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TITLE: Multicenter Clinical Trial of Keratin Biomaterial for
Peripheral Nerve Regeneration

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14. ABSTRACT Common injuries sustained by war fighters in Iraq and Afghanistan result from blast and shrapnel wounds which cause extensive damage to skin, bones, and nerves. The management of damaged peripheral nerves is challenging for patients and surgeons. Peripheral nerve transection injuries may fail to regenerate even when managed surgically. These injuries are associated with long term disability and impaired function. Nerve guidance conduits have been developed for use in surgery to bridge the gap between transected nerve ends and to support nerve regeneration. A team of scientist and clinicians at Wake Forest School of Medicine has developed a keratin biomaterial hydrogel that can be used as luminal filler in nerve guidance conduits to facilitate nerve regeneration. Studies in mice, rabbits, and nonhuman primates have established the feasibility of this keratin hydrogel to promote nerve regeneration. A Phase I prospective, randomized trial is designed to compare nerve regeneration in patients sustaining peripheral nerve injuries treated either with keratin hydrogel and a nerve conduit or with a nerve conduit alone. The clinical trial will be initiated as soon as the FDA provides an IND for the keratin biomaterial hydrogel.					
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INTRODUCTION

While body armor, advanced resuscitation techniques, rapid transportation of wounded soldiers, and damage control surgery have made major contributions to saving lives on the battle field, more can be done to improve the outcomes for soldiers who sustain extremity injuries such as traumatic nerve transections. Extremity trauma with nerve injury can be associated with long term functional limitations and impairments (Rosen 2000; Ruijs 2005). Damaged peripheral nerves may fail to regenerate in patients even when they are managed by surgical intervention. The use of sensory nerve autografts for nerve repair is considered to be the “gold standard”; however, this procedure is associated with donor site morbidity and the possibility that there may be insufficient donor nerve available for extensive repairs involving several nerves (Lohmeyer 2009).

To avoid the issues associated with the use of autografts, nerve guidance conduits have been developed to bridge the gap between the transected nerve ends and to support nerve regeneration (Taras 2008). A team of scientists and clinicians at Wake Forest School of Medicine has developed a keratin biomaterial hydrogel that can be used as luminal filler in nerve guidance conduits in order to facilitate nerve regeneration. Preliminary studies in mouse, rat, rabbit and non-human primate models have established the feasibility and clinical relevance of using a keratin biomaterial filler to promote nerve regeneration (Apel 2008, Hill 2011, Lin 2012, Sierpinski 2008, Pace submitted).

The objective of the clinical trial is to conduct a combined Phase I prospective randomized two center trial that will follow patients who are treated for traumatic peripheral nerve transections. Patients will be randomized to one of two treatment groups in order to compare nerve regeneration following two methods of nerve repair. One group of patients will undergo nerve repair using the keratin hydrogel as filler for a commercially available nerve conduit, and the other group will undergo nerve repair using nerve conduit alone. This trial also will document the safety of the keratin hydrogel. The specific aim of this clinical trial is to determine the safety and efficacy of keratin hydrogel biomaterial as luminal filler in nerve conduits used to manage traumatic peripheral nerve transection.

BODY

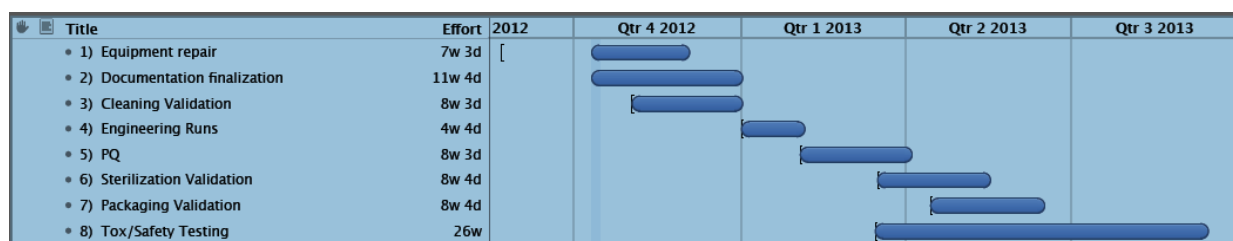
During the past year, our research team has been working with the FDA to obtain a designation for the keratin biomaterial hydrogel to be used in our clinical trial and define the path toward approval of the product. It was initially planned that approval for clinical investigation would best fall under an Investigative Device Exemption (IDE) application but after filing a Request for Designation (RFD) with the FDA’s Office of Combination Products, the KeraGenics Nerve product was designated a biologic. Despite the delays inherent in the RFD process and the unique challenges of regulatory approval for biologics, Dr. Van Dyke (Wake Forest School of Medicine) and Dr. Luke Burnett (KeraNetics, the manufacturer of the keratin hydrogel) have moved the process forward by first meeting with representatives from the FDA, the Center for Drug Evaluation Research (CDER), the Center for Biologics Evaluation Research (CBER), and the Center for Devices and Radiological Health (CDRH) on May 1, 2012. As a result of this meeting, clarity was provided by the Agency on a path forward that would include the filing of an Investigative New Drug (IND) application rather than the IDE. The steps required to obtain the data necessary for a complete IND application were outlined at the meeting.

The plan agreed upon for IND filing for the keratin hydrogel included five main parts.

- 1) The Phase 0 trial included as part of the original clinical trial was designed to evaluate the safety of subcutaneous injection of the gel. This Phase 0 trial was considered to be unnecessary and was eliminated from the trial design. This will result in time savings as no additional patient/volunteer enrollment or post-study waiting period will be necessary.

- 2) The conduits used for the trial will be prefilled with the keratin hydrogel, lyophilized, and packaged for terminal sterilization, rather than filling conduits with sterile hydrogel during surgery as had been originally proposed. This will allow the product to be terminally sterilized and increase shelf-life, thereby simplifying the logistics of the clinical trial vis-à-vis supply of test materials.
- 3) The FDA agreed to review the preclinical animal testing from KeraNetics.
- 4) Required purity and potency tests of the keratin hydrogel were defined: 1. Analytical tests to determine purity and 2. A cell adhesion assay to determine potency.
- 5) The FDA agreed on the design of the fate and distribution study.

Following this FDA meeting, the team at Wake Forest School of Medicine and the CDMRP developed a revised statement of work and a budget to cover the costs of the additional studies requested by the FDA. In July 2012, an additional contract between Wake Forest and the CDMRP was initiated that will provide the funding necessary to comply with the current requests from the FDA in order to obtain an IND for the initiation of the Phase I clinical trial. The CDMRP provided more than \$250,000 of additional funding to cover the majority of the added preclinical costs, with the remaining funding coming from cost-sharing by KeraNetics and WFUSM. A scope of work and timeline for these additional preclinical tests is shown below.



This places the completion of preclinical studies required for the IND application in late 2013 with the formal IND to follow soon thereafter. Provided that the IND is approved without conditions that would require additional testing, the phase I portion of the clinical trial would begin at the end of 2013 (the phase 0 study having been eliminated). Our study team will request another meeting with FDA prior to submitting the formal IND to review these preclinical data and attempt to mitigate the risk of additional questions arising, in an effort to further streamline the process and compress this proposed timeline.

As soon as the IND is available, our team will be able to obtain final approval for the study protocol from the Copernicus Group, an independent review board that has previously granted conditional approval for the protocol. Then, the protocol will be submitted to the University of Virginia School of Medicine IRB (the second study site) and the HRPO for approval.

The Standard Operating Procedures (SOP) Manual and study data forms will be finalized. Training of study personnel at both study sites will be completed, and the study protocol will be initiated at both study sites.

KEY RESEARCH ACCOMPLISHMENTS

- Pre-IDE package submitted to the FDA, June 8, 2010.
- September 28, 2010: Submission of the clinical protocol to the Copernicus Group, an independent IRB located in Research Triangle Park, North Carolina. Due to the conflict of interest policies at the Wake Forest School of Medicine, Dr. Li was asked to send the protocol to an independent review board.
- October 13, 2010: The Copernicus Group granted conditional approval of both Phase 0 and Phase I/II protocols pending the assignment of an IDE number or confirmation of 510K justification acceptance from the FDA.

- October 18, 2010: FDA feedback provided to Dr. Li and Dr. Van Dyke indicated that the FDA's main concern was whether the keratin hydrogel should be classified as a device or a biologic. The FDA suggested that a meeting between the FDA and Drs. Li and Van Dyke should take place; however, the primary reviewer at the FDA was unable to identify a date for a meeting.
- A Request for Designation (RFD) was submitted to the FDA in May 3, 2011. Based on this submission date, the FDA had until July 9, 2011 to reply to the request.
- July 7, 2011: The FDA designated the keratin hydrogel biomaterial as a "therapeutic biological product." The product has been assigned to the Center for Drug Evaluation and Research (CDER) as the lead agency for premarket review and regulation based on the keratin hydrogel's primary mode of action.
- On July 18, 2011, there was a conference call with Miriam Darnell, PhD, Science Officer for Grants Management and the investigators at Wake Forest (Zhongyu Li, MD, PhD, Mark Van Dyke, PhD, and Beth Paterson Smith, PhD). During the call, the submission of the pre-IND package to the FDA and the scheduling of a pre-IND meeting with the FDA were discussed. In addition, the expected request by the FDA for a fate and distribution study of the keratin hydrogel was discussed. Because funding will be required to complete these studies, possible funding sources were discussed.
- July 25, 2011: Dr. Darnell sent an email regarding the possibility of re-budgeting the grant funding to cover the estimated \$250,000 required for the fate and distribution studies in an animal model. Dr. Darnell requested a written statement describing the anticipated animal study, the requirement for the study, the study timeline, and any other pertinent information. These issues also need to be discussed with Ms. Susan Dellinger, the USAMRAA Grants Officer who has the final authority on issues of statement of work and budgets.
- July 25, 2011: Dr. Van Dyke responded to Dr. Darnell's email to provide information that a contract research organization (CRO) had been contacted regarding a quote to cover the costs of the fate and distribution study. Dr. Van Dyke also outlined the reasons why he requested a representative from CDMRP be present at the pre-IND meeting with the FDA.
- July 26, 2011: Dr. Van Dyke sent an email to Dr. Darnell describing the fate and distribution studies including the four to six month period needed to complete the study at a cost of approximately \$250,000.
- August 1, 2011: An email was sent to Brian Garland, Administrative Coordinator of the Human Research Protection Office at USAMRMC containing the June 23, 2011 Clinical Trial Quarterly Technical Progress Report to provide him with the status of our progress on the clinical trial.
- August 8, 2011: The request for a pre-IND meeting with the FDA was submitted.
- On August 19, 2011, Dr. Darnell sent an email to Christopher Baker, CIV USA MEDCOM USAMRAA regarding the request for re-budgeting to cover the costs of preclinical animal studies to determine the fate and distribution of the keratin hydrogel. On August 23, 2011, Mr. Baker requested a revised budget and statement of work for consideration.
- Beginning August 23, 2011, we worked with our Office of Research to develop the re-budgeting plan and statement of work required to complete the keratin hydrogel fate and distribution studies.
- August 31, 2011: The FDA sent a letter providing the date for the pre-investigational new drug application of KeraGenics Nerve. The meeting was scheduled for November 8, 2011 from 12:00-1:00 p.m. in Silver Spring, Maryland. Miriam Darnell, PhD the Science Officer for Grants Management and LTC(P) Leggit, the director of CDMRP agreed to attend this meeting.
- October 7, 2011: The Type B meeting package for KeraNetic's KeraGenics™ Nerve (PIND No. 113077) was sent to Ms. Daughterty at the FDA.
- October 31, 2011: The attorneys at Hogan Lovells received a telephone call from the FDA cancelling the FDA meeting scheduled for November 8, 2011. This meeting cancellation occurred because the FDA was uncertain about how to coordinate our request for the nerve application for the keratin hydrogel given that

there was a co-pending application for a keratin product for use in burn patients. The FDA determined a path for the burn device and is now working on the designation of the nerve application to be used in our clinical trial to study nerve regeneration. An internal FDA meeting was scheduled for January 8, 2012. After this meeting, feedback is expected regarding our request for designation of the keratin hydrogel for use in nerves.

- March 9, 2012: Dr. Van Dyke emailed Dr. Darnell to update her on the conversations he had with the FDA. The FDA is involved in internal discussions regarding the designation of the keratin biomaterial hydrogel. The FDA has scheduled a meeting for March 26, 2012 to finalize recommendations on the designation of the keratin biomaterial.
- May 1, 2012: Dr. Van Dyke and Dr. Luke Burnett (KeraNetics) met at the FDA with representatives from the Center for Drug Evaluation Research (CDER), the Center for Biologics Evaluation Research (CBER), and the Center for Devices and Radiological Health (CDRH) to clarify the designation of the keratin hydrogel. During this meeting, the parties agreed on the next steps required for an IND package for the keratin biomaterial hydrogel.
 - a. The subcutaneous injection trial (Phase 0) was eliminated from the trial design. The FDA determined that the Phase 0 trial was unnecessary.
 - b. Preparation of the keratin hydrogel for use in the clinical trial was discussed. The nerve conduits will be prefilled with keratin; these prefilled conduits will be lyophilized and packaged for terminal sterilization. The use of the prefilled conduits will allow the surgeon to rehydrate the conduit a few minutes prior to implantation. The FDA agreed that this preparation was appropriate because they prefer terminal sterilization of products.
 - c. The FDA agreed on the following purity and potency assays to be completed before beginning the Phase I clinical trial: 1) analytical tests to determine purity (size exclusion chromatography for molecular weight, amino acids analysis, ELISA for protein identification, and gel rheology) and 2) a cell adhesion assay using a rat Schwann cell line to determine the potency of the hydrogel.
 - d. The FDA discussed their preferred experimental design for preclinical animal testing. FDA agreed to review the preclinical data from KeraNetics.
 - e. The FDA agreed on the design of the fate and distribution study. Labeled keratin gel will be placed inside nerve conduits. The ends of the conduits will be closed, and the conduits will be implanted in rat muscle. The rats will be followed to determine the fate and distribution of the labeled keratin biomaterial hydrogel. Depending on the outcomes of this study, additional pharmacokinetic studies may be warranted. The FDA will review the results of the fate and distribution study and will determine if any additional studies will be required.
- May 31, 2012: A revised SOW and budget to reflect the extra funds needed to complete the testing required by the FDA were developed. Wake Forest agreed to provide funding up to the difference of \$107,244 between the total costs of the required studies (\$363,244) and the \$256,000 available from the CDMRP. A letter confirming this arrangement between CDMRP and Wake Forest School of Medicine was sent to Dr. Darnell. In addition, documents were provided to document the breakdown of costs, the timeline for performance of preclinical work for the FDA, and the cost sharing information provided by KeraNetics.
- June 29, 2012: A request was submitted to CDMRP requesting additional funding to perform the purity and potency assays and the fate and distribution studies on the keratin hydrogel.
- July 31, 2012: This is the effective date for the amendment of the solicitation/modification of the contract from CDMRP that provides funding to perform the FDA-requested fate and distribution studies, the analytical tests, and the cell adhesion assay. These studies must be completed in order to obtain an IND from the FDA to initiate the clinical trial.

REPORTABLE OUTCOMES

Publications

Apel PJ, Garrett JP, Sierpinski P, Ma J, Atala A, Smith TL, et al. Peripheral nerve regeneration using a keratin-based scaffold: long-term functional and histological outcomes in a mouse model. *J Hand Surg Am* 2008 Nov;33(9):1541-7.

Hill P, Apel PJ, Barnwell J, Smith TL, Koman LA, Atala A, Van Dyke M. Repair of peripheral nerve defects in rabbits using keratin hydrogel scaffolds. *Tissue Eng Part A* 2011;17(11-12):1499-505

Lin YC, Ramadan M, Van Dyke M, Kokai LE, Philips BJ, Rubin JP, Marra KG. Keratin gel filler for peripheral nerve repair in a rodent sciatic nerve injury model. *Plast Reconstr Surg* 2012;129:67-78.

Pace LA, Plate JF, Mannava S, Barnwell JC, Koman LA, Li Z, Smith TL, Van Dyke M. A human hair keratin hydrogel enhances median nerve regeneration in non-human primates: An electrophysiological and histological study. Submitted to *Science Translational Medicine*.

Sierpinski P, Garrett J, Ma J, Apel P, Klorig D, Smith T, et al. The use of keratin biomaterials derived from human hair for the promotion of rapid regeneration of peripheral nerves. *Biomaterials* 2008 Jan;29(1):118-28.

Presentations

Pace LA, Plate JF, Mannava S, Barnwell JC, Koman LA, Li Z, Smith TL, Van Dyke M. "Peripheral Nerve Repair in Non-human Primates" **Society of Military Orthopaedic Surgeons**: San Diego, CA 12/2011

Pace LA, Plate JF, Mannava S, Barnwell JC, Koman LA, Li Z, Smith TL, Van Dyke M. Peripheral nerve regeneration in non-human primates using a keratin biomaterial hydrogel. **Tissue Engineering and Regenerative Medicine International Society**; Houston, Texas. December 11-14, 2011.

Smith T, Koman LA, Van Dyke M. Translation of biomaterial technologies from academic research to commercial use. **Clinical Orthopaedic Society Annual Meeting**. Charleston, SC. September 29-October 1, 2011

Pace LA, Hill P, Garrett J, Ma J, Apel P, Mannava S, Barnwell J, Smith B, Li Z, Koman LA, Smith T, Van Dyke M. Clinical translation of a keratin biomaterial hydrogel for nerve repair. **Society for Biomaterials Annual Meeting**. Orlando, FL. April 13-16, 2011

Pace LA, Plate JF, Mannava S, Barnwell JC, Koman LA, Li Z, Smith TL, Van Dyke M. "Clinical Translation of a Keratin Biomaterial Hydrogel for Nerve Repair" **North Carolina Tissue Engineering and Regenerative Medicine Society**: Raleigh, NC 11/2010

Barnwell J, Pace L, Li Z, Koman LA, Smith T, Van Dyke M. Peripheral nerve regeneration using keratin biomaterials: From bench to bedside. **Biomedical Engineering Society Annual Meeting**. Austin, TX. October 6-9, 2010

Posters

"A Keratin Biomaterial Hydrogel Improves Median Nerve Regeneration in a Non-Human Primate Model" **Gordon Research Conference in Neural Development**: Newport, RI 8/2012

"Clinical Translation of a Keratin Biomaterial Hydrogel for Nerve Repair" **Gordon Research Conference in Biomaterials and Tissue Engineering**: Plymouth, NH 8/2011; **Orthopaedic Research Society**: San Francisco, CA 2/2012

"Peripheral Nerve Regeneration in Non-Human Primates using a Keratin Biomaterial Hydrogel" **Western North Carolina Society for Neuroscience**: Winston-Salem, NC 11/2011; **North Carolina Tissue Engineering and Regenerative Medicine Society**: Winston-Salem, NC 11/2011

"Human Hair Keratin Hydrogel Enhances Peripheral Nerve Regeneration Following Conduit Repair" **Advanced Technology Applications for Combat Casualty Care**: St. Pete Beach, FL 8/2010; **Society for Neuroscience**: San Diego, CA 11/2010; **Tissue Engineering and Regenerative Medicine Society**: Orlando, FL 12/2010

"Cellular Interactions with a Human Hair Keratin Hydrogel Enhance Peripheral Nerve Regeneration" **Wake Forest Graduate School of Arts and Sciences Graduate Student Research Day**: Winston-Salem, NC 3/2010

CONCLUSION

Significant progress has been made in working with the FDA to obtain the IND necessary to begin the Phase I clinical trial. Our team now has clear direction from the FDA of the steps that must be taken to comply with their recommendations for the IND. In addition, Wake Forest School of Medicine and the CDMRP worked together to identify the funding necessary to complete the studies requested by the FDA. As soon as the FDA provides the IND for the keratin biomaterial hydrogel, final approval of the clinical study protocol will be obtained from Copernicus (the independent review board), Wake Forest School of Medicine, the University of Virginia School of Medicine, and HRPO. Following IRB approval, the clinical trials will be initiated.

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APPENDICES

None