

Pages 1 through 8 redacted for the following reasons:

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From : **Marie Iamothe**

On : De

To : odottwaiver@od.nih.gov

Summary

[Fwd: Request ID No. ##1368## : U.S. Manufacturing Waiver Request for NORTHWESTERN UNIV. EIR: 6144

Description

U.S. MANUFACTURING WAIVER REQUEST

EIR: 6144601-06-0042

EIR TITLE: Noninvasive diagnosis of pancreatic cancer without the need for interrogation of pancreas light scattering fingerprinting (ELF) and low-coherence enhanced backscattering (LEBS

Patent application: 11/803,418, Filing Date 5/14/2007

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 inventions comprising the technology "Low-Coherence Enhanced Backscattering "LEBS"). These are optical detection technol EIBS and LEBS, developed by both Northwestern University and NorthShore University HealthSystem (formerly known as Ev: 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_ 6144601-06-0042_ 12-



Page 11 redacted for the following reason:

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From : **Jannette Wilson**

On : Ja

To : beckyc@northwestern.edu

Summary

US Manufacturing Waiver Request Decision Letter - EIR: 6144601-06-0042 [Request ID No. ##1368##]

Description

Good Morning,

The following referenced U.S. Manufacturing waiver request has been approved:

NIH EIR#: 6144601-06-0042

Invention: Noninvasive Diagnosis of Pancreatic Cancer without the Need for Interrogation of P of Elastic Light Scattering Fingerprinting (ELF) and Low-Coherence Enhanced Backscattering Spectroscopy

NIH Funding Agreement No(s): R21 CA102750, U01 CA111257

Attached is a copy of the decision letter approving the U.S. Manufacturing waiver request for tl technology. Note that the original decision letter has been mailed to your institution.

Please let us know if you have any questions.

Thank you.

The iEdison Waiver HelpDesk Team
Division of Extramural Inventions and Technology Resources (DEITR)

OPERA, OER, OD, NIH, HHS
(301) 435-1986
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Attachments : US Manufacturing Waiver Decison Letter for Northwestern University 6144601-06-0042.

Pages 14 through 19 redacted for the following reasons:

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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 11/803,418, filed 5/14/2007.

EIR No.: 6144601-06-0042

Patent Docket Nos.: NU 26063

NIH Funding Agreements: R21 CA102750, U01 CA111257

EIR 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.

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

This case (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)

(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]

[REDACTED] 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**

Pages 22 through 24 redacted for the following reasons:

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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 [REDACTED]

(b)(4)

[REDACTED] This waiver request is being submitted by Northwestern and NorthShore University HealthSystem, both grantee institutions, on behalf of American BioOptics [REDACTED]

(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 [REDACTED] and manufactured outside the US. [REDACTED]

(b)(4)

[REDACTED] 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. [REDACTED] 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 possibility for cancerous or pre-cancerous lesions. The associated [REDACTED] [REDACTED] 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 [REDACTED]

(b)(4)

[REDACTED] to 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 (b)(4) that incorporate 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)

(b)(4) As described in detail below, requiring that (b)(4) or (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 (b)(4)

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) and 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 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 (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 (b)(4) could 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) 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 (b)(4) 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 (b)(4) 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 (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) (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) 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 (b)(4) 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 (b)(4) ability to integrate it effectively into a widely-used (b)(4)

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

(b)(4)

(b)(4)

[REDACTED] American BioOptics formally engaged boutique investment banking firm Sikich Group to conduct an extensive search of other manufacturers [REDACTED] (b)(4)

(b)(4)

[REDACTED] The process of seeking a partner [REDACTED] of the technology was conducted in the first half of 2010.

Although many of these manufacturers do not participate in the [REDACTED] (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)

[REDACTED] None of these companies presented any alternatives to the [REDACTED] (b)(4) opportunity..

American BioOptics also considered a second potential alternative manufacturer in the United States, but it was not commercially viable [REDACTED] (b)(4)

(b)(4)

(b)(4)

[REDACTED] 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 [REDACTED] (b)(4) success. As a result, American BioOptics believes that Neoguide Systems does not today represent a reasonable commercial alternative to manufacture the EIBS/LEBS [REDACTED] (b)(4) technology in the United States.

Finally, as indicated above, American BioOptics also evaluated [REDACTED]

(b)(4)

[REDACTED] 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 [REDACTED] (b)(4) will be transferred to [REDACTED] (b)(4) Northwestern would then be directly responsible for monitoring [REDACTED] (b)(4) progress and

enforcing the license agreement [REDACTED] including the diligence milestones. Once the agreements are executed, the development of the technology will require significant additional investment from both [REDACTED] 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 [REDACTED] (b)(4) [REDACTED] not commercially feasible include, for example:

(a) *(the relative costs of U.S. and foreign manufacturing)* Modern [REDACTED] [REDACTED] in general are highly complex systems. In particular, [REDACTED]

(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 [REDACTED] (b)(4) [REDACTED] In particular, during operation, the EIBS/LEBS components communicate and interact with the [REDACTED] (b)(4) [REDACTED] As a consequence, it is correspondingly necessary to perform stringent testing of communication, interoperability and quality control of partially and fully assembled combinations of [REDACTED] (b)(4) [REDACTED] and EIBS/LEBS components. This required system testing effectively mandates manufacture of all the components at a common production facility.

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

(b)(4)

(b)(4) presently does not have the manufacturing capabilities in the U.S. to produce (b)(4) 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 (b)(4) or possesses the sophisticated, precision manufacturing capability to manufacture the (b)(4) 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 licensee (b)(4)

(b)(4)

(b)(4) assesses the expertise and manufacturing capability in Japan to develop and commercialize (b)(4) incorporating EIBS/LEBS technologies for commercial distribution and use in the United States patient population (b)(4) 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 (b)(4) United States-based instructors to train clinicians in this country to use the (b)(4) 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 (b)(4) 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 (b)(4) will be restricted to (b)(4) (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 provide support for them to continue their research efforts.

NORTHWESTERN UNIVERSITY INVENTION DISCLOSURE

1. **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.

2. **Inventors**

<u>Name</u>	<u>Department</u>	<u>Position</u>
<u>Vadim Backman</u>	<u>BME</u>	<u>Assistant Professor</u>
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		Postdoc

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 July 2005
Where and how was it documented grant application to NIH (under review), grant application to NSF (funded on August 22, 2005)
- (b) When was the idea reduced to practice August 2005-January 2006

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

- (a) Northwestern University Funds, Facilities laboratory space
- (b) Federal Agency NSF Grant No. BES0547480
- (c) Foundation Steinkoler Pancreatic Cancer Foundation
- (d) Corporate N/A

NIH R21CA102750 to Backman
NIH U01CA111257 to ENH

VB 03/25/08

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- (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 manuscript to be submitted to Cancer Research on March 30, 2006
- (b) Oral Presentation no
- (c) Poster Presentation no
- (d) Conference Abstract no
- (e) Disclosure to Industry no
- (f) Grant Proposal grant application to NSF (funded on August 22, 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

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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.

Description of Invention

We disclose the invention of a new methodology for noninvasive diagnosis of pancreatic cancer without the need for interrogation of the pancreas. This work builds upon our development of two complimentary optical techniques, four-dimensional elastic light scattering fingerprinting (4D-ELF) and low-coherence backscattering (LEBS) spectroscopy, for *in situ* sensing of subtle histologically-undetectable changes in tissue nano/micro-architecture associated with carcinogenesis. The significance of the invention is that it may be used for screening for pancreatic cancer without the need for interrogation or endoscopic visualization of the pancreas, which is extremely complicated and high-risk procedure, by means of a simple examination of duodenal tissue, which is essentially risk-free. Thus, this methodology will enable for the first time screening for pancreatic cancer.

Statement of Problem. Pancreatic cancer is the fourth leading cause of cancer death in the United States and has the worst prognoses of all major cancers as illustrated by essentially the same incidence (32,800) and mortality (31,800) rates and an overall 5-year survival rate <5%. The reason for this grim prognosis is that most pancreatic cancers are diagnosed at a stage when the option of a curative surgical resection is not available. Presently, no current imaging studies including high-resolution CT, MRI, endoscopic ultrasound (EUS), and endoscopic cholangiopancreatography (ERCP) can reliably detect pancreatic tumors at potentially resectable stage (stage 1). Moreover, despite years of research, no clinically effective molecular markers have been developed. Importantly, widespread pancreatic cancer screening by means of examination of the pancreatic duct (e.g., ERCP) is not feasible given that essentially any interrogation of the pancreatic duct including biopsy, fiber-optic evaluation, and brushing may lead to serious complications in ~20% cases, including acute pancreatitis (~5%), which is a potentially life-threatening condition. Clearly, this approach is not suitable for routine screening over successive points in time but may be appropriate for selective situations in which the suspicion for an advanced precursor lesion or early staged tumor is high.

Our New Strategy. Our methodology is to use biophotonics approach for the early detection of pancreatic cancer without the need for direct interrogation of the pancreas, thereby limiting potential complications, most notably pancreatitis. Our strategy is based on detection of the "field-effect" of pancreatic carcinogenesis. The field-effect is the proposition that the genetic/environmental milieu that results in a neoplastic lesion in a particular tissue site should be also detectable outside this location. This opens a possibility to diagnose the presence of pancreatic neoplasia by examination of the duodenal periampullary mucosa (Fig. 1(a)), which can be readily accessed by means of existing upper endoscopy techniques without the risk of pancreatitis or other serious complications. However, no previous studies have demonstrated the feasibility of diagnosis of pancreatic cancer by means of examination of duodenal tissue by any means and, in particular, by means of optical techniques. As discussed below, we have obtained the first data showing such a possibility.

Long-Term Significance. The utilization of the field-effect could potentially revolutionize the diagnosis of pancreatic neoplasms by predicting the presence of pancreatic cancer via assessment of the uninvolved (endoscopically and histologically normal) duodenal mucosa adjacent to the opening of the pancreatic duct (ampulla), which is easy to access during routine endoscopy and without the risk associated with ERCP. This duodenal approach becomes even more clinically attractive giving the advent of ultra-thin endoscopes allowing upper endoscopy to be done safely without discomfort or need for sedation.

Although, in principle, 4D-ELF and LEBS signals can be obtained *in vivo* by means of a specialized fiber-optic probe, future application of this technique will not necessarily require *in vivo* measurements. Indeed, the diagnosis may be based solely on 4D-ELF/LEBS examination of duodenal biopsy obtained during upper endoscopy, which is currently a routine procedure. This test can potentially enable for the first time accurate risk stratification in the general population along with

individuals with genetic/environmental risk factors without the risks associated with the interrogation of the pancreas. 4D-ELF/LEBS test would identify a cohort of patients in whom targeted, intensive examination or treatment of pancreatic cancer is warranted.

Claims. Based on our results (see below), we make the following claims:

- 1) Presence of pancreatic cancer can be detected by examination of endoscopically and histologically normal duodenal tissue, thus avoiding risks associated with interrogation of the pancreas.
- 2) 4D-ELF and LEBS can detect these changes in the duodenal tissue.
- 3) We have discovered 4D-ELF and LEBS signatures capable of accurate diagnosis of pancreatic cancer at a potentially curable stage.

Results

Four-dimensional Elastic Light Scattering Fingerprinting (4D-ELF).¹⁻¹⁰ 4D-ELF can be thought of as an extension of light scattering spectroscopy (LSS). In LSS, light that is elastically scattered by tissue after a single scattering is recorded as a function of wavelength. In 4D-ELF, single scattering is recorded as a function of four parameters: wavelength, angle of scattering, azimuth of scattering, and polarization. Polarization gating is used to increase sensitivity to scattering originating from superficial tissue, e.g. mucosa and epithelium, where carcinogenesis originates. Such 4D data are the most comprehensive light scattering data that have been recorded from tissue to date. 4D-ELF signal contains information about tissue structures with size ranging from $<1\mu\text{m}$ to several microns averaged over $\sim 1\text{ sq. mm}$ areas of tissue. As discussed in the application, we have already demonstrated the feasibility of using 4D-ELF for detection of pancreatic cancer by means of detecting changes in the duodenum adjacent to the ampulla (i.e., in Step 1).

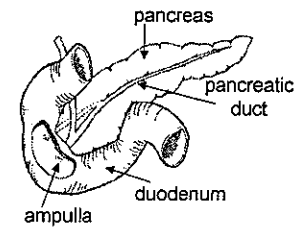


Figure 1(a). Anatomy of duodenal periampullary region and pancreatic duct.

Low-coherence Enhanced Backscattering (LEBS) spectroscopy.¹²⁻¹⁷ LEBS spectroscopy was first developed in our lab. LEBS is a unique optical phenomenon due to weak localization of photons and is manifested by the constructive interference of waves traveling time-reversed paths in tissue.

LEBS enables depth-resolved spectroscopic assessment of tissue with spectral resolution that is much higher than one enabled by spectroscopic OCT-based techniques. In LEBS, diagnostic information is obtained not from images but from LEBS spectra. LEBS signal primarily depends on second-order scattering of weakly localized photons by tissue structures. This contrast mechanism is unique to LEBS and cannot be probed by any other existing techniques including LSS, 4D-ELF, OCT, LCI, confocal microscopy, etc. The signals are sensitive to tissue architecture at scales ranging from a few tens of nanometers to microns averaged over $\sim 1\text{ sq. mm}$ tissue areas. We have already demonstrated the feasibility of using LEBS for detection of pancreatic cancer by means of detecting changes in the duodenum adjacent to the ampulla. Furthermore, our data show that it is the combination of 4D-ELF and LEBS that provides the best sensitivity and specificity.

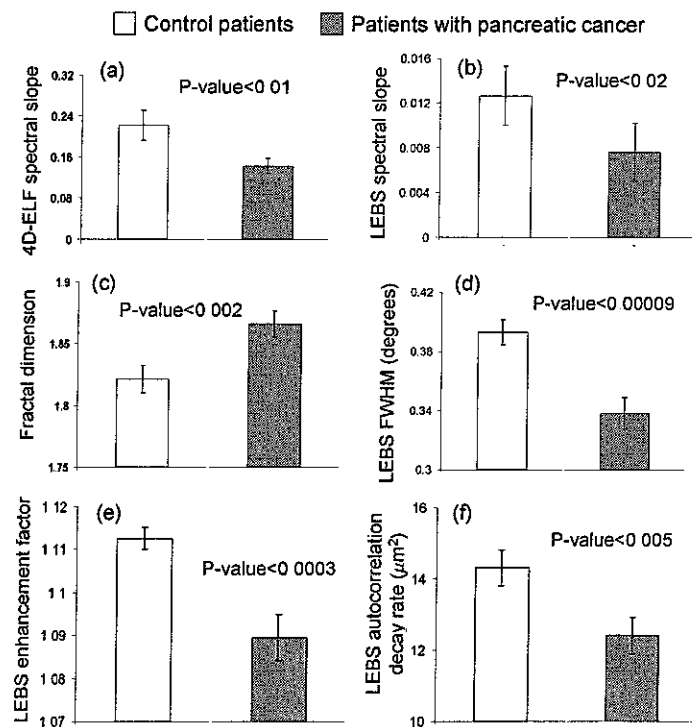


Figure 1. 4D-ELF/LEBS signatures in the periampullary duodenum correlate with presence of pancreatic cancer.

4D-ELF and LEBS Diagnosis of Pancreatic Cancer Without Interrogation of Pancreas.

In order to avoid potentially serious complications associated with interrogation of the pancreatic duct, our strategy is to diagnose pancreatic cancer by detecting alterations in adjacent duodenal tissue. To date we have recruited $n=51$ human subjects. In our study, two biopsies were taken from the histologically normal periampullary region in the duodenum in patients undergoing an upper endoscopic procedure who had pancreatic cancer (positive group) and those with no history of pancreatic disease or cancer (negative controls). All patients had pancreatic cancer confirmed by pathologic examination. The biopsied tissues were analyzed by 4D-ELF and LEBS. After the optical reading, biopsied tissues were examined histopathologically to ensure that the tissues were histologically normal. By correlating the 4D-ELF/LEBS data with this diagnosis we were able to develop a series of optical markers diagnostic for pancreatic neoplasia. Although only a small portion of available 4D-ELF and LEBS data have so far been analyzed, we have already been able to identify six significant optical markers (Fig. 1):

1) 4D-ELF spectral slope is obtained as the absolute value of the linear coefficient of the linear fit to $\Delta I(\lambda, \theta, \phi)$ for fixed θ and ϕ (in our analysis $\Delta I(\lambda, \theta, \phi)$ was integrated over θ for $\phi=0$, $\lambda=500\text{--}650$ nm). The spectral slope depends on the size distribution of scattering structures: abundance of smaller (up to 20 nm) scatterers increases the spectral slope. As shown in Fig. 1(a), 4D-ELF spectral slope assessed from the periampullary mucosa was significantly lower for patients with pancreatic cancer as compared with control patients who were cancer-free ($p\text{-value}<0.01$).

2) LEBS spectral slope. Similar analysis was performed on LEBS spectra $I_{\text{LEBS}}(\lambda)$ for depth of penetration 70 μm . As shown in Fig. 1(b), LEBS spectral slope obtained from the periampullary mucosa was also decreased in patients with pancreatic cancer ($p\text{-value}<0.02$).

3) Fractal dimension of tissue microarchitecture was calculated from the Fourier transform $\text{FT}[\Delta I(\lambda=550\text{nm}, \theta, \phi=0^\circ)](r)=C(r)$. The two-point mass density correlation function $C(r)$ quantifies the correlation between local tissue regions separated by distance r ^{1, 4, 5, 17}. In our data, $C(r) \propto r^{D_f-3}$ for r from 1 to 50 μm , which is characteristic of a fractal-like tissue organization with fractal dimension D_f . As shown in Fig. 1(c), D_f obtained from the periampullary mucosa was elevated in patients with pancreatic cancer ($p\text{-value}=0.002$).

4) LEBS peak width. Angular width of the LEBS peak was decreased in pancreatic cancer patients ($p\text{-value}=0.00009$; Fig. 1(d)), which indicates the increase in the mean free path length of LEBS photons.

5) LEBS enhancement factor was also decreased in patients with pancreatic cancer ($p\text{-value}=0.0003$), which also suggests the increase in the mean free path length (Fig. 1(e)).

6) LEBS autocorrelation decay rate. Autocorrelation of LEBS spectra $C_A(\Delta k) = \int I_{\text{LEBS}}(k) I_{\text{LEBS}}(k + \Delta k) dk$, 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 is sensitive to essentially arbitrary small length scales of refractive index fluctuations and, thus, concentration of tissue solids (up to 1 nm, as confirmed by our numerical FDTD experiments). We found that D was decreased in patients with pancreatic cancer (Fig. 1(f), $p\text{-value}=0.005$).

Sensitivity	95%
Specificity	91%
PPV	86%
NPV	97%

Table 1. Performance characteristics of 4D-ELF/LEBS markers obtained in histologically normal duodenal periampullar mucosa for detection of pancreatic cancer.

Performance Characteristics. The performance of the diagnosis obtained by combining all six optical markers was excellent (Table 1) with sensitivity and specificity $>90\%$. These numbers are even more remarkable given that this is the first demonstration of the feasibility of diagnosing pancreatic cancer without direct visualization of the pancreas. This excellent performance was only attainable when all six markers were included. For example, LEBS alone resulted in specificity and sensitivity of only 74% and 84%. This indicates that both techniques provide complimentary diagnostic information.

Spatial Extent of Field-effect in Pancreatic Cancer. We obtained data to determine the limit of the spatial extent of the field effect in pancreatic cancer by taking optical readings in the gastric mucosa along the lesser curvature of the stomach, which is not adjacent to the pancreas, from the same patients. We found that none of the six 4D-ELF/LEBS markers discussed above was statistically significant when measured from the stomach tissue (Table 2). Furthermore, in the distal duodenum approximately 10 cm from the ampulla, the optical markers were also not significant, although with p-values lower than those from the stomach. This suggests that the field effect is strongest adjacent to the ampulla and propagates to some extent in the duodenum, but does not extend as far as the stomach. Furthermore, these results confirmed that the alterations of optical markers are due to presence of pancreatic cancer rather than a nonspecific predisposition in the mucosa of upper gastrointestinal tract organs.

4D-ELF/LEBS Marker	P-value, Periapillary Duodenum	P-value, Distal Duodenum	P-value, Stomach
4D-ELF Spectral Slope	0.01	0.39	0.17
LEBS Spectral Slope	0.02	0.30	0.40
Fractal Dimension	0.002	0.37	0.12
LEBS FWHM	0.00009	0.08	0.16
LEBS Enhancement Factor	0.0003	0.06	0.14
LEBS Autocorrelation Decay	0.005	0.61	0.69

Table 2. Optical markers obtained from histologically normal duodenal periapillary mucosa but not from distal duodenal/gastric mucosa are significant for pancreatic cancer. This indicates that the field effect associated with pancreatic cancer exists in the periapillary duodenum but does not spread to the distal duodenum and stomach

4D-ELF/LEBS Diagnosis is Not Affected by Confounding Factors. Given that the age and smoking history are the two major risk factors for pancreatic cancer, we wanted to ensure the changes in 4D-ELF and LEBS detect carcinogenesis rather than mere age difference and smoking history among patients with pancreatic cancer and control subjects. We studied how the optical markers vary with patients' age and smoking history. Two-way ANOVA analysis showed that none of the six markers changed significantly with either or age or smoking history (Table 3). Therefore, the changes in the optical markers cannot be attributed to difference in age and smoking history in the patient population.

4D-ELF/LEBS Marker	P-value, Effect of Age	P-value, Effect of Smoking History
4D-ELF Spectral Slope	0.06	0.17
LEBS Spectral Slope	0.20	0.30
Fractal Dimension	0.54	0.10
LEBS FWHM	0.83	0.94
LEBS Enhancement Factor	0.31	0.20
LEBS Autocorrelation Decay	0.91	0.37

Table 3. Diagnostic performance of 4D-ELF/LEBS markers is not affected by patients' age and the history of smoking.

4D-ELF/LEBS Diagnosis is Not Compromised by Tumor Stage and Location. We also wanted to investigate the potential of the optical markers obtained from the periapillary tissue to diagnose not only most proximal pancreatic neoplasms (i.e., those located in the head of the pancreas in the proximity to the ampulla) but also more distal lesions including those in the body and the tail of the pancreas. As shown in Tables 4 and 5, several optical markers obtained from the periapillary duodenum are significant even for the tumors located in the body and the tail of the pancreas as well as small (resectable) tumors of stage 1. Slight increase in p-values for the other optical markers might simply be due to a small number of patients with tumors of small size ($n=5$) and those located in the body/tail ($n=5$). In future multi-center clinical studies we will increase n to address this question and also develop new markers that will be diagnostic for both proximal and distal tumors and tumors of small size.

4D-ELF/LEBS Marker	P-value, Large Tumors (T3)	P-value, Small Tumors (T1)
4D-ELF Spectral Slope	0.026	0.047
Fractal Dimension	0.009	0.039
LEBS FWHM	0.00005	0.290
LEBS Enhancement Factor	0.001	0.030
LEBS Autocorrelation Decay	0.006	0.180

Table 5. The optical markers from the periapillary duodenum are significant not only for large (T3) pancreatic tumors but also small size respectable tumors of stage T1.

4D-ELF/LEBS Marker	P-value, Tumors in Head & Neck	P-value, Tumors in Body & Tail
4D-ELF Spectral Slope	0.036	0.008
Fractal Dimension	0.004	0.056
LEBS FWHM	0.003	0.003
LEBS Enhancement Factor	0.0005	0.099
LEBS Autocorrelation Decay	0.031	0.008

Table 4. The optical markers from the periapillary duodenum are significant not only for pancreatic tumors located most proximally to the ampulla (i.e. head of the pancreas) but also most distally (i.e. body and tail).

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Pages 49 through 224 redacted for the following reasons:

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