In the normal healthy human heart, the atrioventricular node (AVN) is the sole conduction pathway through the fibrous ring of heart between the atria and ventricles. The critical role of the AVN in cardiac conduction means that any dysfunction in this area is likely to lead to cardiac conduction disturbances and arrhythmias, such as heart blocks and re-entrant tachycardias. Heart failure is a severe pathological condition in which the heart is incapable of providing sufficient cardiac output that is needed for the body's metabolic requirement and is associated with high morbidity and mortality. The AVN dysfunction and arrhythmias are commonly seen in heart failure patients with ~50% of patients affected by slow conduction through the AVN and first or second-degree atrioventricular block, a significant risk factor for sudden cardiac death. Heart failure patients with sick AVN have poor outcomes in terms of death, urgent transplantation, or hospitalization. Widespread remodeling of genes has been shown to occur in the tissues of the atrioventricular conduction axis in heart failure, which may contribute AVN conduction dysfunction. Although our knowledge of the structure and function of the AVN has grown significantly over the past few decades, many aspects in this field still remain unclear or undiscovered. We can find gaps in knowledge in both the area of AVN physiology (in healthy hearts) and in the AVN structure and function in sickness (heart failure). Moreover, the overwhelming majority of experimental studies were performed using animal models, not human tissue; thus, the acquired knowledge does not fully correspond to the phenomena observed in humans.

The general scientific aim of this project is to find key morphological, proteomic, and genomic dysfunction of the human AVN that occur in end-stage heart failure based on comparative assessments of human heart samples collected from structurally unchanged hearts and failing explanted organs (ischemic and non-ischemic etiology). Samples will be subject to contrast enhancement micro-computer tomography (CT) scanning with subsequent morphometrical evaluation, histological and immunofluorescence assessments, proteomic profiling (iTRAQ and Western blot), next-generation sequencing (NGS) of mRNA and small-RNA (including mi-RNA), and finally complex bioinformatics analyses with functional validation.

In summary, the proposed project will be highly innovative and the most complex study on the key morphological, proteomic, and genomic dysfunctions of the human AVN in heart failure due to different etiologies. Five important innovations of the project are described: (1) the use of human tissue material instead of animal model, (2) the use of the micro-CT to show the most detailed three-dimensional image of the AVN structure in health and heart failure, (3) delivery of the comparative assessments of the proteomic profile of the AVN in health and heart failure, (4) use of the NGS of mRNA and small-RNA for delivery of the comparative genomic profiles of the AVN in health and heart failure, and (5) identification of key metabolic pathways for AVN that are altered in end-stage heart failure (proteins, mRNAs, small-RNAs, microRNAs, transcription factors, and ion channels).

Improving the understanding of the molecular interactions involved in determining the cardiac conduction system gene expression may contribute to future treatments of cardiac conduction system disorders. Currently, conduction system of the heart dysfunctions in cardiac disease cannot be effectively cured, and while clinical device-based therapies, such as implanted pacemakers, are capable of overcoming the effects of the dysfunctional cardiac conduction system in heart failure, they are associated with significant complications. The development of treatments that reverse dysfunctional remodeling or prevent the changes from occurring in the first instance would offer better outcomes.