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
Boston, MA 02114

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Fort Detrick, Maryland 21702-5012

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Massachusetts Eye and Ear
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243 Charles Street
Boston, MA 02114

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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

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Standard Form 298 (Rev. 8-98)
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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 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 2019. The Sponsor's IRB continuing review documentation was submitted to HRPO and the related Continuing Review Acceptance Memorandum was received from HRPO on June 29th 2018. The Sponsor continues to send FDA yearly reports, the next report will be completed May 2019.

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 met twice during the past review period, once to meet and review the protocol and then at the year anniversary of the first subject enrolled to review all AEs to date. The Committee provided feedback and documentation of their agreement that the study should continue as per the current protocol.

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 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 continues to use the Mass Eye and Ear Infirmary's MyFiles secure file sharing portal for collection of study related optical imaging and for source data verification.

There is 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 1 previously identified sub-site was unable to for fill their commitment to participate due to staff shortage, therefore the Principal Investigator offered the slot to another site. The other site was willing to participate, therefore the list below has been updated to reflect this change. Of the 16 Sites listed below 12 sites are currently open and enrolling subjects and 4 sites are in the approval process.

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
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
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~~	~~Weill Cornell Ophthalmology Dept.~~	~~Dr. Kimberly Sippel~~
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 16 Sub-Sites the following have secured IRB approval:

Site #	**Site Name**	**Principal Investigator**
1	Mass Eye and Ear Infirmary	Dr. Joseph Ciolino
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
11	David and Ilene Flaum Eye Institute	Dr. James Aquavella
12	Shiley Eye Institute	Dr. Natalia Afshari
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 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
11	David and Ilene Flaum Eye Institute	Dr. James Aquavella
12	Shiley Eye Institute	Dr. Natalia Afshari
15	Wills Eye	Dr. Brandon Ayres

An Investigator Meeting was held in Baltimore Maryland on April 13th 2018 following the ASCRS Symposium. Dr. Joseph Ciolino provided a power point presentation which included review of protocol procedures, proper consenting, inclusion criteria, data collection and proper 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 will be held in Chicago Illinois on Oct 26th 2018.

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 most recent FDPs for year 3 were completed by the Sponsor site and counter signed by open sites during this reporting period during the month of August 2018. The chart below lists the open sites and their enrollment to date. Enrollment in the study is currently on going and new subjects are being added at a fairly consistent rate. An additional 20 Subjects have been enrolled and randomized during this reporting period and 1 subject is currently in screening.

Site #	**Site Name**	**Principal Investigator**	**# of Subjects Enrolled**
1	Mass Eye and Ear Infirmary	Dr. Joseph Ciolino	3
3	The Willmer Eye Institute	Dr. Esen Akpek	5
4	W.K. Kellogg Eye Center	Dr. Shahzad Mian	4
5	The Jules Stein Eye Institute	Dr. Anthony Aldave	8
6	Illinois Eye and Ear Infirmary	Dr. Jose De La Cruz	

7	Cincinnati Eye Institute	Dr. Edward Holland	1
8	UC Davis Health System Eye Center	Dr. Mark Mannis	
9	Tauber Eye Center	Dr. Joseph Tauber	3
10	University Hospital Eye Institute	Dr. Pankaj Gupta	1 in screening
11	David and Ilene Flaum Eye Institute	Dr. James Aquavella	1
12	Shiley Eye Institute	Dr. Natalia Afshari	
15	Wills Eye	Dr. Brandon Ayres	1

Major Goal 4: Analysis of photos and images began during this reporting period. All subject photos and images to date have been reviewed by designated staff at the sponsor site. However, analysis on all other data has not yet commenced but will be done so during the next reporting period.

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

The clinical trial design was presented by the study Principal Investigator, Dr. Joseph Ciolino at the 11th annual Kpro Study Group meeting in Barcelona Spain on June 16th 2018.

How were the results disseminated to communities of interest?

Nothing to report

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

During the next reporting period we will.

Regulatory Management: We continue to work with the remaining 4 Sub-Sites to secure IRB approval. The approved site documents and approval letters, once obtained, will be submitted to HRPO for the remaining 4 Sub-Sites

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 protocol plan regarding the activities of the DSMC will be followed.

To ensure enrollment continues at an acceptable pace the Sponsor Site will be conducting monthly tele-conferences with the Sub-Sites to address inclusion questions and to share successful subject identification methods among the sites. Also, the sponsor site is communicating with the Kpro Office for updates on the number of Kpro device orders that come in weekly. Using this information the Sponsor site can check with the Investigator ordering the device to see if the patient may be a potential study subject.

All sub-sites have been invited to attend the scheduled investigators' meeting at AAO in Chicago Illinois on Friday October 26th 2018 where Dr. Ciolino will review the protocol details as well as provide a forum for discussion.

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:

Nothing to report.

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: *12*

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

Name: *Marie Le*

Project Role: *Clinical Study Supervisor*

Researcher Identifier (e.g. ORCID ID): N/A

Nearest person month worked: *1*

*Contribution to Project: Ms. Le Was 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 (KeraLink and Avedro) –**No longer on this project***

Name: *Arden Tesmer*

Project Role: *Project Manager*

Researcher Identifier (e.g. ORCID ID): N/A

Nearest person month worked: 1

Contribution to Project: Ms. Tesmer was 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 (KeraLink and Avedro). ***No longer on this project.***

Name: *Lisa Langone*

Project Role: *Project Manager*

Researcher Identifier (e.g. ORCID ID): N/A

Nearest person month worked: 12

Contribution to Project: Ms. Langonel 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 (KeraLink Int. and Avedro).

Name: *Ellen Fitzgerald*

Project Role: *Clinical Study Supervisor*

Researcher Identifier (e.g. ORCID ID): N/A

Nearest person month worked: 12

Contribution to Project: Ms. Fitzgerald 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 (KeraLink and Avedro). Ms. Fitzgerald assumed these functions upon AnnMarie leaving MEEI.

Name: *Anna Lyczmanenko*

Project Role: *Clinical Research Coordinator*

Researcher Identifier (e.g. ORCID ID): N/A

Nearest person month worked: 1

Contribution to Project: Ms. Lyczmanenko is responsible for enrollment at MEEI, and support of sub-sites with their enrollment goals. She maintains screening and enrollment logs for MEEI and the study sub-sites who report to her weekly via email. ***No longer on this 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 Harvard Medical School	243 Charles Street Boston MA 02114	Joseph Ciolino, MD	Facilities and Collaboration
2	San Antonio Uniformed Services Health and Educational Consortium	2200 Bergquist Drive Lackland AFB, TX 78236	Major Richard Townley, MD	Facilities and Collaboration
3	The Wilmer Eye Institute Johns Hopkins Hospital	600 N. Wolfe Street Baltimore, MD 21287	Esen Akpek, MD	Facilities and Collaboration
4	W.K Kellogg Eye Center University of Michigan	1000 Wall Street Ann Arbor, MI 48105	Shahzad Mian, MD	Facilities and Collaboration
5	The Jules Stein Eye Institute University of California, Los Angeles	100 Stein Plaza Los Angeles, CA 90095	Anthony Aldave, MD	Facilities and Collaboration
6	Illinois Eye and Ear Infirmary University of Illinois College of Medicine	809 S. Marshfield Avenue Chicago, IL 60612	Jose De La Cruz, MD	Facilities and Collaboration
7	Cincinnati Eye Institute University of Cincinnati	580 South Loop Road, Suite 200 Edgewood, KY 41017	Edward Holland, MD	Facilities and Collaboration
8	Health System Eye Centre University of California Davis	4869 Y Street, Suite 2400 Sacramento, CA 95817	Mark Mannis, MD	Facilities and Collaboration
9	Tauber Eye Center	4400 Broadway, Suite 202 Kanas City, MO 64111	Joseph Tauber, MD	Facilities and Collaboration
10	University Hospital Eye Institute	11100 Euclid Ave, Cleveland, OH 44106	Pankaj Gupta, MD	Facilities and Collaboration
11	David and Llene Flaum Eye Institute University of Rochester Medical Centre	210 Crittenden Blvd, Rochester, NY 14642	James Aquavella, MD	Facilities and Collaboration
12	Shiley Eye Institute University of California, San Diego	9415 Campus Point Dr, La Jolla, CA 92093	Natalia Afshari, MD	Facilities and Collaboration
13	Bascom Palmer Eye Institute University of Miami Leonard M. Miller School of Medicine	900 NW 17th St, Miami, FL 33136	Guillermo Amescua, MD	Facilities and Collaboration
~~14~~	~~Weill Cornell Department of Ophthalmology~~	~~1305 York Avenue New York, NY 10021~~	~~Kimberly Sippel, MD~~	~~Facilities and Collaboration~~

14	Duke University Eye Center	Department of Ophthalmology Hudson Building DUHS Box 3802 2351 Erwin Road Durham, NC 27710	Victor Perez, MD	Facilities and Collaboration
15	Wills Eye	100 Presidential Boulevard Suite 200 Bala Cynwyd PA 19007	Brandon Ayres, MD	Facilities and Collaboration
16	New York Eye and Ear Infirmary, Mt Sinai	310 E 14th Street Suite 219 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 Waltham, MA 02451	In-Kind
2	KeraLink International	815 Park Ave Baltimore, MD 21201	In-Kind

Special Reporting Requirements:

Collaborative Awards:

Nothing to Report

Quad Charts:

Please see attached Quad Chart for this reporting period.

Vision restoration with a collagen crosslinked keratoprosthesis unit

MR141163
W81XWH-15-2-0044

PI: Joseph B. Ciolino **Org:** Massachusetts Eye and Ear **Award Amount:** $2,773,704

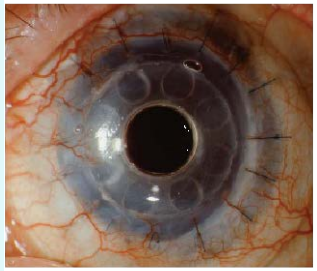
Study/ Product Aims

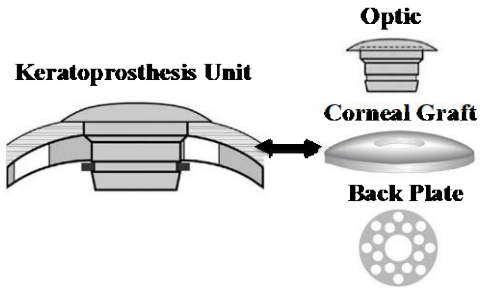
• To determine the **safety** (Aim 1) and **efficacy** (Aim 2) of using a collagen cross-linked cornea as a carrier for the Boston Keratoprosthesis in patients who are at high risk for corneal melts and are not candidates for a standard corneal transplant.

Approach

- This is a phase I/II prospective, randomized, multicenter, double-masked, vehicle-controlled study.
- Treat ½ of eyes with corneal cross-linked cornea and ½ with untreated corneal graft as a keratoprosthesis carrier. Recruit 84 subjects who are high risk for Keratoprosthesis corneal melts across 16 sites.
- Primary endpoint is time to keratoprosthesis loss through 12 months.
- Secondary endpoints include keratoprosthesis retention at 12 months, OCT corneal thickness metrics, etc.

Corneal Cross-linked Keratoprosthesis Unit





FDA approved IND for protocol.

Timeline and Cost

Activities CY	15	16	17	18
FDA IND amendment, Site IRB Approvals, & HRPO				
Subject Enrollment				
Subjects Complete Study				
Data Analysis and Reporting				
Estimated Budget ($)	**$570**	**$729**	**$867**	**$608**

Updated: (14-Sep-2018)

Goals/Milestones

CY15 Goal – To amend the PI's FDA IND to include 16 sites for a multicenter trial. To secure IRB approval at all participating sites.
☑ FDA IND approval for multicenter trial
☑ Secure IRB approval at all sites(12 approved,3 submitted, 1 in process)
☑ Secured signed agreement with supplier of the riboflavin/UV light.

CY16-17 Goals–Activate sub-sites, complete enrollment of 84 subjects.
☑ Submit IRB approved sub sites to HRPO for review
☑ Activate approved sites to begin subject recruitment
☑ 26 subjects randomized into the study this report period
☐ Secured enrollment of 84 subjects by second quarter of 2018.

CY18 Goal – To analyze data and report findings.
☐Complete data analysis
☐Submit findings to FDA and report results in manuscript submission

Budget Expenditure to Date1,100,951.39
Projected Expenditure:$ 2,166,186.12 Actual Expenditure: $1,100,951.39