vitae Pharmaceuticals

Discoveries for life

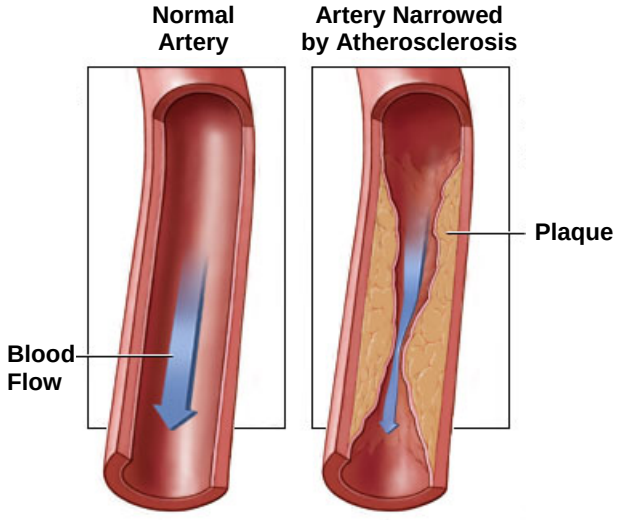
ATHEROSCLEROSIS: FACT SHEET

LXRβ SELECTIVE MODULATORS FOR THE TREATMENT OF ATHEROSCLEROSIS

OVERVIEW

Atherosclerosis is characterized by a progressive build-up of fat and cholesterol (called plaque) in the artery wall. Over time the plaque hardens and narrows the artery, limiting blood flow to organs. Atherosclerosis can affect any artery in the body, including arteries in the heart, brain, arms, legs and pelvis. As a result, different diseases can develop depending on which arteries are affected.

Coronary artery (or coronary heart) disease occurs when plaque builds up in the arteries that supply blood to the heart, which can result in angina (chest pain) and heart attack. Carotid artery disease occurs when plaque builds up in the arteries that supply blood to the brain, which when blocked can lead to a stroke. Peripheral arterial disease occurs when plaque builds up in the major arteries that supply blood to the limbs and pelvis and can lead to numbness, pain when walking, sores or ulcers that may result in infections.



Atherosclerosis is the leading cause of morbidity and mortality in the developed world. In the U.S., Coronary Artery Disease is the leading cause and Stroke is the third leading cause of death. It is a highly prevalent disease – even before the age of 25, two out of three Americans will have some degree of plaque build-up in their arteries.

Current treatment options focus on decreasing cholesterol levels in the blood to limit further advancement of existing plaques. Those options include: lifestyle changes, statins, fibrates and niacin. There are no therapies currently approved specifically targeted to reverse already established plaque build-up.

THE LIVER X RECEPTOR

The liver X receptor (LXR) is an attractive target for atherosclerosis because it acts as a cholesterol sensor. LXR activation can decrease atherosclerotic plaque by promoting cholesterol transport out

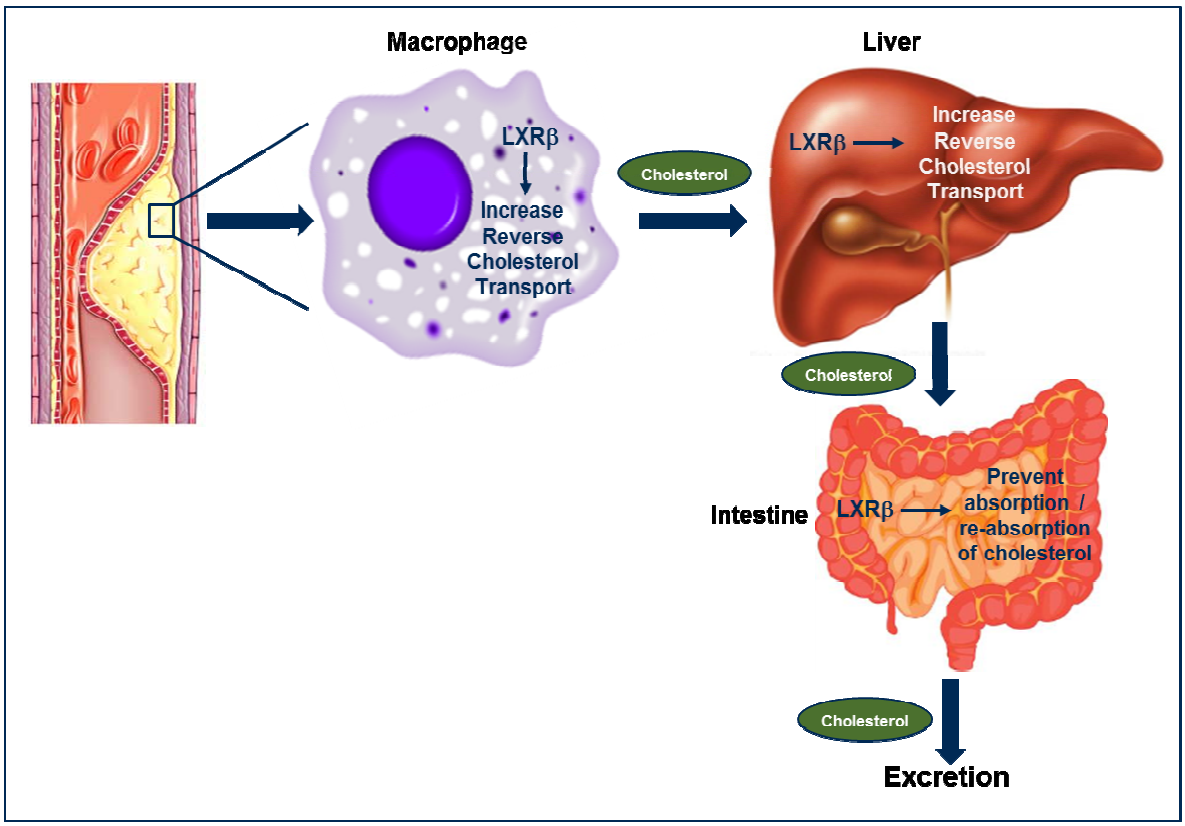
of the plaque (termed reverse cholesterol transport) and directing the cholesterol to the liver and intestine for excretion. LXR activation has also been shown to decrease inflammation in atherosclerotic plaque and to decrease cholesterol absorption in the small intestine. Through these coordinated effects, LXR plays a key role in the body's cholesterol homeostasis.

LXR is a member of the nuclear receptor superfamily with two isoforms, LXRα and LXRβ, which are differentially expressed. LXRα is highly expressed in liver, kidney, intestine, adipose, lung and spleen tissue and in macrophages, while LXRβ is ubiquitously expressed.

In previous clinical trials, LXR agonists have demonstrated a clear benefit in inducing reverse cholesterol transport. But, due to a lack of isoform selectivity, they have also caused an increase in liver triglyceride synthesis, resulting in fatty liver. The major challenge for developing an LXR modulator is achieving activation of LXR to promote reverse cholesterol transport without inducing triglyceride synthesis.

VITAE'S LXRβ SELECTIVE MODULATOR PROGRAM

Researchers at Vitae are working to develop novel compounds that are selective, partial modulators of LXRβ. Preferentially activating LXRβ will promote the desirable reverse cholesterol transport effect, while avoiding the activation of LXRα in the liver that increases triglyceride synthesis. Vitae's proprietary structure-based drug discovery technology is uniquely suited to identify and characterize the subtle differences between LXRα and LXRβ, allowing our structural biologists, modelers, biologists and chemists to develop compounds that take advantage of these differences.



Within 12 months from initiating this program, Vitae scientists discovered novel, selective modulators of LXRβ and demonstrated that these compounds can induce markers of reverse cholesterol transport without increasing triglycerides in multiple animal species. Lead optimization studies are continuing to advance and Vitae expects to select a preclinical candidate by early 2012.