Athera Biotechnologies AB
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Resolving inflammation to tackle cardiovascular disease

With its lead candidate, ATH3G10, a first-in-class antibody indicated for large ST-elevation myocardial infarction (STEMI), Athera Biotechnologies is harnessing the process of efferocytosis to treat a range of vascular diseases.

Vascular diseases are the leading causes of death worldwide, with more than 500 million people currently suffering from vascular conditions affecting the heart as well as blood vessels in the brain, legs and other organs. Although vascular disease is associated with a host of lifestyle factors, from diet and exercise to stress and smoking, inflammation has increasingly taken centre stage in understanding the pathogenesis and course of vascular disease. Athera Biotechnologies, whose mission is to address the large unmet need for anti-inflammatory therapeutics in the treatment of cardiovascular disease, is building on these insights and pursuing the next breakthrough in treating vascular disease with ATH3G10.

The fully human antibody ATH3G10

The monoclonal antibody ATH3G10 is a first-in-class antibody to target phosphorylcholine (PC), the head group of oxidized phospholipids (oxPLs), an epitope on damaged or stressed cells.

ATH3G10 is initially being developed for patients who have had a large ST-elevation myocardial infarction (STEMI) and are at high risk of heart failure. Tissue from infarcted myocardium that has suffered an ischemia–reperfusion injury has large amounts of exposed PC, indicating that the body is not clearing away damaged cells effectively. The resulting non-resolving inflammation can lead to cardiac remodelling and heart failure in 15% of patients with STEMI within 1–2 months. The 5-year mortality in heart failure is 50%—worse than many cancers.

ATH3G10 is currently in a phase 2 proof-of-concept trial for patients with STEMI, who will receive a single dose via intravenous injection in the catheter lab. Patients will have the end-diastolic volume of their left ventricle measured by MRI at the time of dosing, and then again 3 months later, to assess the degree of ventricular expansion, which is associated with heart failure. Results are expected in 2020.

Efferocytosis: resolving inflammation through recycling cells

Every day, in every person, billions of cells in tissues throughout the body become apoptotic and are cleared away through a version of phagocytosis called 'efferocytosis,' the 'burying of dead cells.' When cells become apoptotic, they withdraw 'don't eat me' signals such as CD47 from their surface, and secrete chemotactic 'find me' signals that attract phagocytes. At the same time, apoptotic cells display new epitopes on their surface, including PC on oxPLs, which functions as a damage-associated molecular pattern that is recognized and bound by natural antibodies. Natural antibodies bound to PC act as a potent 'eat me' signal that is recognized by phagocytes, which engulf the apoptotic cell, digest it and recycle the cellular components to maintain tissue homeostasis (**Fig. 1**). Additionally, excessive expression of PC in itself drives local inflammation, which is blocked by PC antibodies. ATH3G10 is designed to act as an analogue of the natural antibodies to PC to increase efferocytosis and resolve inflammation while preserving the body's ability to activate inflammation in response to infection, avoiding potentially dangerous immunosuppression.

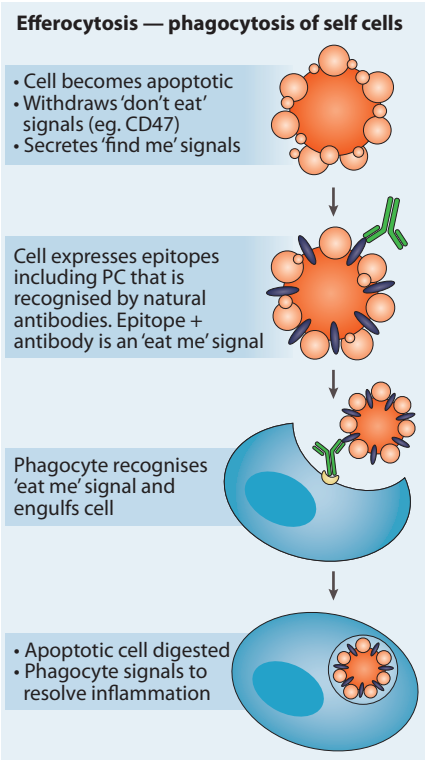

Fig. 1 | The process of efferocytosis. Apoptotic cells withdraw 'don't eat me' signals such as CD47 and secretes chemotactic 'find me' signals that attract phagocytes. Simultaneously, apoptotic cells display new epitopes, including phosphorylcholine (PC) on oxidized phospholipids (oxPLs), which is recognized and bound by natural antibodies. Natural antibodies bound to PC become an 'eat me' signal that is recognized by phagocytes, which engulf, digest and recycle the apoptotic cell.

> **"ATH3G10 is designed to act as an analogue of the natural antibodies to PC to increase efferocytosis and resolve inflammation**

When phagocytes recycle cells and their debris, they induce tolerance for the self-antigens they engulf and promote the resolution of inflammation by suppressing inflammatory mediators. If apoptotic cells are not phagocytosed rapidly, they become necrotic and pro-inflammatory. In this way, impaired efferocytosis leads to chronic inflammation that causes tissue damage and dysfunction. Defective efferocytosis has been implicated in a range of disorders, from heart failure to lung diseases.

The ability to activate inflammation in response to infection means this mechanism is not broadly immunosuppressive. This is a key difference between ATH3G10 and drugs with other anti-inflammatory mechanisms. Many therapies, such as interleukin-1b and tumor necrosis factor inhibitors, broadly suppress inflammation across many tissues. This can create dose-limiting immunosuppression and limit or prevent combination use between classes.

Chronic indications and commercialization

In addition to an intravenous formulation of ATH3G10 for use in acute settings, Athera is developing a subcutaneous version for longer-term, repeat dosing in different conditions. Initially, the subcutaneous formulation will be developed for peripheral artery disease. Subcutaneous ATH3G10, which is easier to administer in an out-of-hospital setting and is more acceptable to patients, has applications in cardiovascular disease and beyond.

Moving forward, Athera is seeking venture investors and is looking to discuss partnering opportunities with pharmaceutical companies that have clinical development and commercialization expertise in the cardiovascular and immunotherapy spaces.

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