

BIOGRAPHICAL SKETCH

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NAME: Simone Puccio

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

POSITION TITLE: Senior Bioinformatician

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Tor Vergata, Rome, Italy	MSc	03/2013	Bioinformatics
University of Milan, Italy	PHD	02/2017	Molecular and Translational Medicine
University of Milan-Bicocca, Italy	Specializing Master	04/2021	Data Analytics

A. Personal Statement

I am a bioinformatician and independent researcher with over a decade of experience in multi-omics data integration, immuno-oncology, and T cell biology. My research focuses on deciphering the molecular and spatial determinants of immune regulation in cancer, with emphasis on regulatory and stem-like T cells. I have contributed to the development of computational pipelines (e.g., CRUSTY, Interctome-Seq, Wopper) and bioinformatics tools for high-dimensional data analysis, enabling discoveries in both basic immunology and clinical oncology. My ongoing projects aim to identify predictive biomarkers of relapse in early-stage NSCLC and uncover the transcriptional and metabolic programs of T cell in cancer.

B. Positions, Scientific Appointments, and Honors**Positions and Scientific Appointments**

2022– Present	Researcher, National Research Council (CNR-IRGB), Milan, Italy
2022– Present	Visiting Researcher, Humanitas Research Hospital, Milan, Italy
2018–2021	Grant Fellow, Humanitas Research Hospital, Milan, Italy
2013 – 2017	Grant Fellow, CNR-ITB, Milan, Italy
2012 – 2013	Student Trainee, Temple University, Fels Institute for Cancer Research, Philadelphia, PA
2008 – 2010	Visiting Research Scholar, Temple University, Department of Pharmacology, Philadelphia, PA

Honors

2018 AIRC fellowship “Francesco Saccon”; project title “Defining the core gene expression of stem-like T cell differentiation to ameliorate the anti-tumor activity of CAR T cells.” (2018-2021) 2019

C. Contributions to Science

1. T cell biology & immunotherapy

My early publications directly addressed the molecular and metabolic programs that regulate T cell differentiation and function in cancer. In particular, these studies demonstrated that transcription factors such as IRF4 drive effector regulatory T cell differentiation and immune suppression in human tumors, while stem-like CD8⁺ T cells represent a heterogeneous population with distinct developmental trajectories and therapeutic potential. Building on these insights, I contributed to work showing that antioxidant metabolism is a critical determinant of CD8⁺ memory stem cell formation and antitumor immunity, providing a mechanistic rationale for metabolic interventions to enhance T cell-based therapies. More recently, my work has extended into translational applications, documenting how depletion of regulatory T cells enhances myeloid cell activation and immunotherapy response in glioblastoma, and how common drugs such as aspirin can restore T cell immunity and prevent metastasis by targeting platelet-derived pathways. Together, this body of work documents fundamental mechanisms of T cell biology while also identifying practical strategies to improve immunotherapy outcomes. By bridging basic immunology with translational relevance, these publications provide a roadmap for leveraging transcriptional, metabolic, and pharmacological interventions to enhance antitumor T cell immunity. I served as co-investigator in all of these studies and contributed to data analysis, interpretation, and manuscript preparation.

- a. Alvisi G, Brummelman J, **Puccio S**, et al. IRF4 instructs a molecular program of effector Treg differentiation and immune suppression in human cancer. *J Clin Invest*. 2020.
- b. Galletti S, De Simone G, Mazza EMC, Puccio S, et al. Two subsets of stem-like CD8⁺ memory T cell progenitors with distinct fate commitments in humans. *Nat Immunol*. 2020.
- c. Pilipow K, Scamardella E, Puccio S, et al. Antioxidant metabolism regulates CD8⁺ T memory stem cell formation and antitumor immunity. *JCI Insight*. 2018.
- d. Galvez-Cancino F, Navarrete M, Beattie G, Puccio S, et al. Regulatory T cell depletion promotes myeloid cell activation and glioblastoma response to anti-PD1 and tumor-targeting antibodies. *Immunity*. 2025.
- e. Yang J, Yamashita-Kanemaru Y, Morris BI, Puccio S, et al. Aspirin prevents metastasis by limiting platelet TXA2 suppression of T cell immunity. *Nature*. 2025.

2. Bioinformatics tools & computational pipelines

My work has consistently addressed the need for robust and accessible computational platforms to analyze high-dimensional biological data. Recognizing the increasing complexity of single-cell and flow cytometry datasets, I have developed CRUSTY, a web-based platform for rapid visualization and interpretation of cytometry data, and Cytophenograph, a pipeline that applies scalable clustering and machine learning approaches to uncover cellular heterogeneity. Earlier, I contributed to the development of WoPPER and Interactome-Seq, webserver designed for prokaryotic and host-pathogen studies. These efforts provided the research community with practical tools that continue to facilitate the analysis of large-scale data across immunology, oncology, and microbiology. By creating accessible platforms and algorithms, this body of work has accelerated discovery and enabled scientists without advanced computational training to engage directly with high-dimensional datasets. I served as developer and co-investigator in these projects, leading software design, pipeline implementation, and dissemination.

- a. **Puccio S**, Grillo G, Alvisi G, et al. CRUSTY: a versatile web platform for high-dimensional flow cytometry data. *Nat Commun*. 2023.
- b. **Puccio S** & Grillo G, et al. WoPPER: webserver for position related data analysis of gene expression in prokaryotes. *Nucleic Acids Res*. 2017.
- c. Di Salvo M, Puccio S, Peano C, et al. RhoTermPredict: an algorithm for predicting Rho-dependent transcription terminators. *BMC Bioinformatics*. 2019.
- d. Soluri MF, **Puccio S**, Caredda G, et al. Interactome-Seq: A Protocol for Domainome Library Construction, Validation and Selection by Phage Display and Next Generation Sequencing. *J Vis Exp*. 2018.

3. High-dimensional single-cell & multi-omics integration

As single-cell technologies emerged, my research focused on integrating multi-modal data to capture the complexity of immune responses in cancer. I contributed to multimodal single-cell profiling of intrahepatic cholangiocarcinoma, which revealed hyperactivated regulatory T cells as a therapeutic target, and to studies characterizing the adaptive immune response during hematopoietic stem cell transplantation through combined transcriptomic and TCR-seq analyses. In other projects, I helped identify circulating mucosal-associated invariant T cells as predictors of response to checkpoint blockade, providing one of the earliest examples of immune correlates derived from high-dimensional profiling. Collectively, these publications document the power of integrating transcriptomic, epigenomic, and repertoire data to uncover new mechanisms of immune regulation and to stratify patients by therapeutic potential. My contributions spanned data integration, computational analysis, and the translation of complex datasets into biologically meaningful hypotheses.

- a. Alvisi G, Puccio S, et al. Multimodal single-cell profiling of intrahepatic cholangiocarcinoma defines hyperactivated Tregs as therapeutic target. *J Hepatol*. 2022.
- b. Van Beek J, Roberto A, Puccio S, et al. Single-cell profiling reveals dynamics of CMV-specific T cells in HSCT. *Haematologica*. 2021.
- c. De Biasi S, Gibellini L, Puccio S, et al. Circulating MAIT cells identify patients responding to anti-PD-1 therapy. *Nat Commun*. 2021.
- d. Mukherjee S, Garda C, Boffa L, Puccio S, et al. Tumor-associated neutrophil precursors impair homologous DNA repair and promote sensitivity to PARP inhibition. *Nat Commun*. 2025.

4. Clinical & translational immunology

I co-authored studies demonstrating an autoimmune-like mechanism in heart failure that enables vaccine-based prevention, showing how immunological insights can be translated into novel therapeutic strategies. I also contributed to research documenting how sodium chloride enhances CD8⁺ T cell effector functions in cancer immunotherapy, and to work establishing that persistence of KIR-negative NK cells after transplantation protects against CMV reactivation. These studies illustrate how combining computational biology with clinical cohorts can reveal actionable immune mechanisms with direct implications for therapy. Together, this body of work advances our understanding of how immune regulation contributes to disease outcome and provides translational avenues to harness these mechanisms for patient benefit. I served as co-investigator in all of these projects, with a focus on study design, computational analysis, and integration of findings into clinical contexts.

- a. Marelli G, Morina N, Puccio S, et al. Chemosensor receptors are lipid-detecting regulators of macrophage function in cancer. *Nat Immunol*. 2025.
- b. Milardi G, Franceschini B, Camisaschi C, Puccio S, et al. Immunosuppressive contribution of tumour-infiltrating B cells in intrahepatic cholangiocarcinoma and their role in chemoimmunotherapy outcome. *Gut*. 2025.
- c. Martini E, Cremonesi M, Puccio S, et al. Autoimmune-like mechanism in heart failure enables preventive vaccine therapy. *Circ Res*. 2025.
- d. Scirgolea C, Sottile R, Puccio S, et al. NaCl enhances CD8⁺ T cell effector functions in cancer immunotherapy. *Nat Immunol*. 2024.
- e. Di Vito C, Coianiz N, Puccio S, et al. Persistence of KIRneg NK cells after HSCT protects from CMV. *Front Immunol*. 2024.
- f. Carnevale S, Ponzetta A, Rigatelli A, Puccio S, et al. Neutrophils mediate protection against colitis and carcinogenesis. *Cancer Immunol Res*. 2024.