

BIOGRAPHICAL SKETCH

NAME: Giorgia, Zadra

eRA COMMONS USER NAME (credential, e.g., agency login): GZADRA

POSITION TITLE: Researcher III (Principal Investigator/Group Leader)

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Milan, Milan, Italy	M.S. cum laude	04/2003	Medical Biotechnology
University of Milan, Milan, Italy	Ph.D.	01/2007	Molecular Medicine (curriculum Molecular Oncology)
Dana-Farber Cancer Institute, Harvard Medical School, Boston, US	Postdoctoral	06/2013	Oncology and Metabolism

A. Personal Statement

I am a Principal Investigator and Group Leader at the Institute of Molecular Genetics, National Research Council (CNR-IGM) in Pavia, Italy, and a Contract Professor in General Pathology, Harvey Medical Course, Medical School, University of Pavia (2021 - 2025). I have extensive expertise in cancer metabolism and translational research, developed over 12 years of international experience, including positions as Junior Faculty in Pathology at Harvard Medical School (Boston, US), Visiting Scientist at the University of Adelaide (Australia), and Postdoctoral Fellow at the Dana-Farber Cancer Institute (Boston, US).

My early research focused on dissecting the mechanisms linking tumor metabolic alterations, particularly lipid metabolism, to prostate cancer progression, with the goal of identifying tumor-specific vulnerabilities to develop more effective and less invasive therapeutic and diagnostic approaches. To achieve this, I combined high-throughput metabolomics and transcriptomics with refined biochemical experiments and digital pathology, applied across *in vitro* and *in vivo* models, patient-derived explants/organoids, and clinical samples. I also employed advanced PET/CT *in vivo* imaging, NMR, and MALDI mass spectrometry imaging to identify predictive and prognostic biomarkers and to monitor therapy response and resistance.

In 2016, supported by U.S. funding (Idea Development Award – U.S. Department of Defense, and Barr Award, DFCI), I developed a holistic approach to explore the role of systemic metabolism in cancer progression. Since then, I have investigated the interplay between genetics, diet, and obesity in reshaping the tumor metabolome, epigenome, and microenvironment, using high-throughput and spatial approaches.

In addition to my primary research, I contribute to projects with significant clinical and social impact. Within the CNR NutrAge project, I focus on lipidomic analyses to identify biomarkers of “inflamm-aging” and support strategies for healthy aging. I am a Unit Head in a PRIN 2022 project with the University of Milan, exploring the role of extracellular vesicles in lung transplant rejection through multi-omic approaches. Most recently, I am CNR partner in the AdvanCed Technologies for Human-centrEd Medicine (Anthem), PNRR-funded project, applying machine learning to integrate clinical, molecular, and imaging data to identify predictive biomarkers and novel therapeutic targets in lung transplantation. Finally, I contribute to the DONO project, recently funded by Regione Lombardia (Bando Collabora&Innova), which aims to develop/characterize pig xenotransplant models for kidney transplantation.

Ongoing and completed projects that I would like to highlight include:

Ongoing

2025 - 2030 Title: *Epigenetic control of MYC-driven metabolic adaptations in aggressive prostate cancer*

Funding Agency: Canadian Institutes of Health Research (CIHR), Canada. Total amount: CAN\$ 1.655.000

Role: **Collaborator** (PI: Prof. David Labbé)

2025 - 2027 Title: *Pig organs to offer hope to patients awaiting transplants*. Multi-institutional grant (industrial partners: Avantea S.R.L, DBA PRO. S.P.A., ROSEBIO S.R.L.; academic partners: National Research Council (CNR), IRCCS-PHARMACOLOGICAL RESEARCH INSTITUTE MARIO NEGRI

Funding Agency: Regione Lombardia, Italy. Total amount: € 3.638.219 (CNR amount: € 782.700,44)

Role: **Co-investigator** (CNR-IGM)

2023 -2027 Title: *Integrating tissue-based spatial information to elucidate how obesity-induced tumour metabolites drive prostate cancer progression*.

Funding Agency: World Cancer Research Fund (WCRF), London, UK. Total amount: UK£ 340.000

Role: **Principal Investigator**

2025 - 2026 Title: *CARELUNG - Multimodal machine learning and OMICs in lung transplantation: charting novel paths for prediction, diagnosis and treatment of chronic rejection*. ANTHEM: AdvANced Technologies for Human-centrEd Medicine

Funding Agency: PNRR, MUR. Total amount: € 511.452 (amount to GZ: € 30.220)

Role: **Partner CNR** (PI: Prof. Valentina Vaira)

2023 - 2026 Title: *New molecular insights on the role of bronchoalveolar lavage-derived extracellular vesicles in lung allograft rejection*. Projects of Relevant National Interest (PRIN) 2022

Funding Agency: Ministry of University and Research (MUR)

Total amount: € 180,000 (amount to GZ: € 95.800)

Role: **Unit Head** (PI: Prof. Valentina Vaira)

2023 – 2025 Title: *Quantitative analysis of the serum lipidome to identify biomarkers of inflammation and define the role of diet in this context* (Subtask 4.4.1, Work package 4). NUTRAGE (Multi-institutional grant)

Funding Agency: FOE 2021, CNR. Amount to GZ: € 47.000

Role: **Leader of Subtask 4.4.1**

Completed (listed only more relevant of the last 6 years)

2019 - 2022: Title: *Lipid elongation via ELOVL5: a novel target for advanced prostate cancer*. Idea Development Award (W81XWH-19-1-0566)

Funding Agency: US-Department of Defense. Total amount: US\$ 736.817

Role: **Co-Investigator** (Multi-PI: Loda M, Butler L, Swinnen JV)

2017 - 2020: Title: *Pharmacologic inhibition of lipogenesis suppresses AR and its splice variants to inhibit progression of castration resistant prostate cancer*. Impact Award (PC160357)

Funding Agency: US-Department of Defense. Total amount: US\$ 2.976.678

Role: **Co-Investigator** (Multi-PI: Loda M; Plymate S; Dehm S)

2017 - 2019: Title: *Identifying key genes that mediate increased prostate cancer cell fitness in metabolic environments perturbed by diet-induced obesity*

Barr Award, Claudia Adams Barr Program in Innovative Basic Cancer Research

Funding Agency: Dana-Farber Cancer Institute, Boston, US. Total amount: US\$ 360.000

Role: **Principal Investigator**

2016 - 2019: Title: *Identify the Metabolic Dependencies of Obesity-Associated Aggressive Prostate Cancer to Develop Tailored Imaging and Therapeutic Approaches*. Idea Development Award (PC150263).

Funding Agency: US-Department of Defense. Total amount: US\$ 414.787

Role: **Principal Investigator**

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2020 - Current	Principal Investigator and Group Leader, CNR-IGM, Pavia, Italy
2019 - Current	CNR Researcher III, CNR-IGM, Pavia, Italy
2021 - Current	Member of the PhD Council in Genetics, Molecular, and Cellular Biology, University of Pavia, Italy
2019 - Current	Member (Junior) of the Editorial Board, Cancer Drug Resistance Journal
2022 - Current	Member, Society for Basic Urologic Research
2018 - Current	Member, International Society of Cancer Metabolism
2018 - Current	Associate member, American Association for Cancer Research
2021 - 2025	Contract Professor in General Pathology, Harvey Medical Course, Master's Degree in Medicine and Surgery, University of Pavia, Italy
Nov 2023	Visiting Researcher, South Australian Health and Medical Research Institute, University of Adelaide, Adelaide, Australia
2019 - 2021	Associate Editor, <i>Cellular Oncology</i> Journal (expertise: oncometabolism)
2013 - 2019	Junior Faculty (Instructor) in Pathology, Harvard Medical School, Boston, US
2019:	Research Scientist II, Dana-Farber Cancer Institute, Boston, US
June 2016	Visiting Scientist, Lipid and Prostate Cancer Group, South Australian Health and Medical Research Institute, University of Adelaide, Adelaide, Australia
2007 - 2013	Post-Doctoral Fellow, Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, US

Prizes/Honors

2017	First Prize-Best Poster “ <i>The diet-induced obesity metabolome propels prostate cancer by rewiring the epigenome</i> ” (Presented by co-first author Dr. Labbé). Multi-Institutional Prostate Cancer SPORE Retreat, Ford Lauderdale, FL, US
2013	Thomas J. Gill and Simon J. Simonian Prize for Research Excellence. Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US
2012	Young Talent Fellowship-CAPES, Ministry of Education, Brazil (declined to continue training in the US)
2010 - 2012	Post-Doctoral Fellowship from Andrea Libi Lorini Foundation for studies and research in Oncology and H.I.V. infection, University of Milan, Milan, Italy
2008 - 2009	American-Italian Cancer Foundation (AICF) International Postdoctoral Fellowship, NY, US

C. Contributions to Science

My main contributions to Science include: *i*) elucidating the role of systemic metabolism in prostate cancer (PCa) progression, *ii*) dissecting the interplay between lipid metabolism and androgen receptor (AR) signaling to identify “non-canonical approaches” to suppress disease progression, *iii*) advancing metabolic-targeted therapies in PCa using clinically relevant models, and *iv*) promoting metabolomics, metabolic imaging, and digital pathology in precision medicine. My work has provided proof-of-concept for clinical trials. My most significant scientific accomplishments are listed.

1. Unravelling the Connection between Diet, Obesity, and Prostate Cancer Progression

- a. *Boufaied N, *Chetta P, Hallal T, Cacciatori S, Lalli D, Luthold C, Homsy K, Imada EL, Syamala S, Photopoulos C, Di Matteo A, de Polo A, Storaci AM, Huang Y, Giunchi F, Sheridan PA, Michelotti G, Nguyen QD, Zhao X, Liu Y, Davicioni E, Spratt DE, Sabbioneda S, Maga G, Mucci LA, Ghigna C, Marchionni L, Butler LM, Ellis L, Bordeleau F, Loda M, Vaira V, *Labbé DP, *Zadra G. *Obesogenic High-Fat Diet and MYC Cooperate to Promote Lactate Accumulation and Tumor Microenvironment Remodeling in Prostate Cancer. Cancer Research.* 2024 Jun 4;84(11):1834-1855. doi: 10.1158/0008-5472.CAN-23-0519. *Equal contribution.

This achievement represents an international, multi-institutional effort that I led. By integrating expertise in metabolomics, transcriptomics, and digital pathology, the team uncovered the role of the oncometabolite lactate in mediating obesity-driven tumor microenvironment remodeling in PCa progression. This discovery highlights oncometabolites as critical mediators in obesity and opens new therapeutic perspectives.

b. *Labbé DP, *Zadra G, Yang M, Reyes JM, Lin CY, Cacciatore S, Ebot EM, Creech AL, Giunchi F, Fiorentino M, Elfandy H, Syamala S, Karoly ED, Alshalalfa M, Erho N, Ross A, Schaeffer EM, Gibb EA, Takhar M, Den RB, Lehrer J, Karnes RJ, Freedland SJ, Davicioni E, Spratt DE, Ellis L, Jaffe JD, D'Amico AV, Kantoff PW, Bradner JE, Mucci LA, Chavarro JE, *Loda M, *Brown M. High-fat diet fuels prostate cancer progression by rewiring the metabolome and amplifying the MYC program. **Nat Commun.** 2019 Sep 25;10(1):4358. doi: 10.1038/s41467-019-12298-z. *Equal contribution.

This groundbreaking study used multi-omics approaches to dissect the link between Western diets and PCa progression. Together with Dr. Labbé, I demonstrated that a diet rich in saturated fat shapes the PCa epigenome through alterations in one-carbon metabolism, resulting in activation of oncogenic signaling (*i.e.*, the MYC transcriptional program) and PCa progression. These findings were recapitulated in PCa patients and laid the groundwork for integrating dietary interventions into oncological management.

2. Dissecting the interplay between lipid metabolism, androgen receptor (AR) signaling, and DNA-damage repair to exploit metabolic targeted therapies for advanced prostate cancer

a. *Ribeiro CF, *Rodrigues S, Bastos DC, Fanelli GN, Pakula H, Foiani M, Zadra G, Loda M. Blocking lipid synthesis induces DNA damage in prostate cancer and increases cell death caused by PARP inhibition. **Sci Signal.** 2024 Apr 9;17(831):eadh1922. doi: 10.1126/scisignal.adh1922. *Equal contribution.

This study elucidated a link between lipid metabolism modulation and the DNA damage response. Inhibition of the key lipogenic enzyme Fatty Acid Synthase (FASN) increased ceramide and sphingomyelin lipid species, causing DNA double-strand breaks. Combining a FASN inhibitor with the PARP inhibitor Olaparib produced stronger anti-tumor effects than either agent alone in human castration-resistant prostate cancer (CRPC) organoids. These findings suggest that FASN inhibition sensitizes prostate cancer cells to PARP inhibitors, supporting combination therapy for CRPC.

b.*Zadra G, Ribeiro CF, Chetta P, Ho Y, Cacciatore S, Gao X, Syamala S, Bango C, Photopoulos C, Huang Y, Tyekucheva S, Bastos DC, Tchaicha J, Lawney B, Uo T, D'Anello L, Csibi A, Kalekar R, Larimer B, Ellis L, Butler LM, Morrissey C, McGovern K, Palombella VJ, Kutok JL, Mahmood U, Bosari S, Adams J, Peluso S, Dehm SM, Plymate SR, Loda M. Inhibition of *de novo* lipogenesis targets androgen receptor signaling in castration-resistant prostate cancer. **Proc Natl Acad Sci U S A.** 2019 Jan 8;116(2):631-640. doi: 10.1073/pnas.1808834116. *Co-corresponding author

This study uncovered, for the first time, a reciprocal crosstalk between lipid metabolism and androgen receptor (AR) signaling mediated by endoplasmic reticulum stress. In collaboration with Infinity Pharmaceuticals (US) and using clinically relevant mouse models alongside patient-derived organoids and explants, we showed that selective inhibition of fatty acid synthase (FASN) downregulates both full-length AR and the splice variant AR-V7, a key driver of resistance to AR inhibitors such as enzalutamide. These findings establish a novel non-canonical therapeutic strategy to overcome or delay resistance. This discovery led to a clinical trial at Weill Cornell Medicine testing the FASN inhibitor TVB-2640 in combination with enzalutamide in patients with metastatic CRPC (NCT05743621).

c. Zadra G, Photopoulos C, Tyekucheva S, Heidari P, Weng QP, Fedele G, Liu H, Scaglia N, Priolo C, Sicinska E, Mahmood U, Signoretti S, Birnberg N, Loda M. A novel direct activator of AMPK inhibits prostate cancer growth by blocking lipogenesis. **EMBO Mol Med.** 2014 Apr;6(4):519-38. doi: 10.1002/emmm.201302734. Epub 2014 Feb 4. Erratum in: **EMBO Mol Med.** 2014 Oct;6(10):1357.

This study identified the energy sensor 5'-AMP-activated kinase (AMPK) as a key modulator of PCa lipid metabolism and showed that AMPK-mediated blockade of *de novo* lipid synthesis halts PCa growth while enhancing the efficacy of current treatments for mCRPC. In collaboration with the US company Mercury Therapeutics and the Molecular Imaging team at Massachusetts General Hospital (US), we characterized a new selective AMPK activator and demonstrated the potential of ¹¹C-

acetate PET imaging as a non-invasive method for patient selection and monitoring drug efficacy. The significance of these findings was recognized with the Thomas J. Gill and Simon J. Simonian Prize for Research Excellence (2013), an editorial in EMBO Molecular Medicine (2014), and an oral presentation at the Italian Embassy in Washington, DC (2012).

3. Advancing the Application of Spatial Metabolomics and Global metabolomics in Clinical Practice

a. Randall EC, **Zadra G**, Chetta P, Lopez BGC, Syamala S, Basu SS, Agar JN, Loda M, Tempny CM, Fennessy FM, Agar NYR. Molecular Characterization of Prostate Cancer with Associated Gleason Score Using Mass Spectrometry Imaging. **Mol Cancer Res.** 2019 May;17(5):1155-1165. doi: 10.1158/1541-7786.MCR-18-1057.

This multidisciplinary study pioneered the use of spatial lipidomics to advance diagnostic workflows in PCa. By applying rapid, ambient mass spectrometry imaging to improve biopsy accuracy, it laid the foundation for integrating spatial metabolic imaging into clinical practice.

b. Cacciatore S, **Zadra G**, Bango C, Penney KL, Tyekucheva S, Yanes O, Loda M. Metabolic Profiling in Formalin-Fixed and Paraffin-Embedded Prostate Cancer Tissues. **Mol Cancer Res.** 2017 Apr;15(4):439-447. doi: 10.1158/1541-7786.MCR-16-0262.

This study demonstrated, for the first time, that meaningful metabolic profiles can be extracted from archival PCa specimens, reflecting pathophysiological mechanisms and hormonal dependencies. These findings pave the way for implementing metabolic biomarkers into personalized medicine approaches for PCa.

The complete list of my publications is available here:

<http://www.ncbi.nlm.nih.gov/pubmed/?term=zadra+g>