The undersigned

SURNAME PIEMONTI

FIRST NAME LORENZO born in *Carate Brianza* Prov. MB on 16 / 08 / 1968

Unit: *Regenerative Medicine and Transplant Unit*

Residency/Postgraduate School[1]: *Internal Medicine*

Email address: *piemonti.lorenzo@hsr.it*

Role:

X 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:

X 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.

X I serve as Supervisor for no. 0 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:

[1] To be indicated only for research projects associated with the Physician Scientist programme

☐ **With a duration of three years**

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

as part of the PhD course in:

X Molecular Medicine

PhD Curriculum:

☐ Basic and Applied Immunology and Oncology

☐ Cell and Molecular Biology

X 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
   X
3. Basic/ Translational research using animal models
   ☐
4. Clinical research
   ☐
5. Clinical research involving interaction with patients
   X

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 _____

X I HAVE NOT YET OBTAINED the approval of the responsible Institutional Animal Care and Use Committee-IACUC (the project consists in translational research w/o use of animal models > no IACUC required)

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

☐ **HAS NOT YET OBTAINED** approval from the Ethics Committee (EC) (project submitted for approval)

X **HAS OBTAINED**, or is part of a broader study that has obtained, approval from the Ethics Committee (EC); study code and date iBETA 22/10/2025 CET 337-2025.

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

X **HAS NOT OBTAINED** the resolution of the Institution

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

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

X 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;

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

X 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.

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

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

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

X 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;

X 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 20/03/2026

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:	Prof Lorenzo Piemonti
Title:	Development of a translational pipeline for patient-derived iPSC generation in type 1 diabetes: from clinical recruitment and source cell procurement to automation and GMP-oriented process development
Curriculum:	Clinical and Experimental Medicine
Link to the personal page of the University or relevant hospital site website:	Dri.hsr.it and https://www.hsr.it/strutture/ospedale-san-raffaele/medicina-interna-trapianti

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

Background/gap of knowledge

Type 1 diabetes (T1D) results from progressive loss of pancreatic beta cells and remains a major unmet need for regenerative medicine. Patient-derived induced pluripotent stem cells (iPSCs) are a promising platform for disease modelling and future beta-cell replacement strategies, but their clinical translation is still limited by heterogeneity of source materials, variable reprogramming efficiency, lack of standardized quality control, and insufficient integration between clinical recruitment, laboratory processing, automation and GMP-oriented development.

Rationale and hypothesis

The approved iBETA clinical protocol offers a unique translational framework for prospective collection of clinically annotated somatic cells through minimally invasive one-time sampling procedures, including skin biopsy, peripheral blood and urine. Within this broader 10-year clinical platform, the PhD project will focus on a realistic 3-year subset of about 20–30 participants, mainly with T1D, to build a patient-to-iPSC workflow integrating source-cell procurement, comparative reprogramming, line qualification, automation and early GMP-oriented process development. The hypothesis is that a clinically embedded and standardized workflow will improve robustness, reproducibility and translational readiness of patient-derived iPSC generation in T1D.

Objectives and specific aims

The project aims to:

1. establish a clinician-scientist workflow for recruitment, phenotyping and biospecimen procurement within iBETA;

2. compare different source materials and reprogramming strategies for T1D iPSC generation;
3. define an expanded quality-control framework beyond minimum protocol thresholds;
4. transfer selected steps to an automated platform;
5. initiate GMP-oriented process translation in collaboration with the PDL at TIGET and European partners.

Expected outcomes

The project is expected to deliver a feasible clinical-laboratory pipeline for T1D donor recruitment and somatic cell collection, comparative evidence on source-cell and reprogramming performance, a structured QC framework for iPSC qualification, an automation pilot, and a GMP-readiness roadmap for future manufacturing development.

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

Clinical research management, informed consent and patient phenotyping; collection and handling of human biospecimens; somatic cell isolation, culture and iPSC reprogramming; pluripotency and quality-control assays; automation and SOP standardization; data integration between clinical and laboratory workflows; translational and GMP-oriented process development in regenerative medicine.

References (max. 15)

- Takahashi K, Yamanaka S. Cell. 2006;126:663-676.
- Yu J et al. Science. 2007;318:1917-1920.
- Stadtfeld M, Hochedlinger K. Genes Dev. 2010;24:2239-2263.
- Shi Y, Inoue H, Wu JC, Yamanaka S. Nat Rev Drug Discov. 2017;16:115-130.
- Pagliuca FW et al. Cell. 2014;159:428-439.
- Rezania A et al. Nat Biotechnol. 2014;32:1121-1133.
- Balboa D et al. Nat Biotechnol. 2022;40:1042-1052.
- Maxwell KG, Augsornworawat P, Velazco-Cruz L, Kim MH, Asada R, Hogrebe NJ, Millman JR. Nat Biotechnol. 2020;38:1032-1036.
- Rizzi R et al. Stem Cell Res Ther. 2024;15: [update final citation if used].
- EMA. Guidelines relevant to Advanced Therapy Medicinal Products.
- Piemonti L. Acta Diabetol. 2021;58:1287-1306.
- Ludvigsson J. Drugs. 2016;76:169-185.
- iBETA Protocol, version 1.0, 06.08.2025.

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):

This is a **clinical-translational, observational prospective study** embedded within the approved iBETA protocol, with a laboratory-based translational component. The parent study is a single-center prospective platform for collection of somatic cells from healthy controls and subjects with diabetes or pancreatic disorders through a single sampling visit. The PhD project will focus on a 3-year subset of approximately 20–30 participants, primarily with T1D and a limited number of controls.

After consent and eligibility assessment within iBETA, participants will undergo one-time collection of one or more source materials according to protocol and technical needs: 3 mm skin punch biopsy, peripheral blood draw up to 20 mL, and/or urine collection up to 300 mL. Clinical and demographic variables relevant to sample quality and interpretation will be recorded.

The translational laboratory component will be carried out at the **Regenerative Medicine and Transplant Unit / associated stem cell laboratory platform at IRCCS San Raffaele**, in collaboration with the PDL at TIGET for GMP-oriented process development. Somatic cells will be isolated and expanded from skin, blood and urine samples. Initial source-cell qualification will build on protocol criteria, including viability greater than 60% and a minimum yield of 1 × 10^6 viable cells prior to reprogramming.

Reprogramming workflows established in the laboratory and within FRAME T1D will be comparatively assessed. The baseline protocol in iBETA foresees RNA-based reprogramming, while the PhD will evaluate robustness, efficiency, timeline and translational suitability across source materials and selected methods. Generated iPSC lines will undergo characterization and quality control. Minimum success criteria will include generation of at least one line positive for SSEA4, OCT4 and NANOG with >80% positivity and post-expansion viability >60%, as already stated in iBETA. The project will extend this by implementing a structured QC framework including clone selection criteria, sterility/mycoplasma testing, identity checks and genomic integrity assessment where feasible.

In the third phase, selected workflow steps will be transferred to an automated platform to assess reproducibility and standardization. Finally, the project will perform a GMP-oriented gap analysis and adapt key SOPs toward regulatory-aligned process development, without aiming to complete full GMP validation within the PhD period.

No drug will be used. No medical device intervention is the object of the study. The clinical part relies on minimally invasive biospecimen collection, while the translational part focuses on iPSC derivation, QC, automation and early manufacturing readiness.

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

Participants (patients and healthy controls) will be prospectively recruited within iBETA. Biological samples will be collected from participants: skin biopsy, peripheral blood and urine, according to the approved protocol. Samples and derived cell lines will be stored within the institutional

biobanking/stem cell infrastructure at IRCCS San Raffaele, as foreseen by the parent study. The project includes additional laboratory procedures beyond routine care, but only one-time minimal-risk sampling on the clinical side.

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

The PhD student will contribute to patient screening, consent support, clinical data collection and biospecimen procurement within iBETA, and will directly perform or coordinate source-cell isolation, reprogramming experiments, iPSC characterization, QC analyses, automation transfer and data integration. The student will work as a clinician-scientist with protected time divided between clinical activity and translational laboratory research.

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

The project will create a practical bridge from clinically annotated donor recruitment to standardized iPSC generation in T1D. Its impact lies in defining reproducible workflows for source-cell selection, reprogramming, QC, automation and GMP-readiness, thereby strengthening translational stem-cell platforms for diabetes modelling and future beta-cell replacement strategies.

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

The project is embedded within the broader iBETA clinical study, which has already obtained Ethics Committee approval. Institutional authorization for the PhD-specific operational implementation will follow internal institutional procedures at IRCCS Ospedale San Raffaele. Recruitment for the PhD project will start within the already approved study framework, after completion of the required institutional steps.

Period of attendance at a foreign institution

Host institution: Leiden University Medical Center (LUMC), Leiden, The Netherlands.
Duration of stay: 3–4 months.
The period abroad will support benchmarking and harmonization of source-cell processing, reprogramming and iPSC quality-control workflows with leading European centers involved in diabetes stem-cell research. It will also strengthen the automation and GMP-oriented translational component of the project and facilitate alignment with shared standards across partner institutions.

For the use by the PhD Office

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

Signature of the Curriculum Supervisor _____ *Date* _____

FOR APPROVAL

Signature of the PhD Course Coordinator

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