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"Biomedical Imaging Using Optical Coherence Tomography"

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Biomedical Imaging using Optical Coherence Tomography

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Abstract Optical coherence tomography (OCT) is a new technology for performing high resolution cross sectional imaging. OCT functions as a type of optical biopsy which provides cross sectional images of tissue structure on the micron scale. In combination with catheters and endoscopes, OCT can perform internal body imaging. OCT is a powerful imaging technology for medical diagnostics because, unlike conventional histopathology, which requires removal of a tissue specimen and processing for microscopic examination, OCT can provide images of tissue in situ and in real time.

Introduction

Optical coherence tomography (OCT) is a recently developed optical imaging technique that performs high resolution, cross-sectional imaging tomographic of microstructure in biological systems[1]. OCT is analogous to ultrasound B mode imaging except that it uses light instead of sound. OCT performs imaging by using low coherence interferometry to measure the optical backscattering of tissue as a function of echo delay and transverse position. The resulting two dimensional data set can be displayed as a gray scale or false color image.

OCT was originally developed and applied by our group for tomographic diagnostics in ophthalmology. OCT can provide images of the retina with resolutions of 10 μm, one order of magnitude higher than conventional ultrasound[2]. Working in collaboration with the New England Eye Center and MIT Lincoln Laboratory, we developed a clinical prototype OCT instrument for ophthalmic diagnosis. Several thousand patients have been examined to date[2-4]. The technology has been transferred to industry and a commercial product was introduced into the ophthalmic market in 1996. More recently, advances in OCT imaging have enabled imaging to be performed in nontransparent tissues, thus enabling its application in a wide range of possible medical specialties[5-7]. Imaging depth is limited by optical attenuation due to scattering and absorption. However, in most tissues, imaging up to 2-3 mm deep can be achieved. OCT has been applied in vitro to image arterial pathology where it can differentiate plaque morphology with superior resolution to ultrasound[8]. Imaging studies have also been performed in vitro to investigate applications in gastroenterology, urology, gynocology, surgery, and neurosurgery[9-12]. OCT has been applied in vivo to image developing biological specimens (African frog, leopard frog, and zebrafish tadpoles and embryos). For applications in developmental biology, OCT can permit the repeated imaging of developing morphology without the need to sacrifice specimens[13].

OCT is a promising and powerful medical imaging technology because it can permit the real time, in situ visualization of tissue microstructure without the need to excisionally remove and process a specimen as in conventional biopsy and histopathology. The concept of "nonexcisional

optical biopsy" provided by OCT and the ability to visualize tissue morphology in real time under operator guidance can be used both for diagnostic imaging as well as to guide surgical intervention. Coupled with catheter, endoscopic, or laparoscopic delivery, OCT holds the promise of having a wide spread impact on medicine ranging from improving the screening and diagnosis of cancer to enabling new microsurgical and minimally invasive surgical procedures.

Principles of operation and technology

OCT is analogous to ultrasound imaging but is based on optical ranging and the high resolution, high dynamic range detection of backscattered light. In contrast to ultrasound, because the velocity of light is extremely high, the echo time delay of reflected light cannot be measured directly. One method for measuring the time delay of light is to use low coherence interferometry or optical coherence domain reflectometry. Low coherence interferometry was first developed for measuring reflections in fiber optics and optoelectronic devices and was first demonstrated in ophthalmology for measurements of axial eye length and corneal thickness[14-17]. Low coherence interferometry uses heterodyne detection of light backscattered from the sample. Interference of the light reflected from the sample arm and reference arm of a Michelson interferometer (Figure 1) can occur only when the optical path lengths of the two arms match to within the coherence length of the optical source. As the reference arm optical path length is scanned, backscattering sites within the sample arm are localized.

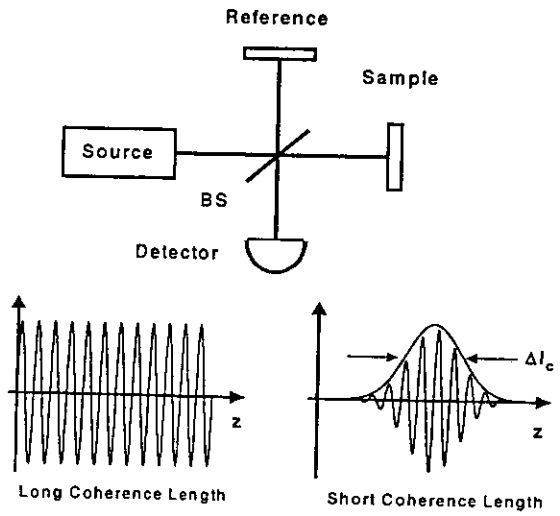

Fig. 1. OCT measures the echo time delay of reflected light by using low coherence interferometry. The system is based on a Michelson type interferometer. Reflections or backscattering from the object being imaging are correlated with light which traverses a reference path.

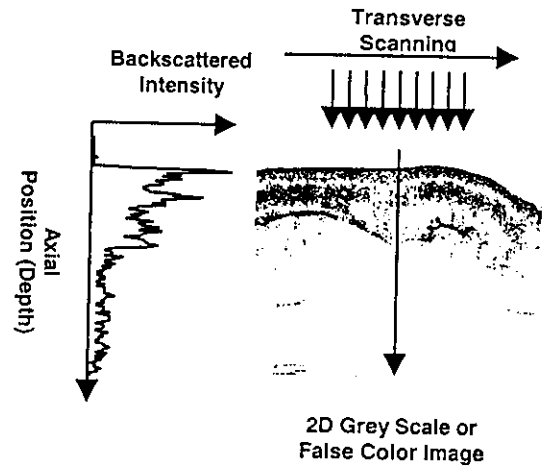

Fig. 2. Cross sectional images are constructed by performing measurements of the echo time delay of light at different transverse positions. The result is a two dimensional data set which represents the backscattering in a cross sectional plane of the tissue.

Figure 2 is a schematic illustrating how OCT performs cross sectional imaging. The optical beam is focussed into the object being imaged and the echo time delay and intensity of the backscatered light is measured to yield an axial backscattering profile. The incident beam is then

scanned in the transverse direction and the axial backscattering is measured at several transverse positions to yield a two dimensional data set. This data set represents the backscattering or back reflection through a cross section of the object being imaging and can be displayed as a gray scale or false color image.

The axial resolution in OCT images is determined by the coherence length of the light source. The interference signal detected at the output port of the interferometer is the electric-field autocorrelation of the source. The coherence length is the spatial width of the field autocorrelation. The envelope of the field autocorrelation is equivalent to the Fourier transform of its power spectrum. Thus the width of the autocorrelation function, or the axial resolution, is inversely proportional to the width of the power spectrum. For a source with a Gaussian spectral distribution, the axial resolution Δz is given: $\Delta z = (2\ln 2/\pi)(\lambda^2/\Delta\lambda)$ where Δz and $\Delta\lambda$ are the full-widths-at-half-maximum of the autocorrelation function and power spectrum, respectively and λ is the source central wavelength. Thus, broad bandwidth optical sources are required to achieve high axial resolution. The transverse resolution achieved with an OCT imaging system is determined by the focused spot size in analogy with conventional microscopy. The transverse resolution is given by: $\Delta x = (4\lambda/\pi)(f/d)$ where d is the spot size on the objective lens and f is its focal length. High transverse resolution can be obtained by using a large numerical aperture and focusing the beam to a small spot size.

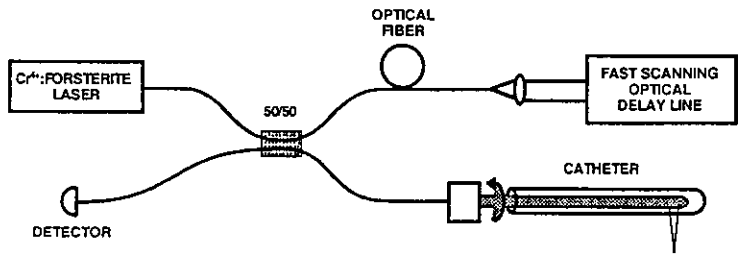

Fig. 3. Schematic of OCT instrument based on a fiber optic implementation of a Michaelson interferometer. One arm of the interferometer is interfaced to the measurement instrument and the other arm has a scanning delay ling. The system shown is configured for high speed catheter-endoscope based imaging.

OCT can be implemented using fiber optic technology. Figure 3 shows a schematic of an OCT system which uses a fiber optic Michelson type interferometer. A low coherence light source is coupled into the interferometer and the interference at the output is detected with a photodiode. One arm of the interferometer emits a beam which is directed and scanned on the object which is being imaging while the other arm of the interferometer is a reference arm with a scanning delay line. Because OCT uses fiber optics, it can easily be interfaced to a wide range of optical instruments.

For research applications, short pulse lasers are used as light sources for OCT imaging because they have extremely short coherence lengths and high output powers, thereby enabling high resolution, high speed imaging. For clinical applications, compact superluminescent diodes or semiconductor based light sources can be used. The laser source for many of our studies was a short pulse Cr^{4+}:Forsterite laser which operates near 1300 nm and achieves an axial resolution of 5-10 μm with a signal to noise ratio of 110 dB[20]. A rapidly scanning optical delay line based

on a grating phase control device, similar to that used in ultrafast optics is used for delay scanning[19]. The grating phase control device is attractive because it permits the phase and group velocity of the scan to be independently controlled and achieves extremely high scan speed. Images of 250 to 500 transverse pixels can be produced at 4-8 frames per second. Future systems will operate at video rates.

Applications

OCT is a promising and powerful medical imaging technique because it can permit the in situ and real time visualization of tissue microstructure with resolutions that are one to two orders of magnitude higher than ultrasound. OCT was initially applied for imaging in the eye and to date, has had the broadest clinical impact in ophthalmology. Figure 4 shows an example of an OCT image of the retina of a human subject[2]. This image is taken at a 10 um resolution and allows the detailed structure of the retina to be differentiated. The retinal thickness can be easily measured as well as the retinal nerve fiber layer which is visible as a highly backscattering layer. Clinical studies in ophthalmology show that OCT is especially promising for the diagnosis and monitoring of diseases such as glaucoma or macular edema associated with diabetic retinopathy where it provides quantitative information on disease progression[4]. In many cases OCT has the ability to detect and diagnose early stages of disease before physical symptoms and loss of vision occurs.

1. OCT can also be used for a variety of applications in internal medicine and internal body imaging of scattering tissues. Although the image penetration depth is limited to a few millimeters, this scale is comparable to the depth over which many biopsies are performed and many diagnostically important changes of tissue morphology occur near tissue or organ surfaces. OCT can resolve changes in architectural morphology which are important for diagnosis of diseases such as early neoplastic changes. Figure 4 shows an example of OCT

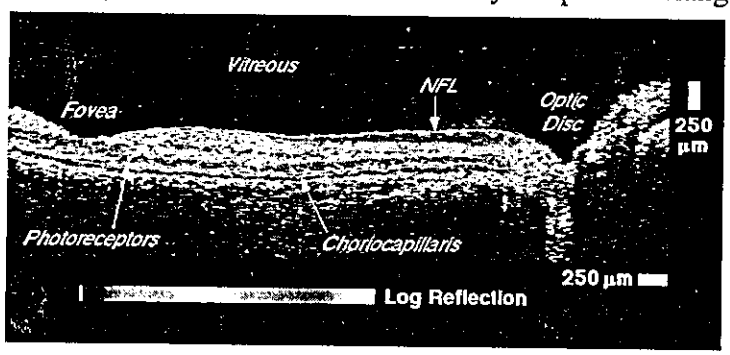

Fig. 4 OCT image of the human retina papillary-macular axis illustrating the ability to discriminate structural morphology *in vivo*. The highly backscattering retinal nerve fiber layer (NFL) and choriocapillaris appear red. The optic disk as well as several of the retinal layers are observed.

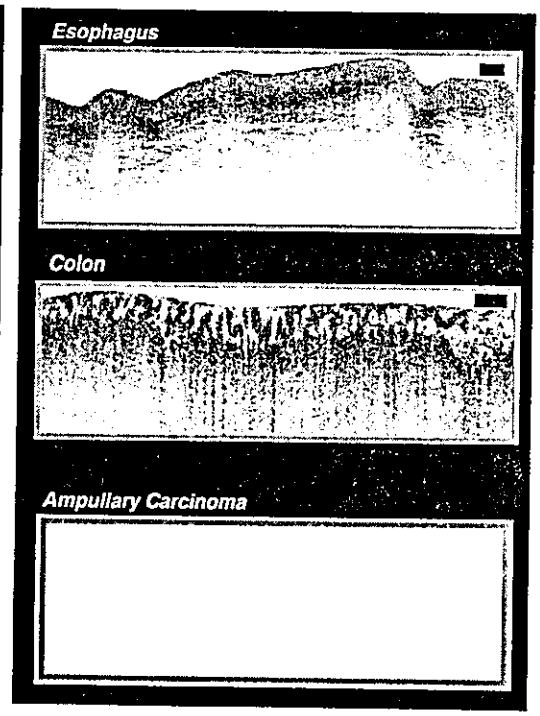

Fig. 5 In vitro images of gastrointestinal tissues and pathology including normal human esophagus, colon, and ampullary carcinoma. These images illustrate the ability of OCT to discriminate architectural morphology.

gastro-intestinal tissues in vitro. These images were performed at 15 um resolution using a 1300 nm wavelength. The top image shows the structure of the normal esophageal mucosal tissue which is characterized by a horizontally organized, squamous epithelial structure. The middle image shows the structure of the normal intestinal mucosal tissue which has a vertically organized, collumnar epithelial structure. Even at modest resolutions of 15 um, the differences between the architectural morphology of these tissue types is evident. The bottom image shows an ampullary carcinoma. The carcinoma is evident in the left one-third of the image and is characterized by a loss of the glandular organization of the tissue. Normal bowel is seen at the right one-third of the image and is characterized by vertically organized, columnar epithelial structure. The center part of the image shows a progressive disorganization and loss of structure. Changes in architectural morphology such as these can be used for the screening and the diagnosis of early neoplastic changes. Conventional excisional biopsy often suffers from high false negative rates because the biopsy process relies on sampling tissue and the diseased tissues can easily be missed. OCT might be used to identify suspect lesions and to guide excisional biopsy in order and reduce the false negative rates. In future applications, when sufficient clinical data is available, OCT may be used directly for diagnosis.

In order to enable OCT imaging in internal organ systems, it is necessary to develop optical delivery technologies[17,18]. Using fiber optics, a catheter-endoscope with an outer diameter of 2.9 French or 1.0 mm has been constructed. Figure 6 shows a schematic of an OCT catheter-endoscope. A single mode optical fiber runs the length of the catheter and the distal end consists of a GRIN lens and a microprism to direct the OCT beam radially. The fiber and distal optics are rotated so that the OCT beam scans an angular, radar like, pattern and image cross sectionally through internal organs.

The catheter-endoscope OCT system enables the acquisition of in vivo images of internal organ systems. Figure 7 shows an example of a cather-endoscope OCT image of the pulmonary tract of a rabbit in vivo. In vivo imaging of the pulmonary tract, gastrointestinal tract, and urinary tract as well as arterial imaging have been performed. These studies demonstrate the feasibility of performing OCT imaging of internal organ systems and suggest the possibility of it application clinically[19]. Other research groups as well as our group are currently beginning OCT imaging studies in patients and we expect results to be published shortly.

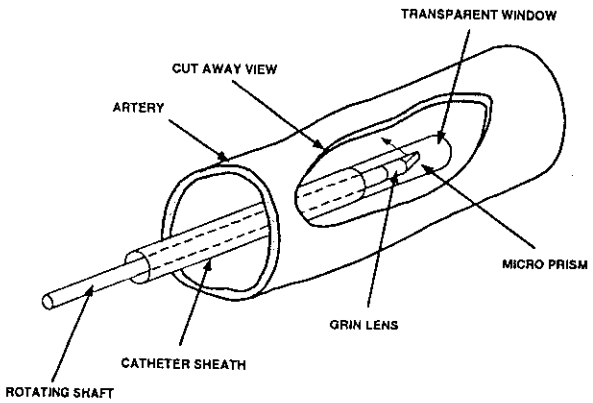

Fig. 6 OCT catheter for transverse, intraluminal imaging. A single-mode fiber lies within a rotating flexible speedometer cable enclosed in a protective plastic sheath. The distal end focuses the beam at 90 degree from the axis of the catheter.

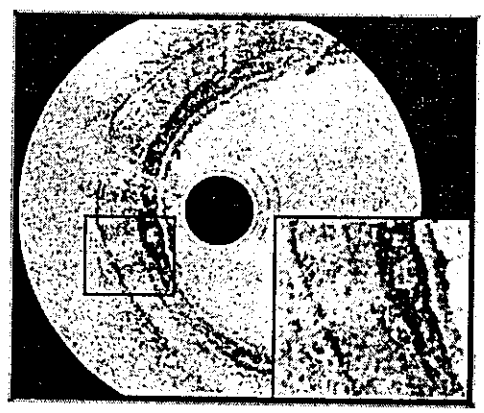

Fig. 7 A. OCT catheter/endoscope image in vivo of the esophagus of a New Zealand White Rabbit. The image clearly shows the layers of the esophagus.

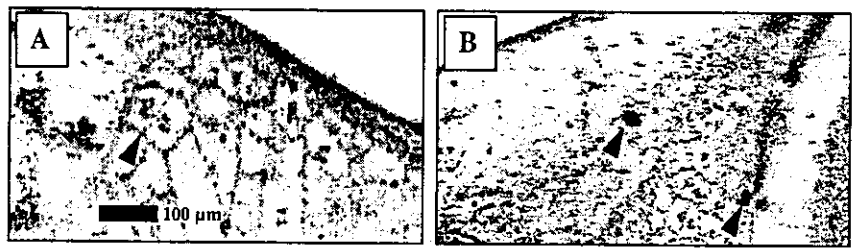

Fig. 8 High resolution OCT images of a Xenopus laevis (African Frog) tadpole in vivo. Figure A shows mesenchymal cells immediately following cell division with two daughter cells (arrow). Cell membranes and individual cell nuclei are apparent. Figure B shows melanin-laden neural crest cells which migrate during development.

The development of high resolution OCT is also an important area of active research. Increasing resolutions to the cellular and subcellular level are important for many applications including the diagnosis of early neoplasias. One of the keys to achieving high resolution is the use of short pulses lasers to obtain short coherence length. High resolution OCT imaging has been demonstrated in vivo in developmental biology specimens. Figure 8 show an example of high resolution OCT images of a *Xenopus laevis* (African frog) tadpole[20]. The OCT beam was focused to a 9 µm diameter spot (100 µm confocal parameter). A short pulse Cr^{4+}:Forsterite laser which operates near 1300 nm was used as the light source for these measurements. The free space axial resolution was 5.1 µm. Assuming an average index of 1.35 for these specimens, the *in vivo* axial resolution was ~ 3.8 µm. In developmental biology, the ability to image subcellular structure can be an important tool for studying mitotic activity and cell migration which occur during development. The extension of these results to humans has important implications for the diagnosis of early neoplasias. Many of these diseases are manifest by changes which occur on a cellular and subcellular level.

The development of high resolution and high speed OCT technology as well as OCT compatible catheter-endoscopes represent enabling steps for many OCT imaging applications including future endoscopic clinical applications. OCT is a powerful technique for optical biopsy because it can perform micron scale imaging of cellular and architectural morphology in situ and in real time. Imaging information is available in real time without the need for excision and histological processing of a specimen. The capability to perform rapid in situ imaging can be used in a variety of clinical scenarios including: 1. To guide conventional biopsy and reduce false negative rates due to sampling errors, 2. To perform imaging of tissue microstructure in situations where conventional excisional biopsy would be hazardous or impossible, and 3. To guide surgical or microsurgical intervention. More research remains to be done and numerous clinical studies must be performed in order to determine in which clinical situations OCT can play a decisive role. However, the unique capabilities of OCT imaging suggest that it has the potential to have a significant impact on the diagnosis and clinical management of many diseases.

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References

1. D. Huang, E.A. Swanson, C.P. Lin, J.S. Schuman, W.G. Stinson, W. Chang, M.R. Hee, T. Flotte, K. Gregory, C.A. Puliafito and J.G. Fujimoto, "Optical coherence tomography," Science 254, 1178, 1991.
2. M.R. Hee, J.A. Izatt, E.A. Swanson, D. Huang, C.P. Lin, J.S. Schuman, C.A. Puliafito, and J.G. Fujimoto, "Optical coherence tomography of the human retina," Arch. Ophthalmol. 113, 325-332, March 1995.
3. C.A. Puliafito, M.R. Hee, C.P. Lin, E. Reichel, J.S. Schuman, J.S. Duker, J.A. Izatt, E.A. Swanson, and J.G. Fujimoto, "Imaging of macular disease with optical coherence tomography (OCT)," Ophthalmology 102, 217-229, February 1995.
4. C.A. Puliafito, M.R. Hee, J.S. Schuman, and J.G. Fujimoto, "Optical Coherence Tomography of Ocular Diseases," Slack, Inc, Thorofare, NJ (1995).
5. J.M. Schmitt, A. Knuttel, M. Yadlowsky, and A.A. Eckhaus, "Optical coherence tomography of a dense tissue: statistics of attenuation and backscattering," Phys. Med. Biol. 39 1705 (1994).
6. J.M. Schmitt, M.J. Yadlowsky, and R.F. Bonner. "Subsurface imaging of living skin with optical coherence microscopy," Dermatology 191: p. 93-98 (1995).
7. M.E. Brezinski, G.J. Tearney, B.E. Bouma, J.A. Izatt, M.R. Hee, E.A. Swanson, J.F. Southern, and J.G. Fujimoto, "Optical coherence tomography for optical biopsy: properties and demonstration of vascular pathology," Circulation 93: p. 1206-1213 (1996).
8. J.G. Fujimoto, M.E. Brezinski, G.J. Tearney, S.A. Boppart, B.E. Bouma, M.R. Hee, J.F. Southern, and E.A. Swanson. "Biomedical imaging and optical biopsy using optical coherence tomography," Nature Medicine 1: p. 970-972 (1995).
9. M.E. Brezinski, G.J. Tearney, N.J. Weissman, S.A. Boppart, B.E. Bouma, M.R. Hee, A.E. Weyman, E.A. Swanson, J. F. Southern, and J. G. Fujimoto, "Assessing atherosclerotic plaque morphology: comparison of optical coherence tomography and high frequency intravascular ultrasound," British Heart Journal 77, 397-404, 1997.
10. G.J. Tearney, M.E. Brezinski, J.F. Southern, B.E. Bouma, S.A. Boppart, and J.G. Fujimoto, "Optical biopsy in human urologic tissue using optical coherence tomography," Journal of Urology 157, 1915-1919, May 1997.
11. M.E. Brezinski, G.J. Tearney, S.A. Boppart, E.A. Swanson, J.F. Southern, and J.G. Fujimoto, "Optical biopsy with optical coherence tomography, feasibility for surgical diagnostics," Journal of Surgical Research 71, 32-40 July 1997.
12. G.J. Tearney, M.E. Brezinski, J.F. Southern, B.E. Bouma, S.A. Boppart, and J.G. Fujimoto, "Optical biopsy in human gastrointestinal tissue using optical coherence tomography," American Journal of Gastroenterology 92, 1800-1804, October 1997.
13. S.A. Boppart, M.E. Brezinski, B. Bouma, G.J. Tearney, and J.G. Fujimoto, "Investigation of developing embryonic morphology using optical coherence tomography," Developmental Biology, 177, 54-63 (1996).
14. K. Takada, I. Yokohama, K. Chida, and J. Noda, "New measurement system for fault location in optical waveguide devices based on an interferometric technique," Appl. Opt. 26, 1603 (1987).
15. A.F. Fercher, K. Mengedoht and W. Werner, "Eye-length measurement by interferometry with partially coherent light," Opt. Lett. 13, 186, 1988.

16. C.K. Hitzenberger, "Measurement of the axial eye length by laser Doppler interferometry," Invest. Ophthalmol. Vis. Sci. 32, 616, 1991.
17. G.J. Tearney, S.A. Boppart, B. Bouma, M.E. Brezinski, N.J. Weissman, J.F. Southern, and J.G. Fujimoto, "Scanning single mode catheter/endoscope for optical coherence tomography," Opt. Lett. 21, 543-545, April 1996.
18. S.A. Boppart, B.E. Bouma, C. Pitris, G.J. Tearney, J.G. Fujimoto, and M.E. Brezinski, "Forward-imaging instruments for optical coherence tomography" Optics Letters 22, 1618-1620, November 1997.
19. G.J. Tearney, M.E. Brezinski, B.E. Bouma, S.A. Boppart, C. Pitris, J.F. Southern, and J.G. Fujimoto, "In vivo endoscopic optical biopsy with optical coherence tomography," Science 276, 2037-2039, June 1997.
20. S.A. Boppart, B.E. Bouma, C. Pitris, J.F. Southern, M.E. Brezinski, J.G. Fujimoto, "In vivo cellular optical coherence tomography imaging," Nature Medicine 4, 861-865, July 1998.