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Global Spotlights

ERC-funded proof of concept grant: targeting imidazoline 1-receptor in atherosclerosis

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Unmet needs in cardiovascular disease management

Cardiovascular disease (CVD) remains the leading cause of death and disability. Lipid-lowering therapies, particularly statins, have long served as the cornerstone of CVD prevention, effectively reducing cardiovascular risk. However, the overall disease burden remains high. Atherosclerosis develops silently, with studies describing prevalence rates of up to 60% in middle-aged individuals.[1] Diagnosis often occurs only when the disease is advanced, in many cases only after the first cardiovascular event. In addition, many individuals experience recurrent events despite optimal control of traditional risk factors.[2] This highlights the urgent need for innovative strategies that address the complex, multifactorial nature of CVD. In recent years, attention has shifted toward non-traditional contributors to CVD, including chronic low-grade inflammation, immune dysregulation, and metabolic dysfunction. Among these, the gut microbiota has emerged as a key player in cardiometabolic health. Microbial metabolites are increasingly recognized for their ability to influence vascular inflammation, endothelial function, and immune cell activation, either promoting or protecting against atherosclerosis.[3] Yet, microbiome-targeted therapies have not been integrated into clinical practice, and current guidelines do not reflect this emerging paradigm.

The ERC Proof-of-Concept funded project ImnovAth aims to address this unmet clinical need by proposing a novel therapeutic strategy for atherosclerosis (*Figure 1*). This approach targets the sensing

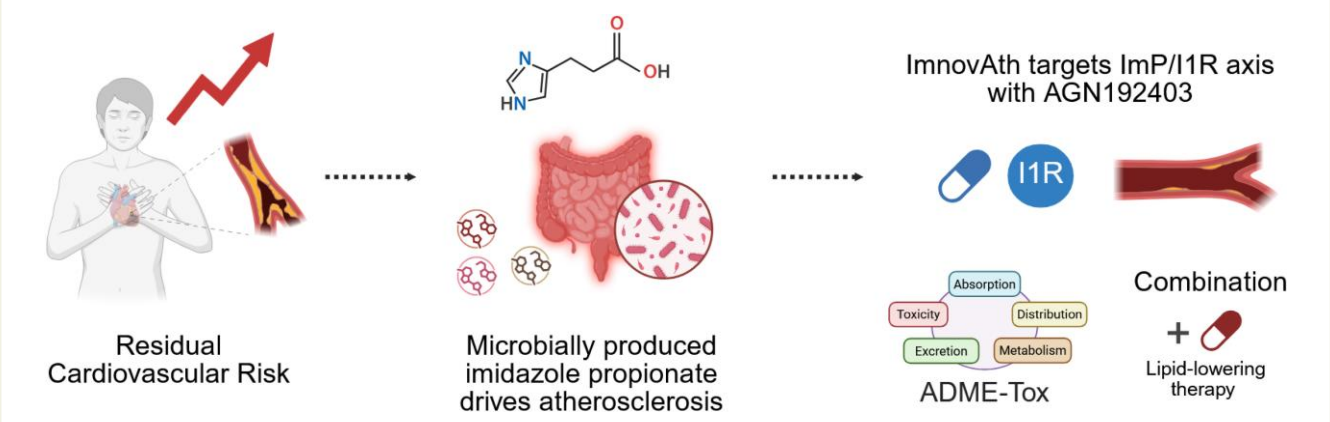

Figure 1 The ImnovAth project introduces a novel therapeutic strategy for atherosclerosis by targeting the sensing pathway of the gut microbiota–derived metabolite imidazole propionate, which drives disease progression independently of lipid metabolism. AGN192403, a selective imidazoline receptor 1 antagonist, is proposed as the therapy acting on the ImP/I1R axis. The strategy includes ADME-Tox profiling and evaluation of combination therapy with standard lipid-lowering agents to improve cardiovascular disease outcomes. Made with BioRender

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pathway of the gut microbiota–derived metabolite imidazole propionate (ImP), which was identified as a key contributor to the development of atherosclerosis.[4,5]

From gut microbiota metabolites to therapeutic targets

ImP is a gut microbiota–derived metabolite produced from histidine, previously linked to insulin resistance through activation of the p38γ/AKT signalling pathway.[6] Recent findings have expanded its pathophysiological relevance to vascular disease, demonstrating its involvement both in subclinical alterations and in more advanced stages of atherosclerosis.[4,5] Beyond atherosclerosis, ImP has been implicated in a broad spectrum of inflammatory and metabolic disorders, including cardiometabolic disease, heart failure, and an increased risk of major adverse cardiovascular events and all-cause mortality[7–10]. These associations underscore the role of the gut microbiota, and ImP in particular, as a critical modulator of cardiovascular risk.

Mechanistic studies have revealed that ImP promotes atherosclerosis through both vascular and immune pathways. Nageswaran *et al.*[5] reported that, in endothelial cells, ImP disrupts the PI3K/AKT/FOXO1 signalling pathway, leading to impaired insulin signalling, increased inflammation, and reduced vascular repair capacity.[5] Additionally, our team demonstrated that ImP activates imidazoline receptor 1 (I1R) in myeloid cells, triggering mTOR-dependent immune activation and chronic inflammation. We further showed that AGN192403, a selective I1R antagonist, effectively blocks ImP-induced atherosclerosis in atheroprone mice. Notably, this protective effect was achieved without altering cholesterol metabolism, suggesting that AGN192403 may serve as a complementary therapy to existing lipid-lowering agents.[4] Building on this mechanistic and preclinical evidence, ImnovAth proposes a novel therapeutic strategy centred on AGN192403, targeting the ImP/I1R axis as a lipid-independent pathway for atherosclerosis treatment.

Toward a new class of cardiovascular therapies

ImnovAth integrates a comprehensive and complementary strategy to bridge scientific innovation with clinical application. The project includes a series of preclinical studies to assess the efficacy and safety of AGN192403 in established models of atherosclerosis, including *ApoE*$^{-/-}$ and *Ldlr*$^{-/-}$ mice fed a high-cholesterol diet, both of which showed elevated ImP levels. First, we will generate a comprehensive pharmacological profile of AGN192403, including absorption, distribution, metabolism, excretion, and toxicity (ADME-Tox) studies, to assess long-term toxicity and tolerability, and provide essential documentation for future regulatory and clinical development. We will then test AGN192403 in both preventive and regression settings, with treatment windows designed to assess efficacy across different stages of disease progression. Therapeutic impact will be assessed through analysis of lipid levels, plaque burden, and plaque composition in the aorta, aortic arch, and heart valves. To further elucidate the mechanism of action, we will characterize immune cell infiltration using single-cell RNA sequencing, enabling identification of transcriptional responses and cellular targets of AGN192403. These studies will be conducted in both male and female mice to ensure sex-specific insights. To explore therapeutic synergy, we will assess the feasibility of combination therapy with statins or other lipid-lowering agents (e.g. ezetimibe and microsomal triglyceride transfer protein inhibitors), aiming to expand the therapeutic potential of the approach. If successful, tolerability and toxicity studies will define safe and effective combination regimens. Together, the findings from ImnovAth will help define the optimal clinical indication, dosing, and safety profile of AGN192403, laying the groundwork for future human trials and informing the design of early-phase clinical studies. In parallel, we will strengthen our intellectual property position, refine our clinical development strategy, and explore industry partnerships to facilitate translation into clinical practice.

As cardiovascular research increasingly embraces precision therapies tailored to the complex, multifactorial nature of the disease, ImnovAth is expected to generate critical preclinical data to inform the design of future clinical trials in humans. While its primary goal is to evaluate the safety and efficacy of AGN192403 in relevant models, the project also serves as a proof-of-concept for a more integrated and personalized approach to CVD management. By focusing on specific biological pathways and patient profiles, particularly those with elevated ImP levels or residual risk despite standard care, ImnovAth is expected to showcase how mechanistic insights can guide the development of novel, personalized interventions.

Declarations

Disclosure of Interest

All authors declare no disclosure of interest for this contribution.

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