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Translating Nobel Prize-winning T_{reg} cell science into cardiovascular therapy

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The 2025 Nobel Prize in Physiology or Medicine honored a scientific breakthrough with hidden cardiovascular potential: regulatory T cells and peripheral immune tolerance. These mechanisms provide a paradigm shift for understanding and treating cardiovascular disease, dampening inflammation without compromising immunity, and offering safer and more effective therapies.

The 2025 Nobel Prize in Physiology or Medicine, awarded to Mary E. Brunkow, Fred Ramsdell and Shimon Sakaguchi "for their discoveries concerning peripheral immune tolerance" recognizes groundbreaking discoveries that have revolutionized our understanding of immune regulation. These findings have major, but largely underappreciated, implications for cardiovascular research and medicine.

Immune tolerance: a fundamental mechanism of body homeostasis

The immune system faces a formidable challenge: it must mount robust defenses against infectious agents while avoiding attacks on the body's own tissues. The latter function, known as immune tolerance, involves several complementary mechanisms. Central tolerance occurs in the thymus, where self-reactive T cells are deleted during development. Peripheral tolerance, mediated by regulatory T cells (T_{reg} cells), provides an essential additional layer of protection by actively suppressing self-reactive T cells that escape thymic deletion. T_{reg} cells exert their immunosuppressive effects through various mechanisms, including direct cell–cell contact inhibition of effector T cells, consumption of survival factors such as interleukin (IL)-2, promotion of tolerogenic dendritic cells and secretion of anti-inflammatory cytokines such as IL-10 and transforming growth factor-β (TGFβ). The Nobel laureates have defined this specific immune cell subset and its transcriptional control by FOXP3, thereby providing a fundamental blueprint for understanding immune homeostasis. Their discovery has also catalyzed extensive research into therapeutic manipulation of T_{reg} cells across multiple disease areas. While the Nobel Committee highlighted the importance of these discoveries to our understanding and treatment of immuno-inflammatory diseases and cancer, cardiovascular diseases (CVD) were not emphasized, despite the major implications of this work for cardiovascular research and medicine.

The underappreciated role of immunity in cardiovascular disease

The cardiovascular research community has long recognized the central role of the immune system in the pathogenesis of CVD, and indeed, a previous chairman of the Nobel Committee was among the first to describe an active adaptive cellular immune response in atherosclerotic plaques[1]. However, compared with other fields, the full integration of immunology into cardiovascular research and medicine has lagged behind, and the relative lack of emphasis on CVD reflects a broader underappreciation of the pivotal role of the immune system in the world's leading cause of death.

Atherosclerosis is fundamentally a lipid-driven immuno-inflammatory disease of medium- and large-sized arteries[2,3]. Beyond modified apolipoprotein B-rich lipoproteins, which act as damage-associated molecular patterns to activate the artery wall, virtually all major cardiovascular risk factors, including obesity, metabolic syndrome, diabetes, smoking, hypertension, stress and sleep disturbances, involve inflammatory components. Experimentally, it is nearly impossible to induce advanced atherosclerosis in the absence of monocytes. The role of the immune system is also supported by genome-wide association studies and downstream mechanistic investigations, which identified causal immune-inflammatory pathways in atherosclerotic cardiovascular disease (ASCVD)[4].

The inflammatory mechanisms of CVD extend well beyond atherosclerosis. The field of cardio-immunology has matured considerably over the past two decades, transitioning from an area often considered marginal to a robust scientific discipline. It now provides a crucial new understanding of the immune drivers behind key cardiovascular conditions, ranging from classical transplant cardiac vasculopathy to the tissue response to ischemic injury (heart and brain), as well as pericarditis, myocarditis, heart failure, atrial fibrillation and vascular dementia[5]. This broad involvement of the immune system across the cardiovascular disease spectrum underscores the substantial therapeutic potential of immune-modulating interventions.

The proof-of-concept journey from innate to adaptive immunity

Initial efforts to target inflammation in CVD focused on innate immune pathways, predominantly the IL-1–IL-6 axis. This approach provided proof-of-concept evidence for the inflammatory hypothesis of ASCVD. The landmark CANTOS trial demonstrated that canakinumab, a monoclonal antibody targeting IL-1β, significantly reduced the occurrence of major adverse cardiovascular events (MACE) in patients with prior myocardial infarction and elevated high-sensitivity C-reactive protein[6]. However, major concerns remain about the long-term benefit–risk profile of targeting upstream innate immune pathways. The IL-1 pathway serves as crucial first-line defense against infections, and the optimal balance between cardiovascular benefit and infection risk remains uncertain, particularly with long-term use in older patients. Subsequent trials with colchicine in patients with stable coronary artery disease further validated the anti-inflammatory approach, showing significant reductions in MACE, although colchicine did not reduce the incidence of MACE after acute myocardial infarction[7]. Ongoing

trials with IL-6 inhibitors will help better define the utility of targeting this innate immune pathway in patients with CVD.

The adaptive immune system plays an equally important part in the pathophysiology of CVD. Early evidence of T cell activation in atherosclerotic lesions, combined with the association between ASCVD and autoimmune diseases[8], suggested an autoimmune component to atherosclerosis. Potential autoantigens have been identified, including components of apolipoprotein B, heat shock proteins and collagens. These observations, together with growing knowledge about counter-regulatory anti-inflammatory mechanisms[9] (for example, involving IL-10 and TGFβ), led to the proposal and discovery that T_{reg} cells have a major atheroprotective role[10]. Studies in mouse models revealed that depletion of T_{reg} cells accelerates atherosclerosis progression and increases plaque vulnerability, whereas T_{reg} cell expansion reduces lesion formation and enhances plaque stability. In humans, reduced T_{reg} cell numbers and impaired T_{reg} cell function have been associated with acute coronary syndromes and adverse cardiovascular outcomes. These findings were later extended to other CVD settings[11]. The mechanisms underlying T_{reg} cell-mediated cardiovascular protection are diverse and include suppression of pro-inflammatory effector T cells, induction of anti-inflammatory and reparative macrophages, regulation of vascular cell activation and proliferation, and modulation of cholesterol metabolism. Importantly, T_{reg} cells also produce growth factors that promote tissue healing and repair, extending their therapeutic potential beyond inflammation resolution.

These discoveries brought the concept of immune tolerance to the forefront of cardiovascular research and therapeutic development, establishing T_{reg} cells as an attractive therapeutic target for limiting cardiovascular inflammation and potentially modifying disease progression.

Clinical translation of the concept of immune tolerance to patients with CVD

Building on preclinical evidence and experience from autoimmune diseases, we recently embarked on testing the clinical relevance of T_{reg} cell-based immunotherapy in patients with ASCVD. The LILACS trial was a phase 1b/2a study that established the safety and biological efficacy of low-dose IL-2 (aldesleukin) in patients with coronary artery disease[12]. We then conducted the IVORY trial to evaluate whether T_{reg} cell expansion using low-dose IL-2 could reduce vascular inflammation in patients with acute coronary syndromes and elevated high-sensitivity C-reactive protein. We demonstrated that low-dose aldesleukin successfully increased T_{reg} cells and significantly reduced vascular inflammation, as measured by ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography. During follow-up, we observed encouraging preliminary signals for reduced cardiovascular events, though larger trials are needed to confirm clinical benefit[13]. Our results align with recent genetic evidence linking the IL-2 signaling pathway to coronary artery disease risk[14], reinforcing the biological rationale for this therapeutic approach.

Why targeting T_{reg} cells may be preferable to other anti-inflammatory strategies

T_{reg} cell-based immunotherapy would offer several potential advantages over other anti-inflammatory approaches for CVD. Firstly, T_{reg} cells promote resolution of diverse inflammatory processes through multiple complementary mechanisms, not only those driven by IL-1 and IL-6, and thus better address the heterogeneous inflammatory pathways implicated in CVD. Secondly, expanding T_{reg} cells appears potentially safer than inhibiting upstream pro-inflammatory pathways that are essential for host defense against infections. The IVORY trial and other studies with low-dose IL-2 have not demonstrated increased infection rates, probably because the selective expansion of T_{reg} cells preserves overall immune competence while specifically enhancing regulatory mechanisms. Indeed, T_{reg} cells are capable of self-nonself discrimination during infections, and although they suppress self-reactive immune responses, they increase the avidity of T cell responses to non-self antigens and promote effective memory.

Another theoretical concern with T_{reg} cells is the potential for impairing anti-tumor immunity and increasing cancer risk. Interestingly, the CANTOS trial demonstrated a substantial reduction in lung cancer deaths, suggesting that certain forms of inflammation inhibition may actually have anticancer effects. However, the relationship between T_{reg} cells, inflammation and cancer in the cardiovascular disease population merits further investigation.

Beyond inflammation resolution, T_{reg} cells produce growth factors and promote tissue healing and repair, contributing to what might be termed tissue tolerance to disease.

Future perspectives and challenges

Mechanistic understanding. We need deeper insight into the mechanisms controlling T_{reg} cell maintenance, activation and function in inflammatory cardiovascular tissues. Understanding the antigen specificity of cardiovascular T_{reg} cells and identifying selective properties for tissue-resident versus circulating T_{reg} cells will be crucial for developing more targeted interventions. Emerging evidence suggests that commensal microbes shape immune tolerance and may influence susceptibility to CVD. Elucidating these interactions could reveal novel preventative and therapeutic strategies.

Next-generation therapeutics. The field is witnessing rapid development of improved IL-2 formulations with enhanced selectivity for T_{reg} cells and reduced off-target effects. Engineered IL-2 variants, IL-2 fusion proteins and IL-2 receptor agonists with differential signaling properties are in various stages of development. Additional approaches use chimeric antigen receptor (CAR)-T_{reg} cells, which could be engineered to specifically target sites of cardiovascular inflammation. For example, a recent study reported the development of CAR-T_{reg} cells engineered to target oxidized low-density lipoproteins[15]. Such antigen- and tissue-targeted approaches might minimize systemic immunosuppression while maximizing therapeutic efficacy at sites of disease. Antigen-specific vaccination and tolerization strategies are also under investigation. The main challenge lies in identifying well-defined antigens and achieving their safe and effective delivery without triggering inflammation. If successful, such approaches could fundamentally transform the management of CVD.

Personalized medicine. Identifying patients who are most likely to benefit from T_{reg} cell-based therapies will be essential for efficient clinical development and implementation.

Long-term safety. Although early data are encouraging, definitive assessment of long-term safety, particularly regarding infection and cancer risks, will require larger trials with extended follow-up.

Conclusion

In conclusion, the convergence of fundamental discoveries in immunology, recognized by the 2025 Nobel Prize of Physiology or Medicine, and

evolving clinical evidence offers new hope for patients with cardiovascular disease. Immune tolerance-based therapies hold the potential to transform how we prevent and treat the world's leading cause of death.

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Competing interests

The author declares no competing interests.