

# [The definite cause of atherosclerosis biology essay](https://assignbuster.com/the-definite-cause-of-atherosclerosis-biology-essay/)

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\n[/toc]\n \nAtherosclerosis, in simple terms, is the hardening or blockage of the arteries, the high-pressure blood vessels that carry oxygenated blood from the heart to the rest of the body. It occurs due to the accumulation of lipids which are retained by extracellular matrix molecules. 1 This leads to the formation of a lesion known as an atherosclerotic plaque, which is cholesterol and fatty acid laden. It builds up in the walls of arteries and over time, it hardens and narrows the arteries, causing an obstruction of oxygen-rich blood flow to the rest of the body. Different diseases may develop due to this condition, based on which artery in the body is affected. For example, atherosclerosis leads to myocardial infarction, when it occurs in the coronary arteries, or stroke, when it occurs in the cerebral arteries. 1 The World Health Organization estimates that cardiovascular diseases are responsible for 30 percent of all deaths worldwide each year, with atherosclerotic vascular disease, the principal cardiovascular disorder responsible for the global rise in mortality (Bonow et al 2002). 2The definite cause of atherosclerosis is unknown. Some may classify it as multi-factorial. The disease may start when certain factors damage the inner layers of the arteries. Such factors include smoking, high blood pressure, high amounts of certain fats and cholesterol in the blood and high amounts of sugar due to diabetes. 3As mentioned above, lipoproteins lead to the formation of plaque. They are the major transporters of both cholesterol and fatty acids. Low density lipoproteins (LDL) is the best known lipoprotein. The pathogenesis of atherosclerosis is associated with the early retention of LDL that are trapped in the extracellular matrix of the arterial intima by interaction with glycosaminoglycan side chains of proteoglycans. 4To best work with the target, we have to understand the mechanism by which LDL attaches itself to damaged intima in the artery. It carries Apo B and proteins like lipoprotein lipase. Proteoglycans aid in the attachment of LDL particles to the vascular wall and act as a docking mechanism for the LDL particles. Platelet derived growth factor (PDGF) is strongly implicated in atherosclerosis as it stimulates proteoglycan synthesis. 5 For evidence, Ballinger ML et al., 6 inhibited PDGF receptor. They demonstrated significant reduction of carotid artery lipid accumulation. The mechanism was through inhibiting glycosaminoglycan (GAG) synthesis on the proteoglycans and thus reducing LDL binding, a possible novel method for reducing atherosclerosis. 5To find the best inhibitors of proteoglycan biosynthesis, various 4-deoxy-4-fluoroxylosides were screened. 12eα and 12eβ were able to reduce GAG production by 80% without affecting cell viability. These novel derivatives can potentially be used to define the biological actions of proteoglycans in model organisms. 7

## Aim

Phase (1): To instil two different 4-deoxy-4-fluoro-xyloside derivatives (12eα and 12eβ) to determine the efficiency of glycosaminoglycan inhibition in mice models. Phase (2): To determine the timeframe of the effects of the 4-deoxy-4-fluoro-xyloside derivatives in glycosaminoglycan inhibition.

## Approach

Phase (1): A total of 40 mice models will be used in this study. 30 mice models (group A) will be fed a high fat-containing diet for 12 weeks. This should increase the level of LDL in the mice. 10 mice (group B) will be kept as controls with the suitable diet. Since atherosclerosis can also be affected genetically, the mice models is best inbred to limit genetic influences. Other factors such as the living conditions will also be kept constant for all 40 mice models. First, the LDL levels of the mice in group A should be recorded. Then, 12eα will be injected into 10 mice that had been fed with a high fat-containing diet (group Aα) and 12eβ will be injected in another 10 mice from group A as well (group Aβ). The level of LDL will be checked throughout this period at 1 week interval using LDL cholesterol assay kit. The proposed hypothesis is that the LDL levels of the mice that were induced with the 4-deoxy-4-fluoro-xyloside derivatives should be lowest, followed the control and lastly the mice without the instilled derivatives from group A should possess the highest LDL levels. We need to observe if group Aα or group Aβ shows the most inhibition as well as any side effects. This will help us determine which of the two 4-deoxy-4-fluoro-xyloside derivatives is more efficient with less risk. Phase (2): This phase will be carried out provided phase (1) is successful. Besides the comparison between LDL levels, the time taken for the LDL levels to decrease as well as by how much it decreases per week will be taken note of. This helps to obtain statistics on how efficient the inhibitors are and how long they take to suppress the expression.

## Significance

Atherosclerosis is the cause of many serious cardiovascular diseases, the largest cause of death in western societies. 1 Treatments for atherosclerosis may include lifestyle changes, medicines, and medical procedures or surgery. The aims of treatment thus far are to alleviate symptoms, decrease or prevent formation of blood clot and prevent cardiovascular diseases. Statins are the best tolerated and most effective way to reduce LDL cholesterol levels and are considered the first-line medication choice. However, a major concern with statins is that they might affect the function of liver. 8This study aims to prevent the accumulation of plaque. Unlike statins, these inhibitors do not only lower the LDL levels but they inhibit GAG synthesis on proteoglycans, and reduce LDL biding. This also reduces the retention of LDL. The success of this study can take the treatment of atherosclerosis and other glycosaminoglycan mediated diseases to the next level. Therapy agents containing these inhibitors may pose to be a better treatment than statins if the efficiency of these inhibitors proves to be higher.