CLAO ERF/Sjögren's Syndrome Foundation
Scientific Research Award
2013

Program Description
The Contact Lens Association of Ophthalmologists Education and Research Foundation (CLAO ERF) in partnership with the Sjögren's Syndrome Foundation (SSF) announces the availability of one Scientific Research Grant to be awarded December 31, 2012. This award will be for $3,000 and is intended to provide support for proposals specifically concerned with issues directly related to dry eye and ocular surface disease. The anticipated research term is three to six months.

Deadline for submission is November 30, 2012

The Award will be made on the basis of scientific merit according to the following criteria:

Eligibility
1. The applicant must be working towards an advanced degree
2. Ophthalmologists, optometrists, technicians, nurses, optometry students, ophthalmology residents and fellows, medical students supervised by a scientist associated with an academic institution in the United States are eligible.

Grant Requirements
1. The research project must be relevant to the mission of the CLAO ERF and SSF as stated in the program description.
2. The award recipient must provide assurance that research protocols comply with appropriate ethical guidelines for the use of experimental animals and human subjects.
3. The principal investigator will prepare a final report describing the progress and status of the research project at the completion of the award interval.
4. Scientific publication resulting from the research grant is encouraged and shall be submitted first to the peer-reviewed Journal Eye and Contact Lens: Science and Clinical Practice for consideration for inclusion in the publication. Any publication is to acknowledge support of the research by the CLAO ERF and SSF.
5. The grant recipient is encouraged to submit an abstract of their research findings for presentation at a CLAO scientific meeting.
6. This award may not be used to support a project already funded by another granting agency.
7. Research funds may not be utilized for Institutional overhead or other indirect costs.
Budget

1. Total budget will be $3,000.

2. Travel, indirect costs, and salary support for the principal investigator must not be included in the budget costs.

3. Financial support is provided for consumable supplies and equipment necessary for the proposed investigation. However, no more than 50% of the research funds may be used for major equipment purchases.

4. This research award is designated for a 3-6 month interval. Unexpended and unobligated funds remaining after the one-year grant period should be returned to the CLAO ERF/SSF.

Application

The application form describing goals, background, methods and materials, and budgetary analysis must be completed. Applications should by typed and returned to the offices of the Contact Lens Association of Ophthalmologists Education and Research Foundation. Applicants in training, residents, fellows, optometric students, technicians, and nurses must submit a letter from the scientific supervisor regarding the capabilities of carrying out the proposed research study. A curriculum vitae of the principal investigator and/or scientific supervisor should be enclosed. This letter must address the applicant's capabilities for carrying out the research and the available facilities.

Completed applications and questions regarding the grants program should be emailed to eyes@clao.org or submitted via regular US mail to:

CLAO ERF
4000 Legato Road, Suite 700
Fairfax, VA 22033

Fax copies are not acceptable. If submitting by US mail, please submit one original and three (3) copies of the completed application. Please do not exceed the space allowed for describing the proposal or your application may not be considered for funding.
APPLICATION FOR CLAO ERF/SSF SCIENTIFIC RESEARCH AWARD

Date 11/30/2012

1. Title of Research Proposal: Novel biomarkers for ocular disease in Sjögren's syndrome (56 characters maximum)

2. Principal Investigator: He Li
   
   Position: Graduate Research Assistant
   
   Address: 825 NE 13th St, Oklahoma City, Oklahoma, 73104

   Telephone: (405) 271-2592       Fax: 
   
   Email address: he-li@omrf.org

3. Scientific Supervisor: Kathy Sivils, Ph.D.
   
   (Needed for applicants-in-training, optometry students, nurses, technicians, residents and fellows)

   Position: Member, Oklahoma Medical Research Foundation
   
   Address: 825 NE 13th St, Oklahoma City, Oklahoma, 73104

   Telephone: (405) 271-2534       Fax: 
   
   Email address: Kathy-sivils@omrf.org

4. *Co-investigator(s):

   *PLEASE ATTACH CONTACT INFORMATION FOR EACH
5. Organization to which award should be made: Oklahoma Medical Research Foundation

Address: Accounting C/O Diana Szeto

825 NE 13th St, MS 18, Oklahoma City, Oklahoma, 73104

Diana-Szeto@omrf.org

Telephone: (405) 271-7453 Fax: (405) 271-7119

ENSURE THAT THIS IS THE PROPER ADDRESS. FUNDS WILL BE SENT TO THE ABOVE ADDRESS ONLY!!

6. Total Budget Request: $3,000

7. IMPORTANT PLEASE READ
   If the project is approved for support, I agree to provide a project report and financial statement at the completion of the research project. I agree to return to the CLAO ERF/SSF any unexpended funds. I agree to acknowledge support of the CLAO ERF and SSF in all publications resulting from this grant. I have not applied nor have been awarded governmental or philanthropic funding to carry out this project.

(Signed) ___________________________
Principal Investigator

(Signed) ___________________________
Department Chairman or Scientific Supervisor (if applicable)

PLEASE USE ONLY THE SPACE PROVIDED. COMPLETE ALL ITEMS. THE ONLY ATTACHMENTS SHOULD BE THE CURRICULUM VITAE FOR PRINCIPAL INVESTIGATOR AND SCIENTIFIC SUPERVISOR(S), IF ANY. ALL APPLICATIONS SHOULD BE TYPED. PLEASE PROVIDE ONE ORIGINAL AND 3 COPIES IF SUBMITTED VIA US MAIL. FAILURE TO COMPLY WITH THESE INSTRUCTIONS MAY DISQUALIFY THE APPLICATION FROM CONSIDERATION.

8. State the specific aim(s) of this study.
   Sjögren's syndrome (SS) is a common, heterogeneous autoimmune disease characterized by keratoconjunctivitis sicca. Diagnosis of SS requires assessment of ocular dysfunction, but is still challenging due to the lack of easily accessible biomarkers. Inflammation contributes to the dysfunction or death of lacrimal glands. For instance, elevated serum levels of interleukin-12, an inflammatory cytokine associated with multiple autoimmune diseases, can promote apoptosis of lacrimal acinar cells in a mouse model and could serve as a serological marker of ocular manifestations in human SS. Our goal of this study is to utilize powerful genomic technologies to characterize the etiology of dry eyes and ocular surface disease in SS, and identify dysregulated genes in peripheral blood that can be potentially used as biomarkers for ocular involvement in SS. Specific Aims: 1) we propose to evaluate the global gene expression profile in SS patients with ocular disease to identify dysregulated genes that can be potentially used as diagnostic serum biomarkers for ocular involvement in SS. 2) We will also integrate the expression data with genotype data from our genome-wide association study (GWAS) to assess genetic determinants

CLAO ERF/SSF Research Award Application 2013
of the dysregulated genes in SS patients with eye disease to provide new insight into the genetic architecture that underlie the etiology of dry eye and ocular surface disease in SS.

9. **Summarize previous studies related to this project.**
Our previous gene expression profiling (GEP) study using microarray data from 260 primary SS patients and 76 healthy controls has revealed 35 dysregulated pathways in SS and heterogeneity among patients. By focusing on specific clinical sub-phenotypes (e.g. compare GEP between anti-Ro positive vs. negative patients), we have identified additional dysregulated genes and pathways that are related to specific disease sub-phenotypes. We have also performed preliminary analysis using only a subset of our data to compare the expression profiles between healthy controls and SS patients with severe eye dryness. Our GWAS has also identified variants that are associated with SS susceptibility. These data will be utilized to focus on ocular phenotypes in this study.

10. **What is the significance of this study to dry eye/or ocular surface disease?**
Dry eye is the most bothersome symptom to many SS patients, but its etiology is largely unknown. Diagnosis of SS is challenging and limited therapeutic options are primarily directed at alleviating symptoms, but do little to halt the progressive decline in gland function. Discovery and characterization of novel serum biomarkers of ocular diseases could greatly advance our ability to diagnose SS. Identification of specific genes and pathways that contribute to inflammation in lacrimal glands may provide novel targets for rapid translation into effective therapies for ocular manifestations in SS.

11. **Research Plan - Provide a concise description of the methodology to be used.**
   
   **Relate the research techniques directly to the specific aim(s).**
   1) Whole blood gene expression profiling analyses will be performed in 260 SS cases and 76 controls after quality control and normalization. Differentially expressed genes will be evaluated via 3 subset analyses: a. lissamine green POSITIVE cases vs. healthy controls; b. lissamine green NEGATIVE cases vs. healthy controls; and c. lissamine green POSITIVE cases vs. NEGATIVE cases. Results from these analyses will be compared to each other to identify genes that can be potentially used as serum biomarkers for impaired ocular function in SS. Pathway analysis will be performed subsequently. Real-time PCR will be carried out to validate the gene expression results.
   2) Genotypes from our genome-wide association study will be used to evaluate expression quantitative trait loci (eQTL) that influence the expression of dysregulated genes related to eye diseases in SS. Taqman assay will be used to validate the result in an independent sample set.

12. **What are your qualifications to carry out this study?**
   1) Part of my dissertation project utilizes gene expression data to characterize interferon pathway dysregulation in SS. We have successfully identified genes that are differentially expressed between cases and controls. Subsequent eQTL analysis using data from our genome-wide association study (GWAS; manuscript in preparation) was also able to identify risk variants that influence the expression of dysregulated genes in SS. We anticipate that using a more homogeneous group of patients defined by traits related to eye symptoms will greatly increase the power to identify genes and pathways that are specifically involved in ocular disease in SS.
   2) I have seven abstracts (3 first author) from the GEP study and GWAS presented this year in two international meetings, and have published 3 papers as co-author during graduate study.

13. **What facilities do you have to carry out this study? List responsibilities of key personnel pertaining to this study.**
The Oklahoma Medical Research Foundation (OMRF) SS group led by Dr. Kathy Sivils has been focusing on SS genetics and gene expression profiling for over a decade. Together with others in our group, we constitute what is arguably the most highly concentrated group of investigators focused on genetics of SS in the world. Dr. Sivils established Sjögren’s Research Clinic in OMRF designed to carefully phenotype and classify patients with primary SS for research studies, and it has thus far evaluated over 1000 participants. Also, our data analysis routines for detecting differentially expressed genes and genetic association are well established and utilize the R package as a primary tool. The Roche LightCycler 480 Real-time PCR instrument in our lab will be used to perform real-time PCR and Taqmen assays for validation of the analyses results.
14. What other funds do you have to assist in the completion of this study (e.g., technician support, equipment, etc.)? List all grant applications pertinent to this study that are currently submitted or planned within the next year.

NA

15. Budget: Itemize all proposed expenditures; provide a brief justification for any item for which the need may not be obvious.

(a) Personnel

NA

(b) Equipment (not to exceed maximum allowed)

NA

(c) Supplies (including cost per individual item)

Real-time PCR kit for validation of the microarray results  $800
Taqman assay kit for validation of the eQTL analysis in an independent sample set  $2,200

(d) Other expenses

TOTAL: __$3,000__

17. Research Safeguards (if applicable): It is desirable to submit this form, completed and signed by a designated representative of the appropriate institutional committee with the original application, but submission of this page may be delayed to November 30.

A. Experimental Animals:

It is the policy of the CLAO ERF/SSF that institutions and organizations using experimental animals in projects or demonstrations supported with funds from the CLAO ERF/SSF grants shall assure the CLAO ERF/SSF in writing of compliance with the Principles for Use of
Laboratory Animals as stated in the regulations of the Department of Health & Human Services.

This is to certify that ___________________________ (Institution) is in compliance with the principles for use of laboratory animals under the regulations of the Department of Health & Human Services.

This is to certify that the research grant entitled ________________________________ submitted by ________________________________ for consideration by the CLAO ERF/SSF has been reviewed by the appropriate institutional committee and approved with the respect to compliance with the principles for the care, use and treatment of experimental animals under the regulations of the Department of Health & Human Services.

(Signed) ________________________________ Date ________________________________

(Institutional Official)

B. Human Subjects:
Safeguarding the rights and welfare of human subjects involved in research supported by the CLAO ERF/SSF is the responsibility of the institution to which the support is awarded. It is the policy of the CLAO ERF/SSF that no grant to support research involving human subjects be made unless the research is given initial and continuing review and approval by an appropriate committee of the applicant's institution. This review should assure that (a) the rights and welfare of the individuals involved are adequately protected, (b) the methods used to obtain informed consent are adequate and appropriate, and (c) the risks to the individual are outweighed by the potential benefit of him or her by the importance of the knowledge to be gained.

This is to certify that Oklahoma Medical Research Foundation (Institution) is in compliance with the U.S. Department of Health and Human Services, Public Health Service requirements regarding the initial and continuing review of research involving human subjects.

This is to certify that the research grant entitled CLAO ERF/Sjögren's Syndrome Foundation Scientific Research Award 2013 submitted by Kathy Sivils on behalf of He Li for consideration by the CLAO ERF/SSF has been reviewed by the appropriate institutional committee and approved with the respect to the study of human subjects as adequately protecting the rights and welfare of the individuals involved, employing adequate methods of securing informed consent from these individuals, and not involving undue risk in the light of the potential medical benefits to be derived therefrom.

(Signed) ________________________________ Date 30 Nov 12

(Institutional Official)

Please attach copies of the consent form and IRB approval statement.