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Research toward world's first vaccine for heart disease advanced

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Research toward the world's first vaccine for heart disease continues to advance at the La Jolla Institute for Allergy and Immunology, with researchers demonstrating significant arterial plaque reduction in concept testing in mice.

Klaus Ley, M.D., a pioneer in vascular immunology, is leading the vaccine effort, which seeks to reduce plaque buildup in the arteries by targeting inflammation. In his latest finding, published recently in the journal *Frontiers in Immunology*, Ley used two mouse peptides, identified by Harley Tse, Ph.D., of Wayne State University, which he incorporated into testing the vaccine approach. In the study, vaccinated mice had about 40 percent less arterial plaque than mice that didn't receive the vaccine.

"Heart disease remains our nation's number one killer," says Mitchell Kronenberg, Ph.D., La Jolla Institute president &chief scientific officer. "We are excited by Dr. Ley's studies, which show promise for creating a vaccine that may one day reduce the incidence of this terrible illness." If successful, the vaccine could be given to aid in preventing heart disease and also to stop or reduce disease progression. In addition to heart disease, the vaccine could target strokes, which are also fueled by plaque buildup in the arteries.

The research drew praise from several cardiology experts. Stanley Hazen, M.D., Ph.D., section head of Preventive Cardiology at the Cleveland Clinic, one of the nation's top cardiology hospitals, called the

research "elegant and tremendously exciting."

"This lays the groundwork for someday being able to prevent or even eradicate heart disease by giving a vaccine. Truly a remarkably important advance," says Hazen, also chairman of the Department of Cellular & Molecular Medicine.

Eric Topol, M.D., chief academic officer of Scripps Health and professor of genomics at The Scripps Research Institute, stressed the importance of Ley's work. "If successful, the potential development of a vaccine to prevent atherosclerosis would be a monumental advance in medicine," says Topol.

About 600,000 Americans die of heart disease every year, amounting to 1 in every 4 U.S. deaths. Most people know that cholesterol is a major factor in creating artery-clogging plaque leading to heart disease. However, many people may not be aware that inflammation is also a very important contributor to arterial plaque buildup. "Many research studies over the last 15 years have demonstrated inflammation's critical role in heart disease," says Ley. "By creating a vaccine to reduce inflammation in the arteries, we hope to significantly lessen the accompanying plaque buildup."

Ley's study was published December 27th in a paper "Atheroprotective vaccination with MHC-II restricted peptides from ApoB-100" in Frontiers in Immunology

Ley says the vaccine type he is exploring is different than those people get for the flu and other infections. "A flu vaccine's purpose is to teach your immune system to launch an attack if it encounters the virus," he says. "Our vaccine works more like the desensitization process used in allergy shots. Allergy shots are designed to teach the individual's immune system to tolerate the allergen. Our vaccine would work on the same

principle—only in this case we'd be teaching the immune system to tolerate certain molecules of our own bodies that it mistakenly attacks, which causes inflammation."

In an earlier study, published August 13, 2012 in the *Journal of Clinical Investigation*, Ley identified that a specific type of immune cells (CD4 T cells) orchestrate the inflammatory attack on the artery wall by receiving antigen-specific signals from other inflammatory cells in the vessel wall. Further, he discovered that these immune cells behave as if they have previously seen the antigen that causes them to launch the attack. An antigen is a peptide derived from a virus, bacteria or, in the case of autoimmune diseases, one of our own proteins that the immune system mistakenly views as foreign and attacks.

Ley says that the discovery was particularly exciting since it meant the immune cells had 'memory' of the molecule brought forth by the antigen-presenting cells. "Immune memory is the underlying basis of successful vaccines," he explains. "This meant that conceptually it was possible to consider the development of a vaccine for heart disease."

Ley collaborated with fellow La Jolla Institute scientist Alessandro Sette, Ph.D. and Dr. Tse of Wayne State University in Michigan, to identify the specific peptides, which prompt the arterial attack in mice – the byproduct of which is inflammation. The mouse peptides were used in the test vaccine to teach the body, through gradual exposure, to tolerate rather than attack those proteins.

In parallel with that research Ley has worked with Sette, who is an internationally recognized vaccine biologist, to identify more candidate peptides with the goal of eventually creating a heart disease vaccine for people. "The next step is to test promising candidate peptides in specially engineered mice with an immune system more similar to humans," he says. If successful, the vaccine could begin human clinical trials in as

little as three years, Ley adds.

The vaccine effort reflects the power of bringing top immunologists together in one institution, Ley notes. "It just shows what can happen when you have an institute like ours dedicated to immunology," says Ley. "Sette is a world renowned expert on vaccines and I have specialized knowledge in cardiovascular immunology. It's the combination of our two areas of expertise that is enabling this vaccine initiative to proceed. I don't think this could have happened anywhere else."