

## **Unraveling proarrhythmic mechanisms of ventricular intramyocardial fat in heart failure through spatial transcriptomics: from bedside to cutting-edge molecular imaging**

Cardiovascular diseases are the leading cause of death in developed countries, with heart failure (HF) being one of the primary contributors, affecting 1–2% of adults. While current treatments for HF can slow the disease's progression, they cannot stop or cure it, highlighting the need for more effective therapeutic options.

Life-threatening ventricular arrhythmias (VAs) are a major cause of mortality in advanced HF. However, the underlying mechanisms of VAs are poorly understood, and treatment is limited to invasive and costly device therapies. Therefore, there is an urgent need for a deeper understanding of the causes of VAs to improve prevention and treatment strategies.

One factor that may contribute to the progression of heart failure (HF) is intramyocardial fat (inFat), a unique type of fat that accumulates between heart muscle cells. Although its precise role is not yet fully understood, inFat can affect local myocardium through secreted proteins and direct communication as well as by creating mechanical barriers that disrupt efficient impulse conduction. In various heart conditions, including HF, inFat undergoes pathological changes that lead to the release of pro-inflammatory molecules, which further disrupt heart function. Research has shown that inFat can cause slow and irregular electrical conduction in the atrial myocardium of patients with atrial fibrillation. However, its role in ventricular arrhythmias (VAs) in heart failure remains unclear.

This project aims to investigate the role of inFat in the development of VAs in HF using a comprehensive, multidisciplinary approach. By combining spatial transcriptomics with histological and functional studies on human heart tissue from HF patients, we will explore how inFat contributes to arrhythmogenesis. Our goal is to uncover new therapeutic strategies that target inFat and its effects on heart tissue, ultimately improving the prevention and treatment of life-threatening arrhythmias in heart failure.