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LLNL-TR-747879

Lasers for Medicine Final Report CRADA No. TC-0436-93

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March 15, 2018

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This work performed under the auspices of the U.S. Department of Energy by Lawrence Livermore National Laboratory under Contract DE-AC52-07NA27344.

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Lasers for Medicine

Final Report
CRADA No. TC-0436-93

Date: 1/20/97 Revision: 1

A. Parties

The project is a relationship between the Lawrence Livermore National Laboratory (LLNL) and Beckman Laser Institute and Medical Center.

University of California
Lawrence Livermore National Laboratory
P.O. Box 808, L-795
Livermore, CA 94551

Beckman Laser Institute and Medical Center
1002 Health Sciences Road East
Irvine, CA ~~92715~~ 92612

B. Project Scope

This project is intended to advance the US position in laser diagnosis and treatment of disease in three thrust areas. A first laser system will advance the US position in photodynamic therapy whereby dyes are introduced into selected tissue and laser treatment with wavelengths matching the dyes' absorption band allows treatment of only the desired tissue. This effort will focus on the development and application of diode arrays delivering up to 10 watts at wavelengths of 657 nm, 675 nm and 695 nm with fiber optic delivery systems. This system would replace existing cumbersome systems with a compact diode array system.

A second laser system is intended to advance the US position in the medical use of lasers in dermatology to remove port wine stains. The project will involve the development of a new all solid-state laser system to deliver light at 585 nm for the direct removal of port wine stains in human skin. This solid-state system would replace the currently used dye laser system with a compact, more efficient, less costly, environmentally benign solid-state laser system. Additionally this new laser system will offer new flexibility in the pulse format allowing treatment on a wider range of patients.

A third laser system is targeted to develop a diode-pumped Tm:YAG laser system operating at 1.9 μm to drill small holes in animal eggs with the goal of improving fertility. This system would replace the current excimer system at 308 nm, which has undesirable mutagenic problems

C. Technical

The initial technical objective of this proposal is to first collaboratively design, construct, and integrate three solid-state laser systems with beam delivery systems. One system is for use in photodynamic therapy, a second system is for use in the removal of port wine stains, and a third system is for gamete manipulation. The new, advanced, LLNL, microchannel-cooled, laser-diode-array technology will allow the building of these three new laser systems. Each system will be a

compact, all solid-state system with outputs uniquely tailored for the intended application. Because of technical difficulties the gamete manipulation system was not pursued.

D. Partner Contribution

Beckman will oversee pre-clinical and animal studies using the laser systems developed at LLNL. See attached articles describing PDT system research.

E. Documents/Reference List

A. Publications

1. R.J. Beach, M.A. Emanuel, B.L. Freitas, J.A. Skidmore, N.W. Carlson, W.J. Benett, and R.W. Solarz, "Applications of Microlens-Conditioned Laser Diode Arrays," SPIE Vol. 2383 p. 283-297 (1995)
2. R.J. Beach, S.B. Sutton, J.A. Skidmore, and M.A. Emanuel, "High power 2 micron wing-pumped Tm:YAG laser," Advanced Solid State Lasers Technical Digest p. 249-252 (1995)
3. E.C. Honea, R.J. Beach, S.B. Sutton, J.A. Speth, S.C. Mitchell, J.A. Skidmore, M.A. Emanuel, and S.A. Payne, "High average power Tm:YAG diode-pumped solid-state laser," UCRL-JC-125109 Preprint, submitted to IEEE Journal of Quantum Electronics

B. Patents and disclosures:

1. "High efficiency 2 micrometer laser utilyzing wing-pumped Tm^{3+} and a laser diode array end-pumping architecture," by R.J. Beach, CIL-9691 LLNL patent application filed October 2, 1996.
2. "Fiber optic coupling of a microlens conditioned, stacked semiconductor laser diode array," by R.J. Beach, W.J. Benett, and S.T. Mills, CIL-9614 LLNL patent application filed February 1996.

F. Acknowledgment

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 attributable to the project have been disclosed or are included on a list attached to this report.
4) The Participant certifies that if real 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.

12/1/97		27-Jan-98	
Michael W. Berns	Date	Raymond Beach	Date
Beckman Laser Institute and Medical Center		Lawrence Livermore National Laboratory	

Attachment I – Final Abstract
Attachment II – Project Accomplishments Summary
Attachment III – Final Quarterly Report

Lasers for Medicine

Attachment I
Abstract
CRADA No. TC-0436-93

Date: Revision: 1

Brief Description:
Lawrence Livermore National Laboratory and the Beckman Laser Institute and Medical Clinic joined forces to design, build, and test three new medical laser systems for laser diagnosis and treatment of cancers, birthmarks, and infertility. The Beckman Clinic has treated 14,000 patients with laser-based medical technologies, more than any other facility in the world. Lawrence Livermore's expertise in laser technology was combined with Beckman's expertise in medical applications of lasers and fiber optic delivery systems. The new technology will be transferred to a third-party manufacturer for commercial packaging and marketing of the laser systems. Because of technical problem the fertility treatment laser which was to be a Q-switched 2 micron Tm:YAG laser was not pursued.

Industrial Partner:
The Beckman Laser Institute and Medical Clinic, based at the University of California in Irvine, Calif., is a non-profit corporation that supports biomedical laser research at the University of California, Irvine. It is affiliated with 15 companies.

Purpose:
Design and construct all-solid-state medical laser systems to diagnose and treat cancer, remove birthmarks and improve fertility.

Benefit to Industry:
Medical lasers that are less costly and more compact, efficient, reliable, flexible, and benign environmentally than existing ones.

Benefit to DOE/LLNL:
Maintain LLNL's 20-year position as a center of expertise in laser system engineering for DOE, other government agencies, and U.S. industry. Develop laser sources applicable to future DOE and Defense Program efforts such as remote sensing and biological activity.

Time Period:
Three years, starting September 28, 1993

LLNL Contact:
Raymond Beach, (510) 423-8986

Lasers for Medicine

Project Accomplishments Summary (Attachment II)
CRADA No. TC-0436-93

Date: Revision:

A. Parties

The project is a relationship between the Lawrence Livermore National Laboratory (LLNL) and Beckman Laser Institute and Medical Clinic.

University of California
Lawrence Livermore National Laboratory
7000 East Avenue, L-795
Livermore, CA 94550

Beckman Laser Institute and Medical Clinic
1002 Health Sciences Rd. East
Irvine, California 92715

B. Background

While part of the medical community is aware of new developments in laser sources, the cost of laser diodes has frequently prevented the demonstration of the usefulness of these devices in medicine, both for diagnosis and treatment. Recent Lawrence Livermore National Laboratory (LLNL) advancements in diode packaging for high average power now offer the potential for these sources to be cost effective in medical treatment and diagnosis systems. Beckman Laser Institute is one of the leading centers in the work in the development of medical applications of lasers and light. Beckman is actively engaged in the development of PDT for both cancer and non-cancer applications, as well as in the development of surgical applications of new solid-state lasers. The ultimate goal of this project is the transfer of LLNL technology in both diode lasers and diode-pumped solid-state lasers to Beckman for application to PDT and to surgery. To this end, LLNL proposes to work jointly with Beckman to accomplish two principle tasks:

1. Diode laser systems for photodynamic therapy.
2. Diode-pumped 1.9 μm solid-state lasers for gamete manipulation.

This effort is targeted toward two TACT areas of emphasis: Microelectronics and Photonics, and Advance Manufacturing and Precision Engineering. To accomplish the goals of this proposed effort requires development of advanced manufacturing techniques for both the laser diode pump source and the solid state laser. This effort will improve domestic diode fabrication and packaging technology. Additionally, the application of laser technology to biomedical treatment involves precision measurements and precision engineering.

Several efforts within this proposed program are of interest to a number of other potential LLNL funding sources. In particular, several of the diode pumped soild-state devices share some commonalty with work being proposed in conjunction with the Wellman Laboratories of Photomedicine (WL). A further example of commonalty are the LLNL current and proposed efforts regarding coupling of high average power diode arrays into fiber optic delivery systems.

C. Description

1. Technical Rationale

This project is designed to take advantage of the combined resources and expertise at LLNL and Beckman Laser Institute to produce new laser systems for PDT and for surgery. The requirements for the new laser systems have been developed by Beckman based on experiments with PDT.

One key requirement is that the laser sources must be amenable to compact and thermally efficient packaging. This focuses interest on the application of semiconductor diode laser technology. Required improvements in this area will be based on the exensive LLNL expertise and experience in processing and fabrication of diode lasers, and high average power thermal management using microchannel cooler packaging technology, as well as LLNL expertise in solid-state laser technology. Beckman's expertise in development and use of PDT and in the investigation of new infrared lasers is pivotal for the evaluation of the new laser systems.

2. Work Plan

This project is broken into two key tasks:

1. Diode-laser systems for photodynamic therapy.
2. Diode-pumped 1.9 μm solid-state lasers for gamete manipulation.

Each task is divided into two parts to reflect the varied experience and expertise of LLNL and Beckman. LLNL will assume lead responsibility for development of the proposed laser systems. The primary LLNL deliverable for each task will be a single laser system that can be coupled to a fiber delivery system. Beckman will be responsible for application and testing of the laser systems in the pre-clinical (in vitro and animal model) and clinical (human studies) environment.

Diode-laser systems for photodynamic therapy (PDT)

Diode-laser systems offer the opportunity of more reliable and ultimately less expensive source technology for PDT. In addition, recent experiments suggest that PDT with mechanically-chopped CW radiation can produce different tissue effect than the same total light dose delivered as continuous wave radiation. Diode lasers are ideally suited for performing experiments of this kind, since they can be modulated to produce a variety of on/off schedules that would be difficult to implement with mechanical shutters.

This task centers on the development and testing of three diode laser systems, operating at wavelengths of 695, 675, and 657 nm. The development and testing efforts are broken into two phases. During phase 1, 0.25-1 W diode systems will be developed and tested. During phase 2, diode array systems delivering up to 10 W will be developed and tested. LLNL is responsible for the development of the the integrated laser diode systems. Each system will consist of an integrated laser package consisting of the diode sources, modulatable power supply, thermal management system, and lensing system suitable for delivery to a Beckman supplied delivery system (possibly a 600 mm multimode fiber). Beckman will be responsible for the application of these systems to the investigation of several photosensitizers (BPD, Chlorine e_6, CASPc, PPIX, etc.) for study of PDT in animal models.

Beckman will use the systems to study the effect of CW versus pulsed format delivery on the effectiveness of treatmen. Ultimately the treatment system should consist of five independently controllable diode lasers, each providing 2 W of optical power out of a 600 micron multimode fiber.

Beckman will be responsible for obtaining approval for modification of the clinical protocols, and for pre-clinical and clinical testing of the new laser system. Should animal trials of pulsed format delivery of the laser light be encouraging, Beckman will investigate the possibility of incorporating this format into the clinical trials; such a change will require FDA.

D. Expected Economic Impact

Economic competitiveness and the rising costs of medical treatment are two of the major issues confronting our nation. One of the more promising fields in the treatment of human cancer employs photosensitive dyes. The use of these dyes to absorb laser light allows the selective destruction of cancerous tissue. Improvements in system reliability and treatment procedure that can be afforded by the introduction of diode laser sources offers the potential for reducing the cost of treatment as well as improving the effectiveness of this treatment procedure. This should allow more widespread treatment as well as treatment at reduced cost.

E. Benefits to DOE

Diode pumped solid state lasers are rapidly becoming the laser of choice in many commercial and military systems. It is anticipated that the demand for these systems will only increase in the future as diode costs and performance improves. The proposed work in the program will extend existing LLNL developed diode processing and packaging technology from largely military based systems to more directly commercial endeavors. The resulting diode source improvements will directly translate to current as well as future DOE and DP efforts. An example is the impact that low-cost diode lasers will have on laser fusion economic viability, as well as future laser isotope separation plants where diode pumped solid state lasers are a candidate for replacing copper vapor lasers. Additionally, the Department of Energy has a long-standing involvement in advanced biomedical technology. To this point, however, DOE developed diode laser technology has not been applied to the biomedical technology area. This effort leverages the investment made in diode technology to the historical DOE involvement in biomedical research.

F. Industry Area

Solid-state lasers, and in particular, diode pumped systems are receiving increasingly more attention with regards to commercial applications in precision manufacturing and medicine. Numerous foreign companies (such as Sony and Panasonic) are actively engaged in the development of diode pumped laser systems. The U.S. still maintains a competitive advantage in the field of diode packaging for high average power. The work propsoed in this research effort enhances the U.S. position by making improvement in packaging technology, as well as implementing a path for domestic commercialization.

G. LLNL Point of Contact for Project Information

Ray Beach, L-441, P.O. Box 808, LLNL; Livermore, CA 94550 (510) 423-8986

H. Company Size and Point(s) of Contact

Michael W. Berns
Beckman Laser Institute and Medical Clinic
1002 Health Sciences Rd. East
Irvine, CA ~~92715~~ 92612
(714) ~~856~~-6996
824

RELEASE OF INFORMATION

I have reviewed the attached Project Accomplishment Summary prepared by Lawrence Livermore National Laboratory and agree that the information about our CRADA may be released for external distribution.

Michael W. Berns
Beckman Laser Institute & Medical Center

12/1/97
Date

RELEASE OF INFORMATION

I certify that all information contained in this report is accurate and releasable to the best of my knowledge.

Karena McKinley, Director
Industrial Partnerships
and Commercialization

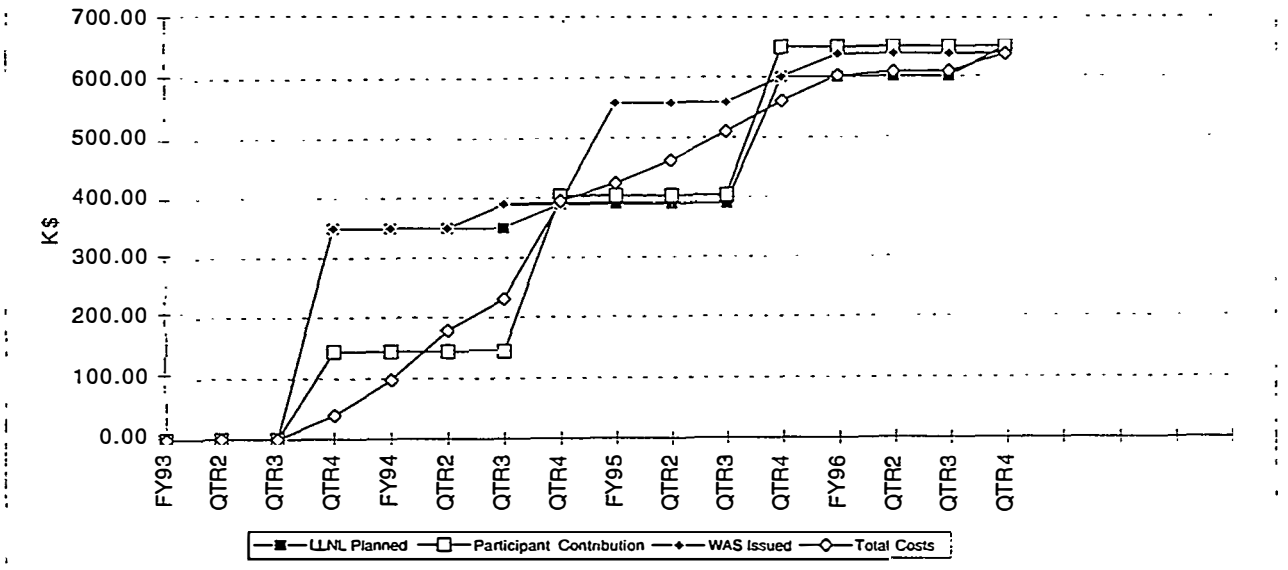
2/18/98
Date

Lawrence Livermore National Laboratory

Title:	Lasers for Medicine	Reporting Period:	07/01/95 - 09/30/96
Participant:	Beckman Laser Institute & Medical Clinic	Date CRADA Executed:	9/28/93
DOE TTI No.:	93-LLNL-003-XX	DOE Approval Date:	9/20/93
CRADA No.:	TC-0436-93	Scheduled Ending Date:	9/28/96
TACT:	BIO	Project Completion:	9/30/96
Account Numbers	4722-53 to 55	B & R Code (S):	DP0301
Accounts Closed:	9/30/96		35DP03

Approved Funding Profile ($K)

	FY93	FY94	FY95	FY96	FYOUT	Total
LLNL Planned	350	40	210	50	0	650
Participant In-Kind	144	259	247	0	0	650
Paticipant Funds-In	0	0	0	0	0	0
WAS DP0301	350	40	210	39	0	639
WAS 35DP03	0	0	0	0	0	0
Total Costs	39	356	165	77	0	637



DP0301	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	July	Aug	Sep	FYTD	637
FY93	0	0	0	0	0	0	0	0	0	0	0	39	39	
FY94	1	27	30	42	31	8	27	14	12	67	84	13	356	
FY95	4	25	0	6	18	14	12	10	26	20	10	20	165	
FY96	24	18	0	5	0	1	0	0	1	6	13	9	77	
FYOUT	0	0	0	0	0	0	0	0	0	0	0	0	0	

35DP03	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	July	Aug	Sep	FYTD	0
FY93	0	0	0	0	0	0	0	0	0	0	0	0	0	
FY94	0	0	0	0	0	0	0	0	0	0	0	0	0	
FY95	0	0	0	0	0	0	0	0	0	0	0	0	0	
FY96	0	0	0	0	0	0	0	0	0	0	0	0	0	
FYOUT	0	0	0	0	0	0	0	0	0	0	0	0	0	

STAFF w/phone:

Lab PI: Ray Beach (510) 423-8986

Resource Manager: Bonnie Zucca (510) 423-9516

DOE OAK: Jerry Scheinberg (510) 637-1653

Participant: Michael W. Berns (714) ~~856~~ 824-6996

DOE HQ: John Uecke (202) 586-5431

Reporting Period: 07/01/95 - 09/30/96
DOE TTI No.: 93-LLNL-003-XX
CRADA No.: TC-0436-93

Milestones and Deliverables:

List the complete set of milestones for all phases of the CRADA. Continue on a separate page if necessary.
Report any changes from the original CRADA or previous quarterly report on the CRADA Change Form.

	Completion Date: Scheduled	Actual
1. Milestone A1 requirements	10-93	10-93
2. Milestone A2 prototype	08-93	06-93
3. Milestone B1 definition	02-94	02-94
4. B2 Laser system design	11-93	06-94
5. B3 System fabrication and performance verification	04-95	*
6. B4 System delivery and test System test	08-95	*
7. Milestone C1 definition requirements	11-93	11-93
8. The third PDT system wavelength has been changed to 732 nm by mutual agreement with Beckman		06-95

* Not completed by mutual agreement with Beckman. Replaced Milestone 8.

Verification of participants' in-kind contribution was made in accordance with LLNL policy. Explain basis of verification:

Please initial: YES X NO ____

The Industrial Participant's in-kind contribution was consistent with the level required and agreed to in the CRADA as evidenced by the progress reported to us by them on work on the port wine stain treatment process.

List any subject inventions by either party (include IL# for LLNL inventions), additional background intellectual property, patents applied for, software copyrights, publications, awards, licenses granted or reportable economic impacts

1. IL-9614 "Fiber Optic coupling of a microlens conditioned, stacked semiconductor laser diode array"
2. IL-9616 "Diode End-Pumped 2 micron Tm:YAG laser"
3. IL-9691 "High efficiency 2 micron laser utilizing wing-pumped Tm3+ and a laser diode array end-pumping architecture"
4. 1995 R&D 100 Award for "All Solid-State Laser with Diode Irradiance Conditioning

Verification that all equipment and proprietary information has been returned to the initial owner or permanently transferred

Please initial: YES X NO ____

Accomplishments

Describe Technical/Non-Technical lessons learned and other observations.
Summarize causes/justification of deviations from original scope of work.

1. Delivered a power supply and utility system for the fiber coupled PDT laser to Beckman.
2. Delivered a 675 nm fiber coupled PDT unit to Beckman.
3. Delivered a 690 nm fiber coupled PDT unit to Beckman.
4. Fabricated a test wafer at ~730 nm for the last Beckman PDT unit. Testing and characterization of this wafer is ongoing.
5. Continued the design of the 2 micron Gamete manipulation laser.
6. Placed orders for the utility system for the 2 micron Gamete manipulation system.
7. We have finished the hardware for the last PDT unit and are presently completing the 732 nm laser diodes.
8. We have attempted to Q-switch a prototype 2 micron Tm:YAG laser similar to the Gamete manipulation laser we are to deliver to Beckman. As a result of the coating damage problem and the limited funding remaining this year, this system will not be completed until next year. Of course the successful completion of the system is predicated on solving the coating problem.

Reviewed by CRADA project Program Manager: _____ Date: _____

Reviewed by Karena McKinley, Acting Director, LLNL/IP&C: _____ Date: _____

Direct questions regarding this Report to IP&C Resource Manager, Susan Springer, at (510) 422-5507