Pages 1 through 7 redacted for the following reasons:
- -
Patent History - not requested

Thanks.

John

Attachments : Manufacturing waiver NORTHWESTERN UNIV 6144601-06-0047 - Ruderman memo.doc

From : **Marie Iamothe** On : **De**

To : odottwaiver@od.nih.gov

Summary

[Request ID No. ##1370## : 6144601-06-0047 U.S. Manufacturing Waiver Request for NORTHWESTERN UN 0047]

Description

U.S. MANUFACTURING WAIVER REQUEST

EIR: 6144601-06-0047

EIR TITLE: Guide-to-colonoscopy by Optical Detection of Colonic Micro-circulation

Patent applications: 11/604,659, Filing Date 11/27/2006

11/604,653, Filing Date 11/27/2006

This technology is planned be licensed by Northwestern University in conjunction with a previously approved U.S. Manufactur 6144601-03-0060. (This technology described by Northwestern University in this request as “Early Increase in Mircovascular I “EIBS””.

Northwestern University is requesting a Waiver of the Preference for United States Industry for the technology indicated above related inventions comprising the technology “Low-Coherence Enhanced Backscattering “LEBS”). These are optical detection both EIBS and LEBS, developed by both Northwestern University and NorthShore University HealthSystem (formerly known a Northwestern Healthcare). (b)(4)

(b)(4) While the EIBS/LEBS technology is expected to generate new product manufactured in the U.S., the technology is also expected to be commercialized the U.S. The requesters are unaware of any manufacturer in the U.S. with the capability of making such complex, precision o instruments (b)(4)

Requiring domestic U.S. manufacture would significantly delay introduction of this product for several years or perhaps indefin
requestors, requiring construction of a new manufacturing facility, as none presently exists in the U.S. Separate manufacture
transportation of mechanically sensitive components increasing risk for costly and labor-intensive repair or adjustment on final

Upon a review of the case and the particular circumstances of this case, the waiver request for this case should be approved,
U.S. industry that are possible are made.

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_ 6144601-06-0047_ 12-

From : **Marie Iamothe** On : **De**

To : odottwaiver@od.nih.gov

Summary

[Request ID No. ##1370## : 6144601-06-0047 U.S. Manufacturing Waiver Request for NORTHWESTERN UN
0047]

Description

U.S. MANUFACTURING WAIVER REQUEST

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EIR TITLE: Guide-to-colonoscopy by Optical Detection of Colonic Micro-circulation

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Please let us know if you have any additional questions.

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Attachments : US Manufacturing Waiver Request for Northwestern University_ 6144601-06-0047_ 12-

Pages 11 through 19 redacted for the following reasons:
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Internal

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 Application Nos. 11/604,659, filed 11/27/2006; 11/604,653, filed 11/27/2006.

EIR No.: 6144601-06-0047
Patent Docket Nos.: NU 26072 A
NIH Funding Agreements: R01 CA109861, U01 CA111257
EIR Title: Guide-to-colonoscopy by Optical Detection of Colonic Micro-circulation
Inventor Names: Vladimir Turzhitzky, Michael Siegel, Ramesh Wali, Vadim Backman, Hemant Roy, Young Kim and Yang Liu

Dear Dr. Crump:

This letter is in response to the US Manufacturing Waiver Request submitted by Northwestern University (Northwestern U.) 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) 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 (b)(4) in the United States. (b)(4) (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 Evanston Northwestern, any consortium issues should be considered in acting on this Waiver Approval. Special Requirements under RFA CA-04-006 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

Pages 22 through 24 redacted for the following reasons:
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Internal

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) (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) 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 (b)(4) display 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) (b)(4) As a consequence, the earliest commercialization of (b)(4) 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 (b)(4) (b)(4) 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 for operation or integration with an endoscope controller/display. 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. In order to more rapidly develop and deploy EIBS or LEBS probe enhanced endoscope systems into the U.S. patient population, it is presently planned that EIBS/LEBS probes will first be employed in the open channels of existing or slightly modified endoscope products, with integration of the EIBS/LEBS processing into the endoscopic system processing components. It is further planned that EIBS/LEBS probes can then be fully integrated into endoscopic systems in the next generation of endoscope products.

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

The endoscope is the most complex of these system components and nearly all of the world's endoscopic system production occurs in a limited number of Japanese manufacturing facilities. Moreover, testing and manufacturing expertise for the endoscopic add-on EIBS/LEBS components resides in the same Japanese endoscopic system 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 manufactured endoscopic systems. Also, development and production of EIBS/LEBS components at one of these facilities will advantageously enable the earliest commercial use of the EIBS/LEBS enhanced endoscopic systems within the United States patient population.

Production of the EIBS/LEBS components at manufacturing facilities in the United States while current endoscope production remains in Japan 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 endoscopic systems in the United States as well. At best, the associated risks and poor business case for constructing manufacturing facilities in the United States to produce endoscopes, endoscopic systems, and 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 enhanced endoscopic systems 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 endoscopic system enhancement 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 endoscopic system, 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 enhanced endoscopic systems that 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 enhanced endoscopic systems to 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 Olympus' ability to integrate it effectively into a widely-used, enhanced endoscopic

system product. After extensive research and discussion, to the best of American BioOptics' knowledge, no U.S. company currently manufactures or sells colonoscopes making it commercially impractical to manufacture colonoscopes and corresponding EIBS/LEBS components in the United States. The market has been dominated for several decades by three major Japanese endoscopic system manufacturers: Olympus, Pentax, and Fujinon, who hold approximate market shares of 70%, 17%, and 13%, respectively.

In its research for potential partners following Olympus initial expression of interest in the technology, American BioOptics formally engaged boutique investment banking firm Sikich Group to conduct an extensive search of other manufactuers of rigid medical endoscopes, imaging companies, and non-endoscope GI device manufacturers with substantially the same commercial terms. The process of seeking a partner for endoscopic applications of the technology was conducted in the first half of 2010. Although many of these manufacturers do not participate in the flexible endoscopic system 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 Pentax Medical, Given Imaging, CR Bard, Abbott Diagnostics, Fujinon, Canon Medical Imaging, Carl Zeiss Microimaging, Covidien, Karl Storz, Siemens Medical, Philips Medical Systems, Boston Scientific, GE Healthcare, Stryker, Welch Allyn, Johnson and Johnson, Medtronic, Baxter, Conmed, Cook Medical, Hitachi Medical Systems, Hologic, Richard Wolfe Medical Instruments, Roache Diagnostics, US Endoscopy, Optiscan Imaging, and Invendo Medical. None of these companies presented any alternatives to the Olympus opportunity..

American BioOptics also considered a second potential alternative manufacturer in the United States, but it was not commercially viable. A startup U.S. company, NeoGuide Systems, planned to market a new, computer-controlled colonoscope and system. Neoguide did not introduce a colonoscope, and it changed its market focus. 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 NeoGuides success. As a result, American BioOptics believes that Neoguide Systems does not today represent a reasonable commercial alternative to manufacture the EIBS/LEBS enhanced endoscopic system technology in the United States.

Finally, as indicated above, American BioOptics also evaluated all three major colonoscope manufacturers who all manufacture in Japan. After discussions with each, American BioOptics chose the world market leader, Olympus, as the preferred company to bring the technology to market because of its engineering expertise, extensive US and worldwide distribution network, and strong market share of 70% in the United States. 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 involving endoscopic systems will be transferred to Olympus. Northwestern would then be directly responsible for monitoring Olympus' progress and

enforcing the license agreement with Olympus, including the diligence milestones. Once the agreements are executed, the development of the technology will require significant additional investment from both Olympus 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 endoscopic probes and endoscopes not commercially feasible include, for example:

(a) *(the relative costs of U.S. and foreign manufacturing)* Modern endoscopes and endoscopic probes in general are highly complex systems. In particular, current endoscopes have specialized optics including miniaturized Charge Coupled Devices (CCDs) for high definition images, fiber optic bundles, and suitable characteristic of insertion tube. As noted above, endoscopes are typically sold for $30,000 or more, and are built and tested in stages and in conjunction with the endoscopic imaging system. 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 endoscopic systems. In particular, during operation, the EIBS/LEBS components communicate and interact with the endoscopic system controller/display. As a consequence, it is correspondingly necessary to perform stringent testing of communication, interoperability and quality control of partially and fully assembled combinations of endoscopes and EIBS/LEBS components. This required system testing effectively mandates manufacture of all the components at a common production facility.

The endoscope is the most complex of these system components and all, or nearly all, of the world's endoscopes are produced at a limited number of Japanese manufacturing facilities. Moreover, the testing and manufacturing expertise for endoscope-based EIBS/LEBS components reside in these same Japanese endoscopic system manufacturing facilities. Thus, requiring production of the EIBS/LEBS components at

manufacturing facilities in the U.S. while current endoscopic system production remains in Japan 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 endoscopic systems 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 enhanced endoscopic system 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 Olympus Corporation, has a significant presence in the United States including non-endoscopic system manufacturing, distribution, and engineering. Olympus Corporation has fourteen subsidiary companies in the U.S., including four companies relating to sales and service for endoscopic systems.

Olympus Corporation also has three U.S. manufacturing facilities for producing ultrasonic testing and eddy current testing instruments outside of the medical field as well as facilities for surgical devices. In addition, Olympus has over 4,200 employees within the U.S., and over 1,400 employees are working in the medical field. However, Olympus presently does not have the manufacturing capabilities in the U.S. to produce endoscopic systems 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 endoscopic systems used in colonoscopy or possesses the sophisticated, precision manufacturing capability to manufacture the enhanced endoscopic systems 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 enhanced endoscopic systems 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 licensee of the enhanced endoscopic system technology, Olympus, is the world's largest endoscopic system manufacturer with 70% of the world market. Olympus possesses the expertise and manufacturing capability in Japan to develop and commercialize enhanced endoscopic systems 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 endoscopic systems, United States-based instructors to train clinicians in this country to use the endoscopic systems, and United States personnel to service the endoscopic systems.

Licensing of the EIBS/LEBS technology to Olympus would further create royalty payments based on each endoscopic system and endoscopic probe sold which would

create a new revenue stream to the United States. Such royalty payments would positively impact the United States– Japan 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 Olympus will be restricted to the use of the EIBS/LEBS technologies in endoscopic systems, 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# 26072
Date Received 5/17/06

NORTHWESTERN UNIVERSITY
INVENTION DISCLOSURE

1. **Invention Title** Guide-to-colonoscopy by Optical Detection of Colonic Micro-circulation

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
Michael Siegel		
Ramesh Wali	ENH	Asst Prof 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** February 2005
Where and how was it documented grant application to NIH (under review), upcoming talk at DDW (May 2006)
(b) **When was the idea reduced to practice** February 2005-May 2006

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

(a) **Northwestern University Funds, Facilities** laboratory space
(b) **Federal Agency** NIH **Grant No.** R01 CA109861
(c) **Foundation**
(d) **Corporate** N/A

NIH U01 CA 111257 to ENH

VB 03/25/08

NU# 26072
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Young Kim	BME	Grad Student
Yang Liu	BME	Grad. Student

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see below

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Where and how was it documented ___grant application to NIH (under review), upcoming talk at DDW (May 2006)_____
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(b) Federal Agency __NIH_____Grant No. __ R01 CA109861_____
(c) Foundation _____
(d) Corporate _____N/A_____

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 __no
(b) Oral Presentation __DDW, May 2006_____
(c) Poster Presentation ___no_____
(d) Conference Abstract __no_____
(e) Disclosure to Industry __no_____
(f) Grant Proposal __ grant application to NIH (under review), _____
(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)

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Signature of Inventor(s) **Date**

Vladimir Turzhitzky 3/4/2008

Michael Siegel

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Personal Info

Please let us know your forwarding address before leaving Northwestern University

Please submit completed disclosure to:

Technology Transfer Program
Northwestern University
1800 Sherman Avenue, Suite 504
Evanston, IL 60201

PRELIMINARY RESULTS

Although it is has been well established that blood supply to neoplastic tissue is increased, very little attention has been given to alterations in blood supply at pre-neoplastic stage, largely due to the methodological difficulties in reliably quantitating microvascular blood supply. Furthermore, previous studies focused on blood supply increase to a neoplastic lesion itself. Our group was the first to observe a new biological phenomenon, EIBS. EIBS manifests itself as an increase in blood supply in the microcirculation (primarily mucosa) supplying blood to epithelium. EIBS occurs very early during the process of colon carcinogenesis. Our data in animal models of colon carcinogenesis showed that EIBS starts far earlier than development of adenomas and aberrant crypt foci (i.e., the earliest marker of carcinogenesis) and precedes the development of currently known molecular markers of colonic neoplasia. Furthermore, EIBS can be detected outside a neoplastic lesion. This opens a possibility to sense a lesion outside its physical extend.

Polarization-gated Fiber-Optic Probe to Detect EIBS. We developed a fiber-optic probe to accurately detect blood supply in tissue mucosa. Figure 1 illustrates the design of the probe. The probe consisted of 100 μm-diameter fibers, one of which was used for delivery of linearly polarized light from a Xe-lamp onto tissue surface and the other fiber two for collecting scattered light from the tissue. A positive aspherical lens was positioned at the focal distance from the fiber tips. We tested several lens types including ball, graded refractive index (GRIN), and aspherical lenses. We determined that the aspherical lens provided improved probe performance compared to the other lens types. This lens focused light backscattered from a sample onto different fibers depending on the angle of backscattering. It also ensured that the collection fibers receive scattered light from the same tissue site (as in our laboratory instrument) and prevents collection of specular reflectance from probe and tissue surfaces. In the distal (i.e., opposite to tissue) end of the probe, the linear array of fibers was coupled to an imaging spectrograph and a CCD. Two thin film polarizers were mounted on the proximal tip of the probe to polarize the incident light and enable collection of both polarization components (i.e. parallel $I_{\parallel}$ and perpendicular $I_{\perp}$ to the incident polarization) of the backscattered light to allow for polarization gating. All components of the probe were made from FDA approved materials.

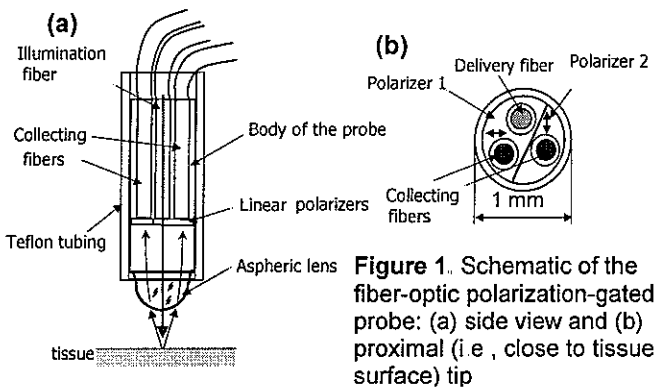

Figure 1. Schematic of the fiber-optic polarization-gated probe: (a) side view and (b) proximal (i.e., close to tissue surface) tip

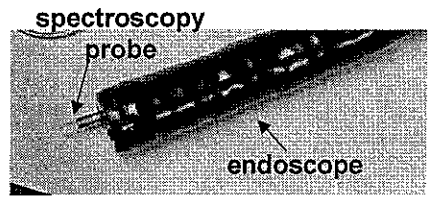

Figure 2. Photograph of the polarization-gated probe in an accessory channel of an endoscope

Polarization-gating[1, 2] Polarization gating has been previously used to selectively record short-traveling photons as well as to increase contrast for photons emerging from deeper tissue. As has been shown by our and other and our groups, the differential polarization signal $\Delta I(\lambda) = I_{\parallel}(\lambda) - I_{\perp}(\lambda)$ is primarily contributed by scatterers located close to the tissue surface and, therefore, particularly sensitive to the properties of the superficial tissues, e.g. epithelia.[1-12] Our experiments showed that the contribution to the differential polarization signal from deeper tissue structures decreases exponentially with "optical distance" τ to the structure and, hence, with depth ($\tau = L/l_S$ with L "physical" depth and l_S photon mean free path length in tissue). Because optical density of epithelium is much smaller than that of underlying connective tissue, in the colon, differential polarization signals are primarily collected from the epithelium plus up to ~50 μm of underlying connective tissue [1-3] This near-surface portion of subepithelial stroma contains a

network of capillaries supplying oxygen to the epithelium. $I_{||}$, diffuse reflectance $I_{||}+I_{\perp}$, and $I_{\perp}$ contain information about progressively deeper tissue, up to several millimeters below the surface.

Measurement of Subepithelial Blood Content.[13, 14] The blood content in the capillaries immediately below epithelium can be quantitatively estimated from the spectral analysis of $\Delta I(\lambda)$. To achieve this, we obtained the scattering images of rats' RBCs. Although Hb primarily absorbs visible light, it is not sufficient to measure only the absorption spectra of Hb molecules. RBCs, which are filled with Hb, are large scatterers approximately 7-8 microns in diameter. Therefore, the contribution from the RBCs couples both absorption and scattering. Our data demonstrate that differential polarization signal measured from a tissue $\Delta I(\lambda)$ can be written as

$$\Delta I(\lambda) = \Delta I_S(\lambda) + \alpha \Delta I_{RBC}(\lambda), \qquad (1)$$

where $\Delta I_S(\lambda)$ is the signal contributed by epithelial cells and other non-RBC components of the superficial tissue (not a priori known), $\Delta I_{RBC}(\lambda)$ is the signal experimentally measured from isolated ref blood cells (thus, this signal is known), and α is the number density of RBCs per mm^2. We have developed an algorithm to find the fitting parameter α by minimizing the Hb absorption bands in $\Delta I_S(\lambda)$.[5, 13] For *in situ* applications, where hemoglobin is present in both oxygenated ($\Delta I_{RBC\text{-}O2}(\lambda)$), and deoxygenated ($I_{RBC\text{-}DO2}(\lambda)$) forms,

$$\Delta I_{RBC}(\chi;\lambda) = \chi \Delta I_{RBC\text{-}O2}(\lambda) + (1-\chi) I_{RBC\text{-}DO2}(\lambda), \qquad (1.a)$$

with χ the oxygen saturation coefficient also determined by means of optimization.

Measurement of Mucosal/Submucosal Blood Content.[13] We also assessed blood supply in the deeper tissue layers, i.e. overall mucosa and submucosa, via $I_{\perp}(\lambda)$ (as opposed to ΔI, this signal is primarily contributed not by single but multiple scattering process) using previously reported and well tested algorithm based on the diffusion approximation.[15] This method was also used previously by our and other groups to detect dysplastic (later-stage) lesions in the colon, esophagus, oral cavity, and cervix.[15-20] We investigated the changes in the blood supply to mucosa/submucosa by means of the analysis of the cross-polarized signal $I_{\perp}(\lambda)$. Briefly, a diffusion approximation model is fit to the data. The model I_M depends on the spectra of the transport scattering $\mu'_s(\lambda)$ and absorption coefficient

$$\mu_a(\lambda) = \chi \mu_{a-O2}(\lambda) + (1-\chi)\mu_{a-DO2}(\lambda), \qquad (2)$$

which is contributed by both oxygenated $\mu_{a-O2}(\lambda)$ and deoxygenated $\mu_{a-DO2}(\lambda)$ Hb species with oxygen saturation χ found as a fitting parameter. μ_a is proportional to the concentration of the respective form of Hb in tissue. It is conventionally assumed that Hb is the only significant absorber of visible light in the mucosa and $\mu'_s(\lambda)$ should not exhibit Hb absorption bands.[5]

Measurement of Oxygen Saturation.[14] As discussed above, due to distinctly different absorption spectra of oxy- and deoxy-hemoglobin, not only does spectral analysis of polarization gated signals enables measurement of blood content but also blood oxygentation (aka. oxygen saturation, $S_{o2}=\chi$). We validated S_{O2} calculations from spectral data using the method reported by Hull and Foster.[21] The accuracy of oxygen saturation measurement was excellent with error < 1%.

<u>*Accuracy of EIBS Assessment Using Fiber-Optic Probe.*</u> We also validated the ability of the probe to assess hemoglobin concentration in studies with tissue models. The tissue models were fabricated and the analysis of spectral data was performed as discussed above. As shown in Figs. 3(a,b), the probe enables accurate assessment of hemoglobin concentration. The root mean square (r.m.s.) error of measurements for concentrations <1.2 g/L for superficial tissue was <0.01 g/L and that for deeper tissue was <0.02 g/L. We point out that according to our EIBS data in animals as well as humans, the dynamic range of Hb concentrations was from 0 to ~0.6 g/L. Thus, we conclude that the range of concentrations for which the probe measurements are sufficiently accurate is at least twice the range within which Hb concentrations vary in control and neoplastic animals/humans. Indeed, the error of measurements was ~5 fold less than the difference between the average concentrations for control and preneoplastic tissue.

As shown in Figs 3(c,d), both "absorption band area" and "absorption band intensity" methods enable accurate assessment of hemoglobin concentration with the error of measurements for concentrations <1 2 g/L 0 02 g/L and 0 03 g/L, respectively, and for concentrations from 1 2 to 1 8 g/L, 0 07 g/L and 0 09 g/L, respectively We conclude that the "absorption band area" approach may indeed provide improvement over the diffusion approximation-based method, particularly for higher Hb concentrations

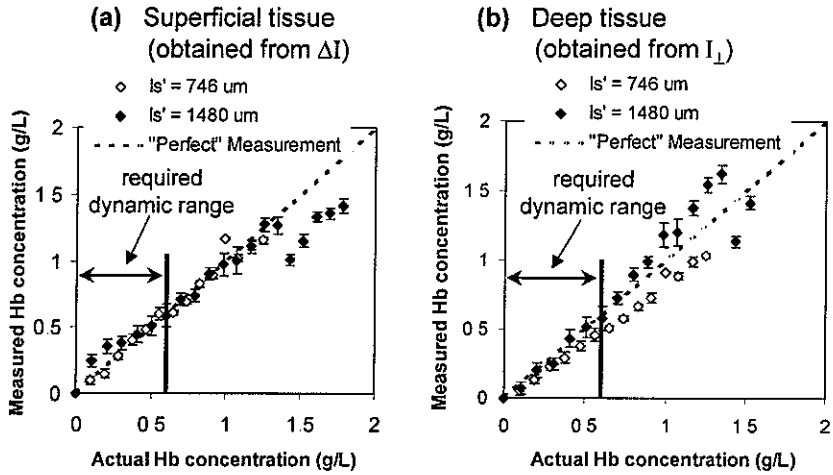

Figure 3. Accuracy of optical measurement of Hb content in (a) superficial tissue (obtained from $\Delta I(\lambda)$ using Eq 1) and in (b-d) deeper tissue (~transport mean free path depth, obtained from $I_{\perp}(\lambda)$) using (b) the diffusion approximation The dashed line shows what the data would look like if the accuracy of measurements were 100%. See text for detail.

EIBS Precedes Formation of Known Markers of Colon Carcinogenesis [13] We have recently reported our results in two animal models of intestinal carcinogenesis that EIBS

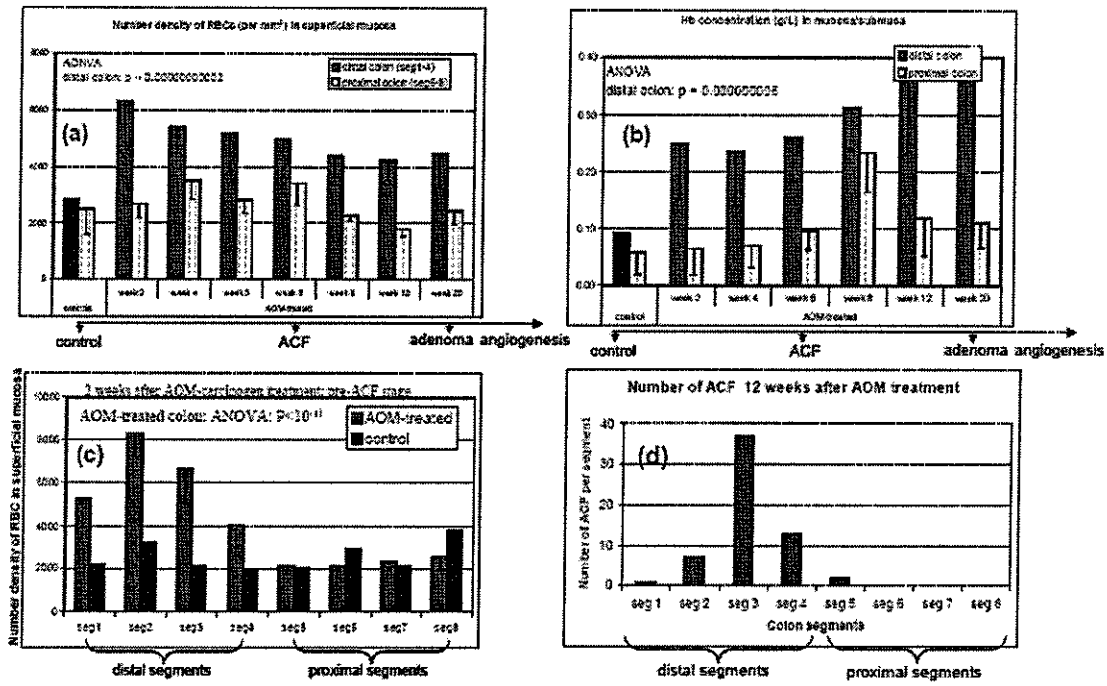

Figure 4. Alterations of blood supply in early experimental carcinogenesis observed using polarization spectroscopy. (a) and (b): Temporal progression of EIBS to the colonic epithelia of carcinogen (AOM)-treated rats obtained from the superficial mucosa (a) and deeper mucosa/submucosa (b). Solid bars – distal colon, shaded bars – proximal colon. Red bars – carcinogen-treated rats; blue bars – control animals. (c): Spatial variations in the distribution of blood supply to the superficial mucosa of the colons of AOM-treated and control (saline-treated) rats. Segments are numbered progressively from the most distal (segment 1) to the most proximal (segment 8). Red bars – carcinogen-treated rats; blue bars – control animals. (c): Spatial variations in the distribution of the earliest biomarker of colon carcinogenesis, abnormal crypt foci (ACF), from distal to proximal rat colons

precedes the development of any currently known histologic or molecular markers of colon carcinogenesis. These results were reported in Ref.[13]

EIBS Is an Accurate Predictor of Colonic Neoplasia: Animal Study.[13] In order to assess whether EIBS may serve as a clinically useful biomarker, we determined the performance characteristics of EIBS to detect future ACF in AOM-treated rats and concurrent adenomas in humans. First, we ascertained whether EIBS in the histologically normal uninvolved mucosa in AOM-treated rats (developing colon cancer) would mirror generalized colonic carcinogenic phenotype. We found that EIBS had excellent ability to distinguish animals at risk for CRC from the negative controls even at the pre-ACF stage of CRC. Indeed, the diagnostic accuracy of EIBS far exceeded conventional markers with high (>90%) sensitivity, specificity, positive and negative predictive values even at the earliest stages of colon carcinogenesis, preceding the development of currently known markers of CRC (Table 1)

Table 1: EIBS diagnosis of predisposition to CRC in AOM-treated rat model.

Sensitivity	94%
Specificity	96%
PPV	97%
NPV	92%

EIBS Gradient Localizes Adenomas: In Vivo Clinical Study. We wanted to prove that EIBS and, importantly, EIBS gradient (i.e., progressive increase in blood content towards an adenoma) can be observed in vivo. We conducted a pilot investigation in human subjects undergoing screening colonoscopies (n=150 subjects including 26 subjects who had adenomas on colonoscopy). All adenomas were diminutive (size<5 mm). There were no significant differences in age or gender between patients with a negative colonoscopy and those who harbored neoplasia. We used an endoscopically-compatible fiber-optic probe discussed in the preceding section. The probe was inserted into the accessory channel of a colonoscope. During colonoscopy, EIBS spectral data were acquired by the probe from the following locations: adenomatous polyp (if present), an endoscopically normal location within 10 cm from the adenoma, from the same colonic segment where the adenoma was located (typically within 30 cm from the adenoma) and the other segments (dubbed "outside" segments). In patients with negative colonoscopy, measurements were taken at random from each of the three colonic segments (i.e., discending colon including rectum and sigmoid colon, mid-transverse colon, and ascending colon including the cecum). On average, three spectra were obtained from each tissue site and more than 10 different tissue sites were probed for each patient.

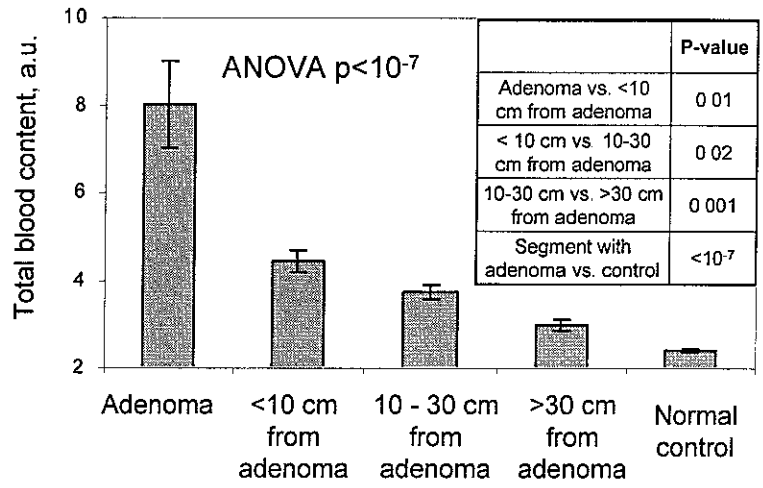

Figure 5. EIBS was observed in our in vivo studies (n=150 patients). The x-axis shows a location of EIBS reading. "Outside segment" stands for a colonic segment adjacent to the one where an adenoma was located. Normal control values were taken from patients with negative colonoscopy from the same colonic segments where adenomas were found in patients with positive colonoscopy

	Sensitivity	Specificity	PPV	NPV
<10 cm vs. 10-30 cm from adenoma	95%	68%	72%	96%
Segment with adenoma vs. normal control	89%	79%	87%	80%
Adenoma vs. normal control	97%	92%	89%	96%

Figure 6. Performance characteristics of EIBS measured from endoscopically normal tissue (except in the case of EIBS recorded from adenomas themselves) to localize diminutive adenomas.

Our data (Fig. 5) demonstrate a marked augmentation of blood content in the uninvolved (endoscopically and histologically normal) colonic mucosal in patients with adenomas compared

to the control subjects. Importantly, EIBS progressively increased when approaching a neoplastic lesion. Indeed, EIBS was noticeable about 30 cm from the location of the adenoma and progressed at 10 cm from the lesion and at the site of the lesion itself. It is this property of EIBS that may potentially guide an endoscopist to identify high-risk colonic segments.

The performance characteristics of EIBS gradient to distinguish colonic segments with and without adenoma as well as differentiate between a tissue site located within 10 cm from the adenoma and between 10 and 30 cm are shown in Figure 6. Although pilot, these characteristics are encouraging. The results are even more impressive given that all adenomas in the study were diminutive and we expect that the diagnostic performance of EIBS will be even better for advanced adenomas, which have greater clinical significance. The performance characteristics of EIBS are even more remarkable given that this is the first technique clinically tested that may be used to guide colonoscopy. The diagnostic performance of EIBS is also superior to conventional CRC screening techniques. For instance, a recent study demonstrated that FOBT and fecal DNA analysis had a sensitivity of 10.8% and 18.2%, respectively, and the sensitivity and positive predictive value of flexible sigmoidoscopy was reported to be only 52% and 6%, respectively. Furthermore, the analysis of our in vivo data showed that there was minor variation in microvascular blood content among the three colonic segments in control subjects, males vs females, and patients of different age (from 40 to 80 years old). The accuracy of EIBS-based colonoscopy guidance may be improved by accounting for these variations.

FUTURE APPLICATIONS

Using 4D-ELF, our group was the first to report a new biological phenomenon, early increase in microvascular blood supply (EIBS) in colonic mucosa in early CRC. Importantly, spatially EIBS extended outside the location of a neoplastic lesion (within ~1/3 of colon from the lesion) and its magnitude increased in the proximity to adenomas. Thus, our data showed that EIBS allowed remarkably accurate determination as to whether a given colonic segment harbors adenoma and could be used to indicate to an endoscopist the proximity of an adenoma. The methodology is to use EIBS to reduce colonoscopic miss rate (15-20% for adenomas and 6-12% for advanced adenomas) by guiding colonoscopy. We propose two applications of EIBS (Fig. 7)

Application A: EIBS assessed from a given colonic segment will signal endoscopist that this segment is at risk for harboring adenomas and requires more rigorous colonoscopic evaluation. If a segment is not at-risk as determined by EIBS measurements, an endoscopist may make decision to focus on other colonic segments that may require more intense examination

Application B: If adenoma is not readily visualized within this segment, increase in EIBS with approaching a lesion will guide an endoscopist in search for a hidden neopalsia.

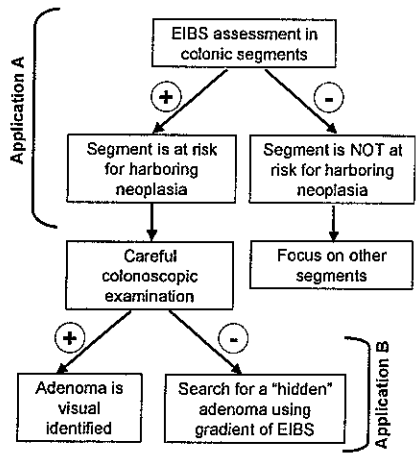

Figure 7. Methodology of EIBS-assisted colonoscopy

CLAIMS

1) We disclose the development of endoscopically compatible fiber-optic probe for EIBS assessment in vivo

2) EIBS is a marker of pre-cancerous lesions (e.g., adenomas) outside their physical extend.

3) The concept of EIBS-assisted colonoscopy (applications A and B) may be used to a) increase the efficacy of colonoscopy and reduce miss rate of detection of adenomas during colonosocpy and b) reduce the time and cost of colonoscopy.

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