

BIOGRAPHICAL SKETCH

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NAME: **Lovisa, Sara**

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

POSITION TITLE: **Junior Group Leader**

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)	END DATE MM/YYYY	FIELD OF STUDY
University of Padua (Italy)	BS	09/2005	Biotechnology
University of Padua (Italy)	MS	03/2008	Medical Biotechnology
University of Udine (Italy)	PHD	05/2012	Clinical Science and Technology
University of Texas MD Anderson Cancer Center (Houston, Texas)	Postdoctoral Fellow	02/2020	Tissue fibrosis and tumor microenvironment
Humanitas Research Hospital (Rozzano, Italy)	Postdoctoral Fellow	03/2021	Tissue fibrosis

A. Personal Statement

I am strongly committed to unravel mechanisms of maladaptive wound repair and tissue fibrosis that will translate into effective predictive and therapeutic solutions for patients with chronic inflammatory diseases and at risk of developing cancer. After my initial training in cancer during my graduate studies, in 2013 I joined the laboratory of Prof. Raghu Kalluri for my postdoctoral training at MD Anderson Cancer Center (Houston, TX). There I gained expertise on fibrosis and the role of the fibrotic microenvironment in tumor progression. My work has led to identifying the functional role of epithelial and endothelial plasticity in fibrosis (Lovisa&LeBleu at al., *Nat Med* 2015; Lovisa et al., *Sci Signal* 2020), and the contribution of distinct cell types to Collagen I deposition (Lovisa et al., *in preparation*; Chen et al. *Nat Comms* 2021). I also worked on epithelial reprogramming mechanisms associated with a genetic form of a fibrotic disease (LeBleu et al., *Life Sci Alliance* 2024). In 2020 I returned to Italy supported by a fellowship to work in the laboratory of Prof. Silvio Danese at Humanitas Research Hospital where I expanded my fibrosis expertise to the field of intestinal disease. In 2021 I started my independent career as Junior Group Leader at Humanitas Research Hospital and Humanitas University where I lead the Plasticity, Fibrosis and Cancer Lab. My laboratory is focused on understanding cellular and molecular mechanisms underlying tissue injury and fibrosis, as well as studying mechanisms of neoplastic transformation associated with chronic inflammatory conditions.

1. LeBleu V, Kanasaki K, **Lovisa S**, Alge J, Kim J, Chen Y, Teng Y, Gerami-Naini B, Sugimoto H, Kato N, Revuelta I, Grau N, Sleeman J, Taduri G, Kizu A, Rafii S, Hochedlinger K, Quaggin S, Kalluri R. Genetic reprogramming with stem cells regenerates glomerular epithelial podocytes in Alport syndrome. ***Life Science Alliance***. 2024 April 01; 7(6):e202402664-. Available from: <https://www.life-science-alliance.org/lookup/doi/10.26508/lsa.202402664> DOI: 10.26508/lsa.202402664
2. Chen Y, Yang S, **Lovisa S**, Ambrose C, McAndrews K, Sugimoto H, Kalluri R. Type-I collagen produced by distinct fibroblast lineages reveals specific function during embryogenesis and Osteogenesis Imperfecta. ***Nature Communications***. 2021 December 10; 12(1):- . Available from: <https://www.nature.com/articles/s41467-021-27563-3> DOI: 10.1038/s41467-021-27563-3

3. **Lovisa S**, Fletcher-Sananikone E, Sugimoto H, Hensel J, Lahiri S, Hertig A, Taduri G, Lawson E, Dewar R, Revuelta I, Kato N, Wu CJ, Bassett RL Jr, Putluri N, Zeisberg M, Zeisberg EM, LeBleu VS, Kalluri R. Endothelial-to-mesenchymal transition compromises vascular integrity to induce Myc-mediated metabolic reprogramming in kidney fibrosis. *Sci Signal*. 2020 Jun 9;13(635) PubMed Central PMCID: PMC7790440.
4. **Lovisa S**, LeBleu VS, Tampe B, Sugimoto H, Vadrnagara K, Carstens JL, Wu CC, Hagos Y, Burckhardt BC, Pentcheva-Hoang T, Nischal H, Allison JP, Zeisberg M, Kalluri R. Epithelial-to-mesenchymal transition induces cell cycle arrest and parenchymal damage in renal fibrosis. *Nat Med*. 2015 Sep;21(9):998-1009. PubMed Central PMCID: PMC4587560.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2021 -	Junior Group Leader, Humanitas Research Hospital and Humanitas University, Milan
2020 - 2021	Research Fellow, Humanitas Research Hospital, Milan
2013 - 2020	Postdoctoral Fellow, The University of Texas MD Anderson Cancer Center, Houston, TX
2012 - 2013	Postdoctoral Intern, CRO National Cancer Institute
2009 - 2012	Ph.D. student, CRO National Cancer Institute
2007 - 2008	M.Sc. student intern and Pre-doctoral fellow, CRO National Cancer Institute
2005 - 2005	B.S. student intern, CRO National Cancer Institute, Aviano

Honors

2021 - 2023	Individual Fellowship, H2020 Marie Skłodowska-Curie Actions
2009 - 2011	Doctoral fellowship, University of Udine (Italy)
2020	Post-Doctoral Fellowship, Umberto Veronesi Foundation
2019	Travel Award, MD Anderson Cancer Center
2019	Thomas H. and Mayme P. Scott Endowed Fellowship Award, MD Anderson Cancer Center
2017	Travel scholarship, Keystone Symposium
2017	Young Investigator Award travel grant, ISSNAF
2017	Hogan Lovells Young Investigator Award Finalist, ISSNAF
2007	Lino Zanussi scholarship award for academic merit, City of Pordenone

C. Contribution to Science

1. Functional contribution of epithelial plasticity to tissue fibrosis. Epithelial-to-mesenchymal transition (EMT) is a critical process during embryonic development relaunched in pathological conditions such as cancer and organ fibrosis. In the context of fibrosis, EMT has been traditionally ascribed as the major process generating fibrosis-associated fibroblasts, although some studies even questioned the existence of this process. To assess the functional contribution of EMT during tissue fibrosis, I have generated novel mouse models to inhibit EMT through the genetic deletion of two EMT driving transcription factors, namely Twist and Snail. My work has led to the finding that EMT is an injury-induced response of the epithelium which contributes to the fibrogenic response by impairing epithelial cell functionality and regenerative capacity. Moreover, EMT further fuels tissue injury by modulating inflammation and the immune response at the site of the damage.
 - a. Rizzo G, Rubbino F, Elangovan S, Sammarco G, **Lovisa S**, Restelli S, Pineda Chavez SE, Massimino L, Lamparelli L, Paulis M, Maroli A, Roda G, Shalaby M, Carvello M, Foppa C, Drummond SP, Spaggiari P, Ungaro F, Spinelli A, Malesci A, Repici A, Day AJ, Armuzzi A, Danese S, Vetrano S. Dysfunctional Extracellular Matrix Remodeling Supports Perianal

Fistulizing Crohn's Disease by a Mechanoregulated Activation of the Epithelial-to-Mesenchymal Transition. **Cell Mol Gastroenterol Hepatol.** **2023**;15(3):741-764. PubMed Central PMCID: PMC9898761.

- b. **Lovisa S.** Epithelial-to-Mesenchymal Transition in Fibrosis: Concepts and Targeting Strategies. **Frontiers in Pharmacology.** **2021**; 12:-. Available from: <https://www.frontiersin.org/articles/10.3389/fphar.2021.737570/full> DOI: 10.3389/fphar.2021.737570
- c. **Lovisa S,** Zeisberg M, Kalluri R. Partial Epithelial-to-Mesenchymal Transition and Other New Mechanisms of Kidney Fibrosis. **Trends Endocrinol Metab.** **2016** Oct;27(10):681-695. PubMed PMID: 27372267.
- d. **Lovisa S,** LeBleu VS, Tampe B, Sugimoto H, Vадnagara K, Carstens JL, Wu CC, Hagos Y, Burckhardt BC, Pentcheva-Hoang T, Nischal H, Allison JP, Zeisberg M, Kalluri R. Epithelial-to-mesenchymal transition induces cell cycle arrest and parenchymal damage in renal fibrosis. **Nat Med.** **2015** Sep;21(9):998-1009. PubMed Central PMCID: PMC4587560.

2. Functional contribution of endothelial plasticity to tissue fibrosis. To assess the functional contribution of Endothelial-to-Mesenchymal Transition (EndMT) during the fibrogenic response, I generated novel mouse models to genetically delete EndMT in the endothelium. When mice were challenged with multiple models of renal fibrosis, conditional knock-out mice displayed an ameliorated phenotype. By utilizing transcriptomic, metabolomic and functional analyses, I discovered that EndMT functionally contributes to tissue fibrosis by provoking vascular leakage and subsequent tissue hypoxia, which in turn are responsible for triggering a cascade of detrimental metabolic changes in the renal parenchyma, mediated by the epithelial upregulation of the transcription factor Myc.

- a. **Lovisa S,** Fletcher-Sananikone E, Sugimoto H, Hensel J, Lahiri S, Hertig A, Taduri G, Lawson E, Dewar R, Revuelta I, Kato N, Wu CJ, Bassett RL Jr, Putluri N, Zeisberg M, Zeisberg EM, LeBleu VS, Kalluri R. Endothelial-to-mesenchymal transition compromises vascular integrity to induce Myc-mediated metabolic reprogramming in kidney fibrosis. **Sci Signal.** **2020** Jun 9;13(635) PubMed Central PMCID: PMC7790440.
- b. **Lovisa S,** Kalluri R. Fatty Acid Oxidation Regulates the Activation of Endothelial-to-Mesenchymal Transition. **Trends Mol Med.** **2018** May;24(5):432-434. PubMed PMID: 29573973.

3. The biology and function of fibroblasts in development and fibrosis. I contributed to providing the first comprehensive functional investigation of the role of Collagen I in distinct fibroblast lineages which led to the identification of the cell of origin of Osteogenesis Imperfecta, a genetic disorder caused by mutated Collagen I. Moreover, I have been involved in collaborative studies to understand the role of fibroblasts associated with intestinal fibrosis, particularly from the perspective of their cross-talk with epithelial and immune cell populations. In fact, in one study, a cross-talk between fibroblasts and epithelial cells was identified underlying mucosal healing. In an other recent study, FAP+Twist+ fibroblasts were identified as the major drivers of transmural fibrosis in Crohn's disease and found originating from a precursor mesenchymal population reprogrammed by inflammatory monocytes.

- a. Ke BJ, Abdurahiman S, Biscu F, Zanella G, Dragoni G, Santhosh S, De Simone V, Zouzaf A, van Baarle L, Stakenborg M, Bosáková V, Van Rymentant Y, Verhulst E, Verstockt S, Klein E, Bislinghi G, Wolthuis A, Frič J, Breynaert C, D'Hoore A, Van der Veken P, De Meester I, **Lovisa S,** Hawinkels LJ, Verstockt B, De Hertogh G, Vermeire S, Matteoli G. Intercellular interaction between FAP+ fibroblasts and CD150+ inflammatory monocytes mediates fibrostenosis in Crohn's disease. **J Clin Invest.** **2024** Jul 23;134(16) PubMed Central PMCID: PMC11324301.

- b. Rizzo G, Pineda Chavez S, Vandenkoornhuyse E, Cárdenas Rincón C, Cento V, Garlatti V, Wozny M, Sammarco G, Di Claudio A, Meanti L, Elangovan S, Romano A, Roda G, Loy L, Dal Buono A, Gabbiadini R, **Lovisa S**, Rusconi R, Repici A, Armuzzi A, Vetrano S. Pomegranate Extract Affects Gut Biofilm Forming Bacteria and Promotes Intestinal Mucosal Healing Regulating the Crosstalk between Epithelial Cells and Intestinal Fibroblasts. **Nutrients**. **2023** April 05; 15(7):1771-. Available from: <https://www.mdpi.com/2072-6643/15/7/1771> DOI: 10.3390/nu15071771
 - c. Chen Y, Yang S, **Lovisa S**, Ambrose C, McAndrews K, Sugimoto H, Kalluri R. Type-I collagen produced by distinct fibroblast lineages reveals specific function during embryogenesis and Osteogenesis Imperfecta. **Nature Communications**. **2021** December 10; 12(1):- . Available from: <https://www.nature.com/articles/s41467-021-27563-3> DOI: 10.1038/s41467-021-27563-3
 - d. D'Alessio S, Ungaro F, Noviello D, Lovisa S, Peyrin-Biroulet L, Danese S. Revisiting fibrosis in inflammatory bowel disease: the gut thickens. **Nature Reviews Gastroenterology & Hepatology**. **2021** December 07; 19(3):169-184. Available from: <https://www.nature.com/articles/s41575-021-00543-0> DOI: 10.1038/s41575-021-00543-0
4. Molecular drivers of cancer development and resistance to therapy. During my post-doctoral training at MD Anderson Cancer Center, I was involved in a collaborative project aimed to generate a new mouse model of malignant rhabdoid tumors (MRTs), a class of aggressive pediatric malignancies caused by the biallelic inactivation of SMARCB1. By using this novel in vivo model, we demonstrated that SMARCB1-dependent malignancies exhibit dramatic activation of the UPR and ER stress responses and therefore are sensitive to agents inducing proteotoxic stress and autophagy inhibition. During my graduate training, I worked on two studies aimed to understanding the molecular mechanisms sustaining Epithelial Ovarian Carcinomas (EOCs) survival and resistance to therapy. I contributed to finding that the microtubule-destabilizing protein stathmin exerts a crucial role in controlling mutant p53 protein stability and is required for the growth and survival of EOC cells carrying a mutant p53 protein. Moreover, we identified SGK2 as a novel mediator of platinum sensitivity in EOCs.
- a. Ranzuglia V, Lorenzon I, Pellarin I, Sonogo M, Dall'Acqua A, D'Andrea S, **Lovisa S**, Segatto I, Coan M, Polesel J, Serraino D, Sabatelli P, Spessotto P, Belletti B, Baldassarre G, Schiappacassi M. Serum- and glucocorticoid- inducible kinase 2, SGK2, is a novel autophagy regulator and modulates platinum drugs response in cancer cells. **Oncogene**. **2020** Oct;39(40):6370-6386. PubMed Central PMCID: PMC7529585.
 - b. Carugo A, Minelli R, Sapio L, Soeung M, Carbone F, Robinson FS, Tepper J, Chen Z, **Lovisa S**, Svelto M, Amin S, Srinivasan S, Del Poggetto E, Loponte S, Puca F, Dey P, Malouf GG, Su X, Li L, Lopez-Terrada D, Rakheja D, Lazar AJ, Netto GJ, Rao P, Sgambato A, Maitra A, Tripathi DN, Walker CL, Karam JA, Heffernan TP, Viale A, Roberts CWM, Msaouel P, Tannir NM, Draetta GF, Genovese G. p53 Is a Master Regulator of Proteostasis in SMARCB1-Deficient Malignant Rhabdoid Tumors. **Cancer Cell**. **2019** Feb 11;35(2):204-220.e9. PubMed Central PMCID: PMC7876656.
 - c. Sonogo M, Schiappacassi M, **Lovisa S**, Dall'Acqua A, Bagnoli M, Lovat F, Libra M, D'Andrea S, Canzonieri V, Militello L, Napoli M, Giorda G, Pivetta B, Mezzanzanica D, Barbareschi M, Valeri B, Canevari S, Colombatti A, Belletti B, Del Sal G, Baldassarre G. Stathmin regulates mutant p53 stability and transcriptional activity in ovarian cancer. **EMBO Molecular Medicine**. **2013** April 22; 5(5):707-722. Available from: <https://www.embopress.org/doi/10.1002/emmm.201201504> DOI: 10.1002/emmm.201201504
5. Molecular mechanisms of cell cycle dysregulation during cancer progression. The tumor suppressor gene p27(Kip1) plays a fundamental role in human cancer progression. Its expression and/or functions are altered in almost all tumor types. p27 exerts a role in both controlling cell cycle, through its N-terminal domain, and modulating cell motility, through its C-terminal domain. During my graduate training, I characterized the role of the post-translation modifications occurring

in p27 C-terminal domain and I discovered a critical role of the last C-terminal aminoacid in regulating p27 stability and its motility function. Moreover I demonstrated for the first time that the post-translational modification SUMOylation modulates p27 function in response to TGF β stimulation. In addition, I have been involved in a collaborative project that described an altered p27 localization as the molecular mechanism by which the E17K mutation in the Akt1 gene, which occurs in approximately 0.6-2% of human lung cancers, is oncogenic.

- a. **Lovisa S**, Citro S, Sonogo M, Dall'Acqua A, Ranzuglia V, Berton S, Colombatti A, Belletti B, Chiocca S, Schiappacassi M, Baldassarre G. SUMOylation regulates p27Kip1 stability and localization in response to TGF β . **J Mol Cell Biol.** **2016** Feb;8(1):17-30. PubMed Central PMCID: PMC5943672.
- b. De Marco C, Malanga D, Rinaldo N, De Vita F, Scrima M, **Lovisa S**, Fabris L, Carriero MV, Franco R, Rizzuto A, Baldassarre G, Viglietto G. Mutant AKT1-E17K is oncogenic in lung epithelial cells. **Oncotarget.** **2015** Nov 24;6(37):39634-50. PubMed Central PMCID: PMC4741851.
- c. Schiappacassi M, **Lovisa S**, Lovat F, Fabris L, Colombatti A, Belletti B, Baldassarre G. Role of T198 modification in the regulation of p27(Kip1) protein stability and function. **PLoS One.** **2011** Mar 14;6(3):e17673. PubMed Central PMCID: PMC3056717.
- d. Belletti B, Pellizzari I, Berton S, Fabris L, Wolf K, Lovat F, Schiappacassi M, D'Andrea S, Nicoloso MS, **Lovisa S**, Sonogo M, Defilippi P, Vecchione A, Colombatti A, Friedl P, Baldassarre G. p27kip1 controls cell morphology and motility by regulating microtubule-dependent lipid raft recycling. **Mol Cell Biol.** **2010** May;30(9):2229-40. PubMed Central PMCID: PMC2863592.