The undersigned

Pappone Carlo nato a Benevento (BN) il 05/12/1961

Unità: Aritmologia & Elettrofisiologia - IRCCS Policlinico San Donato

Scuola di Specializzazione[1]*: Malattie dell'Apparato Cardiovascolare*

Indirizzo email: carlo.pappone@grupposandonato.it

Role:

☑ Vita-Salute San Raffaele University Professor/Lecturer

☐ Vita-Salute San Raffaele University Researcher/Lecturer

☐ Group Leader of the hospital site _____

☐ Project Leader of the hospital site _____

☐ Other

_____

I hereby declare that, within the framework of the PhD Course for which I wish to submit the project described below:

☑I am already a Supervisor;

☐ I am applying for the first time as a Supervisor (CV attached);

☐ I am applying as a Supervisor as three years have elapsed since my last Application as Supervisor and the submission of a research project (CV attached).

I further declare that (select the applicable option(s)):

☑ although I am less than four years away from retirement as a university professor/researcher, I will hold a documented institutional role at the hospital _____, for at least one year beyond the official duration of the course.

☐ I serve as Supervisor for no. __ PhD candidates enrolled at other universities and I comply with the University requirement regarding the maximum number of five PhD candidates that may be supervised.

I would like to present a project:

☐ **With a duration of three years**

[1] Da indicare solo nel caso di progetto di ricerca afferente il programma "Physician Scientist"

☑ **With a duration of two years within the Physician Scientist (PhS) programme**

as part of the PhD course in:

☑ Molecular Medicine

PhD Curriculum: ☐ Basic and Applied Immunology and Oncology

☐ Cell and Molecular Biology

☑Clinical and Experimental Medicine

☐ Neurosciences and Experimental Neurology

☐ Gene and Cell Therapy

☐ Cognitive and Behavioural Sciences

The project consists in:

1. Basic Research ☑
2. Translational Research ☑
3. Basic/ Translational research using animal models ☐
4. Clinical research ☑
5. Clinical research involving interaction with patients ☑

If items 2 and/or 3 is/are selected, I declare that

☐ I HAVE OBTAINED the approval of the responsible Institutional Animal Care and Use Committee-IACUC number _____

☑ I HAVE NOT YET OBTAINED the approval of the responsible Institutional Animal Care and Use Committee-IACUC

If items 4 and/or 5 is/are selected, I declare that the project:

☑**HAS NOT YET OBTAINED** approval from the Ethics Committee (EC)

HAS OBTAINED, or is part of a broader study that has obtained, approval from the Ethics Committee (EC); study code and date _____

If items 4 and/or 5 is/are selected, I declare that the project:

HAS NOT OBTAINED the resolution of the Institution

☑ **HAS OBTAINED** the resolution of the Institution on _____

I further declare (select the applicable option(s)):

☑ that I have the availability of the funds necessary to finance a scholarship for the proposed project and I confirm that I have contacted the Doctoral Office regarding the management of the administrative procedures related to the funding;

☑ that I have the availability of funds to support the research (i.e. funds for materials, reagents, and instruments required for research activities);

☑ that, in the case of a clinical research project, it will include a basic or translational research component to be carried out in a laboratory to be specified in the research plan, whose head will act as co-supervisor.

☑ that I have adequate workspace and a permanent workstation available for the PhD candidate who will be selected to carry out the project;

☑ that the proposed project can be reasonably completed within the three-year legal duration of the programme;

☑ that the PhD student, within the activities of the relevant PhD program, will carry out only their specific doctoral project;

☑ that the PhD student will be the first author/author of the main publication resulting from his/her project and of all publications (also after graduation) that are mainly based on his/her experimental work;

☐ that, in the event that the PhD student is not the recipient of a UniSR grant (i.e. has won a position without a grant), I am willing to cover the cost of their scholarship with funds at my disposal. I am aware that the grant must not amount to less than the minimum required by the Ministerial Decree of 23 February 2022, amounting to € 16,243 gross per year, for three years;

☐ that the study is co-funded by an industrial partner or that a commercial exploitation of the findings resulting from the project's research activity is conceivable, with a potential delay in the publication of the results. I therefore commit to promptly inform potential candidates of such circumstances.

Signature of the Supervisor _____ *Date*
26/03/2026

When applicable:

Group Leader Prof. /Dr. _____

Signature _____ *Date* _____

Please note that the information provided on the following pages (unless otherwise indicated) will be made public on the University website. Therefore, it is important not to include confidential information, in compliance with any confidentiality obligations towards third parties and to protect the potential patenting of such information. For any questions, please consult the PhD Office.

PROJECT

Supervisor:	Pappone Carlo
Title:	"Epicardial Adipose Tissue and Cardiac Arrhythmias: Molecular and Electrophysiological Mechanisms Linking Brady- and Tachyarrhythmogenesis"
Curriculum:	https://www.unisr.it/docenti/p/pappone-carlo
Link to the personal page of the University or relevant hospital site website:	

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

Cardiac arrhythmias impose a major clinical and healthcare burden, encompassing both tachyarrhythmias—most prominently atrial fibrillation (AF)—and bradyarrhythmias, which frequently lead to invasive therapies. The absolute burden of these conditions continues to rise, largely driven by population ageing and the increasing prevalence of cardiometabolic comorbidities. Growing evidence indicates that epi-/pericardial adipose tissue (EAT) is not merely an inert fat depot but a biologically active immunometabolic and paracrine organ in direct contact with the myocardium. This unique anatomic proximity makes EAT a plausible local mediator of electrical and structural remodeling. EAT may influence cardiac electrophysiology through adipokines/cytokines, extracellular vesicles (EVs/exosomes) and microRNAs, inflammatory cell infiltration and fibrosis, and interactions with the cardiac autonomic nervous system, given that atrial ganglionated plexi are frequently embedded within epicardial fat.

Although these mechanisms are increasingly investigated as drivers of arrhythmogenesis, it remains unclear which components are truly causal versus epiphenomena of systemic cardiometabolic risk. Moreover, molecular and functional mechanisms linking EAT to nodal automaticity and AV/His conduction—potentially contributing to bradyarrhythmias—remain largely undefined, and human-relevant causal platforms are lacking.

Clinical translation is further limited by the lack of standardized imaging metrics (total volume versus regional distribution and radiologic "quality"), the absence of EAT-specific circulating biomarkers (including EVs and miRNAs), and the limited validation of their incremental prognostic value beyond established risk factors and conventional atrial measures. Finally, most available evidence is cross-sectional; longitudinal studies integrating imaging, serial biomarker profiling, and quantified arrhythmia burden are needed to establish causality, improve outcome prediction (e.g., post-ablation recurrence and pacemaker requirement), and identify actionable therapeutic targets.

Rationale and hypothesis

Current evidence linking epicardial adipose tissue (EAT) to arrhythmias is largely associative and heterogeneous, leaving uncertainty about (i) which EAT features are clinically actionable, (ii) whether EAT signals can be captured by reproducible imaging and circulating biomarkers, and (iii) whether EAT-related mechanisms differ between tachyarrhythmic and bradyarrhythmic phenotypes. An integrated translational framework—combining standardized EAT imaging, EAT-linked circulating biomarker profiling, and phenotype-specific electrophysiologic readouts—offers a tractable way to move from correlation to mechanistic and prognostic utility. We hypothesize that region-specific EAT characteristics and EAT-derived circulating signatures identify distinct arrhythmogenic pathways: peri-atrial/peri-PV EAT profiles will associate with, and functionally promote, atrial tachyarrhythmia susceptibility, whereas AV-groove/peri-nodal EAT profiles will associate with, and functionally impair, nodal automaticity and AV/His conduction. These EAT markers will provide incremental prediction of clinically relevant outcomes (e.g., post-ablation recurrence and pacemaker requirement) beyond established risk factors.

Objectives and specific aims

The overall objective is to establish a clinically actionable, mechanistic, and prognostic framework linking region-specific epicardial adipose tissue (EAT) phenotypes to the development of tachyarrhythmias (with a focus on atrial fibrillation/atrial tachyarrhythmias) and bradyarrhythmias (sinus node dysfunction and AV/His conduction disease), integrating standardized EAT imaging, EAT-linked circulating biomarkers, and functional electrophysiology.

Specific aims:
-Define standardized EAT imaging phenotypes (total burden, regional distribution, radiologic "quality") and their associations with tachy- and bradyarrhythmic phenotypes.
-Identify EAT-linked circulating biomarker signatures (including EV/miRNA and inflammatory/profibrotic profiles) and quantify their incremental prognostic value for post-ablation recurrence and pacemaker requirement.

-Integrate imaging and biomarkers into an interpretable multimodal risk model to define clinically actionable EAT–arrhythmia endotypes.
-(Exploratory) Test phenotype-specific functional effects of EAT-derived signals in human-relevant electrophysiology platforms and/or evaluate EAT-modifying strategies in longitudinal follow-up.

Expected outcomes

This project is expected to deliver a clinically actionable framework linking epicardial adipose tissue (EAT) to both tachy- and bradyarrhythmic phenotypes. We anticipate defining standardized, reproducible EAT imaging metrics—capturing not only overall burden but also regional distribution and radiologic "quality"—that can be consistently applied across patients and studies. In parallel, we expect to identify EAT-linked circulating biomarker signatures (including EV/miRNA and inflammatory/profibrotic profiles) and demonstrate their incremental prognostic value beyond established risk factors and conventional atrial measures for outcomes such as post-ablation recurrence and pacemaker requirement. By integrating imaging and biomarker findings with functional electrophysiology in human-relevant platforms, the project should strengthen causal inference by demonstrating phenotype-consistent effects of EAT-derived signals on atrial versus nodal/AV conduction electrophysiology. Overall, the work is expected to generate EAT–arrhythmia endotypes suitable for risk stratification and to prioritize actionable pathways and candidate targets within the EAT–heart axis, providing a rationale and measurable readouts for future prospective validation and intervention studies.

Skills that the student should acquire (max. 600 characters including spaces):

-Ability to design and conduct clinical and translational studies, including critical appraisal and interpretation of results.
-Proficiency in the use and interpretation of advanced diagnostic and EP technologies (echocardiography, cardiac MRI, photon-counting CT, electroanatomical mapping).
-Competence in managing and analysing complex clinical and molecular datasets to identify robust associations, patterns, and clinically meaningful trends.
-In-depth understanding of the molecular basis of cardiovascular disease, with focus on key pathogenic pathways and actionable biological targets.
-Knowledge of research ethics and integrity, ensuring responsible conduct of research, informed consent procedures, and appropriate data governance.
-A translational mindset aimed at converting mechanistic and clinical evidence into practical tools to improve risk stratification and patient care.

References (max. 15)

-Ernault AC, et al. Modulation of Cardiac Arrhythmogenesis by Epicardial Adipose Tissue: JACC State-of-the-Art Review. *J Am Coll Cardiol.* 2021.

-Shaihov-Teper O, et al. Extracellular Vesicles From Epicardial Fat Facilitate Atrial Fibrillation. *Circulation.* 2021.

-Yang Y, et al. Association of Epicardial Adipose Tissue With Bradyarrhythmias: A Matched Case-Control Study. *J Am Heart Assoc.* 2025;14(24):e044223.

The information below will not be displayed on the University website in the description of the projects offered for the academic year, and will be used for internal project assessment only.

Experimental plan (Between 2,000 and 3,000 characters including spaces):

To be completed for all types of projects; however, for CLINICAL PROJECTS, please specify:

1. *If Observational prospective, cross-sectional, or retrospective) or retro/prospective, quality of life, pharmacological, pathophysiology, genetics, epidemiological, registry/data collection, biobank, diagnostic accuracy, in vitro diagnostic device (IVD), nutraceutical/supplement, appropriateness; OR interventional (pharmacological, surgical, procedure, or medical device, and if a drug will be used, indicate the phase – I, II, III, or IV);*
2. *If a drug will be used, specify whether it has a marketing authorisation (MA), whether it will be used according to the MA or whether it does not have a MA;*
3. *If the study does not regard a drug, specify what will be studied (e.g. medical device, surgical procedure, diagnostic procedure, food supplement, etc.). If the study will use a medical device, please specify: whether it is CE marked. If CE marked, please indicate whether it will be used according to the approved use or for a new use.*
4. *Indicate the laboratory on which you intend to rely for the basic or translational part.*

Available methods and experimental models (max. 600 characters including spaces):

To be completed for all types of projects; however, for CLINICAL PROJECTS, please specify:

1. *whether participants (patients and/or healthy volunteers) will be recruited;*
2. *whether biological samples will be taken from participants (patients and/or healthy volunteers);*
3. *whether the biological samples will be stored in a Biobank (specify which Biobank);*
4. *whether biological samples are already stored and available in a Biobank (specify which Biobank);*
5. *whether biological samples or data will be collected in addition to those already included in the routine standard of care from routine practice (specify type of samples/data, quantity and timing);*
6. *whether procedures will be required in addition to those already included in the routine standard of care from routine practice (e.g. Consultations, laboratory tests, clinical/instrumental examinations). Specify the additional procedures, quantity and timing).*

Role of the PhD student (max. 600 characters including spaces):

The PhD candidate will take primary responsibility for implementing the experimental work outlined in the project, spanning both the preclinical and clinical components. In parallel with their clinical activity, they will lead patient enrolment and perform the required clinical evaluations. The candidate will also support regulatory and governance processes, including preparation of documentation for Ethics Committee approval, and will contribute to dissemination of the findings through peer-reviewed publications and presentations at international scientific meetings.

Impact of the expected results in the field of research (max. 600 characters including spaces):

This project aims to establish a clinically actionable link between epicardial adipose tissue (EAT) and both tachy- and bradyarrhythmias by defining standardized EAT imaging metrics (burden, distribution, "quality") and identifying EAT-related circulating biomarker signatures (EV/miRNA, inflammatory/profibrotic). These measures are expected to add incremental prognostic value for key outcomes such as post-ablation recurrence and pacemaker requirement.

In the case of clinical research, include the timeline for the project approval process up to the authorizing resolution of the Institution.

Period of attendance at a foreign institution

Mandatory for the PhD course in Cognitive and Behavioral Sciences

The PhD course in Cognitive and Behavioral Sciences encourages attendance at foreign universities and research institutes, promoting the acquisition of advanced skills and methodologies in international contexts.
Please indicate whether a period of activity at a foreign institution is planned. If so, specify:

- *Host institution (name of the University/Institute and country)*
- *Duration of stay (not less than 3 months)*
- *Integration with the research project (describe how this experience will contribute to the objectives of the proposed project)*

The information provided is not binding and may be subject to modifications based on the project's development and available opportunities.

For the use by the PhD Office

FOR OPINION – *(ONLY for Programs divided into Curricula)*

Signature of the Curriculum Supervisor _____ *Date* 26/03/2026

FOR APPROVAL

Signature of the PhD Course Coordinator

_____