Heart failure with preserved ejection fraction (HFpEF) and diastolic dysfunction accounts for more than half of all heart failure (HF) cases in developed countries. HFpEF predominantly affects individuals with type 2 diabetes, hypertension, metabolic syndrome, and obesity, as well as the elderly—more often women than men. In recent years, the number of HFpEF patients has been rapidly increasing, and in the context of aging populations and the growing obesity epidemic, this trend appears difficult to reverse.

In contrast to heart failure with reduced ejection fraction (HFrEF), HFpEF is characterized by considerable clinical heterogeneity, diverse etiology, and a lack of effective therapeutic strategies. Current international cardiology society guidelines recommend sodium-glucose co-transporter 2 inhibitors (SGLT2i) as first-line therapy. These agents have been shown to reduce hospitalization rates; however, their impact on mortality remains limited. Depending on the presence of comorbidities—such as hypertension, type 2 diabetes, or atrial fibrillation—HFpEF patients may also receive mineralocorticoid receptor antagonists, renin–angiotensin–aldosterone system inhibitors, and β-blockers. Additionally, guidelines include non-pharmacological treatments such as cardiac rehabilitation and weight reduction. Increasing attention, in line with WHO recommendations, is also being paid to the impact of therapies on quality of life in patients with chronic diseases. The primary factor impairing quality of life in HFpEF is reduced exercise tolerance, which results not only from impaired cardiac function but also from pathological remodeling of skeletal muscle. Another significant factor is cognitive dysfunction, observed in 25–50% of HFpEF patients, and depression, which affects 40–70% of hospitalized HF patients.

Currently available therapies for HFpEF do not provide satisfactory reductions in mortality or improvements in quality of life. Therefore, there is an ongoing search for new therapeutic options with broad effects aimed at restoring metabolic homeostasis and improving motor, cognitive, and psychological function.

Recently, the fibroblast growth factor 21 (FGF21)/β-Klotho axis has emerged as a promising therapeutic target in HFpEF. Its activation exerts multi-organ metabolic benefits, reduces oxidative stress, and attenuates inflammation in organs such as the brain, heart, kidneys, and liver. Interestingly, patients with HFpEF exhibit elevated circulating levels of FGF21, which strongly correlate with NT-proBNP, a sensitive biomarker of HFpEF. However, intracellular FGF21 signaling appears to be impaired, suggesting the development of tissue resistance, particularly in the myocardium, to FGF21. In this context, administration of stable FGF21 analogues may restore its beneficial protective effects.
To date, FGF21 analogues have demonstrated efficacy and safety profiles in patients with type 2 diabetes and non-alcoholic fatty liver disease. Moreover, FGF21 gene knockout has been shown to exacerbate diastolic dysfunction in HFpEF mouse models, while increasing FGF21 expression via viral transfection significantly reduced diastolic impairment and cardiac injury. These findings clearly identify FGF21 as a potential therapeutic target in HFpEF.

However, no studies to date have investigated the effects of FGF21 analogues on myocardial function, skeletal muscle function, or cognitive and psychological outcomes in the context of HFpEF.
Therefore, we propose an innovative research project aimed at evaluating the effects of an FGF21 analogue on cardiac function, skeletal muscle performance, and cognitive and psychological function in the context of treatment efficacy and quality of life improvement in a murine model of HFpEF. The study will include both male and female animals to assess sex-specific differences in disease progression and treatment response.

We believe that the results of the proposed project will contribute to the development of more effective HFpEF therapies that not only improve clinical outcomes but also enhance the quality of life for both male and female patients.