RESEARCH UPDATE

December 2016 Update on the Research of
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Since 1992, Dr. P.K. Shah and his colleagues have studied the mutant gene (ApoA-1 Milano) which has been found to produce a form of HDL (high-density lipoprotein or "good" cholesterol) that provides greater protection against atherosclerosis and vascular inflammation — processes that lead to clogged arteries, heart attacks, and strokes. In addition, Dr. Shah and his team have pioneered the development of a cholesterol vaccine to reduce cholesterol plaque buildup inside arteries. Through their investigations, he and his team are looking to advance prevention and treatment techniques for the leading cause of death in the United States and a major cause of disability—heart disease.

With the Oppenheimer Atherosclerosis Research Center at Cedars-Sinai Heart Institute serving as home base since 1993, Dr. Shah and his team of 20 researchers work to identify the mechanisms leading to plaque buildup and develop new treatments for atherosclerosis. They continue to push the boundaries of atherosclerosis research, enhancing our understanding of the heart's inner workings and pioneering innovative approaches to combatting heart disease. Following is an update on their major activities.

We are grateful to have you as a vital partner in our mission to increase awareness of this devastating disease and advance medical science.

1) **Development of ApoA-I Milano Gene Transfer and Gene-based Therapy for Prevention and Reversal of Cholesterol-Plaque in the Arteries**

Background: ApoA-I Milano is a naturally occurring mutant gene that encodes the ApoA-I Milano protein. The carriers of this mutant gene are all inhabitants of Limone sul Garda, a northern Italian town. Dr. Shah's laboratory has shown that intravenous injection of this protein (manufactured by genetic engineering technology using bacteria as a factory) dramatically reduces plaque buildup and shrinks pre-existing plaque in animal models.

Due to its apparent efficacy, some have speculated that development of synthetic ApoA-1 Milano may be a key factor in eradicating coronary heart disease. Yet this remarkable discovery has been halted in its use by the fact that it is extremely time consuming and costly to produce in large amounts. Furthermore, protein production in bacteria may result in contamination of the final product by bacterial toxins.

Dr. Shah and his team are exploring direct gene transfer as a way of exploiting the benefits of the ApoA-I Milano gene. The aim is to utilize this direct gene transfer to prompt natural production of the protein, eliminating the need to manufacture and deliver repeated intravenous injections. Over the past year, they have shown that gene transfer can reverse established plaque as well. The ultimate goal is to eventually bring this technology to human application by partnering with an industry partner.

2) Development of ApoA-I Milano Gene Transfer and Gene-based Therapy for Prevention of Alzheimer's Disease

Since inflammation is believed to play a role in the development of Alzheimer's disease, Dr. Shah and his team have begun a pilot experimental project to examine whether the potent anti-inflammatory effects of the ApoA-I Milano gene can be used to ameliorate the devastating effects of Alzheimer's disease, for which no treatment is currently available. They have recently developed preliminary proof of efficacy in mice showing that ApoA-I Milano gene transfer to the brain using an intravenous injection of the gene attached to an innocuous virus reduces Amyloid fibril deposits in those with Alzheimer's disease.

3) Role of the Immune System in Atherosclerosis and Development of a Vaccine for Atherosclerosis

Also on the path to human studies is Dr. Shah's research which has shown that the body's own immune system reacts to high cholesterol by producing antibodies and cellular reactions, some of which have the potential to reduce plaque buildup. Research is currently focused on identifying specific antigens within the cholesterol particles that provoke a protective immune response and which could be used to develop a vaccination strategy against cholesterol-plaque buildup.

Collaborative work has identified parts of the LDL-Cholesterol (so called bad cholesterol) particle that act as antigens to which the immune system reacts. Some of these antigens, when incorporated into a vaccine formulation, were shown to reduce plaque buildup without changes in blood cholesterol levels, thus raising the possibility that a vaccine against plaque buildup could be developed. Work continues to refine these findings and develop a better understanding of the molecular and cellular mechanisms by which the vaccine protects the arteries from plaque buildup. Additional studies have demonstrated that the same vaccine reduces high blood pressure and rupture of aortic aneurysm. Hopes are high to obtain permission from the FDA within the next year or so to start human studies.

4) Identification and Testing of Novel Athero-protective and Athero-permissive Genes using Transcriptional Profiling of Athero-prone and Athero-resistant Arteries

Through current research and future studies, Dr. Shah and his research team are potentially on the path toward important discoveries with major implications for novel gene-based therapeutics to prevent atherosclerosis. It is well-known that coronary and carotid arteries are remarkably susceptible to atherosclerosis; yet internal mammary arteries and radial arteries are almost absolutely resistant to atherosclerosis. By seeking to explain why this is the case, Dr. Shah has examined the genetic expression patterns of athero-prone and athero-resistant arteries and has found novel expression patterns that are unique to either coronary or mammary arteries. Additionally, several novel genes were discovered that may provide clues as to why coronaries develop atherosclerosis and mammaries do not—information necessary to further develop novel gene-based therapeutics on the path toward preventing atherosclerosis. Studies on this topic are currently underway.