Pages 1 through 2 redacted for the following reasons:
- -
Internal documents

6144601-06-0024 US Manufacturing Waiver Request

Request ID : 1369

Requested by **Becky Crump** on Sep 20, 2010 04:51 PM

Subject

6144601-06-0024 US Manufacturing Waiver Request

Description

Attached please find a request for a waiver of the US manufacturing requirement.

Becky L. Crump, Ph.D.
Associate Director
Innovation and New Ventures Office
Northwestern University
1800 Sherman Avenue, Suite 504
Evanston, IL 60201
beckyc@northwestern.edu
voice: 847-491-3630
fax: 847-491-3625

Attachments : 20100914120249136.pdf (1195.32 KB)

Removed by agreement

Pages 3 through 61 redacted for the following reasons:
- -
Removed by agreement (9/7/2012)

Removed by agreement

From : **Marie Iamothe**

To : odottwaiver@od.nih.gov

Summary

[Request ID No. ##1369## : U.S. Manufacturing Waiver Request for NORTHWESTERN UNIV. EIR: 6144601-(

Description

U.S. MANUFACTURING WAIVER REQUEST

EIR: 6144601-06-0024
EIR TITLE: Low-coherence enhanced backscattering spectroscopy for colorectal cancer screening wit

Patent: 7,652,772, Filing Date 1/26/2010

This technology is planned be licensed by Northwestern University in conjunction with a previously approved U.S. Manufactur this request as “Early Increase in Mircovascular Blood Content or Supply, “EIBS””.

Northwestern University is requesting a Waiver of the Preference for United States Industry for the technology indicated above Backscattering “LEBS”). These are optical detection technologies – including both EIBS and LEBS, developed by both Northw Northwestern Healthcare).

(b)(4)

(b)(4)

EIBS/LEBS technology is expected to generate new products that will be manufactured in the U.S., the technology is also exp
outside the U.S. The requesters are unaware of any manufacturer in the U.S. with the capability of making such complex

(b)(4)

Requiring domestic U.S. manufacture would significantly delay introduction of this product for several years or perhaps indefin
none presently exists in the U.S. Separate manufacture would require transportation of mechanically sensitive components in

Upon a review of the case and the particular circumstances of this case, the waiver request for this case should be approved,

Please let us know if you have any additional questions.

Thank you.

The iEdison Waiver HelpDesk Team
Division of Extramural Inventions and Technology Resources (DEITR)
OPERA, OER, OD, NIH, HHS
(301) 435-1986
edison@nih.gov

Attachments : US Manufacturing Waiver Request for Northwestern University_ 6144601-06-0024_12-3

Intra-agency discussion, (b)(4)

Pages 64 through 73 redacted for the following reasons:
- -
Removed by agreement;
Removed by agreement; Intra-agency/DEITR procedural discussion

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

January 25, 2011

Dr. Becky L. Crump
Associate Director, Technology Transfer
Innovation and New Ventures (INVO)
Northwestern University
1800 Sherman Avenue, Suite 504
Evanston, IL 60201

Re: U.S. Patent 7,652,772, issued 01/26/2010.

EIR No.: 6144601-06-0024
Patent Docket Nos.: NU 26034 (25046)
NIH Funding Agreements: R01 CA112315, U01 CA111257
EIR Title: Low-coherence enhanced backscattering spectroscopy for colorectal cancer screening without colonoscopy
Inventor Names: Hemant Roy, Yang Liu, Young Kim, Vadim Backman, Vladimir Turzhitzky, Jeremy Rogers

Dear Dr. Crump:

This letter is in response to the US Manufacturing Waiver Request submitted by Northwestern University (Northwestern) on the above-referenced invention conceived or first actually reduced to practice through an NIH funding agreement. This Manufacturing Waiver is related to a previously-approved Manufacturing Waiver for EIR 6144601-03-0060 in order to incorporate additional improvements on the original technology.

Below is a summary of the scientific, commercialization and licensing reviews of the Subject Invention that is the subject of this Manufacturing Waiver; this Office concurs with those reviews and further agrees that it is in accord with the terms and conditions of the funding agreements under which it was made.

Commercialization Background and Analysis

(b)(4) that directs light to epithelial tissue, and a back-scattered interacted light that reveals the blood content and microstructure of the tissue. (b)(4) (b)(4) There are no current U.S. Manufacturers capable of making the complex, precision optical and mechanical instruments for these systems. (b)(4)

The principal justification for the waiver request is that there is no current manufacturing capability for these type of [redacted] in the United States. [redacted] (b)(4) Requiring U.S. Manufacturing at this time would impact the development of the technology as there are no other manufacturers capable of creating this technology anywhere else in the world. The time and expense of build a U.S.-based facility with the level of expertise and capability would be costly and delay the technology from being manufactured.

Summary

Based on the information you have provided about the current circumstances for this technology, your request for a manufacturing waiver has been approved. By each 3rd year anniversary of the date of this letter, you will need to keep our office apprised of what good faith efforts were continuing to be made during that period to consider substantially manufacturing in the US for this technology. If we do not receive this information for each period, then this approval may need to be revisited. As this invention was made under Funding Agreements that involve Consortium Activity with New York University, the Fox Chase Cancer Center and Creighton University, any consortium issues should be considered in acting on this Waiver Approval. Special Requirements under RFA CA-04-006 and RFA CA-09-017 may also need to be considered. All other terms and conditions of the funding agreements, with the exception of the Preference for United States Industry as outlined in this letter, remain in effect.

Please feel free to contact us should you have any additional questions regarding this issue.

Sincerely,

John Salzman
Assistant Extramural Inventions Policy Officer
Division of Extramural Inventions and Technology Resources
Office of Policy For Extramural Research Administration, OER, OD

Please direct all correspondence to:
6705 Rockledge Drive
Suite 310, MSC 7980
Bethesda, MD 20892-7980

Phone: (301) 435-1986
Fax: (301) 480-0272
e-mail: waiver@nih.gov

NIH Procedures for Requests for Waivers of the U.S. Manufacturing Requirement in Licenses to Extramural Inventions

The NIH has authority to waive the preference for United States industry requirement when a contractor assigns or licenses a contractor owned invention (35 U.S.C. 204). Extramural institutions may request such a waiver on behalf of its licensees. NIH complies with 35 U.S.C. 204 in making determinations regarding the grant of a waiver of the U.S. manufacturing requirement. Section 204 states:

Notwithstanding any other provision of this chapter, no small business or firm or nonprofit organization which receives title to any subject invention and no assignee of any such small business firm or nonprofit organization shall grant to any person the exclusive right to use or sell any subject invention in the United States unless such person agrees that any products embodying the subject invention or produced through the use of such invention will be manufactured substantially in the United States. However, in individual cases, the requirement for such an agreement may be waived by the Federal agency under whose funding agreement the invention was made upon a showing by the small business firm, nonprofit organization, or assignee that reasonable but unsuccessful efforts have been made to grant licenses on similar terms to potential licensees that would be likely to manufacture substantially in the United States or that under the circumstances domestic manufacture is not commercially feasible.

The approval process requires that grantee organizations and contractors provide information and justification for the request as outlined below. In addition to addressing the questions, any other information which the contractor believes pertinent to why the assignment is necessary and in the public interest may be submitted.

After filling out the form, press "Submit" to automatically e-mail the request to the NIH for disposition. Please note that the review by NIH that can lead to the approval of U.S. Manufacturing waiver request will not commence until the answers to the questions and all pertinent information has been received by the NIH. Should you have further questions, or should you prefer to submit information in hard copy, please direct inquiries and information to:

Division of Extramural Inventions and Technology Resources
National Institutes of Health
Attn: U.S. Manufacturing Waiver Request
6705 Rockledge Drive, Suite 6054, Room 6182
MSC 7980
Bethesda, MD 20892
(301) 435-1986
edison@od.nih.gov

Information may be faxed to NIH at (301) 480-0272. To initiate a request for U.S. Manufacturing Waiver, fill out the fields below, then choose "Submit" to send your request to the NIH. All fields marked with an asterisk (*****) are required.

U.S. Manufacturing Waiver Request Form

Prefix: Dr.
***** *First Name:* Becky
Middle Name L.
***** *Last Name* Crump
Suffix
***** *E-mail Address:* beckyc@northwestern.edu

Previously Waived:

***** *Invention Report Number:* 6144601-03-0060
***** *Grantee/Contractor Organization:* Northwestern University
***** *Grant/Contract Number:* 1R21CA102750-01 and U01 CA111257
***** *Invention Title:* Multi-Dimensional Elastic Light-Scattering Fingerprinting For Tissue Diagnosis
***** *Invention Docket Number:* NU 23105
***** *Patent Docket Number:* 03-0060-00
** U.S. Patent Application Number:* 11/261,452 filed October 27, 2005 (and any continuation and/or divisional patent applications claiming this Subject Invention, if any).

Additional Inventions:

First Invention:

***** *Invention Report Number:* 6144601-06-0047
***** *Grantee/Contractor Organization:* Northwestern University and NorthShore University HealthSystem (formerly Evanston Northwestern Healthcare)
***** *Grant/Contract Number:* R01CA109861 to Northwestern University
U01CA111257 to NorthShore University HealthSystem
***** *Invention Title:* GUIDE-TO-COLONOSCOPY BY OPTICAL DETECTION OF COLONIC MICROCIRCULATION
***** *Invention Docket Number:* NU 26072
***** *Patent Docket Number:* NU 26072 A
** U.S. Patent Application Number:* 11/604,659 filed November 27, 2006 (and any continuation and/or divisional patent applications, if any).

***** *Patent Docket Number:* NU 26072 B
** U.S. Patent Application Number:* 11/604,653 filed November 27, 2006 (and any continuation and/or divisional patent applications, if any).

Second Invention:

***** *Invention Report Number:* 6144601-06-0024
***** *Grantee/Contractor Organization:* Northwestern University and NorthShore University HealthSystem (formerly Evanston Northwestern Healthcare)
***** *Grant/Contract Number:* R01CA112315 to Northwestern and U01CA111257 to NorthShore
***** *Invention Title:* LOW-COHERENCE ENHANCED BACKSCATTERING SPECTROSCOPY FOR COLORECTAL CANCER SCREENING WITHOUT COLONOSCOPY
***** *Invention Docket* Number: NU 26034
***** Patent Docket Number: NU 26034 (25046)
** U.S. Patent Number:* 7,652,772 (and any continuation and/or divisional patent applications, if any).

Third Invention:

***** *Invention Report Number:* 6144601-05-0034
***** *Grantee/Contractor Organization:* Northwestern University
***** *Grant/Contract Number:* BES-0238903
***** *Invention Title:* LOW-COHERENCE ENHANCED BACKSCATTERING SPECTROSCOPY (LEBS) FOR TISSUE DIAGNOSIS AND COLONOSCOPY FREE-SCREENING FOR COLORECTAL CANCER
***** *Invention Docket* Number: NU25046
***** Patent Docket Number: NU 26034 (25046)
** U.S. Patent Number:* 7,652,772 (and any continuation and/or divisional patent applications, if any).

Fourth Invention:

***** *Invention Report Number:* 6144601-06-0042
***** *Grantee/Contractor Organization:* Northwestern University and NorthShore University HealthSystem (formerly Evanston Northwestern Healthcare)
***** *Grant/Contract Number:* BES0547480 R21CA102750 to Northwestern, U01CA111257 to NorthShore
***** *Invention Title:* NONINVASIVE DIAGNOSIS OF PANCREATIC CANCER WITHOUT THE NEED FOR INTERROGATION OF PANCREAS BY MEANS OF ELASTIC LIGHT SCATTERING FINGERPRINTING (ELF) AND LOW-COHERENCE ENHANCED BACKSCATTERING (LEBS) SPECTROSCOPY
***** *Invention Docket Number:* NU26063
***** *Patent Docket Number:* NU26063
** U.S. Patent Application Number:* 11/803,418 filed May 14, 2007 (and any continuation and/or divisional patent applications, if any).

Fifth Invention:

***** *Invention Report Number:* 6144601-08-0117
***** *Grantee/Contractor Organization:* Northwestern University and NorthShore University HealthSystem (formerly Evanston Northwestern Healthcare
***** *Grant/Contract Number:* R01CA109861 and R01CA112315 to Northwestern University
***** *Invention Title:* EFFECTIVE MUCOSAL BLOOD VESSEL SIZE AND OXYGENATED HEMOGLOBIN CONCENTRATION IN THE RECTUM ARE MARKERS OF NEOPLASIA IN THE PROXIMAL COLON
***** *Invention Docket Number:* NU 28184
***** *Patent Docket Number:* NU 28184 CIP
** U.S. Patent Application Number:* 12/350,955 filed January 8, 2009 (and any continuation and/or divisional patent applications, if any).

Overview:

Northwestern University has received a waiver of the US manufacturing requirement from NIH for the Invention first listed above (Early Increase in Microvascular Blood Content or Supply, "EIBS").

NorthShore University HealthSystem (formerly, Evanston Northwestern Healthcare) is now joining Northwestern in a request for a waiver for Inventions 1 – 3. This request includes an additional technology (Low-Coherence Enhanced Backscattering, "LEBS"); however, this technology may be combined with and complimentary to the technology for which the requirement has been waived as explained in the required sections below. Since there have also been minor changes in the proposed structure of the license for EIBS, we are also requesting that NIH review these changes and confirm that the waiver originally obtained applies to the altered license structure.

Reasonable but Unsuccessful Efforts to License

***** *Discuss the significance of the technology, including*

(a) the availability of alternative products,

(b) the size of intended patient populations,

(c) whether requiring U.S. manufacture will delay entry of the product into the U.S. or foreign markets, and

(d) the effect such delay may have on the U.S. and foreign public health.

Significance of the Technology

The subject inventions for which a waiver is being sought are part of a portfolio of optical detection technologies – including EIBS and LEBS technologies -- developed through collaboration between biomedical engineers at Northwestern University and physicians at NorthShore University HealthSystem (formerly, Evanston Northwestern Healthcare). The portfolio has been exclusively licensed to American BioOptics, a new small business formed specifically to develop these early stage technologies. (b)(4) This waiver request is being submitted by Northwestern and NorthShore University HealthSystem, both grantee institutions, on behalf of American BioOptics (b)(4)

Whereas the EIBS/LEBS technology is expected to generate new products that will be manufactured in the US, the EIBS/LEBS technology is also anticipated to be commercialized (b)(4) and manufactured outside the US. (b)(4) directs light to epithelial tissue, and back-scattered and interacted light reveals the blood content (EIBS) and tissue microstructure (LEBS) of the tissue. Epithelial blood content increases markedly and tissue microstructure disorder increases in patients at high risk for GI cancers, for example. includes a processing system that receives the back-scattered and interacted light, processes it to detect this increased epithelial blood content (EIBS) or tissue architecture alterations (LEBS), and provides an indication to the clinician of the possiblity for cancerous or pre-cancerous lesions. The associated indicates presence, absence or severity of detected Early Increase in Blood Supply (EIBS) or tissue architectural alterations (LEBS). Improved risk stratification and detection of cancerous or pre-cancerous lesions would assist in reducing the morbidity associated with common GI cancers such as pancreatic cancer, which if found at its earliest stage, offers hope for curative surgery.

(a) *(the availability of alternative products)* Northwestern, NorthShore University HealthSystem, and American BioOptics are unaware of any available alternative technology or devices manufactured in the U.S. or elsewhere to improve the ability (b)(4) o identify patients who likely have cancerous or precancerous lesions based on elevated blood content or tissue architectural changes. More specifically, unlike conventional optical probe technologies, e.g., Narrow Band Imaging and Autofluorescence, that facilitate specific diagnoses of previously located polyps and lesions, the subject complimentary EIBS/LEBS technologies assist in the identification of patients at risk of cancerous or pre-cancerous lesions and polyps.

(b) *(the size of intended patient populations)* In 2007, it was estimated approximately 35,000 Americans would be diagnosed with pancreatic cancer resulting in nearly the same number of deaths and 150,000 Americans would be diagnosed with colorectal cancers (CRC) resulting in 50,000 deaths. The life-time risk for an American to develop CRC is 6% making it the second leading cause of cancer deaths while pancreatic cancer is among the most lethal. While the 5 year survival rate for localized colorectal disease is

excellent (90%), the rate plummets (~11%) for patients who present with advanced disease. Unfortunately, only 37% of CRC patients are diagnosed at the early, curable stage, and this is far less for pancreatic cancer patients. This is largely because the classic symptoms of CRC (hematochezia, anemia, weight loss, abdominal pain) as well as pancreatic cancer (abdominal discomfort) are generally harbingers of advanced, incurable disease, whereas the symptoms of early stage disease are subtle and insidious. This underscores the need to effectively screen and identify high risk patients among the entire, asymptomatic, at-risk population (subjects over age 50).

According to guidelines from the American Cancer Society and the Center for Disease Control, 90 million Americans age 50 and older should be regularly screened for colon cancer, and there is no recognized screening for pancreatic cancer or many other gastro-intestinal (GI) cancers. Colonoscopy is widely recognized as the definitive gold standard for colon cancer screening among the methods available. In 2006, there were an estimated 14 million colonoscopies performed in the United States for screening, follow-up, and related colon disease, and an estimated 3 million upper GI endoscopies. Endoscopy is an expensive and imperfect screening technique, however, and the technology presented here has clear benefits to identify millions of Americans in the at-risk population (b)(4) This technology also represents an opportunity to identify high-risk patients or diagnose pancreatic cancer with a less invasive, lower risk procedure.

(c) *(whether requiring U.S. manufacture will delay entry of the product into the U.S. or foreign markets)* Northwestern, NorthShore University HealthSystem, and American BioOptics are unaware of any manufacturer in the United States with the capability to make such complex, precision optical and mechanical instruments (b)(4) As a consequence, the earliest commercialization of EIBS/LEBS technologies and the maximum benefit to the U.S. patient population would be for American BioOptics and/or Northwestern University (on behalf of NorthShore University HealthSystem) to enter into an agreement with one of these manufacturers. (b)(4)

As described in detail below, requiring that be manufactured in the United States would significantly delay introduction of this important product by several years and perhaps indefinitely. A complex (b)(4) manufacturing facility would have to be constructed, as none exists in this country at present. Newly trained production personnel in these new manufacturing plants might never achieve the high level of quality already existing in the (b)(4) manufacturing plants.

More specifically, the subject EIBS/LEBS technology includes (1) an optical probe, and (2) EIBS/LEBS illumination/processing hardware . The EIBS/LEBS illumination/processing hardware provides light illumination for the probe and processes interacted light detected by the probe for the EIBS or LEBS measurement. (b)(4)

Because of their function and configuration, it is important that the EIBS/LEBS components be manufactured alongside their corresponding (b)(4) In particular, during operation, the EIBS or LEBS components need to communicate and interact with the (b)(4) during operation. As a consequence, it is important to stringently test communication, interoperability and quality control of partially and fully assembled combinations of the (b)(4) EIBS/LEBS components. This required system testing effectively mandates manufacture of the components at a common production facility.

(b)(4) Moreover, testing and manufacturing expertise for the EIBS/LEBS components resides in the same (b)(4) manufacturing facilities. This expertise and skill will facilitate development and production of the EIBS/LEBS components that achieve the same high degree of quality that presently exists for (b)(4) Also, development and production of EIBS/LEBS components at one of these facilities will advantageously enable the earliest commercial use of the EIBS/LEBS (b)(4) within the United States patient population.

Production of the EIBS/LEBS components at manufacturing facilities in the United States would likely require very costly and wasteful transportation of partially/fully assembled components to a common site for system testing. In addition, the EIBS/LEBS components measure small increases in blood content or alterations in tissue structure using optical means and are correspondingly mechanically sensitive devices. The required transportation would correspondingly increase risk for costly and labor intensive repair and adjustment that would otherwise not be necessary and make such multi-country component production impractical and unworkable.

Thus, requiring manufacturing in the United States of the EIBS/LEBS components effectively requires manufacturing of the corresponding (b)(4) n the United States as well. At best, the associated risks and poor business case for constructing manufacturing facilities in the United States to produce (b)(4) EIBS/LEBS components would further delay or permanently

prevent the decision to construct such facilities. As a consequence, at a minimum, a United States manufacturing requirement would delay access by the United States patient population to EIBS/LEBS (b)(4) and improved detection of cancerous and pre-cancerous lesions for many years.

Moreover, an exclusive license to the invention is particularly warranted with regard to the EIBS/LEBS (b)(4) technology. More specifically, as is described in this waiver application, the anticipated market price of the EIBS/LEBS enhancement technologies are a relatively modest portion of the overall (b)(4) and a substantial investment is required for integration and market approval. As a consequence, an exclusive license to the invention is an appropriate mechanism to provide an incentive to the risk taker (i.e., exclusive licensee) to (1) expend the significant resources necessary to develop a commercially useable design of the invention, and (2) assume the cost and risk of the clinical trials needed to obtain the approvals for its use in the United States and establish the database to prove its effectiveness in normal clinical practice. In the medical arts, the incentive to expend such resources traditionally has been accomplished by granting to the risk taker an exclusive license to the invention.

(d) *(the effect such delay may have on the U.S. and foreign public health* As discussed, it would take several years to build manufacturing plants and assemble the necessary technical expertise to manufacture EIBS/LEBS (b)(4) hat meet all necessary federal approvals and regulations for use with the United States patient population. There would be a corresponding delay in the clinical use of the EIBS/LEBS (b)(4) o detect GI-tract cancerous and pre-cancerous lesions in the U.S. patient population and, unfortunately, there will likewise be avoidable deaths and costlier and intrusive treatments of later stage cancers caused by undetected or late detected lesions.

***** *Identify the past marketing strategy and efforts for the technology, including*

the number of companies contacted, the methods used for marketing and contacting companies,

the types of licenses and terms offered to potential licensees,

comparison of terms offered to potential foreign licensee and those offered to U.S. companies, and

the responses of companies to marketing efforts.

The success of the EIBS/LEBS technology will depend on American BioOptics' and ability to integrate it effectively into a widely-used (b)(4)

product. After extensive research and discussion, to the best of American BioOptics' knowledge, no U.S. company currently manufactures or sells making it commercially impractical to manufacture (b)(4) corresponding EIBS/LEBS components in the United States. (b)(4)

(b)(4)

, American BioOptics formally engaged boutique investment banking firm Sikich Group to conduct an extensive search of other manufactuers of (b)(4) . The process of seeking a partner for the technology was conducted in the first half of 2010. Although many of these manufacturers do not participate (b)(4) market today and produce a significantly different and simplified product, American BioOptics nonetheless explored whether such manufacturers might present an alternative. Many of these are also foreign manufacturers and were ruled out. The list of companies with which American BioOptics held direct discussions includes (b)(4) the opportunity..

American BioOptics also considered a second potential alternative manufacturer in the United States, but it was not commercially viable. (b)(4) (b)(4) Proving clinical benefit, achieving the commercial release of a product, and surmounting barriers to entry to an established, competitive market with much larger players posed significant obstacles to (b)(4) success. As a result, American BioOptics believes that (b)(4) does not today represent a reasonable commercial alternative to manufacture the EIBS/LEBS (b)(4) technology in the United States.

Finally, as indicated above, American BioOptics also evaluated (b)(4) . Terms of the final agreement are still under detailed discussion, but it is likely that the license rights of American BioOptics to the EIBS/LEBS technologies in certain fields of use (b)(4) will be transferred to (b)(4) Northwestern would then be directly responsible for monitoring (b)(4) progress and

enforcing the license agreement with , including the diligence milestones. Once the agreements are executed, the development of the technology will require significant additional investment from both (b)(4) and American BioOptics on engineering evaluation, a multi-million dollar clinical trial, and detailed manufacturing development. Northwestern University and NorthShore University HealthSystem are seeking this waiver to provide assurance that such significant additional investment is justified.

Not Commercially Feasible

***** *Discuss the factors that make domestic manufacture not commercially feasible, including*

(a) the relative costs of U.S. and foreign manufacturing,

(b) the licensee's manufacturing capabilities within the U.S. and

(c) the efforts made by to locate, develop, or contract for such manufacturing capabilities, and any other circumstances that make foreign manufacture necessary.

Factors that make domestic manufacture of EIBS/LEBS not commercially feasible include, for example:

(a) *(the relative costs of U.S. and foreign manufacturing)* Modern in general are highly complex systems. (b)(4) The EIBS/LEBS probe technology comprises an optical probe and corresponding illumination/processing hardware that would need to be integrated in this process.

As stated in the response to the above waiver application questions, because of their function and configuration it is important and cost effective for the EIBS/LEBS components be manufactured along side their counterpart (b)(4) In particular, during operation, the EIBS/LEBS components communicate and interact with the (b)(4) As a consequence, it is correspondingly necessary to perform stringent testing of communication, interoperability and quality control of partially and fully assembled combinations of (b)(4) and EIBS/LEBS components. This required system testing effectively mandates manufacture of all the components at a common production facility.

is the most complex of these system components and all, or nearly all, of the world's are produced at a limited number of manufacturing facilities. Moreover, the testing and manufacturing expertise for EIBS/LEBS components reside in these same (b)(4) manufacturing facilities. Thus, requiring production of the EIBS/LEBS components at

manufacturing facilities in the U.S. while current (b)(4) production remains (b)(4) would require very costly and wasteful transportation of the partially/fully assembled components to a common site for system testing. Further, the mechanical sensitivity of the EIBS/LEBS components, which optically measure small increases in tissue blood content, would correspondingly create increased risk for additional costly and labor intensive repair and adjustment that would otherwise not be necessary and make such multi-country component production impractical and unworkable.

Thus, requiring manufacturing in the United States of the EIBS/LEBS components effectively requires manufacturing of the corresponding in the United States as well.

However, establishing a United States manufacturing operation would likewise be prohibitively expensive. Excluding acquisition or development of the highly specialized optics and imaging expertise necessary for system production, the establishment of the manufacturing line itself and hiring, training of employees, and establishing sales/service organization would easily exceed $50 million. This amount could reach $100 million if development or acquisition of underlying technologies is needed. Even if the effort were successful, U.S.-based manufacturing might not be economically competitive with well-established foreign manufacturers. The net result would be a substantial increase in the cost and price of the (b)(4) incorporating the EIBS/LEBS technologies, which would be passed on to the U.S. healthcare system and patient population.

(b) *(the licensee's manufacturing capabilities within the U.S.)* The proposed exclusive licensee (b)(4) on presently does not have the manufacturing capabilities in the U.S. to produce with the EIBS/LEBS enhancements or otherwise.

(c) *(the efforts made by to locate, develop, or contract for such manufacturing capabilities, and any other circumstances that make foreign manufacture necessary)* Northwestern, NorthShore University HealthSystem, and American BioOptics are unaware of any U.S. manufacturing facility that manufactures or possesses the sophisticated, precision manufacturing capability to manufacture the that is the subject of this waiver application.

** Identify the part or percentage of products arising from the invention that would be manufactured outside the U.S.*

For all the reasons stated above, it is cost prohibitive and would substantially delay introduction of EIBS/LEBS (b)(4) into the U.S. patient population if the EIBS/LEBS components are manufactured in the United States. As a consequence, it is proposed that no EIBS/LEBS component will be manufactured in the United States. However, as discussed below the proposed exclusive licensee presently employs and will continue to use U.S. marketing and sales channels, service personnel, and instructors as well as pay royalties to Northwestern University and the NorthShore University HealthSystem.

** Identify any value or benefit to the United States of licensing the technology even if it will not be manufactured in the United States, including*

i) the direct or indirect investment in U.S. plants or equipment, such as for marketing or packaging;

ii) the creation of new or higher quality U.S.-based jobs,

iii) the enhancement of the domestic skills base,

iv) the further domestic development of the technology,

v) a positive impact on the U.S. trade balance considering product and service exports as well as foreign licensing royalties and receipts, or

vi) cross-licensing, sublicensing, and reassignment provisions in the license which seek to maximize benefits to the U.S.

The proposed exclusive license possesses the expertise and manufacturing capability to develop and commercialize incorporating EIBS/LEBS technologies for commercial distribution and use in the United States patient population far more quickly than any other manufacturer. In this manner, the earliest commercial adoption can be achieved and the maximum benefit can be delivered to the United States at-risk for GI cancer, years before any other method.

The proposed exclusive licensee is committed to maximizing the benefits to United States industry to the extent possible, including through the use of United States personnel in market and sales channels for distributing United States-based instructors to train clinicians in this country to use the and United States personnel to service the (b)(4)

Licensing of the EIBS/LEBS technology to (b)(4) would further create royalty payments based on each (b)(4) sold which would

create a new revenue stream to the United States. Such royalty payments would positively impact the United States– trade imbalance and provide funding for future US-based innovation. The business strategy of American BioOptics is to use payments from the EIBS/LEBS agreement to fund the core business which is based in Evanston, Illinois in the further development of related, optical-based, colon cancer screening technologies that were licensed from Northwestern. Northwestern and American BioOptics also intend that the license to will be restricted to (b)(4), leaving American BioOptics free to develop (and manufacture) other embodiments of the technologies claimed in the relevant patent applications and issued patents. It is anticipated that this new research and development activity will lead to economic development through the creation of new, highly skilled biomedical engineering jobs in the United States. Northwestern University and NorthShore University HealthSystem will also share a portion of the license revenue, with the laboratories that have produced these inventions, which will proved support for them to continue their research efforts.

NU# 26034
Date Received 3/7/06

NORTHWESTERN UNIVERSITY
INVENTION DISCLOSURE

1. **Invention Title** Low-coherence Enhanced Backscattering Spectroscopy for Colorectal Cancer Screening without Colonoscopy.

2. **Inventors**

Name	Department	Position
Vadim Backman	BME	Assistant Professor
Hemant Roy	ENH	Associate Professor
Young Kim	BME	Grad. Student
Yang Liu	BME	Grad. Student
Vladimir Turzhitzky	BME	~~Adjunct Professor~~ Grad. Student
Jeremy Rogers	BME	Post doc

VB 03/25/08

3. **Description of Invention**

(a) **Brief summary stating its novelty and utility**
(b) **Background information, how it works, and improvements over existing technologies**
(c) **Detailed description with photographs, drawings, graphs and relevant manuscripts**
(d) **Expected commercial applications**

see below

4. **Date and place where discovery was made**

(a) **When was the idea conceived** ___March 2005_____
Where and how was it documented ___grant application to NIH (under review), grant application to Coulter Foundation (funded in July 2005)_____
(b) **When was the idea reduced to practice** ___partially reduced to practice in October 2005_____

5. **Sources of Support, Research Sponsor and Grant Numbers**

(a) **Northwestern University Funds, Facilities**___Vadim Backman's start-up fund, laboratory space in NU_____
(b) **Federal Agency** __NIH_____**Grant No.** __1R01CA112315_____
(c) **Foundation** _____Coulter Foundation_____
(d) **Corporate** _____N/A_____

Edison # 6144601-06-004

NIH # U01 CA 111257 to ENH

VB 03/25/08

NU# 26034
Date Received 3/7/06

NORTHWESTERN UNIVERSITY
INVENTION DISCLOSURE

1. **Invention Title** Low-coherence Enhanced Backscattering Spectroscopy for Colorectal Cancer Screening without Colonoscopy

2. **Inventors**

Name	Department	Position
Vadim Backman	BME	Assistant Professor
Hemant Roy	ENH	Associate Professor
Young Kim	BME	Grad. Student
Yang Liu	BME	Grad. Student

3. **Description of Invention**

(a) **Brief summary stating its novelty and utility**
(b) **Background information, how it works, and improvements over existing technologies**
(c) **Detailed description with photographs, drawings, graphs and relevant manuscripts**
(d) **Expected commercial applications**

see below

4. **Date and place where discovery was made**

(a) **When was the idea conceived** ___March 2005_____
Where and how was it documented ___grant application to NIH (under review), grant application to Coulter Foundation (funded in July 2005)_____
(b) **When was the idea reduced to practice** ___partially reduced to practice in October 2005_____

5. **Sources of Support, Research Sponsor and Grant Numbers**

(a) **Northwestern University Funds, Facilities**___Vadim Backman's start-up fund, laboratory space in NU_____
(b) **Federal Agency** __NIH_____**Grant No.** __1R01CA112315_____
(c) **Foundation** _____Coulter Foundation_____
(d) **Corporate** _____N/A_____

Edison # 6144601-06-0024

6. **Public Disclosure - Please state if any disclosure has been made or if any is planned in the next six (6) months. Give dates and places.**

(a) Journal article __manuscript to e submitted to Cancer Research ___
(b) Oral Presentation __DDW 2006, May 2006_____
(c) Poster Presentation _____
(d) Conference Abstract __no_____
(e) Disclosure to Industry __no_____
(f) Grant Proposal __Coulter Foundation grant application, funded in July 2005_____
(g) Other __no_____

7. **Prior Art**

Have you done a literature search? YES___X__ NO_____ If yes, include references
What related work in this area by others do you know? __none_____
_____

8. **Commercialization:**

(a) Are you aware of potential licensees for this invention? YES _____ NO __x__
If yes, give names of companies and contact persons known to you on a separate sheet
If no, what industry might have interest in this invention

(b) Would you like to develop this invention further with corporate research support YES___x__ NO_____

(c) Are you willing to participate in the marketing of this invention YES__x___ NO_____

9. **Materials Associated with Invention**

Did this invention use any Materials which were obtained with a Materials Transfer Agreement from a company or another institution YES _____ (Please give details); NO ___x___

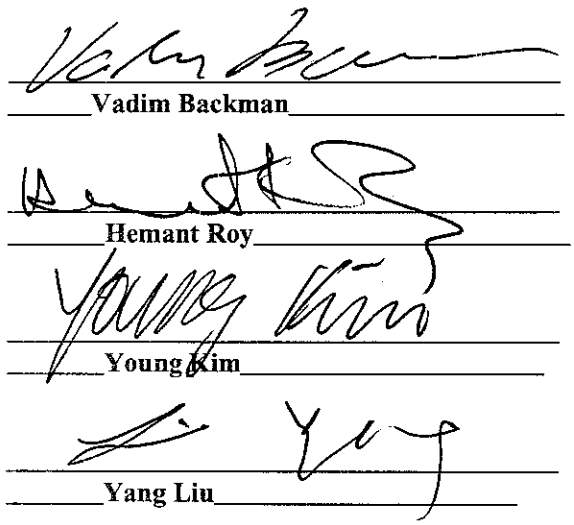
Did this invention use any materials (vectors, cell lines, animals, etc.) containing creDNA and/or lox DNA? YES _____ (Please give details) NO ___x___

Did this invention use information obtained from any Celera database?
YES _____ (Please give details) NO ___x___

Did you transfer to any researcher outside Northwestern any new Materials (DNA, peptides, cell lines, vectors, catalysts, polymers, alloys, etc.) of this invention YES _____ NO ___x___

This disclosure is submitted pursuant to the Northwestern University Patent and Invention Policy and is subject to all the terms of that Policy. If this invention is accepted by Northwestern University's Technology Transfer Program, I/We hereby agree to execute all necessary documents, assigning to Northwestern our rights in any patent application filed on this invention.

Signature of Inventor(s) **Date**



Vadim Backman

Hemant Roy

Young Kim

Yang Liu

Please place an asterisk next to the name of the Principal Investigator(s)

A. **Inventor:** **Name**
SS#
Departmer
Phone/Fax

Home Add **IL**

Citizenship

B. **Inventor:** **Name**
SS# rsonal I
Departmen
Phone/Fax/ western .edu
Home Addı 5
Citizenship

C **Inventor:** **Name**
SS# rsonal I
Departmen
Phone/Fax/

Home Addr
Citizenship

Personal Info

D **Inventor:** **Name**
SS# sonal I
Department
Phone/Fax/e western.edu
Home Addr
Citizenship P.R.China

Signature of Inventor(s) **Date**

Vladimir Turzhitzky — 3/4/2008

Jeremy Rogers — 2/27/08

E. Inventor: **Name** V
Departme
Phone/Fa
Home Ad
Citizensh

Personal Info

F. Inventor: **Name**
Departm
Phone/F
Home A
Citizensl

Personal Info

Please let us know your forwarding address before leaving Northwestern University

Please submit completed disclosure to:

Technology Transfer Program
Northwestern University
1880 Oak Avenue – Suite 100
Evanston, IL 60201
Phone: (847)491-3005
Fax: (847)491-3625

Low-coherence Enhanced Backscattering Spectroscopy for Colorectal Cancer Screening without Colonoscopy

Description of Invention

We disclose the invention of low-coherence enhanced backscattering (LEBS) spectroscopic markers capable of diagnosis of presence of precancerous lesions (adenomas) throughout the colon by means of LEBS examination of rectal surface. The significance of the invention in that it may be used for screening for colon cancer without the need for colonoscopy by means of a simple noninvasive rectal exam.

Rationale. Colorectal cancer remains the second leading cause of cancer death in the U.S Although colonoscopy is effective in preventing colorectal cancer (CRC), screening the entire at-risk population (>60 million Americans over age 50) through colonoscopy is impossible for a variety of reasons including expense (the cost of screening program would be ~$70,000,000,000), patient reluctance and complication rate. Indeed, currently the majority of the population receives no CRC screening whatsoever. Thus, identifying patients at the highest risk for CRC (i.e., risk-stratification) is critical for optimizing utilization of colonoscopy from a cost-benefit and risk-benefit perspective. Many screening techniques exploit the "field effect" of colon carcinogenesis, the proposition that the genetic/environmental milieu that results in a neoplastic lesion in one area of the colon should be detectable in uninvolved (i.e., colonoscopically normal-appearing) mucosa throughout the colon. Unfortunately, the most widely used marker of the field effect (distal colonic adenomatous polyp noted on flexible sigmoidoscopy) is plagued by poor sensitivity and positive predictive value, thus leading to both missed lesions and triggering multiple unnecessary colonoscopies, respectively (see Background and Significance).

Results. LEBS is a self-interference light-scattering phenomenon first discovered in our lab that gives rise to the enhanced backscattering of light in random media in directions close to the backscattering direction In our human studies we demonstrated that the assessment of LEBS signatures in the endoscopically normal rectal mucosa (the most readily accessible colonic mucosa) enabled identifying patients harboring neoplasia elsewhere in their colon. Indeed, the sensitivity of rectal EBS signatures was approaching 100% for diagnosis of colon carcinogenesis elsewhere in the colon, far exceeding any previously described markers. This is in part due to the ability of this technology to perform optical spectroscopic analysis of tissue at different depths ranging from only ~30 mm (e.g. colonic epithelium) to a few hundreds of microns (e.g. deep mucosa) while excluding interference from deeper, arguably less diagnostically significant, tissue layers such as submucosa. This suggests that EBS could be exploited for screening and risk-stratification of CRC. These preliminary results are discussed in detail below.

Long-Term Significance. In the long term, we envision the use of a free-standing LEBS probe during an annual rectal exam by a primary care physician to determine need for colonoscopy. Rectal LEBS test can be performed non-invasively without the need for colonoscopy or patients' colonic preparation. The latter is one of the major reasons for patients' non-compliance. Based on the results of the LEBS test, a patient may be indicated to receive a colonoscopy (which he will be more compliant to). Thus, patients at a higher risk for CRC will receive colonoscopies as appropriate, whereas low-risk patients do not undergo these expensive and uncomfortable procedures.

Results: Detailed Discussion. We assessed LEBS markers from 80 human subjects undergoing colonoscopy. LEBS was recorded from the rectal mucosa as well as from other sites in the colon. All LEBS readings were performed from endoscopically normal tissue at least 15 cm away from any neoplastic lesion. The mean age of the subjects was 56 8 ±10.7 with 53% being female We defined a low-risk group (44 subjects) as those without personal history of neoplasia (both current and previous colonoscopies) and no family history of adenomas/carcinomas. Twenty six (26) patients were noted to have adenomas and 10 patients had adenocarcinomas on current colonoscopy and these lesions were relatively uniformly distributed between the right and left colon. All adenomas were histologically confirmed. On average, 5 tissue sites were assessed per segment per each patient (~1400 LEBS readings total). Adenomas were approximately equally distributed between the sigmoid colon/rectum (28% of all adenomas), transverse colon (35%) and the cecum (38%).

We found that a number of LEBS signatures (obtained from the rectum) that were diagnostic for presence of adenomas elsewhere in the colon.

1) LEBS spectral slope is obtained as the absolute value of the linear coefficient of the linear fit to LEBS spectrum for a given backscattering angle θ. The spectral slope depends on the size distribution of scattering structures: abundance of smaller (up to 20 nm) scatterers increases the spectral slope. LEBS spectral slope was decreased in patients with colon adenomas ($p<10^{-6}$).

2) LEBS peak width. Angular width of the LEBS peak was decreased in patients with adenomas.

3) LEBS enhancement factor was also decreased in patients with adenomas.

4)LEBS autocorrelation decay rate. Autocorrelation of LEBS spectra $C_A(\Delta k) = \int I_{EBS}(k) I_{EBS}(k+\Delta k) dk$, with k the wavenumber, reveals the degree of refractive index fluctuations in tissue microarchitecture. In our data, $C_A(\Delta k) \propto \exp(-\Delta k^2 D)$, which is characteristic of many random mesoscopic systems with D referred to as the decay rate. $D \propto \left(\delta n^2 L_C / L_t\right)^{-1} \lambda^2$, where δn^2 is the variance of refractive index fluctuations, L_C is the refractive index correlation length, and L_t is the temporal coherence length of illumination. We found that D was decreased in patients with adenomas ($p<0.016$).

This is illustrated in Figs. 1 and 2, which show that there was a significant decrease in the spectral slope obtained from essentially any site in the colon including the cecum, transverse colon, and, most importantly, the rectum. These results show that the alteration of LEBS signatures in histolofically and endoscopically normal mucosa in humans (i.e., the field effect) is detectable by LEBS. Furthermore, LEBS markers were expressed in patients with colon cancer even more significantly than in patients with adenomas (Fig. 1(c)).

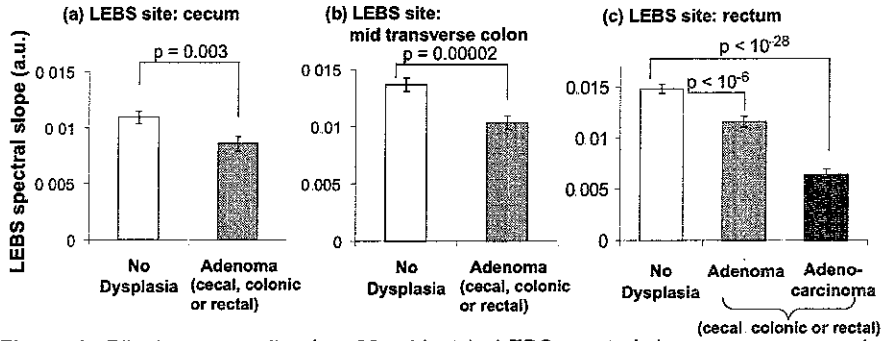


Figure 1. Pilot human studies (n = 80 subjects). LEBS spectral slopes were assessed from colonoscopically normal mocusa in (a) the cecum, (b) the mid transverse colon and (c) the rectum of subjects undergoing colonoscopy. The subjects were divided into three groups: no personal or family history of colonic neoplasia (n=44), subjects with adenomas anywhere in the colon (n=26), and subjects with adenocarcinomas anywhere in the colon (n=10). The LEBS spectral slope recorded from endoscopically normal mucosa was significantly lower in patients with adenomas compared to one recorded from the negative control subjects (p-value < 0.01) in agreement with the similar change observed in the animal studies. Importantly, spectral slope in cancer patients was decreased even more significantly than in patients with adenomas.

Sensitivity	100%
Specificity	60%
PPV	25%
NPV	100%

Table 1. Performance characteristics of rectal LEBS markers obtained from colonoscopically and histologically noral rectal mucosa for diagnosis of advanced adenomas elsewhere in the colon.

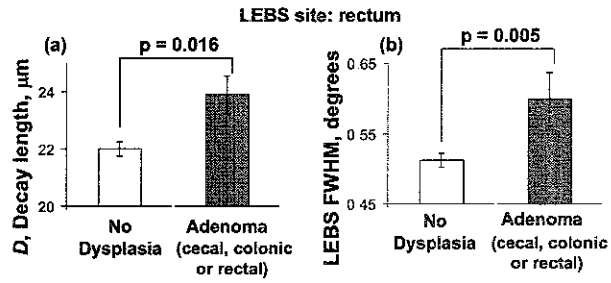


Figure 2. (a) Decay length (see section C8 C) and (b) FWHM of LEBS peak obtained from the rectal endoscopically and histologically normal mucosa can serve as markers of carcinogenesis elsewhere in the colon.

Given that the age is a major risk factor for CRC, in order to ensure that the changes in LEBS detect carcinogenesis as opposed to age difference between patients with adenomas and control subjects, we also studied how the spectral slope varies with age. We found that the spectral slope increases slightly with age, i.e. the opposite trend to the changes in CRC. Therefore, we conclude that the changes in spectral slope cannot be due to age differences in the patient population.

In order for LEBS to be clinically useful for risk-stratification of CRC, the mucosa that is most easily assayed (i.e rectum) would have to accurately reflect neoplastic events throughout the colon.

We, therefore, wanted to ascertain whether spectral signatures from the uninvolved histologically and colonoscopically normal rectal mucosa would mirror generalized colonic carcinogenesis. We confirmed this result in our pilot human studies. The performance of rectal LEBS for adenomas was excellent (Table 1). These numbers are even more remarkable when compared to existing CRC screening techniques. For instance, FOBT and fecal DNA analyses have sensitivities of 10.8% and 18.2%, respectively. It is particularly important to emphasize that high sensitivity and NPV are crucial for a practically useful screening test in order to minimize the false negative rate. Thus, clinically, it is much more acceptable to send some patients for negative colonoscopies rather than have subjects who are enrolled in a screening program develop CRC. We believe the modest specificity and PPV of LEBS will be improved with better markers and development of more sophisticated algorithms. However, even the modest data presented here are still a remarkable improvement over conventional methodologies. As our data show, the sensitivity of LEBS (100%) is much higher to the sensitivity of existing tests including FOBT (10.8%) and fecal DNA analysis (18.2%). From a PPV perspective, the ability of FOBT and flexible sigmoidoscopy to predict advanced adenoma was 9 8 and 6% respectively. Therefore, rectal LEBS already outperforms conventional biomarkers and with refinement promises to offer unprecedented power to risk stratify patients.

The Principal Investigator and the awardee institution shall abide by the Foundation's Intellectual Property Policy, which is as follows:

The Wallace H. Coulter Foundation (WHCF) supports translational research – research that often involves discoveries or inventions that constitute intellectual property in the form of patents, copyrights, or trade secrets. It is the desire of WHCF that such intellectual property be administered in a manner that promotes commercialization and clinical use at the earliest possible time.

Except as provided hereafter, the entire right, title and interest to any invention or discovery, which is or may be patentable under the laws of the United States or any foreign country, and which is conceived or first actually reduced to practice in the course of performance under a grant from WHCF, shall be assigned to and retained by the institution receiving the grant, unless the institution is proscribed from doing so by Federal laws or regulations. If the institution decides not to patent or otherwise develop the invention or discovery, the inventor(s) shall be free to patent or otherwise develop the invention subject to any rights that the institution may retain under its patent policy.

WHCF waives any ownership rights in the patent, or the right to an exclusive or nonexclusive license to practice or assign the invention or discovery. The granting of an exclusive or nonexclusive license by the institution to practice the invention shall be in accordance with the institution's policy on licensing.

In order to protect patent rights or trade secrets, publication or other public disclosure of information about the discovery or invention may be withheld for a reasonable period of time in accordance with the institution's patent policy.

Institutions are expected to have formal safeguards in place for maintaining the highest ethical standards when faced with real or potential conflicts of interest relating to commercialization of discoveries or inventions developed in the course of a research project funded by WHCF. If the principal investigator(s) or any other person being supported under a grant from WHCF, has an arrangement with any organization (non-profit or for-profit), other than the institution receiving the WHCF grant or the government, that would affect patent rights, trade secrets or copyrights for inventions or discoveries arising in whole or in part from the research supported by WHCF, information concerning such an arrangement shall be disclosed in writing at the time of the grant application or at the time such arrangements are agreed upon. In addition, if the principal investigator(s) or any other person being supported under a research grant from the WHCF has any ownership interest in a business that could benefit from the research, or is an employee of such a business, this fact must also be disclosed in the application or as soon as the ownership or employment relationship arises.

Pages 100 through 333 redacted for the following reasons:

Removed by agreement