BIOGRAPHICAL SKETCH

NAME: Nicola Brunetti-Pierri

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

POSITION TITLE: Professor and Principal Investigator

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Federico II University of Naples, Italy	MD cum laude	07/1997	Medicine
Dept. Pediatrics, Federico II Univ. Naples, Italy	Resident	10/02	Pediatrics
Dept. Molecular and Hum Genetics, Baylor College of Medicine, Houston, TX, USA	Post-doc	03/05	Human Genetics

A. Personal Statement

Understanding the pathogenetic mechanisms and developing novel treatments for genetic diseases have been the major goals of my research. During my pediatrics fellowship, I identified and defined the biochemical and molecular bases of a novel inborn error of cholesterol metabolism that I named lathosterolosis. By actively working in the clinic and in the laboratory, I continued to make important contribution in the identification and clinical characterization of novel genetic syndromes, such as 1q21.1 deletion and duplication, 7q11.23 duplication, FOXG1 duplication, BIS and ENDI. My major research effort has been focused on investigation of gene therapy and small molecules for therapies for inherited metabolic diseases (IMDs). The preclinical studies I have generated for small molecule-based therapies of two of them (i.e. maple syrup urine disease and pyruvate dehydrogenase deficiency) have been translated in the clinic. I have also been involved in clinical research, and I am currently the principal investigator of two phase 1/2 liver-directed gene therapy clinical trials. As an independent investigator, I have been able to secure funding from the two major US and European funding agencies (National Institute of Health and European Research Council). My research has also been recognized by awards of both the American and European Societies of Gene and Cell Therapy (ASGCT and ESGCT).

B. Positions, Scientific Appointments and Honors

04/24-to-date Coordinator of the Molecular Therapy Program, Telethon Institute of Genetics and Medicine, Naples, Italy
12/22-to-date Principal Investigator, Telethon Institute of Genetics and Medicine, Naples, Italy
01/21-to-date Professor of Pediatrics, Department of Translational Medicine, Federico II of Naples, Naples, Italy
07/14-to-01/21 Associate Professor, Federico II of Naples, Naples, Italy
01/13-to-11/22 Associate Investigator, Telethon Institute of Genetics and Medicine, Naples, Italy
03/09-to-12/12 Assistant Investigator, Telethon Institute of Genetics and Medicine, Naples, Italy
12/08-to-06/13 Assistant Professor, Department of Translational Medicine, Federico II of Naples, Naples, Italy
03/07-to-2010 Assistant Professor, Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas (USA)
07/07-to-06/08 Biochemical Genetics Fellow, Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas (USA)
07/05-to-06/07 Medical Genetics Resident, Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas (USA)
07/02-to-07/05 Postdoctoral fellow, Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas (USA)
1998- 2002 Resident in Pediatrics at the School of Pediatrics of University of Naples, Italy

Board Certifications: Italian Board of Pediatrics (2002); American Board of Clinical Genetics (2007); American Board of Clinical Biochemical Genetics (2009).

Honors

2005 Telethon Fellowship for Italian Scientists Abroad
2006 K99/R00 NIH Pathway for Independence Award
2010 European Society of Gene and Cell Therapy Young Investigator Award
2011 UMDF Chairman's Award
2012 American Society of Gene and Cell Therapy, Outstanding New Investigator Award
2012 European Research Council, Consolidator Grant Award
2016 UMDF Chairman's Award

Patents:

WO2022184650: Use of micrornas in the treatment of fibrosis; Date: 01/03/2021;
PCT/EP2023/061560: Gene therapy for gyrate atrophy of the choroid and retina; Date: 02/05/2023.

Reviewer Experience

Reviewer for several scientific journals including American Journal of Human Genetics, American Journal of Medical Genetics, Brain, Cell Reports Medicine, EMBO Molecular Medicine, European Journal of Human Genetics, Hepatology, Human Gene Therapy, Human Molecular Genetics, Genetics in Medicine, Journal of Clinical Investigation, Journal of Hepatology, Journal of Inherited Metabolic Disease, Molecular Therapy, Nature Communications, Nature Medicine, Pediatrics, PNAS, Science Translational Medicine.

Reviewer for the scientific agencies including European Research Council (ERC); Association Francaise pour le Myopathies (AFM); Alpha1 Foundation, Agence nationale de la recherche, France; Academia Sinica, Taiwan; Action Medical Research UK; Alpha1 Foundation; Austrian Science Fund; Barth Syndrome Foundation; Citrin Foundation; Dutch Research Council; ELA International; European Science Foundation; GOSH Childrens' Charity, UK; The Israel Science Foundation; IndiaAlliance DBT Wellcome; Italian Ministry of Research; LifeArc Philanthropic Fund; Luxembourg National Research Fund; Metakids, The Netherlands; Michigan Nutrition and Obesity Research Center; Medical Research Council, UK; Myhre syndrome Foundation; Oxalosis and Hyperoxaluria Foundation; Swiss National Science Foundation; UK Research and Innovation; Vici Foundation; McGill University DNA to RNA (D2R) Commercialization Priming Program.

C. Contributions to Science

My career as a physician-scientist has been focused on the elucidation of the pathogenetic mechanisms and treatment of genetic diseases. I identified the clinical and genetic basis of several genetic disorders (lathosterolosis, 1q21.1 deletion and duplication, 7q11.23 duplication, FOXG1 duplication, BIS and ENDI). Moreover, I collaborated on the identification of >20 disease genes. Investigating gene therapy and small molecules for therapies for inherited metabolic disorders (IMDs) has been a major goal of my preclinical and clinical research. In my laboratory, we found that modulation of specific post-translational modifications has therapeutic potential in various IMDs, namely Maple Syrup Urine Disease (MSUD), pyruvate dehydrogenase (PDH) deficiency, and urea cycle disorders. We also found that hepatic autophagy and upregulation of glutamine synthetase are effective mechanisms for ammonia detoxification. Furthermore, my laboratory has also a long-standing interest in understanding the pathogenesis and developing new treatments for the liver disease due to mutant alpha1 antitrypsin deficiency. We showed the efficacy of TFEB and TRPML-1 gene transfer for clearance of the proteotoxic mutant alfa1-antitrypsin and our research has led to the identification of an important therapeutic pathway involved in both genetic and non-genetic forms of liver fibrosis.
In the first part of my research career, I worked extensively on liver gene therapy initially with helper-dependent adenoviral (HDAd) vectors and later I shifted towards Adeno-associated viral (AAV) vectors. My laboratory has generated preclinical proof-of-concept data supporting efficacy of AAV-mediated liver-directed gene therapy for several IMDs and I have been the clinical Principal investigator in the first phase I/II gene therapy clinical trials for mucopolysaccharidosis type VI.

1. **Brunetti-Pierri N**, Corso G, Rossi M, Ferrari P, Balli F, Rivasi F, Annunziata I, Ballabio A, Russo AD, Andria G, Parenti G. Lathosterolosis, a novel multiple-malformation/mental retardation syndrome due to deficiency of 3beta-hydroxysteroid-delta5-desaturase. *Am J Hum Genet*. 2002 Oct;71(4):952-8.

2. **Brunetti-Pierri N**, Liou A, Patel P, Palmer D, Grove N, Finegold M, Piccolo P, Donnachie E, Rice K, Beaudet A, Mullins C, Ng P. Balloon catheter delivery of helper-dependent adenoviral vector results in sustained, therapeutic hFIX expression in rhesus macaques. *Mol Ther*. 2012 Oct;20(10):1863-70.
3. Pastore N, Blomenkamp K, Annunziata F, Piccolo P, Mithbaokar P, Maria Sepe R, Vetrini F, Palmer D, Ng P, Polishchuk E, Iacobacci S, Polishchuk R, Teckman J, Ballabio A, **Brunetti-Pierri N**. Gene transfer of master autophagy regulator TFEB results in clearance of toxic protein and correction of hepatic disease in alpha-1-anti-trypsin deficiency. *EMBO Mol Med*. 2013 Mar;5(3):397-412.
4. Ferriero R, Manco G, Lamantea E, Nusco E, Ferrante MI, Sordino P, Stacpoole PW, Lee B, Zeviani M, **Brunetti-Pierri N**. Phenylbutyrate therapy for pyruvate dehydrogenase complex deficiency and lactic acidosis. *Sci Transl Med*. 2013 Mar 6;5(175):175ra31.
5. Castello R, Borzone R, D'Aria S, Annunziata P, Piccolo P, **Brunetti-Pierri N**. Helper-dependent adenoviral vectors for liver-directed gene therapy of primary hyperoxaluria type 1. *Gene Ther*. 2016 Feb;23(2):129-34.
6. Pastore N, Attanasio S, Granese B, Castello R, Teckman J, Wilson AA, Ballabio A, **Brunetti-Pierri N**. Activation of the c-Jun N-terminal kinase pathway aggravates proteotoxicity of hepatic mutant Z alpha1-antitrypsin. *Hepatology*. 2017 Jun;65(6):1865-1874.
7. Piccolo P, Annunziata P, Soria LR, Attanasio S, Barbato A, Castello R, Carissimo A, Quagliata L, Terracciano LM, **Brunetti-Pierri N**. Down-regulation of hepatocyte nuclear factor-4α and defective zonation in livers expressing mutant Z α1-antitrypsin. *Hepatology*. 2017 Jul;66(1):124-135.
8. Soria LR, Allegri G, Melck D, Pastore N, Annunziata P, Paris D, Polishchuk E, Nusco E, Thöny B, Motta A, Häberle J, Ballabio A, **Brunetti-Pierri N**. Enhancement of hepatic autophagy increases ureagenesis and protects against hyperammonemia. Proc Natl Acad Sci U S A. 2018 Jan 9;115(2):391-396.
9. Ferriero R, Nusco E, De Cegli R, Carissimo A, Manco G, **Brunetti-Pierri N**. Pyruvate dehydrogenase complex and lactate dehydrogenase are targets for therapy of acute liver failure. *J Hepatol*. 2018 Aug;69(2):325-335.
10. Soria LR, Nitzahn M, De Angelis A, Khoja S, Attanasio S, Annunziata P, Palmer DJ, Ng P, Lipshutz GS, **Brunetti-Pierri N**. Hepatic glutamine synthetase augmentation enhances ammonia detoxification. *J Inherit Metab Dis*. 2019 Nov;42(6):1128-1135.
11. Soria LR, Gurung S, De Sabbata G, Perocheau DP, De Angelis A, Bruno G, Polishchuk E, Paris D, Cuomo P, Motta A, Orford M, Khalil Y, Eaton S, Mills PB, Waddington SN, Settembre C, Muro AF, Baruteau J, **Brunetti-Pierri N**. Beclin-1-mediated activation of autophagy improves proximal and distal urea cycle disorders. *EMBO Mol Med*. 2021 Feb 5;13(2):e13158.
12. Piccolo P, Ferriero R, Barbato A, Attanasio S, Monti M, Perna C, Borel F, Annunziata P, Carissimo A, De Cegli R, Quagliata L, Terracciano LM, Housset C, Teckman JH, Mueller C, **Brunetti-Pierri N**. Up-regulation of miR-34b/c by JNK and FOXO3 protects from liver fibrosis. *Proc Natl Acad Sci U S A*. 2021 Mar 9;118(10):e2025242118.
13. Soria LR, Makris G, D'Alessio AM, De Angelis A, Boffa I, Pravata VM, Rüfenacht V, Attanasio S, Nusco E, Arena P, Ferenbach AT, Paris D, Cuomo P, Motta A, Nitzahn M, Lipshutz GS, Martínez-Pizarro A, Richard E, Desviat LR, Häberle J, van Aalten DMF, **Brunetti-Pierri N**. O-GlcNAcylation enhances CPS1 catalytic efficiency for ammonia and promotes ureagenesis. *Nat Commun*. 2022 Sep 5;13(1):5212.
14. **Brunetti-Pierri N**, Ferla R, Ginocchio VM, Rossi A, Fecarotta S, Romano R, Parenti G, Yildiz Y, Zancan S, Pecorella V, Dell'Anno M, Graziano M, Alliegro M, Andria G, Santamaria F, Brunetti-Pierri R, Simonelli F, Nigro V, Vargas M, Servillo G, Borgia F, Soscia E, Gargaro M, Funghini S, Tedesco N, Le Brun PR, Rupar CA, Prasad C, O'Callaghan M, Mitchell JJ, Danos O, Marteau JB, Galimberti S, Valsecchi MG, Veron P, Mingozzi F, Fallarino F, la Marca G, Sivri HS, Auricchio A. Liver-Directed Adeno-Associated Virus-Mediated Gene Therapy for Mucopolysaccharidosis Type VI. *NEJM Evid*. 2022 Jul;1(7):EVIDoa2200052.
15. Consiglieri G, Bernardo ME, **Brunetti-Pierri N**, Aiuti A. Ex Vivo and In Vivo Gene Therapy for Mucopolysaccharidoses: State of the Art. *Hematol Oncol Clin North Am*. 2022 Aug;36(4):865-878.
16. Sorrentino NC, Presa M, Attanasio S, Cacace V, Sofia M, Zuberi A, Ryan J, Ray S, Petkovic I, Radhakrishnan K, Schlotawa L, Ballabio A, Lutz C, **Brunetti-Pierri N**. New mouse models with hypomorphic SUMF1 variants mimic attenuated forms of multiple sulfatase deficiency. *J Inherit Metab Dis*. 2023 Mar;46(2):335-347.
17. Boffa I, Polishchuk E, De Stefano L, Dell'Aquila F, Nusco E, Marrocco E, Audano M, Pedretti S, Caterino M, Bellezza I, Ruoppolo M, Mitro N, Cellini B, Auricchio A, **Brunetti-Pierri N**. Liver-directed gene therapy for ornithine aminotransferase deficiency. *EMBO Mol Med*. 2023 Apr 11;15(4):e17033

18. Pastore N, Annunziata F, Colonna R, Maffia V, Giuliano T, Custode BM, Lombardi B, Polishchuk E, Cacace V, De Stefano L, Nusco E, Sorrentino NC, Piccolo P, **Brunetti-Pierri N**. Increased expression or activation of TRPML1 reduces hepatic storage of toxic Z alpha-1 antitrypsin. *Mol Ther*. 2023 Sep 6;31(9):2651-2661.
19. Rossi A, **Brunetti-Pierri N**. Gene therapies for mucopolysaccharidoses. *J Inherit Metab Dis*. 2024 Jan;47(1):135-144.
20. D'Antiga L, Beuers U, Ronzitti G, **Brunetti-Pierri N**, Baumann U, Di Giorgio A, Aronson S, Hubert A, Romano R, Junge N, Bosma P, Bortolussi G, Muro AF, Soumoudronga RF, Veron P, Collaud F, Knuchel-Legendre N, Labrune P, Mingozzi F. Gene Therapy in Patients with the Crigler-Najjar Syndrome. *N Engl J Med*. 2023 Aug 17;389(7):620-631.
21. Baruteau J, **Brunetti-Pierri N**, Gissen P. Liver-directed gene therapy for inherited metabolic diseases. *J Inherit Metab Dis*. 2024 Jan;47(1):9-21.
22. Wang HH, Lin LL, Li ZJ, Wei X, Askander O, Cappuccio G, Hashem MO, Hubert L, Munnich A, Alqahtani M, Pang Q, Burmeister M, Lu Y, Poirier K, Besmond C, Sun S, **Brunetti-Pierri N**,* Alkuraya FS,* Qi L.* Hypomorphic variants of SEL1L-HRD1 ER-associated degradation are associated with neurodevelopmental disorders. *J Clin Invest*. 2024 Jan 16;134(2):e170054. **co-corresponding authors*.
23. Rossi A, Malvagia S, la Marca G, Parenti G, **Brunetti-Pierri N**. Biomarkers for gene therapy clinical trials of lysosomal storage disorders. *Mol Ther*. 2024 Sep 4;32(9):2930-2938.
24. Rossi A, Romano R, Fecarotta S, Dell'Anno M, Pecorella V, Passeggio R, Zancan S, Parenti G, Santamaria F, Borgia F, Deodato F, Funghini S, Rupar CA, Prasad C, O'Callaghan M, Mitchell JJ, Valsecchi MG, La Marca G, Galimberti S, Auricchio A, **Brunetti-Pierri N**. Multi-year enzyme expression in mucopolysaccharidosis type VI patients after liver-directed gene therapy. *Med*, November 14, 2024,
25. Piccolo P, Ferriero R, Perna C, Nusco E, Monti M, De Cegli R, Barbato A, Sorrentino NC, Viscomi MT, Cariello M, Moschetta A, Campione S, **Brunetti-Pierri N**. Hepatocyte delivery of miR-34b/c reduces hepatic stellate cell activation and improves liver fibrosis. *Mol Ther Nucleic Acids*. 2025 Jun 9;36(3):102593.

Complete List of Published Work in PubMed: http://www.ncbi.nlm.nih.gov/pubmed/?term=brunetti-pierri

Selected book chapters:

1. **Brunetti-Pierri N**, Auricchio A. Gene therapy for inherited diseases. The Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill, New York, 2010.
2. Lee B, **Brunetti-Pierri N**. Management and Treatment of Genetic Disorders. In: Nelson Textbook of Pediatrics. Editors: Kliegman, St Geme, Blum, Shah, Tasker, Wilson. 21st and 22nd Editions, 2019 and 2024.

D. Experience as a research supervisor

Supervision of graduate students and post-doctoral fellows: Dr. Brunetti-Pierri supervised 12 post docs, 9 PhD students and 18 undergraduate students. Former members of the lab are currently employed in both academia and industry, for example: Nunzia Pastore, PhD is Associate Professor of Medical Genetics at the University of Naples, Italy; Pasquale Piccolo, PhD is assistant investigator at TIGEM, Italy; Yu (Ray) Zuo, MD is assistant professor at the University of Michigan, Ann Arbor, USA; Nathan Grove, research scientist, University of Colorado Anschutz Medical Campus, Aurora, USA; Sergio Attanasio, PhD is postdoctoral fellow at MD Anderson Cancer Center, Houston, USA; Riccardo Sangermano, PhD is instructor at Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, USA; Elena De Felice, PhD is Associate Professor at the University Camerino, Italy; Rosa Maria Sepe, PhD is research staff at the Stazione Zoologica Anton Dohrn, Naples, Italy; Valeria Sabatino, PhD is research staff at the University of Zurich, Switzerland; Michele Pinelli, MD, PhD is Associate Professor of Medical Genetics at the University of Naples, Italy; Gerarda Cappuccio is postdoctoral fellow at Baylor College of Medicine, Houston, USA; Virginia Maria Ginocchio, MD, PhD Clinical Program Lead of Chiesi Group, Parma, Italy. In addition, he supervised dozens of Pediatrics and Medical Genetics residents.