Banfi Sandro

Associate Investigator

OTHER POSITION: Full Professor of Medical Genetics, University of Campania Luigi Vanvitelli, Italy

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Medical School, University of Naples Federico II, Italy	MD	1989	Medicine and Surgery
Institute of Neurology, University of Naples Federico II, Italy	Residency Training	1991	Neurology
University of Naples Federico II, Italy	Residency	1993	Neurology
Dept of Pediatrics, Baylor College of Medicine, USA	Postdoctoral Training	1994	Human Genetics

A. Personal Statement

The elucidation of the molecular basis of inherited disorders has always been the primary goal of my research activities. I was trained as an MD and started my scientific career, during the positional cloning era, by working in the field of genetics of neurodegenerative disorders. When I became an independent investigator, I gradually shifted the topic of my research to the elucidation of the molecular basis of another group of neural disorders, namely inherited retinal diseases. To achieve the latter goal, I developed a specific expertise in the exploitation of publicly available bioinformatics resources coupled with functional genomics and gene functional approaches. This integrated strategy allowed me to identify and characterize genes, of high relevance for eye development and function and potentially involved in disease pathogenesis. In the past fifteen years, I have been focusing my research efforts on the study of the functional role of microRNAs in retinal function, both in physiological and pathological conditions. In the latter respect, besides reporting the first example of a microRNA (miR-204) with a pathogenic role in retinal dystrophy in human patients, I am recently dedicating my research efforts to the study of the protective role of microRNAs in models of Inherited Retinal Diseases (IRD). I believe that my longstanding expertise in medical genetics, transcriptomic analysis and gene functional studies applied make me well suited to carry out the proposed research projects finalized to the dissection of the molecular basis of IRDs and to the evaluation of the therapeutic potential of microRNAs.

Ongoing and recently completed projects that I would like to highlight include:

Funding Agency: Foundation Fighting Blindness
Period: 2015 - 2019
Role: PI
Title: MicroRNA miR-204, a new potential therapeutic tool for inherited retinal dystrophies

Funding Agency: Fondazione TelethonPeriod: 2017 - 2018
Role: PI
Title: Systematic search for microRNAs that play a role in photoreceptor degeneration

Funding Agency: European Union H2020-MSCA-ITN-2018 (Grant # 813490)
Period: 2018 - 2022
Role: Beneficiary
Title: StarT - European Training Network to Diagnose, Understand and Treat Stargardt Disease, a Frequent Inherited Blinding Disorder

Funding Agency: Fondazione Roma
Period: 2015 - 2019
Role: PI
Title: Retinitis Pigmentosa: an integrated application of novel strategies towards diagnosis and treatment

Funding Agency: Italian Ministry of research
Period: 2017 - 2020
Role: Partner
Title: Toward new methods for early diagnosis and screening of genetic ocular diseases in childhood

Funding Agency: Foundation Fighting Blindness (Grant # TA-NMT-0619-0764-TIGEM)
Period: 2019 - 2022
Role: PI
Title: AAV-Sponge-mediated modulation of microRNA-181a/b: a potential therapeutic approach for Inherited Retinal Disease

Funding Agency: VALERE: VAnviteLli pEr la RicErca
Period: 2019 - 2022
Role: Coordinator
Title: Beyond the exome: dissecting the missing heritability of mendelian disease with high genetic heterogeneity (DisHetGeD)

Funding Agency: Velux Stiftung Foundation
Period: 2020 - 2023
Role: PI
Title: MicroRNA expression modulation: a new therapeutic avenue for Inherited Retinal Diseases

Funding Agency: EJP-RD 2019
Period: 2020 - 2023
Role:PI
Title: Solve-RET: Solving missing heritability in inherited retinal diseases using integrated omics and gene editing in human cellular and animal models

Citations:

1. 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. miR-181a/b downregulation exerts a protective action on mitochondrial disease models. EMBO Mol Med. 2019;11(5).
2. Karali M, Persico M, Mutarelli M, Carissimo A, Pizzo M, Singh Marwah V, Ambrosio C, Pinelli M, Carrella D, Ferrari S, Ponzin D, Nigro V, Di Bernardo D, **Banfi S**. High-resolution analysis of the human retina miRNome reveals isomiR variations and novel microRNAs. Nucleic Acids Res. 2016;44(4):1525–40.
3. Pinelli M, Carissimo A, Cutillo L, Lai CH, Mutarelli M, Moretti MN, Singh MV, Karali M, Carrella D, Pizzo M, Russo F, Ferrari S, Ponzin D, Angelini C, **Banfi S**, Di Bernardo D. An atlas of gene expression and gene co-regulation in the human retina. Nucleic Acids Res. 2016;44(12):5773–84.
4. Van de Sompele S, Smith C, Karali M, Corton M, Van Schil K, Peelman F, Cherry T, Rosseel T, Verdin H, Derolez J, Van Laethem T, Khan KN, McKibbin M, Toomes C, Ali M, Torella A, Testa F, Jimenez B, Simonelli F, De Zaeytijd J, Van den Ende J, Leroy BP, Coppieters F, Ayuso C, Inglehearn CF, **Banfi S**, De Baere E. Biallelic sequence and structural variants in RAX2 are a novel cause for autosomal recessive inherited retinal disease. Genet Med. 2019;21(6):1319–29.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2019 – Present Full Professor of Medical Genetics - Department of Precision Medicine, University of Campania Luigi Vanvitelli, Italy

2012 – 2019 Associate Professor of Medical Genetics - Department of Biochemistry, Biophysics and General Pathology, University of Campania Luigi Vanvitelli, Italy

2005 – Present Coordinator TIGEM / OPEN UNIVERSITY PhD Program in Human Genetics

2000 – Present Associate Investigator – Telethon Institute of Genetics and Medcine, Italy

1995 – 2000 Researcher – Telethon Institute of Genetics and Medcine, Italy

Honors

1990 Recipient of a Residency Fellowship, Federico II University, Naples, Italy

2009 "Board of Director Awards", Foundation Fighting Blindness, USA

C. Contributions to Science

1. Study of the molecular basis of inherited ataxias and of other neurodegenerative conditions. The main outcome of this work was the elucidation of the molecular mechanisms underlying the pathogenesis of the autosomal dominant Spinocerebellar Ataxia type I (SCA1). We found that this disease was due to the expansion of a poly-glutamine tract in the *SCA1* gene that encodes the Ataxin 1 protein. This was the first evidence that a dynamic mutation caused an inherited ataxia. I was deeply involved as postdoctoral fellow in the identification and characterization of the *SCA1* gene and mutation as well as in the identification of its murine ortholog.

a. Banfi S, Chung MY, Kwiatkowski TJ, Ranum LP, McCall AE, Chinault AC, Orr HT, Zoghbi HY. Mapping and cloning of the critical region for the spinocerebellar ataxia type 1 gene (SCA1) in a yeast artificial chromosome contig spanning 1.2 Mb. Genomics. 1993;18(3):627–35..
b. Orr HT, Chung M, Banfi S, Kwiatkowski TJ, Servadio A, Beaudet AL, McCall AE, Duvick LA, Ranum LPW, Zoghbi HY. Expansion of an unstable trinucleotide CAG repeat in spinocerebellar ataxia type 1. Nat Genet. 1993;4(3).
c. Banfi S, Servadio A, Chung MY, Kwiatkowski TJ, Jr., McCall AE, Duvick LA, Shen Y, Roth EJ, Orr HT, Zoghbi HY. Identification and characterization of the gene causing type 1 spinocerebellar ataxia. Nat Genet. 1994;7:513-520.
d. Banfi S, Servadio A, Chung M, Capozzoli F, Duvick LA, Elde R, Zoghbi HY, Orr HT. Cloning and developmental expression analysis of the murine homolog of the spinocerebellar ataxia type 1 gene (Sca1). Hum Mol Genet. 1996;5:33-40.

2. Data mining of publicly available bioinformatic resources and databases. In particular, I developed approaches that, by taking advantage of either cross-species sequence comparison or careful analysis of genome sequencing data, led to the identification of a large number of genes (both coding and non-coding) of high biological interest. Some of the latter, particularly those associated with ocular function, were also functionally characterized by *in vivo* studies. I served as the primary investigator or co-investigator in most of these studies.

a. **Banfi S**, Borsani G, Rossi E, Bernard L, Guffanti A, Rubboli F, Marchitiello A, Giglio S, Coluccia E, Zollo M, Zuffardi O, Ballabio A. Identification and mapping of human cDNAs homologous to Drosophila mutant genes through EST database searching. Nat Genet. 1996;13:167-174.
b. Barbieri AM, Lupo G, Bulfone A, Andreazzoli M, Mariani M, Fougerousse F, Consalez GG, Borsani G, Beckmann JS, Barsacchi G, Ballabio A, **Banfi S**. A homeobox gene,*vax2*, controls the patterning of the eye dorsoventral axis. Proc Natl Acad Sci USA. 1999;96:10729-10734.
c. Barbieri AM, Broccoli V, Bovolenta P, Alfano G, Marchitiello A, Mocchetti C, Crippa L, Bulfone A, Marigo V, Ballabio A, **Banfi S**. Vax2 inactivation in mouse determines alteration of the eye dorsal-ventral axis, misrouting of the optic fibres and eye coloboma. Development. 2002;129:805-813.
d. Alfano G, Vitiello C, Caccioppoli C, Caramico T, Carola A, Szego MJ, McInnes RR, Auricchio A, **Banfi S**. Natural antisense transcripts associated with genes involved in eye development. Hum Mol Genet. 2005;14:913-923.

3. Functional genomics studies applied to microRNAs towards a reliable prediction of their roles both in normal and in pathological condition. By taking again advantage of a rational exploitation of public datasets, such as transcriptome data, our group developed new algorithms to predict microRNA targets and biological functions. Moreover, we performed systematic gene expression studies that led to the generation of the most comprehensive atlas of microRNA expression in the eye to date. All of the above resources constitute valuable tools for the microRNA research community to gain preliminary insight into the potential role of this class of small non-coding RNAs in many biological processes.

a. Gennarino VA, Sardiello M, Avellino R, Meola N, Maselli V, Anand S, Cutillo L, Ballabio A, **Banfi S**. MicroRNA target prediction by expression analysis of host genes. Genome Res. 2009;19(3):481-490.
b. Karali M, Peluso I, Gennarino VA, Bilio M, Verde R, Lago G, Dollé P, **Banfi S**. miRNeye: a microRNA expression atlas of the mouse eye. BMC Genomics. 2010;11:715.
c. Gennarino VA, D'Angelo G, Dharmalingam G, Fernandez S, Russolillo G, Sanges R, Mutarelli M, Belcastro V, Ballabio A, Verde P, Sardiello M, **Banfi S**. Identification of

microRNA-regulated gene networks by expression analysis of target genes. Genome Res. 2012;22(6):1163-1172.

d. Karali M, Persico M, Mutarelli M, Carissimo A, Pizzo M, Marwah V, Ambrosio C, Pinelli M, Carrella D, Ferrari S, Ponzin D, Nigro V, di Bernardo D, **Banfi S**. High-resolution analysis of the human retina miRNome reveals isomiR variations and novel microRNAs. Nucleic Acids Res. 2016;44(4):1525-1540.

4. Functional characterization of microRNAs with a relevant role in eye function and initial evaluation of their therapeutic potential. By in vivo studies and next generation sequencing approaches, we demonstrated that: i) miR-204 is endowed with an essential role in many aspects of ocular development; ii) plays a pathogenic role in an inherited form of retinal dystrophy (the first example for a microRNA) and iii) its retinal administration in the retina has a protective effect in mouse models of IRD. Moreover, we found that miR-181a/b controls mitochondrial turnover and that their downregulation may represents an effective gene-independent therapeutic strategies for neurodegenerative conditions, including IRD.

a. Conte I, Carrella S, Avellino R, Karali M, Marco-Ferreres Bovolenta P, **Banfi S**. miR-204is required for lens and retinal development via Meis2 targeting. Proc Natl Acad Sci USA. 2010;107(35):15491-15496.

b. Conte I, Hadfield KD, Barbato S, Carrella S, Pizzo M, Bhat RS, Carissimo A, Karali M, Porter LF, Urquhart J, Hateley S, O'Sullivan J, Manson FD, Neuhauss SC, **Banfi S**, Black GC. MiR-204 is responsible for inherited retinal dystrophy associated with ocular coloboma. Proc Natl Acad Sci USA. 2015;112(25):E3236-3245.

c. Karali M, Guadagnino I, Marrocco E, De Cegli R, Carissimo A, Pizzo M, Casarosa S, Conte I, Surace EM, **Banfi S**. AAV-miR-204 Protects from Retinal Degeneration by Attenuation of Microglia Activation and Photoreceptor Cell Death. Mol Ther Nucleic Acids. 2019;19:144-156.

d. 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. miR-181a/b downregulation exerts a protective action on Mitochondrial Disease models. EMBO Mol Med. 2019;11(5):e8734.

5. My strong interest in the study of the molecular mechanisms of eye development and function brought me to undertake studies aimed at unraveling the genetic basis of inherited eye diseases in vast and clinically well-characterized collections of patients. Thanks to a fruitful collaboration with the Ophthalmology clinic at the University of Campania in Naples, our group has played so far the most relevant contribution to the determination of the genetic epidemiology of inherited retinal disorders in the Italian population, also by Next Generation Sequencing approaches. The results of the above studies were instrumental for the identification of new disease genes and to application of the first gene therapy-based clinical trial on a genetic retinal disease.

a. Simonelli F, Ziviello C, Testa F, Rossi S, Fazzi E, Bianchi PE, Fossarello M, Signorini S, Bertone C, Galantuomo S, Brancati F, Valente EM, Ciccodicola A, Rinaldi E, Auricchio A, **Banfi S**. Clinical and molecular genetics of Leber's congenital amaurosis (LCA): a multicenter study of Italian patients. Invest Ophthalmol Vis Sci. 2007;48(9):4284-4290.

b. Testa F, Filippelli M, Brunetti-Pierri R, Di Fruscio G, Di Iorio V, Pizzo M, Torella A, Barillari MR, Nigro V, Brunetti-Pierri N, Simonelli F, **Banfi S**. Mutations in the PCYT1A gene are responsible for isolated forms of retinal dystrophy. Eur J Hum Genet 2017;25(5):651-655.

c. Van de Sompele S, Smith C, Karali M, Corton M, Van Schil K, Peelman F, Cherry T, Rosseel T, Verdin H, Derolez J, Van Laethem T, Khan KN, McKibbin M, Toomes C, Ali M, Torella A, Testa F, Jimenez B, Simonelli F, De Zaeytijd J, Van den Ende J, Leroy BP, Coppieters F, Ayuso C, Inglehearn CF, **Banfi S**, De Baere E. Biallelic sequence and structural variants in RAX2 are a novel cause for autosomal recessive inherited retinal disease. Genet Med 2019;1319-1329.

d. Bedoni N, Quinodoz M, Pinelli M, Cappuccio G, Torella A, Nigro V, Testa F, Simonelli F; TUDP (Telethon Undiagnosed Disease Program), Corton M, Lualdi S, Lanza F, Morana G, Ayuso C, Di Rocco M, Filocamo M, **Banfi S**, Brunetti-Pierri N, Superti-Furga A, Rivolta C. An Alu-mediated duplication in NMNAT1, involved in NAD biosynthesis, causes a novel syndrome affecting multiple tissues and organs. Hum Mol Genet. 2020;29(13):2250-2260.

Complete List of Published Work in MyBibliography