BIOGRAPHICAL SKETCH

NAME: Quadrato, Giorgia

eRA COMMONS USER NAME (credential, e.g., agency login): QUADRATO

POSITION TITLE: Assistant Professor of Stem cell Biology and Regenerative Medicine, University of Southern California

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Milano Bicocca, Italy	B.S.	11/2003	Molecular Biotechnology
University of Milano Bicocca, Italy	M.S.	11/2005	Pharmacogenomics
University of Piemonte Orientale, Italy	Ph.D.	01/2009	Neurobiology, Stem Cell Biology
University of Tuebingen, Germany	Postdoctoral Fellow	06/2014	Neurobiology, Stem Cell Biology
Harvard University and Broad Institute, Cambridge	Research Associate	06/2018	Neurobiology, Stem Cell Biology

A. Personal Statement

My lab focuses on understanding the cellular and molecular basis of human brain development and disease. By combining the use of emerging models of the human brain with single cell omics approaches, we are aiming to identify cell type specific disease mechanisms, and new treatments for human neurodevelopmental disorders. My training and research experiences provide a strong background expertise to carry out the proposed research project. Throughout my career, I have built a solid knowledge of the cellular and molecular mechanisms that drive the development and the function of endogenous neural stem cells, in the embryonic and in the adult central nervous system. In the last part of my training, I have focused on developing 3D *in vitro* models of the human brain that resemble the cellular diversity, and local connectivity, of the developing human cerebral cortex. Specifically, I have developed protocols for the generation of human pluripotent stem cell-derived brain organoids that allow the tissues to grow and develop over periods of nine months or longer, and enable unprecedented levels of cell maturation, including formation of spontaneously active neural networks and the development of light-sensitive retinal photoreceptors. My works has also provided the first molecular map of the diversity and reproducibility of cell types generated in brain organoids, setting new standards in the stem cell field for the use and characterization of stem cell-derived 3D cultures.

a. **Quadrato, G#**, Nguyen, T, Macosko, EZ, Sherwood, JL, Min Yang, S, Berger, DR…Arlotta, P#. Cell diversity and network dynamics in photosensitive human brain organoids. ***Nature.*** 2017;545 (7652):48-53. doi: 10.1038/nature22047. PubMed PMID:28445462 PubMed Central PMC5659341. *(#: corresponding author*)

b. Del Dosso A, Urenda JP, **Quadrato, G#**, "Upgrading the physiological relevance of human brain organoids". ***Neuron****. 2020; Sep 23;107(6):1014-1028.* doi: 10.1-16/j.neuron.2020.08.029 PMID:32970996 *(#: corresponding author);*

c. **Quadrato, G**, Brown, J, Arlotta, P. The promises and challenges of human brain organoids as models of neuropsychiatric disease. ***Nature Medicine.*** 2016;22 (11):1220-1228.
d. Velasco S, Kedaigle AJ, Simmons SK, Nash A, Rocha M, **Quadrato G**, Paulsen B, Nguyen L, Adiconis X, Regev A, Levin JZ, Arlotta P. "Individual brain organoids reproducibly form cell diversity of the human cerebral cortex". ***Nature.*** 2019 Jun;

B. Positions and Honors

Positions and Employment

2009-2014 Postdoctoral fellow, in the lab of Dr. Simone Di Giovanni, University of Tuebingen, Germany
2010-2014 Lecturer in Neuroregeneration and Neuro-tissue engineering, University of Tuebingen, Germany
2014-2018 Research associate, in the lab of Dr. Paola Arlotta, Harvard University, Cambridge, MA
06/2018- Assistant Professor, USC Stem cell, Keck school of Medicine, Los Angeles, CA

Other Experience and Professional Memberships

2009- Member, Society for Neuroscience (SfN)
2016- Member, International Society for Stem Cell Research (ISSCR)
2017- Member, Society for Developmental Biology (SDB)
2018- Abstract Reviewer for the ISSCR Symposium "Stem Cells & Organoids in Develop. & Disease"
2020- Associate Editor for Frontiers in Neuroscience - Neurodevelopment

Honors

2020 **Edward Mallinckdrot**, Jr Foundation Early Career Faculty Award
2020 The Robert E. and May R. Wright Foundation Research Award
2019 **Donald E. and Delia B. Baxter** Foundation Faculty Scholar Award
2017 Poster Award, 12th Annual Harvard Stem Cell Institute, MALKIN RETREAT
2016 Poster Award, ISSCR
2016 Travel award, ISSCR
2012 Postdoctoral fellowship and Start up support for early career scientists with highly innovative projects, the Foertune Programme, University of Tübingen
2010 Poster Award, Best poster of the year, Forschungskolloquium, University of Tübingen
2005 PhD fellowship Institution MIUR (Italian Department for University and Research)

Patents

- (PENDING) **Giorgia Quadrato**, Paola Arlotta. Methods for generating neural tissue and uses thereof. WO2017117547A1 published 2017-07-06
- (PROVISIONAL) Leonardo Morsut, Megan McCain, **Giorgia Quadrato.** Methods and compositions for reproducible derivation of cerebral organoids from stem cell. Filed July 2020

Invited talks (selected last three years)

- **Keystone Symposia on Organoids as tools for Discovery and Translation,** Keystone, Feb 2021
- **Southern California Stem Cell Consortium (SCSCC) Seminar Series**, October 2020
- **From Stem Cell to Human Development,** Wotton House, UK, September 2020
- **ISSCR Workshop on Clinical Translation,** Boston, June 2020
- **ISSCR Ethic Focus Session,** Boston, June 2020
- **British Society for Developmental Biology,** Warwick, March 2020
- **Keystone Symposia on Brain Therapeutics,** Santa Fe, February 2020
- **American Society of Molecular Psychiatry,** San Francisco, October 2020
- **Society for developmental Biology,** Boston, July 2019
- **Michigan Neuroscience Symposium,** Ann Arbor, May 2019
- **Cedars-Sinai,** Los Angeles, 2018
- **International Neuroethics society meeting,** San Diego, November 2018
- **American Society of Nephrology Meeting,** San Diego, October 2018
- Advances in Single Cell genomics to Study Brain cell Types, **Virtual Conference, SFN**, June 2018
- **International Young Investigator Symposium,** Lund Stem Cell, Lund, Sweden, April 2018

- **Stem Cell Symposium in Vienna,** Austrian Society for Stem Cell Research (ASSCR) and IMBA, Vienna, Austria, February 2018
- **Helmholtz Pioneer Campus***,* Munich, Germany, October 2017
- **Neurostemcellrepair consortium***,* Accademia dei Lincei, Rome, Italy, September 2017
- **EMBO conference**, Gene regulatory mechanism in neural fate decision*,* Alicante, Spain, September 2017
- **Center for developmental Neurobiology, Kings college,** London, UK, June 2017
- **Department of Developmental Biology,** Ecole Normale Superieure Paris, France, June 2017
- BioMed21: **Emerging Technology Toward Human Pathway-Based Brain Research**", Rio de Janeiro, Brasil, May 2017
- **Cellular Modeling of Neurological Disease Discussion Group Inaugural Meeting** (Harvard Brain Institute), Boston, USA May 2017
- **Medical and Population Genetics Program Meeting, Crossover meeting** (Broad Institute of MIT and Harvard), Cambridge, USA March 2017
- **University Medical Center Mainz**, Germany, February 2017
- **Keystone Symposia**, Olympic Valley, California, January 2017 (short talk)

C. Contributions to Science

1. Three-dimensional (3D) brain organoids derived from human pluripotent stem cells hold great potential to investigate complex human genetic states and to model aspects of human brain development and pathology. During my postdoc at Harvard University, I optimized a culturing protocol that supports prolonged development of self-organizing 3D human whole brain organoids for over 9 months. Using high-throughput single cell mRNA sequencing I have provided the first molecular map of the diversity and reproducibility of cell types generated in brain organoids. I have discovered that organoids can make a large diversity of cell classes from distinct regions of the brain and from the retina, and that cell types generated in organoids display preferential correlation to the appropriate endogenous counterparts from the human fetal brain and retina. I found that the cellular composition of organoids diversifies over time in culture and displays progressive levels of maturity. This is notably reflected in the acquisition of structural traits characteristic of mature neurons, including dendritic spine-like structures, which have been notoriously difficult to generate by directed differentiation in culture. In agreement with an advanced state of maturation, I have shown that whole brain organoids progressively generate spontaneously-active neuronal networks and that during the same period of time, photoreceptor-like cells mature substantially and become responsive to non-invasive, light-based sensory stimulation that appears capable of affecting neuronal activity. This suggests that co-development of brain and retina cells within the same organoid may in the future serve as a new experimental system to investigate the fine response of neuronal networks to physiological sensory stimuli, in both physiological and pathological setting. A major bottleneck that prevents the use of human brain organoids as a model of neurodevelopmental disease, is the low reproducibility achieved by actual models. We recently have modified current protocols to increase the organoid to organoid reproducibility. Under these conditions virtually all the cells generated in the organoids have cortical identity. Organoids cultured with this protocol also show a high degree of organoid-to-organoid reproducibility in cell type composition comparable to individual endogenous brains.

    a. Del Dosso A, Urenda JP, **Quadrato, G#**, "Upgrading the physiological relevance of human brain organoids". ***Neuron****. 2020; Sep 23;107(6):1014-1028.* doi: 10.1-16/j.neuron.2020.08.029 PMID:32970996 *(#: corresponding author);*
    b. **Quadrato, G**#, Nguyen, T, Macosko, EZ, Sherwood, JL, Min Yang, S, Berger, DR…Arlotta, P#. Cell diversity and network dynamics in photosensitive human brain organoids. ***Nature.*** 2017;545 (7652):48-53. doi: 10.1038/nature22047. PubMed PMID:28445462 PubMed Central PMC5659341. *(#: corresponding author*)
    c. **Quadrato, G**, Brown, J, Arlotta, P. The promises and challenges of human brain organoids as models of neuropsychiatric disease. ***Nature Medicine*** 2016;22 (11):1220-1228. doi: 10.1038/nm.4214. PubMed PMID:27783065 .
    d. Velasco S, Kedaigle AJ, Simmons SK, Nash A, Rocha M, **Quadrato G**, Paulsen B, Nguyen L, Adiconis X, Regev A, Levin JZ, Arlotta P. "Individual brain organoids reproducibly form cell diversity of the human cerebral cortex". ***Nature.*** 2019 Jun;570(7762):523 527.doi:10.1038/s41586-019-1289

2. As PhD student my research has contributed to the identification of signaling pathways that play a role in the transcriptional regulation of adult hippocampal neurogenesis. During my first postdoc, I have discovered expression and transcriptional activity of nuclear factor of activated T cell c4 (NFATc4) in adult hippocampal progenitor cells. I have shown that the NFATc4/calcineurin-dependent activity is required selectively for survival of adult-born neurons in response to BDNF signaling. Furthermore, I have demonstrated that associated with the reduced survival of adult-born neurons, the absence of NFATc4 leads to selective defects in LTP and in the encoding of hippocampal-dependent spatial memories. These findings, consistent with several other reports, have suggested a prominent contribution of adult hippocampal neurogenesis to cognitive processes such as long-term memory formation and retention. I have further contributed to the field by providing a novel molecular insight into the regulation of the innate anxiety response in mice and suggesting the $GABA_AR$/NFATc4 axis as a druggable target for the therapy of emotional disorders. I have shown that selective pharmacological enhancement of $GABA_A$ receptor activity promotes hippocampal neurogenesis via the calcineurin/NFATc4 axis and that the NFATc4-dependent increase in hippocampal neurogenesis following $GABA_A$ receptor stimulation is required for suppression of the anxiety response in mice.
    a. **Quadrato, G#***, Elnaggar, MY*, Duman, C, Sabino, A, Forsberg, K, Di Giovanni, S# *et al.* Modulation of GABAA receptor signaling increases neurogenesis and suppresses anxiety through NFATc4. ***J. Neurosci.*** 2014;34 (25):8630-45. doi: 10.1523/JNEUROSCI.0047-14.2014. PubMed PMID:24948817 . *(#: corresponding author,* equal contribution).*
    b. Ottone C, Krusche B, Whitby A, Clements M, **Quadrato G**, Pitulescu ME, Adams RH, Parrinello S. "Direct cell-cell contact with the vascular niche maintains quiescent neural stem cells." ***Nature Cell Biology.*** 2014 Nov;16(11):1045-56. doi: 10.1038/ncb3045. Epub 2014 Oct 5. PMID: 25283993
    c. Forsberg, K, Wuttke, A, **Quadrato, G**, Chumakov, PM, Wizenmann, A, Di Giovanni, S *et al.*. The tumor suppressor p53 fine-tunes reactive oxygen species levels and neurogenesis via PI3 kinase signaling. **J*. Neurosci***. 2013;33 (36):14318-30. doi: 10.1523/JNEUROSCI.1056-13.2013. PubMed PMID:24005285.
    d. **Quadrato G#**, Benevento M, Alber S, Jacob C, Floriddia EM, Nguyen T, Elnaggar MY, Pedroarena CM, Molkentin JD, Di Giovanni S. Nuclear factor of activated T cells (NFATc4) is required for BDNF-dependent survival of adult-born neurons and spatial memory formation in the hippocampus. ***PNAS*** U S A. 2012 Jun 5;109(23):E1499-508. doi: 10.1073/pnas.1202068109. Pubmed PMID: 22586092 *(#: corresponding author)*.
3. As postdoctoral fellow in the Di Giovanni's lab I focused on understanding the transcriptional machinery regulating CNS repair after acute injury, such as following trauma or stroke. In order to survive and functionally reconnect to the synaptic network, injured neurons activate an intrinsic rescue program aimed to increase their plasticity. In the attempt to switch back to a plastic and growth-competent state, post-mitotic neurons wake up and re-express a set of transcription factors that are also critical for the regulation of their younger brothers, the neural stem cells. Clarification of their common molecular substrate may help simultaneous targeting of both neurogenesis and axonal regeneration with the hope to enhance functional recovery following CNS injury.

    a. Joshi Y, Sória MG, **Quadrato G**, Inak G, Zhou L, Hervera A, Rathore KI, Elnaggar M, Cucchiarini M, Marine JC, Puttagunta R, Di Giovanni S. The MDM4/MDM2-p53-IGF1 axis controls axonal regeneration, sprouting and functional recovery after CNS injury. ***Brain***. 2015 Jul;138(Pt 7):1843-62. doi: 10.1093/brain/awv125. Epub 2015 May 16. PubMed PMID: 25981963.
    b. **Quadrato G#**, Di Giovanni S#. Waking up the sleepers: shared transcriptional pathways in axonal regeneration and neurogenesis. ***Cell Mol Life Sci***. 2013 Mar;70(6):993-1007. doi: 10.1007/s00018-012-1099-x. Epub 2012 Aug 17. Review. PubMed PMID: 22899311. (#: corresponding authors).
    c. Floriddia EM, Rathore KI, Tedeschi A, **Quadrato G**, Wuttke A, Lueckmann JM, Kigerl KA, Popovich PG, Di Giovanni S. p53 Regulates the neuronal intrinsic and extrinsic responses affecting the recovery of motor function following spinal cord injury. ***J Neurosci***. 2012 Oct 3;32(40):13956-70. doi: 10.1523/JNEUROSCI.1925-12.2012. PubMed PMID: 23035104; PubMed Central PMCID: PMC6704782.

Complete List of Published Work in MyBibliography:

https://www.ncbi.nlm.nih.gov/pubmed/?term=quadrato+g

D. Additional Information: Research Support and/or Scholastic Performance

ACTIVE

RECODE (McCain, Morsut, Quadrato) 10/15/20 – 10/14/24 0.96 cal months
NSF
RECODE: Identifying and engineering adhesion-based morphogenesis for reproducible manufacture of cortical organoids
Role: Co-PI
The major goal is to develop new technologies, include fluidic devices and synthetic cell receptors, to improve the reproducibility of cortical organoids.

Mallinckrodt (Quadrato) 01/01/21 – 12/31/23
Edward Mallinckrodt, Jr. Foundation
Role: PI
A human retina-brain organoid-based platform for interrogating neurodevelopmental disease
The major goal of this project is to build a human multi-organ-on-chip (MoC) platform that recapitulates the functional connectivity of the human visual system, for future phenotypic analysis of risk genes associated with complex neurodevelopmental disorders.

Wright Foundation (Quadrato) 07/01/2020 – 06/30/2021
Robert E. and May R. Wright Foundation
A human organoid platform to study cerebellar tumor initiation and development
Role: PI
The major goal of this project is to develop a 3D *in vitro* model of the human cerebellum to study medulloblastoma initiation at the single cell level, and which allows the study of *de novo* medulloblastoma formation by introducing genomic aberrations of the patient's original tumor within their own cerebellar organoids with gene editing techniques.

COMPLETED

HR00111990036 (Sherwood) 04/03/2019 – 09/30/2020 1.
Defense Advanced Research Projects Agency (DARPA)
WILD:CARROT (Wasp Inspired Logic Device: Connectome and RNA profiles Represented On Transistors)
Role: Co-PI
The major goals of this project are to utilize expansion microscopy, lattice light sheet microscopy, and single cell sequencing to more fully characterize the unique neural structure of M. mymaripenne, and work to develop new computational models to represent these architectures.

Baxter Foundation (Quadrato) 07/1/2019 – 09/30/2020
Donald E. and Delia B. Baxter Foundation
The role of Syngap1 in human brain development and disease
Role: PI
The major goal of this exploratory project was to set up a pipeline for the characterization of cell-type specific defects in diseased organoids. Mutant organoids for Syngap1 are used as proof of principle that the pipeline is sensitive enough to detect reproducible patterns of cell-type specific changes in gene expression

RESEARCH SUPPORT TO TRAINEES

Postdoctoral fellowship (Santorelli) 05/2019 – 05/2022
HFSP
Role: Mentor

T32 training grant (Urenda) 10/2019 – 10//2021
NIH
Role: Mentor