Fiber-based Probe Enables High Resolution CARS Imaging of Biological Tissues *in vivo*

Tech ID: 21810 / UC Case 2010-400-0

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BRIEF DESCRIPTION

Researchers at the University of California, Irvine have developed a novel, fiber based imaging probe that is optimized for CARS to enable the label free, in vivo probing of tissues.

Coherent Anti-Stokes Raman scattering (CARS) microscopy, a form of nonlinear optical microscopy, has gained enormous attention in the biomedical community for its potential to provide high resolution images at fast imaging acquisition rates.

Typical applications of CARS include skin and superficial tissue imaging, often in an in vitro setting. Up to this point, a suitable device that enables the CARS imaging of tissues in vivo has not been available.

FULL DESCRIPTION

Nonlinear optical microscopy includes the techniques of two photon excited fluorescence (TPEF), second harmonic generation (SHG) and coherent Anti-Stokes Raman scattering (CARS) microscopy. This imaging approach has gained enormous popularity in biomedical imaging of tissues in vivo, because it provides high resolution images at fast imaging acquisition rates.

While the potential of nonlinear microscopy for in vivo imaging is high, a suitable fiber delivered probe that enables CARS imaging in addition to SHG and TPEF imaging is currently lacking.

CARS microscopy is accomplished by guiding and focusing two laser beams onto a sample. Finding suitable fibers that support delivery of both laser beams without compromising the image quality has been one of the primary design challenges of such a probe to this point. Another issue has been the efficient and noise free collection of the backward scattered signal into the fiber for detection.

The invention is a successful integration of a fiberbased light source with a fiber based multiphoton probe. The combination of the two results in an extremely compact device, which is portable and suitable for applications in the clinic.

To address image quality concerns, the researchers isolated the delivery and collection processes. The collected signals are not affected by spurious anti-Stokes components from the delivery fiber, resulting in images that originate solely from CARS generation in the tissue.

Background

From a design point of view, the development of a fiber delivered or endoscopic probe that supports CARS imaging imposed additional challenges to existing probe designs.

The reason for this is that unlike SHG and TPEF, CARS incorporates two laser beams, called ‘Pump’ and ‘Stokes’, that both need to be guided and focused onto the sample. Finding suitable fibers that support delivery of both laser beams without compromising the image quality had been one of the design challenges.

US Pat. Pub. No. 2007/0088219 “System and Method for Coherent Anti-stokes Raman Scattering Endoscopy” discloses a system and method for fiber based CARS endoscopy. The previously patented invention disclosed a system for guiding both the Stokes and pump wave in one optical fiber and receiving the anti-Stokes signal emitted from the sample with the same fiber or different fiber. However, it was found that strong four-Wave-mixing (FWM)/CARS contribution at the anti-Stokes frequency was generated in the

OTHER INFORMATION

KEYWORDS

Coherent Anti-Stokes Raman scattering microscopy, CARS, SHG, TPEF

CATEGORIZED AS

- **Agriculture & Animal Science**
  - Devices
- **Biotechnology**
  - Other
- **Imaging**
  - Other
- **Medical**
  - Devices
  - Diagnostics
  - Imaging
  - Research Tools

delivery fiber under typical CARS excitation conditions. This fiber-generated FWM/CARS component forms a large background that is typically overwhelming the signal generated in the sample, and severely complicates the interpretation of the image unless removed.

This major problem is not discussed in US Pat. Pub. No. 2007/0088219, and significantly limits the application of the device proposed therein. The mixing the anti-Stokes radiation generated in the delivery fiber with the CARS signal generated from the sample forms a major limitation of the existing technology. In order to get the actual CARS image of the sample, the anti-Stokes frequency generated in the delivery fiber must be filtered out before it is focused onto the sample.

The invention provides a method for eliminating the problem of fiber-generated anti-Stokes radiation. The various embodiments of the invention are based on effectively filtering the fiber-generated anti-Stokes radiation before the excitation beams are focused onto the sample. The CARS signal generated in the sample is then collected by either a different portion of the delivery device (e.g. inner clad of a double clad fiber) or by a different fiber. This method produces high quality CARS images free of detector aperture effects.

» Screening
» **Research Tools**
» Other
» **Sensors & Instrumentation**
» Medical

RELATED CASES

2010-400-0

SUGGESTED USES

The invention can be used for the label free endoscopic imaging of tissue. The invention can provide insight into myelin degradation in the nervous system and in illuminating the role of lipid in mammary tumorigenesis and atherosclerosis. In addition, the invention might also have applications in skin damage assessment, dry eye syndrome diagnosis, and food analysis.

The following is a non-exhaustive list of potential suggested uses:

a. Skin damage assessment. Multiphoton imaging based on SHG/TPEF has proved successful in assessing skin health and damage due to, for instance, sun exposure. Based on optical signals from collagen (SHG) and elastin (TPEF) and index has been developed that can be correlated with age and skin damage. This invention would add CARS contrast as an additional parameter for skin diagnosis. CARS not only identifies dermal adipocytes and details of subcutaneous cells, it also provides a quantitative measure of the density of structural protein in the dermis and the level of skin hydration. Based on this improved index, this probe can be used for a real time assessment of skin health of human subjects in a clinical setting.

b. Dry eye syndrome diagnosis. This invention can be used to establish whether patients with dry eyes are suffering from dry eye syndrome (DES). DES is a condition related to the malfunction of the Meibomian gland, which can be found in the eyelid. The Meibomian gland secretes a lipid tear film that prevents the eye from drying. Upon aging, Meibomian glands may shrink and alter their lipid production, leading to DES. Meibomian glands cannot be seen with standard microscopic in vivo inspection. With CARS, however, Meibomian glands are easily identified and can be assessed. This fiber probe enables a direct inspection of human subjects in vivo by gently lifting the eyelid and visualizing the superficial glands in real time, permitting a direct diagnosis of DES.

c. Food analysis. This invention would be great for inspecting the quality of surfaces of food items. For instance, the CARS modality enables one to identify the onset of ‘blooming’ on chocolate surfaces. Chocolate producing companies are spending millions on controlling blooming, and early identification (small lipid crystals at the chocolate surface) is an important ability in controlling this effect.

d. Photoresists. Quick inspection of photoresists films is important in quality control of these thin polymer films. CARS have proved sensitive to chemical changes at the surface. This invention would enable quick inspection by easily directing the probe to the area of interest.

e. Imaging and diagnose vascular diseases with intravascular CARS imaging and multimodal imaging.

f. Image and diagnose cancers with endoscopic CARS imaging and multimodal imaging.

ADVANTAGES

The device is the first of its kind: a fiber based imaging probe that is optimized for CARS to enable the label free, in vivo probing of tissues. Its compact size also makes it uniquely suitable for clinical applications, both in vivo and in situ.

a) Higher Quality CARS Images: The device produces higher quality images by eliminating fiber-generated four-wave mixing radiation by filtering the fiber-generated four-wave mixing radiation before the Stokes and pump excitation beams are delivered to a sample. The device then collects the CARS signal backscattered from the sample, and returns the CARS signal to a detector by utilizing a different portion of the fiber for the CARS signal or by utilizing a different fiber for the CARS signal. This results in a higher quality image overall that are free of detector aperture effects.

b) Miniaturization: Miniaturization of this fiber-delivered probe results in a practical handheld probe for clinical CARS imaging.

c) In Vivo: The device allows for in vivo imaging as opposed to other devices that require an in vitro setting

d) Label-Free Imaging

e) Fast Image Acquisition Rate

TESTING

The device has been tested on biological tissues *ex vivo.*

PATENT STATUS

Country	Type	Number	Dated	Case
United States Of America	Issued Patent	8,582,096	11/12/2013	2010-400

RELATED MATERIALS

» M. Balu, G. Liu, Z. Chen, B. Tromberg, E. Potma. “Fiber delivered probe for efficient CARS imaging of tissues”. Opt Express. 2010 Feb 1;18(3):2380-8 - 02/01/2010

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