BIOGRAPHICAL SKETCH

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NAME: Saghizadeh Ghiam, Mehrnoosh

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

POSITION TITLE: Associate Professor of Biomedical Sciences

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
California State University, Northridge, CA	M.S.	06/95	Biology
University of California, Los Angeles, CA	Ph.D.	06/07	Ophthalmology
Cedars-Sinai Medical Center, Los Angeles, CA	Postdoctoral	03/11	Ophthalmology

A. Personal Statement

We seek to investigate the role of candidate microRNAs expressed in the limbal epithelial stem cells (LESC)-enriched limbal epithelium in corneal epithelial homeostasis and wound healing *in vitro* and in human organ-cultured corneas. We will employ a variety of molecular, functional tests and ex-vivo human organ-cultured corneas to understand the role of microRNAs in both differentiated epithelial and stem cells of normal and diabetic corneas and their roles in driving LESC activation in normal and diseased cornea. We will focus on determining their targets, and attempt gene therapy with either overexpression or silencing of specific microRNAs to normalize corneal wound healing and LESC marker patterns in diabetic cornea. Our research could lead to the generation of a new cell source for restoring vision in patients with altered LESC.
In addition, Our Laboratory is seeking to investigate the major mechanisms of action of nano-sized limbal extracellular vesicles (EVs), which are taken up by neighboring cells, in stem cell maintenance and wound repair in cell cultures and in normal and diabetic human organ-cultured corneas, and the therapeutic potential of EVs for treatment of corneal injuries and diabetic abnormalities Our goal, ultimately, is to restore stem cell function for future clinical translation.

I have a strong background and expertise in molecular biology, ocular diseases, both corneal and retinal, genetics and cell biology, organ culture, microRNA biology, and miR-based therapeutic approach, as well as training and leadership to carry out the research projects. My laboratory has been in the forefront of the regulatory microRNA field in normal and diabetic cornea. My research experience has been summarized in more than forty peer-reviewed publications in reputed journals, such as *Journal of Clinical Investigation, Journal of Biological Chemistry, American Journal of Pathology, Scientific Reports, Stem Cells.* As PI and co-I on several institute and NIH-funded grants, I have experience managing budgets, organizing research, meet the deadlines, and have collaborated with a number of research groups.

B. Positions and Honors

Positions and Employment

1989-1991 Graduate Assistant, Microbiology Laboratory, California State University, Northridge, CA
1990-1991 Research Assistant, Cancer and Developmental Lab, California State University, Northridge, CA
1991-1995 Research Associate II, Endocrinology, Cedars-Sinai Medical Center, Los Angeles, CA
1995-2002 Research Associate II, Ophthalmology Research, Cedars-Sinai Medical Center, Los Angeles, CA

2002-2007 Research Associate III, Ophthalmology Research, Cedars-Sinai Medical Center, Los Angeles, CA
2007-2011 Postdoc Researcher, Ophthalmology Research, Cedars-Sinai Medical Center, Los Angeles, CA
2011-2015 Research Scientist I, Ophthalmology Research, Cedars-Sinai Medical Center, Los Angeles, CA
2012-2017 Assistant Professor of Biomedical Sciences, Cedars-Sinai Medical Center, Los Angeles, CA.
2014-present Assistant Professor of Medicine, Step II, David Geffen School of Medicine at UCLA, Los Angeles, CA.
2015-present Research Scientist II, Ophthalmology Research, Cedars-Sinai Medical Center, Los Angeles, CA.
2017-present Associate Professor of Biomedical Sciences, Cedars-Sinai Medical Center, Los Angeles, CA.

Other Experience and Professional Memberships

2000-present Member, Association for Research in Vision and Ophthalmology (ARVO)
2003-present Member, International Society for Eye Research (ISER)
2015-present Scientific Review Committee, Dr. Ralph and Marian Falk Medical Research Trust Awards Programs, Scientific Review Committee
2016-present Scientific Review Committee, Science Foundation Ireland (SFI)
2017-2020 ARVO member of the Members-in-Training Committee (MIT), three-year term.
2018-2021 ISER's Membership Committee, three-year term.

Honors

2002-2005 NIH Training Grant
2006-2007 UCLA Dissertation Fellowship
2006 ISER2006 Young Investigator Award, XVIIth ISER Congress, Buenos Aires, Argentina
2006 RD2006 Young Investigator Award, XIIth Symposium, San Carlos de Bariloche, Argentina
2007 APSIH Academic Achievement Award
2009 NEI ARVO Travel Award
2009 ISOV award for best ARVO abstract
2015-2017 ISER Council, Young Investigator Representative

C. Contribution to Science

1. The interregulation of lipoprotein lipase and tumor necrosis factor in obesity.

My early studies as a graduate student toward my master degree in the field of endocrinology focused on the expression of lipoprotein lipase (LPL) and tumor necrosis factor (TNF) in muscle and adipose tissues in relation to obesity, weight loss and insulin resistance. We showed that TNF expression in adipocytes is elevated in most obese subjects and is decreased by weight loss. In addition, we showed that there is an inverse correlation between adipose and muscle TNF and LPL expressions suggesting that TNF is an important locally produced factor that regulates adipocyte metabolism through the local action of increasing insulin resistance and probably limiting the degree of obesity.

a. Ranganathan G, Ong JM, Yukht A, **Saghizadeh M**, Simsolo RB, Pauer A, Kern PA. Tissue-specific expression of human lipoprotein lipase. Effect of the 3'-untranslated region on translation. J Biol Chem 1995, 270:7149-55.
b. Kern PA**, Saghizadeh M**, Ong JM, Bosch RJ, Deem R, and Simsolo RB. The expression of tumor necrosis factor in human adipose tissue. Regulation by obesity, weight loss, and relationship to lipoprotein lipase. J Clin Invest 1995, 95:2111-9.
c. **Saghizadeh M**, Ong JM, Garvey WT, Henry RR, and Kern PA. The expression of TNF alpha by human muscle. Relationship to insulin resistance. J Clin Invest 1996, 15;97:1111-6.

2. Expression analysis and identification of novel molecular markers in common eye diseases.

My earlier studies in the field of ophthalmology were focused on the alterations of extracellular matrix, growth factors and cytokines in common eye diseases including bullous keratopathy (PBK), keratoconus and diabetic human corneas, where new molecular markers of these common corneal diseases were identified. We also discovered the new tenascin splice variants and its interaction with growth factors/cytokines in PBK/ABK pathogenesis.

a. **Saghizadeh M**, Khin HL, Bourdon MA, Kenney MC, Ljubimov AV. Novel splice variants of human tenascin-C mRNA identified in normal and bullous keratopathy corneas. Cornea 1998, 17:326-32.
b. **Saghizadeh M**, Brown DJ, Castellon R, Chwa M, Huang GH, Ljubimova JY, Rosenberg S, Spirin KS, Stolitenko RB, Adachi W, Kinoshita S, Murphy G, WindsorLJ, Kenney MC, Ljubimov AV. Overexpression of matrix metalloproteinase-10 and matrix metalloproteinase-3 in human diabetic corneas: a possible mechanism of basement membrane and integrin alterations. Am J Pathol 2001, 158:723-34.
c. **Saghizadeh M**, Chwa M, Aoki A, Lin B, Pirouzmanesh A, Brown DJ, Ljubimov AV, Kenney MC. Altered expression of growth factors and cytokines in keratoconus, bullous keratopathy and diabetic human corneas. Exp Eye Res 2001, 73:179-89.

3. Identification and characterization of a new gene expressed in cone photoreceptors in retina using microarray gene profiling. During my predoctoral training at the Jules Stein Eye Institute and microarray core facility, University of California, Los Angeles, my studies focused on the identification of genes expressed in cone photoreceptors using microarray gene profiling. I evaluated and showed that two amplification methods, linear RNA amplification by in vitro transcription (IVT) and cDNA amplification by PCR, for microarray gene profiling were comparable in reproducibility and reliability. I produced my own cDNA microarray chips using the cDNA library obtained from subtractive hybridization of retinal cone degeneration (cd) adult dog mRNA from mRNA of normal dog retina. I identify and characterized a novel gene, ZBED4, expressed in human cone and mouse Müller cells. Our studies also showed the patterns of spatial and temporal expression of Zbed4 in the mouse retina suggest a possible involvement of this protein in retinal morphogenesis and Müller cell function.

a. **Saghizadeh M**, Brown DJ, Tajbakhsh J, Chen Z, Kenney MC, Farber DB, Nelson SF. Evaluation of techniques using amplified nucleic acid probes for gene expression profiling. Biomol Eng 2003, 20:97-106.
b. **Saghizadeh M**, Akhmedov NB, Yamashita CK, Gribanova Y, Theendakara V, Mendoza E, Nelson SF, LjubimovAV, Farber DB. ZBED4, A BED-type zinc-finger protein in the cones of human retina. Invest Ophthalmol Vis Sci 2009, 50:3580-8.
c. **Saghizadeh M,** Akhmedov NB, Gribanova Y and Farber DB. ZBED4, a cone and Müller cell protein in human retina, has a different cellular expression in mouse, Mol Vis. 2011, 17:2011-8.

4. The mechanisms of epithelial alterations in diabetic cornea and adenovirus-based gene therapy. During my postdoctoral training at Cedars-Sinai Medical Center, I studied the mechanisms of epithelial alterations in diabetic cornea, which led to translational research on gene therapy treatment for diabetic corneal disease. We were a leading group on gene therapy effects on wound healing and marker distribution in normal and diabetic corneas using adenovirus constructs harboring c-met proto-oncogene or several shRNAs in human organ-cultured cornea. We published exciting results on normalization of wound healing rates and altered marker expression patterns of diabetic corneas by specific adenovirus-based single or combined gene therapy.

a. **Saghizadeh M**, Kramerov AA, Tajbakhsh J, Aoki AM, Wang C, Chai NN, Ljubimova JY, Sasaki T, Sosne G, Carlson MRJ, Nelson SF, Ljubimov AV**.** Proteinase and growth factor alterations revealed by gene microarray analysis of human diabetic corneas. *Invest Ophthalmol Vis Sci*, 2005;46:3604-3615, PMCID: PMC1459105.
b. **Saghizadeh M**, Kramerov AA, Yu FS, Castro MG, Ljubimov AV**.** Normalization of wound healing and diabetic markers in organ cultured human diabetic corneas by adenoviral delivery of *c-met* gene. *Invest Ophthalmol Vis Sci*, 2010;51:1970-1980, PMCID: PMC2846188.
c. **Saghizadeh M**, Epifantseva I, Hemmati DM, Ghiam CA, Brunken WJ, Ljubimov AV**.** Enhanced wound healing, kinase and stem cell marker expression in diabetic organ-cultured human corneas upon MMP-10 and cathepsin F gene silencing. *Invest Ophthalmol Vis Sci*, 2013;54:8172-8180, PMCID: PMC3867183.

5. Limbal epithelial stem cell marker analysis in normal and diabetic corneas and iPSC differentiation to corneal epithelial cells. We documented for the first time-altered expression of limbal epithelial stem cells in human diabetic corneas. We also performed direct gene therapy on diabetic limbal epithelial cells to restore delay wound healing and stem cell marker alterations. Further, an optimized protocol has been established for producing corneal lineage differentiation from iPS cells for reconstruction of corneal surface.

a. **Saghizadeh M**, Soleymani S, Harounian A, Bhakta B, Troyanovsky SM, Brunken WJ, Pellegrini G, Ljubimov AV. Alterations of epithelial stem cell marker patterns in human diabetic corneas and effects of *c-met* gene therapy. *Mol Vis,* 2011;17:2177-2190, PMCID: PMC3159681.
b. **Saghizadeh M**, Winkler MA, Kramerov AA, Hemmati DM, Ghiam CA, Dimitrijevich SD, Sareen D, Ornelas L, Ghiasi H, Brunken WJ, Maguen E, Rabinowitz YS, Svendsen CN, Jirsova K, Ljubimov AV. A simple alkaline method for decellularizing human amniotic membrane for cell culture. *PLoS One,* 2013;8:e79632, PMCID: PMC3827346.
c. **Saghizadeh M**, Dib CM, Brunken WJ, Ljubimov AV**.** Normalization of wound healing and stem cell marker patterns in organ-cultured human diabetic corneas by gene therapy of limbal cells. *Exp Eye Res,* 2014;129:66-73, PMID: 25446319.
d. Sareen D*, **Saghizadeh M***, Ornelas L, Winkler MA, Narwani K, Sahabian A, Funari VA, Tang J, Spurka L, Punj V, Maguen E, Rabinowitz YS, Svendsen CN, Ljubimov AV**.** Differentiation of human limbal-derived induced pluripotent stem cells into limbal-like epithelium. *Stem Cells Transl Med,* 2014;3:1002-1012, PMCID: PMC4149305. * equal contribution.

6. The role of microRNAs in normal and diseased corneal epithelial homeostasis. I identified several miRNAs such as miR-146a and miR-424 with altered expression in diabetic corneas using gene array and deep sequencing, which correlates with their effects on corneal cell wound healing. I showed that downregulation of miR-146a and miR-424 activates wound healing-related signaling molecules *in vitro*. I also showed that inhibition of miRNA-146a accelerates wound healing in organ-cultured diabetic human cornea and normalizes the diabetic marker expression. Therefore, miR-based gene therapy allowed me to successfully treat delayed wound healing in human diabetic organ-cultured corneas.

a. Funari VA, Winkler MA, Brown J, Dimitrijevich SD, Ljubimov AV, **Saghizadeh M**. Differentially Expressed Wound Healing-Related microRNAs in the Human Diabetic Cornea. PLoS One 2013, 8:e84425.
b. Winkler MA, Dib C, Ljubimov AV and **Saghizadeh M.** Targeting miR-146a to Treat Delayed Wound Healing in Diabetic Organ-Cultured Corneas. PLoS One 2014;9:e114692. PMID: 25490205.
c. Kulkarni M, Leszczynska A, Wei G, Winkler MA, Tang J, Funari VA, Deng N, Liu Z, Punj V, Deng SX, Ljubimov AV, **Saghizadeh M.** "Genome-wide analysis of miRNAs suggests a differential microRNAs signature associated with normal and diabetic human corneal limbus",
Sci Rep., 7:3448 (2017) PMID: 28615632.

7. Regulation of Limbal Niche in Normal and Diabetic Cornea by Extracellular Vesicles. The important part of the limbal stem cell niche functioning is interaction between stem cells and their neighboring stromal cells through secreted factors such as nano-sized extracellular vesicles (EVs). These vesicles contain mRNA, miRNA, DNA, and protein cargo mediating physiological intercellular crosstalk. I study limbal EV contribution to corneal regeneration and wound healing and examine possible differences in EV cargos released from normal and diabetic limbal stromal cells (LSCs) and LECs by using different techniques such as next generation sequencing, proteomics, transmission electron and confocal microscopy, and trans-well co-culture system. We show that normal LSC-derived EVs (LSC-EVs) significantly promote epithelial healing in wounded organ-cultured human corneas. In addition, we found that there is a difference in cargos of EVs derived from normal and diabetic LSC. My lab is seeking to investigate the major mechanisms of action of limbal EVs, which are taken up by neighboring cells, in stem cell maintenance and wound repair in cell cultures and in normal and diabetic human organ-cultured corneas, and the therapeutic potential of EVs for treatment of corneal injuries and diabetic abnormalities. Our goal, ultimately, is to restore stem cell function for future clinical translation

a. Leszczynska A, Kulkarni M, Ljubimov AV, **Saghizadeh M**. Exosomes from normal and diabetic human corneolimbal keratocytes differentially regulate migration, proliferation and marker expression of limbal epithelial cells. Sci Rep., 8:15173 (2018) PMID: 30310159.

List of Published Work in My Bibliography at NCBI:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1LWVhzX0fCxAg/bibliography/49207277/public/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

1 R01 EY025377-01 Saghizadeh 08/01/15 – 07/31/20
NIH/NEI
The Role of MicroRNAs in Normal and Diseased Corneal Epithelial Homeostasis
The major goals of this project are to use of quantitative methods to identify and functionally characterize differentially expressed microRNAs in the diabetic human cornea that may be important for wound healing.
Role: **Principal Investigator**
% Effort: 45%

Cedars-Sinai Institution Commitment Grant, Saghizadeh
Biomedical Sciences & Regenerative Medicine Institute, Cedars-Sinai 08/01/15-07/30/18
The Role and Mechanisms of Exosomes in Regulation of Limbal Stem Cells 200,000.00

Major goals: Investigating the role of exsomes in corneal epithelial homeostasis and wound healing in vitro and in human organ-cultured corneas.

Role: **Principal Investigator**
% Effort: 35%

2 R01 EY13431-16 Ljubimov 08/01/01 – 07/31/20
NIH/NEI
Mechanisms of Epithelial Alterations in Diabetic Cornea
Major goals: To change phenotypes of cultured stem cells in human diabetic corneas towards more normal ones using specific gene therapy with *c-met* overexpression and proteinase suppression, and transplant them back to diabetic corneas. Experiments will be conducted in human corneal organ cultures.
Role: **Co-Investigator**

Overlap

There is no scientific or budgetary overlap.

Completed Research Support

1 R21 EY022771-02 Saghizadeh 08/01/12 – 07/31/14
NIH/NEI
The Role and Mechanisms of microRNAs in Diabetic Cornea
The major goals of this project are to use of novel quantitative methods to identify the differentially expressed microRNAs in the epithelial cells of diabetic cornea may be important for wound healing and to examine their roles and mechanisms of actions using adenovirus-driven microRNA-based gene therapy.
Role: PI

1 R01 EY023429-03 Ljubimov 06/01/13 – 05/31/16
NIH/NEI
Transplantable Limbal Cells from Induced Pluripotent Stem Cells
The major goal of this project is to generate transplantation grade limbal stem cells from limbal-derived induced pluripotent stem cells in culture.
Role: Co-Investigator