BIOGRAPHICAL SKETCH

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NAME: Ljubimov, Alexander Vladimir

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

POSITION TITLE: Professor of Biomedical Sciences and Neurosurgery

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
Moscow State University, Moscow, Russia	M.S.	06/1974	Biochemistry/Virology
Cancer Research Center, Moscow, Russia	Ph.D.	10/1979	Experimental Oncology
International Agency for Research on Cancer, Lyon, France	Postdoctoral	05/1983	Experimental Oncology

A. Personal Statement

The goal of the proposal is to develop novel translational gene therapy approaches to diabetic corneal disease, focusing on improving corneal wound healing. We have successfully tested in whole corneas and cultured limbal cells adenoviral therapy that normalized marker protein expression and wound healing. My lab has also discovered stem cell dysfunction in human diabetic corneas. We are currently working on novel therapies involving (1) generation of normal-like induced pluripotent stem cells (iPSC) from human diabetic limbal cultures in order to differentiate them to limbal progenitor cells, and (2) new nanobiopolymers for gene therapy of cultured diabetic cells. Both approaches aim at creating reliable ways to transplant normalized limbal cells to diabetic corneas in advanced diabetic corneal disease with severely compromised and dysfunctional stem cells. My laboratory is at the forefront of studies of corneal stem cells as it relates to diabetic disease. We were the first group to identify targets for gene therapy in diabetic corneas and developed this approach effectively normalizing compromised corneal wound healing in organ-cultured human corneas. We have first described epithelial stem cell alterations in these corneas, and repaired them with gene therapy, which was a pioneering study in a common corneal disease. My lab is developing efficient ways of making corneal epithelium from induced pluripotent stem cells (iPSC) in order to apply them for generating autologous limbal cells for diabetic patients. My laboratory has discovered the role of protein kinase CK2 in angiogenesis. In collaboration with the Department of Neurosurgery, we are developing a nanomedicine approach to treat diabetic corneal abnormalities based on the results of brain and breast cancer treatment in animal models. The laboratory is also conducting cutting edge studies of microRNA functionally involved in wound healing. Overall, my expertise and research directions are geared towards translational stem cell investigations, iPSC generation to normalize diabetic corneal stem cells, and nanotechnology for corneal diabetes. Over the past 20 years, I have been fully funded by the NIH and currently hold 2 R01 grants. I have directly supervised and mentored over 20 premed, undergrad and grad students, as well as postdoctoral fellows and scientists. I am currently mentoring several junior faculty members, and participating in PhD student admissions, qualifying exams, curriculum lectures, and dissertation defenses. I have a long record of successful management of NIH-funded projects as PD/PI including staff, research, and budget administration. For 13 years, I have managed a unit of several laboratories that successfully obtained and renewed a number of NIH grants. I have trained many students. I encourage communication within my research team, creation of innovative and feasible goals, and enforce adherence to timelines, regulations, and budget. I have a documented record of leading collaborative interdisciplinary research projects to success and feel that my experience and various strengths of our team will help directing this proposal to success.

B. Positions and Honors

Positions and Employment

1977-1979 Research Associate, Cancer Research Center, Moscow, Russia
1979-1988 Junior Researcher, Cancer Research Center, Moscow, Russia
1988-1991 Leading Researcher, Cancer Research Center, Moscow, Russia
1991-1993 Visiting Scientist, La Jolla Cancer Research Foundation, La Jolla, CA
1993-1998 Research Scientist II, Department of Surgery, Cedars-Sinai Medical Center, Los Angeles, CA
1998-2002 Research Scientist III, Department of Surgery, Cedars-Sinai Medical Center, Los Angeles, CA
2002-present Research Scientist IV, Department of Surgery, Cedars-Sinai Medical Center, Los Angeles, CA
2002-2013 Director, Ophthalmology Research Laboratories, Department of Surgery, Cedars-Sinai Medical Center, Los Angeles, CA
2003-present Professor of Medicine, Department of Medicine, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA
2009-2013 Professor of Surgery & Biomedical Sciences, Cedars-Sinai Medical Center, Los Angeles, CA
2013-present Director, Regenerative Medicine Institute Eye Program, Department of Biomedical Sciences, Cedars-Sinai Medical Center, Los Angeles, CA
2013-present Professor of Biomed. Sciences & Neurosurgery, Cedars-Sinai Medical Center, Los Angeles, CA

Other Experience and Professional Memberships

1985 Consultant, International Agency for Research on Cancer, Lyon, France
1991 D.Sc. degree in experimental oncology from Cancer Research Center, Moscow, Russia
1991-present Life Member, Association of International Union Against Cancer Fellows
1993-present Member, Association for Research in Vision and Ophthalmology
1995-present Member, American Diabetes Association
2000-present Member, International Society for Eye Research; Chair of the Membership Committee
2000-present Member, American Society for Matrix Biology
2002 Member, NIDDK ZDK1 GRB-9 O1 R Study Section
2003-2006 Member, Research Grant Review Committee of the American Diabetes Association
2005-2007 Member, NEI ZRG1 CB-G (90) Study Section
2006 Member, NIDDK ZDK1 GRB-4 02 Study Section
2007 Member, NEI ZRG1 BDCN-F (02) M Study Section
2008-2011 Ad Hoc member, NEI AED and BDPE Study Sections
2008,2010 Member, Grant Review Committee, Juvenile Diabetes Research Foundation International
2009 Member, NEI ZRG1 ETTN-E (12) B and ZRG1 BDCN-F (02) M Study Sections
2010,2011 Member, NEI ZRG1 BST-Z (90) R Study Section
2012-2013 Ad Hoc member, NEI DPVS Study Section
2012-2013 Member, VA RRD8 1 and RRD3 1 Study Sections
2013-2017 Standing Member, NEI DPVS Study Section

Honors

1974 *Summa cum laude* M.S. in Biochemistry from Moscow State University, Moscow, Russia
1982-1983 International Agency for Research on Cancer Research Training Fellowship, Lyon, France
1987-1995 Editorial Board Member, *Invasion and Metastasis*
1991-1992 American Cancer Society-Eleanor Roosevelt International UICC Fellowship, La Jolla, CA
1999 Young Investigator Award, Cedars-Sinai Medical Center, Los Angeles, CA
2003-present Executive Editor, *Experimental Eye Research*
2004-2007 Editorial Board Member, *Investigative Ophthalmology and Visual Science*
2006-present Editorial Board Member, *Brain Research Bulletin*
2007-2009 Winnick Family Foundation Research Scholar Award
2008-2011 Editorial Board Member, *Diabetes*
2009-present Editorial Board Member, *Vascular Cell*
2009-present Editorial Board Member, *Experimental Biology and Medicine*
2010 Silver Fellow of ARVO
2012-present Editorial Board Member, *PLoS One*
2012-present Editorial Board Member, *Molecular Vision*
2012-present Editorial Board Member, *Conference Papers in Medicine*

2013-present Editorial Board Member, *Investigative Ophthalmology and Visual Science*
2014 Gold Fellow of ARVO
2014 Overseas Fellow, Royal Society of Medicine (London)
2015 Visiting Professor, Harvard University
2016 Advisory Board member, *Progress in Retinal and Eye Research*

C. Contribution to Science

1. My earlier publications dealt with alterations of extracellular matrix in common eye diseases including bullous keratopathy, keratoconus, and diabetic retinopathy, where new extracellular protein markers of these common diseases were identified. In 1995 I published a landmark paper on the composition of normal corneal basement membrane that showed its heterogeneity between compartments harboring stem cells and differentiated cells. It became highly cited and inspired many studies on the special structure, composition and functions of limbal stem cell niche extracellular matrix.

a. **Ljubimov AV,** Burgeson RE, Butkowski RJ, Michael AF, Sun T-T, Kenney MC. Human corneal basement membrane heterogeneity: topographical differences in the expression of type IV collagen and laminin isoforms. *Lab Invest,* 1995;72:461-473, PMID: 7723285.

b. **Ljubimov AV**, Burgeson RE, Butkowski RJ, Couchman JR, Zardi L, Ninomiya Y, Sado Y, Huang Z, Nesburn AB, Kenney MC. Basement membrane abnormalities in human eyes with diabetic retinopathy. *J Histochem Cytochem,* 1996;44:1469-1479, PMID: 8985139.

c. Kenney MC, Nesburn AB, Burgeson RE, Butkowski RJ, **Ljubimov AV.** Abnormalities of the extracellular matrix in keratoconus corneas. *Cornea,* 1997;16:345-351, PMID: 9143810.

2. I have described novel markers of human diabetic corneas including several upregulated proteinases and a decrease in c-met proto-oncogene. My laboratory then developed the first gene therapy for altered diabetic wound healing using human organ-cultured corneas. This adenovirus-based gene therapy normalized aberrant marker expression patterns and wound healing rates in diseased corneas. The organ culture model is used in several labs now to study wound healing mechanisms and screen drugs.

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.

3. I have documented novel alterations of stem cells in human diabetic corneas and designed successful gene therapy that reversed these alterations. Additionally, gene therapy of stem cell compartment was found sufficient for the restoration of normal corneal epithelial wound healing. We have designed a novel fast and efficient method for denuding amniotic membrane for stem cell culture, which will have a significant impact on the use of this membrane for limbal stem cell transplantation. We also made iPSC from cultured human limbal cells and were able to differentiate them back to limbal cells.

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.

4. I have been actively collaborating with the Department of Neurosurgery in the design and therapeutic use of a new class of nanodrug conjugates based on non-toxic and non-immunogenic polymalic acid. These nanoconjugates were successfully used for treatment of brain and breast cancers and brain metastases. As a continuation of this collaboration, we have designed and tested for the first time a similar new drug for corneal epithelial cell gene therapy.

a. Ding H, Inoue S, **Ljubimov AV,** Patil R, Portilla-Arias J, Hu J, Konda B, Wawrowsky KA, Fujita M, Karabalin N, Sasaki T, Black KL, Holler E, Ljubimova JY. Inhibition of brain tumor growth by intravenous poly (β-L-malic) acid nanobioconjugate with pH-dependent drug release. *Proc Natl Acad Sci U S A,* 2010;107:18143-18148. PMCID: PMC2964197.

b. Inoue S, Ding, H, Portilla-Arias J, Hu J, Konda B, Fujita M, Espinoza A, Suhane S, Riley M, Gates M, Patil R, Penichet, ML, **Ljubimov AV,** Black KL, Holler E, Ljubimova JY. Polymalic acid-based nanobioconjugate provides efficient systemic breast cancer treatment by inhibiting both HER2/neu receptor synthesis and activity. *Cancer Res,* 2011;71:1454-1464. PMCID: PMC3428373.

c. Patil R, **Ljubimov AV,** Gangalum PR, Ding H, Portilla-Arias J, Wagner S, Inoue S, Konda B, Rekechenetskiy A, Chesnokova A, Markman JL, Ljubimov VA, Li D, Prasad RS, Black KL, Holler E, Ljubimova JY. MRI virtual biopsy and treatment of brain metastatic tumors with targeted nanobioconjugates: nanoclinic in the brain. *ACS Nano,* 2015;9:5594-5608. PMID: 25906400.

5. My laboratory has shown for the first time that inhibition of protein kinase CK2 dramatically reduced pathological retinal neovascularization as exemplified by proliferative diabetic retinopathy. This inhibition also precluded bone marrow-derived endothelial progenitor cells to home to neovascularization sites, which may open new avenues for drug development and use against CK2 in neovascular diseases and cancer. We have further discovered that CK2 inhibitors rounded cells, and this effect was mediated by alterations in cytoskeleton involving myosin light chain kinase. CK2 inhibitors were also shown to synergize with other drugs to inhibit retinal neovascularization in a combination therapy approach.

a. **Ljubimov AV,** Caballero S, Aoki AM, Pinna LA, Grant MB, Castellon R. Involvement of protein kinase CK2 in angiogenesis and retinal neovascularization. *Invest Ophthalmol Vis Sci,* 2004;45:4583-4591, PMCID: PMC2917328.

b. Kramerov AA, Saghizadeh M, Caballero S, Shaw LC, Li Calzi S, Bretner M, Montenarh M, Pinna LA, Grant MB, **Ljubimov AV.** Inhibition of protein kinase CK2 suppresses angiogenesis and hematopoietic stem cell recruitment to retinal neovascularization sites. *Mol Cell Biochem,* 2008;316:177-186, PMCID: PMC2913688.

c. Kramerov AA, Ahmed K, **Ljubimov AV.** Cell rounding in cultured human astrocytes and vascular endothelial cells upon inhibition of CK2 is mediated by actomyosin cytoskeleton alterations. *J Cell Biochem,* 2012;113:2948-2956, PMCID: PMC3430847.

List of Published Work in My Bibliography at NCBI:

http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40946551/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

2 R01 EY013431-14 Ljubimov (PI) 8/1/01 – 3/31/16
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: PI

1 R01 EY023429-03 Ljubimov (PI) 6/1/2013 – 5/31/2016
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: PI

1 R01 EY025377-01 Saghizadeh (PI) 8/1/15 – 7/31/20
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: Co-Investigator

LSP1-08235 Wang (PI) 8/1/15 – 7/31/2017
California Institute for Regenerative Medicine (CIRM)
IND-enabling Study of Subretinal Delivery of Human Neural Progenitor Cells for the Treatment of Retinitis Pigmentosa
The major goal of this project is to conduct and finalize preclinical experiments aimed at stabilizing disease progression and maintain ocular integrity and vision for retinitis pigmentosa (RP) using human fetal cortex-derived neural progenitor cells (CNS10-NPC).
Role: Co-Investigator

T32 DK00770-12 Melmed (PI) 8/1/99 – 6/30/17
NIH/NIDDK
Training Program in Endocrinology and Diabetes
Major Goals: To provide an outstanding training environment for post-doctoral students pursuing research careers in fields related to endocrinology, endocrine cancers and metabolism at CSMC/UCLA.
Role: Mentor

Overlap

There is no scientific or budgetary overlap. The grant 2 R01 EY013431-14 is a previous round of the current application. The grant 1 R01 EY023429-03 uses the same technology for iPSC generation as the present application. However, there is no overlap because (1) the EY023429-03 will expire before the new funding for the current proposal starts, and (b) the EY023429-03 does not deal with generating and studying diabetic iPSC, which is the main topic of the present application. Therefore, no adjustments will be necessary.

Completed Research Support

1 R21 EY022771-02 Saghizadeh 8/1/12-7/31/14
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: Co-Investigator