New Rheumatoid Arthritis Drug Developed At UCSD Promises Improved Treatment Option

October 14, 2005

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Researchers at the UCSD School of Medicine have announced successful completion of Phase II clinical trials of a novel drug for the treatment of rheumatoid arthritis (RA), one that works without suppressing the patient's immune system.

Salvatore Albani, M.D., Ph.D, professor of medicine and pediatrics and Director of the Translational Research Unit of the Clinical Investigation Institute (CII) at the UCSD School of Medicine, recently presented a summary of the findings at the "Frontiers of Clinical Investigation Symposium." The symposium, sponsored by the CII and *Nature Medicine*, was held in La Jolla, California in September.

The new drug, dnaJP1, is a peptide derived from a naturally occurring protein, dnaJ, which generates inflammation in RA patients, whose inflammatory-control mechanisms are impaired. The impairment causes the body's T cells - which trigger inflammation to kill and clear foreign pathogens in the body - to attack the body's own tissues.

"In essence, we re-educated the immune system T cells to be tolerant of the dnaJP1 amino acid sequence, which would usually contribute to inflammation in rheumatoid arthritis patients," Albani said.

DnaJP1 works by resetting the ability of the patient's immune system to tolerate dnaJ, thus transforming a potentially damaging trigger into a tool for controlling the disease. Oral ingestion of dnaJP1 is key, because the mucosal immune system found in the gut has the ability to "teach" the body to view a protein as one that isn't dangerous or foreign. Much as food is ingested into the body and not rejected, the body tolerates dnaJP1.

Current medications for treating RA range from anti-inflammatory drugs, such as aspirin, to corticosteroids and medicines that alleviate symptoms by suppressing or killing the body's immune response, basically crippling the body's ability to defend itself against other infectious diseases or cancer.

"Such drugs are costly, have potentially dangerous side effects and are inconvenient to administer," Albani said. "Our drug leaves the patient's natural immune responses intact. This differs profoundly from what is currently available to patients."

DnaJP1 was found effective in a double-blind, placebo-controlled trial sponsored by the National Institutes of Health, which took place between 2000 and 2005 and involved 160 patients enrolled in centers nationwide including UCSD, Stanford University, Johns Hopkins University, the Mayo Clinic, and Virginia Mason Medical Center in Seattle. The technology was developed at UCSD and has been licensed for further development to Androclus Therapeutics, a biotechnology company located in San Diego and Milan, Italy. Dr. Albani is one of the company's co-founders.

Patients received 25mg of dnaJP1 daily by mouth for six months, and the treatment was found to be safe and well-tolerated. When compared with a placebo, patients in the treatment group experienced lessening

of symptoms such as swollen joints, tenderness, pain and decreased mobility. Improvement was particularly significant at the follow up visits, indicating a lasting effect of the drug. Efficacy was quantified in data generated from physicians, patients and laboratories, measuring improvement according to standards set by the American College of Rheumatology (ACR) from the beginning to later points in the trial. For instance, "ACR 20" indicates a 20% improvement in standardized symptoms. ACR 20 response was in the 50-55% range; ACR 50 in the 30-40% range; and ACR 70 in the 15-20% range of patients completing the trial.

Rheumatoid arthritis, or inflammation of the joints, is a chronic, painful disease affecting one percent of the U.S. population, or more than 2 million people. It occurs three times more often in women than men, targeting people of every age. The condition simultaneously strikes joints on both sides of the body, such as the hands or feet or knees but can also affect the skin, eyes, lungs, heart, blood, nerves or kidneys. It is an incurable disease, with most therapies focusing on symptom relief.

"Although the current available drugs pose risks to patients, the first two trials of dnaJP1 have not raised any significant safety concerns and offer an improved treatment option for patients with rheumatoid arthritis," said Albani. The next step, according to Albani, is to get approval and funding to move into Phase III clinical trials.

"This is a very exciting and novel therapeutic approach, which holds the promise to be an entirely new type of immunomodulatory drug - one that can shape a patient's immune system, rather than suppressing it," said Gary S. Firestein, M.D., Director of CII (http://cii.ucsd.edu/), which provides UCSD faculty with an infrastructure to support the translation of fundamental biology into novel therapeutic interventions. "It is also an Institute success story because it represents a true 'bench to bedside' research model."

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