

BIOGRAPHICAL SKETCH

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NAME: **Salvatore Piscuoglio**

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

POSITION TITLE: **Associate Professor of Genetics**

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 Naples, "Federico II", Naples, Italy	B.Sc.	12/2005	Biotechnology for the Health
University of Naples, "Federico II", Naples, Italy	M.Sc.	03/2008	Medical and Pharmaceutical Biotechnology
University of Basel, Basel, Switzerland	Ph. D.	11/2012	Human Genetics
Memorial Sloan Kettering Cancer Center, New York, US	Postdoctoral	02/2016	Cancer omics
Certificate of Advanced Studies Clinical Research I	Post graduate education	09/2019	Clinical Trial Planning and Conduct
Executive MBA Candidate	Master degree	07/2025	Executive MBA

A. Personal Statement

I obtained my degree in Medical Biotechnology from the University of Naples "Federico II" in 2008, followed by a PhD in Genetics at the University of Basel (Switzerland) in 2012. After completing my doctoral studies, I joined the Memorial Sloan Kettering Cancer Center in New York as a postdoctoral researcher in 2013. There, I focused on characterizing human cancers using omics technologies to discover new biomarkers, identify therapeutic targets, and elucidate genotype-to-phenotype associations. This foundational experience fueled my commitment to understanding cancer biology through cutting-edge technologies.

In 2016, I transitioned to the role of group leader at the Institute of Medical Genetics and Pathology at the University Hospital Basel. By 2019, I expanded my responsibilities as a group leader in the Department of Biomedicine at the University of Basel and as co-director of research at the Institute of Medical Genetics and Pathology. These roles allowed me to delve deeper into translating genetic insights into actionable therapeutic strategies. In 2024, I joined Humanitas as an Associate Professor of Genetics, where I continue to pursue research at the intersection of genetics and oncology.

My current research is focused on defining clinically relevant predictive biomarkers of therapeutic response and resistance while identifying novel drug targets. To achieve these goals, I employ a multi-modal approach that integrates computational predictions, multi-omics profiling, and ex-vivo drug testing. This comprehensive methodology enables a deeper understanding of cancer biology and facilitates the identification of therapeutic strategies tailored to individual tumors. Recognizing the need for models that replicate the molecular diversity and microenvironment of cancer, my lab has processed over 1,000 tumors and successfully developed more than 150 patient-derived organoids across various cancer types. We are advancing this effort by creating 3D models that preserve tumor tissue architecture, thereby better mimicking the pathophysiological context of

cancers. These models serve as valuable platforms for multi-omics profiling, large-scale drug screening, toxicity studies, and the discovery of critical cellular interactions that drive tumor progression.

Cancer's complexity arises from alterations in numerous genes and pathways, posing challenges for effective treatment development. My research seeks to address these challenges by uncovering novel cancer genes, identifying biomarkers of therapy response and resistance, and discovering new drug targets. By leveraging high-throughput technologies—genomics, transcriptomics, proteomics, and metabolomics—we explore the genetic and biochemical pathways that become dysregulated in cancer cells. These insights guide the identification of potential therapeutic targets, which we further characterize through cell-based assays, in vitro and in vivo models, and structural biology techniques.

Our approach culminates in testing therapeutic compounds, including small molecule inhibitors, monoclonal antibodies, and gene therapies, on patient-derived organoids and tumor fragments. This strategy ensures that we target specific molecular pathways essential for cancer cell survival, enabling selective eradication of malignant cells. By bridging foundational research with clinical applications, my work aims to pave the way for innovative and effective treatments for cancer patients.

B. Positions, Scientific Appointments, and Honors

• Current positions

2024 - present **Associate Professor in Genetics**, Humanitas University, Pieve Emanuele, Milan, Italy
2024 - present **Head of the Precision Medicine Research Laboratory**, Humanitas Research Hospital, Rozzano, Milan, Italy

• Previous positions

2019 - 2023 **Head of Research**, Institute of Pathology and Medical Genetics, University Hospital Basel, Basel, Switzerland
2019 - 2023: **Group Leader** (Visceral Surgery and Precision Medicine Research Laboratory), Department of Biomedicine, Basel, Switzerland
2016 - 2023: **Principal Research Investigator**, Institute of Pathology and Medical Genetics, University Hospital Basel, Basel, Switzerland
2013 - 2016: **Research Fellow**, Memorial Sloan Kettering Cancer Center, New York, US

• Honors

07/2021 Professor Dr. Max Cloetta Foundation Medical Fellowship (Switzerland)
01/2020 Swiss Foundation against Liver Cancer 2019 Award (Switzerland)
01/2017 Swiss National Science Foundation: Ambizione Grant Award (Switzerland)
05/2014 Susan G Komen Basic/Translational Research Fellowship Award (United States)
02/2013 Swiss National Science Foundation (early post-doc mobility) Award (Switzerland)

C. Contributions to Science

My lab has made significant contributions to cancer treatment through the development of clinically relevant predictive biomarkers and the discovery of novel therapeutic targets. By combining computational predictions, multi-omics, and ex-vivo drug profiling, we have pioneered a targeted approach that uncovers critical genetic and biochemical pathways involved in cancer. One of our most notable achievements is the development of the APSiC and SLiDr frameworks, which enable high-throughput analysis of perturbation screens. These methods have allowed us to systematically identify synthetic lethal interactions and crucial pathway drivers, such as those within Wnt/ β -catenin and Hippo signaling, that are essential for tumor growth and survival. Using this methodology, our lab was the first to establish synthetic lethality between GATA3 and MDM2 in estrogen receptor-positive breast cancers, positioning MDM2 as a promising target for GATA3-mutant patients. clinical trial ongoing (NCT04872166).

Our work has significant implications for integrating multi-omics data in precision oncology. We demonstrated this by combining whole-exome sequencing and DNA methylation analysis in prostate cancer brain metastasis (PCBM), where we identified that the methylation landscapes are closely associated with specific driver mutations, such as SPOP and TMPRSS2-ERG fusions. This integration reveals that genetic backgrounds significantly influence the epigenetic landscape, providing valuable insights for targeted therapy development. In hepatocellular carcinoma (HCC), we further integrated methylation, transcriptomic, and genomic data to illustrate how chronic liver disease (CLD) epigenetically primes cells, creating a landscape conducive to oncogenesis and poor prognosis in HCC. This comprehensive multi-omics approach underscores the role of epigenetic priming in cancer progression and highlights new avenues for therapeutic intervention.

Additionally, in all our studies, we have pioneered the use of patient-derived organoids (PDOs) as robust preclinical models. Having processed over 1,000 tumor samples and generated more than 150 PDOs, our lab has created a unique repository that mirrors patient tumor diversity, facilitating high-throughput drug screening and toxicity studies. For instance, in colorectal cancer, we identified adenylosuccinate lyase (ADSL) as a driver of tumor growth, using PDOs to validate its utility as a predictive biomarker for antimetabolite response. This discovery is opening new pathways for precision treatment in colorectal cancers overexpressing ADSL. In cancer immunotherapy, our lab has leveraged PDOs to assess the toxicity of T-cell-engaging bispecific antibodies. By co-culturing PDOs with immune cells, we successfully modeled on-target, off-tumor toxicities, providing a more accurate platform for assessing immunotherapy safety and efficacy, especially in cancers with complex immune profiles.

Through these achievements, my lab has positioned itself at the forefront of translational oncology, significantly advancing cancer therapy and facilitating new personalized treatment strategies.

Selected research outputs (last 5 years)

1	Borrelli C, Roberts M, Eletto D, Hussherr MD, Fazilaty H, Valenta T, Lafzi A, Kretz JA, Vinzoni EG, Karakatsani A, Adivarahan S, Mannhart A, Kimura S, Meijs A, Mhamedi FB, Acar IE, Handler K, Ficht X, Platt RJ, Piscuoglio S, Moor AE. In vivo interaction screening reveals liver-derived constraints to metastasis. <i>Nature</i>. 2024 Aug;632(8024):411-418. <i>In this study, we utilized in vivo interaction screening combined with organoid models to uncover liver-derived factors that impose constraints on metastasis. Our findings demonstrate how the liver microenvironment, as modelled in organoids, influences and restricts metastatic spread, offering new insights into potential therapeutic strategies to limit metastasis progression. Relation to proposed project: organoid modelling, drug screening.</i>
2	Harter MF, Recaladin T, Gerard R, Avignon B, Bollen Y, Esposito C, Guja-Jarosz K, Kromer K, Filip A, Aubert J, Schneider A, Bacac M, Bscheider M, Stokar-Regenscheit N, Piscuoglio S, Beumer J, Gjorevski N. Analysis of off-tumour toxicities of T-cell-engaging bispecific antibodies via donor-matched intestinal organoids and tumouroids. <i>Nat Biomed Eng</i>. 2024 Apr;8(4):345-360. <i>In this study, we analysed the off-tumor toxicities of T-cell-engaging bispecific antibodies using donor-matched intestinal organoids and tumoroids. This research demonstrates that the use of organoids allows for precise assessment of potential adverse effects on healthy tissues while retaining the therapeutic effectiveness against tumor cells, contributing to the development of safer and more effective cancer immunotherapies. Relation to proposed project: organoid modelling.</i>
3	Gallon J, Rodriguez-Calero A, Benjak A, Akhoundova D, Maletti S, Amstutz U, Hewer E, Genitsch V, Fleischmann A, Rushing EJ, Grobholz R, Fischer I, Jochum W, Cathomas G, Osunkoya AO, Bubendorf L, Moch H, Thalmann G, Feng FY, Gillissen S, Ng CKY, Rubin MA and Piscuoglio S. DNA Methylation Landscapes of Prostate Cancer Brain Metastasis Are Shaped by Early Driver Genetic Alterations. <i>Cancer Res</i>. 2023 Apr 14; 83(8): 1203–1213. <i>We explored the DNA methylation landscapes of prostate cancer brain metastasis, revealing that early driver genetic alterations play a crucial role in shaping these epigenetic patterns. Our findings highlight the interplay between genetic mutations and DNA methylation in brain metastases, offering potential avenues for therapeutic intervention and understanding disease progression in metastatic prostate cancer. Relation to proposed project: methylome analysis.</i>

4	Srivatsa S, Montazeri H, Bianco G, Coto-Llerena M, Marinucci M, Ng CKY, Piscuoglio S*, Beerenwinkel N*. Discovery of synthetic lethal interactions from large-scale pan-cancer perturbation screens. Nat Commun. 2022 Dec 14;13(1):7748. *Co-corresponding <i>The study leverages large-scale pan-cancer perturbation screens to identify synthetic lethal interactions across diverse cancer types. Using CRISPR and RNAi-based approaches coupled with a novel statistical framework, we systematically investigated perturbed cancer cell lines, uncovering novel gene pairs whose co-inhibition leads to selective cancer cell death. By integrating genomic and transcriptomic data, the study highlights key vulnerabilities in cancer cells, paving the way for precision medicine strategies aimed at co-targeting these synthetic lethal pairs. This research provides a comprehensive resource for identifying therapeutic targets that could be exploited across various cancer subtypes. Relation to proposed project: Synthetic lethality, patient-derived organoids, drug testing, multi-ome analysis.</i>
5	Rodriguez-Calero A, Gallon J, Akhoundova D, Maletti S, Ferguson A, Cyrt J, Amstutz U, Garofoli A, Paradiso V, Tomlins SA, Hwer E, Genitsch V, Fleischmann A, Vassella E, Rushing EJ, Grobholz R, Fischer I, Jochum W, Cathomas G, Osunkoya AO, Bubendorf L, Moch H, Thalmann G, Ng CKY, Gillesen S, Piscuoglio S*, Rubin MA*. Alterations in homologous recombination repair genes in prostate cancer brain metastases. Nat Commun. 2022 May 3;13(1):2400. *(Co-corresponding) <i>This study focuses on the genomic landscape of prostate cancer brain metastases, particularly alterations in homologous recombination repair (HRR) genes. By utilizing comprehensive genomic profiling, including whole-exome sequencing and copy number analysis, we identified recurrent mutations and deletions in key HRR pathway genes such as BRCA1, BRCA2, and ATM. These alterations may confer increased vulnerability to DNA-damaging agents, such as PARP inhibitors, offering potential therapeutic avenues for patients with advanced metastatic prostate cancer. The study emphasizes the clinical significance of HRR deficiencies in brain metastases, providing insights into precision oncology strategies. Relation to proposed project: Omics analysis.</i>
6	Bianco G, Coto-Llerena M, Gallon J, Kancherla V, Taha-Mehlitz S, Marinucci M, Konantz M, Srivatsa S, Montazeri H, Panebianco F, Tirunagaru VG, De Menna M, Paradiso V, Ercan C, Dahmani A, Montaudon E, Beerenwinkel N, Kruithof-de Julio M, Terracciano LM, Lengerke C, Jeselsohn RM, Doebele RC, Bidard FC, Marangoni E, Ng CKY*, Piscuoglio S*. GATA3 and MDM2 are synthetic lethal in estrogen receptor-positive breast cancers. Commun Biol. 2022 Apr 19;5(1):373. *Co-corresponding <i>By mining a high-throughput shRNA screen, we discovered and validated the synthetic lethal interactions between GATA3 and MDM2 in breast cancer. We demonstrated that depletion and pharmacological inhibition of MDM2 significantly impaired tumor growth in GATA3-deficient models in vitro, in vivo and in patient-derived organoids/xenograft (PDOs/PDX) harboring GATA3 somatic mutations. Our results present MDM2 as a therapeutic target in a substantial fraction of breast cancer patients. Relation to proposed project: synthetic lethality, patient-derived organoids, drug testing, transcriptomic analysis.</i>
7	Gallon J, Coto-Llerena M, Ercan C, Bianco G, Paradiso V, Nuciforo S, Taha-Melitz S, Meier MA, Boldanova T, Pérez-Del-Pulgar S, Rodríguez-Tajes S, von Flüe M, Soysal SD, Kollmar O, Llovet JM, Villanueva A, Terracciano LM, Heim MH, Ng CKY, Piscuoglio S. Epigenetic priming in chronic liver disease impacts the transcriptional and genetic landscapes of hepatocellular carcinoma. Mol Oncol. 2022 Feb;16(3):665-682. <i>This study investigates how epigenetic changes in chronic liver disease (CLD) influence the transcriptional and genetic landscape of hepatocellular carcinoma (HCC). By analyzing patient-derived samples, we identified that chronic liver injury primes the epigenome, rendering liver cells more susceptible to malignant transformation. The study uncovers key epigenetic alterations that drive transcriptional dysregulation in HCC, providing insights into the progression of CLD to cancer. Integrating multi-omic approaches, the research highlights potential biomarkers and therapeutic targets for HCC, emphasizing the role of epigenetic priming in the development of liver cancer. Relation to proposed project: multi-ome analysis, AI-model.</i>
8	Taha-Mehlitz S, Bianco G, Coto-Llerena M, Kancherla V, Bantug GR, Gallon J, Ercan C, Panebianco F, Eppenberger-Castori S, von Strauss M, Staubli S, Bolli M, Peterli R, Matter MS, Terracciano LM, von Flüe M, Ng CKY, Soysal SD, Kollmar O, Piscuoglio S. Adenylosuccinate lyase is oncogenic in colorectal cancer by causing mitochondrial dysfunction and independent activation of NRF2 and mTOR-MYC-axis. Theranostics. 2021 Feb 15;11(9):4011-4029.

	<i>In this study, we identified adenylosuccinate lyase (ADSL) as a novel oncogenic driver in colorectal cancer (CRC). By integrating genomic, transcriptomic, and functional assays, we demonstrated that ADSL overexpression leads to mitochondrial dysfunction, triggering a metabolic shift that promotes tumorigenesis. The study uncovers a dual mechanism where ADSL independently activates the NRF2 antioxidant pathway and the mTOR-MYC axis, both of which are critical for cancer cell survival and proliferation. These findings suggest that ADSL plays a central role in CRC pathogenesis and could be a potential therapeutic target. This research provides valuable insights into CRC metabolic vulnerabilities, providing opportunities for targeted interventions. Relation to proposed project: patient-derived organoids, drug testing, multi-ome analysis.</i>
9	Montazeri H, Coto-Llerena M, Bianco G, Zangene E, Taha-Mehlitz S, Paradiso V, Srivatsa S, de Weck A, Roma G, Lanzafame M, Bolli M, Beerenwinkel N, von Flöe M, Terracciano LM, Piscuoglio S*, Ng CKY*. Systematic identification of novel cancer genes through analysis of deep shRNA perturbation screens. Nucleic Acids Res. 2021 Sep 7;49(15):8488-8504. *Co-corresponding <i>We developed APSiC (Analysis of Perturbation Screens for identifying novel Cancer genes) to identify genetic drivers and effectors in perturbation screens even with few samples. Applying APSiC to a large shRNA screen, we identified well-known and novel putative mutational and amplified cancer genes. We also discovered tumor-promoting and tumor-suppressive effectors, including genes involved in cell cycle control, Wnt/β-catenin and hippo signalling pathways. We functionally demonstrated that LRRC4B is a novel tumor-suppressive effector in breast cancer. Relation to proposed project: algorithm development, statistical methods, perturbation screens.</i>
10	Cyrtta J, Augspach A, De Filippo MR, Prandi D, Thienger P, Benelli M, Cooley V, Bareja R, Wilkes D, Chae SS, Cavaliere P, Dephoure N, Uldry AC, Braga Lagache S, Roma L, Cohen S, Jaquet M, Brandt LP, Alshalalfa M, Puca L, Sboner A, Feng F, Wang S, Beltran H, Lotan T, Spahn M, Kruithof-de Julio M, Chen Y, Ballman KV, Demichelis F, Piscuoglio S, Rubin MA. Role of specialized composition of SWI/SNF complexes in prostate cancer lineage plasticity. Nat Commun. 2020 Nov 3;11(1):5549. *(Co-senior) <i>This study investigates the role of SWI/SNF chromatin remodelling complexes in driving lineage plasticity in prostate cancer, a key mechanism enabling cancer cells to adopt treatment-resistant phenotypes. By analysing prostate cancer models, including patient-derived organoids and xenografts, we uncovered how specific subunit compositions of the SWI/SNF complex influence the transition from androgen receptor (AR)-dependent states to neuroendocrine-like states. We demonstrate that alterations in these complexes contribute to therapy resistance, shedding light on molecular mechanisms underlying cancer progression and offering potential new therapeutic targets for overcoming resistance in prostate cancer. The study emphasizes the importance of SWI/SNF dynamics in maintaining cancer cell plasticity, particularly in response to AR-targeting therapies. Relation to proposed project: organoids, chromatin remodelling, multi-omic analysis and drug testing.</i>

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