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TITLE: A Dual Antibiotic-Steroid Drug-Eluting Contact Lens for Treatment of Eye Injuries That Can Be Used in an Austere Environment or Prolonged Field Care Setting

PRINCIPAL INVESTIGATOR: Joseph B. Ciolino, M.D.

CONTRACTING ORGANIZATION: Schepens Eye Research Institute, Boston, MA

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A Dual Antibiotic-Steroid Drug-Eluting Contact Lens for Treatment of Eye Injuries That Can Be Used in an Austere Environment or Prolonged Field Care Setting

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Joseph B. Ciolino

E-Mail: joseph_ciolino@meei.harvard.edu

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

Schepens Eye Research Institute
20 Staniford St
Boston MA 02114

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12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

We have developed a therapeutic contact lens that releases BOTH a broad spectrum antibiotic (moxifloxacin [MXF]) and a steroid (dexamethasone [DEX]). The drug-eluting contact lens consists of a thin drug-polymer film encapsulated within the periphery of a standard contact lens. Importantly, the MXF-DEX TCL is available for immediate On-Demand use. We achieved this significant advantage over the prior approach by using a non-degradable polymer to help modulate the drug release. The non-degradable polymer allows the lenses to be stored for 1-2 years at room temperature in a hydrated state within a blister pack or bottle. This application will test MXF-DEX TCLs in both infectious and inflammatory animal model

15. SUBJECT TERMS
None listed.

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
Unclassified	Unclassified	Unclassified	Unclassified	14	19b. TELEPHONE NUMBER *(include area code)*

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1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

Both steroid and antibiotic eye drops are typically frequently given after ocular surgery or injury to prevent infection and excessive inflammation. In our previous work, we developed a DEX-TCL for inflammatory ocular conditions. In this project, we have developed a combined steroid and antibiotic TCL to further simplify treatment regimens after surgery or injury.

2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

Inflammation, contact lens, sustained release, dexamethasone, keratitis

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Aim 1. *In vitro* assessment of the MXF-DEX TCL

Aim 2. *In vivo* evaluation of drug flux and biocompatibility

Aim 3. *In vivo* evaluation of efficacy

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Aim 1: Perform *in vivo* efficacy testing for of the steroid eluting therapeutic contact lens (TCL) in back of the eye animal models

1. Aim 1. Characterization of the TCL

We demonstrated the TCL can be stored for six months without compromising release. TCLs were fabricated, sterilized, and stored either at 4°C or room temperature. All TCLs were protected from light during storage. Release was tested by immersing the TCLs in phosphate buffered saline (PBS) and incubating at 37°C and 64 rpm. At regular intervals, the TCLs were removed and placed in fresh PBS. Results (n=4-5/group) were quantified by HPLC.

Through six months, the TCL demonstrated stable release kinetics in both storage conditions. There was no significant difference in cumulative release among the groups.

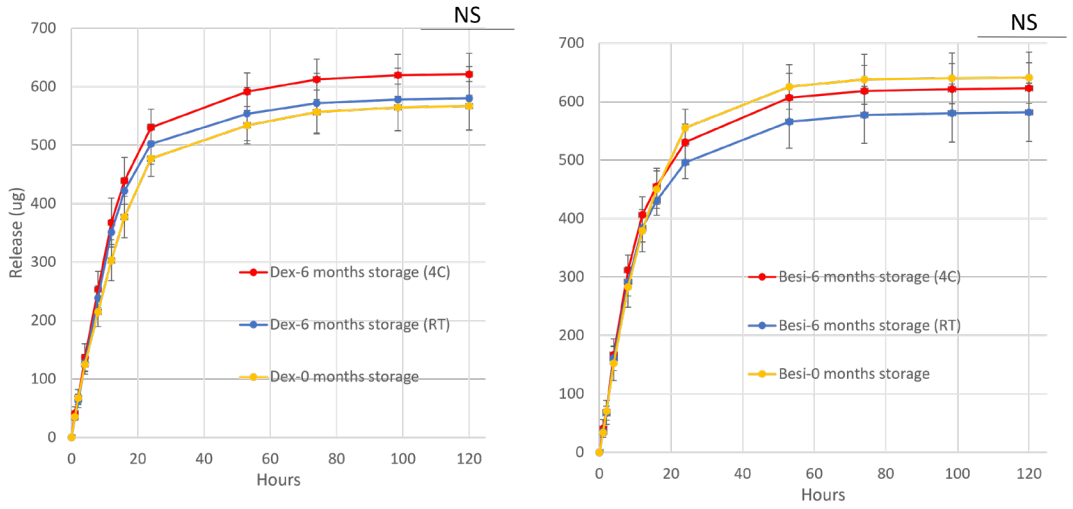

Figure 1. *In vitro* release of TCLs after six months of storage.

Water content-We demonstrated TCLs have similar water content compared to methafilcon hydrogels. Water content is a key indicator of both contact lens comfort, and can serve as a surrogate for oxygen permeability.

TCLs at equilibrium swelling were weighed, then dried at 60°C overnight to remove water. They were then weighed again. Each weight, both swollen and in the dry state, was taken three times. TCLs (n=4) had a water content of 58.3±1.7%. This is similar to the theoretical value for commercial methafilcon contact lenses (55%), and slightly higher than our research group's previous measurements for commercial methafilcon contact lenses (53±1.6%, Chen. et. al., *Pharmaceutics*, 2022)

Cytotoxicity-cytotoxicity of TCLs was measured using HCLE cells and comparing the results to untreated (control cells). PrestoBlue™ was used to measure cell viability. TCLs had a mean cell survival of 76±15.% (n=24), greater than the ISO standard of 70% for a medical device. Previously, we have noted dexamethasone decreased cell viability, even at doses considered safe in humans (Bengani et. al., *Acta Biomaterialia*, 2020), which likely accounts for the decreased viability compared to controls. Vehicle CLs (with polymer but no drug) demonstrated cell viability of 101±19%.

Aim 2. *In vivo* evaluation of drug flux and biocompatibility

To measure tear concentrations, New Zealand White rabbits (NZWs) were given 0.6% besifloxacin drops for four hours, concurrently with hourly dexamethasone eye drops for three hours, Eye drops were given five minutes apart to maximize absorption and mimic real-world instructions. After eye drop administration, tears were collected by Schirmer strip at 1, 2, 4, 8 and 24h.

For TCLs, NZWs received a permanent lateral tarsorrhaphy to aid contact lens retention. NZWs wore the TCL for a predetermined amount of time (1,2,4,8, or 24 hours). Tears were collected using Schirmer strips as described in the previous paragraph. Aqueous humor was collected by inserting a 31 gauge needle into the anterior chamber and withdrawing 100 µL of fluid. Results are forthcoming.

Aim 3. *In vivo* evaluation of efficacy

CNV study:

CNV can occur after surgery or injury. Blood vessels grow throughout the normally avascular cornea, obstructing patient vision. Steroids are a mainstay for treatment. We have previously demonstrated the dexamethasone-only TCL was effective at preventing CNV in a rabbit model (Bengani et. al., *Acta Biomateralia*, 2020) We proposed the Besi-Dex TCL could also prevent CNV, while providing the added benefit of antibiotic release to prevent postsurgical or post-injury infections.

NZWs received a figure-8 suture using 7-0 silk through the corneal stroma of the study eye. Sutures were approximately 1 mm high x 2 mm long. NZWs were randomly assigned to one of four groups: 1) no treatment, 2) Besi-Dex TCL, 3)besifloxacin and dexamethasone eye drops, or 4) vehicle contact lens, which contained a polymer but no drug. Eye drops were given hourly for 8 hours for dexamethasone, every other hour for besifloxacin (4 drops total). Eye drop administration was limited to 8 hours per day for practical and humane reasons.

This study is currently in progress. Results to date: we measured CD45+ corneal cells by flow cytometry, as a measure of corneal inflammation (Figure 2).

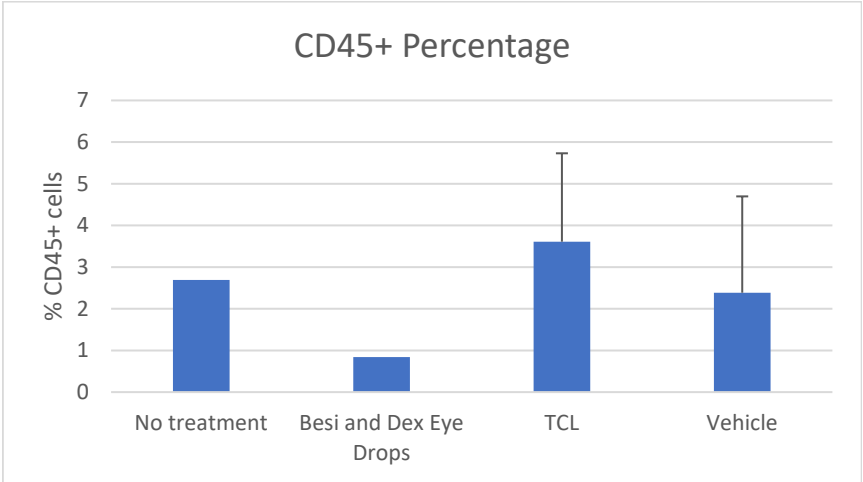

Figure 2. CD45+ corneal cells by flow cytometry (n=1-2/group).

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to report.

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

Complete corneal neovascularization, and bacterial keratitis studies. Continue storage studies.

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to report

What was the impact on other disciplines?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to report.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

The drug eluting contact lens patent has been licensed to a company, TherOptix, which was founded to commercialize the technology.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to report

5. **CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

Nothing to report

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Nothing to report

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or

equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Not applicable

Significant changes in use or care of vertebrate animals

Significant changes in use of biohazards and/or select agents

Not applicable

6. **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to report

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to report

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

- **Other Products**

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Joseph B Ciolino
Project Role: PI
Nearest person month worked: 3.00
Contribution: Oversight, experimental design

Name: Amy Ross
Project Role: Technician
Nearest person month worked: 12.0
Contribution: fabrication of TCLs, writing and submission of protocols, animal studies

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report

What other organizations were involved as partners?

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES: