The undersigned

SURNAME BRIGANTI

FIRST NAME ALBERTO

born in Milan Prov. *(Milan)* on 27 / 11 / 1977

Unit: *Urological Research Institute (URI)*

Residency/Postgraduate School[1]:

- *Residency in Urology*

Email address: *briganti.alberto@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.

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

☐ 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**

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 evaluation is ongoing).

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:

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;

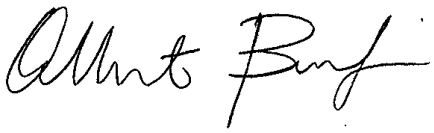
X that the PhD student, within the activities of the relevant PhD program, will carry out only their specific doctoral project;

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;

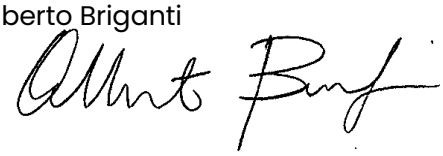
☐ that the study is co-funded by an industrial partner or that a commercial exploitation of the findings resulting from the project's research activity is conceivable, with a potential delay

in the publication of the results. I therefore commit to promptly inform potential candidates of such circumstances.

Signature of the Supervisor 
Date 21/03/2026

When applicable:

Group Leader Prof. Alberto Briganti

Signature 
Date 21/03/2026

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. Alberto Briganti
Title:	**Development and First-in-Human Use of a Dual-Modality PSMA-Targeted Approach in Prostate Cancer**
Curriculum:	Clinical and Experimental Medicine
Link to the personal page of the University or relevant hospital site website:	https://www.unisr.it/en/docenti/b/briganti-alberto

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

Background/gap of knowledge

Prostate cancer (PCa) remains a leading cause of cancer morbidity and mortality worldwide (1,2). While PSMA PET/CT has significantly improved staging accuracy, its sensitivity for detecting microscopic disease remains limited (3). Intraoperative techniques such as radioguided surgery (RGS) and fluorescence-guided surgery (FGS) offer complementary advantages but suffer from intrinsic limitations when used independently, including poor spatial resolution, limited depth penetration, and lack of preoperative imaging integration (4–6). Consequently, there is an unmet need for a unified imaging strategy capable of improving both preoperative planning and intraoperative tumor detection, particularly for micro-metastatic and residual disease.

Rationale and hypothesis

We hypothesize that a novel dual-modality PSMA-targeted tracer ([64Cu]Cu-P3) combining PET imaging with intraoperative fluorescence and beta-radioguidance will enhance detection of prostate cancer lesions (7,8). By integrating diagnostic and surgical imaging into a single platform, this approach will overcome current limitations, improve tumor localization, and ultimately optimize surgical outcomes.

Objectives and specific aims.

The overall objective is to develop and clinically translate a dual-modality PSMA-targeted imaging agent. Specific aims are:

1. To evaluate in vitro and in vivo pharmacokinetics, biodistribution, and specificity of [64Cu]Cu-P3 (10,11).
2. To assess safety, feasibility, and dosimetry in a first-in-human Phase 0 clinical trial (5,6).
3. To determine intraoperative diagnostic performance in detecting lymph node metastases and residual disease (14,15).
4. To correlate imaging findings with histopathology and molecular profiling, including spatial transcriptomics (9).

Expected outcomes

This project is expected to demonstrate the feasibility and safety of a dual-modality imaging approach in prostate cancer. It will provide evidence that combining PET, fluorescence, and radioguided surgery improves detection of microscopic disease and surgical precision (7,15). Additionally, integration with molecular profiling will enhance understanding of PSMA expression heterogeneity and tumor biology (9). Ultimately, the study may establish a new paradigm for image-guided oncologic surgery and support broader applications in other PSMA-expressing malignancies.

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

The student will acquire multidisciplinary skills in molecular imaging, radiochemistry, and translational oncology. Training will include in vitro and in vivo experimental design, PET/CT and fluorescence imaging, data analysis, and clinical research methodology. Additional expertise will be gained in histopathology, spatial transcriptomics, and bioinformatics, alongside regulatory and ethical aspects of first-in-human trials.

References (max. 15)

1. Culp MB et al. Eur Urol. 2020.
2. Rebello RJ et al. Nat Rev Dis Primers. 2021.
3. Hofman MS et al. Lancet. 2020.
4. van Leeuwen FW et al. Radiology. 2020.
5. Maurer T et al. J Nucl Med. 2019.
6. Gandaglia G et al. Eur Urol. 2022.
7. Baranski AC et al. J Nucl Med. 2018.
8. Zhang J et al. J Nucl Med. 2018.
9. McBriar JD et al. Clin Nucl Med. 2024.
10. Iannone MN et al. EJNMMI Radiopharm Chem. 2024.
11. Li Y et al. Bioorg Med Chem. 2022.
12. Mapelli P et al. Diagnostics. 2021.
13. Ghosh A et al. Cancer Res. 2005.
14. Quarta L et al. Eur J Nucl Med Mol Imaging. 2024.
15. Collamati F et al. Eur J Nucl Med Mol Imaging. 2024.

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 (2,000–3,000 characters)

This is a prospective interventional clinical study (Phase 0) involving a novel investigational radiopharmaceutical ([64Cu]Cu-P3) used for diagnostic purposes in combination with a surgical procedure. The tracer does not currently have marketing authorization (MA) and will be administered under an Investigational Medicinal Product Dossier (IMPD) according to EU regulations. The study evaluates a dual-modality diagnostic approach combining PET imaging, fluorescence-guided surgery, and beta radioguided detection.

The project follows a translational design with two phases:

Preclinical phase: in vitro validation of PSMA-targeting specificity and uptake in prostate cancer cell lines, followed by in vivo studies in murine xenograft and patient-derived xenograft models. PET/CT and fluorescence imaging will assess biodistribution, pharmacokinetics, tumor retention, and specificity. Toxicity and dosimetry studies will be performed to support clinical translation.

Clinical phase: a first-in-human Phase 0 trial enrolling 10 patients with high-risk localized prostate cancer undergoing robot-assisted radical prostatectomy (RARP) and extended pelvic lymph node dissection (ePLND). Patients will receive [64Cu]Cu-P3 preoperatively. PET/CT imaging will guide surgical planning. During surgery, a CE-marked beta probe and the Firefly™ fluorescence system integrated in the da Vinci platform will be used for intraoperative detection of tumor lesions.

The study evaluates diagnostic accuracy, safety, and feasibility, correlating imaging findings with histopathology and molecular analyses (PSMA expression, spatial transcriptomics).

The project will rely on the Nuclear Medicine Department, Urological Research Institute, and Center for Omics Sciences at Università Vita-Salute San Raffaele / IRCCS Ospedale San Raffaele.

Available methods and experimental models (max. 600 characters)

Patients will be prospectively recruited (n=10). Blood and tissue samples (prostate and lymph nodes) will be collected intraoperatively and stored in the San Raffaele Biobank. Additional

samples will be obtained beyond routine care for molecular analyses (RNA-seq, spatial transcriptomics). Extra procedures include preoperative PET/CT with [64Cu]Cu-P3 and intraoperative fluorescence and beta-probe detection. Preclinical models include PSMA+/- cell lines, xenografts, and PDX models.

Role of the PhD student (max. 600 characters)

The PhD student will participate in both preclinical and clinical phases, including experimental design, radiotracer validation, imaging acquisition and analysis (PET/fluorescence), and data interpretation. The student will contribute to patient recruitment, intraoperative data collection, and integration of histopathological and molecular results. Additional responsibilities include statistical analysis, dissemination of findings, and coordination between multidisciplinary teams.

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

The project may establish a novel paradigm in prostate cancer surgery by integrating preoperative and intraoperative imaging into a single platform. Improved detection of micro-metastatic and residual disease could enhance surgical precision, reduce recurrence, and refine staging strategies. The dual-modality approach may also be extended to other PSMA-expressing tumors, advancing translational imaging and precision oncology.

Timeline for approval process (clinical research)

- Months 1–6: Submission to Ethics Committee and AIFA
- Months 7–12: Regulatory approval and study setup (GCP training, eCRF)
- Month 12-18: Institutional authorization and trial initiation

Period of attendance at a foreign institution

A research period abroad is planned at a leading institution in molecular imaging and robotic institution

Duration: 6-12 months

- Integration: The student will gain expertise in advanced PET imaging, radiochemistry, and image analysis, strengthening the translational component of the project and supporting data interpretation and international collaboration.

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 _____