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UCSD Develops Rheumatoid Arthritis Therapy That Re-Educates Body's Immune Response

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Sue Pondrom

A promising new therapy for rheumatoid arthritis (RA) developed by researchers at the University of California, San Diego (UCSD) School of Medicine re-educates the body's immune system to prevent an attack against healthy joint tissue.

In patients with RA, the immune system that is supposed to protect the body, instead attacks it for unknown reasons. In a Phase I/IIa clinical trial recently described in Proceedings of the National Academy of Sciences *****, the UCSD researchers report that a peptide called dnaJP1, taken orally for six months by a group of patients with early RA, caused no side effects and actually changed the action of the immune system's T cells, preventing them from attacking the body's own tissues.

The new therapy is currently in Phase II clinical trials with 160 RA patients at UCSD, Johns Hopkins University, the Mayo Clinic, and Virginia Mason Medical Center in Seattle. It is expected to be completed by the end of 2004, with enrollment still open for interested study participants. RA is a chronic, painful disease that causes joint inflammation and destruction, progressive disability and premature death. Affecting an estimated 2.1 million Americans, RA causes substantial economic burden, with 50 percent of patients unable to work within 10 years of onset, and lifetime costs of the disease rivaling those of coronary artery disease or stroke. ****** RA is incurable, with most therapy focused on symptom relief. Unfortunately, current therapies can have serious side effects and work by suppressing the immune system, which increases the risk of infection.

While the precise cause of the disease is unknown, researchers believe that RA is influenced by an abnormal reaction to environmental factors such as infection, which initiate the autoimmune response in genetically susceptible individuals.

The immune-modulation therapy developed by Salvatore Albani, M.D., Ph.D., UCSD professor of medicine and pediatrics, takes advantage of both the genetic and environmental components of RA. In studies over the past 12 years, he has focused on the immune system's T cells, which trigger inflammation to kill and clear foreign pathogens from the body. Albani reasoned that if the immune system of RA patients could be altered, T cells might be less likely to cause chronic inflammation.

His research involved several components of the immune response, beginning with a sequence of amino acids (segments that comprise proteins) expressed on the surface of cells during an immune response. Called a human leukocyte antigen (HLA), this sequence is designed to recognize self- from non-self cells. In a normal immune response, HLA acts as a "natural dimmer" to prevent over-stimulation of the inflammatory response. In RA patients, however, the dimmer is broken and excessive inflammation ravages tissue and joints. Interestingly, researchers have determined that 70 percent of RA patients, and not normal individuals, share a specific sequence of five amino acids within their HLA.

Albani's current findings were further supported by previous studies he conducted with Dennis Carson, M.D., UCSD professor of medicine and director of the Sam and Rose Stein Institute on Aging at UCSD, that showed

immune-system T cells in RA patients become confused by the body's natural HLA sequence on cell surfaces, thinking it is a foreign invader. In an attempt to protect the body, the T cells attack the HLA sequence by inducing inflammation.

To prevent T cells from attacking the body's own HLA sequence, Albani sought to develop a vaccine therapy that could re-educate the diseased immune system in RA patients to prevent rampant inflammation. He focused on a naturally occurring protein called dnaJ that is used by T cells to help initiate the inflammation process. A section of the dnaJ protein, called dnaJP1, contains the same sequence of five amino acids as those within the HLA of RA patients. Bacterial, non-human forms of the dnaJP1 peptide also contained the same sequence of RA-susceptible HLA amino acids, and were found by the UCSD team to be targets of pro-inflammatory T cell responses in RA patients.

"Therefore, we believed that if we could administer the bacterial dnaJP1 as a vaccine to patients with early RA, it would affect the autoimmune inflammation," Albani said. "A key to the treatment was oral administration of dnaJP1."

The researchers determined that an injection of dnaJP1 caused a typical RA-inflammatory immune response, because T cells recognize the peptide as a foreign invader. When the peptide was ingested by patients, however, the special properties of the digestive system's mucosal cells recognized dnaJP1 as a "self-peptide," rather than foreign, and tolerated it. It's the same mechanism the digestive system uses with food, which is also a foreign invader to the body. The mucosal system is designed to tolerate the food, or medications, that enter the body in this manner.

"In essence, we re-educated the immune system T cells in RA patients to be tolerant of the dnaJP1 amino acid sequence that would usually trigger inflammation," Albani said. "In turn, the immune system became tolerant of the HLA sequence, thus avoiding a T cell attack against the body's own tissue."

He added that "the findings with dnaJP1 offer a strategy and the tools to develop a new therapy for RA that focuses on immune modulation rather than immune suppression."

Immune modulation may be particularly helpful in delaying, or possibly abolishing the need for RA patients to take currently available drugs called disease modifying antiarthritic drugs (DMARDs), which provide significant improvements in RA but have potentially serious side effects such as skin rash; mouth sores; stomach, eye and kidney problems; and low blood counts.

The University of California has licensed to Androclus Therapeutics, a biotechnology company located in Milan, Italy and San Diego, California, exclusive rights to further develop a new therapy based on these discoveries

In addition to Albani, authors of the paper in Proceedings of the National Academy of Sciences were first author Berent J. Prakken, M.D., Ph.D., UCSD Departments of Medicine and Pediatrics and IACOPO Institute for Translational Medicine; and Rodrigo Samodal, M.D., Tho D. Le, M.S., Francesca Giannoni, M.S., Gisella Puga Yung, M.S., John Scavulli, M.D., Diane Amox, R.N., Sarah Roord, M.D., Isme de Kleer, M.D., Dustan Bonnin, M.S., Charles Berry, Ph.D., and Margherita Massa, Ph.D., UCSD Departments of Medicine and Pediatrics and IACOPO Institute for Translational Medicine; and Paola Lanza, M.S. and Rosario Billetta, M.S., Androclus Therapeutics, Milan, Italy and San Diego, California. Prakken, Roord, and de Kleer are also affiliated with the Department of Pediatric Immunology, University Medical Center Utrecht, The Netherlands. Massa is also affiliated with Istituo de Ricovero e Cura a Carattere Scientifico, Pavia, Italy. Albani is affiliated with Androclus Therapeutics.

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***** Proceedings of the National Academy of Sciences, March 23, 2004, Vol. 101, No. 12, pages 4228-4233. ****** Journal of the American Medical Association, Vol. 285, No. 5, Feb. 7, 2001, pages 648-650.

Media Contact: Sue Pondrom (619) 543-6163