

## Atherosclerosis Vaccine: A Review

Sidhi Laksono<sup>1,2</sup>, Hillary Kusharsamita<sup>3</sup>

<sup>1</sup> Department of Cardiology and Vascular Medicine, RS Pusat Pertamina, South Jakarta, Indonesia

<sup>2</sup> Faculty of Medicine, Universitas Muhammadiyah Prof. DR. Hamka, Tangerang, Indonesia

<sup>3</sup> Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia

**Abstract:** Atherosclerosis is the world's largest pathological contributor to cardiovascular morbidity and mortality. Since atherosclerosis is an inflammatory disease in which the immune system plays an important role, it would be interesting to consider new techniques for targeting immune or inflammatory components as a novel approach to inflammation and atherosclerosis. Vaccination against atherosclerosis has been tested as a potential approach to overcome the condition. This study aims to review the current potential types of antigens for the atherosclerosis vaccine. We also aim to examine the challenges of the atherosclerosis vaccine for future research since there were significant gaps in evidence for human samples for vaccination testing and side effects in the atherosclerosis vaccine. The various potential of antigens for atherosclerosis vaccine includes lipid-related antigens (OXLDL apoB100, CETP, PCSK9) and non-lipid-related antigens (MHC II deprived peptides, HSP, S. Pneumoniae, interleukin, oral DNA vaccination, fibronectin, B2 glycoprotein, C5a receptor, plant base). The current study shows that atherosclerosis vaccination may not be used to treat humans since most studies have been done on animals and very few on humans. Further study in humans is required, in addition to continuing animal research, to evaluate atheroprotective efficacy and side effects.

**Keywords:** atherosclerosis, inflammation, vaccination, antigen.

## 動脈粥樣硬化疫苗：綜述

**摘要：**動脈粥樣硬化是世界上導致心血管發病率和死亡率的最大病理因素。由於動脈粥樣硬化是一種免疫系統在其中發揮重要作用的炎症性疾病，因此考慮將靶向免疫或炎症成分的新技術作為治療炎症和動脈粥樣硬化的新方法會很有趣。已經測試了針對動脈粥樣硬化的疫苗接種作為克服該病症的潛在方法。本研究旨在回顧目前用於動脈粥樣硬化疫苗的潛在抗原類型。我們還旨在檢查動脈粥樣硬化疫苗對未來研究的挑戰，因為用於疫苗接種測試的人體樣本和動脈粥樣硬化疫苗的副作用的證據存在顯著差距。動脈粥樣硬化疫苗的各種潛在抗原包括脂質相關抗原（氧化低密度脂蛋白載脂蛋白乙 100、膽固醇酯轉移蛋白、前蛋白轉化酶枯草桿菌蛋白酶/可心 9 型）和非脂質相關抗原（主要組織相容性複合體 II 剝奪肽、人血清蛋白、肺炎鏈球菌、白細胞介素、口服脫氧核糖核酸疫苗、纖維連蛋白、乙 2 糖蛋白, C5a 受體, 植物基)。目前的研究表明，動脈粥樣硬化疫苗可能無法用於治療人類，因為大多數研究都是在動物身上進行的，而對人類的研究很少。除了繼續進行動物研究外，還需要對人體進行進一步研究，以評估動脈粥樣硬化保護功效和副作用。

**关键词：**動脈粥樣硬化、炎症、疫苗接種、抗原。

## 1. Introduction

According to the World Health Organization (WHO), coronary atherosclerotic disease is the leading cause of death worldwide [1]. Atherosclerosis is a chronic inflammatory condition in which arterial walls are hardened by atherosclerotic plaque accumulation. These plaques tend to form thrombi, the main cause of acute ischemic events in coronary and brain vessels [2, 3].

Based on the calculation by WHO, there are 20 million deaths every year due to this disease, whereas the treatment itself entails high costs for the national health system. The significance of mortality caused by this disease emphasizes the importance of developing an effective preventive strategy [4].

Vaccination, a principal method of prevention that creates an aimed immune response against antigens, has been used for many years [5]. The study of autoimmune and inflammatory components of atherosclerosis provides compelling reasons to develop a vaccine as a preventive method [6]. Nevertheless, at first glance, this method is not as simple as it looks. Atherosclerosis is a multifactorial, chronic, and complex process that evolves over time [5]. Although treatment of atherosclerosis has been for years based on lipid-lowering therapies reducing a series of risk factors, and its success rate has been limited because cardiovascular complications related to the evolution of atherosclerotic lesions continue to appear in the population worldwide [4]. Vaccination can be an alternative approach expected to reduce disease burden.

Over the years, several studies have been conducted to ascertain the best atherosclerosis vaccine. Undeterred by substantial efforts in this field, vaccination against atherosclerosis is still in its early stages [6]. It appears that the most challenging step in this zone is finding a proper atherogenesis-related antigen [4-7]. In this literature review, we aim to discuss the types of antigens which hold promising potentials for atherosclerosis vaccine development and their future challenges

## 2. Pathogenesis

Atherosclerosis begins with the endothelium build-up of LDL-carrying cholesterol, activating innate and adaptive immune responses. LDL, especially oxidized-LDL and subclass B of LDL, manifest the properties of associated molecular pattern damage and trigger endothelial cell activation, thus inducing an inflammatory response [8]. A single cell layer covering the surface of blood vessels called the endothelium is not static [9]. Naturally, a healthy endothelium can inhibit the adhesion of platelets and leukocytes to the vascular surface and maintain a balance of profibrinolytic and prothrombotic activities. Hypercholesterolemia, hypertension, diabetes, and smoking, are conditions predisposing to atherosclerosis. These predisposing conditions are

correlated with endothelium dysfunction, which leads to a proinflammatory and prothrombotic phenotype endothelium [10]. This implies that changes in endothelial function play a significant aspect in the development of atherosclerosis and its clinical complications.

The earliest feature of atherosclerosis is endothelial dysfunction, followed by an inflammatory reaction and lipid deposit [9]. Consistent laminar shear stress develops an 'atheroprotective state' in endothelial cells. The endothelium that encounters laminar shear stress within the bloodstream stimulates vasodilation and antithrombotic. However, activated endothelial cells become less efficient. This event leads to endothelial dysfunction characterized by diminished nitric oxide bioavailability and excessive endothelin-1 production that interferes with the function of vascular hemostasis, increased expression of adhesive molecules such as vascular cell adhesion molecule 1 (VCAM-1), also intercellular adhesion molecule 1 (ICAM-1), P-selectin, and E-selectin. Leukocytes decelerate through interaction with P-selectin and E-selectin. The interface between VCAM-1 and ICAM-1 with very late antigen-4 (VLA-4) and lymphocyte function-associated antigen-1 (LFA-1), separately, leads to a stronger adhesion of leukocytes [10].

The following step is a process called diapedesis when leukocytes migrate through the inter-endothelial junction into the sub-endothelial space. This process is facilitated by several adhesion molecules such as platelet/endothelial adhesion molecule-1 (PEAM-1), junctional adhesion molecule-1 (JAM-1), chemokines, and interleukins secreted by the activated endothelial cells. Among chemokines, the two most critical chemoattractants for leukocytes are monocyte chemoattractant protein-1 (MCP-1), which is responsible for the migration of monocytes into the intima, and T cell chemoattractant, which supports the infiltration of lymphocytes into the intima [5, 13].

When monocytes enter the intima, they are converted to macrophages and express scavenger receptors with the mediation of macrophage colony-stimulating factor (M-CSF), formed by activated endothelial cells and smooth muscle cells (SMCs). This element facilitates phagocytosis of modified lipoproteins and multiplication of monocytes into macrophage foam cells, leading to the development of fatty streaks [11].

Foam cells recruit extra inflammatory cells, including proinflammatory cells such as T-helper type 1 (Th1) lymphocytes, as an abortive effort to suppress or sequester irregular lipids. Th1 lymphocytes secrete cytokines that activate monocytes to form M1 polarized inflammatory macrophages, such as interferon- $\gamma$  (IFN $\gamma$ ) and interleukin 2 (IL-2). These inflammatory macrophages, in particular, secrete significant quantities of reactive oxygen species and extracellular catabolic enzymes, including matrix

metalloproteinases (MMPs) and myeloperoxidase (MPO) [12].

Although the inflammatory mechanism may be counterbalanced by regulatory T lymphocytes (T-regs) and, in some cases, antibody-producing B lymphocytes, leukocytes begin to accumulate in a typically proinflammatory setting. As a result, more foam cells are produced, and more cytokines, proteases, and reactive oxygen species are expressed [9].

Such cytokine production drives smooth muscle cell and fibroblast proliferation and encourages endothelial activation, generating a positive feedback loop that activates atherosclerotic plaque development. In some cases, this mechanism may gradually stabilize, while in other cases, it may intensify. The main step in transforming from a fatty streak to a more progressive atherosclerotic plaque is the deposition of extracellular lipid. Initially, this extracellular lipid is interdigitated between the intimal smooth muscle cells. When a lesion progresses, the extracellular lipid is deposited form large pools, which become the core of the atheroma [4, 9].

The core also includes necrotic material from dead foam cells and macrophages and is also referred to as the necrotic lipid core. The necrotic core is protected by a fibrous cap formed by SMCs and extracellular matrix proteins under the impact of cytokines and T cell and macrophage growth factors that preserve the lesion from blood flow. Rupture-prone plaques usually contain a large, soft, lipid-rich necrotic core with a thin (approximately 65  $\mu\text{m}$ ) and an inflamed fibrous cap [3]. Progression of the atherosclerotic plaque would limit the passage of blood and would be compensated for by an internal remodeling. However, the adaptability of vascular remodeling is limited. Decreased luminal diameter limits blood flow to the downstream tissue, but in most situations, this will not become functionally restricted until 75% of the lumen is affected. At this stage, distal perfusion can be insufficient to meet the demands of perfused tissue, leading to manifest clinical symptoms [9].

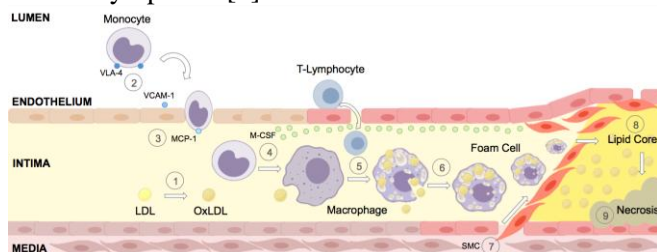


Fig. 1 Pathogenesis of atherosclerosis

Fig. 1 demonstrates pathogenesis of atherosclerosis: (1) Atherosclerosis begins with the endothelium build-up of LDL-carrying cholesterol, especially Ox-LDL; (2) The Ox-LDLs stimulate the activation of endothelial cells and the expression of various leukocyte adhesion molecules (such as VLA-4) and endothelial monocyte adhesion (VCAM-1); (3)

Transmigration of monocytes into the intima assisted by MCP-1; (4) Monocyte differentiate into macrophages with the mediation of M-CSF facilitates phagocytosis of modified lipoproteins; (5) Multiplication of monocytes into foam cells, leading to the development of atherosclerotic plaque; (6) Foam cells recruit extra inflammatory cells such as T lymphocytes to meet macrophages in the intima during plaque evolution and secrete cytokines; (7) Cytokine production drives SMCs and fibroblast proliferation, encourages endothelial activation, generating a positive feedback loop that activates the development of the atherosclerotic plaque; (8) When the plaque progresses, the extracellular lipid deposits form large pools which become the core of the atheroma; (9) The core also includes necrotic material from dead foam cells and macrophages and is also referred to as the necrotic lipid core protected by a fibrous cap formed by SMCs.

### 3. Innate and Adaptive Immune System in Atherosclerosis

Innate and adaptive immune systems play a part in the development of atherosclerosis. Innate immunity responds rapidly to PAMP determinants such as gram-negative lipopolysaccharide bacteria. Innate immunity includes macrophages, natural killer (NK) cells, mast cells, complement, various chemokines. Adaptive immunity responds slower by recognizing particular antigen epitopes. Cellular elements consist of B- and T-cells, cytotoxic T-cells, and chemokines as the effector. The activity of both adaptive and innate immune cells has been reported to be associated with preventing atherosclerosis lesions [13].

It is now clear that atherosclerosis leads to an inflammatory disease in which the immune system plays an important role in its progress, both during the early stages and during the late complications of the disease. Therefore, at least one of the following points must be reached by an effective immunomodulatory therapeutic strategy: 1) stop the development of the atherosclerotic plaque; 2) present the ability to achieve complete or partial regression of the plaque; 3) preserve the plaque, and 4) promote factors that reduce the inflammatory process associated with the formation of the atherosclerotic plaque [4].

Since atheroprotective immunity is established throughout the disease, producing immunomodulation approaches and developing a vaccine in the prevention and/or treatment of atherosclerosis, have been assumed a feasible strategy. There are two important points of a vaccine against atherosclerosis: 1) Selective repression of the pro-atherogenic immune response 2) Specific activation of the anti-atherogenic immune response [4]. Based on the above, many methods have been developed and analyzed with the possibility of inhibiting atherosclerosis by active immunization or specifically delivering antibodies to proteins related to the development of the disease. The most challenging

and complicated stage in immunization against atherosclerosis has always been identifying effective antigens to provide sufficient protection against atherosclerosis [4, 5, 7].

## **4. Lipid-Related Antigens: OXLDL apoB100, CETP, PCSK9**

### **4.1. OXLDL and apoB100**

LDL and other lipoprotein-containing apoB100 are the main perpetrators with the greatest causative link to atherothrombosis, and lipoprotein-derived antigens have been at the forefront of vaccine production [5]. Oxidized LDL (OxLDL) plays a significant function in the production of atherosclerosis. Modification of LDL to its oxidized form happens through many different pathways. One clinically important pathway is myeloperoxidase (MPO) and its oxidant product hypochlorite (HOCl). MPO tends to estimate well in the susceptible population and be well associated with the seriousness of the disease. In mice and humans, increased titers of HOCl-OxLDL autoantibodies have been observed during atherogenesis. The use of OxLDL immunization in animals has shown a strong association between the elevated titers of anti-OxLDL antibodies and the level of defense against atherosclerosis [14]. Anti-OxLDL antibodies can provoke an adaptive immune response leading to inflammation. Various subclasses of anti-OxLDL antibodies with various pathogenic effects have been identified in humans, which are remarkable candidates to investigate immune modulation [7].

Two main subclasses of OxLDL antigens have been used for atherosclerosis vaccination and considered atheroprotective are unique MDA-modified peptide sequences in apoB-100 and oxidized phospholipids containing a PC head group, either as isolated lipids or as directly bind to apoB-100 peptide sequences [15].

A study at Lund University in Sweden has made a large effort to identify possible antigenic epitopes within apoB-100, the main protein element of LDL, and other atherogenic lipoproteins, which could then be used as antigens to promote atheroprotective effects by vaccination. They examined a complete 4536-amino acid human apoB-100 protein and created a library of 302 peptides covering the entire apoB-100 sequence. 102 peptides were chosen based on the humoral immune response found in pooled human plasma as potential candidates for the next round of screening [16].

Several experiments have been performed with differences in the p210 vaccine. These distinct cellular immune responses triggered by p210 may be explained by the differences in 1) the type of p210 delivered (conjugated carrier, recombinant with CTB, or free form); 2) the route of delivery subcutaneous versus mucosal; 3) the dosage of p210 or 4) the duration of delivery of p210 (long term depot effect of carrier-

conjugated p210 in subcutaneous tissue versus infusion for two weeks. However, a substantial decrease in p210 atherosclerosis, regardless of how and what type it was given, strongly implies that p210 is a promising candidate for potential vaccine development for possible future human use [5].

### **4.2. CETP**

Cholesteryl ester transfer protein (CETP) is a hydrophobic glycoprotein secreted in the liver and circulates in plasma, bound primarily to HDL. In rabbits, vaccination CETP, one of the enzymes involved in HDL metabolism, has shown to increase the development of HDL-C and minimize atherosclerosis. However, no improvements in CETP and CETP vaccine HDL were seen in Phase 1 human trials [17].

### **4.2. PCSK9**

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is mainly secreted in the liver and binds to the LDL receptor, thereby preventing the recycling of further LDL take-up particles and contributing to an increase in the circulating LDL-C. Vaccination against PCSK9 has been produced by passive immunization with PCSK9 monoclonal antibodies, decreasing LDL cholesterol concentration. The FDA approved Alicurumab in July 2015 for adult patients with heterozygous familial hypercholesterolemia or in patients with clinically significant atherosclerotic CVD requiring further LDL lowering following diet management and maximally tolerated statin therapy. However, they need to be injected intermittently due to their brief half-lives in vivo, which require a high cost [18]. Given the need for repeated administration of anti-PCSK9 monoclonal antibodies at high doses associated with side effects, low medication adherence, and high cost, active immunization against PCSK9 may be a possible route to addressing the downside of passive immunization [5].

## **5. Nonlipid Antigens: MHC II Deprived Peptides, HSP, S. Pneumoniae, Oral DNA Vaccination, Fibronectin, B2 Glycoprotein, C5a Receptor, Plant Base**

### **5.1. MHC II Deprived Peptides**

Peptides eluted from murine class II MHC molecules are another type of antigen derived from non-apoB100 proteins. Apolipoprotein E (ApoE) is a lipid transport protein with various functions in cellular responses to tissue damage, immune modulation, and cell development. Ep1.B (239e252) of eluted peptides has been shown to suppress early atherosclerosis when delivered intravenously. When given during early plaque development in ApoE-deficient mice, Ep1.B injections also inhibited plaque formation. Treatment

with Ep1.B, however, did not minimize the growth of the developed plaque in older mice. Afterward, S. M. Bellemore and his colleagues showed plasmacytoid DC (pDC) induced by Ep1.B treatment. They have shown that Ep1.B-induced pDCs stimulate Treg cells' production that enhances peripheral tolerance in adaptive immunity and potentially contributes to its anti-atherogenic effect [19].

## 5.2. HSP

Heat shock protein (HSP) is a protein expressed at a high level in response to stress, such as low oxygen levels or pH alterations. HSPs restore or inhibit denatured proteins in these conditions and improve cell viability under severe stimuli. HSPs are also reported to be associated with atherosclerosis [2]. HSP antigen is detected on the surface of endothelial cells, mononuclear cells, and vascular SMCs in human atherosclerotic plaques. Circulating antibodies toward HSPs have been identified in patients with atherosclerosis, and HSP60-specific T cells have been identified in atherosclerotic plaques [20].

Immunization trials have reported contradictory findings, partially due to various adjuvants and routes of administration. G. Foteinos et al. have demonstrated that IV injection of blood-derived anti-HSP antibodies in patients with coronary heart disease significantly improved atherosclerotic lesions in the aorta after eight weeks in apolipoprotein E-deficient mice [21]. But on the other hand, mucosal administration of HSP-based vaccines achieves a downmodulation of immune reactions to particular antigens. For example, intranasal vaccines using either plasmid DNA encoding HSP65, whole protein HSP65, or both in phosphate-buffered saline (PBS) in rabbits induced HSP65 IgG reactions, increased serum IL-10, decreased IFN- $\gamma$ , and decreased atherosclerosis along with decreased cholesterol levels. The effects of these types of HSP65 were distinct and complex, and thus the precise action mechanisms remained to be identified. However, intranasal administration of the Hsp65 protein alone is an advisable approach to interact with the progression of atherosclerosis compared to the other two immunization approaches [7].

## 5.3. *S. Pneumoniae*

Molecular mimicry between *Streptococcus pneumoniae* (*S. pneumoniae*) and OxLDL has been indicated. For the first time, C. J. Binder and his colleagues observed that certain OxLDL autoantibodies originating from "naive" atherosclerotic mice share full genetic and structural characteristics with antibodies from the classical anti-PC B-cell clone, T15, which have defensive effects against certain infectious pathogens, including pneumococci. Pneumococcal immunization has been found to decrease the extent of atherosclerosis. The plasma of these mice had a superior tendency to inhibit the binding of OxLDL to

macrophages [5].

In contrast, with regard to minimizing myocardial infarction or stroke as endpoints, human observational cohort studies have not shown consistent benefits of pneumococcal vaccination. However, a systematic study and meta-analysis of cohort studies found that pneumococcal vaccination was correlated with a reduced risk of cardiovascular incidents and mortality. This advantage was greater in older age and subjects at high cardiovascular risk [22].

## 5.4. Oral DNA Vaccination

The baseline of oral DNA vaccine is the target of some cell-surface proteins known to lead to atherosclerosis. In this technique, the word plasmid encoding the antigen moves the genetic material from the carrier to the host phagocytes in the gastrointestinal tract. The phagocytes then release the antigen de novo in the cytosol and present it to MHC molecules. Vascular endothelial growth factor receptor 2 (VEGFR2), which is not expressed in stable arteries and veins, is highly expressed both in endothelial cells during angiogenesis and in luminal endothelial cells in human atherosclerotic vessels. Interaction between VEGF and VEGFR2 is a crucial factor in the abnormal angiogenesis of plaque stimulation, endothelial cell migration, and proliferation [23].

One of the experiments using the oral DNA vaccine system was conducted by A.D. Hauer and his colleagues. They used live attenuated bacterium *S. Typhimurium* containing VEGFR2-encoding plasmid, resulting in the activation of a cytotoxic CD8 T cell response to VEGFR2 over-expressing cells in atherosclerosis-prone mice. Vaccination against VEGFR2 has been shown to reduce the onset of atherosclerosis by 77% substantially and to reduce the development of pre-existing atherosclerotic lesions in apoE mice by 66% [5].

## 5.5. Fibronectin

LDL preservation by an extracellular matrix such as fibronectin in the arterial wall is an early stage in the formation of atherosclerotic lesions. The association of apoB-100 protein in LDL with extracellular matrix proteoglycans plays a key role in this process. In comparison, mice that express LDL-binding deficient proteoglycan produce less atherosclerosis [24]. Extracellular matrix proteins such as collagen, laminin, and fibronectin have been found to bind lipoproteins. LDL oxidation is consistent with aldehyde modulation of extracellular matrix proteins such as fibronectin. MDA-fibronectin is found in human atherosclerotic plaques, and autoantibodies to MDA-fibronectin can also be found in human plasma. In a prospective case-control analysis, antibodies to MDA-modified fibronectin were associated with a lower risk of cardiovascular events [5].

### 5.6. 2-Glycoprotein I (b2-GPI)

B2-GPI is an intensely glycosylated plasma protein ready to bind negatively charged surfaces and compounds. It is used to target antiphospholipid antibodies in patients with procoagulant and related immune disorders. It has also been shown that apoptotic cells bind, act as a regulator of cell flow, and are also involved in atherogenesis. Anti-b2-GPI has a growing impact on the *in vitro* absorption of OxLDL by macrophages, which exacerbates atherosclerosis.

In research performed by J. De Haro et al., LDLR mice stayed on a high-fat diet for eight weeks after b2-GPI vaccination. Thoracic aorta thickening was completely different between immunized and control populations. The aortic wall thickness of the vaccinated population was slightly smaller than the aortic wall thickness in the control group [25].

### 5.7. C5a Receptor

Anaphylatoxin C5a, formed by activating the innate immune complement part C5, is a potent protein fragment. It has proinflammatory properties as it binds to the C5a receptor in immune-inflammatory cells, including monocytes, macrophages, neutrophils, and T cells. Among the innate immune elements, C5, C5a, and C5aR are common and are suggested to play critical roles in atherogenesis. In a study to assess the impact of C5aR vaccination on mice, X. Lu et al. observed that C5a or C5aR was expressed in aorta sinus lesions. In immunized mice, the lesion size was slightly smaller. They also observed that immunization with C5aR peptides had decreased lesion production although peptides had little effect on both C5a and C5aR expression, indicating that immunization with C5aR peptides may affect the activity of the inflammatory cells rather than the expression of C5aR and C5a. They noted that in immunized mice, C5a could not effectively bind to C5aR expressed in inflammatory cells present in the lesions, suggesting a possible mechanism that C5aR antibody produced by immunization can occupy the site of C5a binding to the surface cells in the lesions, thereby blocking C5a binding to C5aR [26].

### 5.8. Plant-Based Vaccination

The theory of using transgenic plants to develop and distribute subunit vaccines was proposed by Dr. Arntzen and his colleagues and stated that this idea could solve the limitations of conventional vaccine manufacturing.

Plant-based vaccine development requires, in particular, the incorporation of a transgene into plant cells. Direct and indirect methods could generate genes. Direct approaches essentially include the direct injection of DNA or RNA into plant cells. At the same time, indirect gene transmission requires the use of plant bacteria, particularly *Agrobacterium* species and plant viruses, which normally infect plant cells and are

capable of introducing the gene of interest into the plant genome [27].

The plants widely used as bioreactors are tobacco, potatoes, tomatoes, corn. Several transgenic plants have been used to develop four distinct forms of vaccines: bacterial vaccines, virus vaccines, parasitic vaccines, and immunocontraceptive vaccines. A plant-based vaccine may also be a vaccination option for atherosclerosis and could offer a new window in this sector. Consideration of plant-based vaccinations stems from a clear sense of the need to establish low-cost vaccination strategies as a key concern to achieve robust platforms for large-scale vaccination campaigns, especially in developed countries [5, 27].

## 6. Challenges in Atherosclerosis Vaccine Development

The best time for vaccination is also a major issue to address when the vaccine is ready for use. Most experimental immunization trials using LDL or OxLDL antigens have demonstrated important prevention of early atherosclerotic lesions. Theoretically, the optimal target for the administration of atherosclerosis vaccine is children between 5 and 15 years of age based on the initiation of fat deposition in the blood vessel within that range. Other than that, in children aged 5 to 15 years, the body's immune response begins to grow. It is also challenging to assess the atheroprotective efficacy of vaccines clinically in humans. Atherosclerosis is a progressive disease that thus takes a very long duration. However, further research on the efficacy of the vaccine is expected. Possible side effects include fever and swelling in the injection area. Further studies are still required [13].

## 7. Conclusion

The vaccination method to modulate highly prevalent atherosclerotic cardiovascular disease is interesting and challenging but still in its infancy. Vaccination with atherosclerosis has a great deal of potential. It has multiple candidate antigens, including lipid-related antigens (OxLDL apoB100, CETP, PCSK9) and non-lipid-related antigens (MHC II peptide-free, HSP, *S. Pneumoniae*, interleukin, oral DNA vaccination, fibronectin, B2 glycoprotein, C5a receptor, plant base) with contrasting efficacy. We believe that vaccination against atherosclerosis is interesting because it is antigen-specific, does not compromise host defense, and offers long-term protection. Currently, atherosclerosis vaccination may not be applied to treat atherosclerosis in humans due to most research being conducted in animals and extremely few in humans. It is necessary to do further human research in addition to the ongoing animal research. More studies are also still required to determine the efficacy of vaccines in preventing the development of atherosclerotic plaques at a very early

stage.

## 8. Limitations and Further Study

This study was limited by the number of prior studies identified and the insufficient evidence of an atherosclerosis vaccination in human trials and its side effects. Further study is required to determine the choice of dosage and technique, side effects, the efficacy of atherosclerosis vaccine in clinical trials.

## References

- [1] WORLD HEALTH ORGANIZATION. *Cardiovascular diseases (CVDs)*. WHO Press, 2016.
- [2] FAVA C., and MONTAGNANA M. Atherosclerosis Is an Inflammatory Disease which Lacks a Common Anti-inflammatory Therapy: How Human Genetics Can Help to This Issue. A Narrative Review. *Frontiers in Pharmacology*, 2018, 9: 55.
- [3] BERGHEANU S.C., BODDE M.C., and JUKEMA J.W. Pathophysiology and treatment of atherosclerosis: Current view and future perspective on lipoprotein modification treatment. *Netherlands Heart Journal*, 2017, 25(4): 231-242.
- [4] WANG F., ZHANG Z., FANG A., JIN Q., FANG D., LIU Y., WU J., TAN X., WEI Y., JIANG C., and SONG X. Macrophage Foam Cell-Targeting Immunization Attenuates Atherosclerosis. *Frontiers in Immunology*, 2019, 10(9): 3127. DOI: 10.3389/fimmu.2018.03127.
- [5] SOIZA R.L., DONALDSON A.I.C., and MYINT P.K. Vaccine against arteriosclerosis: an update. *Therapeutic Advances in Vaccines*, 2018, 9(6): 259-61.
- [6] SORCI-THOMAS M.G., and THOMAS M.J. Microdomains, Inflammation, and Atherosclerosis. *Circulation Research*, 2016, 118(4): 679-691.
- [7] AMIRFAKHRYAN H. Vaccination against atherosclerosis: An overview. *Hellenic Journal of Cardiology*, 2020, 61(2): 78-91.
- [8] LI T.B., ZHANG J.J., LIU B., LUO X.J., MA Q.L., and PENG J. Dysfunction of endothelial progenitor cells in hyperlipidemic rats involves the increase of NADPH oxidase derived reactive oxygen species production. *Canadian Journal of Physiology and Pharmacology*, 2017, 95(5).
- [9] DAIBER A., STEVEN S., WEBER A., SHUVAEV V.V., MUZYKANTOV V.R., LAHER I., LI H., LAMAS S., and MÜNZEL T. Targeting vascular (endothelial) dysfunction. *British Journal of Pharmacology*, 2017, 174(12): 1591-1619.
- [10] LINTON M.R.F., YANCEY P.G., DAVIES S.S., JEROME W.G., LINTON E.F., SONG W.L., DORAN A.C., and VICKERS K.C. *The Role of Lipids and Lipoproteins in Atherosclerosis*. MDText.com South Dartmouth, MA, 2019. <https://www.ncbi.nlm.nih.gov/books/NBK343489/>
- [11] SZENTES V., GAZDAG M., SZOKODI I., and DÉZSI C.A. The Role of CXCR3 and Associated Chemokines in the Development of Atherosclerosis and During Myocardial Infarction. *Frontiers in Immunology*, 2018, 27(9): 1932.
- [12] IBRAHIM N.I., and MOHAMED I.N. Interdependence of Anti-Inflammatory and Antioxidant Properties of Squalene-Implication for Cardiovascular Health. *Life (Basel)*, 2021, 11(2): 103.
- [13] PUTRI D.K.S.C., AL-FARABI M.J., and SURYAWAN I.G.R. Antigen Candidates for Atherosclerosis Vaccine Development. *IOP Conference Series: Earth and Environmental Science*, 2020, 441(1).
- [14] NILSSON J., and SHAH P.K. Promoting atheroprotective immunity by vaccination with low density lipoprotein-derived antigens. *Atherosclerosis*, 2021, 335: 89-97.
- [15] AMELI S., HULTGÅRDH-NILSSON A., REGNSTRÖM J., CALARA F., YANO J., CERCEK B., YANO J., CERCEK B., SHAH P.K., and NILSSON J. Effect of Immunization With Homologous LDL and Oxidized LDL on Early Atherosclerosis in Hypercholesterolemic Rabbits. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 2021, 16(8): 1074-1079.
- [16] HU W., ZHANG X., HAN Y., WANG Y., LEI M., MEGSON I.L., WEI J., and JIN Y. Associations between circulating IgG antibodies to Apolipoprotein B100-derived peptide antigens and acute coronary syndrome in a Chinese Han population. *Bioscience Reports*, 2018, 38(6): 20180450.
- [17] AL-FARABI M.J. Development of Candidate Antigens for Atherosclerosis Vaccination. *Atherosclerosis*, 2016, 43(11): 836-842.
- [18] CHAUDHARY R., GARG J., SHAH N., and SUMNER A. PCSK9 inhibitors: A new era of lipid-lowering therapy. *World Journal of Cardiology*, 2017, 9(2): 76.
- [19] BELLEMORE S.M., NIKOPOUR E., AU B.C.Y., KROUGLY O., LEE-CHAN E., HAERYFAR S.M., and SINGH B. Anti-atherogenic peptide Ep1.B derived from apolipoprotein E induces tolerogenic plasmacytoid dendritic cells. *Clinical and Experimental Immunology*, 2014, 177(3): 732-742.
- [20] WICK C. Tolerization against atherosclerosis using heat shock protein 60. *Cell Stress and Chaperones*, 2016, 21(2): 201-211.
- [21] CHYU K.Y., DIMAYUGA P.C., and SHAH P.K. Vaccine against arteriosclerosis: an update. *Therapeutic Advances in Vaccines*, 2017, 5(2): 39-47. DOI: 10.1177/2051013617693753.
- [22] SHIMADA K., MORINAGA H., KIYANAGI T., MIYAZAKI T., NISHITANI-YOKOYAMA M., OKAI I., TAMURA H., KONISHI H., KURATA T., MIYAUCHI K., and DAIDA H. Safety and Efficacy of Simultaneous Inoculations of Pneumococcal and Influenza Vaccines in Patients with Coronary Artery Disease. *Journal of Atherosclerosis and Thrombosis*, 2021, 28(8): 826-834.
- [23] XU J., LU X., and SHI G.P. Vasa vasorum in atherosclerosis and clinical significance. *International Journal of Molecular Sciences*, 2015, 16(5): 11574-11608.
- [24] AMIRFAKHRYAN H. Vaccination Against Atherosclerosis: A Brief Review and Update. *Journal of Cardiology and Cardiovascular Sciences*, 2020, 4(1): 35-40.
- [25] MARCHINI T., HANSEN S., and WOLF D. ApoB-Specific CD4+ T Cells in Mouse and Human Atherosclerosis. *Cells*, 2021, 10(2): 446.
- [26] NETTERSHEIM F.S., DE VORE L., and WINKELS H. Vaccination in Atherosclerosis. *Cells*, 2020, 9(12): 2560.
- [27] SHARMA S., and NEGI N.P. Production and Challenges of Plant based Vaccines. *Annals of the Romanian Society for Cell Biology*, 2021: 3625-3639.

## 參考文:

- [1] 世界衛生組織。心血管疾病。世衛組織出版社，2016年。



- [2] FAVA C. 和 MONTAGNANA M. 動脈粥樣硬化是一種缺乏常見抗炎療法的炎症性疾病：人類遺傳學如何幫助解決這個問題。敘事評論。藥理學前沿，2018，9：55。
- [3] BERGHEANU S.C.、BODDE M.C. 和 JUKEMA J.W. 動脈粥樣硬化的病理生理學和治療：脂蛋白修飾治療的當前觀點和未來觀點。荷蘭心臟雜誌，2017，25 (4)：231-242。
- [4] WANG F.、ZHANG Z.、FANG A.、Jin Q.、FANG D.、LIU Y.、WU J.、TAN X.、WEI Y.、JIANG C. 和 SONG X. 巨噬細胞泡沫細胞-靶向免疫可減輕動脈粥樣硬化。免疫學前沿，2019，10(9)：3127。DOI: 10.3389/fimmu.2018.03127。
- [5] SOIZA R.L.、DONALDSON A.I.C. 和 MYINT P.K. 抗動脈硬化疫苗：更新。疫苗的治療進展，2018，9(6)：259-61。
- [6] SORCI-THOMAS M.G. 和 THOMAS M.J. 微區、炎症和動脈粥樣硬化。循環研究，2016，118(4)：679-691。
- [7] AMIRFAKHRYAN H. 抗動脈粥樣硬化疫苗：概述。希臘心臟病學雜誌，2020年，61 (2)：78-91。
- [8] LI T.B.、ZHANG J.J.、LIU B.、LUO X.J.、MA Q.L. 和 PENG J. 高脂血症大鼠內皮祖細胞功能障礙涉及煙酰胺腺嘌呤二核苷酸磷酸，還原形式氧化酶衍生的活性氧物質產生的增加。加拿大生理學和藥理學雜誌，2017，95 (5)。
- [9] DAIBER A.、STEVEN S.、WEBER A.、SHUVAEV V.V.、MUZYKANTOV V.R.、LAHER I.、LI H.、LAMAS S. 和 MÜNZEL T. 針對血管 (內皮) 功能障礙。英國藥理學雜誌，2017，174 (12)：1591-1619。
- [10] LINTON M.R.F.、YANCEY P.G.、DAVIES S.S.、JEROME W.G.、LINTON E.F.、SONG W.L.、DORAN A.C. 和 VICKERS K.C. 脂質和脂蛋白在動脈粥樣硬化中的作用。南達特茅斯，馬薩諸塞州，2019年。<https://www.ncbi.nlm.nih.gov/books/NBK343489/>
- [11] SZENTES V.、GAZDAG M.、SZOKODI I. 和 DÉZSI C.A. 白細胞介素 8 受體， $\beta$  和相關趨化因子在動脈粥樣硬化發展和心肌梗死期間的作用。免疫學前沿，2018，27(9)：1932。
- [12] IBRAHIM N.I. 和 MOHAMED I.N. 角鯊烯的抗炎和抗氧化特性的相互依賴性——對心血管健康的影響。生活 (巴塞爾)，2021，11 (2)：103。
- [13] PUTRI D.K.S.C.、AL-FARABI M.J. 和 SURYAWAN I.G.R. 動脈粥樣硬化疫苗開發的抗原候選者。物理研究所會議系列：地球與環境科學，2020年，441(1)。
- [14] NILSSON J. 和 SHAH P.K. 通過接種低密度脂蛋白衍生抗原來促進動脈粥樣硬化保護性免疫。動脈粥樣硬化。2021年，335：89-97。
- [15] AMELI S.、HULTGÅRDH-NILSSON A.、REGNSTRÖM J.、CALARA F.、YANO J.、CERCEK B.、YANO J.、CERCEK B.、SHAH P.K. 和 NILSSON J. 同源低密度脂蛋白免疫的效果和氧化低密度脂蛋白對高膽固醇血症家兔早期動脈粥樣硬化的影響。動脈硬化、血栓形成和血管生物學，2021，16(8)：1074-1079。
- [16] HU W.、ZHANG X.、HAN Y.、WANG Y.、LEI M.、MEGSON I.L.、WEI J. 和 JIN Y. 循環免疫球蛋白 G 抗體對載脂蛋白 B100 衍生肽抗原與急性冠狀動脈綜合徵的關聯在中國漢族人群中。生物科學報告，2018，38 (6)：20180450。
- [17] AL-FARABI M.J. 動脈粥樣硬化疫苗候選抗原的開發。動脈粥樣硬化，2016，43 (11)：836-842。
- [18] CHAUDHARY R.、GARG J.、SHAH N. 和 SUMNER A. 前蛋白轉化酶枯草桿菌蛋白酶/可心 9 型抑制劑：降脂治療的新時代。世界心臟病學雜誌，2017，9 (2)：76。
- [19] BELLEMORE S.M.、NIKOPOUR E.、AU B.C.Y.、KROUGLY O.、LEE-CHAN E.、HAERYFAR S.M. 和 SINGH B. 源自載脂蛋白 E 的抗動脈粥樣硬化肽 Ep1.B 誘導耐受性漿細胞樣樹突狀細胞。臨床和實驗免疫學，2014，177(3)：732-742。
- [20] WICK C. 使用熱休克蛋白 60 耐受動脈粥樣硬化。細胞應激和伴侶，2016，21(2)：201-211。
- [21] CHYU K.Y.、DIMAYUGA P.C. 和 SHAH P.K. 抗動脈硬化疫苗：更新。疫苗的治療進展，2017，5(2)：39-47。DOI：10.1177/2051013617693753。
- [22] SHIMADA K.、MORINAGA H.、KIYANAGI T.、MIYAZAKI T.、NISHITANI-YOKOYAMA M.、OKAI I.、TAMURA H.、KONISHI H.、KURATA T.、MIYAUCHI K. 和 DAIDA H. 安全冠狀動脈疾病患者同時接種肺炎球菌和流感疫苗的療效和療效。動脈粥樣硬化和血栓形成雜誌，2021，28(8)：826-834。
- [23] XU J.、LU X. 和 SHI G.P. 血管滋養管在動脈粥樣硬化中的臨床意義。國際分子科學雜誌，2015，16(5)：11574-11608。
- [24] AMIRFAKHRYAN H. 抗動脈粥樣硬化疫苗：簡要回顧和更新。心臟病學和心血管科學雜誌，2020，4(1)：35-40。
- [25] MARCHINI T.、HANSEN S. 和 WOLF D. 小鼠和人類動脈粥樣硬化中的載脂蛋白 B 特异性 CD4+ T 抑制細胞。細胞，2021年，10 (2)：446。
- [26] NETTERSHEIM F.S.、DE VORE L. 和 WINKELS H. 動脈粥樣硬化疫苗接種。細胞，2020年，9 (12)：2560。
- [27] SHARMA S. 和 NEGI N.P. 植物疫苗的生產和挑戰。羅馬尼亞細胞生物學學會年鑑，2021：3625-3639。