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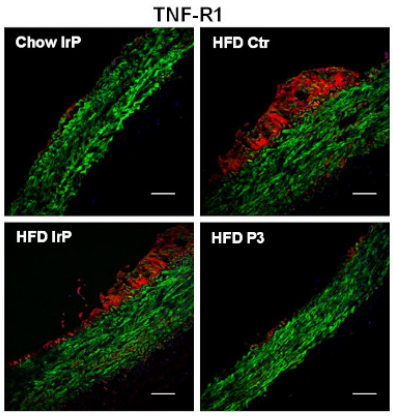
Innovative Antibodies to treat Cardiovascular Disease



According to the World Health Organisation, cardiovascular disease is the leading cause of death worldwide. Current treatments are mainly aimed at reducing the concentration of cholesterol in the blood plasma, but more than half of those affected still suffer acute ischemic events due to the silent internalization of this lipoprotein in the coronary arteries. Now, the research group led by Vicenta Llorente-Cortés (IIBB-CSIC-IIB SantPau-CIBERcv) has developed antibodies that in animal models work more efficiently and specifically by sequestering cholesterol in the arteries and in the heart, without no loss in functionality. It is presented as a possible therapy for those cases which do not respond to medication.

Cardiovascular disease (CVD) is presently a leading cause of death and its impact is even increasing due to CVD complications in surviving oncology (cardio-oncology) and HIV patients. Current treatments are focused on lowering plasma cholesterol levels traditionally through statins and more recently through PCSK9 inhibitors. However, approximately **60% of patients treated with the classic treatment, with on-target plasma cholesterol levels are still suffering acute ischemic events** (ACS) due to the silent internalization of cholesterol in their coronary arteries.

Cellular cholesterol internalization is a critical currently untreated step. That is why patients with low plasma cholesterol levels suffer ACS episodes. The cellular internalization of

cholesterol has to be interrupted. In this scenario, **we have developed antibodies that efficiently and specifically treat the entrapment of cholesterol** in vasculature and heart.

The group of Dra Llorente identified a critical receptor, low-density lipoprotein receptor (LRP1) that is key for intracellular entrapment of colesterol. LRP1 is strongly upregulated in coronary arteries and myocardium of patients exposed to prevalent cardiovascular factors. In this receptor we have identified the epitope (P3) and the specific aminoacidic sequence in charge of cholesterol internalization. Anti-P3 antibodies, developed by SCAC, scientific and technical service of the UAB, **specifically interrupt the interaction of the receptor with atherogenic lipoproteins without altering other essential functions** of the receptor.

In the article, we demonstrate that P3 immunization raised anti-P3 antibodies that are therapeutically efficient in atherosclerosis. Anti-P3 antibodies block cholesterol accumulation in vascular cells and counteract high-fat diet induced atherosclerosis in rabbits. The therapeutic effect was evidenced b**y molecular and immunohistochemical studies and, importantly, by non-invasive clinical methods** including 18F-FDG PET/CT and Doppler Ultrasound Ecography showing a reduction in the standardized uptake value (SUV) and in the resistive index (RI), imaging read-outs currently used for atherosclerosis diagnosis in humans.

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