CNIC researcher William Joyce receives an ERC Starting Grant for the TROPOSplice project

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TROPOSplice proposes an evolution-inspired strategy to improve cardiac relaxation in patients with hypertrophic cardiomyopathy and heart failure with preserved ejection fraction.

The TROPOSplice project, coordinated by researcher William Joyce at the Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), has been awarded an ERC Starting Grant and will receive funding of *1.5M €*.

TROPOSplice proposes an evolution-inspired strategy to improve cardiac relaxation in patients with hypertrophic cardiomyopathy (HCM) and heart failure with preserved ejection fraction (HFpEF).

Diastolic dysfunction, defined as impaired relaxation and filling of the heart, is a common feature of several cardiovascular diseases, including HCM and HFpEF. This dysfunction is often caused by excessive calcium sensitivity of the cardiac myofilaments and, in both HCM and HFpEF, is associated with altered adrenergic signalling, which leads to a reduced cardiac response to adrenaline.

According to William Joyce, the project seeks to develop a new generation of RNA therapies targeting diastolic dysfunction, a condition that prevents the heart from relaxing properly and is present in prevalent cardiac diseases such as hypertrophic cardiomyopathy and heart failure with preserved ejection fraction.

Over the course of five years, the project aims to lay the foundations for a completely novel therapeutic strategy based on antisense oligonucleotides capable of modifying the RNA processing of the TNNI3 gene, which encodes cardiac troponin I, a protein essential for regulating the contraction and relaxation of cardiac muscle.

The project builds on a discovery made by Joyce and his collaborators, who identified that small mammals such as bats and shrews have evolved a natural mechanism that enables them to maintain extremely rapid cardiac relaxation despite their very high heart rates. Although this mechanism does not occur naturally in humans or most mammals, it could be induced therapeutically through antisense oligonucleotides to increase the relaxation rate of the myocardium.

TROPOSplice proposes to reproduce this mechanism in the human heart through an RNA-based therapy, using what Joyce describes as a “from bats to patients” strategy.

The therapy works by inducing the controlled skipping of exon 3 in the TNNI3 gene, thereby reducing the calcium sensitivity of cardiac muscle fibres and improving cardiac relaxation. “By bypassing adrenaline receptors, this strategy would be compatible with widely used therapies such as beta-blockers,” says Joyce.

To validate this approach, the project will combine studies in cardiomyocytes derived from human pluripotent stem cells with experimental models of cardiovascular disease. The aim will be to optimise the design and delivery of antisense oligonucleotides, evaluate their effects on cardiac function, and conduct a comprehensive assessment of their safety before progressing towards clinical application.

The researcher expects that TROPOSplice could open a new therapeutic avenue for diseases that currently have few therapies specifically targeting impaired cardiac relaxation. In addition to its potential in HCM and HFpEF, this strategy could have applications in other disorders characterised by excessive calcium sensitivity of cardiac muscle.

William Joyce holds a BSc in Zoology from the University of Manchester (UK) and a PhD in Bioscience from Aarhus University (Denmark). He initially joined Borja Ibáñez’s group at CNIC in September 2023 through a CIBER-funded position (Biomedical Research Networking Centre) and since June 2024 has held a “la Caixa” Foundation Junior Leader fellowship.

ERC Starting Grants support highly innovative projects led by early-career researchers, with the aim

of advancing transformative ideas at the frontiers of knowledge. The TROPOSplice project combines evolutionary biology, molecular biology, and translational medicine to explore a new therapeutic concept for cardiovascular disease.

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