PERSONAL INFORMATION

Serenella Pupa

(39)02-23902573

serenella.pupa@istitutotumori.mi.it

WORK EXPERIENCE

2023-present

Head of the Microenvironment and Biomarkers of solid tumors, Dept of Experimental Oncology

Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Her studies performed in collaboration with her experimental team, our Medical Oncology Department, Department of Diagnostic Pathology and Laboratory Medicine, University of Milan, University of Palermo, IFOM ETS, Istituti Clinici Scientifici Maugeri (Pavia) and IRCCS Ospedale San Raffaele Milan are focused to investigate the pathobiological roles exerted by the rewiring of the key enzyme regulating fatty acid biosynthesis (FASN) in both HER2-positive breast and gastric cancer stem cells as potential resistance mechanism to HER2-targeted therapy; the reprogramming of fatty acid transporters regulating both fatty acid uptake (CD36) and their beta-oxidation (CPT-1A) as novel metabolic biotargets to potentiate the efficacy of anti-HER2 agents in therapy-resistant HER2-positive breast cancer models. Her studies performed in collaboration with her experimental team, University of Milan and Biophysics Institute of CNR-IBF (Milan) are addressed to the in silico design and biological characterization of novel CD36 inhibitors to be used as innovative therapeutic strategy in dual combination with anti-HER2 agents to increase anti-HER2 therapy efficacy in HER2-positive breast cancer models.

1998 - 2023

Staff Scientist, Molecular Targeting Unit, Department of Experimental Oncology

Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

- Scientific coordination of research groups studying: efficacy of naked DNA-based anti- tumor vaccines in the field of HER2-positive breast cancer in *ad hoc* transgenic mouse strains; breast tumor-restricted antigens by serological analysis of expression cDNA libraries; immunological and pathobiological roles exerted by the extracellular matrix protein fibulin-1; antibody response in vaccinated non-Hodgkin's B-cell lymphoma patients and novel biotargets of therapy; role of d16HER2 splice variant in the carcinogenesis, invasiveness, stemness and therapy susceptibility of HER2-positive breast and gastric cancers; pathobiological features of cancer stem cells in HER2-positive and triple negative breast and in HER2-positive gastric cancers; targeting biomarkers of rewired fatty acid lipid metabolism to revert therapy resistance to anti-HER2 agents in HER2-positive breast and gastric cancers

- Principal Investigator of many funded grants and fellowships funded to own collaborators

- Principal Investigator of distinct animal projects authorized by the Italian Ministry of Health

- Principal Investigator/collaborator in distinct Institutional clinical studies

- Mentoring activity of numerous Bachelor and Master of Science graduates

- Supervisor of students of the PhD Programme, Open University, Milton Keynes (UK), and External Examiner of PhD student (NewCastle University, Professor A. Tyson-Capper).

Business or sector Experimental Oncology

1991 - 1998 **Staff Scientist, Division of Experimental Oncology E, Department of Experimental Oncology**

Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

- Scientific coordination of research groups, designing and executing experiments studying: antibody response directed to the HER2 oncoprotein and other tumor-restricted antigens in pre-clinical and clinical models of HER2-positive breast cancer; association of intratumor inflammatory infiltrate with the prognosis of HER2-positive breast cancer patients;
- 3 months period spent as Visiting Scientist at the Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA, USA (1995) to study the role of Rb2/p130 oncosuppressor in HER2-positive breast cancer
- Supervisor of some Master of Science graduates

Business or sector Experimental Oncology

1990 - 1988 **Staff Fellow, Division of Experimental Oncology E, Department of Experimental Oncology**

Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

- Designing and executing experiments in the fields of cell biology and tumor immunology; production of murine monoclonal and human antibodies directed against breast cancer-restricted antigens and generation of anti-idiotypic monoclonal antibodies in the context of ovarian cancer; cellular, biochemical and histological characterization of all produced monoclonal antibodies in different solid cancers and normal tissues

1988 **Post-doctoral fellow of the Department of Microbiology and Immunology**

New York Medical College, Valhalla, New York

- Designing and executing experiments in the field of tumor immunology, production of anti-idiotypic monoclonal antibodies directed against melanoma-restricted antigens and their biological and biochemical characterization; purification of immunoreactive radiolabeled monoclonal antibodies using matched sepharose-immobilized anti-idiotypic monoclonal antibodies

Business or sector Experimental Oncology

1984- 1987 **Post-doctoral fellow , Division of Experimental Oncology E**

Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

- Designing and executing experiments in the field of tumor immunology, production of monoclonal antibodies directed against tumor-restricted antigens and characterization of bispecific monoclonal antibodies as potential therapeutic tools in ovarian cancer

Business or sector Experimental Oncology

EDUCATION AND TRAINING

1985 **Passed the Government Exam and Licensed as a Professional Biologist**

1978-1983 **Degree in Biological Science**

University of Milan, Italy

1973-1978 **Baccalaureate**

High School, Liceo “A. Manzoni”, Milan , Italy

- Classical Studies

Mother tongue(s) Italian

Other language(s)	UNDERSTANDING		SPEAKING		WRITING
	Listening	Reading	Spoken interaction	Spoken production	
English	Good	Good	Good	Good	Good

Communication skills
- good communication skills gained through experience as Senior Staff Researcher

Organisational / managerial skills
- Tutor (currently responsible for a team of 1PhD, 1PhD student and 1 junior Fellow)
- At present Principal Investigator of a grant AIRC IG (call 2019) and active Collaborator in different Experimental and Clinical Research Projects. Currently, Principal Investigator of one FUV Fellowship (call 2022).
- Ad hoc Reviewer for different peer-reviewed International Journals: Oncogene, Theranostics, MDPI journals, Neoplasia, Cell Death and Disease, and others

From 2021 Editor for Cancers (6.639)
-Guest Editor for Cancers Special Issue entitled "Latest basic, translational and clinical advancements in HER2-positive breast cancer" (IF: 6.639)

Job-related skills
- good command of quality control processes

Computer skills
- good command of Microsoft Office™ tools

Other skills
- Personal hobbies and Mother of Alessandro (09/08/1990) and Camilla (16/02/2000)

Driving licence
- B

ADDITIONAL INFORMATION

Presentations
Projects
Conferences
Seminars
Honours and awards
Memberships
References

Early in her research career, Dr. Serenella Pupa focused on the production and characterization of murine monoclonal antibodies (MAbs) and human antibodies (HuAbs) directed to tumor-restricted antigens (ags), and on the production and characterization of anti-idiotypic M Abs for use in cancer diagnosis and immunotherapy in both ovarian cancer and melanoma fields (in collaboration with Professor S. Ferrone, New York Medical College, Valhalla, New York, USA). Further, she characterized bispecific MAbs targeting cytotoxic T cells and tumor ags for immunotherapeutic strategies of ovarian cancer (in collaboration with Professor A. Lanzavecchia, Basel Institute for Immunology, Basel, Switzerland) and applied the molecular serological analysis of recombinant cDNA expression libraries, defined "SEREX" strategy, in the context of HER2-positive human breast cancer to identify novel tumor ags as potential targets for immunotherapy (in collaboration with Professor LJ Old and Dr MJ Scanlan, Memorial Sloan Kettering Cancer Center, New York, USA). In her pivotal studies, Dr. Pupa showed that the extracellular domain (ECD) of HER2 (HER2/ECD) is released into circulation by a proteolytic cleavage and that circulating HER2/ECD fragment can be considered a marker of worst prognosis, a parameter currently tested in the HER2 metastatic setting to follow patients' outcome. She was the first to demonstrate that HER2-positive breast carcinoma patients mount an antibody response to HER2 itself thus shedding light on HER2 *in vivo* immunogenicity and opening a new field of research related to the targeting of HER2 in immunotherapeutic interventions/strategies; in this context, she also started to collaborate with Professor MA Cheever and Dr ML Disis (University of Washington,

Seattle, WA, USA). She also tested the efficacy of naked DNA-based vaccination strategies in mice transgenically expressing the rat HER2/neu gene and demonstrated the validity of xenogeneic vaccination in preventing mammary tumor development, as evidenced by several scientific publications developed in collaboration with several Italian Universities. Dr. Pupa's research has contributed in revealing the immunological and pathobiological roles exerted by the extracellular matrix (ECM) protein fibulin-1 in drug responsiveness of breast cancers (in collaboration with Professor WS Argraves, Medical University of South Carolina, Charleston, USA) and produced *ad hoc* MAbs subsequently distributed commercially.
She was involved in the study of antibody response in non-Hodgkin's lymphoma (NHL) patients vaccinated with autologous dendritic cells (DCs); in the discovery of potential novel NHL-restricted biotargets using the serological proteome analysis, defined "SERPA" strategy; and identification of predictive factors of immunogenic cell death after DC-based vaccination in B-cell lymphoma patients undergoing different chemotherapeutic and immunotherapeutic treatments.
During her career she mainly conducted several pre-clinical and clinical studies aimed at addressing the implication of full-lenght HER2 in breast cancer immunogenicity, tumorigenesis, progression, response to therapy and cancer stemness.
Dr. Pupa collaborated and continues to collaborate with many national and international clinical and translational research national and international groups to investigate different experimental oncologic fields. In the last years, her work mainly applied to unveil the role of d16HER2 variant in HER2-driven tumorigenesis, aggressiveness, response to targeted therapy and stemness. In particular, Dr. Pupa's research unveiled that the d16HER2 variant is the "true oncogenic driver" of the HER2 signalling in HER2-positive breast cancer. Recently, she expanded this specific pre-clinical area of research into the clinic of HER2-positive breast and gastric cancers and together with her team actively collaborates with medical oncologists of INT-MI. She studied cancer stemness and mechanisms of immune-evasion also in *in vitro* and *in vivo* models of Triple Negative Breast Cancer (TNBC) reporting a key study demonstrating the expression of the immunosuppressive molecule Programmed death-ligand 1 (PDL-1) in human TNBC stem cells.
She started to study the rewiring of fatty acid lipid metabolism in the response to anti-HER2 agents in both HER2-positive breast and gastric cancers. Currently, her studies performed in collaboration with our Medical Oncology and Pathology and Laboratory Medicine Departments, University of Milan, University of Palermo, Biophysics Institute of CNR-IBF (Milan) and Istituti Clinici Scientifici Maugeri (Pavia) are focused to investigate the pathobiological role of key molecules linked to the fatty acid uptake and fatty acid oxidation pathways as metabolic biomarkers of anti-HER2 therapy resistance and to explore their inhibition as an innovative therapeutic strategy to increase anti-HER2 therapy efficacy in HER2-positive breast cancer patients.

Mentoring activity of Dr. Pupa has led to numerous Bachelor and Master of Science graduates as well as Doctors in Philosophy.

Scientific Associations:
Active Member since 1996 of American Association for Cancer Research (AACR), European Association of Cancer Research (EACR) and Italian Society of Cancer (SIC).

Dr. Pupa count numerous invitations to national and international conferences.

Il sottoscritto è a conoscenza che, ai sensi dell'art. 26 della legge 15/68, le dichiarazioni mendaci, la falsità negli atti e l'uso di atti falsi sono puniti ai sensi del codice penale e delle leggi speciali. Inoltre, il sottoscritto autorizza al trattamento dei dati personali, secondo quanto previsto dalla Legge 196/03
-

Firma

Milano, 7 April 2025

The results obtained throughout her career are reported in more than 90 papers published in peer-reviewed journals-data according to Scopus: total n. citations without self citations: **5.167**; H-index **37.**

References (last 5 years)

Castagnoli L, Franceschini A, Cancila V, Dugo M, Bigliardi M, Chiodoni C, Toneguzzo P, Regondi V, Corsetto PA, Pietrantonio F, Mazzucchelli S, Corsi F, Belfiore A, Vingiani A, Pruneri G, Ligorio F, Colombo MP, Tagliabue E, Tripodo C, Vernieri C, Triulzi T, **Pupa SM**. CD36 enrichment in HER2-positive mesenchymal stem cells drives therapy refractoriness in breast cancer. J Exp Clin Cancer Res. **2025** Jan 20;44(1):19.

Bianchi F, Le Noci V, Bernardo G, Gagliano N, Colombo G, Sommariva M, Palazzo M, Dalle-Donne I, Milzani A, **Pupa S**, Tagliabue E, Sfondrini L. Cigarette smoke sustains immunosuppressive microenvironment inducing M2 macrophage polarization and viability in lung cancer settings. PLoS One **2024**;19(5):e0303875.

Mazzucchelli S, Signati L, Messa L, Franceschini A, Bonizzi A, Castagnoli L, Gasparini P, Consolandi C, Mangano E, Pelucchi P, Cifola I, Camboni T, Severgnini M, Villani L, Tagliaferri B, Carelli S, **Pupa SM**, Cereda C, Corsi F. Breast cancer patient-derived organoids for the investigation of patient-specific tumour evolution. Cancer Cell Int. **2024** Jun 27;24(1):220.

Sommariva M, Dolci M, Triulzi T, Ambrogi F, Dugo M, De Cecco L, Le Noci V, Bernardo G, Anselmi M, Montanari E, **Pupa SM**, Signorini L, Gagliano N, Sfondrini L, Delbue S, Tagliabue E. Impact of in vitro SARS-CoV-2 infection on breast cancer cells. Sci Rep. 2024 Jun 7;14(1):13134.

Bernardo G, Le Noci V, Di Modica M, Montanari E, Triulzi T, **Pupa SM**, Tagliabue E, Sommariva M, Sfondrini L. The Emerging Role of the Microbiota in Breast Cancer Progression. *Cells* **2023** Jul 27;12(15):1945.

Castagnoli L, Corso S, Franceschini A,·Raimondi A,·Bellomo SE, Dugo M, Morano F, Prisciandaro M, Brich S, Belfiore A, Vingiani A, Di Bartolomeo M, Pruneri G, Tagliabue E, Giordano S, Pietrantonio F, **Pupa SM**. Fatty acid synthase as a new therapeutic target for HER2-positive gastric cancer. *Cell. Oncol.* **2023;** Jun;46(3):661-676

Pietrantonio F, Manca P, Bellomo SE, Corso S, Raimondi A, Berrino E, Morano F, Migliore C, Niger M, Castagnoli L, **Pupa SM**, Marchiò C, Di Bartolomeo M, Restuccia E, Lambertini C, Tabernero J, Giordano S. HER2 copy number and resistance mechanisms in patients with HER2-positive advanced gastric cancer receiving initial trastuzumab-based therapy in JACOB trial. *Clin Cancer Res*. **2023**; 29(3):571-580.

Ligorio F, Di Cosimo S, Verderio P, Ciniselli CM, Pizzamiglio S, Castagnoli L, Dugo M, Galbardi B, Salgado R, Loi S, Michiels S, Triulzi T, Tagliabue E, El-Abed S, Izquierdo M, de Azambuja E, Nuciforo P, Huober J, Moscetti L, Janni W, Coccia-Portugal MA, Corsetto PA, Belfiore A, Lorenzini D, Daidone MG, Vingiani A, Gianni L, **Pupa SM**, Bianchini G, Pruneri G, Vernieri C. Predictive role of CD36 expression in HER2-positive breast cancer patients receiving neoadjuvant trastuzumab. *J Natl Cancer Inst* **2022**, djac126.

De Santis F, Romero-Cordoba, SL, Castagnoli L, Volpari, T, Faraci S, Fucà, G, Tagliabue E, De Braud F, ***Pupa SM,** *Di Nicola M. BCL6 and the Notch patway: a signaling axis leading to a novel druggable biotarget in triple negative breast cancer. *Cell. Oncol.* **2022**, 45(2):257-274.

Fucà G, Ambrosini M, Agnelli L, Brich S, Sgambelluri F, Mortarini R, **Pupa SM,** Magni M, Devizzi L, Matteucci P, Cabras A, Zappasodi R, De Santis F, Anichini A, De Braud F, Gianni AM, Di Nicola M. Fifteen-year follow-up of relapsed indolent non-Hodgkin lymphoma patients vaccinated with tumor-loaded dendritic cells. *J Immunother. Cancer* **2021**, 9, e002240.

Lecchi M, Verderio P, Cappelletti V, De Santis F, Paolini B, Monica M, Sangaletti S, **Pupa SM,** Iorio MV, Bianchi G, Gennaro M, Fucà G, De Braud F, Tagliabue E, Di Nicola M. A combination of extracellular matrix- and interferon-associated signatures identifies high-grade breast cancers with poor prognosis. *Mol Oncol* **2021**, 15, 1345-1357.

Ligorio F, Zambelli L, Bottiglieri A, Castagnoli L, Zattarin E, Lobefaro R, Ottini A, Vingiani A, **Pupa SM,** Bianchi G, Capri G, Pruneri G, de Braud F, Vernieri C. Hormone receptor status influences the impact of Body Mass Index and hyperglycemia on the risk of tumor relapse in early-stage HER2-positive breast cancer patients. *Ther. Adv. Med. Oncol* **2021**, 13, 17588359211006960.

Ligorio F, Pellegrini I, Castagnoli L, Vingiani A, Lobefaro R, Zattarin E, **Pupa SM,** Pruneri G, De Braud F, Vernieri C. Targeting lipid metabolism is an emerging strategy to enhance the efficacy of anti-HER2 therapiesin HER2-positive breast cancer. *Cancer Lett* **2021**, 511, 77-87.

Morello G, Cancila V, La RM, Germano G, Lecis D, Amodio V, Zanardi F, Iannelli F, Greco D, La Paglia L, Fiannaca A, Urso AM, Graziano G, Ferrori F, **Pupa SM,** Sangaletti S, Chiodoni C, Pruneri G, Bardelli A, Colombo MP, Tripodo C. T Cells Expressing Receptor Recombination/Revision Machinery Are Detected in the Tumor Microenvironment and Expanded in Genomically Over-unstable Models. *Cancer Immunol Res.* **2021**, 9, 825-837.

Pupa SM, Ligorio F, Cancila V, Franceschini A, Tripodo C, Vernieri C, Castagnoli L. HER2 signaling and breast cancer stem cells: The Bridge behind HER2-positive breast cnacer aggressiveness and therapy refractoriness. *Cancers* **2021**, 13, 4778.

Castagnoli L, De Santis F, Volpari T, Vernieri C, Tagliabue E, Di Nicola M, **Pupa SM**. Cancer Stem Cells: Devil or Savior-Looking behind the Scenes of Immunotherapy Failure. *Cells* **2020** Feb 27;9(3):E555.

Castagnoli L, Tagliabue E, **Pupa SM**. Inhibition of the Wnt signalling pathway: an avenue to control breast cancer aggressiveness. *Int J Mol Sci.* **2020**; 21: E9069.

Volpari T, De Santis F, Bracken AP, **Pupa SM**, Buschbeck M, Wegner A, Di Cosimo S, Lisanti MP, Dotti G, Massaia M, Pruneri G, Anichini A, et al. Anticancer innovative therapy: Highlights from the ninth annual meeting. *Cytokine Growth Factor Rev* **2020** Feb;51:1-9.