University of Pennsylvania

Annual Progress Report: 2009 Nonformula Grant

Reporting Period

July 1, 2011 – June 30, 2012

Nonformula Grant Overview

The University of Pennsylvania received $4,600,000 in nonformula funds for the grant award period June 1, 2010 through May 31, 2014. Accomplishments for the reporting period are described below.

Research Project: Project Title and Purpose

Improving Vision and Preventing Visual Impairment in Rural Amish and Urban African Americans - We propose to assess methods for improving treatment of visual impairment for Age-Related Macular Degeneration; determine the genes associated with Age-Related Macular Degeneration in African Americans; phenotype Amish and African American subjects with Age-Related Macular Degeneration to determine characteristic retinal signs associated with genetic risk variants; determine the extent of cortical plasticity in advanced Age-Related Macular Degeneration; and identify disparities in vision care within the African American community.

Anticipated Duration of Project

6/1/2010 - 5/31/2014

Project Overview

The overall goal of this project is to investigate the genetic and environmental determinants of Visual Impairment, to develop new methods of treatment to delay its progression, and enhance the use of remaining residual vision. In particular, this project will focus on Age-related Macular Degeneration (AMD), which is the leading cause of Visual Impairment in Pennsylvania. The research aims are to (1) enhance vision rehabilitation for African Americans with central visual impairment, (2) determine the genetic and environmental modifiers in AMD, (3) determine visual cortex function in response to the central visual deficit seen in AMD, and (4) identify the barriers for minorities that prevent access to vision care.

To address the need for enhancing vision rehabilitation, a clinical trial will be performed comparing home vs. office-based rehabilitation in 60 African American subjects with visual impairment to determine if there is an advantage of one method over another. To assess the genetic and environmental modifiers in AMD, African American and Amish case-controls will be genotyped for risk variants and phenotyped for retinal changes with advanced imaging technology. To address the need to understand visual cortex function in AMD subjects with
central visual deficits, 40 subjects will undergo extensive testing with functional MRI to
determine if there has been any remapping and shift of visual cortical responsiveness. To
identify the reasons for minorities having poor access to vision care, faculty at Lincoln
University in collaboration with other faculty participating on this project, will develop and test a
study protocol to identify the hurdles that impede access to vision care in African Americans.

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**Other Participating Researchers**

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Ellenberg, PhD, Rui Feng, PhD, David Brainard, PhD, Sashank Prasad, MD – employed by
University of Pennsylvania
Elise Ciner, OD, Sarah Appel, PhD, Marcy J. Graboyes, MSW, LSW, ACSW, Ruth Y. Shoge,
OD, Erin Draper, OD – employed by Salus University
Daniel Weeks, PhD – employed by University of Pittsburgh
Judith Thomas, PhD, Patricia Joseph, PhD – employed by Lincoln University
Jeffrey Henderer, MD – employed by Temple University Health System
Omesh Gupta, MBA, MD – employed by Temple University School of Medicine

**Expected Research Outcomes and Benefits**

(1) Of the 50 states, Pennsylvania has the 4th highest prevalence of visual impairment and
blindness. Age-related Macular Degeneration is the leading cause of Visual Impairment in
Pennsylvania. The outcome of our project will be improved methods to treat and diagnose Age-
related Macular Degeneration resulting in earlier therapeutic intervention to prevent and slow
progression of this blinding disease. Slowing progression will lead to less advanced disease
which will impact the overall prevalence of Visual Impairment in Pennsylvania.

(2) Ethnic, cultural and socio-economic factors contribute to the poor access of African
Americans (AAs) to essential visual rehabilitative services and must be addressed to ensure that
individual needs, rather than these modifiable factors, determine the potential for AAs to achieve
successful outcomes. We expect that an understanding of these factors will lead to increased
access to essential vision rehabilitative services and improved vision.

(3) There is a need to empower the African American community in Philadelphia to perform
vision screening and refer subjects to appropriate facilities for continued vision care if needed.
We will train lay screeners from the community to educate their communities so services can be
continued beyond the grant period. This will result in less visual impairment long-term due to
better education and access for community members.

(4) The future of stopping visual impairment will depend on preventing progression from early disease to later blindness. This project will identify modifiable risk factors in Age-related Macular Degeneration, such as diet and smoking behavior, and target subjects with these risks with interventions to reduce these risk factors. This reduction in risk factors will result in a decrease in prevalence of Visual Impairment.

Summary of Research Completed

Aim 1: Vision Rehabilitation Research for African Americans with Central Vision Impairment (VISRAC)

Recruitment has been facilitated through interagency cooperation via the ‘recruitment advisory committee’ meeting of agency representatives and community members, visits, calls and presentations to referring organizations servicing individuals with visual impairment in PA. The advisory committee met on 3/20/12. Internal recruitment has been fostered through strategy sessions at various levels with Salus University and VISRAC study personnel. Efforts were made to train multiple personnel to provide maximum accommodation of study subject’s schedules thereby improving participation, compliance and retention. Ongoing VISRAC personnel meetings are held bimonthly to review study successes and challenges and plan for Year 03. A review of study activity was accepted and presented at the Pen-Del Association for the Education and Rehabilitation of the Blind and Visually Impaired on 4/19/12.

Participation in the VISRAC study requires 5 visits over a 2 to 3 month period. Of the 34 subjects that were initially enrolled, 22 have completed all 5 visits. (Table 1)

Aim 2. Genetic and Environmental Modifiers in AMD

Subaim 2A. Genotyping of Candidate Genes in African Americans

Recruitment toward our goal of 400 cases/400 controls over the 4-year funding period is progressing as shown by our current totals of 238 cases and 363 controls (Table 2). In terms of genotyping, we have completed targeted sequencing of 90 cases and 90 controls.

Subaim 2B. Genotyping of Candidate Genes in the Amish

Recruitment toward our goal of 200 cases and 100 controls over the funding period is going well with a total of 200 cases and 100 controls. No individuals have been genotyped.

Subaim 2C. Phenotyping of AMD subjects

Phenotyping by Jacobson group. Recruitment for the phenotyping (Jacobson group) has consisted of 10 African Americans and 50 Amish individuals. Both the current period enrollment (60) and the total enrollment to date (114) are appropriate to the proposed schedule of enrolling a total of 160 patients, both African American and Amish, in the phenotyping study during the whole 4-year grant period. For the 60 patients enrolled in the current reporting period, age range was 50-86 years for the Amish and 60-87 years for the African-American populations, respectively. At the beginning of each visit, full ocular and medical histories were taken and
there was noting of all current medications, vitamin supplements, and modifiable risk factors, such as smoking, hypertension and adiposity. Height, weight, resting blood pressure, and pulse were measured; BMI was calculated. Visual acuities (VA) using the Early Treatment of Diabetic Retinopathy (ETDRS) chart were measured using the subject’s current prescription, followed by manifest refraction to achieve best-corrected visual acuity (BCVA). New glass prescriptions were provided if there was improvement of VA with refraction. VA ranged from 20/16 to LP across all enrolled patients. Evaluation of pupils, extra-ocular eye movements, and full anterior segment examination with slit lamp were performed and pupils were dilated. Stages of AMD evaluated ranged from grade 1 (few signs of early AMD with small, hard discrete drusen) to grade 4 (late stage wet AMD with active central retinal bleeding at the time of their exam).

Cross-sectional imaging included a spectral-domain optical coherence tomography (OCT) protocol with overlapping line scans covering the central 60° along the horizontal and vertical meridians, and overlapping raster scans providing wide-field coverage of the retina. En face imaging with a confocal scanning laser ophthalmoscope included near infrared reflectance (NIR-REF), near infrared autofluorescence (NIR-AF), and short wavelength autofluorescence (SW-AF). Imaging was done with high-speed mode where overlapping 30°x30° regions of the retina were sampled for later digital mosaicing. Focus settings were optimized and NIR, NIR-AF, and SW-AF images were acquired in 25 consecutive frames and a single ART (Automatic-Real-Time) average of 20 frames were obtained.

After all imaging was accomplished, a clinical retinal exam was performed followed by discussion of the findings with the patient. In these two underserved populations, it was especially important to provide clinical care in addition to the retinal research. Of note, based on imaging and clinical examination findings, 12 Amish and 4 African-American patients were recommended for follow-up either as emergencies or for more routine care.

Phenotyping by Contrast sensitivity. Over the past year we have refined our methods significantly and have studied 9 control subjects and 4 experimental subjects. In order to increase the precision of the projection of the stimulus on the retina, we have developed a new technique for stitching together fundus photographs that takes into account and corrects for image distortions that are the result of pointing a fixed-aperture camera at the inside of a sphere. By projecting the fundus images onto the inside of a sphere and aligning their features with a general nonlinear search, we can create very high-fidelity maps of the retina that preserves angle from the fovea. Additionally, we have improved our software to take into account the displacement and angle of the eye relative to the fixation point when calculating the position of a stimulus. Using these new techniques have resulted in improved perimetry performance relative to the previous year. For targets placed over a blood vessel, only 2 of 9 control subjects failed to exhibit a contrast sensitivity dip while only 2 of 9 subjects showed a significant dip in sensitivity for targets placed over normal fundus (1 subject overlapped between the two failure groups). In experimental subjects, only one subject failed to exhibit a dip in sensitivity over a blood vessel, and all subjects except one, for whom normal fundus target data was not collected, showed no dip across normal fundus positions. All experimental subjects, except for the subject who showed no evidence of a drop in sensitivity over the blood vessel, showed a drop in sensitivity over the druse. A drop in sensitivity was considered to be significant when the leave-one-out RSS of a best-fit inverted Gaussian model was lower than the leave-one-out RSS of a horizontal
line. These results are preliminary but suggest that drusen do in fact interfere with contrast sensitivity even in very early AMD. These results were presented at the 2012 annual meeting of the Association for Research in Vision and Ophthalmology.

**Aim 3. Brain structure and function in response to changes in visual experience**

We have continued to refine our ability to identify the location and organization of cortical visual regions without the need for explicit visual stimulation. We have to date conducted 28 control subject MRI scanning sessions with both visual retinotopic mapping and with resting-state fMRI data (brain activity measured from awake subjects in darkness). As previously reported, the retinotopic mapping data have been used to create a predictive map of primary visual cortex organization based upon anatomy alone. We have further refined and extended this anatomical template in a replication data set, confirming our ability to specify retinotopic organization with a precision of approximately 1° of eccentricity (within the central 20° of vision) and approximately 15° of polar angle. This template approach allows us to predict the cortical location of the “lesion projection zone” for patients with homonymous vision loss, and test for alterations in cortical organization at that site. A manuscript describing this work is in revision at the journal Current Biology.

We have extended this anatomical prediction approach to extra-striate visual areas, and have shown that similar prediction of retinotopic organization may be achieved for visual areas V2, V3, and hV4. This work was presented at the annual Human Brain Mapping meeting.

We have used resting-state data from control subjects to examine the intrinsic functional connectivity of primary visual cortex within and across hemispheres, and have generated an algebraic model for the connectivity structure found. This allows an assessment of the functional organization of visual cortex without the need for explicit visual stimulation, which is of enormous value in patients with fixation impairments. This work was presented at the annual Human Brain Mapping meeting, and selected for recognition with a student travel award and highlighted presentation.

We are applying these techniques now to patients with advanced AMD. To date, we have studied the four patients with advanced AMD who have been identified by our collaborators in the other aims of this project. Of those four, two had the required combination of demarcated, homonymous central scotomas and the ability to participate with the scanning study. We have studied these two patients on each of two occasions. Preliminary analyses of these data—combining our ability to target cortical regions with an anatomical template and assess functional connectivity with resting-state data—suggest altered cortical functional connectivity between the lesion projection zone in the occipital pole and the cortical region sub-serving a preferred retinal locus.

**Aim 4: Collaboration with Lincoln University (LU)**

The continuance of the LU pilot study involved analysis of collected data, report writing and presenting research findings during the Pennsylvania Department of Health Interim Performance Review. This pilot study of the developed questionnaire was designed to ferret out bugs in the
questionnaire design and its actual implementation, to make sure that the questionnaire was efficient in that the least number of questions were used to assess the needed information, and to assess its ability to provide similar results when repeated in a second sample of the same cohort (reliability). The questionnaire highlighted four categories of questions that, based on prior evidence, were thought to be related to one of four different impediments (or enablers) related to access to eye care.

In the preliminary analysis initial results indicate that questions directed to each of the four categories of potential impediments of access to health care were on target, and that that these assessments were consistent between the two time periods the questionnaires were administered (November 2010 and March 2011).

Table 1.

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<thead>
<tr>
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<th>Cumulative Total as of 6/30/2012</th>
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<tbody>
<tr>
<td>New Enrollees</td>
<td>34</td>
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<tr>
<td>Withdrew</td>
<td>3</td>
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<tr>
<td>Active/In Progress</td>
<td>9</td>
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<tr>
<td>Completed Trial (Target=48)</td>
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Table 2.

African American AMD Genotyping – Aim 2, Sub Aim 2A

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<tr>
<th>Cumulative (to date totals)</th>
<th>All Sites</th>
<th>Penn</th>
<th>Temple</th>
<th>Salus</th>
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<tr>
<td>Enrolled Controls</td>
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<td>290</td>
<td>34</td>
<td>39</td>
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<tr>
<td>Enrolled Controls – Genotyped</td>
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<tr>
<td>Enrolled Cases</td>
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<td>177</td>
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<td>31</td>
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<tr>
<td>Enrolled Cases – Genotyped</td>
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