BIOGRAPHICAL SKETCH

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NAME: Shariati, Ali

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POSITION TITLE: Assistant Professor of Bimolecular Engineering

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)	END DATE MM/YYYY	FIELD OF STUDY
Kharazmi University, Tehran	BS	06/2005	Molecular and Cellular Biology
Tarbiat Modares University, Tehran	MS	06/2008	Genetics
KU Leuven, Leuven	PHD	01/2014	Biomedical Sciences

A. Personal Statement

The overarching goal of my laboratory is to determine *molecular feedback mechanisms between the cell division cycle and differentiation in pluripotent embryonic stem cells (ESCs).* ESCs have great therapeutic potential for regenerative medicine because they can self-renew to unlimited numbers and can be instructed to differentiate into any cell type. However, a major challenge for therapeutic applications of ESCs is development of efficient and reproducible differentiation methods. Detailed insight into molecular mechanisms linking the cell cycle and differentiation of ESCs will allow for development of novel strategies for robust differentiation of ESCs for therapeutic applications.

I received my PhD in Biomedical Sciences in 2014 under supervision of Professor Bart De Strooper at the University of Leuven in Belgium. My PhD thesis was focused on determining the role of Amyloid Precursor Protein (APP) family in differentiation and migration of neural stem cells during brain development. After completing my PhD, I started my postdoctoral training in the laboratory of Professor Jan Skotheim in the Department of Biology at Stanford University where I received interdisciplinary training across stem cell biology and bioengineering disciplines. I was co-advised by Professor Marius Wernig from the Stem Cell Institute and Professor Stanley Qi from the Bioengineering Department. During my postdoctoral work, **I developed a new CRISPR-based method, named CRISPRd, to precisely disrupt the binding of transcription factors to specific binding sites**. I used CRISPRd to uncover regulatory principles that govern pluripotency transcription network.

Despite unusual challenges of the past two years, I succeeded in establishing my laboratory at University of California, Santa Cruz (UCSC), recruiting excellent researcher to my laboratory and pushing forward with our research program. The goal of my laboratory is to determine molecular feedback mechanisms between the cell division cycle and differentiation of ESCs. My team combines emerging genome-editing technologies, protein engineering and single cell quantitative live imaging to determine molecular mechanisms linking the cell cycle and cell fate decisions in pluripotent cells. A notable early success for my laboratory was the **development of a new software for automated analysis of single-cell time lapse microscopy**, termed DeepSea, that allows us to monitor the dynamics of cell cycle progression and pluripotency in individual cells. Currently, I have two postdoctoral fellows, one graduate students, one technician and two undergraduate lab assistants in my laboratory. I would like to note that both of my postdoctoral fellows **have received prestigious fellowships**: NIH IRACDA fellowship and the Rubicon fellowship.

In my new role as a faculty member at UCSC, I am committed to mentor students and postdoctoral fellows from diverse backgrounds to become independent scientists with skills that will allow them to pursue different career opportunities. My training at Stanford University and KU Leuven has prepared me to train a new generation of independent, confident and creative scientists. I was fortunate enough to be supported by my PhD and postdoctoral advisors to succeed in academia and I am excited to pay it forward.

B. Positions, Scientific Appointments, and Honors

Positions and Employment

2006 - 2008	Research Assistant, Stem Cell Technology Center, Tehran
2014 - 2019	Postdoctoral Researcher, Stanford University, Stanford, CA
2019 -Now	Assistant Professor of Bimolecular Engineering, University of California, Santa Cruz

Honors

2004	Ranked 1st in National Graduate School Entrance Exam (among more than 7000 students)
2009	KU Leuven Greatest Distinction for Predoctoral Studies, KU Leuven
2017	National Research Service Award (F32), NIH/NIGMS
2018	Transition to Independence Award (K99/R00), NIH/NIGMS
2019	Selected Talk, Stem Cell Biology Meeting, Cold Spring Harbor Laboratory
2019	Invited Speaker, Department of Biological Sciences, San Jose State University
2020	New Faculty Research Award, UCSC
2021	Invited Speaker, Faculty Bootcamp Preparation, Chan Zuckerberg Initiative (CZI)
2021	Invited Speaker, Department of Biology, Tehran University, Tehran

C. Contribution to Science

1. Early Career:

   As a master student, I focused on development of accessible and cost-effective molecular biology techniques for profiling of small RNAs. In order to detect small RNAs, we used a ligation based PCR amplification in which size coded probes were used to distinguish the expression of several small RNAs in one reaction. This method was used to measure expression of Let7 family of MicroRNAs during differentiation of stem cells as well as in young and aged tissues. We showed that this method can be applied for specific and quantitative measurement of small RNAs expression in various samples.

   a. Ahmadbeigi N, Soleimani M, Gheisari Y, Vasei M, Amanpour S, Bagherizadeh I, Shariati SA, Azadmanesh K, Amini S, Shafiee A, Arabkari V, Nardi NB. Dormant phase and multinuclear cells: two key phenomena in early culture of murine bone marrow mesenchymal stem cells. Stem Cells Dev. 2011 Aug;20(8):1337-47. PubMed PMID: 21083430.
   b. Arefian E, Kiani J, Soleimani M, Shariati SA, Aghaee-Bakhtiari SH, Atashi A, Gheisari Y, Ahmadbeigi N, Banaei-Moghaddam AM, Naderi M, Namvarasl N, Good L, Faridani OR. Analysis of microRNA signatures using size-coded ligation-mediated PCR. Nucleic Acids Res. 2011 Jul;39(12):e80. PubMed Central PMCID: PMC3130289.

2. Graduate work:

   For my PhD thesis, I focused on understanding the role of Alzheimer's linked gene family, amyloid precursor protein (APP), in physiological development of the brain. In addition to APP itself, APP protein family has two other members in mouse and human: APLP1 and APLP2. Single deletion of any of the three APP results in very minor phenotypes likely due to functional redundancy. However, deletion of all the three genes (triple knockout) results in developmental lethality. To avoid lethality and compensation, we used in vitro neuronal differentiation of triple knockout mouse ESCs which allowed us to generate enough mature neurons to be studied in vitro. Our analysis of neuronal migration, neuronal maturation and synaptic activity showed that triple knockout neurons behave to large extent similar to their wild type counterparts in vitro.

   Using cell specific genetic manipulation, I found that members of the APP family proteins regulate distinct cellular processes during brain development. While APLP2 promotes differentiation of neural

stem cells, APP and APLP1 are involved in neuronal migration and maturation. Despite sequence homology, differential expression of these proteins in distinct cell types confer specificity to their function. Computational analysis of these proteins revealed that the functions of APP, APLP1 and APLP2 have diverged after duplication to contribute distinctly to different neuronal events. Overall, I uncovered a new function for amyloid precursor protein (APP) family in neuronal stem cells of the brain.

I was also involved in understanding the role of membrane protease, γ-secretases, in cleaving and processing of schizophrenia associated gene, NRG1. In this work we showed that γ-secretases mediated processing of NRG1 is required for the proper development of neurons by regulating dendritic spine formation.

a. Fazzari P, Snellinx A, Sabanov V, Ahmed T, Serneels L, Gartner A, Shariati SA, Balschun D, De Strooper B. Cell autonomous regulation of hippocampal circuitry via Aph1b-γ-secretase/neuregulin 1 signalling. Elife. 2014 Jun 2;3 PubMed Central PMCID: PMC4073283.
b. Shariati SA, De Strooper B. Redundancy and divergence in the amyloid precursor protein family. FEBS Lett. 2013 Jun 27;587(13):2036-45. PubMed PMID: 23707420.
c. Shariati SA, Lau P, Hassan BA, Müller U, Dotti CG, De Strooper B, Gärtner A. APLP2 regulates neuronal stem cell differentiation during cortical development. J Cell Sci. 2013 Mar 1;126(Pt 5):1268-77. PubMed PMID: 23345401.
d. Bergmans BA, Shariati SA, Habets RL, Verstreken P, Schoonjans L, Müller U, Dotti CG, De Strooper B. Neurons generated from APP/APLP1/APLP2 triple knockout embryonic stem cells behave normally in vitro and in vivo: lack of evidence for a cell autonomous role of the amyloid precursor protein in neuronal differentiation. Stem Cells. 2010 Mar 31;28(3):399-406. PubMed PMID: 20049903.

3. Postdoctoral work:

In my postdoctoral work, I developed a novel method termed CRISPR Disrupt (CRISPRd) that allows rapid functional analysis of specific transcription factor-promoter interactions by site-specific disruption of transcription factor binding sites (Shariati et al, Molecular Cell, 2019). Typical mammalian transcription factors target hundreds of genes, a small subset of which may have a functional role in cell biological processes such as stem cell division and differentiation. However, it is difficult to determine the function of single transcription factor binding sites within larger transcription networks. I developed a new method, termed CRISPRd, that allows for disruption of the transcription factor to specific sites in the genome. CRISPRd uses deactivated version of Cas9 nuclease, dCas9, to compete for endogenous binding sites of transcription factors. I have shown that CRISPRd can be used to efficiently and reversibly outcompete pluripotency transcription factors at specific binding sites in the genome of mouse ESCs. My work revealed the functional importance of individual binding sites of pluripotency transcription factors, Oct4 and Nanog, in cell cycle progression and differentiation of ESCs. CRISPRd may offer a novel strategy to control lineage differentiation by specific perturbation of key nodes in transcriptional nodes.

a. Shariati SA, Dominguez A, Xie S, Wernig M, Qi LS, Skotheim JM. Reversible Disruption of Specific Transcription Factor-DNA Interactions Using CRISPR/Cas9. Mol Cell. 2019 May 2;74(3):622-633.e4. PubMed Central PMCID: PMC6599634.
b. Jukam D, Shariati SAM, Skotheim JM. Zygotic Genome Activation in Vertebrates. Dev Cell. 2017 Aug 21;42(4):316-332. PubMed Central PMCID: PMC5714289.
c. Treutlein B, Lee QY, Camp JG, Mall M, Koh W, Shariati SA, Sim S, Neff NF, Skotheim JM, Wernig M, Quake SR. Dissecting direct reprogramming from fibroblast to neuron using single-cell RNA-seq. Nature. 2016 Jun 16;534(7607):391-5. PubMed Central PMCID: PMC4928860.

4. Ongoing work in my laboratory at UCSC:

An early success of my laboratory was development of a novel deep-learning based software, termed

DeepSea, that allows for automated analysis of live imaging microcopy data. Single-cell quantitative live microscopy can directly capture both dynamics and heterogeneity of stem cell fate decisions by continuous long-term measurements of cellular features. However, a major bottleneck is automated analysis of hundreds of images that are typically generated over a course of few days. We successfully developed an efficient deep learning model, termed DeepSear, that can detect single cells with high precision and track them over a long period of time accurately. We demonstrated the application of our software by quantifying and tracking several cell biological features of mouse ESCs, such as cell division cycle, mitosis, cell morphology, and cell size, using phase-contrast image sequences. Currently, we are using our automated single cell live imaging method to rapidly monitor cell cycle progression and differentiation of ESCs.

Abolfazl Zargari, Gerrald A. Lodewijk, Celine W. Neudorf, Kimiasadat Araghbidikashani, Najmeh Mashhadi, Stefany Rubio, Lindsay Hinck, S. Ali Shariati, DeepSea: An efficient deep learning model for automated cell segmentation and tracking, bioRxiv, 2021, https://doi.org/10.1101/2021.03.10.434806

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

Ongoing Research Support

R00GM126027, NIH/NIGMS Shariati, Ali (PI) 07/01/20-06/30/23
Determining feedback mechanisms between cell cycle and cell fate in pluripotent cells
Role: PI

UCSC Startup Fund Shariati, Ali (PI) 07/01/19-06/30/25
Role: PI

Completed Research Support

1K99GM126027, NIH/NIGMS Shariati, Ali (PI) 07/01/18-09/30/19
Determining feedback mechanisms between cell cycle and cell fate in pluripotent cells
Role: PI

1F32GM123576, NIH/NIGMS Shariati, Ali (PI) 07/01/17-06/01/18
Determining feedback mechanisms linking cell cycle control and stem cell pluripotency using an engineered CRISPR/dCas9 system
Role: PI