

BIOGRAPHICAL SKETCH			
NAME Vania Broccoli		POSITION TITLE Head of Research Unit, San Raffaele Scientific Institute and CNR Institute of Neuroscience	
EDUCATION/TRAINING			
INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
Bologna University	BSc	1993	Molecular biology
San Raffaele Scientific Institute	PhD	1997	Genetics
Helmholtz Centre and Max Planck for Psychiatry	Post-doc	1997-1999	Molecular Neurobiology
Telethon Institute of Genetics and Medicine	Staff scientist	2000	Mouse transgenics
University of California (San Francisco, UCSF)	Guest Scientist	2003	Molecular Neurobiology

A. Personal statement

Vania Broccoli was trained as a neurodevelopmental geneticist interested in unraveling the function of developmental transcription factors during neuronal differentiation and brain morphogenesis. He generated the second knock-in mouse ever made by knocking the *Otx2* gene into the *En1* locus which led to a spatial reconfiguration of the brain with loss of the cerebellar structures (Broccoli et al., Nature 1999). Starting his own research in 2005 at the San Raffaele Scientific Institute, his group was among the first worldwide to establish the Yamanaka's method to reprogram somatic cells into induced pluripotent stem cells (iPSCs). Using this procedure, his lab has generated multiple iPSC lines from patients with Alzheimer's and Parkinson's disease, neurodegeneration with brain accumulation (NBIA), mitochondrial disorders and neurodevelopmental diseases (autism, epilepsies and encephalopathies). Subsequently, his group identified a minimal combination of three transcription factors (*Mash1*, *Nurr1* and *Lmx1a*) able to directly convert mouse and human fibroblasts into functional dopaminergic neurons (Caiazzo et al., Nature, 2011). Since then, his lab has established multiple procedures for generating different neuronal and glial subtypes by direct cell reprogramming. Since these approaches skip out the pluripotency stage they promote cell conversion preserving the biological age of the starting cells providing a powerful system to study brain aging and related disorders. In the last 5 years, his group established a solid experience in AAV production and delivery to design new gene therapy approaches for incurable neurodevelopmental disorders. In particular, he described the first applications of the novel AAV synthetic variant PHP.eB for a widespread brain delivery of therapeutic genes for treating infantile and age-related neurological disorders. His team is now further developing AAV capsids, routes of delivery and applications for implementing a cure for Rett syndrome, genetic ataxia and Parkinson's disease. In particular, his group uncovered key inflammatory processes leading to neurodegeneration in Parkinson's disease and established gene-based immunomodulating applications. By rational engineering, his team has developed transcription factor epigenetic silencers which are able to repress the entire downstream gene network of a given transcription factor. His group is developing epigenetic silencers as new and potent tools to defeat cancer malignancy through in situ viral delivery.

B. Positions, Scientific Appointments, and Honors

2006 - 2010: **Group Leader**, San Raffaele Scientific Institute, Milan, Italy.

2010 - present: **Head of Research Unit**, San Raffaele Scientific Institute, Milan, Italy.

2015 - present: **Director of Research**, CNR Institute of Neuroscience, Milan, Italy.

2014 - present: **Associated scientist**, Sant'Anna School of Advanced Studies, Life Science Center, Pisa, Italy.

- 2020-present: Member of the Scientific Advisory Board of Science Translational Medicine.
- Member of the Armenise Foundation's Italian Scholarship Advisory Committee – Armenise Harvard Foundation (2015 - 2018)
- Member of the evaluating committee for the Consolidator European Research Council (ERC) awards, Panel LS7 (2015 - present).
- Member of the Reviewer Scientific Panel of the California Institute of Regenerative Medicine (CIRM) (2013 – present), California, USA
- Member of the European Scientific Advisory Board of the FP7-ERANET Neuron-II program (2011 - 2018)
- Member of the external Scientific Advisory Board of the University of Lund (Sweden) (2012 – 2016) – Life Science
- Recipient of the European Research Council (ERC) Advanced grant (2014 – 2019).
- 2023: Abstract Review Chair for Neurological Disease of the American Society of Gene and Cell Therapy Meeting (LA, USA)
- 2023: Chair of the Scientific Committee on cell therapy/iPS cells/organoids of the European Society for Gene and Cell Therapy (ESGCT).
- 2023-2020: Member Scientific Committee for evaluation of the Academy of Finland grants, Program of Neuroscience.
- 2022: Member of the HCERES Committee for the evaluation of the Neuroscience Institutes of CNRS and INSERM in France (INCI, INP, INMED and UNIS).
- 2022: Member Scientific Advisory Board of I-STEM (AFM-Telethon Institute), Evry-Paris.
- 2021: Member of the HCERES Committee for the evaluation Stem Cell and Brain Research Institute in Lyon (France).
- Ad-hoc reviewer for scientific journals: Nature, Nature Neuroscience, Nature Communication, Nature Structural and Molecular Biology, Nature Chemical Biology, Cell, Cell Stem Cell, Cell Reports, Neuron, Science Translational Medicine, J. Neuroscience, EMBO Molecular Medicine, Genes & Development, Stem Cell Reports, Gene Therapy, Stem Cells, Development, Eur. J. Neuroscience, PNAS, Journal of Cell Science, Neuroscience, Cell Death and Differentiation, PloS One, Mechanisms of Development, Developmental Dynamics, Developmental Biology.
- Ad-hoc reviewer for scientific proposals: California Institute of Regenerative Medicine (CIRM), National Science Foundation (USA), Agence Nationale de la Recherche (ANR, France), CNRS, DFG, The Israel Science Foundation (ISF), AFM (France), Academy of Finland, Italian Telethon Association, MRC, BSSCR, Parkinson UK, Danish Council for Independent Research.
- Supervisor of 14 PhD students who have finished their thesis.
- 1999 - HFSP long-term fellowship
- 1998 - EMBO short-term fellowship

C. Contributions to Science

Starting by own lab in 2005 at the San Raffaele Scientific Institute, my group pioneered the Yamanaka's method to reprogram somatic cells into induced pluripotent stem cells (iPSCs) for disease modeling. Using this procedure, we established iPSC lines from patients with Alzheimer's and Parkinson's disease, neurodegeneration with brain accumulation (NBIA), mitochondrial disorders and autism. Patient iPSC-derived neurons were instrumental to elucidate new molecular mechanisms in these diseases. In particular, we established the first human iPSC-derived dopaminergic-striatal neuronal circuit in microfluidic devices. This model enabled us to discover that Parkinson's disease-associated mutations in the OPA1 gene cause stalling of axonal mitochondria in dopaminergic neurons with consequent loss of synaptic terminals. In addition, OPA1-mutated neuronal cultures showed reduced survival that could be substantially rescued by inhibiting necroptosis. We extended these results showing that necroptosis inhibition reduced dopaminergic neuronal demise in MPTP treated mice and enhanced activation of this pathway in the nigral tissue of Parkinson's disease patients.

1. Iannielli A, Ugolini GS, Cordiglieri C, Bido S, ..., Valtorta M, Cabassi T, Rasponi M, **Broccoli V**. Reconstitution of the Human Nigro-striatal Pathway on-a-Chip Reveals OPA1-Dependent

Mitochondrial Defects and Loss of Dopaminergic Synapses. **Cell Reports** 29:4646-4656.e4, 2019. PMID: 31875567.

2. Iannielli A, Bido S, Folladori L, Segnali A, Bezard E, Carelli V, Tiranti V, **Broccoli V**. Pharmacological Inhibition of Necroptosis Protects from Dopaminergic Neuronal Cell Death in Parkinson's Disease Models. **Cell Reports** 22:2066-2079, 2018. PMID: 29466734.

Since 2016 I have been focused my group on designing and validating novel gene therapy approaches for the neurological diseases we have been interested over many years. During that time CRISPR tools for gene targeting and engineered AAV capsids for efficient gene transfer in the brain were optimized providing unprecedented opportunities for treating human diseases. Reaching efficient disease gene correction enables to fix the primary genetic cause and possibly its phenotypic manifestations. On this perspective, these experiments enabled us also to answer to fundamental questions on the symptomatic reversibility of these disorders in time and space. My group established a new MECP2 gene replacement vector for treating Rett syndrome mice and determined the thresholds of gene correction necessary to achieved marked symptomatic rescue. My team established the first CRISPR-based gene augmentation strategy to restore physiological levels of genes encoding for ion channels and rescue seizures in murine models of human genetic epilepsies. We also provided unexpected evidence that recurrent seizures in Dravet mice can be fully extinguished when the mutant Scn1a gene is corrected to any post-natal stage.

3. Luoni M, Giannelli S, Indrigo MT, Niro A, ..., Calamita P, Gregori S, Deverman B, **Broccoli V**. Whole brain delivery of an instability-prone Mecp2 transgene improves behavioral and molecular pathological defects in mouse models of Rett syndrome. **Elife** 9:e52629, 2020. PMID: 32207685.
4. Colasante G, Qiu Y, Massimino L, Di Berardino C, ..., Schorge S*, Kullmann DM, **Broccoli V***, Lignani G*. *Co-last authors. In vivo CRISPRa decreases seizures and rescues cognitive deficits in a rodent model of epilepsy. **Brain** 143:891-905, 2020. PMID: 32129831.
5. Valassina N, Brusco S, Salamone A, Serra L, ..., D'Adamo P, Lignani G, **Broccoli V***, Colasante G.* *Co-last authors. Scn1a gene reactivation after symptom onset rescues pathological phenotypes in a mouse model of Dravet syndrome. **Nature Commun.** 13:161, 2022. PMID: 35013317.

My lab has pioneered new approaches of direct neuronal and glial cell reprogramming for the fast and straightforward generation of functional mouse and human brain cells. Initially, we identified a new set of transcription factors capable to convert mouse and human fibroblasts into midbrain dopaminergic neurons. This was the first time ever that a human neuronal subtype was produced by direct neuronal reprogramming. We, next, set up methodologies to generate GABAergic neurons, astrocytes and Schwann cells by identifying a minimal set of transcription factors for the direct conversion of fibroblasts. We also demonstrated that the same factors can be used to accelerate the commitment of human stem cells toward these particular cell types. Finally, my team showed that directly reprogrammed dopaminergic neurons can functionally integrated into neuronal circuits after brain transplantation in adult mice and release dopamine on-demand through DREADD remote control.

6. Colasante G, Lignani G, Rubio A, Medrihan L, ..., Taverna S, Benfenati F, **Broccoli V**. Rapid conversion of fibroblasts into functional forebrain GABAergic interneurons by direct genetic reprogramming. **Cell Stem Cell** 17:719-734, 2015. PMID: 26526726.
7. Dell'Anno MT, Caiazzo M, Leo D, Dvoretzkova E, ..., Taverna S, Dityatev A, **Broccoli V**. Remote control of induced dopaminergic neurons in parkinsonian rats. **J Clin Invest.** 124:3215-29, 2014. PMID: 24937431.
8. Caiazzo M, Dell'Anno MT, Dvoretzkova E, Lazarevic D, ..., Gustincich S, Dityatev A, **Broccoli V**. Direct generation of functional dopaminergic neurons from mouse and human fibroblasts. **Nature** 476:224-7, 2011. PMID: 21725324.

My team generated the first viral conditional system for the cell type-specific overexpression of a-Synuclein (aSYN). Surprisingly, we reported that microglia-specific aSYN overexpression is sufficient to induce dopaminergic neuron (DAN) degeneration through non-cell autonomous mechanisms. In fact, inflamed aSYN overexpressing microglia, together with recruited peripheral T cells, establishes a pathological amplifying inflammatory crosstalk, leading to the release of cytotoxic molecules and undermining neuronal survival. More recently, we showed a consistent correlation between neuroinflammation, brain parenchymal

lymphocytes and DAN cell loss among several commonly used mouse models of PD generated by a variety of pathological triggers. We validated a viral therapeutic approach for the microglia-specific expression of Interleukin 10 (IL-10) that sustained a robust neuroprotection against α SYN-induced neurodegeneration. IL-10 promoted microglia phagocytotic and clearance activities and stimulated the differentiation of CD4⁺ T lymphocytes into active T regulatory cells. Finally, CD8⁺ T cells exhibited enhanced inhibitory characteristics in the presence of IL-10. **These results offer insights into the therapeutic benefits induced by IL-10, showcasing a promising gene delivery approach that minimizes undesired side effects and has a strong translational relevance. Moreover, these findings led me to consider T regulatory cells as promising and unexplored targets to develop novel neuroprotective therapies for fighting PD progression.**

9. Bido S, Nannoni M, Muggeo S, Gambarè D, ..., Giannese F, Lazarevic D, Gregori S, **Broccoli V.** Microglia-specific IL-10 gene delivery inhibits neuroinflammation and neurodegeneration in a mouse model of Parkinson's disease. **Science Transl. Med.** 16(761):eadm8563. PMID: 39167665
10. Bido S, Muggeo S, Massimino L, Marzi MJ, ..., Bacigaluppi M, Gregori S, Nicassio F, **Broccoli V.** Microglia-specific overexpression of α -synuclein leads to severe dopaminergic neurodegeneration by phagocytic exhaustion and oxidative toxicity. **Nature Commun.** 12:6237, 2021. PMID: 34716339.

D. Publications

V. Broccoli has published 157 articles in international peer-reviewed scientific journals with a total of 13.168 citations (SCOPUS, Dec 2025), with an average citation index of 83/Journal. *h-index*: Google scholar, 71; SCOPUS, 61; WoS, 56 (Dec. 2025).

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He is the lead author of publications in journals with the highest scientific reputation, visibility and impact such as Nature (2), Nature Communications (5), Nature Cell Biology (1), Science Advance (1), Cell Reports (2), Cell Stem Cell (1), Neuron (3), Journal of Clinical Investigation (1), Brain (2), Genes & Development (1) and EMBO Molecular Medicine (1).

He has also co-authored high-impact publications in the work-frame of scientific consortia in Cell (1), Nature Communications (4), Nature Methods (1), Cell Reports (3), PNAS (2), Neuron (2), Brain (1). At the present time, 49,7% of his articles have IF higher than 7.