Application

01962 - The GEM Challenge 2015

02127 - A Biological Bandage for Dry Eye Treatment

Collaborative awards with IEM

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Primary Contact

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Area of Specialty	Ophthalmology		

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Information

PI Name (Last Name, First Name)	*Afshari, Natalie*
CO-PI Name (Last name, First name)	
Project Title	*A Biological Bandage for Dry Eye Treatment*
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PI Biosketch

File Name	Description	File Size
Afshari Biosketch.pdf	*PI Natalie Afshari's Biosketch*	

Narrative

File Name	Description	File Size
Biological Bandage_NAfshari.pdf	*GEM 2015 Proposal: A biological bandage for dry eye treatment by Natalie Afshari*	

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Afshari, Natalie	POSITION TITLE Professor of Ophthalmology (With Tenure)
eRA COMMONS USER AFSHA003	

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of California at Berkeley	BA	1990	Biophysics
	BA	1990	Near Eastern Studies
University of California at Berkeley	MA	1991	Endocrinology
Stanford University School of Medicine	MD	1995	Medicine
Harvard University, Brigham & Women's Hospital	Intern	1995-1996	Internal Medicine
Harvard University, Mass Eye & Ear Infirmary	Resident	1996-1999	Ophthalmology
Harvard University, Mass Eye & Ear Infirmary	Fellow	1999-2001	Cornea & Refractive Surgery

A. Personal Statement

As a clinician-scientist specializing in ocular surface diseases, I am keenly aware of the growing problem/increasing prevalence of dry eye disease. The current treatment options are limited to artificial solutions and autologous serums, both of which are inconvenient and, more importantly, inadequate in resolving this condition. There exists a need for a simpler and more durable therapeutic option. Given recent advancements in 3D bioprinting technology and tissue engineering, we plan to develop novel methods for the creation of a biological bandage that would be placed on the surface of the eye like a contact lens, and would be more versatile than our current options because of its capacity to integrate live cells, bioactive molecules, and other therapeutic agents. Working along with Dr. Zhao and in collaboration with UCSD engineers, my goal is to create a dynamic, long-lasting solution for dry eye disease that also has potential for broader application in the treatment of other ocular surface diseases.

B. Positions and Honors

Positions and Employment

2001-2006 Assistant Professor, Department of Ophthalmology, Duke University Medical Center
2006-2009 Associate Professor, Department of Ophthalmology, Duke University Medical Center
2006-2012 Director of Cornea and Refractive Surgery Service Fellowship, Duke University
2009-2012 Tenured Associate Professor, Department of Ophthalmology, Duke University Medical Center
2011-2012 Director of Centers of Excellence at Duke Eye Center
2012-2012 Professor of Ophthalmology, Duke University Medical Center
2012-present Professor of Ophthalmology and Chief of Cornea and Refractive Surgery, University of California San Diego
2013-present Stuart I. Brown MD Chair in Ophthalmology in Memory of Donald P. Shiley

Other Experience and Professional Memberships

1997-2001 Chair, Premedical Committee, Kirkland House, Harvard University

2003- FDA Consultant to the Ophthalmic Drug Advisory Panel
2005- Associate Examiner for the American Board of Ophthalmology
2005-2011 Editorial Board Member, EyeNet
2005-2008 ARVO Cornea Program Committee Member
2006- 2011 Councilor American Academy of Ophthalmology
2006 Reviewer NIH Grants (special study section)
2007-2010 Invited mentor Examiner for the American Board of Ophthalmology
2009- Editor Current Opinion in Ophthalmology Cataract Section
2010- Editorial Board Member EyeWiki
2011-2012 Leadership Development Program of American Academy of Ophthalmology
2011- Chief Scientific Posters Judge for American Academy of Cataract and Refractive Surgery
2011-2012 Editorial Board Member Clinical & Experimental Ophthalmology
2011-2012 Co-Director Cornea Day American Academy of Ophthalmology
2011-2013 CPE Cornea Fellows National Course Director
2011-present Editorial Board Member, *Cornea (Basic & Clinical Science Series)*
2012-present Board of Directors, Cornea Society
2013-present Board of Directors, San Diego Eye Bank
2013-present Editorial Board Member Investigative Ophthalmology & Visual Science (IOVS)

Honors

1990 Valedictorian Commencement Speaker, University of California at Berkeley
1990 Extraordinary Honors Award, University of California at Berkeley
1991 Outstanding Graduate Student Instructor Teaching Award, University of California at Berkeley
1993 Stanford Medical Scholars Research Award
1995 Dean's Research Award, Stanford University School of Medicine
1999-2000 HEED Foundation Ophthalmic Fellowship
2002 Teacher of The Year Duke University Eye Center (awarded during first year as faculty)
2003-2007 Research to Prevent Blindness Career Development Award
2007 Achievement Award American Academy of Ophthalmology
2008 Elected Deputy Section Leader of Council of American Academy of Ophthalmology
2008 ARVO Chair of Cornea Program Committee
2003-2012 Best Doctors in America ® (Cornea)
2004-2012 The Best Doctors in North Carolina: Business North Carolina
2009-2010 Horizon Grant Research Award from Allergan
2010 Secretariat Award of American Academy of Ophthalmology
2012 Inaugural *Top 10 Women in Medicine* by Triangle Medical News
2012 Co-editor of a Two-Volume Cornea Book, Jaypee Brothers
2013 U.S. News and World Report Top Doctors List for 2013 (1% in the nation)
2014 Senior Achievement Award of American Academy of Ophthalmology

C. Selected Peer-Reviewed Publications:

1. **Afshari NA**, Mullally JE, Afshari MA, Steinert RF, Adamis AP, Azar DT, Talamo JH, Dohlman CH, Dryja TP. Survey of patients with granular, lattice, Avellino, and Reis-Bucklers corneal dystrophies for mutations in the BIGH3 (TGFBI) and gelsolin genes. *Arch Ophthalmol* 2001; 119:16-22. PMCID: PMC11146721
2. Klintworth GK, Bao W, **Afshari N**. Two mutations in the TGFBI (BIGH3) gene associated with lattice corneal dystrophy in an extensively studied family. *Invest Ophthalmol Vis Sci* 2004; 45:1382-8. PMCID: PMC15111592
3. **Afshari NA**, Duncan SM, Tanhehco T, Azar DT. Optimal size and locations of corneal rotational autograft. A simplified mathematical model. *Arch Ophthalmol* 2006; 124:410-3. PMCID: PMC16534062
4. **Afshari NA**, Pittard AB, Siddiqui A, Klintworth GK. Clinical study of Fuchs corneal endothelial dystrophy over a thirty-year period (1972-2001). *Arch Ophthalmol* 2006; 124:777-80. PMCID: PMC16769829

5. Johnson CS, Mian S, Moroi S, Epstein D, Izatt J, **Afshari NA**. Role of Corneal Elasticity in Damping of Intraocular Pressure. *Invest Ophthalmol and Vis Sci* 2007; 48:2540-4. PMCID: PMC17525182
6. Kuo AN, Harvey TM, **Afshari NA**. Novel delivery method to reduce endothelial injury in descemet stripping automated endothelial keratoplasty. *Am J Ophthalmol 2008*; 145:91-6. (PMCID: PMC17996209
7. **Afshari NA**, Bahadur RP, Eifrig DE Jr, Thogersen IB, Enghild JJ, Klintworth GK. Atypical asymmetric lattice corneal dystrophy associated with a novel homozygous mutation (Val624Met) in the TGFBI gene. *Mol Vis* 2008;14:495-9. PMCID: PMC18385782
8. Hong A, Caldwell M, Kuo AN, **Afshari NA**. Air-bubble associated endothelial trauma in descemets stripping automated endothelial keratoplasty. *Am J Ophthalmol* 2009; 148:256-9. (PMCID # 19426961)
9. **Afshari NA**, Li YJ, Gregory S, Pericak-Vance M, Klintworth GK. Genome wide linkage scan in Fuchs endothelial corneal dystrophy. *Invest Ophthalmol Vis Sci* 2009; 50:1093-97. PMCID: PMC18502986
10. Riazuddin SA, Zaghloul NA, Al-Saif A, Davey L, Diplas BH, Meadows DN, Eghrari AO, Minear MA, LI YJ, Klintworth GK, **Afshari N**, Gregory SG, Gottsch JD, Katsanis N. Missense mutations in TCF8 cause late-onset Fuchs corneal dystrophy and interact with FCD4 on chromosome 9p. *Am J Hum Genet* 2010; 86:45-53. PMCID: PMC20036349
11. Hwang RY, Gauthier DJ, Wallace D, **Afshari NA**. Refractive changes after descemet stripping endothelial keratoplasty: a simplified mathematical model. *Invest Ophthalmol Vis Sci* 2011; 22:52:1043-54. PMCID: PMC21051729
12. Rebong RA, Santaella RM, Goldhagen BE, Majka CP, Perfect JR, Steinbach WJ, **Afshari NA**. Polyhexmethylene biguanide and calcineurin inhibitors as novel antifungal treatments for Aspergillus keratitis. *Invest Ophthalmol Vis Sci* 2011; 52:7309-15. PMCID: PMC21849421
13. Li YJ, Minear MA, Rimmler J, Zhao B, Balajonda E, Hauser MA, Allingham RR, Eghrari AO, Riazuddin A, Katsanis N, Gottsch JD, Gregory SG, Klintworth GK, **Afshari NA**. Replication of TCF4 through association and linkage in late-onset Fuchs endothelial corneal dystrophy. *PLoS One* 2011; 6:18044. PMCID: PMC21533127
14. Minear MA, Li YJ, Rimmler J, Balajonda E, Watson S, Allingham RR, Hauser MA, Klintworth GK**, Afshari NA***, Gregory SG*. (*contributed equally) Genetics screen of African American with Fuchs Corneal Dystrophy. *Mol Vis.* 2013;19:2508-16. PMCID: PMC3859630
15. Li YJ, Minear MA, Qin X, Rimmler J, Hauser MA, Allingham RR, Igo RP Jr, Lass JH, Iyengar SK, Klintworth GK, **Afshari NA**, Gregory S. Mitochondrial Polymorphism A10398G and Haplogroup I Are Associated With Fuchs' Endothelial Corneal Dystrophy. *Invest Ophthalmol Vis Sci.* 2014; 55:4577-84.

D. Research Support

Ongoing Research Support

R01EY023196 (Afshari & Iyengar) PI
NIH/ NEI 03/01/2013-02/28/2016
Integrative Genetic Analyses in Fuchs Endothelial Corneal Dystrophy
The major goal of his study is to delineate the genetic architecture of Fuchs Endothelial Corneal Dystrophy by pursuing detailed secondary analysis of the genome-wide association study (GWAS) and to perform robust replication of the genome-wide significant loci via meta-analysis.
Role: PI

X01 HG006619-01 (Afshari & Iyengar) PI
NIH/NEI X01
A Genome Wide Association Study of Fuchs Endothelial Corneal Dystrophy
To perform genome wide association study (GWAS) for Fuchs Endothelial Corneal Dystrophy in 2206 samples with the Illumina Omni2.5 array.
Role: PI

R01EY016514 (Klintworth) PI 09/15/07-08/31/2012
NIH /NEI R01 No Cost Extension
Study of Genetic Basis of Fuchs Corneal Dystrophy

This is a genetic association study to detect the genetic basis for Fuchs Endothelial Corneal Dystrophy which is a common debilitating age-related disorder that affects women much more commonly than men. The long term objective of this study is to understand the basic pathobiology of FCD and to identify genetic comments of the disorder that will be valuable from the standpoint of developing molecular diagnostic tests for early diagnosis and for developing novel therapeutic procedures for this debilitating disease.
Role: Co-I (50%)

Completed Research Support

5K23-EY021522-02
NIH-NEI 4/1/2011-3/31/2014
Kuo PI
Imaging to Predict Refractive Outcomes after Corneal Endothelial Keratoplasty
Role: Afshari Mentor to Kuo
This project will use new technology to study and improve corneal transplantation. Knowledge gained from this project may help to customize grafts optically for individual patients

Allergan Horizon Grant (Afshari) PI 07/01/09-06/30/2010
To support cornea fellowship and cornea research.
Role: PI

Research to Prevent Blindness (Afshari) PI 07/01/03-06/30/2007
Career Development Award
To better understand the process of corneal inflammation, vascularization and transplant rejection and to utilize this knowledge to decrease the rate of corneal transplant rejection through gene therapy.
Role: PI (25%)

HL-2002-01(Afshari) PI 09/25/02-05/31/2004
Holles Laboratories, Inc.
NIH (sub)
DEHYDREX for Treatment of Recurrent Corneal Erosions
To evaluate in a quantitative manner the symptoms and clinical signs of corneal erosion in an appropriately stratified and randomized group of patients when treated with topical dextran (DEHYDREX).
Role: Duke-PI (50%)

5R01 EY012712-05 (Klintworth) PI 08/01/99-07/31/2004
NIH/NEI
Percent effort: 10%
Study of BIGH3 Wild-type and Mutant Protein
To investigate the molecular structure of the protein product of the TGFB1 (BIGH3) gene).
To purify and characterize wild-type and mutant transforming growth factor beta induced protein and thereby gain a better understanding of the fundamental steps that lead to the debilitating conditions in which the mutant protein accumulates in the cornea.
Role: Co-I (10%)

GEM 2015 Proposal: A Biological Bandage for Dry Eye Treatment

PI: Natalie Afshari, M.D., F.A.C.S., Professor of Ophthalmology, Chief of Cornea & Refractive Surgery, Shiley Eye Center, UCSD

AIM: To use 3D bioprinting technology to construct a biological bandage for dry eye treatment.

RATIONALE: Dry eye is one of the most common ocular complaints, reported by about 25% of patients who visit an eye clinic. The disease is estimated to affect approximately 20 million people in the US alone, with the majority of those individuals over the age of 50. Dry eye has been characterized as "a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface" (The Report of the International Dry Eye Workshop 2007). Severe cases can lead to complications such as corneal scarring and permanent vision loss, but even mild cases can have a high impact on quality of life due to discomfort and visual disability. Though it is highly prevalent and costs billions of dollars to manage, treatments are limited to artificial tears and autologous serums (AS), which have largely been inadequate, making it a frustrating condition, both for physicians and patients alike. Therefore, a material, which combines features such as bio-compatible polymers, bio-engineered cells, capacity for moisture retention on the ocular surface, and potential for incorporation of additional agents, would be ideal for treating dry eye. 3D bioprinting technology has revolutionized tissue engineering and affords us with a unique opportunity to produce an ocular surface biological bandage, which is more effective than our current therapeutic options.

CHALLENGE/NEED AND SIGNIFICANCE: Based on epidemiological studies, dry eye is not only common in the United States, it is also a prevalent public health issue in many parts of the world. Currently there is no cure, and existing clinical approaches are either inadequate or lacking in efficacy.

The most common method of managing symptoms is using artificial tear solutions, which may require frequent application. Not only is this inconvenient, posing a challenge for compliance, but it has also been found to induce toxic and allergic reactions, especially among those with sensitive eyes, because of the chemical preservatives in the solutions. Another option, autologous serums (AS), is unique among ophthalmic therapies in that they are manufactured specifically for each individual from that person's own blood. The rationale is based on the fact that vitamins or growth factors present in tears are also present in serum. However, preparation, storage, and special regulations regarding blood products by the FDA and other regulatory agencies make this option cumbersome. Recently, amniotic membrane-based ocular bandages have been introduced as a higher endurance solution to treat severe dry eye disease, but it is not a material intrinsic to the eye and often leads to cloudy vision.

An effective treatment option would address the shortcomings of the current treatments while maintaining their beneficial properties. A bio-fabrication technology could be utilized to generate a cell-encapsulated biological bandage that would be placed on the ocular surface similar to an amniotic membrane, thus retaining high moisture for a long period and eliminating the need for frequent re-application. Live cells within the bandage could be engineered to release growth factors and other nutrients that promote ocular surface healing without the complexity of blood product regulation. The scaffold of the bandage can be made from a natural, transparent polymer such as hyaluronic acid (HA), a class of negatively charged polysaccharides and a major constituent of the extracellular matrix (ECM). It was recently demonstrated that CD44, a hyaluronate receptor, is expressed in corneal and conjunctival cells and that its activation

promotes the interaction with cytoskeletal proteins, suggesting easy assimilation and tissue compatibility during wear. The size, thickness, and shape of the biological bandage can be custom-made by laser-induced photolithographic techniques. Moreover, the possibility of mass production could eventually lower costs and make it more readily available around the world.

Besides dry eye, potential indications for the use of a biological bandage could include ocular surface diseases such as neurotrophic keratitis, herpes simplex keratitis, microbial keratitis, filamentary keratitis, recurrent corneal erosions, and Salzmann's nodular degeneration. Additional indications include corneal abrasions, scarring and erosions, chemical burns, corneal defects, partial limbal stem cell deficiencies, high-risk corneal transplants, and Stevens–Johnson syndrome.

INNOVATION: A hyaluronate scaffold biological bandage offers a number of advantages:

1) **Stability**: HA is a naturally stable, inert, and transparent polymer that has receptors on the cornea. It exhibits extraordinary rheological properties in solution, making it a very flexible material to work with. The size, thickness, and shape of the bandage can be predetermined and fabricated by 3D bioprinting techniques.
2) **Prolonged Moisture**: The properties that make HA flexible also make it very hydrophilic, and thus an ideal lubricant.
3) **Personalization**: The scaffold can be customized to integrate cells and a variety of bioactive molecules, depending on the patient's needs.
4) **Broad Applications**: In the future, this model could be extended to diseases other than dry eye. A biological bandage could be used as a new vector for drug therapy, or could be further customized to incorporate a patient's own cells.
5) **Convenience**: The biological bandage can be administrated in the eye doctor's office rather than the operating room.

FEASIBILITY:

1) The concept of an ocular bandage is not new. Collagen bandages are used frequently after ocular surgery to help wound healing and soothe corneal discomfort and dry eye. However, they disintegrate after 24-72 hours.
2) 3D bioprinting technology has been successfully used to fabricate cell-laden hydrogels. The bio-compatible hydrogel can be made entirely of FDA-approved materials such as HA polymers. Sodium hyaluronate has already been used in artificial tears because of its viscous formation and excellent ocular surface retention time, along with beneficial effects in corneal wound healing.

INVESTIGATOR QUALIFICATIONS: The PI is a clinician-scientist sub-specializing in cornea and external disease. She is Chief of Cornea and Refractive Surgery at UCSD. Prior to this position, she was Professor of Ophthalmology and Director of Centers of Excellence at Duke University Eye Center. She is an international expert on corneal endothelium and epithelium, and is an active clinician and surgeon who serves on the Board of Directors of the Cornea Society. She has a dedicated dry eye and ocular surface disease clinic. Her extensive work on Fuchs dystrophy during the past decade has led to multiple publications leading to better understanding of this disease and enhanced treatments for these patients.