The undersigned

SURNAME: Bianchini

FIRST NAME: Giampaolo

born in *Bergamo* Prov. *BG* on 24 / 05 / 1971

Unit: *Oncologia Medica*

Residency/Postgraduate School[1]*: Oncologia Medica*

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

as part of the PhD course in:

- ☒ Molecular Medicine

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

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

☒ There will be no use of animal models

☒ The data used in this project are publicly available and do not require ethics committee (EC) approval

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;

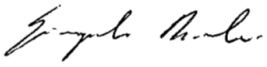
☒ that the proposed project can be reasonably completed within the three-year legal duration of the programme;

☒ 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* ____*30/3/2026*__

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. Giampaolo Bianchini
Title*:*	Integrative Biomarker Discovery to Optimize Precision Medicine in Breast Cancer
Curriculum:	Basic and Applied Immunology and Oncology
Link to the personal page of the University or relevant hospital site website:	https://www.unisr.it/docenti/b/bianchini-giampaolo

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

Background/gap of knowledge

Despite significant therapeutic advances, breast cancer management still relies largely on clinicopathological features, resulting in a persistent "one-size-fits-all" approach and consequent under- and overtreatment. This limitation is particularly evident in early-stage disease, where current tools inadequately capture tumor heterogeneity and immune contexture. As a result, many patients receive ineffective therapies or are exposed to unnecessary toxicity. The rapid integration of novel agents, including immunotherapy(1) and antibody–drug conjugates (ADCs)(2), has further increased the urgency for robust predictive biomarkers to guide treatment selection and sequencing. However, clinically applicable biomarkers—especially in the post-neoadjuvant setting—remain scarce.

Rationale and hypothesis

Large-scale, publicly available multi-omics datasets represent a unique opportunity to systematically identify and validate predictive biomarkers. Integrative analyses of genomic, transcriptomic, and immune-related data across cohorts can reveal molecular determinants of recurrence risk in patients with residual disease after neoadjuvant therapy, as well as mechanisms of response and resistance to immunotherapy and ADCs. We hypothesize that integrative bioinformatic approaches will identify clinically actionable biomarkers capable of predicting treatment benefit, with particular relevance for high-risk patients with residual disease after neoadjuvant chemo-immunotherapy. All analyses will leverage publicly available or previously approved datasets and will not require additional ethical approval. Advanced bioinformatics expertise from the candidate, including proficiency in R, is essential for project execution as well as a strong knowledge background in breast cancer.

Objectives and Specific Aims

The overall objective is to optimize treatment strategies in breast cancer through biomarker-driven patient stratification. Specific aims are: (i) to perform integrative analyses of publicly available datasets to identify molecular and immune signatures associated with recurrence risk after neoadjuvant therapy, with a focus on residual disease; (ii) to develop and validate predictive models of treatment benefit from immunotherapy and ADCs, particularly in patients with residual disease after neoadjuvant chemo-immunotherapy, a high-risk setting where treatment escalation strategies are actively evolving (3,4).

Expected outcomes

This project will generate robust predictive biomarkers and integrative models to improve risk stratification and guide treatment selection in breast cancer. By enabling precise identification of patients most likely to benefit from immunotherapy or ADCs, it aims to minimize both under- and overtreatment. Ultimately, the results will support biomarker-driven therapeutic strategies and advance the implementation of precision oncology in breast cancer.

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

The PhD student must demonstrate a basic bioinformatics knowledge being confident with R environment and able to write codes. During the period of thesis the student will acquire advanced skills in bioinformatics and computational biology, including multi-omics data integration, statistical modeling, and machine learning applied to translational oncology. Additional competencies will include critical interpretation of large-scale datasets, biomarker discovery, and validation strategies. The student will also develop scientific writing, interdisciplinary collaboration, and project management skills in a precision medicine framework.

References (max. 15)

1. Schmid P, Cortes J, Dent R, et al. Overall Survival with Pembrolizumab in Early-Stage Triple-Negative Breast Cancer. New England Journal of Medicine. Published online September 15, 2024. doi:10.1056/NEJMoa2409932

2. Spring LM, Tolaney SM, Fell G, et al. Response-guided neoadjuvant sacituzumab govitecan for localized triple-negative breast cancer: results from the NeoSTAR trial. Annals of Oncology. 2024;35(3):293-301. doi:10.1016/j.annonc.2023.11.018

3. Bardia A, Pusztai L, Albain K, et al. TROPION-Breast03: a randomized phase III global trial of datopotamab deruxtecan ± durvalumab in patients with triple-negative breast cancer and residual invasive disease at surgical resection after neoadjuvant therapy. Ther Adv Med Oncol. 2024;16. doi:10.1177/17588359241248336

4. Tolaney SM, DeMichele A, Takano T, et al. ASCENT-05/OptimICE-RD (AFT-65): Phase 3, randomized, open-label study of adjuvant sacituzumab govitecan (SG) + pembrolizumab (pembro) vs pembro ± capecitabine (cape) in patients (pts) with triple-negative breast cancer (TNBC) and residual disease after neoadjuvant therapy (NAT) and surgery. Journal of Clinical Oncology. 2023;41(16_suppl):TPS619-TPS619. doi:10.1200/JCO.2023.41.16_suppl.TPS619

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.*

This is a retrospective observational translational study based exclusively on publicly available datasets. The project's focuses are biomarker discovery and predictive modeling.

The study will analyze existing multi-omics datasets, including genomic, transcriptomic, and immune-related data derived from breast cancer cohorts treated with various treatment regimens including chemotherapy and the combination of chemo and immunotherapy.

The experimental workflow will consist of: (i) systematic identification and curation of relevant publicly available datasets (e.g., TCGA, METABRIC, and clinical trial-associated datasets, including personal data from Michelangelo Foundation, where public accessible), focusing on early-stage breast cancer patients with available treatment and outcome data; (ii) harmonization and preprocessing of multi-omics data (iii) characterization of molecular subtypes, tumor microenvironment features, and immune signatures associated with residual disease following neoadjuvant therapy; (iv) development of predictive models for recurrence risk and treatment response using statistical and machine learning approaches (e.g., penalized regression, random forest, and survival models) implemented in R; (v) internal and external validation of identified biomarkers and models across independent datasets to ensure robustness and reproducibility.

Emphasis will be placed on patients with residual disease after neoadjuvant chemo-immunotherapy, a high-risk population in which treatment escalation strategies are evolving. The project will also explore mechanisms of resistance and sensitivity to immunotherapy and ADCs through integrative analyses.

No prospective enrollment, interventional procedures, or quality-of-life assessments are planned. No drugs, medical devices, or interventional procedures will be used. Therefore, marketing authorization (MA), investigational drug phase, and CE marking are not applicable.

The translational component of the project will be conducted within a computational and bioinformatics research environment, without the need for wet laboratory experimentation. The candidate will rely on institutional

computational resources and collaborate with the "Translational and immunotherapy research group" under the supervision of Prof. Giampaolo Bianchini.

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).*

The project is based exclusively on publicly available dataset (e.g., TCGA, METABRIC, and clinical trial-associated datasets, including personal data from Michelangelo Foundation, where public accessible). No biobank access or storage is required. No participants will be recruited and no biological samples will be collected. No procedures, interventions, or examinations outside are planned. Analyses will be conducted using bioinformatic and statistical methods on existing multi-omics data.

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

The PhD student will lead the integrative analysis of publicly available multi-omics datasets, focusing on identifying predictive biomarkers of response to immunotherapy and ADCs. The student will design and implement bioinformatic pipelines, perform data integration and model development, and validate findings across independent cohorts. The student will actively contribute to result interpretation and dissemination in a translational research environment.

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

The project will advance precision medicine in breast cancer by identifying robust predictive biomarkers for immunotherapy and ADCs. These findings may improve patient stratification, reduce under- and overtreatment, and support more tailored therapeutic strategies, particularly in the post-neoadjuvant setting. Additionally, the generated evidence may inform the design of future biomarker-driven clinical trials and accelerate the translation of integrative data approaches into clinical decision-making.

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.

Currently, the PhD project does not include a period of research at an external institution abroad.

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 _____