural binding partner) called RORa and ROR? involved in both autoimmune and metabolic diseases.

These particular receptors play a critical role in the development of TH17 cells, a form of T helper cells that make up part of the immune system. A relatively new discovery, TH17 cells have been implicated in the pathology of numerous autoimmune diseases, including multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, and lupus. TH17 cells produce Interleukin-17, a natural molecule that can induce inflammation, a characteristic of autoimmunity.

"If you eliminate TH17 cell signals, you basically eliminate the disease in animal models," Burris said. "Our compound is the first small-molecule orally active drug that targets this specific cell type and shuts it down. Once SR1001 is optimised, chances are it will be far more potent and effective."

No significant metabolic impact

The compound works without affecting other types of T helper cells and without any significant metabolic impact, Burris added.

The first author of the study, *Inhibition of TH17 Differentiation and Suppression of Autoimmunity by a Selective Synthetic ROR Ligand*, is Laura A. Solt of Scripps Research. In addition to Burris, Griffin, Roush, Kamenecka, Drew, and Solt, other authors include Naresh Kumar, Philippe Nuhant, Yongjun Wang, Janelle L. Lauer, Jin Liu, and Monica Istrate of Scripps Research; Dušica Vidovic, Stephan C. Schürer of Scripps Research and the Centre for Computational Science, University of Miami; and Jihong Xu and Gail Wagoner of the University of Arkansas for Medical Sciences. See http://www.nature.com/nature/journal/vaop/ncurrent/abs/nature10075.html.

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