AWARD NUMBER: W81XWH-15-2-0044

TITLE: Vision Restoration with a Collagen Cross-linked Boston Keratoprosthesis Unit

PRINCIPAL INVESTIGATOR: Joseph B. Ciolino, MD

CONTRACTING ORGANIZATION: Massachusetts Eye and Ear Infirmary

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TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Material Command
Fort Detrick, Maryland 21702-5012

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Vision Restoration with a Collagen Cross-linked Boston Keratoprosthesis Unit

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**6. AUTHOR(S)**

Elizabeth Grimm, Clinical Research Project Manager
Dr. Joseph Ciolino

**5d. PROJECT NUMBER**

**5e. TASK NUMBER**

**5f. WORK UNIT NUMBER**

**7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)**

Massachusetts Eye and Ear
Infirmary
243 Charles Street
Boston, MA 02114

**8. PERFORMING ORGANIZATION REPORT NUMBER**

**9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)**

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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**13. SUPPLEMENTARY NOTES**

**14. ABSTRACT**

The Boston Keratoprosthesis is the most widely used keratoprosthesis worldwide and is implanted in the eyes of patients who are not candidates for a traditional corneal transplant. Unfortunately, the most common cause of keratoprosthesis failure is due to keratolysis (corneal melts), which can result in devastating sight-threatening complications and /or loss of the eye. Within the keratoprosthesis unit, corneal melts typically develop in the corneal graft that serves as a carrier for the optic. We have developed a method to reduce the incidence or potentially eliminate corneal melts by strengthening the keratoprosthesis carrier tissue by collagen-crosslinking the cornea graft ex vivo using vitamin B2 (riboflavin) and ultraviolet light. The overall objective of this study is to prevent sight-threatening keratoprosthesis corneal melts and identify an improved treatment for patients who are not candidates for traditional corneal transplants.

**15. SUBJECT TERMS**

Boston Keratoprosthesis, corneal melts, collagen-crosslinking

| 16. SECURITY CLASSIFICATION OF: | | | 17. LIMITATION OF ABSTRACT | 18. NUMBER OF PAGES | 19a. NAME OF RESPONSIBLE PERSON |
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# Table of Contents:

## Introduction:

The goal of this proposal is to evaluate the safety and efficacy of a new method for preparing and transplanting an artificial cornea (keratoprosthesis) unit by using a novel procedure, known as corneal cross-linking, to reduce the incidence of corneal melts and improve the outcomes of keratoprosthesis surgery. The Boston Keratoprosthesis (KPro) is the most widely used keratoprosthesis worldwide and is implanted when patients are not candidates for a traditional corneal transplant. Unfortunately, the most common cause of keratoprosthesis failure is due to corneal melts, which can lead to permanent vision loss. We have developed a method to reduce the incidence or potentially eliminate corneal melts by strengthening the keratoprosthesis carrier cornea using tissue that has been cross-linked using vitamin B2 (riboflavin) and ultraviolet light prior to prosthesis assembly. This study's population will include patients who are both candidates for a Boston KPro and had either a history of corneal melting (keratolysis) or have high risk for corneal melting.

## Key Words:

Keratoprosthesis

Corneal Cross-Linking

Corneal Melting (Keratolysis)

## Accomplishments:

**What were the major goals of the project?**

This project has four major goals that are listed below.

1. IRB, HRPO and FDA Approval of the study protocol
2. Study Start-Up with DSMB, contractors and sub-sites
3. Enrollment and Completion of Study Assessments
4. Data Analysis and Publications

**What was accomplished under these goals?**

The following tasks (numbered to correspond with Gantt chart in the SOW) have been completed or are in progress.

Major Goal 1: The Sponsor Site completed its yearly IRB continuing review and is currently approved through March 2021. The Sponsor's IRB last continuing review documentation was submitted to HRPO and the related Continuing Review Acceptance Memorandum was received from HRPO on April 30, 2020. The Sponsor continues to

send FDA yearly reports. The most recent FDA annual report was sent June 18, 2020, and the next report will be completed in May 2021.

Major Goal 2: The Sponsor Site identified personnel to be included on the Data Safety Monitoring Committee, which included the study Medical Monitor, the Study Biostatistician and an Ophthalmologist not associated with the study. The Committee has met on October 24, 2019 and April 23, 2020. The Committee recommended that the study continue with the modifications described to the Committee in the DSMC report.

The Sponsor Site continues to work with Avedro Incorporated for supply of the study solution and UB light device. The Sponsor also continues to work with CorneaGen (formerly KeraLink International) which is the tissue bank providing corneal tissue according to the randomization schematic. The Sponsor continues to use the StudyTrax secure electronic data capture program for collecting all subject related data. The Sponsor now also uses StudyTrax as a secure way for sites to send study related optical imaging. The Sponsor uses hospital provided systems for secure encrypted e-mail to receive documents from sites for source data verification.

There are a total of 16 sites participating in this study. 1 site is the Sponsor Site, Massachusetts Eye and Ear Infirmary, and 15 Sub-Sites listed below. During this past reporting period enrollment was completed. Of the 16 Sites listed below, 14 sites are currently open and actively following subjects.

Complete list of Sub-Sites and Principal Investigators:

| **Site #** | **Site Name** | **Principal Investigator** |
|---|---|---|
| 1 | Mass Eye and Ear Infirmary | Dr. Joseph Ciolino |
| ~~2~~ | ~~San Antonio Uniformed Services~~ | ~~Dr. James Townley~~ |
| 2 | Columbia New York Presbyterian Harkness Eye Institute | Dr. Danielle Trief |
| 3 | The Willmer Eye Institute | Dr. Esen Akpek |
| 4 | W.K. Kellogg Eye Center | Dr. Shahzad Mian |
| 5 | The Jules Stein Eye Institute | Dr. Anthony Aldave |
| 6 | Illinois Eye and Ear Infirmary | Dr. Jose De La Cruz |
| 7 | Cincinnati Eye Institute | Dr. Edward Holland |
| 8 | UC Davis Health System Eye Center | Dr. Mark Mannis |
| 9 | Tauber Eye Center | Dr. Joseph Tauber |
| 10 | University Hospital Eye Institute | Dr. ~~Pankaj Gupta~~ Ahmed Omar |
| 11 | David and Ilene Flaum Eye Institute | Dr. James Aquavella |
| 12 | Shiley Eye Institute | Dr. Natalia Afshari |
| 13 | Bascom Palmer Eye Institute | Dr. Guillermo Amescua |
| 14 | Duke Eye Center | Dr. Victor Perez |
| 15 | Wills Eye | Dr. Brandon Ayres |
| 16 | New York Eye and Ear Infirmary of Mt Sinai | Dr. John Seedor |

Of the Sub-Sites, the following have secured IRB approval:

| Site # | Site Name | Principal Investigator |
|---|---|---|
| 1 | Mass Eye and Ear Infirmary | Dr. Joseph Ciolino |
| 3 | The Wilmer Eye Institute | Dr. Esen Akpek |
| 4 | W.K. Kellogg Eye Center | Dr. Shahzad Mian |
| 5 | The Jules Stein Eye Institute | Dr. Anthony Aldave |
| 6 | Illinois Eye and Ear Infirmary | Dr. Jose De La Cruz |
| 7 | Cincinnati Eye Institute | Dr. Edward Holland |
| 8 | UC Davis Health System Eye Center | Dr. Mark Mannis |
| 9 | Tauber Eye Center | Dr. Joseph Tauber |
| ~~10~~ | ~~University Hospital Eye Institute~~ | ~~Dr. Pankaj Gupta~~ |
| 11 | David and Ilene Flaum Eye Institute | Dr. James Aquavella |
| 12 | Shiley Eye Institute | Dr. Natalia Afshari |
| 13 | Bascom Palmer Eye Institute | Dr. Guillermo Amescua |
| 14 | Duke Eye Center | Dr. Victor Perez |
| 15 | Wills Eye | Dr. Brandon Ayres |

Of the above IRB approved Sub-Sites the following have secured HRPO approval:

| Site # | Site Name | Principal Investigator |
|---|---|---|
| 1 | Mass Eye and Ear Infirmary | Dr. Joseph Ciolino |
| 3 | The Wilmer Eye Institute | Dr. Esen Akpek |
| 4 | W.K. Kellogg Eye Center | Dr. Shahzad Mian |
| 5 | The Jules Stein Eye Institute | Dr. Anthony Aldave |
| 6 | Illinois Eye and Ear Infirmary | Dr. Jose De La Cruz |
| 7 | Cincinnati Eye Institute | Dr. Edward Holland |
| 8 | UC Davis Health System Eye Center | Dr. Mark Mannis |
| 9 | Tauber Eye Center | Dr. Joseph Tauber |
| ~~10~~ | ~~University Hospital Eye Institute~~ | ~~Dr. Pankaj Gupta~~ |
| 11 | David and Ilene Flaum Eye Institute | Dr. James Aquavella |
| 12 | Shiley Eye Institute | Dr. Natalia Afshari |
| 13 | Bascom Palmer Eye Institute | Dr. Guillermo Amescua |
| 14 | Duke Eye Center | Dr. Victor Perez |
| 15 | Wills Eye | Dr. Brandon Ayres |

An Investigator Meeting was held in San Francisco, CA on October 11, 2019 following the Cornea Society Meeting. An additional Investigator Meeting was held virtually on June 10, 2020. At both meetings, Dr. Joseph Ciolino provided a power point presentation which included review of protocol procedures, proper consenting, inclusion criteria, data collection and proper adverse event reporting requirements. Also Dr. Ciolino provided an enrollment update to the Investigators, Sub-Investigators and study coordinators who attended the meeting. The next meeting is planned to occur before the end of calendar year 2020 and will be held virtually.

Major Goal 3: Study Sub-Sites that secured IRB and HRPO approval also have FDP Contracts in place. The FDPs are reviewed and reissued annually. The study received a one year No Cost Extension from the DoD as of 9/24/2019. An additional one year No Cost Extention from DoD has been requested and is pending with the GMO for sign off. The sponsor site will be reissuing FDPs to all current active sites. The chart below lists

the open sites and the number of subjects that have had the keratoprosthesis surgery through September 15, 2020. Enrollment in the study is complete.

| Site # | Site Name | Principal Investigator | # Subjects who Received KPro surgery |
|---|---|---|---|
| 1 | Mass Eye and Ear Infirmary | Dr. Joseph Ciolino | 5 |
| 3 | The Wilmer Eye Institute | Dr. Esen Akpek | 9 |
| 4 | W.K. Kellogg Eye Center | Dr. Shahzad Mian | 13 |
| 5 | The Jules Stein Eye Institute | Dr. Anthony Aldave | 14 |
| 6 | Illinois Eye and Ear Infirmary | Dr. Jose De La Cruz | 3 |
| 7 | Cincinnati Eye Institute | Dr. Edward Holland | 1 |
| 8 | UC Davis Health System Eye Center | Dr. Mark Mannis | 1 |
| 9 | Tauber Eye Center | Dr. Joseph Tauber | 6 |
| ~~10~~ | ~~University Hospital Eye Institute~~ | ~~Dr. Pankaj Gupta~~ | ~~0~~ |
| 11 | David and Ilene Flaum Eye Institute | Dr. James Aquavella | 2 |
| 12 | Shiley Eye Institute | Dr. Natalia Afshari | 5 |
| 13 | Bascom Palmer Eye Institute | Dr. Guillermo Amescua | 1 |
| 14 | Duke Eye Center | Dr. Victor Perez | 7 |
| 15 | Wills Eye | Dr. Brandon Ayres | 2 |
| | | Total | 69 |

Major Goal 4: Analysis of photos and images by designated staff is ongoing. Analysis of all other data is also ongoing.

**What opportunities for training and professional development has the project provided?**

Nothing to Report

**How were the results disseminated to communities of interest?**

The number of enrolled study subjects across the study has been distributed to all sites each time new subjects are scheduled for KPro surgery.

**What do you plan to do during the next reporting period to accomplish the goals?**

Regulatory Management: We will continue to work with all sites to ensure ongoing IRB approval. The approved site documents and approval letters, once obtained, will then be submitted to HRPO.

Continue to work with the sites to collect and maintain all required regulatory documentation. Continue to monitor all subject data entered into the electronic data base for accuracy, and track all events entered into the system including any protocol deviations that occur. All reportable events will be forwarded to the IRB, HRPO and FDA as required.

Data Safety Monitoring Committee: The Data Safety Monitoring Committee will continue to meet annually to review all events and protocol deviations. The DSMC met

on October 24, 2019 and on April 23, 2020. The protocol plan regarding the activities of the DSMC will be followed.

## Impact:

**What was the impact on the development of the principal disciplines(s) of the project?**

As a result of our proposed study and the technique that it describes, some keratoprosthesis surgeons around the world have begun cross linking tissue used as a carrier for the keratoprosthsesis. During presentations, the investigators have cited our previous work that was included in our preliminary data for this grant application. At this time, it is not known whether this approach is effective which is what we intend to evaluate with this study. Through personal correspondence with cornea surgeons from around the world, MEEI has been told that they are eager to see the results from our study to help guide their clinical practice.

**What was the impact on other disciplines?**

Nothing to Report

**What was the impact on technology transfer?**

Nothing to Report

**What was the impact on society beyond science and technology?**

Nothing to Report

## Changes/Problems:

**Changes in approach and reasons for change:**

Nothing to report

**Actual or anticipated problems or delays and action or plans to resolve them:**

The COVID-19 pandemic necessitated a slow down in enrollment. As a result, we extended the time available for sites to complete their last surgery through the end of June 2020. An additional one year No Cost Extention from DoD has been requested and is pending with the GMO for sign off.

**Changes that had a significant impact on expenditures:**

Nothing to Report

**Significant Changes in use of care of human subjects, vertebrate animals, biohazards, and/or select agents:**

Nothing to Report

**Significant changes in use of care of human subjects:**

Nothing to Report

**Significant changes in use of care of vertebrate animals:**

Nothing to Report

**Significant Changes in use of care of biohazards:**

Nothing to Report

## Products:

**Publications, conference papers, and presentations:**

Nothing to Report

**Website(s) or other Internet site(s):**

Nothing to Report

**Technologies or Techniques:**

Nothing to Report

**Other Products:**

Nothing to Report

## Participants & Other Collaborating Organizations:

### What individuals have worked on the project?

*Name:* Joseph Ciolino, MD
*Project Role:* Principal Investigator
*Researcher Identifier (e.g. ORCID ID):* N/A
*Nearest person month worked:* 3 in this reporting period

*Contribution to Project: Dr. Joseph Ciolino is the Principal Investigator of this study and assumes all the roles associated with a principal investigator.*

*Name:* Ellen Fitzgerald
*Project Role:* Clinical Study Supervisor
*Researcher Identifier (e.g. ORCID ID):* N/A
*Nearest person month worked:* 2 in this reporting period

*Contribution to Project: Ms. Fitzgerald is responsible for overseeing study staff employed by the Center for Clinical Research Operations, as well as working on QA/QI and compliance.*

*Name:* Odeta Dyrmishi, MPA
*Project Role:* Project Manager
*Researcher Identifier (e.g. ORCID ID):* N/A
*Nearest person month worked:* 10 in this reporting period

*Contribution to Project: Ms. Dyrmishi is responsible for overseeing all aspects of the project, including enrollment, site coordination, data collection activities, regulatory compliance, IRB/FDA submissions, and working with key collaborators (CorneaGen/KeraLink. and Avedro).*

*Name:* Elizabeth Grimm, JD
*Project Role:* Project Manager (Back-Up)
*Researcher Identifier (e.g. ORCID ID):* N/A
*Nearest person month worked:* 2 in this reporting period

*Contribution to Project: Ms. Grimm is responsible for providing back-up support while the primary Project Manager is not available. This includes site coordination, data collection activities, regulatory compliance, and IRB/FDA submissions.*

*Name:* Xiudi Chen, MS
*Project Role:* Clinical Research Coordinator
*Researcher Identifier (e.g. ORCID ID):* N/A
*Nearest person month worked:* 5 in this reporting period

*Contribution to Project: Ms. Chen is responsible for enrollment at MEEI, and support of sub-sites with their enrollment goals. She reviews screening and enrollment logs, and she communicates directly with sites regarding study-wide enrollment.*

*Name:* *Matthew Sorial*
*Project Role:* *Clinical Research Coordinator*
*Researcher Identifier (e.g. ORCID ID):* *N/A*
*Nearest person month worked:* *1 in this reporting period*

*Contribution to Project: Mr. Sorial reviews StudyTrax data entry for MEEI and the study sub-sites. He communicates directly with sites regarding data entry.*

*Name:* *Vijeeta Tadla, PhD*
*Project Role:* *Study Monitor*
*Researcher Identifier (e.g. ORCID ID):* *N/A*
*Nearest person month worked:* *7 in this reporting period*

*Contribution to Project: Ms. Tadla is responsible for monitoring conduct of the study at sub-sites, including periodic monitoring calls and review of source documentation.*

*Name:* *Moona Abulkerim*
*Project Role:* *Clinical Research Coordinator*
*Researcher Identifier (e.g. ORCID ID):* *N/A*
*Nearest person month worked:* *3 in this reporting period*

*Contribution to Project: Ms. Abdulkerim is responsible for enrollment at MEEI, and support of sub-sites with their enrollment goals. She reviews StudyTrax data entry for MEEI and the study sub-sites. She communicates directly with sites regarding data entry. –* ***no longer on the project***

*Name:* *Ridwan Ahmed*
*Project Role:* *Clinical Research Coordinator*
*Researcher Identifier (e.g. ORCID ID):* *N/A*
*Nearest person month worked:* *1 in this reporting period*

*Contribution to Project: Mr. Ahmed is responsible for enrollment at MEEI, and support of sub-sites with their enrollment goals. He reviews StudyTrax data entry for MEEI and the study sub-sites. He communicates directly with sites regarding data entry. –* ***no longer on the project***

**What other organizations were involved as partners?**

List of Sub-Sites

| Site # | Site Name | Site Location | Site PI | Contribution |
|---|---|---|---|---|
| 1 | Massachusetts Eye and Ear Infirmary<br>Harvard Medical School | 243 Charles Street<br>Boston MA 02114 | Joseph Ciolino, MD | Facilities and Collaboration |
| 2 | Columbia/New York Presbyterian<br>Harkness Eye Institute | 635 West 165th Street, Box 25<br>New York, NY 10032 | Danielle Trief, MD | Facilities and Collaboration |
| 3 | The Wilmer Eye Institute<br>Johns Hopkins Hospital | 600 N. Wolfe Street<br>Baltimore, MD 21287 | Esen Akpek, MD | Facilities and Collaboration |
| 4 | W.K Kellogg Eye Center<br>University of Michigan | 1000 Wall Street<br>Ann Arbor, MI 48105 | Shahzad Mian, MD | Facilities and Collaboration |
| 5 | The Jules Stein Eye Institute<br>University of California, Los Angeles | 100 Stein Plaza<br>Los Angeles, CA 90095 | Anthony Aldave, MD | Facilities and Collaboration |
| 6 | Illinois Eye and Ear Infirmary<br>University of Illinois College of Medicine | 809 S. Marshfield Avenue<br>Chicago, IL 60612 | Jose De La Cruz,MD | Facilities and Collaboration |
| 7 | Cincinnati Eye Institute<br>University of Cincinnati | 580 South Loop Road,<br>Suite 200<br>Edgewood, KY 41017 | Edward Holland, MD | Facilities and Collaboration |
| 8 | Health System Eye Centre<br>University of California Davis | 4869 Y Street, Suite 2400<br>Sacramento, CA 95817 | Mark Mannis, MD | Facilities and Collaboration |
| 9 | Tauber Eye Center | 4400 Broadway, Suite 202<br>Kanas City, MO 64111 | Joseph Tauber, MD | Facilities and Collaboration |
| 10 | University Hospital Eye Institute | 11100 Euclid Ave, Cleveland, OH 44106 | ~~Pankaj Gupta, MD~~ Ahmed Omar, MD | Facilities and Collaboration |
| 11 | David and Llene Flaum Eye Institute<br>University of Rochester<br>Medical Centre | 210 Crittenden Blvd, Rochester, NY 14642 | James Aquavella, MD | Facilities and Collaboration |
| 12 | Shiley Eye Institute<br>University of California, San Diego | 9415 Campus Point Dr, La Jolla, CA 92093 | Natalia Afshari, MD | Facilities and Collaboration |
| 13 | Bascom Palmer Eye Institute<br>University of Miami Leonard M. Miller School of Medicine | 900 NW 17th St, Miami,<br>FL 33136 | Guillermo Amescua, MD | Facilities and Collaboration |
| 14 | Duke University Eye Center | Department of Ophthalmology<br>Hudson Building DUHS Box 3802<br>2351 Erwin Road Durham, NC 27710 | Victor Perez, MD | Facilities and Collaboration |
| 15 | Wills Eye | 100 Presidential Boulevard Suite 200<br>Bala Cynwyd PA 19007 | Brandon Ayres, MD | Facilities and Collaboration |
| 16 | New York Eye and Ear Infirmary,<br>Mt Sinai | 310 E 14th Street Suite 219<br>New York, NY 10003 | John Seedor, MD | Facilities and Collaboration |

List of Partnering Institutions:

| Number | Partner Name | Location | Contribution |
|---|---|---|---|
| 1 | Avedro Incorporated | 201 Jones Rd, Suite 5<br>Waltham, MA 02451 | In-Kind |
| 2 | CorneaGen (previously known as KeraLink International) | 815 Park Ave<br>Baltimore, MD 21201 | In-Kind |

## Special Reporting Requirements:

### Collaborative Awards:

Nothing to Report

### Quad Charts:

Please see attached Quad Chart for this reporting period.