BIOGRAPHICAL SKETCH

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NAME: Lomvardas, Stavros

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

POSITION TITLE: Professor of Biochemistry and Molecular Biophysics and Neuroscience

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Crete, Heraklion, Greece	B.S	06/1998	Molecular Biology
Columbia University, New York, NY	M.A.	09/1999	Genetics and Development
Columbia University, New York, NY	Ph.D.	09/2002	Biochemistry and Molecular Biophysics
Columbia University, New York, NY	Postdoctoral	12/2006	Biochemistry and Molecular Biophysics

A. Personal Statement

My research program explores the mechanisms that organize the genome in the 3D nuclear space and to elucidate the influence of nuclear architecture in gene expression. As a model system for our studies we use the genetically tractable main olfactory epithelium, which provides an ideal system for the interogation of neural development in adult mice. What is appealing for this system is that every olfactory sensory neuron expresses one out of a thousand olfactory receptor (OR) genes in a seemingly stochastic fashion. My lab revealed that the key step in singular OR transcription is the assembly of multi-chromosomal compartments consisted of OR genes from 18 different chromosomes. These compartmens which form gradually during differentiation lead to the assembly of a multi-enhancer interchromosomal hub that associates only with one OR allele leading to the robust activation of singular OR transcription. Genetic manipulations that interfere with the assembly or stability of these compartments result in loss of OR transcription and/or loss of transcriptional singularity, highlighting the role of genomic compartmentalization in OR gene choice. We have a track record of developing and/or implemending cutting edge imaging and genomic technologies for the study of nuclear architecture, and integrating them with sophisticated genetic experiments. Thus, I have the conceptual and technical expertise to lead this U01 proposal, seeking to identify developmental trajectories of genome folding during neuronal differentiation

1. Clowney E.J., LeGross M.A., Mosley C.M., Clowney F.G., Markenskoff-Papadimitriou E.C., Myllys M., Barnea G., Larabell C.A. and **Lomvardas, S.** (2012). Nuclear aggregation of olfactory receptor genes regulates their monogenic expression. *Cell*, 151(4), 724-737. PMCID: PMC3659163.
2. Lyons, B.D., Allen, W.E., Goh, T., Tsai, L., Barnea, G. & **Lomvardas, S.** (2013). An epigenetic trap stabilizes singular olfactory receptor expression. *Cell*, 154(2), 325-336. PMCID: PMC3929589.
3. Markenscoff-Papadimitriou, E.C., Allen, W.E., Colquitt, B.M., Goh, T., Monahan, K., Murphy, K.K., Mosley, C.P., Ahituv, N., & **Lomvardas S.** (2014). Enhancer interaction networks as a means of singular olfactory receptor expression. *Cell*, 159(3), 543-557. PMCID: PMC4243057.
4. Monahan, K., Horta A., and **Lomvardas S** (2019)**.** Lhx2/Ldb1-mediated trans interactions regulate olfactory receptor choice. *Nature*, 565(7740): 448-453. PMCID: PMC6436840.

B. Positions and Honors

Positions and Employment

2007-2013 Assistant Professor, Department of Anatomy, University of California, San Francisco, CA
2013-2014 Associate Professor, Department of Anatomy, University of California, San Francisco, CA
2014- Professor, Biochemistry and Molecular Biophysics and Neuroscience, Columbia University, NY
2014- Principal Investigator, Zuckerman Mind Brain Behavior Institute, Columbia University, NY

Other Experience and Professional Memberships

2010-2014 Scientific Board of the International Rett Syndrome Foundation
2011-2014 European Research Council: Referee in Peer Review Evaluations
2013 NIDA CEBRA review roster member (NIH)
2012-2015 Somatosensory and Chemosensory Study Section, Ad Hoc Roster member (NIH)
2015-2018 NIDA AVENIR phase II review roster member (NIH)
2015 Simons Foundation Autism Research Initiative (SFARI) review roster member
2015 4D Nucleome Program, review roster member for the Nucleomics Tools RFA (NIH)
2015-2021 Chemosensory Study Section (NIH), regular member (chairperson from 2019)

Honors

2002 Harold M. Weintraub Award for outstand achievement during graduate studies in Biological Sciences, Fred Hutch Cancer Center, Seattle, WA
2002 Ph.D. with highest distinction from Department of Biochemistry and Molecular Biophysics, Columbia University, New York, NY
2002 Samuel W. Rover and Lewis Rover Awards for outstanding achievement in Biochemistry and Molecular Biophysics, Columbia University, New York, NY
2003 Helen Hay Whitney Foundation Fellowship, Helen Hay Whitney Foundation, New City, NY
2007 Innovations in Basic Sciences Award, Program for Breakthrough Biomedical Research, San Francisco, CA
2008 Rett Syndrome Trust New Investigator Award, Rett Syndrome Research Trust, Trumbull, CT
2009 NIH Director's New Innovator Award, National Institutes of Health, Bethesda, MD
2010 EUREKA Award, National Institutes of Health, Bethesda, MD
2010 McKnight Scholar Award, McKnight Endowment for Neuroscience, Minneapolis, MN
2014 Vilcek Prize for Creative Promise in Biomedical Promise, Vilcek Foundation, New York, NY
2014 Young Investigator Award for Research in Olfaction, Association for Chemoreception Sciences, Glenview, IL
2016 HHMI Faculty Scholar, Howard Hughes Medical Institute
2017 Blavatnik Foundation National Award Finalist, Blavatnik Foundation

C. Contribution to Science

My scientific career is focused on deciphering regulatory mechanisms of gene expression, with major contributions in the understanding of mechanisms of inducible and stochastic gene activation.

1. As a graduate student I examined the role of chromatin structure in the transcriptional activation of the IFNβ gene. My experiments revealed the order of events that lead to the activation of IFNβ transcription *in vivo,* established the role of histone acetylation in recruitment of nucleosome remodeling complexes, and demonstrated that TBP binding induces nucleosome sliding away from the core promoter, providing a novel mechanism by which general transcription factors facilitate transcription. Moreover, I showed that chromatin imposes specificity in gene activation; the position of a nucleosome determines the range of stimuli that lead to activation of IFNβ expression and defines the order of molecular events required for initiation of transcription. These experiments provided the first insight into the role of chromatin in regulation of inducible gene transcription and constitute the textbook view of transcriptional activation in the context of chromatin. I had major conceptual and technical contribution to most of these experiments.
    a. Agalioti, T*., **Lomvardas, S*.**, Parekh, B., Yie, J., Maniatis, T., & Thanos, D. (2000). Ordered recruitment of chromatin modifying and general transcription factors to the IFN-beta promoter. *Cell*, 103(4), 667-678. *Equally contributing authors

b. **Lomvardas, S**. & Thanos, D. (2001). Nucleosome sliding via TBP DNA binding in vivo. *Cell,* 106(6), 685-696.
c. **Lomvardas, S**. & Thanos, D. (2002). Modifying gene expression programs by altering core promoter chromatin architecture. *Cell*, 110(2), 261-271.

2. As an independent investigator I study the regulatory mechanisms of the monogenic and monoallelic olfactory receptor (OR) choice. Our experiments revealed an elegant molecular pathway that starts with the heterochromatic silencing of OR genes, continues with enzymatic de-silencing of one OR allele by lysine demethylase Lsd1, and culminates with the OR-dependent downregulation of Lsd1 expression, which stabilizes the singular OR choice. We also discovered that OR elicit this feedback signal via components of the unfolded protein response pathway, which detect OR protein expression in the endoplasmic reticulum. This regulatory loop, combined with our analysis of the unusual organization of OR loci in nuclei of olfactory sensory neurons provide molecular insight to a process that remained elusive since the cloning of olfactory receptor genes. These experiments, which I supervised and designed, provided significant insight to the elusive process of olfactory receptor choice, which remained mysterious since the discovery of olfactory receptor genes by Buck and Axel.
    a. Magklara, A., Yen, A., Colquitt, B.M., Clowney, E.J., Allen, W., Markenscoff-Papadimitriou, E., Evans, Z.A., Kheradpour, P., Mountoufaris, G., Carey, C., Barnea, G., Kellis, M., & **Lomvardas, S**. (2011). An epigenetic signature for monoallelic olfactory receptor expression. *Cell*, 145(4), 555-570. PMCID: PMC3094500.
    b. Lyons, B.D., Allen, W.E., Goh, T., Tsai, L., Barnea, G. & **Lomvardas, S.** (2013). An epigenetic trap stabilizes singular olfactory receptor expression. *Cell*, 154(2), 325-336. PMCID: PMC3929589.
    c. Dalton, P.R., Lyons, B.D & **Lomvardas S**. (2013). Co-opting the unfolded protein response to elicit olfactory receptor feedback. *Cell,* 155(2), 321-32 PMCID: PMC3843319.
    d. Lyons, B.D., Magklara, A., Goh, T., Sampath, S., Schaefer, A., Schotta, G. & **Lomvardas, S**. (2014). Heterochromatic silencing facilitates the diversification of olfactory neurons. *Cell Rep*, 9(3), 884-892. PMCID: PMC4251488.

3. In addition to our epigenetic studies focused on OR gene regulation we have performed comprehensive analyses on the epigenetic transitions occurring during the differentiation of olfactory neurons in vivo. By performing ChIP-seq and DIP-seq on FACsorted cells we provided the first detailed description of the changes in DNA methylation, DNA hydroxymethylation, chromatin accessibility occurring during differentiation. With genetic manipulation (loss of function and overexpression experiments) we demonstrated the role of hydroxylmethylcytosine in neuronal transcription as a facilitator of transcriptional elongation than a mere intermediate of cytosine de-methylation. Finally, more recently by performing ChIP-seq for transcription factors we showed that transcription factors Lhx2 and Ebf bind cooperatively to OR enhancers and enable their function.
    a. Colquitt, B.M., Allen, W.E., Barnea, G., **Lomvardas, S.** (2013). Alteration of genic 5-hydroxymethylcytosine patterning in olfactory neurons correlates with changes in gene expression and cell identity. *Proc Natl Acad Sci U S A*, 110(36), 14682-14687 PMCID: PMC3767503.
    b. Colquitt, B.M., Markenscoff-Papadimitriou, E., Duffié, R., **Lomvardas, S.** (2014). Dnmt3a regulates global gene expression in olfactory sensory neurons and enables odorant-induced transcription. *Neuron*, 83(4), 823-838. PMCID: PMC4153871.
    c. Monahan K.,Schieren I., Cheung J., Mumbey-Wafula A., Monuki E.S., and **Lomvardas S**. (2017). Cooperative interactions enable singular olfactory receptor expression in mouse olfactory neurons. *Elife* PMCID: PMC5608512.
    d. Canzio D., Nwakeze C.,L., Horta A., Rajkumar S., M., Coffey E., L., Duffy E., E., Duffie R., Monahan K., O'Keeffe S., Simon M., D., **Lomvardas S**., and Maniatis T., (2019) Antisense lncRNA transcription mediates DNA demethylation to drive stochastic Protocadherin a promoter choice. *Cell*. 2019 Apr 18;177(3):639-653.e15. PubMed PMID: 30955885.

4. Importantly, my research program has revealed significant insight to the understanding of the role of nuclear architecture in epigenetic processes and gene regulation during neuronal differentiation. Using sequence capture technologies to generate a complex DNA FISH probe that detects the thousands of olfactory receptor alleles simultaneously we showed that during neuronal differentiation olfactory receptor loci converge to unique heterochromatic nuclear foci that contribute to the complete transcriptional

silencing of olfactory receptor genes. Our experiments revealed that essential for this unusual nuclear reorganization is the downregulation of lamin b receptor from the differentiating neurons, which normally tethers olfactory receptor genes to the nuclear envelope. In each olfactory neuron, the transcriptionally active olfactory receptor allele resides outside of these repressive foci and is surrounded by a large number of intergenic enhancers that converge over the active allele from many different chromosomes, a discovery that constitutes the continuation of work that I started as post-doc in Richard Axel's lab. These findings demonstrate the decisive role of nuclear architecture in gene regulation in vivo. I designed and supervised the experiments that led to these discoveries from my own lab and designed and executed the experiments that I published as post-doc.

a. Clowney E.J., LeGross M.A., Mosley C.M., Clowney F.G., Markenskoff-Papadimitriou E.C., Myllys M., Barnea G., Larabell C.A. and **Lomvardas, S.** (2012). Nuclear aggregation of olfactory receptor genes regulates their monogenic expression. *Cell,* 151(4), 724-737. PMCID: PMC3659163.
b. Markenscoff-Papadimitriou, E.C., Allen, W.E., Colquitt, B.M., Goh, T., Monahan, K., Murphy, K.K., Mosley, C.P., Ahituv, N., & **Lomvardas S.** (2014). Enhancer interaction networks as a means of singular olfactory receptor expression. *Cell*, 159(3), 543-557. PMCID: PMC4243057.
c. Le Gros, M.A., Clowney, E.J., Magklara, A., Yen, A., Markenscoff-Papadimitriou, E., Colquitt, B., Myllys, M., Kellis, M., **Lomvardas, S.,** & Larabell, C.A. (2016). Soft X-Ray Tomography reveals gradual chromatin compaction and reorganization during neurogenesis in vivo. *Cell Rep*, 17(8), 2125-2136. PMCID: PMC5135017.
d. Monahan, K., Horta A., and **Lomvardas S** (2019)**.** Lhx2/Ldb1-mediated trans interactions regulate olfactory receptor choice. *Nature* 565(7740): 448-453. PMCID: PMC6436840.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/stavros.lomvardas.1/bibliography/40755668/public/?sort=date&direction=descending

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

Ongoing Research Support

U01 DA040582 Lomvardas, Brown, Larabell (MPI) 09/01/2015–08/30/2020
Deciphering nuclear bodies and compartments that govern singular olfactory receptor expression
This grant seeks to develop new technologies for the imaging, genomic, and biochemical analysis of the heterochromatic nuclear bodies formed by silent olfactory receptor genes.
Role: MPI

R56 AG062454 Lomvardas (PI) 08/15/2019–07/31/2020
Anosmia as a predictor of preclinical Alzheimer's disease
This grant seeks to we explore the possibility that olfactory neurons could be used as early molecular sensors for neurodegenerative disorders.
Role: PI

R01 DC015451 Lomvardas (PI) 07/01/2016–06/30/2021
Deciphering the Molecular Principles of Olfactory Receptor Gene Choice
This grant seeks to decipher the molecular mechanisms by which transcription factors Lhx2 and Ebf activate intergenic transcriptional enhancers towards the singular olfactory receptor transcription.
Role: PI

HHMI Faculty Scholar Lomvardas (PI) 11/01/2016–10/31/2021
Molecular Mechanisms of Stochastic Gene Expression
Role: PI

NSF 1921500 Narlikar (PI), Larabell, Lomvardas 08/01/2019–07/31/2024
Collaborative Research: URoL: Epigenetics 2: Phase separated genome compartments as drivers of epigenetic phenotypes
This grant seeks to decipher how droplet mediated DNA organization is regulated by cellular signals and how it impacts epigenetic phenotypes.
Role: Co-PI

R01DC018744 Lomvardas (PI) 04/01/2020-03/31/2025
Olfactory receptor mRNAs as lnRNAs that regulate genomic interactions
This grant seeks to decipher the mechanism by which OR mRNA transcription recruits OR enhancers from other chromosomes and biases OR gene choice
Role: PI

R01DC018745 Lomvardas (PI) 03/01/2020-02/28/2025
Principles of zonal olfactory receptor expression
This grant seeks to identify gradients of transcription factors along the dorsoventral axes of the olfactory epithelium responsible for the zonal expression of olfactory receptor genes.
Role: PI

Completed Research Support

R01 DC014144 Lomvardas (PI) 08/01/2014–07/31/2019
The Unfolded Protein Response as an Organizer of Chemosensory Response
This grant seeks to characterize a newly discovered molecular pathway that uses components of the unfolded protein response for the stabilization of olfactory receptor gene choice.
Role: PI

R01 DC013560 Lomvardas (PI) 08/01/2014–07/31/2019
Understanding the Nuclear Architecture in Olfactory Receptor Choice.
This grant seeks to characterize a network of interchromosomal interactions formed between the transcriptionally active OR allele and distant regulatory enhancers in olfactory neurons.
Role: PI

R01 DA036894 Lomvardas, Barnea (MPI) 09/15/2013–9/14/2018
Controling epigenetic states and nuclear architecture in the brain
This grant seeks to develop technologies that will allow the cell type and sequence specific manipulation of gene loci, either at the level of epigenetic regulation and at the level of relative nuclear positioning.
Role: MPI