BIOGRAPHICAL SKETCH

NAME: Indrieri, Alessia

POSITION TITLE: *Assistant Investigator*, Telethon Institute of Genetics and Medicine (TIGEM) and *Researcher* (tenured), Institute for Genetic and Biomedical Research (IRGB), National Research Council (CNR)

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
University of Naples "Federico II", Italy	MS	12/2005	Molecular Biology
SEMM (European School of Molecular Medicine) and University of Naples "Federico II" Naples, Italy	PhD	04/2011	Molecular Medicine
TIGEM, Pozzuoli (NA), Italy	Postdoctoral Fellow	01/2017	Human Genetics, Neuroscience

A. Personal Statement

I worked for several years in the field of Biomedicine at the Telethon Institute of Genetics and Medicine (TIGEM), where I first got a PhD in Molecular Medicine, and then I continued my work as postdoctoral fellow. I also spent part of my PhD training in Madrid, in the laboratory of Prof. Paola Bovolenta at the Cajal Institute, Consejo Superior de Investigaciones Científicas (CSIC), where I developed first-rate skills in neurobiology and in the generation and characterization of disease models in the medakafish. During the PhD I studied a rare Mitochondrial Disease, the Microphthalmia With Linear Skin Lesions syndrome, characterized by a severe neurodevelopmental phenotype. As Postdoctoral Fellow I focused my research interest on the study and therapy of Mitochondrial Disorders and of mitochondrial-associated neurodegeneration. Moreover, I acquired a strong expertise in the biology of non-coding RNA and in their application in disease therapy. My expertise and research interests are quite extensive, including human genetics, neuroscience, molecular therapy, molecular and cellular biology, with a particular interest in mitochondrial biology. Very recently I started my own laboratory at TIGEM and current research interests are mainly focused on the development of new therapeutic strategies for Mitochondrial Optic Neuropathies and common disorders associated to mitochondrial dysfunctions such as Parkinson's Disease, Glaucoma and Diabetic Retinopathy.

B. Positions and Honors

Positions and Employment

2004 - 2006 **Research Fellow**, Department of Structural and Functional Biology, University of Naples "Federico II", Italy.

2006 - 2006 **Research Fellow**, TIGEM, Pozzuoli (NA), Italy.

2006 - 2007 **Research Fellow / PhD student**, Cajal Institute, Consejo Superior de Investigaciones Científicas (CSIC), Madrid, Spain.

2007 - 2011 **PhD student**, TIGEM, Pozzuoli (NA), Italy.

2011 - 2017 **Postdoctoral Fellow**, TIGEM, Pozzuoli (NA), Italy.

2017 - 2019 **Junior Principal Investigator**, Department of Translational Medical Science, University of Naples "Federico II", Italy.

2019 - present **Researcher (tenured),** Institute for Genetic and Biomedical Research (IRGB), National Research Council (CNR), Milan, Italy.

2020 - present **Lecturer**, European School of Molecular Medicine (SEMM), Naples – Milan, Italy

2020 - present **Assistant Investigator**, TIGEM, Pozzuoli (NA), Italy.

Honors

2006	Development travelling fellowship, The Company of Biologist
2007	Short-term fellowship, European Molecular Biology Organization (EMBO)
2007	PhD student fellowship, European School of Molecular Medicine (SEMM)
2012	Award for the best talk at SIGU 2012 meeting (Sorrento, Italy), Italian Society Human Genetics (SIGU)
2012 - 2014	Fellowship for Advance Training Course in Molecular and Cellular Biology, Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR)
2013	Travel Grant for ESHG 2013 meeting (Paris, France), European Society Human Genetics (ESHG)
2013	Young Investigator Award for Outstanding Science, European Society Human Genetics (ESHG)
2015	Post-Doctoral Fellowship, Fondazione Umberto Veronesi

C. Contribution to Science

1) During the PhD and the first years of the postdoctoral training I studied a rare neurodevelopmental disease, the Microphthalmia With Linear Skin Lesions (MLS) syndrome, contributing to the identification of disease genes and to the characterizations of the molecular mechanisms that underlie this disorder. In particular we discovered that actually MLS syndrome is a mitochondrial disease and that the disease phenotype is due to activation of a non-canonical cell death pathway in the brain and in the eye. These results provided the first experimental evidence for a mechanistic link between mitochondrial dysfunction, intrinsic apoptosis and developmental disorders.

a. **Indrieri A**, Conte I, Chesi G, Romano A, Quartararo J, Tatè R, Ghezzi D, Zeviani M, Goffrini P, Ferrero I, Bovolenta P, Franco B. *The impairment of HCCS leads to MLS syndrome by activating a non-canonical cell death pathway in the brain and eyes.* EMBO Mol Med. 2013 Feb;5(2):280-93.

b. **Indrieri A**, van Rahden VA, Tiranti V, Morleo M, Iaconis D, Tammaro R, D'Amato I, Conte I, Maystadt I, Demuth S, Zvulunov A, Kutsche K, Zeviani M, Franco B. *Mutations in COX7B cause microphthalmia with linear skin lesions, an unconventional mitochondrial disease.* Am J Hum Genet. 2012 Nov 2;91(5):942-9.

c. **Indrieri A**, Franco B. *Microphthalmia with linear skin lesions (MLS) syndrome, an unconventional mitochondrial disorder*. Chapter in Epstein's Inborn Errors of Development: The Molecular Basis of Clinical Disorders of Morphogenesis, 3rd ed. Eds. RP Erickson, A Wynshaw-Boris 2016. Oxford University Press, New York. pp.1449-1451

2) During the last years I acquired a strong expertise in the biology of non-coding RNA and in their application in disease therapy. First in collaboration with Prof. Gustincich group we demonstrated that synthetic antisense long non-coding RNAs [SINEUPs] are able to up-regulate the translation of selected transcripts in vivo and rescue haploinsufficient gene dosage in a medakafish model of a mitochondrial disease. Our results demonstrate that SINEUPs can be successfully applied *in vivo* as a new research and therapeutic tool for gene-specific up-regulation of endogenous functional proteins.
Then we identified the microRNA 181a and b as potential therapeutic target for mitochondrial diseases characterized by neuronal degeneration. We demonstrate that miR-181a/b regulate key genes involved in mitochondrial biogenesis and function. We also show that these miRNAs are involved in the global regulation of mitochondrial turnover in the central nervous system through the simultaneous and fine-tuning modulation of mitochondrial biogenesis and mitophagy. We found that miR-181a/b downregulation strongly protects neurons from cell death and significantly ameliorates the phenotype in different *in vivo* models of mitochondrial disease. This work paves the way for a novel gene-independent therapeutic approach for mitochondrial diseases and neurodegeneration associated mitochondrial disfunction. With my collaborators I've also projected and patented approaches to test the miR-181a/b inhibition as therapeutic approach in neurodegenerative diseases associated to mitochondrial dysfunction.

a. **Indrieri A**, Grimaldi C, Zucchelli S, Tammaro R, Gustincich S, Franco B. *Synthetic long non-coding RNAs [SINEUPs] rescue defective gene expression in vivo*. Sci Rep. 2016 Jun 6;6:27315.

b. **Indrieri A***, Carrella S*, Romano A, Spaziano A, Marrocco E, Fernandez-Vizarra E, Barbato S, Pizzo M, Ezhova Y, Golia FM, Ciampi L, Tammaro R, Henao-Mejia J, Williams A, Flavell RA, De Leonibus E, Zeviani M, Surace EM, Banfi S, Franco B (2019). *miR-181a/b downregulation exerts a protective action on mitochondrial disease models*. EMBO Mol Med 11(5). *co-first authors

c. **Indrieri A.***, Carrella S., Carotenuto P., Banfi S.*, and Franco B*. (2020). The Pervasive Role of the miR-181 Family in Development, Neurodegeneration, and Cancer. Int J Mol Sci 21(6). doi: 10.3390/ijms21062092. *co-corresponding authors

d. Carrella S, **Indrieri A**, Franco B, and Banfi S. (2020). *Mutation-Independent Therapies for Retinal Diseases: Focus on Gene-Based Approaches*. Front Neurosci *14*, 588234.

e. **Patent:** "mir-181 inhibitors and uses thereof" (registered in 20th of April, 2018)

3) Recently I also contribute to describe visual defects in the “Parkinsonian Eye”. Retina abnormalities are being considered powerful non-invasive biomarkers for Parkinson’s Disease. Moreover, our results support the idea to use retina as useful complementary experimental model for the identification and study of pathways involved in the disease pathogenesis or to test novel therapeutic approaches for Parkinson’s Disease.

a. Marrocco E*, **Indrieri A***, Esposito F, Tarallo V, Carboncino A, Alvino FG, De Falco S, Franco B, De Risi M, and De Leonibus E. (2020). *alpha-synuclein overexpression in the retina leads to vision impairment and degeneration of dopaminergic amacrine cells*. Sci Rep 10, 9619. *co-first authors

b. **Indrieri A***, Pizzarelli R, Franco B, De Leonibus E*. *Dopamine, Alpha-Synuclein, and Mitochondrial Dysfunctions in Parkinsonian Eyes.* Front Neurosci *In press.* *co-corresponding authors

4) Other publications

a. Ventre S*, **Indrieri A***, Fracassi C, Franco B, Conte I, Cardone L, di Bernardo D. *Metabolic regulation of the ultradian oscillator Hes1 by reactive oxygen species*. J Mol Biol. 2015 May 22;427(10):1887-902. *co-first authors

b. Polishchuk EV, Merolla A, Lichtmannegger J, Romano A, **Indrieri A**, Ilyechova EY, Concilli M, De Cegli R, Crispino R, Mariniello M et al (2019) *Activation of Autophagy, Observed in Liver Tissues From Patients With Wilson Disease and From ATP7B-Deficient Animals, Protects Hepatocytes From Copper-Induced Apoptosis.* Gastroenterology 156: 1173-1189 e1175

c. Iaconis D., Crina C., Brillante S., **Indrieri A**., Morleo, M., and Franco, B. (2020). *The HOPS complex subunit VPS39 controls ciliogenesis through autophagy*. Hum Mol Genet *29*, 1018-1029.

d. Botta, C., Indrieri, A., Garofalo, E., Biamonte, F., Bruni, A., Pasqua, P., Cesario, F., Costanzo, F.S., Longhini, F., and Mendicino, F. (2020). COVID-19: High-JAKing of the Inflammatory "Flight" by Ruxolitinib to Avoid the Cytokine Storm. Front Oncol 10, 599502.

D. Additional Information:

Commission of trust

2012- Ad-hoc reviewer for peer-review journals including *American Journal of Human Genetics, Human Molecular Genetics, Neuroscience, Frontiers.*

2019- Reviewer for the The French National Research Agency (ANR)

Supervision of students and postdoctoral fellows

Since 2006 6 Master students, 3 PhD student and 2 Postdocs

Research Support:

Ongoing:

Telethon Core Grant
Evaluation of miR-181a/b as new therapeutic targets for neurodegeneration associated to mitochondrial dysfunction
210.000€; 09/2020 - 08/2023
Role: **PI**

BrightFocus Foundation Grant
miR-181a/b modulation as potential therapeutic approach for AMD treatment
180.000€; 10/2020 - 09/2022
Role: **co-PI**

The United Mitochondrial Disease Foundation: Roadmap Project focused on Leigh's Syndrome
Therapeutic efficacy of miR-181a/b down regulation in Leigh syndrome
25.000$ 12/2019 - 03/2021
Role: **co-PI**

Roche per la Ricerca, Fondazione Roche
Evaluation of the role of microRNAs 181 a e b in Parkinson Disease
50.000€; 01/2019 - 12/2021
Role: **PI**

Completed:

Bando STAR, 16-CSP-UNINA-048, Compagnia di San Paolo, Istituto Banco di Napoli
Evaluation of microRNAs 181 a e b as new therapeutic targets in neurodegeneration associated to mitochondrial dysfunction
100.000€; 01/2017 - 05/2019
Role: **PI**