

## Sabrina Carrella, PhD



Born in Naples (Italy), 25/03/1985

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**Current Position:** Tenured Researcher (III level)

**Current Affiliation:**

Ecosustainable Marine Biotechnology Department, Stazione Zoologica Anton Dohrn, Napoli (Italy)

### Education/Training/Experience

INSTITUTION AND LOCATION	DEGREE	YEAR	FIELD OF STUDY
University of the Study of Naples Federico II, Naples, Italy	MS	07/2008	Molecular Biology
University of the Study of Naples Federico II, Naples, Italy	PhD	12/2012	Molecular Medicine
Telethon Institute of Genetics and Medicine (TIGEM), Pozzuoli (NA) and University of Campania Luigi Vanvitelli, Naples, Italy	Postdoctoral Associate Researcher	2013-2021	Human Genetics, Neuroscience
Stazione Zoologica Anton Dohrn, Naples, Italy	Tenured Researcher	2021-present	Ecosustainable Marine Biotechnology

### Honors

2008	Winner of PhD Fellowship, European School of Molecular Medicine (SEMM)
2010	Graziella Persico Travel Award, Institute of Genetics and Biophysics “A. Buzzati-Traverso” – CNR Naples
2010	ESHG Young Investigator Award, Scientific Programme Committee at European Human Genetics Conference 2010
2013	Winner of two-year fellowship, MIUR and TIGEM
2015	Winner of three-year Research Associate fellowship, Università della Campania Luigi Vanvitelli
2019	Winner of one-year Research Associate Fellowship Università della Campania Luigi Vanvitelli

2021 Winner of tenured researcher position at the “Stazione Zoologica-Anton Dohrn”, Naples, Italy

### **Additional Information**

#### **Research Support:**

- “AAV-Sponge-mediated modulation of microRNA-181a/b: a potential therapeutic approach for Inherited Retinal Disease.” Foundation Fighting Blindness. Funding period: 1/6/19-31/5/22. Role: Participant
- “miR-181a/b modulation as potential therapeutic approach for AMD treatment” BrightFocus Foundation. Funding period: 1/11/20-31/10/22. Role: Principal Investigator (until 30/11/2021)
- “MicroRNA expression modulation: a new therapeutic avenue for Inherited Retinal Diseases” Velux Stiftung Foundation. Funding period: 1/11/20-31/10/23. Role: Co-Principal Investigator
- "CRISPR/Cas9 microRNAs Editing as gene-independent therapeutic approach in Inherited Retinal Dystrophies (IRDs)" AFM-Telethon Trampoline grant. Funding period: 1/12/20-30/11/21. Role: Principal Investigator
- “MicroRNAs-mediated environmental adaptation in marine microalgae: from physiological responses to biotechnology applications”. SZN-OU PhD Fellowship. Funding period: 1/10/2022-30/9/2025

#### **Supervision and Training Activities:**

2012-2013: training activity for Dr Ylenia D’Agostino, Master Degree in Biology, University of Naples Federico II, Naples (Italy)

2015-2017: training activity for Dr Ludovica Ciampi, Master Degree in Medical Biotechnology, University of Naples Federico II, Naples (Italy)

2017-2018: training activity for Dr Davide Piccolo, Master Degree in Biology, University of Naples Federico II, Naples (Italy)

2019-present: co-tutor activity for Dr Georgios Petrogiannakis, PhD program in “Molecular Life Science-Human Genetics”, University of Campania "Luigi Vanvitelli" and TIGEM (Telethon Institute of Genetics and Medicine), Naples (Italy)

2020-present: co-tutor activity for Dr Martina Di Guida, PhD program in “Scienze Biomolecolari”, University of Campania "Luigi Vanvitelli" and TIGEM (Telethon Institute of Genetics and Medicine), Naples (Italy)

2021: training activity for Dr Dalila Capasso, PhD program in “Genomic and Experimental Medicine”, Scuola Superiore Meridionale, Naples (Italy)

2020-present: supervisor activity for Dr Simona Brillante, postdoc in the project “miR-181a/b modulation as potential therapeutic approach for AMD treatment” (BrightFocus Foundation)

2020-2021: supervisor activity for Dr Irene Guadagnino, postdoc in the project “MicroRNA expression modulation: a new therapeutic avenue for Inherited Retinal Diseases” (Velux Stiftung Foundation)

2021-2022: thesis tutor and training activity for Dr Eva Cipollaro, Master Degree in Genetics and Molecular Biology, Sapienza University, Rome (Italy)

2021-2022: training activity for Dr Paola Quadrano, pre-doctoral fellow in the project "CRISPR/Cas9 microRNAs Editing as gene-independent therapeutic approach in Inherited Retinal Dystrophies (IRDs)" (AFM-Telethon Trampoline)

2021: supervisor and training activity for Dr Marta Molinari, pre-doctoral fellow in the project “miR-181a/b modulation as potential therapeutic approach for AMD treatment” (BrightFocus Foundation)

2022-present: Director of the Studies and supervisor for Gabriele De Falco, PhD program Open University-SZN, Naples (Italy)

2020-present: External member of the thesis committee in the PhD program at Centre for Genomic Regulation (CRG) in Barcelona. Student name: Dr Ludovica Ciampi, Title of the thesis project: “MIRAS: bringing the Microexons Retina-specific Alternative Splicing program to light”

2020, 2021: Lecturer for the specialistic course “miRNAs in mitochondrial diseases” of second year in the PhD program at TIGEM (SEMM-European School of Molecular Medicine, Genomic and Experimental Medicine, Federico II, Vanvitelli and OPEN University)

2021: Lecturer in the Research Training workshop as part of an “Innovative Training Network” grant. Title of the course: “Implementation of Novel Therapies for IRD”

2022: Lecturer in the course “Marine Genomics – Module of Marine Genomics” at Federico II University. Title of the lesson: “non-coding RNAs in marine organisms”

### **Other:**

- Patent: "mir-181 inhibitors and uses thereof" (WO/2019/202162) 20th of April, 2018

- Member of the examining commission for the public competition number IRGB/AR/002/2021MI; Project: SAC.AD002.020.031, and for the public competition number IRGB/AR/008/2022MI; Project: PRIN 2020 2020XBCMHI - CUP B49I22000550006; at IRGB- Istituto di Ricerca Genetica e Biomedica (CNR)

- Topic Editor: Research Topic” Rare and common neurodegenerative retinal diseases: from molecular mechanisms to the identification of novel mutation-independent therapeutic strategies”. Frontiers In Aging Neuroscience

- Reviewer activities: MDPI (International Journal of Molecular Science, Genes, Pharmaceuticals and Cells), Inflammation Research, European Journal of Neuroscience, and Molecular Therapy

- Dissemination activities: From 2014 to 2019, Scientific dissemination at TIGEM laboratories to schools and/or to civil society; December 5<sup>th</sup> 2015, Participation at “Il non vedente del terzo millennio” Convention, Naples, Italy; December 21st 2018, Scientific dissemination about Retinitis Pigmentosa at “Uno Mattina”, Studi Rai, Rome, Italy; 2022, Scientific dissemination at SZN laboratories at Molosiglio to schools

- 2019-2020: Member of Association for research Vision and Ophthalmology (ARVO)

- 2015-2016: Member of American Society of Cell Biology

- June-October 2016: Maternity leave

- January-June 2019: Maternity leave

### **Publications**

1. Conte I, **Carrella S**, Avellino R, Karali M, Marco-Ferreres R, Bovolenta P, Banfi S. (2010) “miR-204 is required for lens and retinal development via Meis2 targeting.” Proc Natl Acad Sci U S A 107: 15491-15496
2. R. Avellino, **S. Carrella**, M. Pirozzi, M. Risolino, Salierno FG, P. Franco, P. Stoppelli, P. Verde, S. Banfi, I.Conte (2013) “miR-204 targeting of Ankrd13A controls both mesenchymal neural crest and lens cell migration” PLoS One 8: e61099
3. Poulter JA, Al-Araimi M, Conte I, van Genderen MM, Sheridan E, Carr IM, Parry DA, Shires M, **Carrella S**, Bradbury J, Khan K, Lakeman P, Sergouniotis PI, Webster AR, Moore AT, Pal B, Mohamed MD, Venkataramana A, Ramprasad V, Shetty R, Saktivel M, Kumaramanickavel G, Tan A, Mackey DA, Hewitt AW, Banfi S, Ali M, Inglehearn CF,

- Toomes C. (2013) "Recessive Mutations in SLC38A8 Cause Foveal Hypoplasia and Optic Nerve Misrouting without Albinism." *Am J Hum Genet* 93: 1143-1150
4. Ivan Conte, Stefania Merella, Jose Manuel Garcia Manteiga, Chiara Migliore, Dejan Lazarevic, **Sabrina Carrella**, Raquel Marco-Ferrerres, Raffaella Avellino, Davidson Nathan Paul, Warren Emmett, Remo Sanges, Nicholas Bockett, David Van Heel, Germana Meroni, Paola Bovolenta, Sandro Banfi, Elia Stupka. (2014) "The combination of transcriptomics and informatics identifies pathways targetted by miR-204 during neurogenesis and axon guidance". *Nucleic Acids Res* 42: 7793-7806.
  5. **Sabrina Carrella**, Ylenia D'Agostino, Sara Barbato, Sabina P. Huber-Reggi, Francesco Giuseppe Salierno, Anna Manfredi, Stephan C.F. Neuhauss, Sandro Banfi, Ivan Conte (2015). "miR-181a/b control the assembly of visual circuitry by regulating retinal axon specification and growth". *Dev Neurobiol* 75: 1252-1267.
  6. Ivan Conte, Kristen D Hadfield, Sara Barbato, **Sabrina Carrella**, Mariateresa Pizzo, Louise F Porter, Sofie Hateley, James O'Sullivan, Forbes Manson, Stephan C.F. Neuhauss, Sandro Banfi, Graeme C M Black (2015). "MiR-204 is responsible for inherited retinal dystrophy associated with ocular coloboma". *Proc Natl Acad Sci U S A* 112: E3236-3245.
  7. **Sabrina Carrella**, Sara Barbato, Ylenia D'Agostino, Francesco Giuseppe Salierno, Anna Manfredi, Sandro Banfi, Ivan Conte (2015). "TGF- $\beta$  controls miR-181/ERK regulatory network during retinal axon specification and growth." *PlosOne* 10(12):e0144129.
  8. Alessia Indrieri†, **Sabrina Carrella**†, Alessia Romano, Alessandra Spaziano, Elena Marrocco, Erika Fernandez-Vizarra, Sara Barbato, Mariateresa Pizzo, Yulia Ezhova, Francesca M. Golia, Ludovica Ciampi, Roberta Tammara, Jorge Henao-Mejia, Adam Williams, Richard A. Flavell, Elvira De Leonibus, Massimo Zeviani, Enrico M. Surace, Sandro Banfi\*, Brunella Franco\*. "miR-181a/b downregulation exerts a protective action on Mitochondrial Disease models". *EMBO Molecular Medicine*, 2019 † co-first authors; \*co-corresponding authors
  9. Alessia Indrieri, **Sabrina Carrella**, Pietro Carotenuto, Sandro Banfi and Brunella Franco. "The Pervasive Role of the miR-181 Family in Development, Neurodegeneration, and Cancer." *Int J Mol Sci*. 2020
  10. **Sabrina Carrella**\*, Alessia Indrieri, Brunella Franco, Sandro Banfi\*. "Mutation-Independent Therapies for Retinal Diseases: Focus on Gene-Based Approaches". *Front Neurosci*. 2020 \*co-corresponding authors
  11. **Sabrina Carrella**\*, Sandro Banfi\*, Marianthi Karali \*. "Sophisticated gene regulation for a complex physiological system: the role of non-coding RNAs in photoreceptor cells". *Front Cell Dev Biol*. 2021 \*co-corresponding authors
  12. Anna Barbato, Antonella Iuliano, Mariagrazia Volpe, Romina D'Alterio, Simona Brillante, Filomena Massa, Rossella De Cegli, **Sabrina Carrella**, Massimiliano Salati, Annapina Russo, Giulia Russo, Sara Riccardo, Davide Cacchiarelli, Mariaelena Capone, Gabriele Madonna, Paolo A. Ascierio, Brunella Franco, Alessia Indrieri and Pietro Carotenuto. "Integrated Genomics Identifies miR-181/TFAM Pathway as a Critical Driver of Drug-resistance in Melanoma" *Int. J. Mol. Sci*. 2021
  13. **Sabrina Carrella**\*, Filomena Massa, Alessia Indrieri\*. "microRNAs in mitochondrial-related eye diseases" *Front Cell Dev Biol*. 2021 \*co-corresponding authors
  14. Brillante S, Galasso C, Lauritano C, **Carrella S**\*. From the Sea for the Sight: Marine Derived Products for Human Vision. *Front Aging Neurosci*. 2022 May 9;14:892764. doi: 10.3389/fnagi.2022.892764. PMID: 35615590; PMCID: PMC9124809. (\*corresponding author)
  15. Ciampi L, Mantica F, López-Blanch L, Permanyer J, Rodriguez-Marín C, Zang J, Cianferoni D, Jiménez-Delgado S, Bonnal S, Miravet-Verde S, Ruprecht V, Neuhauss SCF, Banfi S, **Carrella S**, Serrano L, Head SA, Irimia M. Specialization of the photoreceptor transcriptome by Srrm3-dependent microexons is required for outer segment maintenance

- and vision. Proc Natl Acad Sci U S A. 2022 Jul 19;119(29):e2117090119. doi: 10.1073/pnas.2117090119. Epub 2022 Jul 12. PMID: 35858306; PMCID: PMC9303857.
16. Nocera GM, Viscido G, Criscuolo S, Brillante S, Carbone F, Staiano L, **Carrella S**, di Bernardo D. The VersaLive platform enables microfluidic mammalian cell culture for versatile applications. Commun Biol. 2022 Sep 29;5(1):1034. doi: 10.1038/s42003-022-03976-8. Erratum in: Commun Biol. 2022 Oct 13;5(1):1090. PMID: 36175545; PMCID: PMC9522807.
  17. **Carrella S\***, Di Guida M, Brillante S, Piccolo D, Ciampi L, Guadagnino I, Garcia Piqueras J, Pizzo M, Marrocco E, Molinari M, Petrogiannakis G, Barbato S, Ezhova Y, Auricchio A, Franco B, De Leonibus E, Surace EM, Indrieri A, Banfi S\*. miR-181a/b downregulation: a mutation-independent therapeutic approach for inherited retinal diseases. EMBO Mol Med. 2022 Oct 4:e15941. doi: 10.15252/emmm.202215941. Epub ahead of print. PMID: 36194668. (\*co-corresponding authors)

### **ATTENDACES at NATIONAL and INTERNATIONAL CONFERENCES**

- Conte I, **Carrella S**, Avellino R, Karali M, Marco-Ferreres R, Bovolenta P, Banfi S. "The microRNA miR-204 is required for vertebrate eye development". ESHG. Gothenburg, Sweden (June, 2010) Oral presentation (**presenting author: Sabrina Carrella**)
- **Sabrina Carrella**, Ylenia D'Agostino, Sara Barbato, Francesco Giuseppe Salierno, Stephan C.F. Neuhauss, Sandro Banfi, Ivan Conte. "Study of miRNA roles in retinal axon specification and growth" 8th European Zebrafish meeting, Barcelona (July, 2013). Oral presentation
- **Sabrina Carrella**, Ylenia D'Agostino, Sara Barbato, Francesco Giuseppe Salierno, Stephan C.F. Neuhauss, Sandro Banfi, Ivan Conte. "Study of miRNA roles in retinal axon specification and growth" British Society for Developmental Biology Autumn Meeting 2013\_Axon guidance and Regeneration, University of Aberdeen, Aberdeen, Scotland, UK (August, 2013).
- **Carrella S**, Indrieri A, Golia F, Romano A, Pizzo M, Marrocco E, Giordano N, Carboncino A, Tammaro R, De Leonibus E, Surace E, Banfi S, Franco B. "miR-181 modulation has a protective effect in in vivo models of mitochondria-mediated neurodegeneration". 1st Tri-Retreat meeting. May 2016, Rome, Italy Oral presentation
- **Carrella S.**, Indrieri A., Piccolo D., Ciampi L., Pizzo M., Barbato S., Marrocco E., Ezhova Y., Franco B., Surace E.M., Banfi S. "MicroRNAs miR-181a and miR-181b (miR-181a/b) downregulation as potential therapeutic approach for Inherited Retinal Diseases (IRDs)". TIGEM Retreat 2019, Paestum. Oral presentation
- **Carrella S.**, Indrieri A., Piccolo D., Ciampi L., Pizzo M., Barbato S., Marrocco E., Ezhova Y., Franco B., Surace E.M., Banfi S. "MicroRNAs miR-181a and miR-181b (miR-181a/b) downregulation as potential therapeutic approach for Inherited Retinal Diseases (IRDs)" IX Neapolitan Brain Group Meeting, December 2019, Naples, Italy. Oral presentation
- **Sabrina Carrella**, Alessia Indrieri, Davide Piccolo, Ludovica Ciampi, Mariateresa Pizzo, di Guida Martina, Petrogiannakis Georgios, Sara Barbato, Elena Marrocco, Yulia Ezhova, Brunella Franco, Enrico Maria Surace, Sandro Banfi "miR-181a/b downregulation: a possible gene-independent therapeutic approach for inherited retinal diseases". ARVO 2020 meeting in Baltimore Oral presentation ARVOLearn platform (on-line due to COVID-19).
- **Sabrina Carrella**, Alessia Indrieri, Davide Piccolo, Ludovica Ciampi, Mariateresa Pizzo, di Guida Martina, Petrogiannakis Georgios, Sara Barbato, Elena Marrocco, Yulia Ezhova, Brunella Franco, Enrico Maria Surace, Sandro Banfi "miR-181a/b downregulation: a possible gene-independent therapeutic approach for inherited retinal diseases". 2nd Genetics

of Ocular Development meeting 2020, 7th September 2020 On-line Oral presentation (due to COVID-19)

- **Sabrina Carrella**, Martina Di Guida, Davide Piccolo, Ludovica Ciampi, Mariateresa Pizzo, Georgios Petrogiannakis, Sara Barbato, Elena Marrocco, Yulia Ezhova, Brunella Franco, Enrico Maria Surace, Alessia Indrieri, Sandro Banfi. miR-181a/b downregulation: a possible gene-independent therapeutic approach for inherited retinal diseases (IRDs). (EMBO workshop- Mitochondrial homeostasis and human disease 2021)
- **Sabrina Carrella**, Martina Di Guida, Davide Piccolo, Ludovica Ciampi, Mariateresa Pizzo, Marta Molinari, Simona Brillante, Elena Marrocco, Irene Guadagnino, Georgios Petrogiannakis, Sara Barbato, Yulia Ezhova, Brunella Franco, Enrico Maria Surace, Alessia Indrier, Sandro Banfi. “AAV-Sponge-mediated modulation of miR-181a/b as a gene-independent therapeutic approach for inherited retinal diseases (IRDs)” (ESGCT 2021)
- **Sabrina Carrella**, Martina Di Guida, Davide Piccolo, Ludovica Ciampi, Mariateresa Pizzo, Marta Molinari, Simona Brillante, Elena Marrocco, Irene Guadagnino, Georgios Petrogiannakis, Sara Barbato, Yulia Ezhova, Brunella Franco, Enrico Maria Surace, Alessia Indrier, Sandro Banfi. “Modulation of miR-181a/b as a gene-independent therapeutic approach for inherited retinal diseases (IRDs)” (SIGU 2021, oral presentation)

#### **ABSTRACTS at NATIONAL and INTERNATIONAL CONFERENCES**

- Marianthi Karali, Alessandro Gennarino, Raffaella Avellino, Ivan Conte, Antonietta Carola, Silvia Catuogno, **Sabrina Carrella**, Vincenza Maselli, Sandro Banfi. “MicroRNAs involved in eye development and function.” Human health foundation & CELBIO meeting (2008).
- Ivan Conte, **Sabrina Carrella**, Raffaella Avellino, Marianthi Karali, Sandro Banfi. “Mir-204 Modulates Optic Cup Patterning During Medaka Fish Embryonic Eye Development”. ARVO meeting, Invest.Ophthalmol.Vis.Sci. (2009).
- Conte I, **Carrella S**, Avellino R, Karali M, Marco-Ferrerres R, Bovolenta P, Banfi S. “miR-204 is required for vertebrate eye development via Meis 2 targeting and Pax6 regulation” 6th European Zebrafish Genetics and Development Meeting.Rome, Italy (2009).
- Banfi S, **Carrella S**, Avellino R, Karali M, Marco-Ferrerres R, Bovolenta P, Conte I.” miR-204 is required for vertebrate eye development”. 59th Annual ASHG Meeting, Hawaii. (2009)
- R. Avellino, **S. Carrella**, M. Karali, M. Pirozzi, R. Marco-Ferrerres, P. Franco, P. Stoppelli, P. Bovolenta, S. Banfi, I.Conte “miR-204 is required for lens morphogenesis”. ISER (2012) Oral presentation
- Ivan Conte, **Sabrina Carrella**, Sara Barbato, Raffaella Avellino, Francesco Giuseppe Salierno, Ylenia D’Agostino, Sandro Banfi. “Mir-204 as a ‘key regulator’ of vertebrate eye development and function. 8th European Zebrafish meeting, Barcelona (July, 2013) Oral presentation
- A Indrieri\*, **S Carrella\***, A. Romano, F Golia, M Pizzo, R Tammaro, E Marrocco, N Giordano, A Carboncino, A Spaziano, L Ciampi, J Henao-Mejia, A Williams, R Flavell, E De Leonibus, EM Surace, S Banfi, B Franco. miR-181a and miR-181b downregulation protects from Mitochondria-associated Neurodegeneration by enhancing mitochondrial biogenesis and mitophagy. Keystone Symposia - Mitochondrial Biology - Kyoto, Japan - April 24, 2018
- **S Carrella\***, A Indrieri\*, A Romano, F Golia, M Pizzo, R Tammaro, E Marrocco, N Giordano, A Carboncino, A Spaziano, L Ciampi, J Henao-Mejia, A Williams, RA Flavell, E De Leonibus, EM Surace, S Banfi, B Franco. “miR-181a and miR-181b downregulation

- protects from Mitochondria-associated Neurodegeneration by enhancing mitochondrial biogenesis and mitophagy. European Society of Human Genetics meeting 16-19 June, 2018, Milan, Italy. Session: Metabolic and Mitochondrial disorders. Oral presentation
- Indrieri Alessia\*, **Carrella Sabrina\***, Romano Alessia, Spaziano Alessandra, Golia Francesca, Pizzo Mariateresa, Tammaro Roberta, Marrocco Elena, Giordano Nadia, Carboncino Anna, Ciampi Ludovica, Barbato Sara, De Leonibus Elvira, Surace Enrico Maria, Banfi Sandro, Franco Brunella. MIR-181a AND MIR-181b DOWNREGULATION PROTECTS FROM MITOCHONDRIA-ASSOCIATED NEURODEGENERATION BY ENHANCING MITOCHONDRIAL BIOGENESIS AND MITOPHAGY. VIII° MEETING NEAPOLITAN BRAIN GROUP, december 13 2018, Naples, Italy. Oral presentation
  - Indrieri A.\*, **Carrella S.\***, Barbato S, Spaziano A, Marrocco E., Fernandez-Vizarra E., Volpe M.G., Pizzo M.,Ezhova Y, Golia F.M, Ciampi L, Tammaro R, Giordano N, Carboncino A, Zeviani M, De Leonibus E., Surace E.M.2, Banfi S., Franco B. miR-181a/b downregulation as new therapeutic strategy in mitochondria-associated neurodegeneration IX Neapolitan Brain Group Meeting, December 12 2019, Naples, Italy. Oral presentation
  - Martina Di Guida, Irene Guadagnino, Mariateresa Pizzo, Marta Molinari, **Sabrina Carrella**, Sandro Banfi. “AAV-sponge mediated downregulation of miR-181a/b exerts a gene-independent protection on photoreceptors degeneration in inherited retinal dystrophies” Genetics of ocular development (Good) meeting 2021- oral presentation
  - Simona Brillante, Eva Cipollaro, Marta Molinari, Sandro Banfi, Alessia Indrieri, **Sabrina Carrella**. “miR-181a/b modulation as potential therapeutic approach for AMD treatment.” Genetics of ocular development (Good) meeting 2021- oral presentation
  - **Sabrina Carrella**, Martina Di Guida, Georgios Petrogiannakis, Dalila Capasso, Mariateresa Pizzo, Marta Molinari, Simona Brillante, Eva Cipollaro, Paola Quadrano, Karla Ruiz, Santiago Negueruela, Marianthi Karali, Alessia Indrieri, Sandro Banfi. Modulation of microRNA expression: a new therapeutic avenue for inherited retinal disease? (Sandro Banfi, Invited speaker ESGCT 2021)