

BIOGRAPHICAL SKETCH

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NAME: ANDREA CAVAZZONI

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

POSITION TITLE: associate professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date MM/YYYY	FIELD OF STUDY
University of Parma	BS	03/2000	Biology
University of Parma	PhD	03/2005	Molecular pathology
University of Parma	Post Doc	12/2013	Molecular and cellular Oncology

A. Personal Statement

I am an Associate Professor of General Pathology at the University of Parma. My primary research focus is on translational studies in solid tumors, particularly non-small cell lung cancer (NSCLC).

During my PhD course (2001-2004), I focused on the inducible expression of tumor suppressor genes FHIT and p53. This work was carried out in collaboration with the National Cancer Institute of Milan.

During my postdoc position (2005-2013), my studies focused on a novel class of epidermal growth factor receptor (EGFR) inhibitors for the treatment of lung cancer (5-benzylidene-hydantoins), in partnership with the Department of Pharmacy at the University of Parma. I then participated in studies investigating drug combinations targeting epidermal growth factor receptor (EGFR) in non-small cell lung cancer (NSCLC) cell lines in collaboration with The Medical Oncology Unit of the Azienda Ospedaliero-Universitaria of Parma (AIRC GRANT PI Ardizzoni, 2010-2012). This teamwork has led to numerous research papers focused on drug combination therapies, with a particular emphasis on the squamous histotype of NSCLC (AIRC GRANT, PI Ardizzoni 2014-2016).

In 2014, I was successful in a comparative call for an RTD position SSD06/A2, MED/04 at the University of Parma, Department of Medicine and Surgery.

My international experience at the Department of Medical Oncology at Vrije University Amsterdam (The Netherlands) in 2015 expanded my knowledge of different aspects of molecular cancer, enhancing my background and experience.

In 2018 I obtained the national scientific qualification for associate professor in SSD 06/A2 MED04 General Pathology.

During my university research experience, I focused on the mechanisms of action of immune checkpoint inhibitors, specifically on the PD-1/PD-L1 interaction, in NSCLC. Our published research has demonstrated the rationale underlying the enhanced efficacy of these therapeutic modalities when employed in conjunction with chemotherapy. This manuscript was a collaboration with Prof. Ardizzoni, Department of Medical and Surgical Sciences (DIMEC), University of Bologna (AIRC GRANT PI Ardizzoni 2017-2019).

In 2021, I moved to tenure-track faculty member (associate professor SSD06/A2 MED/04). I have collaborated with Prof. Ferracin from the Department of Medical and Surgical Sciences (DIMEC), University of Bologna, on a study exploring combination therapies in tumor cells from patients with cancer of unknown primary origin (AIRC GRANT PI Ferracin 2022-2027).

My research is currently focused on understanding the mechanisms of acquired resistance to KRAS^{G12C} inhibitors, specifically sotorasib and adagrasib, in NSCLC cell lines. This study is at an advanced stage, and the results will be published soon. In the last year, a new research project was initiated, focusing on the role of the KRAS^{G12D} and KRAS^{G12V} mutations in non-small cell lung cancer (NSCLC). My scientific background, the establishment of national and international collaborations, and my sustained motivation provide the solid foundation needed to execute the proposed research project successfully.

B. Positions, Scientific Appointments, and Honors

2022 present: Associate Professor of General Pathology, University of Parma

2013-2021: Senior Researcher General Pathology, University of Parma

2018: National scientific qualification for associate professorship in SSD 06/A2 MED04 General Pathology

2017: National scientific qualification for associate professorship in SSD 06/D3 MED06 Medical Oncology

2015-2015: visiting professor Department of Medical Oncology, Vrije University, Amsterdam (NL)

2011-2013: Post Doc: *Molecular targets in non-small cell lung cancer treatment*. Department of Clinical and Experimental Medicine, University of Parma- PARMA, Italy

2010-2011: Post Doc: *Comparison between 3-MCPD and its palmitic esters in a 90-day toxicological study*. Department of Experimental Medicine University of Parma- PARMA, Italy (In collaboration with European Food Safety Authority)

2009-2010: Post Doc: *Control of the of lung and mammary tumor progression by interference with molecular targets*. Department of Experimental Medicine, University of Parma- PARMA, Italy

2005-2009: Post Doc: *Molecular targets in non-small cell lung cancer treatment*. Department of Experimental Medicine, University of Parma- PARMA, Italy

Selected Speaker "40th EORTC-PAMM Winter Meeting", Verona, Italy, 2019.

Invited speaker CELLSEARCH® + DEPAArray™ User Meeting (Menarini Silicon Biosystem) September 26-27, 2017 | MAST - Bologna, Italy.

Speaker at the Italian Congress "Translational research in pulmonary neoplasms: state of the art and research experiences" December 6, 2017, Parma

Invited speaker 37th EORTC-PAMM Winter Meeting, Antwerp, Belgium 2016.

Organizer of International Meeting "Translational research in pleuro-pulmonary tumors: overview and new experimental data", Parma 2009.

Selected speaker XXVIII^o Meeting "Italian Society of Pathology", "Beyond the bench...preparing your career transition" Napoli 2009.

Organizer of National Meeting "XX Annual Meeting ABCD. Cellular stress and apoptosis", Parma 2009.

Speaker, National Congress " Prevention, early diagnosis and new lung cancer therapies ", Montichiari (BS) 2006.

Ordinary member of SIPMeT (Italian Society of Pathology and Translational Medicine).

Ordinary member of SIC (Italian Society of Cancer).

Ordinary member EACR (European Association for Cancer Research).

C. Contributions to Science

During my four-year PhD program, I successfully generated an inducible expression system for the FHIT and p53 tumor suppressor genes in NSCLC cells lacking both genes. This research aimed to precisely examine their role in tumor biology. Our results unequivocally demonstrated their cumulative function in a double expression inducible system.

- **CAVAZZONI A**, et al. Dose-dependent effect of FHIT-inducible expression in Calu-1 lung cancer cell line *Oncogene*. 2004;23(52), pp.8439-8446.
- **CAVAZZONI A**, et al. Effect of inducible FHIT and p53 expression in the Calu-1 lung cancer cell line *Cancer Letters*. 2007; 246 (1-2), pp. 69-81.

During my postdoctoral position (2005-2013), I acquired many skills in translational medicine, especially regarding the role of a novel class of epidermal growth factor receptor (EGFR) inhibitors. This study focuses on the chemical compounds 5-benzylidene-hydantoin.

- Carmi C, **CAVAZZONI A**, et al. 5-Benzylidene-hydantoin as new EGFR inhibitors with antiproliferative activity *Bioorganic and Medicinal Chemistry Letters*. 2006;16(15), pp.4021-4025
- **CAVAZZONI A**, et al. Dual mechanisms of action of the 5-benzylidene-hydantoin UPR1024 on lung cancer cell lines *Molecular Cancer Therapeutics*. 2008; 7 (2), pp. 361-370

The impact of EGFR-targeted therapy in NSCLC cells presented a valuable opportunity for our laboratory to engage in national grants (AIRC grants) in collaboration with the Medical Oncology Unit of the Azienda Ospedaliero-Universitaria of Parma. This ongoing collaboration has resulted in the publication of a paper in 2012, which demonstrates that the combination of the tyrosine kinase inhibitor erlotinib and the monoclonal antibody cetuximab on non-small cell lung cancer (NSCLC) wild-type for epidermal growth factor receptor (EGFR) produces a synergistic effect in terms of reducing tumor growth.

- **CAVAZZONI A**, et al. Combined use of anti-ErbB monoclonal antibodies and erlotinib enhances antibody-dependent cellular cytotoxicity of wild-type erlotinib-sensitive NSCLC cell lines *Molecular Cancer*. 2012; 11(1):91.

The subsequent project was based on the study of new pharmaceutical therapies in the squamous subgroup of NSCLC, with a focus on the role of PI3KCA mutations and PTEN loss. This project resulted in the production of two papers. In the first study, the role of monotherapy with a specific PI3K-targeting agent was examined, while the second study investigated the role of PTEN loss. These results globally confirm that monotherapy is unsuccessful in inhibiting tumor cell growth in NSCLC cells carrying PI3KCA mutations or PTEN loss, making a second specific targeted agent mandatory to obtain a reliable result.

- Bonelli MA, **CAVAZZONI A**[#], et al. Inhibition of PI3K Pathway Reduces Invasiveness and Epithelial-to-Mesenchymal Transition in Squamous Lung Cancer Cell Lines Harboring PI3KCA Gene Alterations. *Molecular Cancer Therapeutics*. 2015;14(8):1916-27 [#] co-first
- **CAVAZZONI A**, et al. Enhanced efficacy of AKT and FAK kinase combined inhibition in squamous cell lung carcinomas with stable reduction in PTEN. *Oncotarget* 2017; 8(32):53068-53083.

The advent of the immunotherapy approach, particularly in the context of NSCLC, has led us to concentrate our research efforts on this subject. The current treatment for patients with NSCLC (adenocarcinoma subtype) involves a combination of immunotherapy directed at the PD-L1/PD-1 axis with chemotherapy. Based on our results, chemotherapy may increase PD-L1 levels in cancer cells, which could potentially enhance the effect of antibodies directed toward PD-L1. Our research has identified an intrinsic role of membrane-bound PD-L1, which appears to be involved in the activation of intracellular signaling pathways that enhance the secretion of pro-inflammatory cytokines and angiogenesis-related proteins. These findings have provided the rationale for exploring combinatorial treatments involving PD-1/PD-L1 inhibitors and anti-angiogenic agents.

- **CAVAZZONI A**, et al. Pemetrexed Enhances Membrane PD-L1 Expression and Potentiates T Cell-Mediated Cytotoxicity by Anti-PD-L1 Antibody Therapy in Non-Small-Cell Lung Cancer. *Cancers (Basel)*. 2020;12(3):666.
- **CAVAZZONI A**, et al. PD-L1 overexpression induces STAT signaling and promotes the secretion of pro-angiogenic cytokines in non-small cell lung cancer (NSCLC). *Lung Cancer* 2024 Jan; 187:107438

In recent years, a collaboration has been started with Prof Ferracin from the Department of Medical and Surgical Sciences (DIMEC), University of Bologna. This collaborative endeavor is supported by an AIRC grant, which is dedicated to the investigation of the tumor biology of cancers of unknown primary origin. Our research paper included an extensive genetic analysis of cancer cells from patients with unknown primary tumors. We proposed a pharmaceutical approach combining FGFR2 and MEK inhibitors in cancer cells with FGFR2 gene amplification.

- **CAVAZZONI A**, et al. Synergic activity of FGFR2 and MEK inhibitors in the treatment of FGFR amplified cancers of unknown primary. *Mol Ther*. 2024 Oct 2;32(10):3650-3668.

My current research is focused on the study of the resistance mechanisms to specific KRAS^{G12C} inhibitors in NSCLC cells.

Our new study will explore the role of KRAS mutations non-G12C (G12D and G12V), which are less frequent in NSCLC, but for which there is currently no targeted specific strategy. The project is a collaboration with the Medical Oncology Unit of the Azienda Ospedaliero-Universitaria of Parma, and it received a grant from the Berlucchi Foundation (PI Digiacoimo) and Sanofi S.r.l. (PI Mazzaschi).

My publication list can be found at the following link:

<https://pubmed.ncbi.nlm.nih.gov/?term=cavazzoni+a&size=50>

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