Society for Acquired Resilience Meeting

AR 2026

Fourth Meeting

2 – 4 September 2026

Genova

Università di Genova

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Program
AR 2026

Wednesday, 2nd September 2026

14:00 – 15:00	**Registration**
15:00 – 15:15	**Welcome**
15:15 – 15:40	**Prof. Fabio Benfenati, Italian Institute of Technology (IIT)** Promoting functional integration of retinal prosthetic interventions in photoreceptor degeneration prostheses through environmental enrichment
15:40 – 16:00	**Mattia Di Paolo, PhD, University of Louisville** Functional Resilience of Rod-Mediated Vision Under Photopic Conditions in the Absence of Cone Phototransduction
16:00 – 16:10	**Poster Quick Fire Talks**
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Thursday, 3rd September 2026

08:30 – 09:00	**Registration**
09:00 – 09:50	**Prof. Silvia Bisti, National Institute of Biostructures and Biosystems (INBB)** The Story Behind the Founding of the Society for Acquired Resilience
09:50 – 10:15	**Prof. Jonathan Stone, The University of Sydney** A look at the mechanisms of resilience that protect against neurodegeneration
10:15 – 10:35	**Andrew Daoud, Philadelphia College of Osteopathic Medicine** Role of Brain-Specific Angiogenesis Inhibitor 1 (BAI-1) in Retinal Neovascularization and Visual Function in a Murine Model of Retinopathy of Prematurity
10:35 – 11:05	**Coffee Break**
11:05 – 11:30	**Prof. Piera Versura, University of Bologna** Cord Blood Serum Eye Drops: Fifteen Years of Translational Research toward Retinal Neuroprotection
11:30 – 12:30	**Business meeting Society**
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14:00 – 14:25 **Prof. Ann Liebert, Shepherd University, WV, Australia**
Acquired resilience to reduce the progression of intractable diseases: The potential of photobiomodulation for chronic kidney disease.

14:25 – 14:45 **Alessandra La Terra, PhD, Italian Institute of Technology**
Mechanisms of adaptive resilience to neuroinflammation in a mouse model of Multiple Sclerosis

14:45 – 15:10 **Alessandra Puddu, University of Genova**
RPE Resilience: From Physiological Adaptation to Retinal Disease

15:05 – 15:20 **Rocco Mastromartino, Catholic University of Sacred Heart (Rome)**
Functional Visual Effects of Saffron, Photobiomodulation, and Subthreshold Laser in Age-Related Macular Degeneration: A Retrospective Review

15:20 – 15:50 **Coffee Break**

15:50 – 16:15 **Francesca Corsi, PhD, University of Pisa**
From Neuroprotection to Resilience: Targeted and Nutraceutical Approaches in Retinal Degeneration

16:15 – 16:30 **Federica De Cecco, PhD, IRCCS AOM San Martino (Genova)**
Retinal Network Dysfunction and Neuroprotection in the Ins2Akita Mouse Model of Diabetic Retinopathy

16:30 – 16:55 **Camille Monchaux de Oliveira, PhD, University of Bordeaux & Activ'Inside**
A Standardized Saffron Extract (Safr'Inside™) for Stress Resilience: Clinical and Mechanistic Evidence Across Mood, Sleep and Stress Regulation

16:55 – 17:20 **Prof. Stefano Di Marco, University of Genova**
Matching the Prosthesis to the Disease: Interfacing Injectable and Optical Retinal Rescue Strategies with Distinct Modes of Photoreceptor Degeneration

Friday, 4th September 2026

09:00 – 09:30 **Registration**

09:30 – 10:20 **Prof. Jonathan Stone, The University of Sydney**
The Evolutionary Origins of Dementia

10:20 – 10:45 **Vicky Chrysostomou, PhD, Duke-NUS Medical School, Singapore**
Acquired Resilience in the Retina and Exercise: An Overview

10:45 – 11:00 **Siena Hasson, Philadelphia College of Osteopathic Medicine**
Neuroprotective Effect of Intravitreal Administration of Noggin in Mice with Retinitis Pigmentosa (RP)

11:00 – 11:30 **Coffee Break**

11:30 – 11:45	**Leo McLean, Philadelphia College of Osteopathic Medicine** Role of BAI1 in Diabetic Wound Healing: A Mouse Model Using Streptozotocin-Induced Diabetes
11:45 – 12:10	**Prof. Arturo Bravo Nuevo, Philadelphia College of Osteopathic Medicine** Myo/Nog Cells: What Are They and Their Neuro-Protective Dilemma
12:30 – 13:00	**Prizes and Greetings**
13:00 – 14:30	**Lunch**

List of the posters:

1. **Alessia Galante**, J. Di Pierdomenico, I. Piano, M. Norte Muñoz, F. Corsi, M. A. Maggi, S. Bisti, C. Gargini, D. Garcia Ayuso
   Saffron and tepal extracts (Repron®) exert model-specific neuroprotective effects in retinal degeneration

2. **Alessandra La Terra**, Giorgio Grasselli
   Mechanisms of adaptive resilience to neuroinflammation in a mouse model of Multiple Sclerosis

3. **Federica De Cecco**, N. Telitsyn, G. Ferrara, A. La Terra, T. Vigo, A. Uccelli, F. Benfenati, G. Grasselli, S. Di Marco
   High-density multielectrode array recordings uncover early retinal ganglion cell dysfunction in EAE

4. **Daoud, Andrew**; Riaz, Tabish; Margulies, Kyle; Perez, Naheed; Heist, Brian; Crispin, Mara; Van Meir, Erwin G.; George-Weinstein, Mindy; and Bravo-Nuevo, Arturo
   Role of Brain-Specific Angiogenesis Inhibitor 1 (BAI-1) in Retinal Neovascularization and Visual Function in a Murine Model of Retinopathy of Prematurity

5. **Siena Hasson**
   Neuroprotective Effect of Intravitreal Administration of Noggin in Mice with Retinitis Pigmentosa (RP)

6. **Leo McLean and Jeshur Thangaraj**
   Role of BAI1 in Diabetic Wound Healing: A Mouse Model Using Streptozotocin-Induced Diabetes

7. **Maggi Maria Anna**, Silvia Bisti
   The Chemical Characterization of Natural Substances: A Fundamental Requirement for Ensuring Their Quality, Safety, and Efficacy in Human Use

Abstracts & Authors

Prof. Fabio Benfenati

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AFFILIATION & CURRENT POSITION

Director of the Center for Synaptic Neuroscience and Technology (NSYN)
at the Italian Institute of Technology (IIT)

Brief CV

Fabio Benfenati graduated in Medicine in 1979 at the Alma Mater University of Bologna, where he specialized in Neurology in 1983. He began his research track first at the Neuroscience Department of the Karolinska Institutet, Stockholm, and then at the Rockefeller University, New York, in the laboratory of Nobel laureate Paul Greengard, with whom he established a long-lasting collaboration. Benfenati is a professor of Neurophysiology at the University of Genoa from 2000 to 2026, and Research Director at the Italian Institute of Technology (IIT) since 2006. Within IIT, he is currently coordinating the Center for Synaptic Neuroscience and Technology, leading a group of 30 young neuroscientists. Over the years, he has made important contributions to the physiological mechanisms of synaptic transmission and plasticity, as well as to the pathogenetic mechanisms of human neurological disorders. More recently, he started the field of hybrid light-sensitive interfaces between neurons and nanomaterials, at the border between neuroscience, nanotechnology and neuroprosthetics. Fabio Benfenati is the author of over 400 research papers in peer-reviewed international journals, including several in Science, Nature, and Cell, with an h-index of 86 and over 27,000 citations. He is a co-inventor of 5 patents. He is member of Academia Europæa and of the Academy of the International Union of Physiological Sciences. During his career, he was President of the Italian Society for Neuroscience and of the Italian Physiological Society, and he is currently President of the Federation of European Physiological Societies and a member of the Council of Scientists of Human Frontiers Science Program Organization. In 2024, he was awarded the Feltrinelli Prize by the Accademia Nazionale dei Lincei for his contributions in Physiology and Neuroscience.

Promoting functional integration of retinal prosthetic interventions in photoreceptor degeneration prostheses through environmental enrichment

E. Porzano[1,2], C. Ciani[1], G. Mantero[1], C. Michetti[1,2], L. Ciano[1], S. Di Marco[1,2], E. Colombo[1,3], F. Benfenati[1,3]

[1]Center for Synaptic Neuroscience and Technology, Istituto Italiano di Tecnologia, Genova, Italy; [2]Department of Experimental Medicine, University of Genova, Italy; [3]AOM IRCCS Ospedale Policlinico San Martino, Genova, Italy.

Visual loss in neurodegenerative conditions, such as Retinitis Pigmentosa, is characterized by the progressive death of photoreceptors and subsequent inner retina remodeling. In our laboratory, we utilize the *rd10* mouse model of Retinitis pigmentosa to develop innovative neuro-prosthetic strategies, through the subretinal injection of organic photovoltaic nanoparticles (NP, composed of poly(3-hexylthiophene, P3HT) or membrane-targeted photochromic compounds, such as Ziapin2. While restoring light sensitivity is the primary goal, functional recovery strongly relies on the visual cortex's capacity to process the new visual prosthetic signals. Visual cortical plasticity is high during early life and progressively decreases afterward. Interestingly, environmental enrichment (EE), a non-invasive condition of enhanced sensory stimulation and social interaction, increases cortical plasticity and cognitive abilities.

We recently implemented such an EE protocol in our visual restoration studies and discovered that enriched housing dramatically enhances neurorehabilitation and neural rewiring following P3HT-NP injection. Following subretinal microinjection, *rd10* mice underwent a two-month EE protocol designed to promote sensory, motor, and cognitive stimulation. Visual recovery was assessed using a range of behavioral and neurophysiological assays.

We have found a positive effect in visually guided behaviors when combining the treatment with P3HT-NPs with EE. Mice exposed to EE showed improved performance in OMR scores, suggesting enhanced visuo-motor acuity, and stronger responses in fear-conditioning paradigms, consistent with more effective processing of learned visual cues. In parallel, VEP recordings revealed a tendency toward increased cortical responsiveness to light stimulation, with larger evoked responses in the combined treatment group. We are currently planning to apply this strategy to the visual recovery observed after intravitreal administration of the photochromic compound Ziapin2.

This study demonstrates that coupling a retinal prosthetic strategy with sensory stimulation and enhancement of visual cortical plasticity can effectively optimize neurorehabilitation in retinal dystrophies caused by photoreceptor degeneration.

Mattia Di Paolo, PhD

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AFFILIATION & CURRENT POSITION

Postdoctoral Associate in the Department of Ophthalmology and Visual Sciences at the University of Louisville

Brief CV

Mattia Di Paolo is a neuroscientist specializing in visual neurophysiology and retinal neurodegeneration, with over a decade of experience investigating mechanisms underlying retinal dysfunction and developing strategies to preserve visual function. He currently works as a Postdoctoral Associate in the Department of Ophthalmology and Visual Sciences at the University of Louisville, where his research focuses on humanized animal models of P23H rhodopsin-associated Retinitis Pigmentosa and the evaluation of disease progression and therapeutic strategies.

His research combines retinal electrophysiology, in vivo imaging, behavioral assessment, histology, molecular biology, and quantitative image and data analysis to characterize structural and functional changes associated with retinal degeneration. His current work includes the phenotypic characterization of novel humanized mouse models and the study of retinal gene-therapy approaches, as well as the coordination of transgenic porcine preclinical studies for translational ophthalmic research.

He received his PhD in Neurobiology of Neurodegenerative Diseases, Neuronal Development and Plasticity from the University of L'Aquila, Italy, with a thesis focused on visual function preservation in animal models of retinal neurodegeneration. During his doctoral and postdoctoral training, he investigated retinal neuroprotective approaches including photobiomodulation and saffron-based treatments, retinal prostheses, and mechanisms of light-induced retinal degeneration.

His work has resulted in peer-reviewed publications and presentations at international scientific meetings, including ARVO and European Retina Meeting, spanning retinal degeneration, retinal prosthetics, neuroprotection, and translational retinal research.

Functional Resilience of Rod-Mediated Vision Under Photopic Conditions in the Absence of Cone Phototransduction

Di Paolo M. [1], Hasan N [2], Frye KE [1], Gregg RG [2], McCall MA [1,3]

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Purpose: The visual system must maintain function across a broad range of lighting conditions despite challenges to photoreceptor signaling. Rod- and cone-mediated vision depends on ambient light intensity, wavelength, and visual contrast, although the limits of rod function under photopic conditions remain incompletely understood. Previous electrophysiological studies have shown that rods can partially recover responsiveness during sustained bright illumination despite initial saturation. Here, we investigated whether rod-mediated signaling contributes to photopic visual function in the absence of cone phototransduction and whether this represents a form of functional resilience within the visual system.

Methods: Visual acuity (VA) and contrast sensitivity were assessed in GNAT2 knockout (Gnat2−/−) mice under scotopic and photopic conditions using the Visual Water Task (Prusky et al.). Retinal function was evaluated by flash electroretinography across increasing stimulus intensities.

Results: Photopic ERG responses were absent in Gnat2−/− mice, confirming the loss of cone-mediated phototransduction. Nevertheless, knockout animals successfully learned and performed the Visual Water Task under photopic illumination, although photopic training was facilitated by prior scotopic training. Both scotopic and photopic visual acuity were significantly reduced compared with wild-type controls. Photopic contrast sensitivity was lower than scotopic contrast sensitivity but improved following prolonged light adaptation.

Conclusion: Our findings demonstrate that visual behavior can be maintained under photopic conditions despite the absence of cone phototransduction, highlighting an unexpected capacity for functional resilience within the visual system.

Alessia Galante, PhD

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AFFILIATION & CURRENT POSITION

PhD Candidate, Department of Pharmacy, University of Pisa
Laboratory of Physiology, Prof. Maria Claudia Gargini. Research focused on neuroprotective strategies for retinal degenerative diseases, with particular interest in oxidative stress, neuroinflammation and cellular resilience. PhD project: Valorization of Crocus sativus L. by-products for the sustainable development of phytocomplexes with potential neuroprotective action.

PUBLICATIONS

• Carullo G., Orsini N., Piano I., Pozzetti L., Papa A., Fontana A., Napoli D., Corsi F., Di Marco B., Galante A., et al. – "Targeting Relevant HDACs to Support the Survival of Cone Photoreceptors in Inherited Retinal Diseases: Identification of a Potent Pharmacological Tool with In Vitro and In Vivo Efficacy" - J Med Chem. 2024 Sep 12;67(17):14946-14973.
• Corsi F., Galante A., Maggi MA., et al. – "The efficacy of Saffron Repron® in counteracting the progression of retinitis pigmentosa: Neuroprotection and resilience." Asia Pac J Ophthalmol (Phila). 2025 Mar 22:100192.
• Galante A, Corsi F, Cioni E, Di Stasi M, Maggi MA, Bisti S, Piano I, Gargini C. In Vitro Evaluation of the Protective Efficacy of Crocus sativus L. Waste for the Sustainable Development of Bioactive Phytocomplexes. Molecules. 2025; 30(14):2894.
• Carullo G., Piano I., Salamone G., Corsi F., Orsini N., Dichiara M., Cursaro I., Fontana A., Galante A., Contri C., Guadagno L., Caroli J., Mattevi A., Vincenzi F., Varani K., Brogi S., Gemma S., Butini S., Gargini C., Strettoi E., Campiani G.; Uncovering a Mutation-Independent Therapeutic Strategy against Inherited Retinal Diseases: Development of Class I HDAC/LSD1 Hybrid Inhibitors. ACS Chem. Neurosci. 3 September 2025; 16 (17): 3364–3384.
• Corsi F, Castagnoli J, Galante A, Fabiano A, Nuti E, Piras AM, Taliani S, Piano I, Gargini C. TSPO Modulation Prevents Photoreceptor Degeneration and Produces Neuroprotective Effects in an Animal Model of Retinitis Pigmentosa. Cells. 2025; 14(22):1778.
• Galante A, Corsi F, Amato R, Taliani S, Da Settimo F, Cammalleri M, Piano I, Dal Monte M, Gargini C. TSPO Modulation by PIGA-1138 Attenuates Oxidative Stress and Preserves Retinal Function in Experimental Diabetic Retinopathy. Antioxidants. 2026; 15(8):1000.

Saffron and tepal extracts (Repron®) exert model-specific neuroprotective effects in retinal degeneration

Alessia Galante[1], J. Di Pierdomenico[2], I. Piano[1,3,4], M. Norte Muñoz[2], F. Corsi[1,3], M. A. Maggi[5,6], S. Bisti[3,5], C. Gargini[1,3,4], D. Garcia Ayuso[2]

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[2] Department of Ophthalmology, Universidad de Murcia e IMIB-Arrixaca, Murcia, Spain.
[3] National Institute of Biostructures and Biosystems (INBB), Via Medaglie d'Oro 305, 0136 Rome, Italy;
[4] CISUP, Center for Instrument Sharing of the University of Pisa, University of Pisa, Lungarno Pacinotti 43/44, 56126 Pisa, Italy;
[5] Hortus Novus srl, Via Campo Sportivo 2, 67050 Canistro, Italy;
[6] Department of Physical and Chemical Sciences, University of L'Aquila, 67100 Coppito, Italy.

Several studies have demonstrated that saffron (REPRON®) exerts neuroprotective effects in retinal degenerations. These beneficial effects have been mainly attributed to the presence of bioactive compounds known for their antioxidant and anti-inflammatory properties. In the context of a circular economy approach, saffron floral by-products (tepals), which are usually discarded during spice production, were investigated as a potential source of bioactive molecules capable of exerting protective effects in retinal degeneration.

Two rat models were used: P23H-1, carrying a rhodopsin mutation that induces protein misfolding, endoplasmic reticulum stress, and rod cell death; and RCS, with an excessive mutation in Mertk that impairs phagocytosis by the retinal pigment epithelium, leading to debris accumulation and secondary photoreceptor degeneration.

Pregnant females received either saffron or tepal extract (os, 10 mg/kg) starting from gestational day 10 until weaning. Treatment was subsequently continued in the offspring until postnatal day 60 (P60).

Retinal function and morphology were longitudinally evaluated at P24, P30, P45, and P60 using electroretinogram (ERG) and optical coherence tomography (OCT). At the end of the experimental period, immunohistochemistry was performed to investigate cellular and structural changes within the retina.

Overall, a protective effect on retinal structure was observed in treated animals; however, this effect varied depending on the stage of disease progression and differed between the two experimental models. ERG recordings showed only limited functional improvement in P23H-1 rats, suggesting that the treatment had a modest impact on retinal function in this model characterized by primary photoreceptor degeneration. In contrast, in the RCS model the protective effect appeared more pronounced, although transient, indicating that the treatment may partially delay the progression of degeneration associated with impaired RPE phagocytosis.

Alessandra La Terra, PhD Alessandra.LaTerra@iit.it

AFFILIATION & CURRENT POSITION

PhD Student at the University of Genoa (Italy)

EDUCATION

PhD student in Neuroscience (Curriculum: Clinical and Experimental Neuroscience)
University of Genoa | Genoa | 2023-present
Supervisors: Giorgio Grasselli & Antonio Uccelli
Master's degree in Medical-pharmaceutical biotechnology
University of Genoa | Genoa | 2021-2023
Final grade: 110/110 cum laude
Supervisors: Fabio Benfenati & Giorgio Grasselli
Thesis title: Study of activity-dependent neuronal plasticity in mouse cerebellum through the design and use of viral vectors and immunohistochemistry
Bachelor's degree in Biotechnology
University of Genoa | Genoa | 2018-2021
Supervisors: Fabio Benfenati & Giorgio Grasselli
Final grade: 110/110 cum laude
Thesis title: Study of activity-dependent spinogenesis in Purkinje neurons via in vivo silencing in climbing fibers

TECHNICAL SKILLS

- Histology and microscopy (immunohistochemistry, RNAscope, optical and confocal microscopy)
- Molecular Biology and Biochemistry (basic cloning methods and bacterial transformation, PCR, enzymatic digestion, qPCR)
- Image analysis (ImageJ)
- Electrophysiology (patch-clamp recordings on acute cerebellar slices)
- Animal surgery and treatments (stereotaxic cerebellar injections and pups' intracisternal magna injections, intraperitoneal injections)
- Behavior (open field, rotarod, beam balance, climbing test, grooming test, social recognition test, clinical motor score assessment of EAE- experimental autoimmune encephalomyelitis, Eyeblink conditioning)
- Data analysis and statistics (MS Excel, GraphPad Prism, Jamovi)

Mechanisms of adaptive resilience to neuroinflammation in a mouse model of Multiple Sclerosis

Alessandra La Terra, Giorgio Grasselli

University of Genova, DIFAR department;
Center for Synaptic Neuroscience and Technology, Istituto Italiano di Tecnologia
IRCCS AOM Ospedale Policlinico San Martino, Genova

Neuroinflammation causes neuronal dysfunctions that contribute to the pathogenesis of multiple sclerosis and of its mouse model, the experimental autoimmune encephalomyelitis (EAE). Neuroinflammation is also associated with the upregulation of the transcriptional repressor REST (RE1-silencing transcription factor), a master regulator of neuron-specific genes, including ion channels involved in the regulation of intrinsic excitability. Its contribution to promoting or protecting from the pathology remains to be clarified. Here, we found that REST is upregulated in neurons in the spinal cord during EAE in association with a consistent downregulation of REST-repressed genes. We knocked out REST in neurons of the lower central nervous system of mice, by injecting AAV vectors expressing CRE or its recombinase-defective variant (deltaCRE) intra cisterna magna at birth, and induced EAE after 8 weeks by immunization with the autoantigen myelin-oligodendrocyte glycoprotein peptide 35-55 (MOG35-55). We observed that REST depletion is associated with an experience-dependent decrease in the latency-to-fall time on an accelerating Rotarod compared to deltaCRE-treated EAE mice, and with lower walking performance in the open field. Although the treatment did not significantly affect clinical score and weight changes in female EAE mice, in males it was associated with a higher peak score and trends towards a larger relative weight loss and a higher disease incidence.
The treatment was not associated with differences in serum levels of major cytokines confirming purely neuronal mechanisms underlying the observed behavioural effects. Our data therefore show that, during EAE, REST is upregulated in neurons and indicate that this may protect from EAE-induced motor impairments through its role in gene regulation by promoting an adaptive response to neuroinflammation.

Federica De Cecco, PhD

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AFFILIATION & CURRENT POSITION

Postdoctoral researcher, IRCCS AOM San Martino Genova, Italy

Brief CV

Postdoctoral researcher
IRCCS AOM Azienda Ospedaliera Metropolitana, *Genoa (Italy)*
Scientific supervisor: Prof. Stefano Di Marco
Topic: Modulation of neuronal excitability as an early therapeutic target to prevent neurodegeneration in EAE.
Study of early neuroinflammatory dysfunction in multiple sclerosis using the EAE mouse model. *Ex vivo* electrophysiological characterization of retinal circuits and axonal conduction tracking in retinal ganglion cells (RGCs) using high-density multielectrode arrays (HD-MEAs).
The research activity was conducted in the laboratory of Professor Fabio Benfenati, at Center of the Center for Synaptic Neuroscience and Technology (NSYN), Istituto Italiano di Tecnologia (IIT), located at the IRCCS Ospedale Policlinico San Martino in Genoa.

Postdoctoral researcher
University of Genoa, *Genoa (Italy)*
Scientific supervisor: Prof. Stefano Di Marco
Topic: Investigation of neurodegenerative diseases associated with the retina.
Evaluation of disease progression using different murine models to test therapeutic efficacy on molecular pathways. Preparation of histological samples for microscopy analysis (fixation, dehydration, inclusion, cutting, staining), immunofluorescence, immunohistochemistry, experience with animal models (retina dissection, flat mount, subretinal injection, intravitreal injection). Behavioral tests in rat and mouse models. The research activity was conducted in the laboratory of Professor Fabio Benfenati, at the Center for Synaptic Neuroscience and Technology (NSYN), Istituto Italiano di Tecnologia (IIT), located at the IRCCS Ospedale Policlinico San Martino in Genoa.

PhD student
University of G. D'Annunzio Chieti-Pescara, Chieti (Italy)
Scientific supervisor: Prof. Lorenza Speranza
Title of thesis: "Valorization and biofunctional characterization of the petals of Crocus Sativus (saffron) from Navelli and potential use in the antiinflammatory therapy of IBD". The main purpose of this study is to evaluate Saffron Petal Extract (SPE) as a potential complementary therapeutic agent for the treatment of Inflammatory Bowel Disease (IBD). In vitro cell treatments with natural compounds, PBMC isolation from peripheral blood, MTT metabolic activity assay, Bradford Protein Assay, Western Blot, ELISA assays, colorimetric enzymatic assays, RT-PCR real time. Data analyses and data presentation. The research was done in collaboration with the University of L'Aquila.

High-density multielectrode array recordings uncover early retinal ganglion cell dysfunction in EAE

F. De Cecco[1,2], N. Telitsyn[1,2], G. Ferrara[1], A. La Terra[1,2,3], T. Vigo[1], A. Uccelli[1,3], F. Benfenati[1,2], G. Grasselli [1,2,5], S. Di Marco[1,2,4]

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2. Center for Synaptic Neuroscience and Technology, Istituto Italiano di Tecnologia, Genova, Italy.
3. Department of Neurosciences, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), University of Genova, Genova, Italy
4. Department of Experimental Medicine (DIMES), University of Genova, Genova, Italy
5. Department of Pharmacy (DIFAR), University of Genova, Genova, Italy

Introduction: One of the main challenges in finding new therapeutic strategies for progressive multiple sclerosis is detecting neuronal dysfunction before irreversible degeneration is established. The retina offers a particularly informative model, as retinal ganglion cell axons are unmyelinated within the retinal tissue and can therefore reveal early inflammatory effects independently of demyelination. In this study, we asked whether experimental autoimmune encephalomyelitis (EAE) induces early alterations in retinal ganglion cell axonal signaling before conventional measures of retinal damage become abnormal.

Methods: EAE was induced in female C57BL/6J mice through MOG immunization. Mice receiving mock immunization, with only complete Freund's adjuvant (CFA) without antigen, served as controls. Animals were assessed at baseline and during the presymptomatic (6–11 dpi), acute (14–19 dpi), and chronic (21–30 dpi) phases. Full-field electroretinography (f-ERG) was used to examine photoreceptor and bipolar cell function in vivo, and visual behavior was tested with the optomotor response. To probe retinal ganglion cells more specifically, retinal explants were analyzed ex vivo with high-density multielectrode arrays (HD-MEA), enabling direct measurement of action potential propagation along intraretinal axons at the same time points.

Results: f-ERG responses remained stable during the early stages of disease, and optomotor deficits were not evident until the chronic phase. In contrast, high-density multielectrode array analysis detected an early decrease in conduction velocity in retinal ganglion cell axons during the symptomatic phase. Because these axons are not myelinated within the retina, this impairment likely reflects inflammation-related disruption of axonal function rather than classical demyelination.

Conclusions: These results suggest that retinal ganglion cell axonal conduction is affected early in EAE, whereas conventional retinal and behavioral measures remain initially preserved. HD-MEA-based axonal tracking may thus serve as a useful electrophysiological biomarker of early neuroinflammatory damage and a potential tool for evaluating neuroprotective interventions.

Retinal Network Dysfunction and Neuroprotection in the Ins2Akita Mouse Model of Diabetic Retinopathy

F. De Cecco[1,2], N. Telitsyn[1,2], M. Dionisi[2], G. Zerbini[3] F. Benfenati[1,2], S. Di Marco[1,2,4]

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2. Center for Synaptic Neuroscience and Technology, Istituto Italiano di Tecnologia, Genova, Italy.
3. Diabetes Research Institute, I.R.C.C.S. San Raffaele, Milano, Italy
4. Department of Experimental Medicine (DIMES), University of Genova, Genova, Italy

Introduction: Diabetic retinopathy (DR) is increasingly recognized as a neurovascular unit disorder where retinal neurodegeneration precedes microvascular breakdown. This study evaluated early inner retinal network dysfunction in the Ins2Akita mouse model and explored the neuroprotective potential of Saffron, Aspirin, and their combination.
Methods: Controls, untreated diabetic Akita mice, and Akita mice treated with Saffron (10 mg/kg/day), Aspirin (30 mg/kg/day), or both were monitored for up to 24 weeks. Retinal ganglion cell (RGC) pathophysiology was assessed using patch-clamp and HD-MEA. Visual acuity, inner retinal function, and layer thickness were tracked in vivo using optomotor response (OMR), electroretinography (f-ERG), and OCT. Trypsin digestion quantified acellular capillaries and pericyte loss.
Results: Electrophysiology revealed prominent RGC network hyperexcitability at P80, before gross anatomical damage. Ex vivo electrophysiological analyses indicated that chronic treatment with Saffron or Aspirin, as well as the combination therapy, effectively attenuates this early network excitotoxicity. In parallel, long-term in vivo assessments showed that Saffron and co-administration significantly improved visual performance (OMR), supported the recovery of oscillatory potential amplitudes (f-ERG), and helped preserve the thickness of the RNFL/GCL layer (OCT). Conversely, Aspirin alone showed no significant benefits in vivo, likely restricted by systemic side effects. Structurally, Saffron limited pericyte loss and reduced downstream acellular capillary formation.
Conclusions: Dysfunction of the inner retinal network arises well before capillary degradation. Early oral intervention with Saffron, alone or combined with low-dose aspirin, offers a safe, low-cost, multi-target neuroprotective strategy that preserves visual function and halts progressive vascular failure in DR.

Andrew Daoud

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AFFILIATION & CURRENT POSITION

Philadelphia College of Osteopathic Medicine, Philadelphia, PA, USA
Second-year medical student | Ophthalmology Laboratory, Dr. Arturo Bravo-Nuevo

Research focus: Retinal vascular development, pathological neovascularization, and visual function in murine models of retinopathy of prematurity. Current work examines Brain-Specific Angiogenesis Inhibitor 1 (BAI-1) in oxygen-induced retinopathy.

Techniques: Electroretinography, optical coherence tomography, retinal flat-mounting, immunohistochemistry, quantitative vascular analysis (AngioTool, ImageJ).

Previous Work: Cell Migration Laboratory, University of Pittsburgh (2022–2024) — profilin-1 and angiogenesis in renal cell carcinoma; co-author, *Journal of Biological Chemistry* (2023).

Service: Vice President, PCOM Ophthalmology Club.

Role of Brain-Specific Angiogenesis Inhibitor 1 (BAI-1) in Retinal Neovascularization and Visual Function in a Murine Model of Retinopathy of Prematurity

Daoud, Andrew[1]; Riaz, Tabish[1]; Margulies, Kyle[1]; Perez, Naheed[1]; Heist, Brian[1]; Crispin, Mara[1]; Van Meir, Erwin G.[2]; George-Weinstein, Mindy[1]; and Bravo-Nuevo, Arturo[1]

1Philadelphia College of Osteopathic Medicine, Philadelphia, PA, United States,
2Heersink School of Medicine, University of Alabama at Birmingham

INTRODUCTION: Retinopathy of prematurity (ROP) affects infants born prematurely or weighing under 3 pounds. Supplemental oxygen for underdeveloped lungs suppresses angiogenic signaling; on return to room air these signals rapidly reactivate, driving pathological neovascularization, retinal detachment, and irreversible vision loss. Brain-specific Angiogenesis Inhibitor 1 (BAI-1), expressed in Myo/Nog cells, regulates angiogenesis and is a potential therapeutic target in ROP.

OBJECTIVES: This study assesses neovascularization and visual capacity in BAI-1 −/− mice exposed to hyperoxia postnatally. METHODS: BAI-1 −/−, +/−, and WT mice were housed in room air from birth (P0) to P7, then assigned to 75% oxygen or continued normoxia until P12, and returned to room air until P17. Pups underwent ERG, retro-orbital Tomato Lectin injection, enucleation, and retinal flat-mounting; vascular morphology was quantified using AngioTool.

RESULTS: Under normoxia, BAI-1 KO mice showed elevated b-wave amplitude relative to WT ($p=0.0014$) and Het ($p=0.0046$), with no genotype difference in a-wave ($p=0.77$), indicating preserved photoreceptor function. AngioTool analysis of normoxic flat-mounts revealed more total vessel endpoints in KO than WT ($p=0.024$) or Het ($p=0.016$). Following OIR, KO a- and b-wave amplitudes fell below their own normoxic baselines ($p<0.0001$), and the KO a-wave fell below OIR Het ($p=0.013$). Hyperoxia also reduced b-wave amplitude in Het mice ($p=0.0003$) but not significantly in WT. Genotype-by-environment interactions were significant for both waveforms (a-wave $p=0.0008$; b-wave $p=0.0012$). KO pups occurred at 9.7% (6/62) from Het-Het matings.

CONCLUSION: Loss of BAI-1 enhances inner retinal function in room air, likely reflecting unopposed angiogenesis supporting the metabolic demands of the developing inner retina. Under OIR, this advantage reverses, supporting our hypothesis that BAI-1 knockout exacerbates hyperoxic injury by removing an endogenous brake on pathological neovascularization. The sub-Mendelian KO frequency suggests BAI-1 may also be required for normal prenatal or perinatal viability.

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AFFILIATION & CURRENT POSITION

Philadelphia College of Osteopathic Medicine, Philadelphia, PA, USA
Third-year medical student | Ophthalmology Laboratory, Dr. Arturo Bravo-Nuevo

Neuroprotective Effect of Intravitreal Administration of Noggin in Mice with Retinitis Pigmentosa (RP)

Siena Hasson

Philadelphia College of Osteopathic Medicine, Philadelphia, PA, United States,

Retinitis pigmentosa (RP) is the most common inherited retinal disorder globally, impacting roughly 1 in 4,000 people.1 The disease results in the gradual loss of photoreceptor cells within the retina. Although causative genetic mutations have been identified, treatment options remain limited and largely focus on managing visual impairment rather than addressing the underlying disease. RP typically presents with difficulty seeing at night and progressive loss of peripheral vision, gradually advancing to complete, irreversible blindness. Rod cells, which are sensitive to low levels of light, degenerate first followed by cone cells that detect color and are responsible for visual acuity.

One approach to the treatment of RP is to protect neurons in the retina. Noggin, a protein that inhibits bone morphogenetic protein (BMP) signaling, has been shown to be neuroprotective in the brain and spinal cord. The source of Noggin in the brain and retina is Myo/Nog cells. Depletion of Myo/Nog cells in the retina results in increased cell death, whereas their addition into the vitreous reduces cell loss and improves vision in an animal model of light damage. We hypothesize that intravitreal injection of Noggin will reduce photoreceptor loss, lower retinal stress, and enhance retinal function in the mouse model of RP.

Jeshur Thangaraj jt4000@pcom.edu

AFFILIATION & CURRENT POSITION

Philadelphia College of Osteopathic Medicine, Philadelphia, PA, USA
Second-year medical student | Ophthalmology Laboratory, Dr. Arturo Bravo-Nuevo

EDUCATION

- Philadelphia College of Osteopathic Medicine, Philadelphia, PA (June 2025 – present)
  Second Year Osteopathic Medical Student
- Stony Brook University, Stony Brook, NY (August 2020 – May 2024)
  Bachelor of Science in Chemistry (Concentration: Biological Chemistry)

RESEARCH

Student Researcher, Bravo Lab – Philadelphia College of Osteopathic Medicine (Nov 2025 – present)

EMPLOYMENT

Certified Nursing Assistant at Stony Brook University Hospital, Stony Brook, NY (2023-2024)

Leo McLean lm3934@pcom.edu

AFFILIATION & CURRENT POSITION

Philadelphia College of Osteopathic Medicine, Philadelphia, PA, USA
Second-year medical student | Ophthalmology Laboratory, Dr. Arturo Bravo-Nuevo

EDUCATION

- Philadelphia College of Osteopathic Medicine, Philadelphia, PA (June 2025 – present)
  Second Year Medical Student
- University of Washington, Seattle, WA (Sept 2020 – present)
  Bachelor of Science in Biology (Molecular, Cellular, and Developmental), Minor in Bioethics and Humanities
- Edmonds College, Lynnwood, WA (Sept 2018 – June 2020)
  Associate of Science

RESEARCH

Student Researcher, Bravo Lab (PCOM Division of Research) – Philadelphia College of Osteopathic Medicine (Oct 2025 – present)

Role of BAI1 in Diabetic Wound Healing: A Mouse Model Using Streptozotocin-Induced Diabetes

Leo McLean and Jeshur Thangaraj

1Philadelphia College of Osteopathic Medicine, Philadelphia, PA, United States,

Previous research has shown brain angiogenesis inhibitor 1 (BAI1), which is naturally produced in humans and mice, as an inhibitor of blood vessel growth. Previous studies have localized BAI1 protein to Myo/Nog cells in tissues in the skin, eye and brain. It has also been shown that Myo/Nog cells increase in number after epidermal abrasion specifically in follicles and the wound itself. Insufficient angiogenesis is a key factor in delayed wound healing in diabetes. Because of this, our target is to analyze the effects of the absence of BAI1 on wound healing in a diabetic mouse model. We established a murine model of streptozotocin-induced diabetes based on Bourdot et al. Mice were separated into BAI1+/- control, BAI1+/- hyperglycemic, BAI1-/- control, and BAI1-/- hyperglycemic groups. Bourdot et al. provided data on wild type groups. In all groups, wound healing rates, epidermal height, and dermal height were measured. Wound healing rates in BAI1+/- normoglycemic vs hyperglycemic groups were slower in the hyperglycemic group, but not to a level that is statistically significant. In WT mice, Bourdot et al. found that histological analysis showed greater epidermal height in diabetic wounds. Using BAI1+/- and BAI1-/- mice in the streptozotocin model has been cumbersome, with lowest mouse survival rates in Bai1+/- mice, as well as mice in hyperglycemic groups.

MARIA MAGGI, PhD m.maggi@hortusnovus.it

AFFILIATION & CURRENT POSITION

Head of Research and Research & Development at Hortus Novus S.r.l.

BRIEF CV

Dr. Maria Anna Maggi is Head of Research and Research & Development at Hortus Novus S.r.l., a position she has held since 2012. She coordinates the company's research activities, carried out in collaboration with universities, research institutions, and national and international scientific partners, with particular focus on the chemical characterization, quality assessment, and valorization of saffron (*Crocus sativus* L.) and its by-products.Her scientific activity includes the study of saffron bioactive compounds, the optimization of cultivation, drying, and processing conditions, the development of analytical methods, and the application of chemometric approaches. She is also a co-inventor of the international patent WO2015/145316 – "Compositions based on saffron for the prevention and/or treatment of degenerative eye disorders", which underpins the characterization of REPRON® saffron, associated with a specific chemical composition and neuroprotective properties.

She is author and co-author of several international scientific publications, including:

- 2020 – *Saffron: Chemical Composition and Neuroprotective Activity*;
- 2020 – *Saffron Shifts the Degenerative and Inflammatory Phenotype in Photoreceptor Degeneration*;
- 2023 – *Saffron and Retinal Neurodegenerative Diseases: Relevance of Chemical Composition*;
- 2023 – *Efficacy of Hydroponically Cultivated Saffron in the Preservation of Retinal Pigment Epithelium*;
- 2025 – *The Efficacy of Saffron Repron® in Counteracting the Progression of Retinitis Pigmentosa: Neuroprotection and Resilience*;
- 2026 – *Saffron as a Retinal Neuroprotectant: A Narrative Review of Preclinical Studies and Clinical Results*.

As Head of Research, her activities also include participation in national and international research and innovation projects, addressing the development and valorization of saffron and its bioactive compounds, neuroprotection in degenerative retinal diseases, innovative cultivation and processing technologies, and the valorization of saffron by-products. Among these activities is her involvement in the PRIN 2022 project "Saffron and Tepals Nanodrugs as a Novel Therapeutic Approach for Inflammatory Bowel Disease: A Pilot Study", focused on investigating saffron and saffron tepals through innovative formulations for potential applications in inflammatory bowel diseases.

The Chemical Characterization of Natural Substances: A Fundamental Requirement for Ensuring Their Quality, Safety, and Efficacy in Human Use

Maggi Maria Anna[1], Silvia Bisti[2]

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[2] Istituto Nazionale di Biostrutture e Biosistemi (INBB), Via delle Medaglie D'Oro, 305, 00132 Roma

Natural substances are a valuable source of bioactive compounds; nevertheless, their natural origin does not automatically guarantee efficacy, safety, or appropriateness for human use. Their biological properties are closely linked to their chemical composition, which can be affected by several factors, including botanical origin, cultivation methods, harvesting conditions, processing, and storage. For this reason, standardized chemical characterization and the quantification of relevant bioactive compounds, together with biological evaluation, are essential to establish reliable correlations between chemical composition and biological activity.

In this context, we present a Design of Experiments (DoE) study focused on assessing the effect of saffron drying conditions on its chemical composition and, consequently, on its neuroprotective properties. Particular attention was given to the main bioactive compounds that define the chemical profile described in the international patent PCT/IB2015/052053 (WO2015/145316). Saffron (*Crocus sativus* L.) is a sterile plant propagated vegetatively, and its chemical profile may be influenced by cultivation practices and, in particular, by post-harvest treatments. Among these factors, drying is a crucial step in determining both the content and composition of its bioactive constituents. The DoE approach therefore represents a systematic strategy for identifying the most appropriate processing conditions to obtain chemically standardized saffron with reproducible neuroprotective activity.

Prof.ssa Silvia Bisti

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AFFILIATION & CURRENT POSITION

Retired Professor of Physiology,
External Collaborator NetS Laboratory, Neuroscience and Brain
Technologies (NBT) Fondazione Istituto Italiano di Tecnologia (IIT) Genova (Italy); member of INBB and scientific director BIO AURUM start-up

Professor Bisti started her career as a researcher at the Institute of Neurophysiology of the CNR in Pisa, directed by Prof L. Maffei, studying adult visual function. She trained further at University of Pennsylvania (Prof J. Sprague) and at Max-Plank Institute fur Psychiatrie, Munich (Prof H. Holländer). Later she became interested in mechanisms of the pre and post-natal development of the visual system. She studied the role of neurotransmitter release in collaboration with Prof L. Chalupa and environmental stress (Dr D. Protti). Her main interest during the last decades is concentrated on the mechanisms involved in retinal degeneration and protection. She was enrolled in a research program in collaboration with colleagues from Università Cattolica in Rome (Prof Falsini) and University of Sydney (Prof J. Stone) focused on the relationship between: 1) genetic background, environmental factors and disease progression; and 2) efficacy of antioxidant/neuroprotective treatments.
Her most recent work is increasingly therapy-oriented. A successful clinical trial on the therapeutic effects of saffron on Age Related Macular Degeneration patients was carried out in collaboration with Prof B. Falsini at Policlinico Gemelli (Università Cattolica di Roma). She was partner PI in a Telethon Project “Development and application of opto-neural prosthetic devices as a therapeutic approach for Retinitis pigmentosa” coordinated by Prof. Lanzani at the Politecnico di Milano and Prof Benfenati at IIT and the University of Genova. She was full professor of physiology at University of L’aquila, Dean of the faculty of Biotechnology and External Collaborator NetS Laboratory Neuroscience and Brain Technologies (NBT) Fondazione Istituto Italiano di Tecnologia (IIT) Genova (Italy).

The Story Behind the Founding of the Society for Acquired Resilience

Silvia Bisti

The Acquired Resilience Society was founded primarily through Jonathan's intuition, spurred by the results obtained in experiments with saffron and photobiomodulation (PBM). Analysis of experimental evidence and discussions among colleagues have led to the idea that it is possible to increase individual's resilience to cope with pathological processes using various strategies. This process began almost twenty years ago but it is leading to a new vision of how to address, for example, age-related degenerative processes. I will summarize the key events and advance hypotheses on the critical procedures to follow and the importance of early diagnosis.

Prof. Jonathan Stone

jonathanston@gmail.com

Degrees

BSc (Med) - 1962; PhD – 1966; DSc – 1977

Positions held

1966:	Lecturer, University of Sydney
1966 – 1967:	Lecturer, Hadassah Medical School, Hebrew University of Jerusalem
1967 – 1970:	Postdoctoral positions in Chicago and Munich
1970 – 1975:	Research Fellow, Australian National University
1976 - 1986:	Senior Lecturer, Ass. Professor, Professor University of NSW
1987 - 2003:	Challis Professor of Anatomy, University of Sydney.
2001 - 2003	Director, Institute for Biomedical Research, University of Sydney.
2003 - 2007:	Director, Research School of Biological Sciences, ANU
2007 - 2019:	Professor of Retinal and Cerebral Neurobiology, University of Sydney
2010 - 2019:	Executive Director, Bosch Institute, University of Sydney
2019 -	Emeritus, University of Sydney
1984	Fellow, Australian Academy of Sciences
1986-90	Secretary (Biological Sciences), Australian Academy of Science

Scholarly publications

250 research and scholarly articles, reports, reviews and several monographs.

Some recent reviews related to acquired resilience:

Stone, J., et al. (2026). "The evolutionary origins of dementia." J Alzheimers Dis https://doi.org/10.1177/25424823261470053.

Stone, J. (2025). "What is frustrating the search for treatment of dementia? Fraud or ideas?" J Alzheimers Dis: 13872877251346044.

Stone, J., et al. (2024). "A Triple Mystery of Insidious Organ Failure: Are the Lung, Kidney and Brain All Damaged by the Ageing Pulse?" Biomedicines **12**(9).

Stone, J., et al. (2024). The Catastrophe of Intracerebral Hemorrhage Drives the Capillary-Hemorrhage Dementias, Including Alzheimer's Disease. J Alzheimers Dis **97**(3): 1069-1081.

Stone, J., et al. (2024). "Trace Toxins: The Key Component of a Healthful Diet." Dose Response **22**(3): 15593258241271692.

Stone, J., et al. (2023). "Twelve protections evolved for the brain, and their roles in extending its functional life." Front Neuroanat **17**: 1280275.

Johnstone, D. M., et al. (2023). "The brain's weakness in the face of trauma: How head trauma causes the destruction of the brain." Front Neurosci **17**: 1141568.

Andersson, M. J. and J. Stone (2023). "Best Medicine for Dementia: The Life-Long Defense of the Brain." J Alzheimers Dis **94**(1): 51-66.

Stone, J., et al. (2018). "Acquired Resilience: An Evolved System of Tissue Protection in Mammals." Dose Response **16**(4): 1- 40.

Stone, J., et al. (2015). "The mechanical cause of age-related dementia (Alzheimer's disease): the brain is destroyed by the pulse." J Alzheimers Dis **44**(2): 355-373.

A look at the mechanisms of resilience that protect against neurodegeneration

Jonathan Stone

Professor Emeritus in Neurobiology, University of Sydney

This talk will attempt to summarise the mechanisms of cell death and cell protection that have been identified in the ageing human brain, and whose actions – some destructive, some protective – determine the rate of brain damage and loss of cognition that occur in every aging person. In this understanding, the brain damage that results in dementia begins with the hardening of the aorta and the great distributing arteries, as the elastin in their walls with denatures with age. Elastin is ~30% of the dry weight of the tissue that forms the wall of the aorta (far more than in any other tissue) and it allows the aortic wall to stretch and contract with every beat, softening the pulse.

Elastin has a long half-life in the body (70 years) but is not replaced and, by the time humans reach the three score and ten of human life (the biblical view of how long humans live), the elastin in arteries is ~50% degraded, systolic and pulse pressures are rising and damage is becoming evident in the brain in the form of capillary bleeding.

The senile plaques that characterise the ageing brain form at sites of these capillary bleeds. The sites are small (~100μm in diameter) but increase in number (but not size) with age and dementia. Each forms near or around a capillary and each contains a residue of haem, presumably derived from haemoglobin spilt into the neuropil. It will be argued that, at each site of a capillary bleed, four toxicities stress and kill neurones: hypoxia, the toxicity of haem, glutamate excitoxicity and immune-mediated cytotoxicity. Mitigating mechanisms have evolved to counter these toxicities – storage of oxygen, peptides that mitigate the toxicity of haem and molecules that sequester pathogens to prevent their infecting neurones; these will be described.

Of these protective mechanisms, Aβ expression by stressed neurones and glia meets the criteria for acquired resilience: its expression is upregulated by stress and it acts of protect the functional cells of the brain. This understanding (which goes back 25 years) of Aβ as a protective, first responder molecule contrasts with the neurotoxic role posited for Aβ in the long-debated amyloid cascade hypothesis of the causation of dementia. The implications of the present evidence for the understanding and management of dementia will be discussed.

The Evolutionary Origins of Dementia

Jonathan Stone[1], Daniel M. Johnstone[2], Rebecca S. Mason[3], John Mitrofanis[4,5], Stephen R. Robinson[6,7]

[1]Faculty of Medicine and Health, University of Sydney, Sydney, Australia

[2]School of Biomedical Sciences and Pharmacy, University of Newcastle, Newcastle, Australia

[3]School of Life and Environmental Sciences and Charles Perkins Centre, University of Sydney, Sydney, Australia

Evidence has grown that the core pathology of age-related dementias, including Alzheimer's disease, is microvascular— small, symptomless bleeds from cerebral capillaries, accelerated by the hypertension of age. Each such bleed, this evidence suggests, damages a patch of brain, causing the death of neurons. This review asks how this vulnerability of the brain emerged from evolution, to cause age-related dementia? And has the vulnerability spurred the evolution of mitigating mechanisms? It will be argued that seven features of human evolution contribute to the cause of dementia: the dependence of our tissues, especially the brain, on oxygen; the toxicity of the molecule (heme) that binds to oxygen to enable its transport; the pulsatility of the heart; the danger of glutamate as an excitatory neurotransmitter; the irreparability of elastin; the low level of adult neurogenesis in humans; and the breakdown, in late life, of the blood-brain barrier. Also discussed will be mechanisms that have evolved to counter these threats to the brain. We argue that the vulnerabilities of the brain to damage that accumulates throughout life, and leads to dementia in the aged, were established early in the evolution of vertebrates. Human cognition fails when and because, with age, the damage that results from these vulnerabilities overwhelms the evolved protections.

Prof.ssa Piera Versura

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AFFILIATION & CURRENT POSITION

Associate Professor at the University of Bologna.

BRIEF CV

1981 – Degree *cum laude* in Biological Sciences, University of Bologna.
Since obtaining her degree, she has been affiliated with the University of Bologna, initially at the Institute of Ophthalmology and currently at the Ophthalmology Unit, Department of Medical and Surgical Sciences (DIMEC).
Since 2018, she has held the position of **Associate Professor** in the scientific disciplinary sector MEDS 17/A – Diseases of the Visual System.
Since 1990, she has been Head of the **Cornea and Ocular Surface Analysis Laboratory**, a Unit operating within a clinical agreement with the IRCCS Azienda Ospedaliero-Universitaria di Bologna – Policlinico di Sant'Orsola, where she conducts research, diagnostic and clinical activities, and clinical trials focused on the efficacy of innovative ophthalmological therapies.
Since 1996, she has served as Senior Biologist (Dirigente Biologo).
At the departmental level, **since 2023**, she has been **Delegate for Communication** and Coordinator of the Communication Working Group.

LABORATORY ACTIVITY

Design, planning, and implementation of biomedical and clinical research projects, in accordance with Evidence-Based Laboratory Medicine (EBLM) principles.
Specific expertise and research interests include:

- Primary and continuous cell cultures derived from ocular tissues
- Conventional and advanced (high-tech) morphological analysis of ocular cells and tissues
- Molecular analysis techniques: RNA, DNA, and protein extraction from cells and tissues; RT-PCR, real-time PCR, Western blot, ELISA
- Proteomic analysis of biological fluids, with particular focus on human tears for biomarker identification for diagnostic and therapeutic purposes

SCIENTIFIC INTERESTS

- Preclinical studies and clinical applications of biomaterials, with reference to ophthalmology
- Functional pathophysiology of the ocular surface
- Laboratory medicine applied to diagnostics on small-volume biological fluids, with particular focus on human tears
- Mechanisms of neuroprotection

PUBLICATIONS

Author or co-author of more than **200 full-length publications** (over 100 in peer-reviewed journals; cumulative impact factor >150; H-index 31) in the field of ophthalmology.
Co-Editor of the book “Biomaterials in Ophthalmology: An Interdisciplinary Approach.”
Editor of the journal “Cells and Materials” from 1991 to 1996.

Cord Blood Serum Eye Drops: Fifteen Years of Translational Research toward Retinal Neuroprotection

Piera Versura [1, 2], Marina Buzzi [2,] and Silvia Bisti [3]

1 - Ophthalmology Unit, DIMEC, Alma Mater Studiorum Università di Bologna, Italy.
2 - IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy.
3 - Istituto Nazionale di Biostrutture e Biosistemi (INBB), Roma, Italy.

Cord blood serum (CBS) eye drops are a biologically complex, growth factor-rich preparation initially developed for ocular surface diseases. CBS represents a naturally occurring mixture of growth and neurotrophic factors generated at birth, a physiological phase characterized by exceptionally high metabolic demands. Over the past fifteen years, our research has progressively explored whether this unique biological profile may extend its activity beyond the ocular surface and support retinal cell homeostasis and survival.

Biological characterization of CBS demonstrated a distinctive profile of trophic and neurotrophic factors, including brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), glial cell-derived neurotrophic factor (GDNF), epidermal growth factor (EGF), and transforming growth factor-α (TGF-α), providing the rationale for investigating CBS in retinal models of oxidative and inflammatory injury.

In vitro studies showed that CBS improved survival of Müller glial cells exposed to oxidative and inflammatory stress, with evidence supporting the involvement of neurotrophin/Trk signaling. In a light-induced retinal degeneration model, topical CBS preserved retinal function and outer retinal morphology while reducing microglial activation. More recently, studies in retinal pigment epithelial and photoreceptor-like cells confirmed protective effects against oxidative stress, including preservation of mitochondrial integrity and involvement of BDNF-TrkB signaling.

These converging findings supported translation into a prospective pilot clinical study in patients with open-angle glaucoma. Sixty-day topical CBS administration proved safe and well tolerated. Although no significant overall structural or functional improvement was demonstrated, exploratory electrophysiological findings suggested potential neuroretinal biological activity and provided the rationale for larger controlled studies. This translational pathway also resulted in patent protection across major international jurisdictions

CBS eye drops are part of the emerging field of Eye Drops of Human Origin (EDHO), encompassed within the new European regulatory framework for Substances of Human Origin (SoHO), which emphasizes standardization, quality, safety, and traceability. Overall, fifteen years of multidisciplinary research support further investigation of CBS as a multifactorial biological strategy toward retinal neuroprotection.

Prof. Ann Liebert

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AFFILIATION & CURRENT POSITION

Professor of Research and Development at Shepherd University, WV,
Research Fellow at the Kolling Institute, Sydney University, Australia
Coordinator of Photomolecular Research at the Sydney Adventist Hospital, Australia.

Brief CV

Dr Ann Liebert is an Australian clinician scientist, and a Professor of Research and Development at Shepherd University, WV, a Research Fellow at the Kolling Institute, Sydney University, Australia, and the Coordinator of Photomolecular Research at the Sydney Adventist Hospital, Australia. She has over 30 years' experience using photobiomodulation in a clinical setting, treating previously intractable conditions such as Parkinson's disease, Alzheimer's disease and chronic headache. Ann's major research interests are translational clinical studies using photobiomodulation for Parkinson's disease, chronic kidney disease, traumatic brain injury and supportive cancer care. She also conducts theoretical research into the photo-molecular mechanisms of the action of light on cells, including light absorption and transmission, and endogenously generated light (biophotons), and the interaction of light with the microbiome. She received a Global Discovery Award for her theoretical work on photobiomodulation mechanisms ans was a 2022 recipient of the Rosalind Franklin Award honouring women in science for her clinical studies on treatment of Parkinson's disease symptoms using remote photobiomodulation. Ann is the Vice-president of the Australian Medical Photobiomodulation Association, a Board Member of the PBM Foundation in WV, a convenor for the Photobiomodulation conference of the SPIE Photonics West Conference held annually in San Francisco, a member of the scientific board of the World Association of Photobiomodulation Therapy (WALT) and teaches on a medical specialist photobiomodulation post-graduate diploma at Montpellier University. Ann continues to treat patients in her clinic for Parkinson's disease, chronic pain, migraine headaches, supportive cancer care, and sports performance.

Acquired resilience to reduce the progression of intractable diseases: The potential of photobiomodulation for chronic kidney disease.

Ann Liebert

The use of light therapy for over 120 years, and especially in the last 60 years since the advent of laser therapy, has been shown to have a profound effect on numerous conditions, due to the cellular mechanism of action. Photobiomodulation, as it is now known, has been increasingly used for musculoskeletal conditions and injuries, chronic pain and inflammatory conditions, wounds, and in the last decades, for neurological conditions and supportive cancer care; all of which result in an increase in acquired resilience. New developments from pre-clinical research at Sydney University have led to encouraging clinical studies in Parkinson's disease. More recently, positive pre-clinical studies of PBM for chronic kidney disease have resulted in the development and ethical approval of a world first proof-of-concept translational clinical trial to assess the feasibility, safety and tolerability of using PBM to treat the symptoms of chronic kidney disease. This talk will give an overview of the preclinical experimental data, both in vivo and in vitro, that has formed the basis of the translational study. Evidence from in vitro experiments using human proximal tubule cells, from a folic acid induced chronic kidney disease in vivo model and from a high fed diet induced diabetic kidney disease model have shown that PBM can improve renal function, reduce kidney damage, reduce fibrosis, and reduce inflammatory processes. Results have also demonstrated a clear biphasic dose response. Results will be explained in the context of potential mechanisms of action of the PBM therapy in kidney disease, including the biphasic and bystander effects, action on the mitochondria and microbiome, as well as conformational change of proteins including the cytoskeleton. Implications for senescence of cells and bodily resilience will be discussed.

Dr.ssa Alessandra Puddu

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AFFILIATION & CURRENT POSITION

University of Genova (Italy), Dep. of Internal Medicine and Medical Specialties
Senior Biomedical Research Technician

PROFESSIONAL EXPERIENCE

Senior Biomedical Research Technician, University of Genova, 22/09/2020-present
Research Fellow, University of Genova, 3/03/2014-2/03/2020
Senior Biology Research Technician, University of Genova, 1/03/2011-28/02/2014
Research Fellow, University of Genova, 01/07/2008-28/02/2011
Contract Biotechnologist, University of Genova, 01/01/1996-30/06/2008

RECENT PUBLICATIONS

1: Puddu A, Balbi M, Ravera S, Panfoli I, Maggi D. Insulin production in the retina drives autocrine signalling and metabolism reprogramming of the ARPE-19, a retinal pigment epithelium cellular model. Cell Mol Life Sci. 2026 May 1;83(1):259.
2: Balbi M, Puddu A, Amaroli A, Maggi D, Panfoli I, Ravera S. Local Insulin for Local Needs? Insights into Retinal Insulin Signaling and RPE Metabolism. Biomolecules. 2025 Nov 8;15(11):1570.
3: Puddu A, Maggi DC. Molecular Research on Diabetes. Int J Mol Sci. 2025 Feb 21;26(5):1873.
4: Puddu A, Nicolò M, Maggi DC. Combination of Saffron (Crocus sativus), Elderberry (Sambucus nigra) and Melilotus officinalis Protects ARPE-19 Cells from Oxidative Stress. Int J Mol Sci. 2025 Feb 11;26(4):1496.
5: Ravera S, Puddu A, Bertola N, Verzola D, Russo E, Maggi D, Panfoli I. IGF-1 Signaling Modulates Oxidative Metabolism and Stress Resistance in ARPE-19 Cells Through PKM2 Function. Int J Mol Sci. 2024 Dec 20;25(24):13640.
6: Ravera S, Bertola N, Puddu A, Bruno S, Maggi D, Panfoli I. Crosstalk between the Rod Outer Segments and Retinal Pigmented Epithelium in the Generation of Oxidative Stress in an In Vitro Model. Cells. 2023 Aug 30;12(17):2173.
7: Puddu A, Maggi DC. Klotho: A new therapeutic target in diabetic retinopathy? World J Diabetes. 2023 Jul 15;14(7):1027-1036.
8: Puddu A, Maggi D. Anti-Inflammatory Effects of GLP-1R Activation in the Retina. Int J Mol Sci. 2022 Oct 17;23(20):12428.
9: Puddu A, Ravera S, Panfoli I, Bertola N, Maggi D. High Glucose Impairs Expression and Activation of MerTK in ARPE-19 Cells. Int J Mol Sci. 2022 Jan 20;23(3):1144.
10: Puddu A, Sanguineti R, Maggi D. Caveolin-1 Down-Regulation Reduces VEGF-A Secretion Induced by IGF-1 in ARPE-19 Cells. Life (Basel). 2021 Dec 28;12(1):44.

RPE Resilience: From Physiological Adaptation to Retinal Disease

Alessandra Puddu

University of Genova (Italy), Dep. of Internal Medicine and Medical Specialties

The retinal pigment epithelium (RPE) is one of the most metabolically active tissues in the human body and is continuously exposed to metabolic and oxidative stress while performing essential functions, including photoreceptor outer-segment (POS) phagocytosis, visual cycle support, barrier maintenance, and regulation of the retinal microenvironment. Despite this demanding workload, the RPE normally maintain homeostasis by balancing energy demand, oxidative stress and cellular repair. We can refer to these coordinated adaptive responses as RPE resilience.

In our studies, we used ARPE-19 cells as an in vitro model of RPE cells. The results indicate that physiological POS phagocytosis acts not only as a clearance mechanism but also as a bioenergetic and adaptive stimulus, promoting glucose utilization, mitochondrial activation, ATP production, antioxidant defenses, and local insulin signaling. Together, these responses allow RPE cells to adapt their metabolism according to the energetic demands while limiting oxidative damage. In contrast, when metabolic, oxidative or inflammatory challenges exceed the capacity of endogenous adaptive mechanisms, RPE resilience can become impaired. In particular, under hyperglycemic conditions, disruption of these adaptive mechanisms is associated with impaired POS phagocytosis, altered metabolism, oxidative damage, and a shift toward a pro-angiogenic phenotype characterized by increased VEGF secretion. Our findings further identify dietary supplements, miR-126, IGF-1, and GLP-1 pathways as potential modulators of RPE adaptation and resilience.

Together, these observations suggest that retinal disease may arise not only from direct cellular damage but also from a progressive loss or maladaptation of endogenous resilience mechanisms. Therefore, preserving or restoring these mechanisms may represent a complementary therapeutic strategy for retinal diseases such as diabetic retinopathy and age-related macular degeneration.

Dr. Rocco Mastromartino

rocco.mastromartino01@icatt.it

AFFILIATION & CURRENT POSITION

Residency in Clinical Genetics, Catholic University of Sacred Heart

ABOUT ME

Young physician starting his residency in Clinical Genetics, with a keen interest in Electrophysiology of Vision, Inherited Retinal Diseases and Regenerative Medicine in Neurobiology.
My objectives in the framework of Electrophysiology and Psychophysics are improving the diagnosis of IRD, developing composite outcomes to evaluate the effects of Gene Therapies and Target Therapies. From a neurobiological perspective, a deep understanding of the mechanisms of disease will lead to improvement in clinical practice.

RECENT PUBLICATIONS

Maggi, M.A.; Mastromartino, R.; Piccardi, M.; Minnella, A.M.; Marangoni, D.; Di Marco, S.; Falsini, B.; Bisti, S. Saffron as a Retinal Neuroprotectant: A Narrative Review of Preclinical Studies and Clinical Results. *Antioxidants* **2026**, *15*, 501. https://doi.org/10.3390/antiox15040501

Functional Visual Effects of Saffron, Photobiomodulation, and Subthreshold Laser in Age-Related Macular Degeneration: A Retrospective Review.

Background: Intermediate and dry age-related macular degeneration (AMD) require early interventions to preserve photoreceptors.
Emerging therapies such as saffron supplementation, photobiomodulation (PBM), and subthreshold micropulsed laser (STL) aim to enhance cellular function prior to irreversible anatomical loss.
Objective: To evaluate the clinical efficacy of saffron, PBM, and STL in AMD patients, focusing on best-corrected visual acuity (BCVA), retinal sensitivity (microperimetry), and electrophysiological responses (fERG/mfERG).
Methods: A retrospective review of indexed clinical trials (minimum follow-up: 3–24 months) was performed. Data regarding changes in BCVA letters, ERG amplitude/latency, and macular sensitivity thresholds via microperimetry were extracted and compared.
Results: Saffron (20–50 mg/day) demonstrates robust neuroprotection, reflected in enhanced mfERG metrics. Multi-wavelength PBM protocols yield the highest quantifiable letter gains, backed by clinical trial data showing sustained improvements in macular sensitivity. Micropulsed STL effectively preserves BCVA and local retinal sensitivity by triggering RPE cellular repair mechanisms without structural tissue destruction.
Conclusions: All three modalities present an excellent safety profile.
While saffron provides biochemical neuroprotection measurable via fERG, PBM and STL deliver localized biostimulation that boosts BCVA and macular sensitivity, validating the implementation of functional endpoints alongside purely anatomical metrics.

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Francesca Corsi, PhD francesca.corsi@farm.unipi.it

AFFILIATION & CURRENT POSITION

• July 2024 - Today

Research Fellow, Department of Pharmacy, University of Pisa, Italy, SSD BIOS-06/A – Physiology. Research focused on retinal neurodegeneration, neuroinflammation and neuroprotection.

• Jan. 2026 – May 2026

Academic Visitor, Department of Pharmacology, University of Oxford, UK. Research on sensory and functional mechanisms of light-responsive head-direction cells.

• Nov. 2023 – June 2024

Research Fellow, Department of Pharmacy, University of Pisa, Italy, SSD BIOS-06/A – Physiology Research on pharmacological and epigenetic approaches to photoreceptor protection in Retinitis Pigmentosa.

• Nov. 2022 – March 2023

Visiting Researcher, University Eye Hospital Tübingen, Germany. Research in retinal degeneration under the supervision of Dr. Sven Schnichels.

• Oct. 2020 – March 2024

PhD Researcher in Science of Drug and Bioactive Substances, Department of Pharmacy, University of Pisa, Italy - SSD BIOS-06/A – Physiology

RECENT PUBLICATIONS:

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3. Guidotti L., Lapi D., Lucchesi M., Valori S., Corsi F., Giambastiano L., Vornoli A., Gargini C., Cammalleri M., and Dal Monte M. – “An Acebuche Oil-Enriched Diet Prevents Early-Stage Cerebrovascular Alterations in the 5xFAD Mouse Model of Alzheimer's Disease” - Nutrients. 2026 Jan 5;18(1):172.

4. Corsi F., Castagnoli J., Galante A., Fabiano A., Nuti E., Piras A.M., Taliani S., Piano I., and Gargini C. – “TSPO Modulation Prevents Photoreceptor Degeneration and Produces Neuroprotective Effects in an Animal Model of Retinitis Pigmentosa” - Cells. 2025 Nov 12;14(22):1778.

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From Neuroprotection to Resilience: Targeted and Nutraceutical Approaches in Retinal Degeneration

Francesca Corsi[1], Alessia Galante[1], Ilaria Piano[1] and Claudia Gargini[1]

[1] Department of Pharmacy, University of Pisa, Italy

Background: Retinal degenerative disorders arise from different primary causes but share common mechanisms of cellular stress, including oxidative imbalance, mitochondrial dysfunction, and chronic neuroinflammation. Enhancing the intrinsic ability of retinal cells to adapt to and withstand stress may represent a complementary therapeutic strategy. We compared two different approaches to retinal protection: the synthetic TSPO ligand PIGA-1138, targeting mitochondrial and inflammatory pathways, and Saffron Repron®, a nutraceutical intervention with broader effects on cellular stress responses and epigenetic regulation.

Methods: Experimental studies were performed in models of Retinitis Pigmentosa (RP) and Diabetic Retinopathy (DR). PIGA-1138 was evaluated systemically (i.p. injection) in DR and as a topical ophthalmic formulation in rd10 mice, from P18 to P90. Saffron Repron® was administered orally using chronic treatment regimens in both RP and DR models, including treatment from gestation through P120 in the RP model. Saffron Repron® was administered orally using chronic treatment regimens in both RP and DR models, including treatment from gestation through P120 in the RP model.

Results: Both interventions increased retinal resistance to disease-associated stress, although through distinct mechanisms. In DR models, PIGA-1138 reduced pathological responses associated with mitochondrial dysfunction and oxidative stress, while Saffron Repron® attenuated hyperglycemia-related retinal alterations. In rd10 mice, topical PIGA-1138 preserved retinal function and visual performance and reduced photoreceptor degeneration. Chronic Saffron Repron® treatment provided sustained functional protection and modulated molecular pathways associated with cellular adaptation, including SIRT1 and inflammatory signaling.

Conclusions: Our results support a resilience-oriented view of retinal neurodegeneration, in which increasing the capacity of retinal cells to withstand metabolic, inflammatory, and genetic stress may complement conventional disease-targeted therapies. PIGA-1138 and Saffron Repron® represent distinct but potentially convergent strategies, highlighting mitochondrial regulation and adaptive cellular responses, respectively, as relevant targets for strengthening retinal resilience.

Camille Monchaux de Oliveira, PhD **c.monchaux@activinside.com**

AFFILIATION & CURRENT POSITION

Nutrition & Health Research Project Manager at Activ'Inside

Brief CV

Camille Monchaux de Oliveira holds a PhD in Neuroscience from the University of Bordeaux, where her doctoral research, conducted in collaboration with Activ'Inside and the NutriNeuro laboratory (INRAE), focused on depressive disorders and therapeutic response, with a particular focus on the mechanisms underlying the effects of saffron bioactives as a nutritional approach. She is now a Nutrition & Health Research Project Manager at Activ'Inside, where she leads preclinical research and contributes to the R&D strategy for plant-derived ingredients targeting the dietary supplement market. Her work involves collaborating with academic and industrial partners to investigate the mechanisms of action and efficacy of bioactive ingredients.

A Standardized Saffron Extract (Safr'Inside™) for Stress Resilience: Clinical and Mechanistic Evidence Across Mood, Sleep and Stress Regulation

Stress resilience depends on the ability to adapt to challenging situations, regulate the physiological stress response and restore emotional and physiological homeostasis. Because stress, mood and sleep are closely interconnected, interventions targeting multiple components of this network may represent a promising approach to support resilience.

Saffron (*Crocus sativus* L.) has emerged as a botanical ingredient with potential benefits for emotional well-being and sleep. Safr'Inside™ is a standardized, full-spectrum saffron extract with a broad profile of bioactive compounds, investigated for its potential role in stress regulation and sleep quality. Clinical studies with Safr'Inside™ provide evidence of effects across several domains relevant to stress resilience. In adults with subclinical mood disturbances, 8 weeks of supplementation improved mood and attenuated the reduction in heart rate variability induced by a psychosocial stressor, suggesting a more adaptive physiological response to stress. Consistent with these findings, an acute stress study showed that a single dose of Safr'Inside™ modulated both subjective and physiological responses to stress. The clinical evidence also extends to sleep: in a 4-week randomized controlled trial in adults with moderate insomnia, Safr'Inside™ improved insomnia symptoms, with improvements in subjective sleep quality emerging after three weeks and accompanied by reduced perceived stress. Complementary findings from another study in older adults with sleep complaints showed improvements in both subjective sleep quality and objectively measured sleep parameters.

Evidence from both clinical and preclinical studies further supports a multi-target mode of action involving pathways relevant to emotional regulation, stress adaptation and sleep, including monoaminergic signaling, modulation of autonomic nervous system activity, the gut-brain axis, and protection against oxidative and inflammatory processes.

Together, these clinical and mechanistic findings suggest that Safr'Inside™ may support stress resilience through coordinated effects on stress regulation, emotional balance and sleep homeostasis, providing a multi-target botanical approach to support adaptation to stress and maintain psychological well-being.

Prof. Stefano Di Marco

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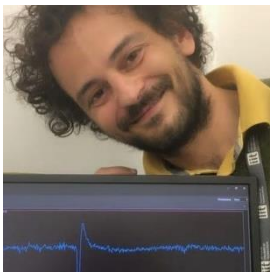

AFFILIATION & CURRENT POSITION

Associated Professor, University of Genova

Brief CV

Stefano Di Marco graduated in Biological Sciences from the University of Genoa in 2004 and obtained a PhD in Biochemical Sciences and Neuroscience from the University of L'Aquila in 2008, with research focused on visual electrophysiology and the development of the visual system.
From 2008 to 2012, he was a postdoctoral researcher at the University of Sydney, Australia, where he studied contrast adaptation in the visual system and implemented patch-clamp techniques with two-photon microscopy. He then worked as a postdoctoral researcher at IIT, contributing to the development of experimental platforms based on high-density CMOS microelectrode arrays.
From 2015 to 2019, he was an RTDA Researcher in Physiology, teaching neurophysiology and studying saffron-based neuroprotection in retinal degeneration. From 2019 to 2024, he worked at the IIT NSYN Center on innovative strategies for neural modulation, including nanoparticles and photochromic molecules for light-dependent activation of the nervous system.
Since 2024, he has been an Associate Professor of Physiology at the University of Genoa and remains affiliated with IIT NSYN, where he continues to work on neural photostimulation in the retina and cortex. He is also a co-PI of projects funded by FISM and the Italian National Health System on neurodegeneration and diabetic retinopathy.

RECENT PUBLICATIONS

- Ziraldo, G.; Cupini, S.; Sesti, V.; Delfino, E.; Lanzani, G.; Bertarelli, C.; Benfenati, F.; Di Marco, S.; A Membrane-Targeted Photoswitch Restores Physiological ON/OFF Responses to Light in the Degenerate Retina. (2025) Nature Communications.
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Matching the Prosthesis to the Disease: Interfacing Injectable and Optical Retinal Rescue Strategies with Distinct Modes of Photoreceptor Degeneration

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Retinal degenerations converge on photoreceptor loss but diverge widely in mechanism, kinetics, and residual circuitry, challenging the notion that a single prosthetic solution can rescue vision across disease types. Using genetically and environmentally distinct rodent models — RCS rats with MerTK-dependent combined rod/cone loss and impaired RPE/microglial phagocytosis, rd10 mice with primary rod-specific Pde6b-driven degeneration and intact RPE, and light-damage models recapitulating AMD-like oxidative stress with region-specific dorsal/ventral progression — we show that the surviving retina presents fundamentally different substrates for intervention. Injectable subretinal poly(3-hexylthiophene) nanoparticles and graphene-enhanced nanoimplants restore light-driven cortical and behavioral responses in both RPE-deficient and RPE-intact models, demonstrating that healthy phagocytic clearance does not compromise nanoparticle-mediated phototransduction, while graphene oxide doping improves photovoltaic efficiency and lowers the luminance threshold for rescue. In parallel, antioxidant platinum nanozymes and neuroprotective saffron formulations counteract oxidative and inflammatory cascades characteristic of light damage and AMD-like degeneration, a mechanism distinct from the genetic mutations driving retinitis pigmentosa. Because inner retinal neurons downstream of photoreceptor loss undergo degeneration-dependent remodeling — including loss of bipolar cell synaptic output, retinoic acid receptor-driven ganglion cell hyperactivity, and partial structural resilience of surviving synaptic circuits — the functional window and efficacy of any prosthetic or optogenetic strategy are inherently time- and disease-dependent. A membrane-targeted photoswitch capable of reinstating physiological ON/OFF segregation in the degenerate retina further illustrates that rescue strategies must respect, rather than uniformly override, the surviving circuit architecture. Together, these findings argue that acquired resilience in the degenerating retina is itself a design constraint: effective vision restoration requires prostheses tailored to the specific cellular and circuit-level signature of each degeneration, not a one-size-fits-all approach.

Vicki Chrysostomou, PhD

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AFFILIATION & CURRENT POSITION

Duke-NUS Medical School, Singapore, and
Singapore Eye Research Institute (SERI)

Brief CV

Vicki Chrysostomou obtained a PhD in medical science from the Australian National University, Canberra, Australia. Under the supervision of Jonathan Stone, her doctoral studies focused on mechanisms of cone and rod dysfunction in inherited retinal diseases. She continued her studies of retinal cell biology as a postdoctoral fellow at the Centre for Eye Research Australia (CERA) and University of Melbourne, Australia, focusing on the identification of lifestyle interventions and novel neuroprotective strategies to prevent age-related vision loss. Her major interest has been to develop and lead studies investigating the impact of exercise on the aged retina and optic nerve, and its response to injury. Currently, she holds a dual appointment at Duke-NUS Medical School, Singapore, and Singapore Eye Research Institute (SERI), where she continues to work on neurorecovery and neuroprotective therapies for inherited retinal diseases, with a focus on regenerative medicine, including gene and cell therapy.

Acquired Resilience in the Retina and Exercise: An Overview

Vicki Chrysostomou

Duke-NUS Medical School, Centre for Vision Research, Singapore, and Singapore Eye Research Institute, Singapore

Our studies in mouse models over the past 20 years provide strong evidence that exercise promotes robust resilience in the retina and optic nerve. We show that exercise-mediated resilience is dependent on BDNF signalling in the retina and is independent of local or systemic AMPK activation. While increased levels of physical activity by either voluntary or forced modalities can provide protection, we found that the greatest benefits are seen when exercise is performed in a continuous manner, before and after the onset of retinal insult or injury. Exercise can increase the rate of neurorecovery when the retina is exposed to an acute recoverable injury, and it can also prevent cell loss and structural degeneration when the retina is exposed to a more severe injury or insult. We found that overexercising can eliminate the benefits of exercise to the retina and is associated with systemic pathology such as cardiac hypertrophy. These results suggest that exercise holds promise as a neuroprotective strategy to promote retinal resilience. However, considerations about the type, timing and quantity of physical activity must be made.

Prof. Arturo Bravo Nuevo

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AFFILIATION & CURRENT POSITION

Professor of Neuroanatomy and Neuroscience,
Philadelphia College of Osteopathic Medicine.

Brief CV

Dr. Arturo Bravo Nuevo is a Full Professor of Neuroanatomy and Neuroscience at the Philadelphia College of Osteopathic Medicine, where his laboratory studies mechanisms of retinal cell death, neuroprotection, and the biology of Myo/Nog cells in ocular disease. He earned his PhD at the Australian National University and completed postdoctoral training at Harvard University before joining the faculty at PCOM.

His current research program spans several fronts. His group investigates RhoB signaling in retinal apoptosis, the antiangiogenic and antifibrotic roles of profilin 1, and the contribution of Myo/Nog cells to conditions including proliferative vitreoretinopathy, corneal transplant failure, and glaucoma. He is also leading a clinical trial evaluating saffron supplementation in glaucoma, and participates in the ACEYE2 Spanish national grant alongside collaborators in Valladolid and Sevilla.

Dr. Bravo Nuevo has combined his academic career with senior industry leadership, serving as Chief Scientific Officer at Heritage Therapeutics and Myo Therapeutics. That dual perspective shapes a research philosophy oriented toward translation, moving findings from cell and animal models toward interventions that can reach patients.

At PCOM he teaches neuroanatomy and a HEENT and Neuroscience course for first year osteopathic medical students, and he developed and teaches a Medical Spanish curriculum aimed at improving care for Spanish speaking patients. He mentors graduate students and trainees pursuing careers in ophthalmology and vision science, and maintains active research collaborations across Europe and the United States.

Myo/Nog Cells: What Are They and Their Neuro-Protective Dilemma

Arturo Bravo Nuevo

Philadelphia College of Osteopathic Medicine, Dept. of Biomedical Sciences, Philadelphia, U.S.

Purpose: Myo/Nog cells were identified over two decades ago by Dr. Mindy George-Weinstein and Jacquelyn Gerhart and are defined by their expression of MyoD mRNA, the BMP inhibitor Noggin, and Brain Angiogenesis Inhibitor 1 (BAI1). They are present at low numbers in nearly every tissue and expand rapidly in response to injury. Our laboratory has spent the last decade asking a simple question: are these cells good or bad for the retina? The answer, it turns out, depends on the context.

Methods: We assessed the role of Myo/Nog cells in several rodent models of ocular and CNS injury. Endogenous cells were depleted using a BAI1 antibody conjugated to complement. Exogenous Myo/Nog cells were purified from rat brain (>99% purity) and delivered intravitreally or intracamerally. Outcomes included TUNEL labelling, ganglion cell counts, electroretinography, and OCT.

Results: Depletion of endogenous Myo/Nog cells in a murine model of oxygen-induced retinopathy significantly increased apoptosis in the inner retina. Conversely, exogenous Myo/Nog cells preserved photoreceptor structure and ERG amplitudes after light damage in albino rats, protected retinal ganglion cells in a magnetic microsphere model of ocular hypertension, and reduced apoptosis after needlestick injury to the rat brain. The same cells, however, drive fibrotic complications by differentiating into myofibroblasts in posterior capsule opacification, proliferative vitreoretinopathy, and corneal transplant failure. Noggin alone reproduced much of the neuroprotection without the fibrotic liability in the rd1 retina.

Conclusions: Myo/Nog cells are a double edged population. Targeting Noggin rather than the cells themselves may resolve this therapeutic dilemma.

Prof.ssa Maria Angela Bagni mangela.bagni@unifi.it

AFFILIATION & CURRENT POSITION

Full Professor of Physiology at the Experimental and Clinical Medicine Department, University of Florence. Head of the Muscle Mechanics Laboratory.

Brief CV

Full Professor of Physiology at the Experimental and Clinical Medicine Department, University of Florence. Head of the Muscle Mechanics Laboratory. PI in the project: The study on changes in eye movements in neurodegenerative diseases. Member of the Scientific Committee of the Biomedical Area Museum and Head of the Physiology Section of the Museum. Invited speaker at international and national symposia and congresses. Peer review for impacted international Journals.

Expert researcher at molecular level of force generation mechanisms of the contractile apparatus in single skeletal muscle fibers in wild-type or genetically modified animals. These researches using fast mechanics techniques with isometric or "length-clamp" methodology associated with X-ray diffraction techniques (with synchrotron source) have been the first in muscle physiology in which a temporal resolution lower than millisecond was reached. The results obtained made it possible to precisely identify some structural aspects related to the formation of the acto-myosinic bonds responsible for the generation of force. The expertise in muscle field is now applied: 1) to study movement and motor control in humans to identify the physiological mechanism involved in the physiotherapy techniques developed for example in post-stroke rehabilitation and rheumatology; 2) in a multidisciplinary and innovative approach to design and use of a prototype for the early diagnosis of neurodegenerative diseases. The research findings have been published in over 70 papers in international impacted journals.

Cristiana Picco, PhD

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AFFILIATION & CURRENT POSITION

Senior researcher at Biophysics Institute (IBF)
National Research Council (CNR)

BRIEF CV

Dr. Cristiana Picco joined the Institute of Biophysics at the Italian National Research Council (CNR) as a researcher, developing extensive expertise in the structure-function relationships of membrane proteins. Her research focuses mainly on the functional role of proteins, ion channels, and membrane receptors in human diseases, including Cystic Fibrosis (CFTR), Brugada Syndrome, epilepsy, muscular dystrophies, and neurodegenerative disorders.
She has acquired a notable expertise on electrophysiological techniques, such as patch-clamp and two electrodes voltage-clamp (TEV). She has combined these techniques with cell biology (primary and secondary cell cultures, cell transfection, preparation of Xenopus laevis oocytes and microinjection with cRNA), molecular biology (recombinant DNA manipulation, PCR, mutagenesis) and fluorescence microscopy techniques (calcium imaging). This approach has enabled her to electrophysiologically characterized both animal and plant potassium channels and cytochromes.
She has been involved in different national (San Paolo, Telethon, PRIN) and international projects (EU Marie Curie Programme, Horizon 2020). Her productivity and contributions to the field are reflected in 55 peer-reviewed publications in international scientific journals, more than 80 abstracts submitted to national and international meetings. She has been supervisor of both graduate and PhD students.
She serves as a referee for several international journals, including the *British Journal of Pharmacology*, *Biophysical Journal*, *PLOS ONE*, *Scientific Reports*, *Vision*, *Neural Regeneration Research*, *Molecules*, and *The Plant Journal*. Additionally, she is an active member of the Biophysical Society (USA), the Italian Society for Pure and Applied Biophysics (SIBPA), and the National Interuniversity Consortium for Biostructures and Biosystems (INBB). Her international experience includes scientific visit abroad at Columbia University in New York with Prof. Firestein in 1996 and at the University of Cuernavaca in Mexico with Prof. Possani in 2010.

Prof. Giorgio Grasselli

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AFFILIATION & CURRENT POSITION

Associate Professor of Physiology at the Department of Pharmacy of the University of Genoa
Affiliated Researcher at the Center for Synaptic Neuroscience and Technology of the Italian Institute of Technology (IIT)
San Martino Research Hospital, Genoa

BRIEF CV

Giorgio Grasselli, PhD, is Associate Professor of Physiology at the Department of Pharmacy of the University of Genoa and Affiliated Researcher at the Center for Synaptic Neuroscience and Technology of the Italian Institute of Technology (IIT) and San Martino Research Hospital, Genoa. After completing his training in Cellular and Molecular Biology at the University of Rome Tor Vergata, he carried out most of his postdoctoral training at the University of Chicago.

His research focuses on the physiology and pathophysiology of neural circuits, with particular interest in neuronal plasticity, intrinsic excitability, and the cellular mechanisms underlying learning and memory. Using the cerebellum as a model system, his work investigates how functional and structural plasticity contribute to circuit adaptation in both healthy and diseased conditions. A major line of his current research addresses neurological and neuroinflammatory disorders, including multiple sclerosis, cerebellar ataxias, and autism spectrum disorders. His group combines electrophysiology, imaging, neuroanatomical approaches, and animal models to study disease-related alterations in neuronal function and connectivity.