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TITLE: Thermoresponsive Reversible Adhesive for Temporary Intervention of Ocular Trauma - II

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14. ABSTRACT A pre-clinical research and development project to advance a novel technology for temporary treatment of ocular trauma in austere environments. Open globe injuries, e.g. penetrating injuries to the sclera (the white surface of the eye) require microsurgical instrumentation, trained ocular surgery specialists to perform the closure and time to perform the procedure. We have developed a reversibly deployable, thermo-responsive hydrogel adhesive that can be placed, in a liquid gel form, through the penetrating injury to fill the laceration in the wall of the eye. As the hydrogel adhesive's temperature rises with body temperature, it transitions from a fluid gel into a viscous semi-solid that bridges and seals the penetrating injury for up to thirty days. The entire procedure from injection to fixation can take less than five minutes. Once transported to a ROC4 facility, a specialist can easily remove the adhesive by rehydrating with cold water and aspirating the adhesive away and perform a complete revision. This project pursues four objectives: 1) refine and manufacture a 2 nd prototype of the hydrogel and accompanying instrument for subsequent GLP validation testing. 2) Perform GLP biocompatibility and in vivo performance testing of these devices to support a subsequent regulatory package. 3) Hold a pre-submission meeting with the FDA to get preliminary feedback on the product designs, proposed indications and clinical safety assessment strategy. 4) Further explore improvements to the adhesive properties of the hydrogel for potential future developments. To date we have made advanced in all four areas in line with our set goals.					
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1. INTRODUCTION:

This is a pre-clinical research and development project to further advance a novel technology for temporary treatment of ocular trauma in austere environments. Open globe injuries, e.g. penetrating injuries to the sclera (the white surface of the eye) require microsurgical instrumentation, trained ocular surgery specialists to perform the closure and time to perform the procedure. We have developed a reversibly deployable, thermo-responsive hydrogel adhesive that can be placed, in a liquid gel form, through the penetrating injury to fill the laceration in the wall of the eye. As the hydrogel adhesive's temperature rises with body temperature, it transitions from a fluid gel into a viscous semi-solid that bridges and seals the penetrating injury for up to thirty days. The entire procedure from injection to fixation can take less than five minutes. Once the patient can be seen by the appropriate specialist with the necessary equipment and time, the hydrogel can be easily removed by simply cooling and rehydrating the adhesive with cold water. This project seeks to accomplish four primary goals: 1) refine and manufacture a first prototype of the hydrogel and accompanying injector instrument for subsequent GLP safety and performance testing. 2) Performance of GLP biocompatibility and in vivo performance testing on the manufactured prototypes to support a subsequent regulatory package. 3) Hold a pre-submission meeting with the FDA to get preliminary feedback on the product designs, proposed indications and clinical safety assessment strategy. 4) Further explore improvements to the adhesive properties of the hydrogel for potential future developments.

2. KEYWORDS:

- Thermoresponsive reversible hydrogel
- Open globe injury
- Penetrating injury
- First point of care
- Ocular trauma
- Intraocular pressure
- Preclinical evaluation
- In vivo validation

3. ACCOMPLISHMENTS:

Project Major Goals for 2018:

	Deliverables due by Q3 2018 (project year end)	Status
1. Collect used needs and product specifications from combat medical community	Define new specs and integrate into Gen 2.0 concept	100% Complete.
2. Hydrogel plug chemistry refinement to meet new needs	- Complete refinement of hydrogel into Gen 2.0 specs - Begin hydrogel packaging verification	70% Complete ^a .
3. Tool design for hydrogel deployment will be refinement to meet new needs	- Design, build and benchtop verify new Gen 2.0 injector tool - Build out design history file	70% Complete ^b .
4. In vivo validation of Gen 2.0 Hydrogel Plug System	- Draft and submit animal protocol for in vivo validation of Gen 2.0 system - Produce Gen 2.0 devices for testing	70% Complete ^c .
5. GLP In vitro and in vivo biocompatibility validation	- Get quotes for GLP biocompatibility testing - Produce samples for GLP testing	70% Complete ^d .
6. Research & Development of Supported Patch Chemistry	Propose/Identify best candidates for modifying/improving hydrogel adhesive performance for supported patch	70% Complete.
7. Research & Development of Unsupported Patch Chemistry	Propose/Identify best candidates for modifying/improving hydrogel adhesive performance for unsupported patch	80% Complete.
8. Draft Regulatory Package Preparation	Awaiting delivery of manufactured prototypes for GLP testing.	70% Complete.

- Waiting on Gen 2.0 hydrogel from manufacturer. Hydrogel production has been verified. Just waiting on delivery. Development work has expanded thus the reduction in completed effort from year prior.
- Waiting on Gen 2.0 injector tool SLA from design house. Injector tool design is complete. Component production has started. Development work has expanded thus the reduction in completed effort from year prior.
- Waiting on delivery of Gen 2.0 components for starting testing. Development work has expanded thus the reduction in completed effort from year prior.
- Waiting on delivery of Gen 2.0 components for starting testing. Development work has expanded thus the reduction in completed effort from year prior.

3.A. SPECIFIC AIM 1: COLLECT USED NEEDS AND PRODUCT SPECIFICATIONS FROM COMBAT MEDICAL COMMUNITY.

3.A.1. SA1 MAJOR ACTIVITIES.

In Year 2, no additional activities were performed with respect to Specific Aim 1 as it was completed in Year 1 of the program.

3.A.2. SA1 SPECIFIC OBJECTIVES.

N/A.

3.A.3 SA1 SIGNIFICANT RESULTS.

N/A.

3.A.4. SA1 OTHER ACHIEVEMENTS

N/A.

SPECIFIC AIM 2: HYDROGEL PLUG CHEMISTRY REFINEMENT TO MEET NEW NEES.

3.B.1. SA2 MAJOR ACTIVITIES.

In Year 2 of this project, we completed the following key activities related to Specific Aim 2:

- We engaged a contract manufacturer to begin development of a GMP manufacturing route for the hydrogel adhesive's production.
- Hydrogel adhesive synthesis SOPs were transferred from USC to the contract manufacturer, as well as specifications and requirements.
- Three synthesis approaches were performed, successively, by the contract manufacturer at 30g batch size to finally reproduce the USC-synthesize copolymer.
- **20-Jan-2018:** The first Polysciences-produced hydrogel samples were shipped and received by USC for analysis. Samples were analyzed and feedback reported to Polysciences for revision of process. Hydrogel failed performance bench testing.
- **06-Mar-2018:** The second Polysciences-produced hydrogel samples were shipped and received by USC for analysis. Samples were analyzed and feedback reported to Polysciences for revision of process. Hydrogel failed performance bench testing. Next sample shipment scheduled for April 2018.
- **26-Apr-2018:** Polysciences delivered the 3rd batch of hydrogel to USC for our comparison testing against the university prepared hydrogels.
- GCP testing of the 3rd batch suggests that the molecular weight distribution is near the same as the hydrogels prepared by USC.

- **01-Jun-2018:** Polysciences has begun with process expansion from 30g batch preparation to 100g batch preparation. The focus will be on determining if synthesis processes will scale.
- Strategies for purifying the polymer and ensuring monomer content minimization were developed.
- First-pass price estimates were put together for next steps towards design for manufacturing (quality control build out, spec requirements definition, etc.).

3.B.2 **SA2 SPECIFIC OBJECTIVES.**

Specific Objectives	Month
Major Task 1: Identify a better working Gen 2.0 hydrogel	
1.) Place order for, receive, setup and calibrate new rheometer	1
2.) Synthesize new 30% hydrogel for testing	2
3.) Establish benchmark viscosity of the current 30% hydrated co-polymer hydrogel	2
4.) Create a matrix of hydrogel chemistries to be synthesized; Axes: hydrogel molecular weight, other alkyl groups on the acrylate co-monomer, and adhesion enhancing additives.	2
5.) Deliver a lower MW hydrogel formulations that can be prepared <10min with similar viscosity to current solution.	1
Major Task 2: Identify a working strategy for preparing and packaging hydrogel Gen 2.0	
1.) Synthesize "best candidate" Gen 2.0 hydrogels.	1-24
2.) Conduct characterization studies to verify and validate study.	12-24

3.B.3 **SA2 SIGNIFICANT RESULTS.**

Approaches to manufacturing medical grade hydrogel have been initiated.

The USC Team has engaged Polysciences Inc. (Warrington, PA) to provide contract manufacturing services for the hydrogel material. The USC team identified a handful of contract medical grade polymer manufacturers and selected one to work through the design for manufacturing and manufacturing development of the hydrogel polymer. The manufacturing contractor was selected for the following primary reasons:

- US-based manufacturer.
- ISO-90001 certification.
- ISO-13485 certification.
- FDA-registered.
- Experience with hydrogel synthesis and R&D.
- The scale of our envisioned manufacturing programs fits within the size scale that the contractor typically engages. (Note: the size is significantly smaller than the those typically handled by larger manufacturers, e.g. Dupont) Specifically, we are targeting < 100 gallon reaction chambers.
- The estimated costs were lower than the other proposals received.

Establishment of Polymer Specifications. Work was initiated in Q4 2017 with a preliminary transfer of knowledge from USC to the manufacturer. This included sharing of synthesis routes used, characterization data collected as well as preliminary requirements and criteria developed by the USC team. Four specific criteria were shared with the manufacturing team to help with defining the manufacturer polymer's acceptable properties. They were:

- Co-polymer composition (PNIPAM & butylacrylate)
- Molecular weight distribution as determined by GPC
- Rheometric (viscosity) properties.
- Phase Transition (LCST) characteristics of the hydrogel.

The manufacturing development project was laid out in 3 primary stages. Our development plan followed three stages: Stage 1) replicate the hydrogel production at the same small (<100g scale) as USC. Stage 2) replicate the hydrogel production at an intermediate size production (1-5kg scale). Stage 3) replicate the hydrogel production at large scale without loss of properties.

3 attempts to synthesize a 30g batch of the USC hydrogel composition were attempted, in succession, in order to successfully reproduce the copolymer hydrogel using manufacturing equipment.

Two iterations of hydrogel synthesis by Polysciences were performed and delivered to USC for evaluation in an attempt to manufacture the co-polymer (Warrington, PA). The Polysciences team delivered the first batch of hydrogel chemistries in **late January (26-JAN-2018)**, for evaluation. Three different samples (S1, S2 and S3) were shipped, with minor modifications to the synthesis conditions. Characterization tests performed by USC were reported back to Polysciences and used collaboratively to prepare a second series of hydrogels that were delivered in **mid-March (13-MAR-2018)**

The USC team use three bench top characterization tests to determine if the hydrogel is appropriate: 1) Gas permeation chromatography is first performed to evaluate the molecular weight distribution of the hydrogel, a characteristic that is critical to the hydrogel adhesive performance; 2) A rheometer is used to perform dynamic viscoelastic characterization of the mechanical properties; 3) Lower Critical Solution Temperature (LCST) transition characterization was tested to properly characterize LCST and reversibility. If these three tests are successful, then the hydrogel will be slated for in vivo performance and safety testing.

Figure 1 shows the summary of the GPC tests performed for the seven samples of hydrogel, prepared in two series, by Polysciences, Inc. For both series, at least one USC sample GPC was performed and included in the plot (labeled USC xx/xx/2017) for comparison. Note, it is important that the GPC profile of the Polysciences samples nearly match the profile of the USC hydrogels GPC scans. This ensures that the molecular weight distributions are similar in both cohorts.

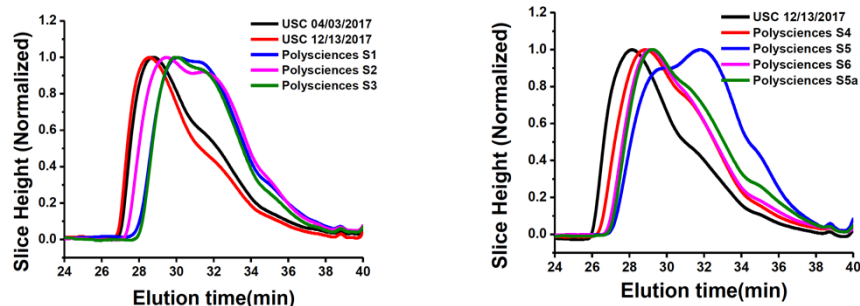


Figure 1. Gas permeation chromatography analyses performed on hydrogels prepared by Polysciences Inc., and compared against the USC prepared hydrogels for quality.

The seven hydrogels prepared by Polysciences in the first two batches do not have the same molecular weight distribution as the USC chemistries. The first series had both a significantly different GPC distribution as well as significantly smaller molecular weight distribution. Of the second series, S4, S6 and S5a all possess GPC profiles with shapes that more closely approximate the molecular weight distribution of the USC-prepared hydrogels. However, all four samples from the second series still possessed lower molecular weights than the USC samples.

Rheometer characterization of hydrogel viscosities on Series 2 prepared by Polysciences showed that the manufactured hydrogels are lower in viscosity than those prepared by USC. **Figure 2.** Shows the viscosity characterization measures performed on the hydrogel samples prepared in the second series (March samples). Across the entire shear rate range, the hydrogels prepared by Polysciences show significantly lower viscosity, consistent with the GPC results. However, we did note that for our application, we are most concerned with the lowest end of the shear rate axis, and in this range, the Polysciences samples are less than 5x lower than the desired viscosity range. **The conclusion here is that we are significantly closer to having Polysciences deliver a hydrogel formulation that will meet our requirements.**

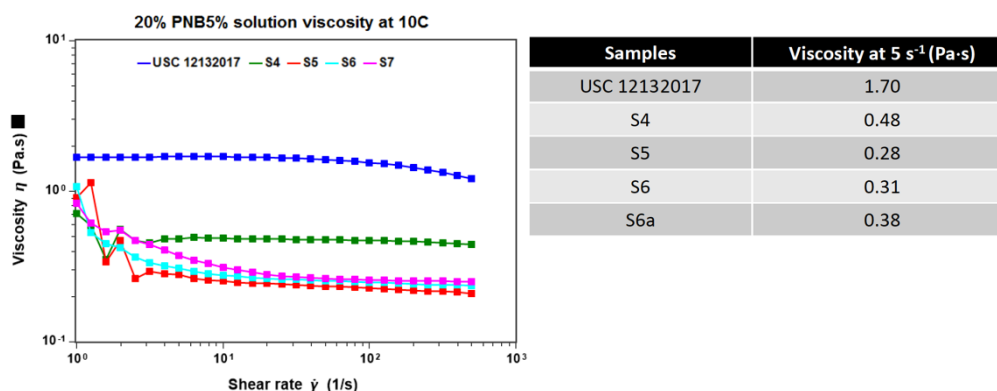


Figure 2. Rheometer measurements of hydrogel viscosity as a function of shear rate. For our application, the critical viscosity measures are in fact at the lowest shear rates.

All samples received from Polysciences, to date have exhibited LCST temperatures within the desired range. Data not shown.

A third iteration of the hydrogel production from Polysciences has produced manufacturable hydrogels in small quantities (30g runs) that are comparable to the preferred compositions prepared by the USC Thompson Group.

A concern raised by the Polysciences team has been with the non-linear increases in exothermic energy released during polymer synthesis, which can affect the molecular weight distribution. Through tailoring the temperature modulation and polymerization catalysts, it appears that Polysciences have matched the molecular weight distribution. **Figure 3** shows the gas permeation chromatography scans for the two hydrogel series (S7 and S8) shipped on **26-APR-2018**. It can be seen that both GPC scans show similar molecular weight distributions to the USC sample.

Similarly, rheometric tests (not shown) were within acceptable performance limits compared to our USC-prepared hydrogels. Based on these results, we began preparations for in vivo performance testing.

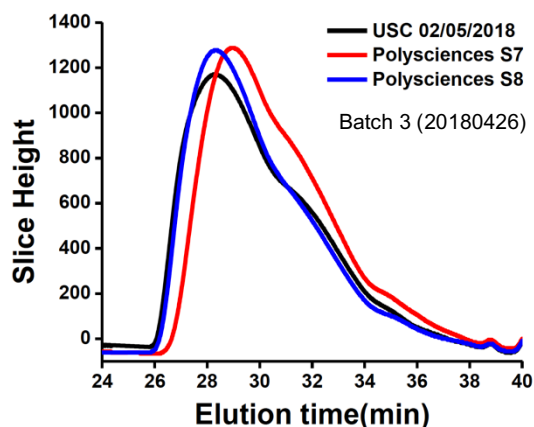


Figure 3. GPC molecular weight scans for S7 and S8 hydrogel series prepared by Polysciences and tested by USC.

3.B.4 **SA2 OTHER ACTIVITIES.**

No additional activities in this year.

SPECIFIC AIM 3. TOOL DESIGN FOR HYDROGEL DEPLOYMENT WILL BE REFINED TO MEET NEW NEEDS.

3.C.1 **SA3 MAJOR ACTIVITIES.**

In year 2, the following key activities were completed with respect to Specific Aim 3:

- A number of contract medical device design houses were vetted for engaging to develop our injector tool.
- Symbient Product Development (PD) was selected for having a number of qualifications.
- Technical kickoff meeting held with Symbient on **15-Dec-2017** at Symbient.
- Prototype concepts and project summary reviewed with Symbient team.
- USC given specification requirements sheet to complete with known design requirements.
- **09-Jan-2018:** Technical review of the specification requirements sheet was held via teleconference. Symbient was instructed to develop up to 4 concepts based on the design requirements.
- **31-Jan-2018:** Symbient provided four concepts for the injector tool based on the design requirements. Each design was scored on a number of characteristics, and those scores were presented with each design to help with evaluation (see details in detailed Accomplishments section).

- **22-Feb-2018:** One of the four designs was selected for further development and production work. An order was submitted for production of several (10-20) SLA units for in vivo testing.
- **12-Mar-2018:** Symbient provided the USC team with artistic renderings of the finished injector tools, and payment was issued to begin SLA production work.
- **22-May-2018:** Basic design and Bill-of-Materials build out has begun. First component challenge identified was the water reservoir (ampule).
- **15-Jun-2018:** Water reservoirs have been designs from a crystalline polymer (exhibits brittle characteristics). Key challenge is sonic welding of system. This is key focus of development for the project right now.
- Challenges with product development led to some delays so the first prototype devices have not yet been delivered.
- Time and cost estimates have been generated to deliver 20-25 SLA prototype injector tools based on the preferred design.

3.C.2 **SA3 SPECIFIC OBJECTIVES.**

Specific Objectives	Month
1.) Distill feedback from military medical personnel into Gen 2.0 Tool design specs	1
2.) Draft Gen 2.0 tool design and conduct design review to get signoff that specs are met.	1-2
3.) Draft validation testing strategy along with success criteria - get stakeholder signoff	1
4.) Fabricate SLA working prototypes of Gen 2.0 tool for testing	2-3
5.) Conduct benchtop validation to determine if ready for in vivo validation	3-4
6.) Finalize draft Design History File (DHF) for transfer to contract manufacturer	4

3.C.3 **SA3 SIGNIFICANT RESULTS.**

In Q4 2017, the USC team engaged a medical device product development team and began injector tool Gen 2.0 design. The USC team signed a preliminary agreement with an FDA compliant development house (Symbient PD, Inc.) to begin concept build out of the Gen 2.0 injector tool based on the design requirements captured by the team. Design requirements and all known, pre-defined specifications were aggregated by the USC team for transfer to Symbient in early 2018. The plan will be to generate first concepts in early 2018.

The Symbient PD team provided four concepts with associated development/production “scores” which allow the USC team to assess the risks with development each concept. Following the kickoff meetings with USC, the Symbient team has drafted four concepts based on the USC prototype design as well as additional requirements specifications provided in their worksheet. The following schematics, **Figure 4**, shows four different injector tool concepts generated by Symbient. Additional details of each concept are contained in the Appendix.

Each concept addressed the basic specification requirements. For example, all contained up to a 1cc hydrogel storage chamber insulated by an external jacket filled with sodium ammonium nitrate particles. All designs incorporated a separate, sequestered chamber for holding water for mixing

with the ammonium nitrate to catalyze the cooling process. All devices also used a thumb-driven plunger to drive the hydrogel from the instrument into the eye. All four devices were also assigned a risk-for-development score. The higher the score, the higher the probability of success.

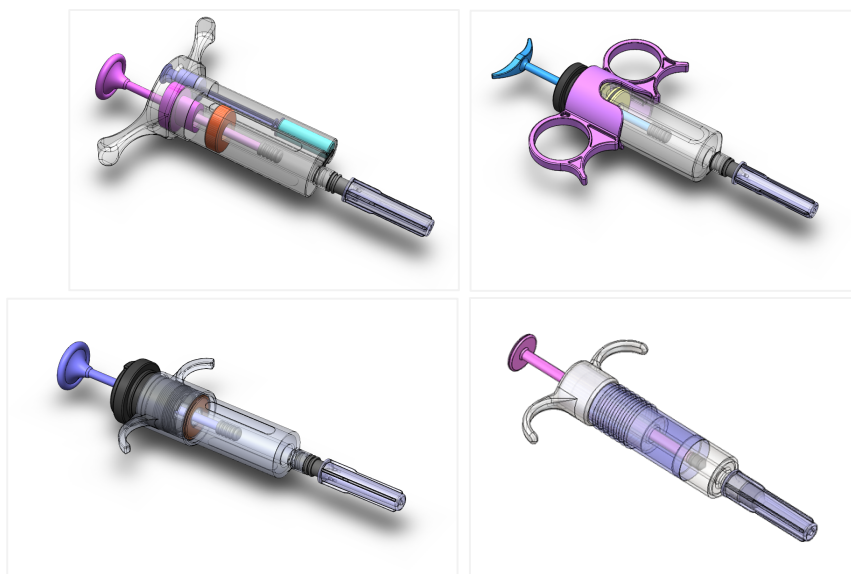


Figure 4. Four injector tool concept schematics created by Symbient Inc. for the USC IBT Research Team. All four designs capture the required specifications for the injector tool design, but employ different approaches. From left to right starting from the top, these designs are ordered with decreasing risk to development.

The USC team has worked with the product development team at Symbient to rank the properties of each of the four prototype designs created by Symbient, **Figure 4 and 5**. The four designs were generated using product engineering and performance requirements defined by USC. 3-dimensional concepts were generated for each concept in the previous period, showing key components and modes of action.

Each concept was scored on five criteria that were mutually agreed to by the development team and USC: 1) Ease of Assembly, 2) Shelf Life, 3) Technical Risk (Fluid accuracy, leaking), 4) Cost of Disposal, and 5) Development Risk. All five attributes were scored on a scale of 1 to 5 with 1 being the lowest (most negative score) and 5 being the highest (most desirable) score. A cumulative score out of 25 was given to each device, **Figure 5**.

The following definitions were used for each characteristic:

Ease of Assembly: The work associated with the manufacturing building these parts was assessed and ranked on a scale of 1 to 5, with 1 being “extremely challenging”, and 5 being “very easy”.

Shelf Life: An assessment of what the material stability of the design may be. Chambers which sequester hygroscopic cooling salts, water, and the thermoresponsive hydrogel.

Technical Risk. Risks with deviation from technical requirements for the design, e.g. ability to hold the correct volume of water and hydrogel; ability to repeatably mix the water and salt reactants to get the correct temperature profile, etc. High risk for missing specs will be scored a 1. No risk for missing requirements will be scored a 5.

Cost of Disposable: The COGS for parts and materials comprising the completed assembly. This will vary based on the ability to use existing components, vs. having the manufacture custom pieces. Expensive will be scored a 1. Significant cost savings will be scored a 5.

Development Risk: Challenges associated with the actual development work required to deliver actual prototypes. This includes challenges like inability to design tooling capable of producing a component, or inability to demonstrate proper mixing of cooling reactants using the design. Significant development risk is scored a 1. No apparent development risk is scored a 5.

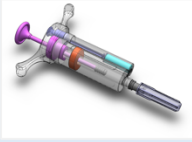
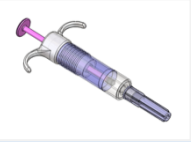
				
Ease of Assembly	3	3	4	5
Shelf Life	3	3	3	3
Technical Risk	2	2	4	4
Cost of Disposable	3	4	4	4
Development Risk	3	3	3	4
Cumulative Score	14	15	18	20

Figure 5. Score cards for each concept prior to investing in development.

A list of advantages and disadvantages were also generated for each concept design. Additional diagrams and schematics of each device are provided in the Appendix. Following discussions between USC and the engineering team leader, it was decided that the 4th design (Figure 3, far right) would serve as the basis for the product development.

Preliminary development work has started with development of the water reservoir. Currently, the first major manufacturing challenging is the development of a water reservoir that can sequester the water for on-demand cooling, but in a container that is easily ruptured to enable mixing for the endothermic reactions. Currently, there is a plan to create a two-component (cup with top) reservoir which will be sonically welded to seal the two components. Other components for the system are relatively easy to develop, therefore attention will be focused first on the water reservoir.

3.C.4 **SA3 OTHER ACHEIVEMENTS.**

No additional achievements to report this period.

SPECIFIC AIM 4. IN VIVO VALIDATION OF GEN 2.0 HYDROGEL PLUG SYSTEM.

3.D.1 **SA4 MAJOR ACTIVITIES.**

In year 2 of this project, the following key activities were completed with respect to Specific Aim 4:

- The non-GLP animal protocol was submitted to USC IACUC for review and approval (**03-Nov-2017**).
- The USC approved protocol was then submitted for ACURO review (**11-Dec-2017**)

- Revisions requested by ACURO were submitted for review to USC (**07-Mar-2018**).
- Following USC and ACURO approval, planning for first in vivo procedures started in **Q2Y2018**.
- A first series of animals (New Zealand rabbit, n=4) underwent in vivo testing procedures with some of the new hydrogel Gen 2.0 embodiments (May through June).
- Imaging data and histology data were prepared and aggregated for analysis.

3.D.2 **SA4 SPECIFIC OBJECTIVES.**

Specific Objectives	Month
1.) Draft and submit ACURO review for approval	2
2.) Produce and sterilize Gen 2.0 products for in vivo validation	5
3.) Perform implantation studies; track tool performance, IOP outcomes, and tissue response	5-7
4.) Perform statistical analysis of data: 95% CI new system (tool + hydrogel) works effectively	6-8
5.) Compile data for integration into regulatory package	8

3.D.3 **SA4 SIGNIFICANT RESULTS.**

The non-GLP animal protocol for performing preliminary in vivo assessments of the Gen 2.0 manufactured hydrogel was submitted to both USC and ACURO in year 2 and was approved in early 2018. The following list enumerates the key accomplishments with respect to our in vivo work:

- **09-May-2018:** Four preliminary rabbits were ordered for first implantation studies on the manufactured hydrogels from Polysciences (manufactured)
- **25-May-2018:** Baseline IOP measures initiated to collect at least 3 days of baseline IOP measures on both eyes for all four rabbits.
- **30-May-2018:** First rabbit implantation (**R1016**) procedure was performed as well as evaluation of the new, commercially manufactured hydrogel adhesive and also using tannic acid modifications for improved adhesion.
- **01-Jun-2018:** First implant was lost at 48-hours follow-up. Rabbit was still followed for one week as a control (laceration with no intervention).
- **04-Jun-2018:** **R1016** was euthanized and enucleated eyes were prepared for histology.
- **04-Jun-2018:** **R1017** underwent in vivo implantation test using the commercially manufactured hydrogel (rabbit 2 of 4). A hydrogel plug was placed into a 4mm full thickness pars plana scleral laceration.
- **04-Jun-2018:** Tannic acid adhesion enhancement was tested with the hydrogel and this time it was found to improve attachment of the hydrogel to the scleral surface (no conjunctiva). Video of procedure was taken.
- **06-Jun-2018:** Hydrogel plug was missing in eye at 48hr evaluation. Rabbit **R1017** was followed to 7-day endpoint for histology.
- **11-Jun-2018:** **R1017** euthanized at study endpoint and eyes enucleated for histology.

The first animal implantation tests were performed this period, using the first series of hydrogels produced by our contract manufacturer. During this period four rabbits were ordered and two of them underwent surgical procedures, **Figure 6**.

	Day-0	Day-7	Total Days	
R1016	5/30/2018	6/06/2018	8	
R1017	6/04/2018	06/11/2018	8	

Figure 6. Table of rabbits undergoing procedures to date.

All animals underwent the same stepwise procedures illustrated in **Figure 7**. On the day of surgery, animals were anesthetized and a baseline imaging series (slit lamp exam, posterior and anterior segments OCT, fundus photography and confocal corneal microscopy). After baseline imaging, a 3-5mm full thickness laceration was created approximately 3mm radial from the limbus in the superior temporal quadrant. Once the laceration was created, time was given to allow the pressure in the eye to drop and for vitreous to partially leak from the rupture. A sterile non-woven swab was used to remove moisture from the scleral surface.

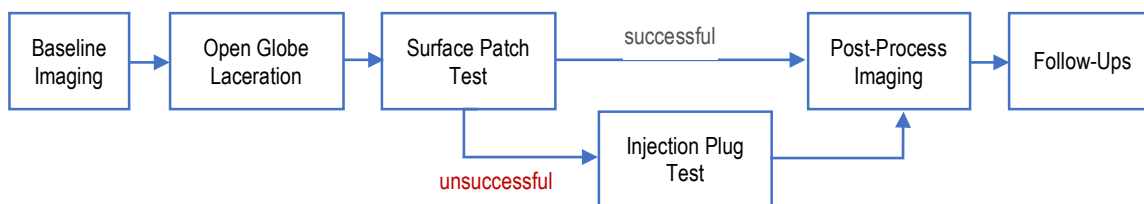


Figure 7. Flow chart of steps planned and performed on each study animal.

R116 Test Series 1. Unsuccessful Tannic Acid Adhesion Promoter Test. A first attempt was made at globe closure via direct adhesion of the hydrogel to the exterior surface of the sclera (direct adhesion) using the latest hydrogel chemistries developed. The scleral surface was first dried with compressed air, then an aqueous solution of tannic acid was applied to the scleral surface to improve hydrogel adhesion, **Figure 8**. The hydrogel was then applied to the external surface and given 5 minutes to fix on the surface. Different combinations of removal of excess moisture and waiting for different intervals for drying, activation solution placement, and hydrogel fixation time were tried with both animals, **Figure 8**, and the success of these tests are reported here.

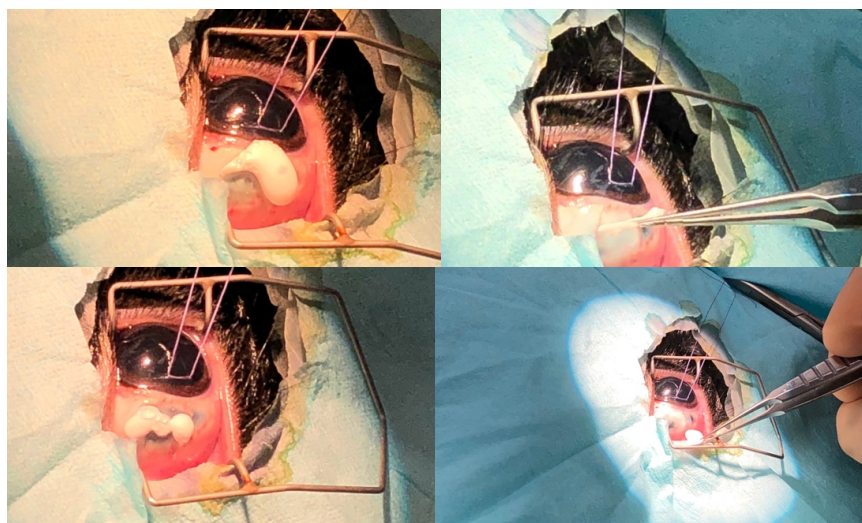


Figure 8. Two photo series (top row and bottom row) of injectable hydrogel placement with tannic acid primer treatment of the scleral surface on R116. (top row, left to right): Test 1 - applying injectable hydrogel adhesive to the scleral surface after first preparing with tannic acid primer solution. Testing adhesion by pulling hydrogel adhesive with forceps shows weak surface adhesion. (bottom row, left to right): Test 2 - Second attempt at adhesion test with tannic acid priming, using a different TA application protocol. Still no adhesion.

R116 Test Series 2. Successful Laceration Occlusion with Injectable Hydrogel. After the tannic acid adhesion tests, we ran the standard laceration occlusion test, **Figure 9**. A 5mm full-thickness laceration was created in the sclera, approximately 3mm from the limbus. Once characterized, the Gen 1.0 injector tool was prepped for use by the surgical assistant and then the surgeon applied the manufactured hydrogel per the usual approach.

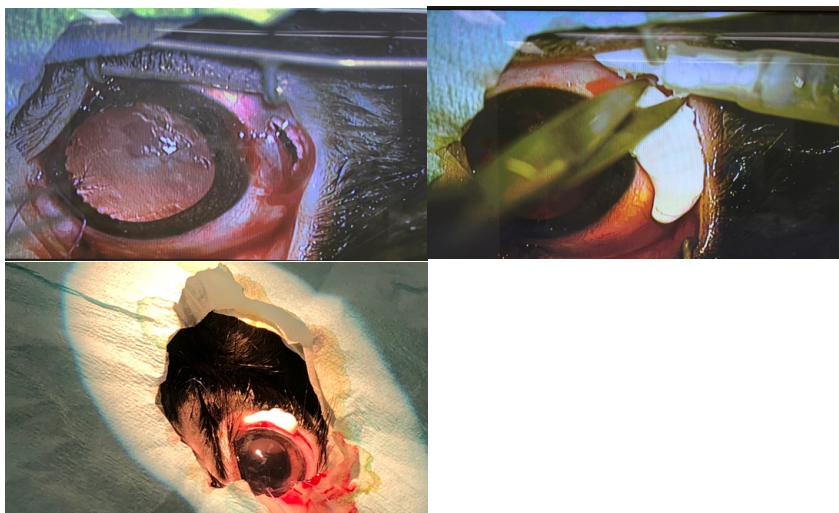


Figure 9. Photographic series of laceration occlusion experiment on R116 showing (left to right, starting at top), creation of the 5mm laceration, followed by trimming of the injected hydrogel after its placement and fixation; and a final photograph of the complete hydrogel placement after fixation in the eye.

R117 Test Series 1. Successful Tannic Acid Adhesion Promoter Test. We repeated the same tannic acid surface priming procedure with fresh solution, **Figure 10**. This time, we applied several drops from a syringe onto a completely dry scleral surface. The droppered tannic acid was allowed 5 minutes to soak on the surface before the hydrogel was applied ovetop. The hydrogel was removed from the site after video documentation. The eye was then prepped for a laceration occlusion test.

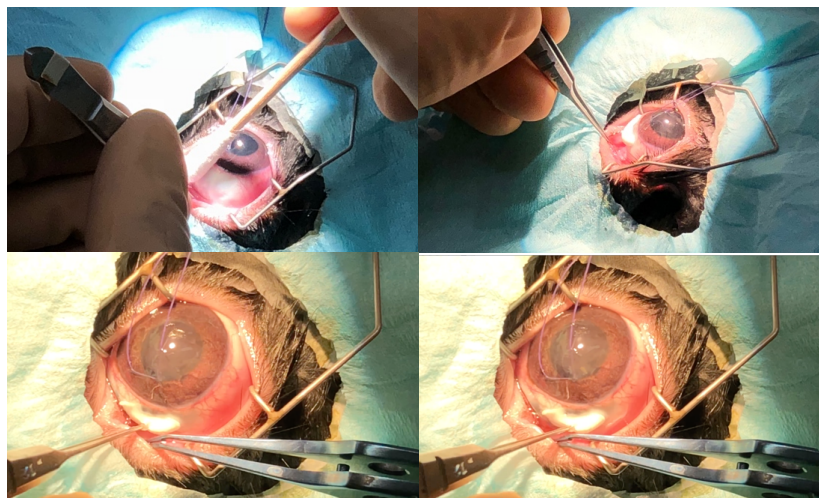


Figure 10. Photo series (left to right, from top) of a successful tannic acid primed placement of hydrogel adhesive with good adhesion performance. The bottom two photos are time-laps showing the eye rotating in its orbit by grasping the hydrogel and rotating the eye.

117 Test Series 2. Successful Laceration Occlusion with Injectable Hydrogel. After the successful tannic acid adhesion tests, we ran the standard laceration occlusion test on the opposite side of the eye, **Figure 11**. A 5mm full-thickness laceration was created in the sclera (similar to **R116**).



Figure 11. Photographic series for the laceration occlusion test on rabbit R117, showing (from left to right, top row first), a full thickness scleral laceration was created and swabbed until bleeding was controlled; next the injector tool was prepared by the surgical assistant by adding water to the ammonium nitrate cooling chamber; next the hydrogel was placed and allowed to set.

Intraocular pressure was tracked as well as ocular imaging series were taken over a 7-day period, post-procedure to track ocular tissue conditions. These data are being compiled and reviewed and will be included in our next report.

3.D.4 SA4 OTHER ACHIEVEMENTS.

Nothing to report this period. We have been slightly delayed on completion of these objectives by the opportunity to host our expanded end user workshop at Walter Reed Medical Center.

SPECIFIC AIM 5. GLP IN VITRO AND IN VIVO BIOCOMPATIBILITY VALIDATION

3.E.1 SA5 MAJOR ACTIVITIES.

GLP in vitro and in vivo biocompatibility testing is waiting for delivery of the hydrogel produced by our contract manufacturer. We have only been able to engage the contract laboratories to secure price quotes for the work, but have not been able to initiate testing. This part of the program has been delayed.

3.E.2 **SA5 SPECIFIC OBJECTIVES.**

Specific Objectives	Month
1.) Draft and submit ACURO review for approval	2
2.) Team meeting with contract biocompatibility lab to define SOW and deliverables	4
3.) Produce and sterilize Gen 2.0 hydrogel for biocompatibility; delivery to biocompatibility lab	5
4.) Conduct MEM elution/extraction cytotoxicity testing on selected “best candidate” chemistries.	6
5.) Results review - select formulations for in vivo biocompatibility testing; Fabricate/deliver	7
6.) Conduct GLP <i>in vivo</i> biocomp testing in accordance with ISO-10993 protocol standards.	8-12
7.) Statistical analysis of data and interpretation	11-12
8.) Results review and next steps determination	12

3.E.3 **SA5 SIGNIFICANT RESULTS.**

Nothing to report this period as we are awaiting delivery of the Gen 2.0 products for GLP testing.

3.E.4 **SA5 OTHER ACHIEVEMENTS.**

Draft of a biocompatibility study for future submission to IACUC and ACURO has been initiated, but is awaiting review with regulatory consultant.

SPECIFIC AIM 6. RESEARCH & DEVELOPMENT OF SUPPORTED PATCH CHEMISTRY.

3.F.1 **SA6 MAJOR ACTIVITIES.**

In Year 2, the following key activities were completed with respect to Specific Aim 6:

- The Thompson Group continues to work on developing supported patch-based approaches to the ocular sealant.
- Dr. Bin Li continues to work on enhancing the hydrogel adhesion to ocular tissues by modification with tannic acid and other additives.
- Preliminary data measuring hydrogel adhesion to cadaveric porcine eyes showed improvement with the use of tannic acid.
- The Thompson Group continues to study the physical characteristics of tannic acid (TA) modification of the copolymer hydrogel.
- Sol-Gel transition as a function of temperature was studied for the TA-modified copolymer hydrogel to evaluate the kinetics of the temperature dependence.
- The temperature transition behavior of the TA-modified hydrogels perform within the required temperature range.
- Work of adhesion for the TA-pretreated hydrogels was also characterized.
- Mechanical adhesion testing on different ocular tissues shows significant enhancement of adhesion to porcine cornea as well as sclera.

- Preliminary in vivo tests of adhesion enhancement of hydrogels to eye tissues were performed to compare performance vs. standard hydrogel in vivo.
- We observed adhesion improvement success in priming the scleral surface with tannic acid on one (R117) of the two rabbits in the two test studies.

3.F.2 SA6 SPECIFIC OBJECTIVE.

Specific Objectives	Month
1.) Identify (on-paper) a series of “best candidates” hydrogel-on-substrate patches to investigate	9
2.) Fabricate patches (different cross-linking densities and anchoring strategies) for testing	9-12
3.) Perform benchtop verification (Bose, IOP testing)	12-15

3.F.3 SA6 SIGNIFICANT RESULTS.

Thermally reversible Tannic Acid Pretreated Adhesive (tr-TAPA) hydrogels were prepared with different compositions and tested against different biological tissues of interest. Figure 12, (A) Chemical formula of tannic acid. (B) Screening of commercial available thermo-responsive polymers as the cohesive matrix based on sol-gel transition behavior, opacity and cohesion and adhesion strength. (C) Two-step deployment method of tr-TAPA formulated with different thermo-responsive polymers (TRP). ‘Cool glue’ refers to polymers showing a gel state above a critical temperature, and ‘warm glue’ refers to polymers showing a gel state below a critical temperature. (D) The versatile adhesion performance of tr-TAPA with altered TRPs and substrates. The substrates without TA pretreatment serve as the blank control group. An asterisk indicates a cohesive failure of the TRP gel. (E) The tr-TAPA joint between two Ca-alginate/PAAm hydrogel cylinders can withstand different deformations. Specifically, the tr-TAPA is formulated of 20 w/w% PNB_{0.1}, and used at room temperature.

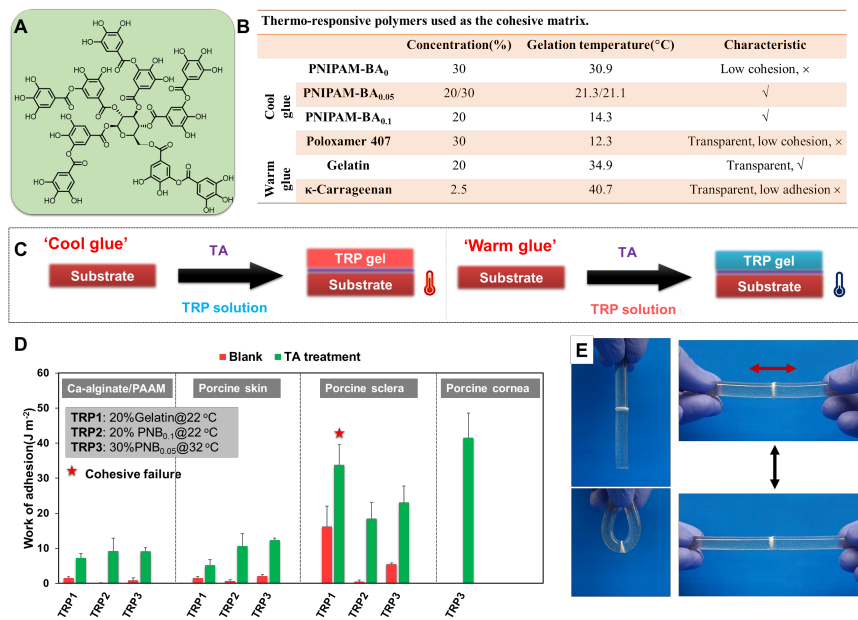
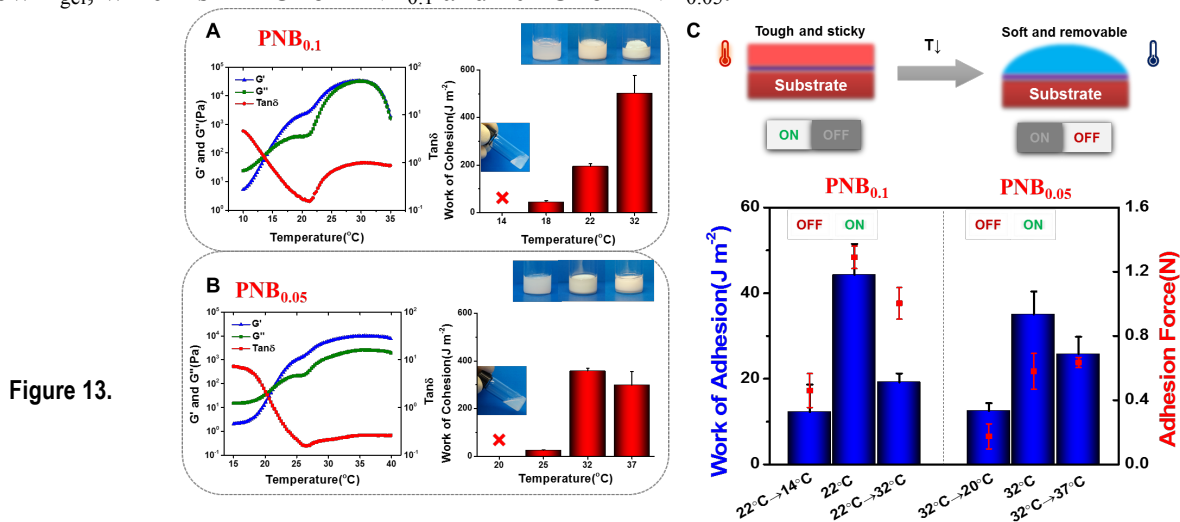
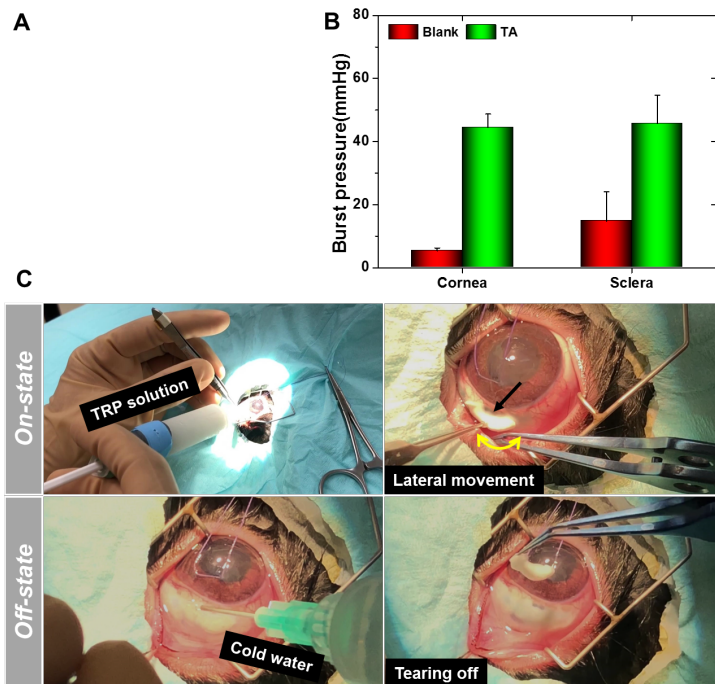


Figure 12. Study of the adhesive behavior of different hydrogel preparations with additives tested on different biological tissues.

Adhesion performance testing of PNIPAM-butylacrylate (PNBx) with ratios (x) of 0.1/0.9 and 0.5/0.5, Figure 13. Reversible phase behavior and adhesion of ‘cool glue’. Rheological properties and cohesion strength of PNB_{0.1}/water mixture (A) and PNB_{0.05}/water mixture (B). Rheology analysis is performed by oscillatory temperature ramp within the linear viscoelastic region, and gelation temperature (T_{gel}) is determined as the crossover point of storage modulus (G') and loss modulus (G''). Cohesion strength is measured by an isothermal tensile test, and expressed as work of cohesion (WOC). The photograph of the phase state at each temperature is given in the inset. (C) Simulated application procedure and outcome of ‘cool glue’ for bonding scleral tissue *ex vivo*. High adhesion in an *on-state* is triggered by raising the temperature above T_{gel} , which is 22 °C for PNB_{0.1} and 32 °C for PNB_{0.05} in this case, and low adhesion in an *off-state* is induced by cooling below T_{gel} , which is 14 °C for PNB_{0.1} and 20 °C for PNB_{0.05}.



Tannic acid improved hydrogel adhesion to scleral surface in vivo. Ex vivo and in vivo evaluation of the sealing capability and reversible adhesion of tr-TAPA to ocular tissue, **Figure 14.** (A) A custom-built intraocular pressure (IOP) device to measure the burst pressure of tr-TAPA to ocular wound *ex vivo*. (B) Burst pressure results of ‘cool glue’ to wounded ocular tissues *ex vivo*. The ‘cool glue’ is formulated of 30 w/w% PNB_{0.05}, and the environmental temperature is maintained in the range of 32-35 °C. The blank control group represents the ones without TA pretreatment. (C) A performance validation of tr-TAPA in vivo in a rabbit model. The PNB_{0.05} gel in place shows arbitrary lateral movement



together with the underneath tissue without detachment, and can be easily torn off by rinsing cold water.

Study of tannic acid (TA) absorption behaviors on tissue substrate ex vivo. **Figure 15**, (A) Photograph of porcine skin surface after sequential TA and TRP gel coating. The deposited TA layer is colorless, but can be validated by staining with transition metal ions such as Fe(III). (B) SEM observation of the skin tissue before and after TA coating from the surface and cross section views. The insets show zoom-in images. Scale bar is 100 μm , and 10 μm in the insets. (C) Cross sectional SEM image of the skin tissue bonded with tr-TAPA formulated of TA and PNB_{0.1} gel. Scale bar is 100 μm , and 10 μm in the zoom-in image. (D) Contact angle measurement of porcine skin surface after coating with TA of different concentration. (E) Quantitative measurement of TA absorption on porcine skin surface using a bicinchoninic acid (BCA) assay. (F) Hydrodynamic diameter of TA in aqueous solution determined by DLS measurement.

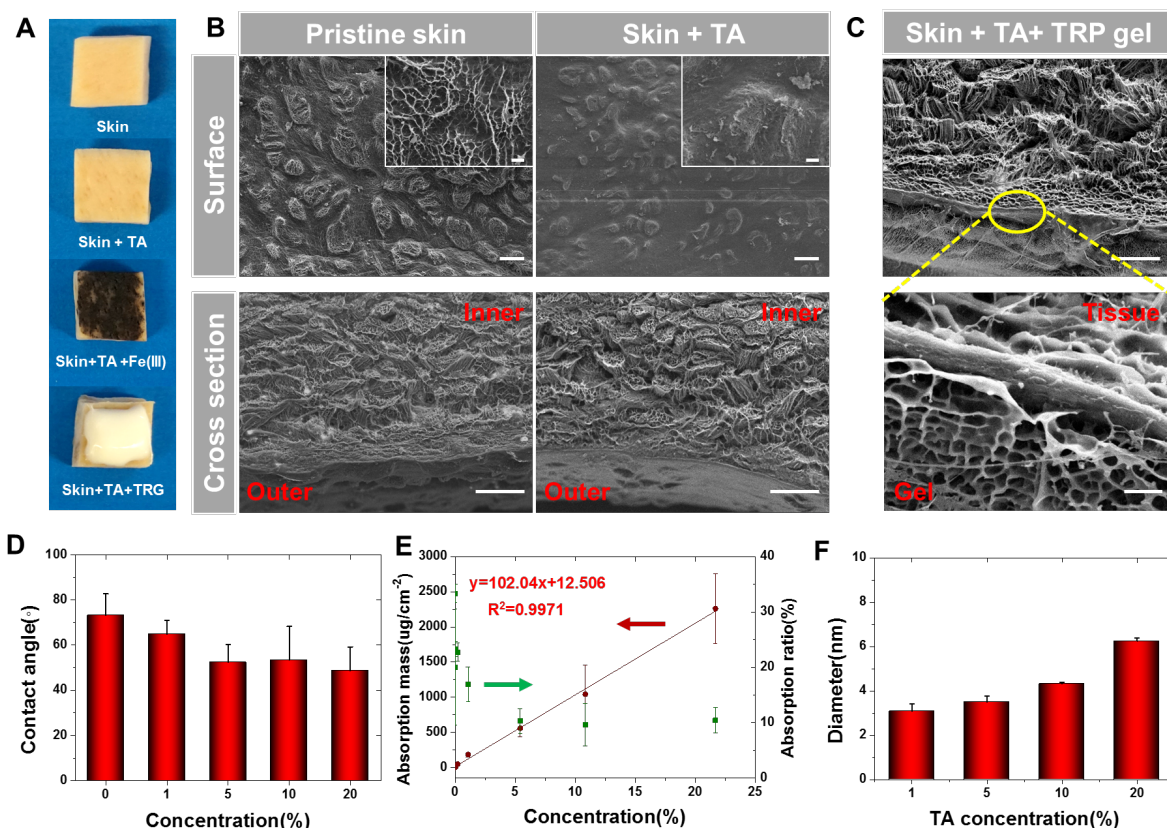


Figure 15.

The molecular interaction of TA with polymers and biomolecules. **Figure 16**, UV-vis absorption spectra of TA solution with a base titration(A) and an acid titration (C). (B) Proposed structural change of TA during acid/base titrations. Plot of the enthalpy change of injectant (ΔH , kJ mol⁻¹) against the molar ratio of the polymer pair, which is obtained by ITC titration of PNIPAM into gelatin (D), TA into gelatin (E) and TA into PNIPAM (F), respectively. The titration curve is fitted to a One Set of Sites binding model, and the thermodynamic parameters of the interactions between different polymer pairs are calculated and summarized in the table below (G). (H) Enthalpic and entropic contributions to free energy changes of the binding events between TA and different molecules estimated by ITC analysis.

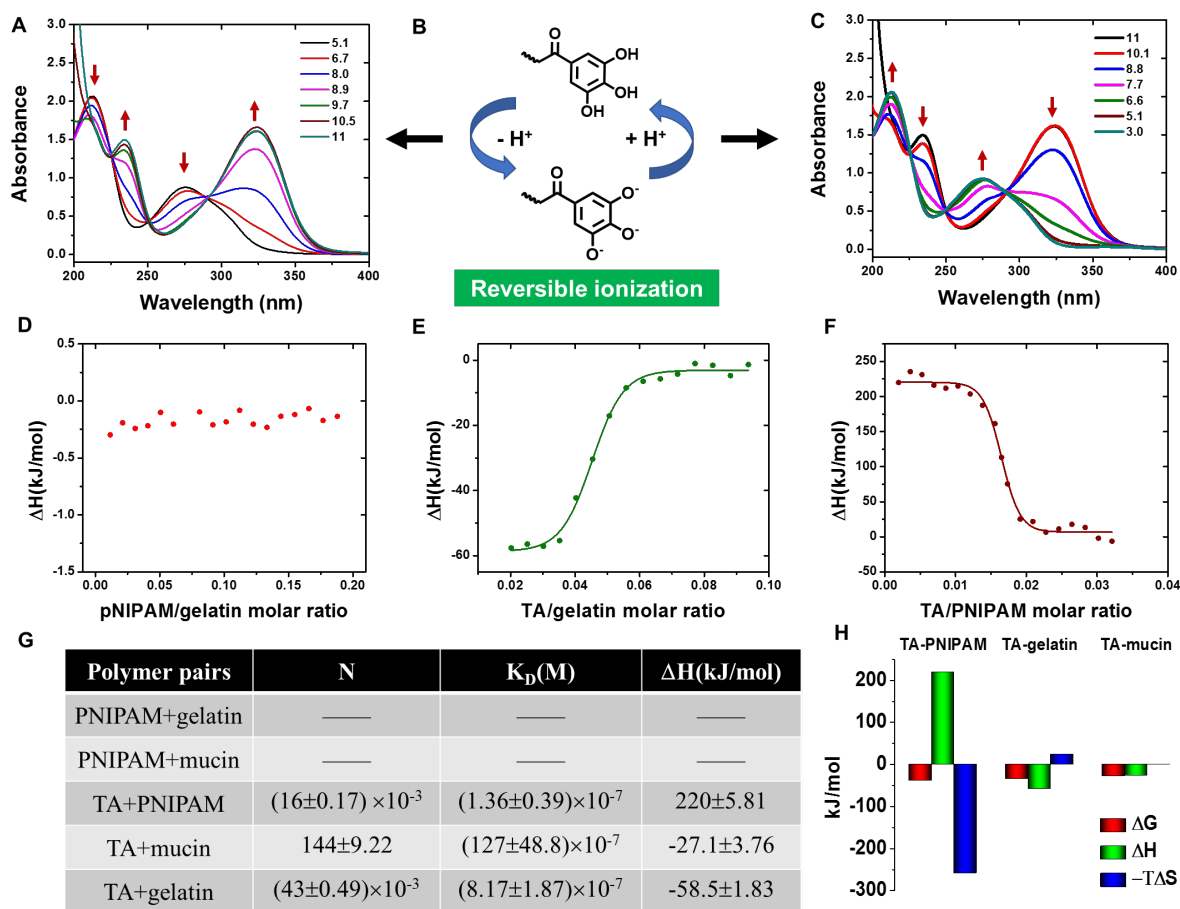


Figure 16.

We generated a proposed model of how the tannic acid promotes our copolymer hydrogel adhesion to tissues. **Figure 17**, Proposed molecular mechanism of reversible adhesion of tr-TAPA to tissue surface exemplified using poly(NIPAM-co-BA). The possible binding site within the TA-tissue interface, TA layer, TA-polymer interface and polymer gels are considered, and are classified into different intermolecular interactions.

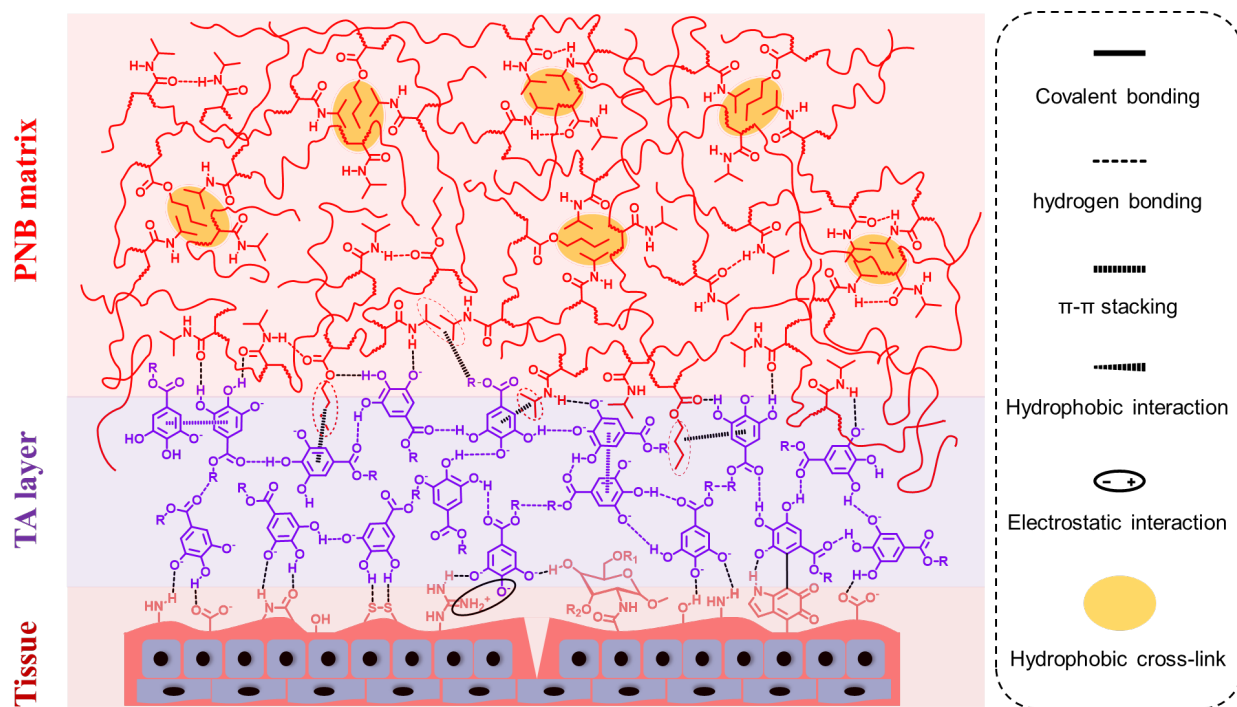


Figure 17.

3.F.4 **SA6 OTHER ACHIEVMENTS.**

- Nothing additional to report.

SPECIFIC AIM 7. RESEARCH & DEVELOPMENT OF UNSUPPORTED PATCH CHEMISTRY.

3.G.1 **SA7 MAJOR ACTIVITIES.**

In year 2, the following key activities were completed with respect to Specific Aim 7:

- The majority of the supported patch research findings (Specific Aim 6) pertain also to the work in Specific Aim 7.
- Hydrogel cohesion was characterized by molding uniaxial test pieces and performing conventional pull tests.

3.G.2 **SA7 SPECIFIC OBJECTIVES.**

Specific Objectives	Month
1.) Identify (on-paper) a series of “best candidates” hydrogel-on-substrate patches to investigate	9
2.) Fabricate patches (different cross-linking densities and anchoring strategies) for testing	9-12
3.) Perform benchtop verification (Bose, IOP testing)	12-15
4.) Perform preliminary in vivo validation study (rabbit model, n < 3) on versions that pass subtask 3	15-18

3.G.3 **SA7 SIGNIFICANT RESULTS.**

Hydrogel Patches were molded using a new casting-polymerization technique. The Thompson Group along with another USC group have been exploring the casting of hydrogel patches using a glass mold. Comonomer solution is loaded into the mold and polymerized in situ. One polymerized the hydrogel is then rinsed and hydrated. These first pieces, **Figure 18**, are the first pieces produced and will be in vivo tested in the next performance period.

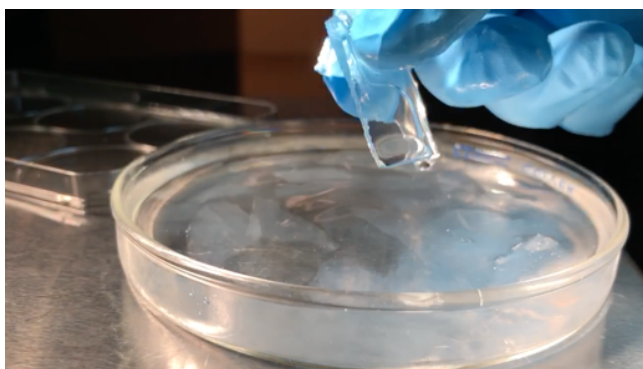


Figure18. Photograph of cast hydrogel patches soaking in petri dish with saline solution. Patch thicknesses were approx. 2-3mm.

3.G.4 **SA7 OTHER ACHIEVEMENTS.**

No additional achievements to report this period.

SPECIFIC AIM 8: RESULTS OF THE PRECIEEDING SPECIFIC AIMS WILL BE COMPILED INTO A DRAFT IDE PACKAGE FOLLOWED BY IDE PACKAGE AT THE END OF THE PROGRAM.

3.H.1 **SA8 MAJOR ACTIVITIES.**

Our draft regulatory package is awaiting release of our manufacturing development efforts. We have not made any significant efforts on Specific Aim 8, pending completion of these other activities.

3.H.2 **SA8 SPECIFIC OBJETIVES.**

No objectives/deliverables to report, as we are awaiting delivery of the Gen 2.0 prototypes from the contract manufacturers.

3.H.3 **SA8 SIGNIFICANT RESULTS.**

No significant results to report this period, as we are awaiting delivery of the Gen 2.0 prototypes from the contract manufacturers. We continue to have our regulatory consultant engaged and available to begin work.

3.H.4 **SA8 OTHER ACHIEVEMENTS.**

None. Nothing to report.

3.I.1 **TRAINING & PROFESSIONAL DEVELOPMENT OPPORTUNITIES.**

In 2017, the following graduate students made significant contributions to the efforts performed:

- Bin Li (Chemistry, Post-Doc): Dr. Li has taken over the majority of the polymer synthesis and characterization research. Recently, he has begun to learn how we perform our benchtop ex-vivo tissue tests with the porcine eye tissues. This is an expansion and augmentation of his skills from only polymer chemistry research.
- Alejandra Gonzalez PhD (Ophthalmology, Post-doc): Dr. Gonzalez joined the team in March 2018 with the primary responsibility of supporting the in vivo validation testing and data analysis. In addition to these efforts Dr. Gonzalez is helping with management of the manufacturing development efforts and regulatory strategy planning, which are expanding her skill sets.

3.J.1 **RESULTS DISSEMINATION.**

- Our primary efforts in year 2 have been focused on manufacturing development to deliver the Gen 2.0 system. We have not pursued any results dissemination activities. We do have a new manuscript that is in draft and will likely be submitted in early 2019.

3.K.1 **PLANS FOR NEXT REPORTING PERIOD.**

The following table lists all deliverables for completion by the next annual report

Specific Aim	Deliverables due by Q4 2019
1. Collect used needs and product specifications from combat medical community	• No new deliverables.

2. Hydrogel plug chemistry refinement to meet new needs	• Rebudget to allocate more funds to manufacturing development of the hydrogel. • Delivery of scaled up (100-300g) batch samples of hydrogel using contract manufacturing approach. • Verification testing of large batch hydrogel by USC, including monomer content assessment. • Development and validation of monomer purification/extraction approach (if required) • Build out of plan for scale up to GMP process (flex test of processing parameters, build out of quality control testing protocols) • Complete storage/package stability testing on hydrogels
3. Tool design for hydrogel deployment will be refined to meet new needs	• Rebudgeting of funds to allocate additional support to the injector tool production. • Complete delivery of the water ampule for verification testing. • Produce first SLA, rapid prototype Gen 2.0 injector tool for design review by USC, verification testing and approval to serial production. • Produce 15-20 rapid prototype SLA units for in vivo validation testing with the manufactured hydrogels. • Build out of project plan and refine cost estimates for mold tooling for manufactured units. • Draft Design history file for regulatory package & tracking
4. In vivo validation of Gen 2.0 Hydrogel Plug System	• Continue with in vivo evaluations on hydrogel patches and hydrogel additives produced by Thompson group. • Complete in vivo performance and safety validation of Gen 2.0 injector tool and hydrogel adhesive. (non-GLP testing)
5. GLP In vitro and in vivo biocompatibility validation	• Setup and perform GLP cytotoxicity and biocompatibility testing on selected Gen 2.0 concepts.
6. Research & Development of Supported Patch Chemistry	• Produce supported patch chemistry hydrogels for testing • Perform bench testing for direct adhesion to cadaveric porcine sclera • Perform in vivo testing for topical adhesive closure of ocular trauma
7. Research & Development of Unsupported Patch Chemistry	• Produce unsupported patch chemistry hydrogels for testing • Perform bench testing for direct adhesion to cadaveric porcine sclera • Perform in vivo testing for topical adhesive closure of ocular trauma
8. Compile a draft IDE package for submission to FDA for pre-submission meeting feedback.	• Compile all supporting information, documentation and data for preparation of draft IDE package. • Review results with regulatory consultant to identify missing materials and build plan for completing draft • Draft and review clinical trial documentation for pilot safety study. • Submit with questions to FDA for pre-submission meeting

4. IMPACT:

4.A. IMPACT ON PRINCIPAL DISCIPLINES DEVELOPMENT.

This project continues to make an impact in two different disciplines: 1) hydrogel chemistries 2) ocular trauma management.

Hydrogel Chemistries. The Thompson Group continues to conduct significant work in synthesizing a variety of different base hydrogel chemistries coupled with different additives, and then performed characterization studies on those formulations. This library of information is helping to expand the greater community's understanding of thermo-responsive hydrogels and how their properties can be modulated.

- Distinctive Contributions: Our first publication has shed some light on how different synthesis approaches have produced hydrogels with difference properties. Follow-on papers will be added to this knowledge base.
- Major Accomplishments & Innovations: We have identified which chemistries are optimal for implantation and occlusion of ocular trauma.
- Successes: We have published a preliminary paper and will be producing at least one more paper that focuses on relating performance characteristics to chemistries.
- Changes in Behaviors/Practices. None.

Ocular Trauma Management. Previously we have held workshops to get our technology in the hands of end users. Once the new Gen 2.0 system is produced, our plan is to organize another workshop to put our new design system in the hands of clinical end users. The goal of these workshops is to familiarize

- Distinctive Contributions: We have proposed a novel approach to managing ocular trauma which expedites preliminary intervention and allows intervention under significantly austere environments.
- Major Accomplishments & Innovations: We have allowed end users to test our concept and many have been receptive to the idea of rethinking how ocular trauma is managed.
- Successes: We have advanced our preliminary concept an approach into a 2nd stage of refinement and development.
- Changes in Behaviors/Practices. None to date.

4.B. IMPACT ON OTHER DISCIPLINES.

Nothing to report this period. We have received inquiries about employing our adhesive sealant for other (non-ophthalmologic) penetrating injuries management.

4.C. TECHNOLOGY TRANSFER IMPACT.

Medical device technology commercialization is a primary motivation of this project. We continue to build an intellectual property portfolio which is already under examination by the USPTO. This year we started speaking with venture capital groups as we start to plan for translating this technology out of the university. We continue to have dialog with larger medical device manufacturers about our development efforts. The USC team plans to leverage our experience in

medical technology commercialization to begin to translate this technology from the university into a commercial entity, once we have de-risked the technology to an acceptable level.

4.D. SOCIETAL IMPACT.

The USC Team believes this project, if successful, may have at least one impact on society beyond the scientific and technological contributions.

Impact on Trauma Management Paradigms. If successful, this technology would enable healthcare to rethink how healthcare is administered for ocular trauma patients and in particular in mass casualty events where time, resources and facilities may be heavily strained. This technology allows interventions to be performed in austere environments which would free up resources and facilities to manage other life threatening conditions.

5. CHANGES/PROBLEMS:

CHANGES IN APPROACH.

We have not encountered any challenges that have required a change in our approach. We are continuing with the same approach.

ACTUAL/ANTICIPATED PROBLEMS/DELAYS.

Our manufacturing development has encountered small technical challenges which have required additional time and effort to deliver the Gen 2.0 hydrogel and the Gen 2.0 injector tool. For example, we have found that the exothermic reactions of copolymer polymerization scale non-linearly with increasing volume. This required additional experiments to dial in the reaction parameters to produce the correct polymer molecular weight distribution. These are not significant problems, however they have added a few months to our original project plan.

We have also been slightly delayed with our project because of a need to rebudget our program to allocate more support to our manufacturing development. This is discussed below.

SIGNIFICANT CHANGES TO EXPENDITURES.

The hydrogel manufacturing development and our injector tool manufacturing development have encountered additional challenges in development that have added extra costs to these efforts. We have looked at the balance of our budgets and have made a plan to rebudget and reallocate some of our budget for personnel and travel to cover the additional costs. We anticipate needing approximately \$45,000 each for the hydrogel manufacturing development and the injector tool production to get us to begin GLP testing. The details will be submitted in a rebudget request in early Year 3, following our extension request.

SIGNIFICANT CHANGES IN USE OF VERTEBRATE ANIMALS.

None.

HUMAN SUBJECTS.

Not applicable.

SIGNIFICANT CHANGES TO CARE AND USE OF VERTEBRATE ANIMALS.

We have begun the process of securing approvals for our proposed in vivo safety and performance assessment studies (rabbit model). No significant changes to report.

CHANGES TO BIOHAZARD OR SELECT AGENTS.

Not Applicable.

6. PRODUCTS:**PUBLICATIONS, CONFERENCE PAPERS, PRESENTATIONS.****JOURNAL PUBLICATIONS.**

Bayat N, Zhang Y, Falabella P, Menefee R, Whalen JJ, 3rd, Humayun MS, Thompson ME. **A Reversible Thermoresponsive Sealant for Temporary Closure of Ocular Trauma.** *Sci Transl. Med.* 2017 Dec 6; 9(419).

ONE-TIME PUBLICATIONS (BOOKS, OTHER PERIODICALS).

Nothing to report.

OTHER PUBLICATIONS, CONFERENCE PAPERS AND PRESENTATIONS.

No publications or presentations were given in year 2, as we are seeking to reallocate travel budget towards the additional M&S costs associated with our manufacturing development.

WEBSITE(S) OR OTHER INTERNET SITE(S)

The team's Science Translational Medicine article led to several follow-up press notifications published on a variety of websites in Q4 2017 and through the beginning of 2018. The university posted a front page piece about this project on the University of Southern California's main homepage (<http://www.usc.edu>), **Figure 19**. The additional webpage publications are listed in the hyperlinks that follow.



Figure 19.

List of subsequent press releases that were generated from the release of this publication are listed below:

December 6, 2017: USC university press release:

<https://news.usc.edu/132588/a-new-portable-gel-that-could-save-an-injured-eye/>

December 6, 2017: USC Keck School of medicine press release:

<http://hscnews.usc.edu/a-new-portable-gel-that-could-save-an-injured-eye/>

December 6, 2017: Ureka Alert press release:

https://eurekalert.org/pub_releases/2017-12/uosc-cei120417.php

December 6, 2017 on HealthDay: <https://consumer.healthday.com/eye-care-information-13/eye-and-vision-problem-news-295/coming-soon-a-gel-that-could-help-save-soldiers-eyes-729155.html>

December 6, 2017 on RT: <https://www.rt.com/news/412216-reversible-superglue-eye-injuries/>

December 6, 2017: Newswise press release:

<https://www.newswise.com/articles/combating-eye-injuries-with-a-reversible-superglue-seal>

December 7, 2017 on Optometry Today: <https://www.aop.org.uk/ot/science-and-vision/research/2017/12/07/sealing-battlefield-injuries-with-reversible-superglue>

December 7, 2017 on IFL Science: <http://www.iflscience.com/health-and-medicine/injecting-smart-glue-could-be-a-temporary-fix-for-severe-eyeball-injury-on-the-battlefield/>

December 7, 2017 on Science Alert: <http://www.sciencealert.com/superglue-gel-protects-wounded-eyeballs-saving-sight-vision>

December 7, 2017 on Med India: <http://www.medindia.net/news/healthinfocus/gel-to-fix-eye-injuries-175310-1.htm>

December 7, 2017 on Med Gadget: <https://www.medgadget.com/2017/12/novel-transforming-hydrogel-treats-emergency-battlefield-eye-injuries.html>

December 8, 2017 on Alphr: <http://www.alphr.com/science/1007922/superglue-for-your-eyeballs-is-now-a-thing>

December 8, 2017 on Digital Trends: <https://www.digitaltrends.com/cool-tech/injured-eyeballs-superglue/>

December 8, 2017 on Press Trust of India: <https://economictimes.indiatimes.com/magazines/panache/future-of-health-this-temperature-sensitive-gel-treatment-could-seal-eye-injuries/articleshow/61981314.cms>

December 8, 2017 on Zee News: <http://zeenews.india.com/health/scientists-just-developed-a-gel-to-treat-eye-injuries-2064219>

December 9, 2017 on International Business Times: <http://www.ibtimes.co.uk/eyeball-superglue-that-washes-off-water-can-prevent-vision-loss-1650711>

December 9, 2017: CBS This Morning (aired on more than 150 CBS affiliate stations): <http://mms.tveyes.com/PlaybackPortal.aspx?SavedEditID=51cad940-ad20-4ef9-9205-070b3d197969> (also on YouTube at timepoint 3:50: <https://www.youtube.com/watch?v=qTysmI-Ptqs>)

December 12, 2017 on Eye Smart: <https://eyesmart.com.au/newsarticle/5420-novel-gel-developed-to-treat-eye-injuries>

December 21, 2018 “Eye on Vision” Radio Interview 89.3 WYPL-FM <http://eyeonvision.blogspot.com/2017/12/hydrogel-for-battle-wounds-and-plextalk.html>

January 9, 2018 “Top of Mind with Julie Rose” BYU Radio <http://www.byuradio.org/episode/492c99ad-95ff-4084-bcb7-8cb71ddd56a0?playhead=2443&autoplay=true>

March 1, 2018 interview article in EyeNet (AAO) Magazine <https://www.aao.org/Assets/2c6be5aa-b1f5-4db1-acec-309169a2f8b5/636539016536730000/march-2018-eyenet-pdf?inline=1>

March 1, 2018 Eye World Magazine <https://www.eyeworld.org/heat-activated-reversible-and-temporary-new-sealant-works-ocular-trauma>

TECHNOLOGIES OR TECHNIQUES.

Our efforts continue to drive delivery of a medical device technology to temporarily treat ocular trauma. This will be a medical device and the details have been explained elsewhere in this report.

INVENTIONS, PATENT APPLICATIONS OR LICENSES.

Our provisional application filed last year was converted to a full application.

OTHER PRODUCTS.

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

INDIVIDUALS ON THE PROJECT.

<i>Name:</i>	<i>Mark S. Humayun MD PhD</i>
<i>Project Role:</i>	<i>Principal Investigator, Professor</i>
<i>Research Identifier:</i>	<i>ORCID: 0000-0002-5830-5208</i>
<i>Nearest person month worked:</i>	<i>1</i>
<i>Contribution to Project:</i>	<i>Dr. Humayun provides clinical expertise and guidance and overall oversight on activities of the program.</i>
<i>Funding Support:</i>	<i>N/A.</i>
<i>Name:</i>	<i>Mark E. Thompson PhD</i>
<i>Project Role:</i>	<i>Co-Investigator, Professor</i>
<i>Research Identifier:</i>	<i>ORCID: 0000-0002-7764-4096</i>
<i>Nearest person month worked:</i>	<i>1</i>
<i>Contribution to Project:</i>	<i>Dr. Thompson is responsible for overseeing hydrogel synthesis, hydrogel adhesion properties R&D, and supporting the transition to manufacturing.</i>
<i>Funding Support:</i>	<i>N/A.</i>
<i>Name:</i>	<i>John J. Whalen PhD</i>
<i>Project Role:</i>	<i>Co-Investigator, Assistant Professor</i>
<i>Research Identifier:</i>	<i>ORCID: 0000-0002-5202-4747</i>
<i>Nearest person month worked:</i>	<i>6</i>
<i>Contribution to Project:</i>	<i>Dr. Whalen is responsible for project management of the project, setup and execution of the in vivo testing; and transition towards manufacturing and regulatory package preparation.</i>
<i>Funding Support:</i>	<i>N/A.</i>
<i>Name:</i>	<i>Alejandra Gonzalez PhD</i>
<i>Project Role:</i>	<i>Post-doctoral Research Assistant</i>
<i>Research Identifier:</i>	<i>N/A</i>
<i>Nearest person month worked:</i>	<i>3</i>
<i>Contribution to Project:</i>	<i>Dr. Gonzalez is responsible for conducting the in vivo validation studies of the hydrogel injectable adhesives and the hydrogel patches. She is performing some of the surgical procedures and the imaging procedures as well as IOP monitoring.</i>
<i>Funding Support:</i>	<i>N/A</i>
<i>Name:</i>	<i>Bin Li PhD</i>
<i>Project Role:</i>	<i>Post-doctoral Research Assistant</i>
<i>Research Identifier:</i>	<i>N/A</i>
<i>Nearest person month worked:</i>	<i>6</i>
<i>Contribution to Project:</i>	<i>Dr. Li has synthesized many of the new additive hydrogel chemistries and has been performing many of the characterization studies on the new hydrogels he prepares.</i>
<i>Funding Support:</i>	<i>N/A.</i>

CHANGES IN ACTIVE SUPPORT FOR PI OR KEY PERESONNEL.

Nothing to report.

PARTNERING ORGANIZATIONS.

No other organizations. Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

QUAD CHART.

Please see the attached 2017 annual quad chart in the Appendix.

9. APPENDICES:

CONTENTS:

Appendix 1: Annual Report Quad Chart 2018 (Year 2)

Thermoresponsive Reversible Adhesive for Temporary Intervention of Ocular Trauma II

ERMS/Log Number
W81XWH-16-C-0086



PI: Mark S. Humayun MD PhD

Org: University of Southern California

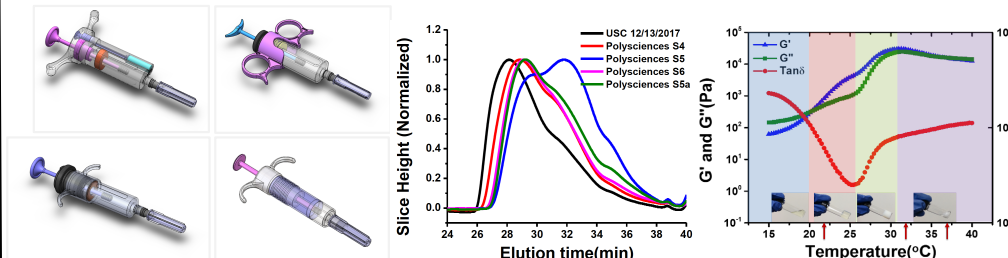
Award Amount: \$1,599,999

Study/Product Aim(s)

- Refine hydrogel adhesive & tool design to optimize for clinical testing
- Conduct preclinical feasibility validation on Gen 2.0 system
- Conduct GLP biocompatibility on Gen 2.0 hydrogel to support regulatory submission
- Source vendors & roadmap production strategy
- Prepare regulatory package to initiate FDA IDE submission process.

Approach

This program advances the commercialization of a prototype hydrogel and tool system designed to temporarily occlude open globe injuries. This second phase of development includes: design refinement through end user feedback from army, road-mapping of component production/ manufacturing, collection of data to support regulatory submission and ultimately preparation of a regulatory package in support of an FDA investigational device exemption application.



- Four injector tool concepts have been created based on the specification requirements from the USC IBT team. These will be down-selected to one.
- GCP scans of first series of manufactured copolymer hydrogel adhesive are approaching the physical properties of the USC synthesized samples.
- Our animal protocol was submitted to IACUC with the requested modifications from ACURO for approval.
- The Thompson Group continues exploration of co-polymer hydrogel modification to enhance surface adhesion strength

Timeline and Cost

ACTIVITY	2016	2017	2018	
User needs/prod. specs from military physicians				
Hydrogel chemistry refinement				
Tool design refinement				
Gen 2.0 hydrogel in vivo validation				
GLP in vivo/in vitro validation studies				
R&D to develop supported hydrogel patch				
R&D to develop unsupported hydrogel patch				
Compile IDE package for submission				
Estimated Budget (\$K)	\$1,600	\$53	\$758	\$117

Goals/Milestones

CY16 Goal – Program Initiation/ Setup & Planning

- ☒ Purchase, setup and initiate calibration of new rheometer
- ☒ Initiate new polymer chemistry production for user testing
- ☒ Engage Water Reed Ophthalmology to plan for first workshop

CY17 Goals – System validation

- ☒ Conduct first user feedback workshop with army
- ☒ Identify Gen 2.0 hydrogel and tool for validation testing
- ☒ Initiated engagement w/ reg. strategist to produce FDA reg. package

CY18 Goal – Planning for future clinical phase.

- ☐ Produce Gen 2.0 hydrogel and tool for validation testing
- ☐ Setup and conduct in vivo validation testing & compile reg. pack
- ☐ Compile all data into FDA regulatory package and submit.

Comments/Challenges/Issues/Concerns

- Manufacturing development costs will require a rebudgeting increase

Cal. Year Budget Expenditure, to Date

- Projected Expenditure: \$925,000
- Actual Expenditure: \$927,791

Updated: (September 2018)