

University of Pennsylvania

Annual Progress Report: 2009 Nonformula Grant

Reporting Period

July 1, 2010 – June 30, 2011

Formula 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.

Principal Investigator

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Other Participating Researchers

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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)

Research activities to date for the VISRAC Study include 1) hiring/training of personnel, 2) acquisition of clinical research space, supplies/equipment, 3) establishment and meeting of community advisory committee, 4) finalization of study protocols including inclusion/exclusion criteria, sequence of eligibility assessments, development of streamlined two-step process of informed consent, 5) human subjects certification of study personnel, 6) attainment of IRB approval for study and personnel, 7) development of manual of procedures (MOP) including online MOP portfolio, 8) establishment and use of university electronic blackboard for calendars, schedules, information and forms by all study personnel, 9) development of assessment forms for each study visit, 10) development of recruitment materials for patients, referring doctors and community leaders, 11) recruitment and enrollment of subjects to attain Year 01 milestones (Table 1).

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. 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. A year end summary meeting of VISRAC personnel was held on 5/12/11 to review study successes and challenges and plan for Year 02.

The VISRAC study will require 5 visits over a 2 to 3 month period. Of the 10 subjects that were initially enrolled, 7 have completed all 5 visits, 1 has completed 4 visits, 1 has completed 3 visits and 1 withdrew from the study at the second study visit.

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 157 cases and 376 controls (Table 2). In terms of genotyping, we have completed targeted sequencing of 45 cases and 50 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 100 cases and 100 controls. No individuals have been genotyped.

Subaim 2C. Phenotyping of AMD subjects

A total of 160 patients aged ≥ 50 years, both African American and Amish, will be enrolled in the phenotyping study during the 4-year grant period.

Recruitment for the phenotyping (Jacobson group) has consisted of 10 African Americans and 44 Amish individuals while 1 African American and 2 Amish have participated in Contrast sensitivity exams (Brainard group).

Phenotyping by Jacobson group

Age range was 55-84 years for the Amish and 52-83 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 glasses prescriptions were provided if there was improvement of VA with refraction. VA ranged from 20/20 to LP. 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, 6 Amish and 3 African-American patients were sent for follow-up either as emergencies or for more routine care. Two Amish patients and one African-American patient were treated for active choroidal neovascularization and subretinal bleeding seen at their examination in our clinic.

Phenotyping by Contrast sensitivity

We have, to date, studied four control subjects and two experimental subjects. Our procedure reliably measures a drop in sensitivity at the location of a blood vessel for two of our four control subjects. This result demonstrates that in principle our method can measure changes in sensitivity across identified retinal structures. For the other two control subjects, however, the data were noisier and did not show a reliable dip at the predicted blood vessel location, and we have begun to investigate the subject-to-subject factors that might mediate this variability. We examined parameters of control subject performance to try to identify factors that might be diagnostic of decreased reliability for some subjects. Optic disc calibrations were reliable for all four control subjects and seem unlikely to be the source of subject differences. On the other hand, Control Subject 3's mean c1/2 value was 0.81 as compared to 0.23, 0.34, and 0.44 for subjects 1, 2, and 4 respectively. Control Subject 4 was well-fixated for only 53.5% of trials, compared to 72.4%, 60.4%, and 63.4% for the other three subjects. These observations, as well as our experience with experimental subjects, indicate that further refinements in subject screening and stimulus parameter choice may lead to improved reliability.

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

We have collected retinotopic mapping data from 15 control subjects. These data have been analyzed to create a predictive map of normal retinotopic organization based solely upon cortical surface topology. We have found that anatomy alone may be used to specify retinotopic organization with a precision of approximately 1° of eccentricity (within the central 20° of vision) and approximately 10° 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. These results are the subject of a manuscript in preparation for publication.

To date, two AMD patients have been identified with homonymous, central scotomas suitable for study with functional MRI. The first of these subjects has been scanned. The second, recently identified patient will be studied this Fall. It is anticipated that more candidate patients will be identified in coming years as the phenotyping studies examine additional patients with advanced AMD.

Aim 4: Collaboration with Lincoln University (LU)

In order to meet the aims of the proposed pilot study, *Identifying Barriers for Routine Eye Care*, the LU team completed a literature review, developed a questionnaire designed to elicit barriers to eye care (Visual Health and Access to Eye Care), consulted with study focus group members (students, parents, eye-care physicians) who reviewed the questionnaire for its ability to answer questions it is designed to answer (face validity), secured LU Institutional Review Board (IRB) approval, and trained student assistants.

This pilot study of the developed questionnaire was designed to ferret out bugs in the questionnaire design and its actual implementation as well as to assess its ability to provide similar results when repeated in a second sample of the same cohort (reliability). The

questionnaire was administered to targeted minority groups during two major campus events where significant numbers of parents and relatives of students were present (approximately 100 participated in November 2010 and approximately 76 participated in March 2011).

Subaim 4D Student Internships

The goal of research grant Aim 4D (Student Internships) is to provide opportunities for select Lincoln University (LU) students to participate in a 12 week summer experience where they engage in hospital based research, training and education in clinical and scientific study. Toward that end, the LU staff team members recruited and selected 4 students interns; 2 for summer 2010 and 2 for summer 2011.

The two LU students selected for the summer 2010 internship were Chimerze Nwachuku and Dony Benjamin. They worked at Salus University under the direction of Drs. Audrey Smith and E. Cinar. Their primary activities included attending classes and labs, participating in simulations of problems experienced by low vision patients, and visiting the Franklin Institute. In addition, they accompanied Dr. Audrey Smith on clinic visits and vision screenings at local schools where they assisted in performing tests on the students. Lastly, the young men performed literature reviews and research. Dr. E. Cinar noted that their work contributed greatly to an ongoing study project.

During the summer 2011 two LU graduating seniors were selected to participate in summer internships. Ms. Kaylene Baugh worked under the supervision of LU team members Drs. Joseph and Major. Her primary duties and responsibilities included reviewing relevant literature and drafting annotated bibliographies, studying grant related data and writing a final report of her work. She also spent several days shadowing a noted ophthalmologist, Dr. Alexander J. Brucker of PennMed. Nikoia Fredickson was assigned to U of Penn Stellar Chance Labs under the direction of Dr. Dwight Stambolian. Her immediate supervisor was Dr. Murthy Chavali. Among other laboratory duties she received official training in microinjection for zebrafish embryos and earned certification.

Table 1: VISRAC Recruitment Sequence and Year 01 Activity

| Initial Eligibility Interviews (IEI) → | Eligible for Clinical Eligibility Exam (CEE) → | Clinical Eligibility Exams Completed→ | Enrolled in VISRAC Study as of 6/1/11 | Milestones Accomplished for enrollment Year 01 |
|--|--|---------------------------------------|---------------------------------------|--|
| 30 patients | 24 patients | 15 patients | 10 subjects | 10 subjects |

Table 2. Summary of African Americans Recruited at Penn, Salus and Temple

| Sites | Total Cases | Controls |
|--------|-------------|----------|
| Penn | 121 | 288 |
| Salus | 18 | 65 |
| Temple | 18 | 23 |