LAWRENCE LIVERMORE NATIONAL LABORATORY

LLNL-TR-739178

Interventional Application of Shape Memory Polymer Foam Final Report CRADA No. TC-02067-03

D. Maitland, M. F. Metzger

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Interventional Application of Shape Memory Polymer Foam

Final Report
CRADA No. TC-02067-03
Date Technical Work Ended: August 16, 2006

Date: September 14, 2006 Revision: 2

A. Parties

This project was a relationship between Lawrence Livermore National Laboratory (LLNL) and Sierra Interventions.

The Regents of the University of California
Lawrence Livermore National Laboratory
7000 East Avenue
Livermore, CA 94550
Duncan Maitland, Principal Investigator
Tel: (925) 423-6697
Fax: (925) 424-2778

Sierra Interventions, LLC
2425 Fulton St. Unit 1
Berkeley, CA 94704
Melodie F. Metzger
Tel: (925) 788-1519

B. Project Scope

This was a collaborative effort between The Regents of the University of California, Lawrence Livermore National Laboratory (LLNL) and Sierra Interventions, LLC, to develop shape memory polymer foam devices for treating hemorrhagic stroke. The project consisted of five major tasks and the following major deliverables:

1. Establish a foam process for SMP that produces foams with controlled porosity (relative densities 0.01 to 0.1), pore size (10 to 200 mirons), and pore size distribution (monodispers through continuous borakd) via the templated foam process. (LLNL)
2. Measure and document SMP foam structure and thermomechanical properties. (LLNL)
3. Fabricate foam actuator delivery system. (LLNL/Sierra)
4. Demonstrate SMP foam device actuation in vascular model with flow. (Sierra)

This project was originally designated as a six-month project. A no-cost time extension request was executed on April 22, 2004, extending the CRADA to September 16, 2004 to negotiate a possible amendment to the CRADA, and to allow enough time for Sierra Interventions to submit Phase II proposals and await confirmation of grant funding. A second no-cost time extension request was executed on January 13, 2005, extending the CRADA to March 16, 2005 to allow enough time to prepare and execute Amendment One to the CRADA.

An amendment to the CRADA was executed on February 24, 2005, which added four tasks, deliverables and associated funding, and extended the project for an additional six months. The following major deliverables were added under Amendment One:

5. Establish a foam process for SMP that produces cylindrical SMP foam devices with radial controlled expansivities up to 10x, average pore size (20 to 100 microns), and narrow pore size distribution via the templated foam process. Due at the end of the Month 1 (LLNL)
6. Measure and document SMP foam structure and thermomechanical properties. Due at the end of Month 2 (LLNL)
7. Design and fabricate SMP foam thrombectomy system. Due at the end of Month 4 (LLNL/Sierra)
8. Demonstrate SMP foam device actuation in vasculature model (glass, silicon, or PDMS) with accurate anatomical geometries and flows. Due at the end of Month 6 (Sierra)

A twelve-month no-cost time extension request was executed on August 29, 2005, extending the project through August 16, 2006 to allow enough time to complete the remaining tasks and deliverables under the current Statement of Work.

All of the tasks and deliverables for this project were successfully completed.

C. Technical Accomplishments

The goal of the CRADA partnership was to develop, fabricate and deliver prototype embolic foam actuator devices that can begin pre-clinical trials. This goal and the specific milestones were all accomplished during this CRADA for both the embolic foam for filling aneurysms and the foam thrombectomy devices. This initial work was supported at LLNL as a subcontract from Sierra Interventions, LLC, based on two Phase I SBIR grants from the National Institutes of Health (NIH) to Sierra Interventions, LLC. The long-term goal of this research is to deliver clinical prototype devices that can begin FDA clinical trials. Financial support for the longer-term goal of developing a clinical prototype device for the embolic foam application was submitted to NIH as a Phase II SBIR application but this application was not funded.

The specific technical accomplishments of the CRADA were:

1. Established a foam process for SMP that produces foams with controlled porosity. The research included both templated and chemically blown foams using commercially available

polyurethanes purchased from Diaplex Co. Ltd., a wholly owned subsidiary of Mitsubishi Heavy Industries Ltd.

2. Measured and documented SMP foam structure and thermomechanical properties. Pore size and size distribution will be determined by optical and scanning electron microscopy on foam sections. Computer based image analysis software allowed for a statistical description of these properties. Dynamic scanning calorimetry (DSC) and dynamic mechanical thermal analysis (DMTA) was used to define the temperatures necessary for thermal actuation. The non-linear mechanical behavior relevant to actuation forces and strains was obtained via Instron compression testing, combined with free strain recovery.
3. Demonstrated SMP foam device actuation. An SMP foam actuator that can be compressed to a diameter deliverable through a size 4 French catheter and expands to 20 times its size upon actuation, a ratio to make it suitable for aneurysm occlusion. Demonstrated the device in a silicone model of a cerebrovascular aneurysm with accurate anatomical geometries and flows.
4. Established a foam process for SMP that produces cylindrical SMP foam devices with radial controlled expansivities up to 10x. The Diaplex materials limited the radial expansions to 7x, which is sufficient for the medical devices described. These expansions, as obtained by LLNL staff (Dr. Wilson) were better than the expansions reported by the SMP inventor at Diaplex Co. Ltd, Dr Hayashi.
5. Measured and documented SMP foam structure and thermomechanical properties.
6. Designed and fabricated SMP foam thrombectomy system. A cylindrically shaped SMP foam actuator was demonstrated which can be compressed to a diameter deliverable through a catheter and expands to 10 times its initial diameter upon actuation, a ratio that would make it suitable for catheter based removal of arterial occlusions.
7. Demonstrated SMP foam device actuation. The device was demonstrated in a model of the vasculature (glass, silicone, or PDMS) with accurate anatomical geometries and flows. We specifically demonstrated both the ability of the device to dislodge and remove thrombus as well as allow for through flow of whole blood.

D. Expected Economic Impact

The economic impact of the shape memory polymer foam technology is difficult to predict. Even though Sierra Interventions, LLC has withdrawn interest in further pursuit of this technology, the shape memory foam technology continues to receive commercialization interest from medical device companies. Since LLNL retains the rights for all of the background intellectual property, the pathway for a new industrial partner is clear.

The work supported under this CRADA was critical in demonstrating that SMP foams could be fabricated. This demonstration has supported the scientific and innovative reputation of the LLNL and Sierra Interventions, LLC staff that facilitates continued academic and industrial support for both parties.

D.1 Specific Benefits

<u>Benefits to DOE</u>
This CRADA supports the efforts of the Medical Technology Program in the Physics and Advanced Technology Directorate at LLNL. It is anticipated that additional knowledge on this technology will be obtained as a result of this CRADA and thus further improve the LLNL capabilities and generate new inventions for DOE. This CRADA project will enhance LLNL's capabilities in developing microactuators, specifically shape memory polymer actuators. While the application of this CRADA is medical, the technology has broad application to volume expansion microactuators including micro pumps and filters, which are potentially beneficial to LLNL's biosecurity mission. The work with fabricating polymer foam structures contributes to other programmatic needs relating to the weapons complex of DOE.

<u>Benefits to Industry</u>
Development of this device will lead to a product with clinical significance and high commercial potential. Stroke is a major cause of mortality and the primary cause of long-term disability in the United States. Each year there are an estimated 700,000 occurrences of stroke, from which 150,000 people will die and 400,000 will be left with a significant deficit. Since an estimated four percent (4%) of aneurysm/AVMs rupture each year, a significant number of people (up to 3.5 million) have aneurysm/AVMs for years prior to stroke occurrence, indicating significant benefit from early preventative treatment. The costs of caring for victims of stroke in the acute phase, for chronic care, and lost productivity amount to forty billion dollars ($40B) per year.

The taxpayer will benefit from the development of a device that will improve and reduce the costs of medical treatment of aneurysms and arteriovenous malformations (AVMs). Such a device should significantly improve aneurysm/AVM cure rates and reduce complications due to relative ease and speed of delivery, ability to pre-shape the device to match the aneurysm/AVM geometry, ability to fill and seal the aneurysm/AVM volumes, dramatic reduction in mechanical stiffness relative to solid polymer occlusions and metal coils, and enhanced biocompatibility due to microporous structure.

At present, the highest success rates are achieved using standard microsurgery in which the aneurysm/AVM is removed. However, microsurgery involves a great deal of trauma (cutting a hole in the skull), long recovery times, and cannot be used for a significant minority of aneurysm/AVMs due to insufficient access or patient refusal. Radiosurgery involves applying a focused beam of radiation to vessel walls, resulting in shrinkage of the aneurysm/AVM.

E. Partner Contribution

Sierra Interventions, LLC contributed to several technical areas in addition to managing the overall project and budget as well as coordinating activities between three sites including LLNL and UC Davis. Sierra Interventions, LLC staff worked with LLNL personnel on a daily basis to fabricate foams, test foam material properties and demonstrate the deployment of the foams in silicone or glass vascular models. Further, Sierra Interventions, LLC worked with subcontractors at UC Davis to perform preliminary (in vitro) biocompatibility studies with the foams developed in cooperation with LLNL. Sierra Interventions, LLC also presented business plans to potential investors as well as led the submission of follow-on funding from the National Institutes of Health.

There were no subject inventions created during the CRADA performance period.

F. Documents/Reference List

Reports

Unpublished

Metzger, M.F. NIH Phase I SBIR final report, "Interventional Applications of Shape Memory Polymer Foam" December, 2003.

Published

Small, W., IV, M.F. Metzger, T.S. Wilson, and D.J. Maitland, "Laser-Activated Shape Memory Polymer Microactuator for Thrombus Removal Following Ischemic Stroke," *IEEE J. Quantum Electronics* **11**(4), July/August 2005 pp. 892-901.

Copyright Activity

No copyright protected documents or data were generated during this CRADA.

Subject Inventions

There were no subject inventions generated through this CRADA.

Background Intellectual Property

LLNL disclosed the following Background Intellectual Property for this project:

U.S. Patent No. 6,418,252 (LLNL Docket IL-10478) - *Light Diffusing Fiber Optic Chamber*; Issued: 7/9/02; Duncan J. Maitland

U.S. Patent No. 6,740,094 (LLNL Docket IL-10492) - *Shape Memory Polymer Actuator and Catheter*; Issued 5/25/04; Duncan J. Maitland, Abraham P. Lee, Daniel L. Schumann, Dennis L. Matthews, Derek E. Decker, Charles Jungreis (non-LLNL)

LLNL Docket IL-10819 – patent pending

LLNL Docket IL-11176 – patent pending

Sierra Interventions has not expressed an interest in licensing any of the above Background Intellectual Property.

Sierra Interventions did not disclose any Background Intellectual Property for this project.

G. Acknowledgement

Industrial Participant's signature of the final report indicates the following:

1) The Participant has reviewed the final report and concurs with the statements made therein.
2) The Participant agrees that any modifications or changes from the initial proposal were discussed and agreed to during the term of the project.
3) The Participant certifies that all reports either completed or in process are listed and all subject inventions and the associated intellectual property protection measures generated by his/her respective company and attributable to the project have been disclosed and included in Section E or are included on a list attached to this report.
4) The Participant certifies that if tangible personal property was exchanged during the agreement, all has either been returned to the initial custodian or transferred permanently.
5) The Participant certifies that proprietary information has been returned or destroyed by LLNL.

11/6/06

Melodie F. Metzger, President — Date
Sierra Interventions, LLC

11-22-06

Duncan J. Maitland, LLNL Principal Investigator — Date
Lawrence Livermore National Laboratory

12/7/06

Karena D. McKinley, IPAC Director — Date
Lawrence Livermore National Laboratory

Attachment I – Final Abstract

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Final Abstract (Attachment I)
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E. Project Dates

September 16, 2003 to August 16, 2006