BIOGRAPHICAL SKETCH

NAME: Pasquale Piccolo

POSITION TITLE: Group Leader

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date MM/YYYY	FIELD OF STUDY
Federico II Univ. of Naples, Italy	B.Sc.	07/05	Medical biotechnology
Dept. of Pediatrics Federico II Univ. of Naples, Italy	Ph.D.	01/09	Inherited metabolic disorders
Dept. of Human Molecular Genetics Baylor College of Medicine, Houston TX	Post-doctoral	07/09	Adenoviral gene therapy
Telethon Institute of Genetics and Medicine, Italy	Post-doctoral	07/16	Liver gene therapy

A. Personal Statement

Since its beginnings, my research activity has been focused on the investigation of pathomechanisms underlying liver genetic disorders and in developing novel therapeutic strategies. My research initially focused on understanding the role of transcription factors and microRNAs in the development of liver diseases associated with α1-antitrypsin deficiency. This work garnered me significant recognition, including the α1-Antitrypsin Laurell's Training Award and the Gordon L. Snider Scholar Award. As an independent researcher, I have since dedicated my efforts to developing novel adeno-associated viral vector (AAV)-based liver-directed gene therapy approaches for genetic disorders characterized by liver damage and fibrosis. My work in this field has been recognized with the Daniel Alagille Award, delivered by the European Association for the Study of the Liver (EASL). My research continues to focus on creating innovative therapeutic strategies for inherited liver diseases, with the primary goal of translating scientific discoveries into effective treatments for patients.

B. Positions and Honors

Positions and Scientific Appointments

2005 – 2008 Graduate student, Department of Pediatrics, Univ. of Naples Federico II, Italy

2008 – 2009 Post-doctoral fellow, Department of Molecular and Human Genetics, Baylor College of Medicine, USA

2009 – 2016 Post-doctoral fellow, Telethon Institute of Genetics and Medicine, Italy

2016 – 2018 Staff scientist, Telethon Institute of Genetics and Medicine, Italy

2018 – 2020 Junior Principal Investigator, STAR program, Department of Translational Medicine, Univ. of Naples Federico II, Italy

2019 – to date Assistant Investigator, Telethon Institute of Genetics and Medicine, Italy

2024 – to date Executive Board Member, Telethon Institute of Genetics and Medicine, Italy

Honors

2013	Travel award (American Society of Gene and Cell Therapy - ASGCT)
2016	Alpha-1 Antitrypsin Laurell's Training Award (Grifols, S.A.)
2017	Gordon L. Snider Scholar Award (Alpha-1 Foundation)
2018	Young Investigator Bursary (European Association for the Study of the Liver)
2022	Daniel Alagille Award (European Association for the Study of the Liver)

Patents

2022	Patent application n. WO2022/184650 A1 – Brunetti-Pierri N, *Piccolo P*, Ferriero R. Use of microRNAs in the treatment of fibrosis
2025	Patent application n. IT102025000011368 – *Piccolo P*, Battipaglia M, Vivenzio S. Therapeutic strategy for treating diseases associated with copper toxicity
2025	Patent application n. IT102025000004800 – *Piccolo P*, Ferriero R. Materials and methods for gene therapy in subjects with liver fibrosis

Reviewer Experience

Cell Stem Cell; Nature Communications; Molecular Therapy; EMBO Molecular Medicine; Clinical Chemistry and Laboratory Medicine; Molecular Therapy – Methods & Clinical Development; Gene Therapy; Communications Biology; iScience; Bioengineered; Frontiers in Cell and Developmental Biology; Frontiers in Pediatrics; Frontiers in Oncology; Scientific Reports.

C. Contribution to science

My research focuses on developing and mechanistically understanding gene therapy strategies for inherited liver diseases, with particular emphasis on AAV-based platforms for in vivo gene transfer and genome editing. I have contributed to overcoming key translational barriers, including AAV cargo limitations, by implementing split-intein technology to reconstitute full-length ATP7B for Wilson disease (WD).
I subsequently developed nuclease-free and CRISPR-based genome editing strategies targeting the albumin locus, demonstrating that corrected hepatocytes can acquire a proliferative advantage and repopulate the diseased liver, leading to sustained phenotypic rescue. More recently, I contributed to the development of homology-independent targeted integration (HITI), achieving therapeutic efficacy at clinically relevant vector doses.
A central aspect of my work has been the study of disease context as a determinant of gene therapy outcome. In particular, I demonstrated that liver fibrosis significantly impairs AAV-mediated gene transfer by reducing hepatic uptake and altering vector biodistribution in a capsid-dependent manner.
Earlier in my career, I investigated the molecular pathogenesis of α1-antitrypsin deficiency (AATD), identifying transcriptional and stress-response pathways (HNF4α, CHOP/c-JUN, JNK–FOXO3–miR-34b/c axis) that contribute to liver disease and fibrosis. These studies led to the identification of miR-34b/c as an anti-fibrotic therapeutic candidate. I also contributed to defining autophagy–lysosomal pathways (TFEB, TRPML1, SESTRIN2) as targets for the clearance of misfolded proteins.
Additionally, I have contributed to vector biology by identifying key receptors mediating adenoviral vector uptake and developing strategies to improve hepatocyte transduction. My work also extends to rare genetic diseases and translational approaches, including drug repurposing and gene discovery, highlighting how rare disorders can reveal fundamental biological mechanisms

1. Piccolo P, Annunziata P, Soria LR, […], Brunetti-Pierri N. **Downregulation of HNF-4α and defective zonation in α1-antitrypsin-deficient liver.** *Hepatology* 2017

2. Attanasio S, Ferriero R, Gernoux G, […], Piccolo P*, Brunetti-Pierri N*. **CHOP and c-JUN up-regulate mutant Z α1-antitrypsin, exacerbating liver proteotoxicity.** *J Biol Chem* 2020 — **co-corresponding authors*
3. Piccolo P*, Ferriero R, Barbato A, […], Brunetti-Pierri N*. **Up-regulation of miR-34b/c by JNK and FOXO3 protects from liver fibrosis.** *PNAS* 2021 — **co-corresponding authors*
4. Padula A, Petruzzelli R, Philbert SA, […], Piccolo P. **Full-length ATP7B reconstituted through protein trans-splicing corrects Wilson disease in mice.** *Mol Ther Methods Clin Dev.* 2022
5. Padula A, Spinelli M, Nusco E, […], Piccolo P. **Genome editing without nucleases confers proliferative advantage to edited hepatocytes and corrects Wilson disease.** *JCI Insight* 2023
6. Pastore N, Annunziata F, Colonna R, […], Piccolo P, Brunetti-Pierri N. **TRPML1 activation reduces hepatic storage of mutant α1-antitrypsin.** *Mol Ther* 2023
7. Esposito F, […], Piccolo P, Trapani I, Cathomen T, Auricchio A. **Safe and effective liver-directed AAV-mediated homology-independent targeted integration in mouse models of inherited diseases.** *Cell Rep Med* 2024
8. De Leonibus C, Maddaluno M, Ferriero R, […], Piccolo P, Settembre C. **Sestrin2 drives ER-phagy in response to protein misfolding.** *Dev Cell* 2024
9. Ferriero R, Bruno G, Padula A, […], Piccolo P. **Impact of liver fibrosis on AAV-mediated gene transfer to mouse hepatocytes.** *Nat Commun* 2025
10. Piccolo P*, Ferriero R, Perna C, […], Brunetti-Pierri N*. **Hepatocyte delivery of miR-34b/c reduces hepatic stellate cell activation and fibrosis.** *Mol Ther Nucleic Acids* 2025 — **co-corresponding authors*

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/1hiHik7vcuj/bibliography/public/

D. Past and Ongoing Research Support

2025 – 2027 Title: Development of RNA aptamers inhibiting polymerization of mutated Z α-1-antitrypsin
Funding agency: Alpha-1 Foundation
Role: Principal investigator

2024 – 2025 Title: HITI-based promoterless genome editing for the treatment of PFIC3
Funding agency: PFIC Network
Role: Principal investigator

2023 – 2025 Title: Mitochondrial dysfunction in α1-antitrypsin deficiency-associated liver disease
Funding agency: Alpha-1 Foundation
Role: Principal investigator

2022 – 2024 Title: Promoterless liver genome editing for PFIC3
Funding agency: European Association for the Study of the Liver
Role: Principal investigator

2022 – 2026 Title: AAVolution-Next-generation AAV vectors for liver-directed gene therapy
Funding agency: European Innovation Council-Pathfinder
Role: co- Principal investigator

2021 – 2024 Title: WilsonMed-Multi-molecular targeting of copper overload in Wilson disease
Funding agency: European Joint Program-Rare Diseases

Role: co- Principal investigator

2020 – 2022 Title: Micro-RNA based therapy for Primary Sclerosing Cholangitis
Funding agency: PSC Partners Seeking a Cure
Role: Principal investigator

2018 – 2020 Title: Metabolic alterations in liver disease due to Z a1-antitrypsin
Funding agency: Alpha-1 Foundation
Role: Principal investigator

2018 – 2020 Title: miRNA therapy for liver fibrosis
Funding agency: Federico II University of Naples/Compagnia di S. Paolo
Role: Principal investigator

2017 – 2020 Title: Regulation of autophagy in liver disease due to Z a1-antitrypsin
Funding agency: Alpha-1 Foundation
Role: Principal investigator

2016 – 2017 Title: miRNAs as biomarkers for AATD-related liver disease
Funding agency: Grifols, S.A.
Role: Principal investigator

2011 – 2014 Title: Gene therapy for inborn errors of liver metabolism
Funding agency: Italian Ministry of Health
Role: Research unit coordinator

E. Experience as a research supervisor

5 postdocs
4 PhD students
2 undergraduates