# RESEARCH ACTIVITY SHEET

2025 PhD selections

## YOUR DETAILS

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| * Name & Surname | Federica Di Nicolantonio |

* Affiliation UNITO

## PHD PROJECT DETAILS

* Title of the proposed project

The molecular bases of liquid biopsy tests for precision oncology

* Short description of the project (up to 300 words)

Precision oncology relies on the early diagnosis of cancer, detection of minimal residual disease, and timely characterization of the tumor molecular landscape to identify actionable alterations that can guide patient treatment. Blood from most cancer patients contains cell-free DNA (cfDNA) released predominantly by neoplastic cells. Tumor-derived cfDNA has emerged as a minimally invasive biomarker to guide precision oncology interventions. However, a full understanding of the mechanisms contributing to tumor cfDNA release is still missing. We hypothesize that a better elucidation of these mechanisms could unveil essential knowledge to improve the clinical implementation of liquid biopsy tests. We will address fundamental - yet translationally relevant - questions concerning tumor cfDNA. 1) What governs the fluctuations and the pattern in the cfDNA levels in the blood? 2) Is it possible to distinguish between cfDNA shed by dying cells in response to treatment and that actively secreted by drug-tolerant resistance cells? 3) What is the kinetic of cfDNA release in relation to specific therapeutic interventions?
We will employ a combination of computational methods, as well as molecular and cell biology techniques to address the above questions in cancer cell lines and murine models, followed by validation in patient plasma. We will explore whether and how intracellular DNA damage (either spontaneous or caused by exogenous factors), can lead to cfDNA release and affect its fragmentation patterns. Using drug-sensitive and drug-persistor cancer cell lines, we will investigate whether the analyses of cfDNA fragment lengths and specific end features could differentiate cfDNA from dying cells from actively secreted cfDNA. We will also measure the kinetic of cfDNA release from cancer cells undergoing treatment with different chemotherapy and/or targeted therapies.
Overall, this project will provide guidance on the features of cfDNA to be analyzed and the most appropriate timing of blood draw based on specific treatments.

* Indicate the main research area for the project described above Cancer Biology

If needed indicate a second research area for the project described above Genomic medicine

* Provide up to 3 key words for project:

Molecular diagnostics, liquid biopsy, cancer biomarkers

# YOUR LABORATORY ACTIVITIES DETAILS

* Main topic/s of the lab

Identification of biomarkers of drug response/drug resistance in solid tumors, with a focus on colorectal cancer, but ongoing projects include also preclinical research in malignant pleural mesothelioma and pancreatic cancer.

Development and implementation of liquid biopsy tests for precision oncology.

* Short description of the lab activity (up to 500 words)

I have been active in cancer research for almost 25 years, throughout which I have demonstrated an established record of accomplishments in the field of translational oncology. My research interests have always been inspired by the observation that the 'one-size-fits-all' approach should not be applied to treat cancers of the same histological type; since tumors affecting the same tissue often display individual and peculiar morphological and molecular features. My studies on the molecular mechanisms of cell transformation have been consistently aimed at identifying individualized targets amenable for therapeutic intervention as well as cancer prognostic and/or predictive biomarkers. Throughout my career, I have shown that it is possible to deliver precision cancer medicine by coupling tumor molecular profiling with functional studies in clinically relevant preclinical models.

I contributed to establish that activated RAS-BRAF signalling can by-pass EGFR targeted inhibition in metastatic colorectal cancer, a notion that led to restricting the use of EGFR targeted monoclonal antibodies to RAS wild-type metastatic colorectal cancer patients. In this regard, I am the leading author of a highly cited manuscript that first described BRAF V600E mutations as a biomarker of adverse prognosis and of resistance to EGFR targeted therapies in metastatic colorectal cancer patients.

In the same field, I contributed as a co-first author to the discovery that lack of efficacy of BRAF inhibitors could be mediated by feedback re-activation EGFR in colon tumors, and proved that combinations of EGFR and BRAF inhibitors were effective in restraining growth of BRAF mutant colorectal cancer xenografts. Importantly, my preclinical works have also provided the rationale for the design of clinical trials testing BRAF and EGFR inhibitor combinations in BRAF mutant metastatic colorectal cancer patients, a regimen that is now clinically approved. My laboratory has then further shown that it possible to individualize treatment of BRAF mutant metastatic colorectal cancer patients, by studying mechanisms of primary and acquired resistance to molecularly targeted agents in tumor samples as well as in liquid biopsies.

Finally, we have developed an interest in epigenetics of colorectal cancer, since methylation changes can serve as tumor-specific changes for monitoring tumor burden in plasma circulating tumor DNA, as well as modifiers of drug response. In this regard, my team has implemented a digital PCR based assay to provide a quantitative assessment of MGMT methylation in tissue and liquid biopsies for prediction of response to alkylating agents in advanced CRC patients.
Along this research topic, we have also completed genome-wide assessment of DNA methylation of a collection of over 200 colorectal cancer cell lines and compared it to normal mucosa and blood cells, in order to define a highly specific and sensitive gene methylation signature to be employed in liquid biopsy tests. We have evidence that assessment of methylated markers in cell-free circulating DNA allows non-invasive monitoring of disease burden in metastatic colorectal cancer patients. Methylation changes over time correlate with tumor response evaluated by CT-scan in patients treated with chemotherapy or targeted agents.

* Recent bibliography (max 5 references)

Pessei V, (…) Di Nicolantonio F. DNA demethylation triggers cell free DNA release in colorectal cancer cells. Genome Med. 2024 Oct 9;16(1):118. https://pmc.ncbi.nlm.nih.gov/articles/PMC11462661/

Mirandola A, (…) Di Nicolantonio F, Thierry A. Post-surgery sequelae unrelated to disease progression and chemotherapy revealed in follow-up of patients with stage III colon cancer. Lancet EBioMedicine. 2024 Oct;108:105352. https://pmc.ncbi.nlm.nih.gov/articles/PMC11437914/

Sartore-Bianchi A, et al.,. Circulating tumor DNA to guide rechallenge with panitumumab in metastatic colorectal cancer: the phase 2 CHRONOS trial. Nat Med. 2022 Aug;28(8):1612-1618.

Di Nicolantonio F, Precision oncology in metastatic colorectal cancer - from biology to medicine. Nat Rev Clin Oncol. 2021 Aug;18(8):506-525.

* Group composition: total members, and roles distribution (PhD, postdoc, technician, etc.)

Main group members at the University of Torino, Department of Oncology and Candiolo Cancer Institute-FPO

Federica Maione, Assistant Professor
Marco Macagno, Laboratory Manager
Daniele Forte, Technician
Alessandro Cavaliere, Fariha Idrees, PhD Students
Wiktoria Bienek, Research assistant
Chiara Baretta, Anita Brignacca, Master Students

Institutional page link

https://www.irccs.com/it/cancer-epigenetics

Lab website link, if any

Social media links, if any

X: fdinicolantonio

If you prepare a video to promote your lab/project, please include the link below