原子力研究所の初期のレーザー

http://www.optronics.co.jp/optworld/spring11/list/company/27

パルスレーザーの小型化
超音波診断装置の発展

日本無線・内田六郎開発、1955 年

1956年

2011年

http://www.jira-net.or.jp/vm/chronology_ultrasonic.html

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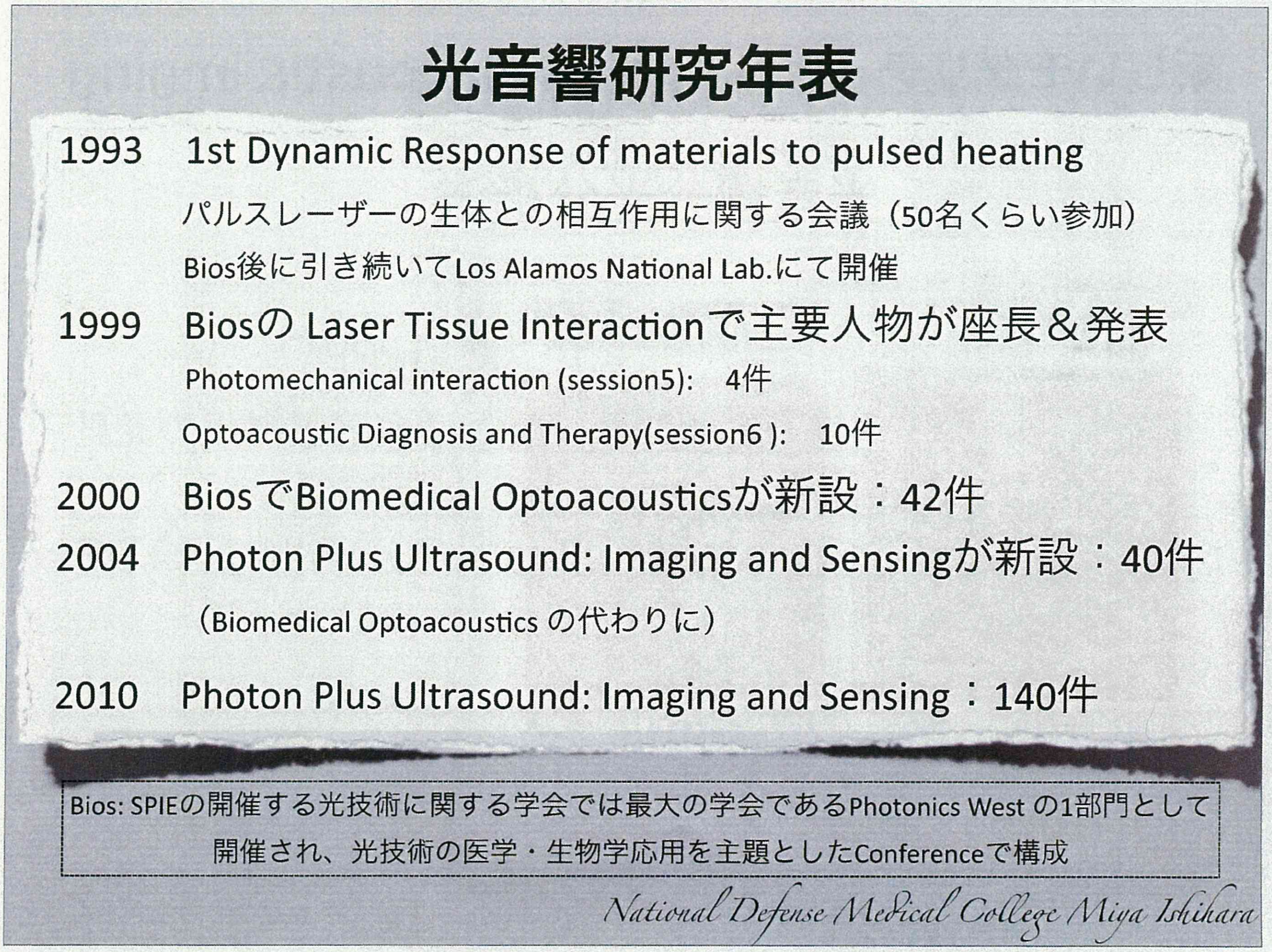

光音響研究年表

1993　1st Dynamic Response of materials to pulsed heating

パルスレーザーの生体との相互作用に関する会議（50名くらい参加）

Bios後に引き続いてLos Alamos National Lab.にて開催

1999　BiosのLaser Tissue Interactionで主要人物が座長＆発表

Photomechanical interaction (session5):　4件

Optoacoustic Diagnosis and Therapy(session6):　10件

2000　BiosでBiomedical Optoacousticsが新設：42件

2004　Photon Plus Ultrasound: Imaging and Sensingが新設：40件

（Biomedical Optoacoustics の代わりに）

2010　Photon Plus Ultrasound: Imaging and Sensing：140件

Bios: SPIEの開催する光技術に関する学会では最大の学会であるPhotonics West の1部門として開催され、光技術の医学・生物学応用を主題としたConferenceで構成

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世界の光音響研究グループ

- Washington Univ. St. LouisのL. V. Wangのグループ
- Texas Univ. のS. Emelianovのグループ
- Univ. College LondonのC. Beardのグループ
- Univ. MichganのL. J. Guoのグループ
- Fairway Medical Technologies, Incの A. A. Oraevsky
- その他、ヨーロッパ勢多数

日本の光音響研究人口は極少

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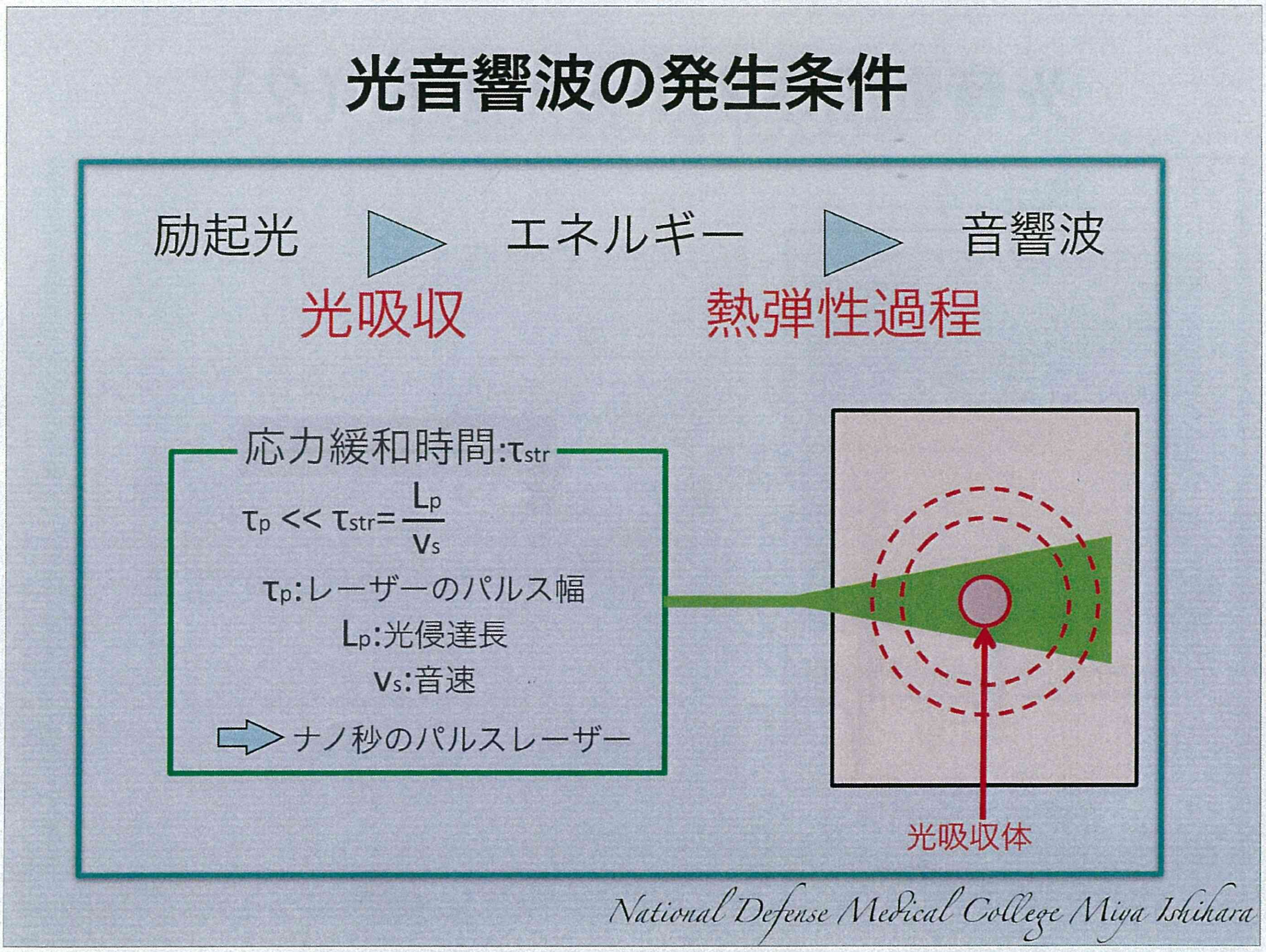

光音響波の発生条件

励起光 ▷ エネルギー ▷ 音響波

光吸収　熱弾性過程

応力緩和時間:τ_{str}

$$\tau_p << \tau_{str} = \frac{L_p}{V_s}$$

τ_p:レーザーのパルス幅

L_p:光侵達長

V_s:音速

⇨ ナノ秒のパルスレーザー

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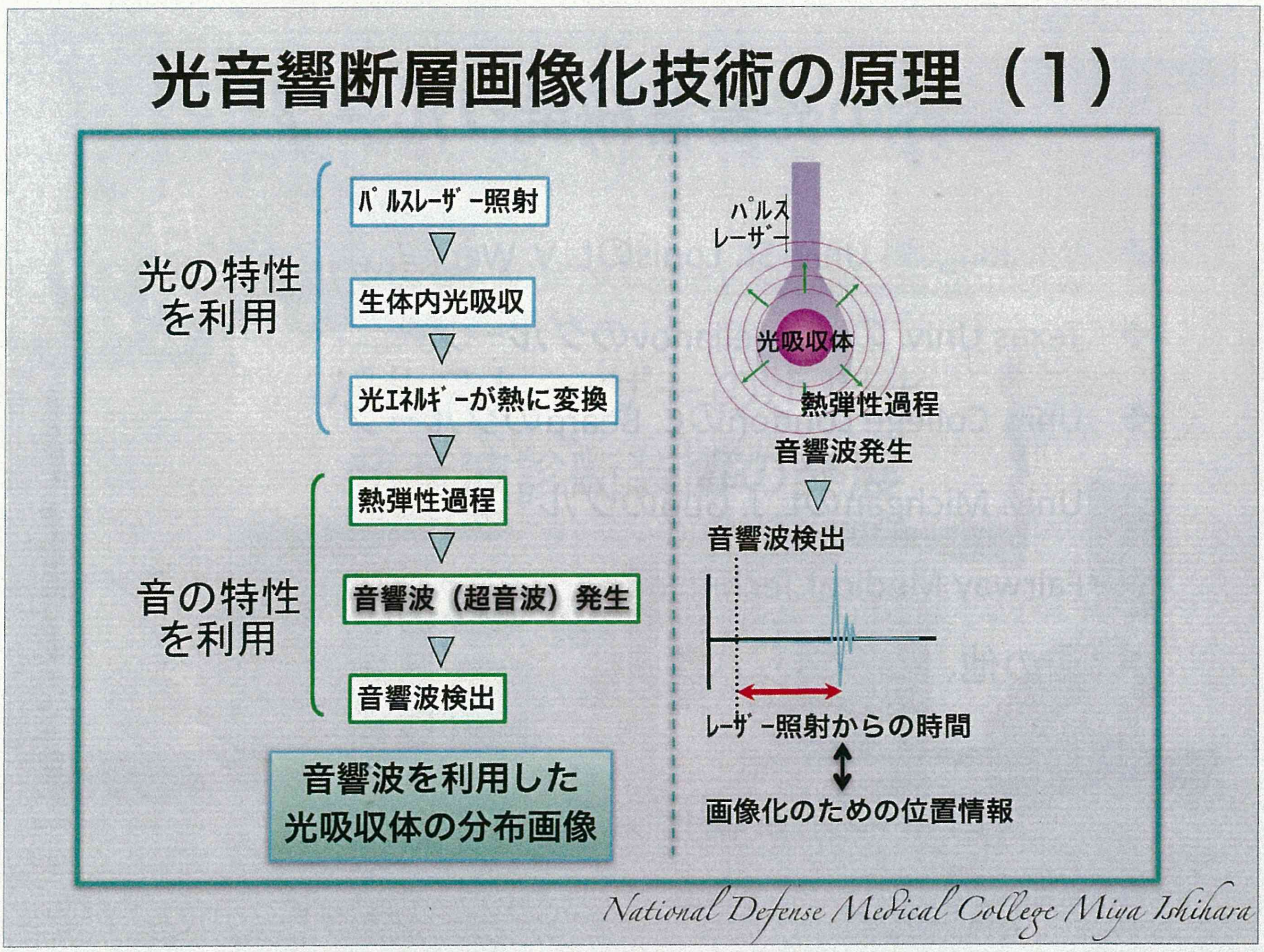

光音響断層画像化技術の原理（1）

光の特性を利用

ﾊﾟﾙｽﾚｰｻﾞｰ照射

▽

生体内光吸収

▽

光ｴﾈﾙｷﾞｰが熱に変換

▽

音の特性を利用

熱弾性過程

▽

音響波（超音波）発生

▽

音響波検出

音響波を利用した光吸収体の分布画像

ﾊﾟﾙｽﾚｰｻﾞｰ

光吸収体

熱弾性過程

音響波発生

▽

音響波検出

ﾚｰｻﾞｰ照射からの時間

↕

画像化のための位置情報

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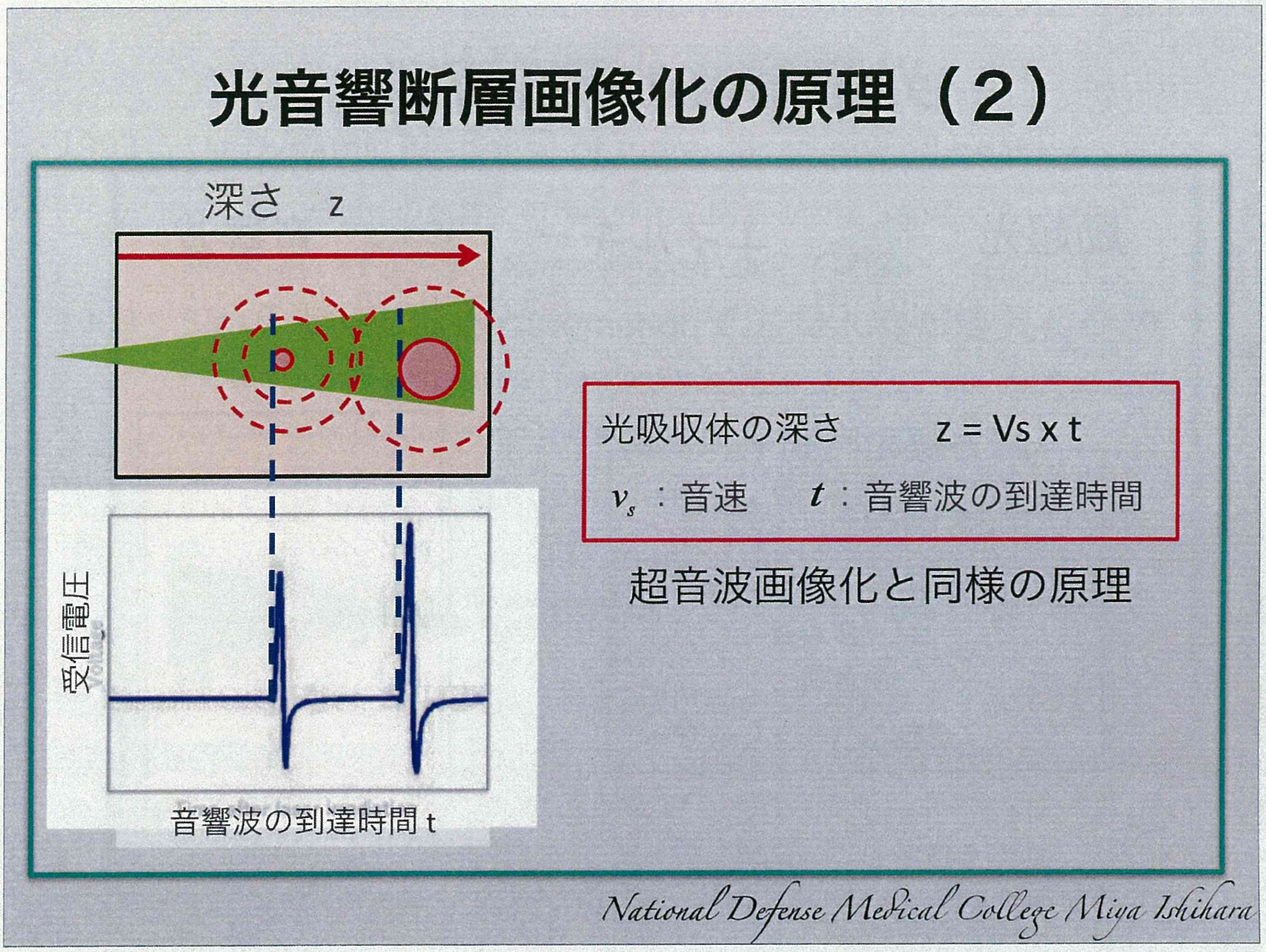

光音響断層画像化の原理（2）

光吸収体の深さ　$z = V_s \times t$

v_s：音速　t：音響波の到達時間

超音波画像化と同様の原理

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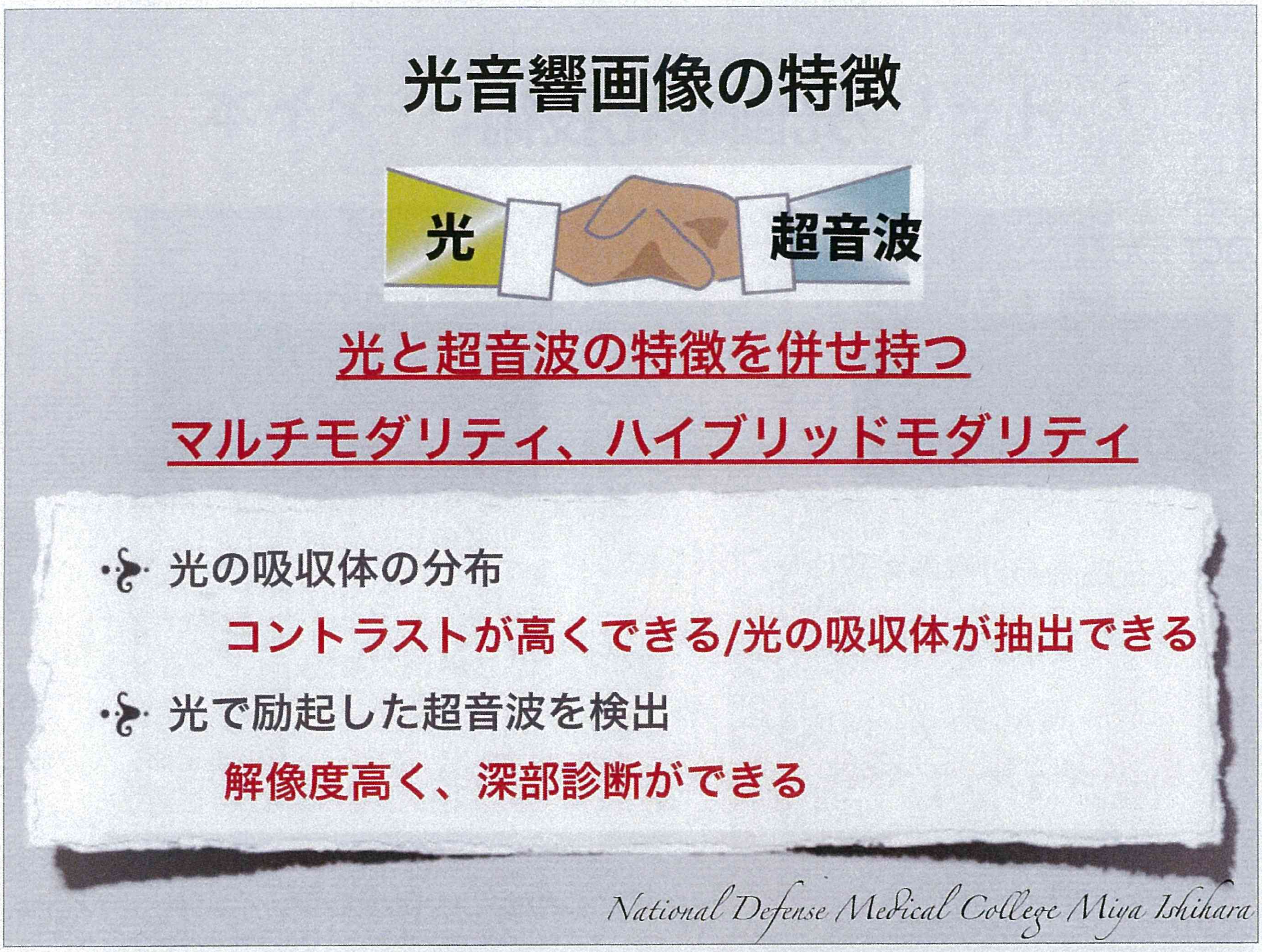

光音響画像の特徴

光と超音波の特徴を併せ持つ

マルチモダリティ、ハイブリッドモダリティ

- 光の吸収体の分布
  コントラストが高くできる/光の吸収体が抽出できる
- 光で励起した超音波を検出
  解像度高く、深部診断ができる

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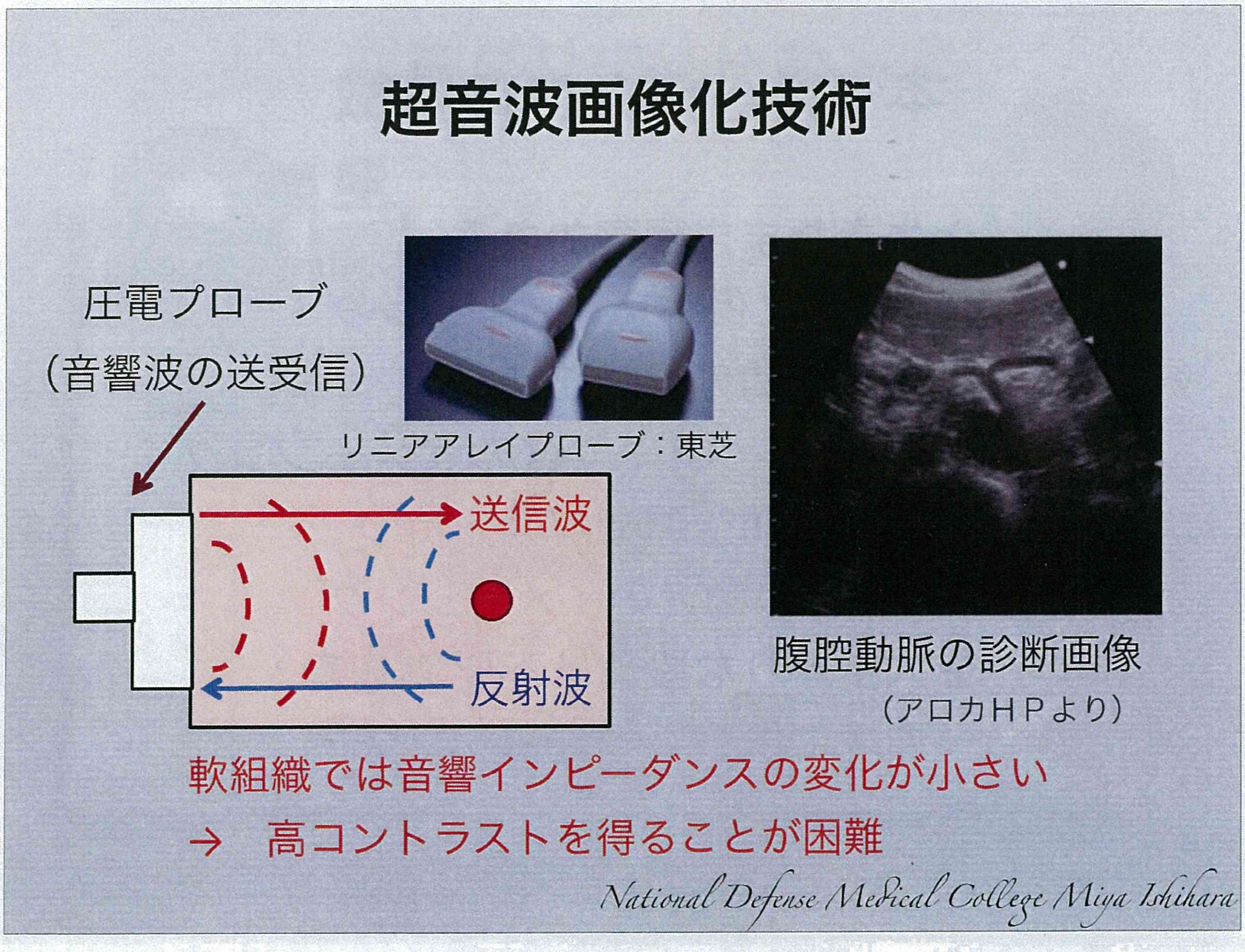

超音波画像化技術

リニアアレイプローブ：東芝

腹腔動脈の診断画像
（アロカＨＰより）

軟組織では音響インピーダンスの変化が小さい
→　高コントラストを得ることが困難

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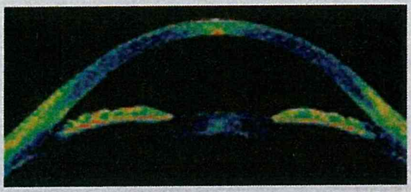
光画像化技術

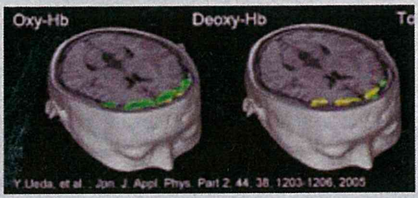
OCT : 光コヒーレンストモグラフィ



角膜のＯＣＴ画像（Carl Zeiss社）

- 表在部を高分解能で画像化
- 既に眼科診断で実用化

DOT : 拡散光トモグラフィ



Y Ueda, et al : Jpn. J. Appl. Phys. Part 2, 44, 38, 1203-1206, 2005

酸素飽和度の診断画像　（浜松ホトニクス）

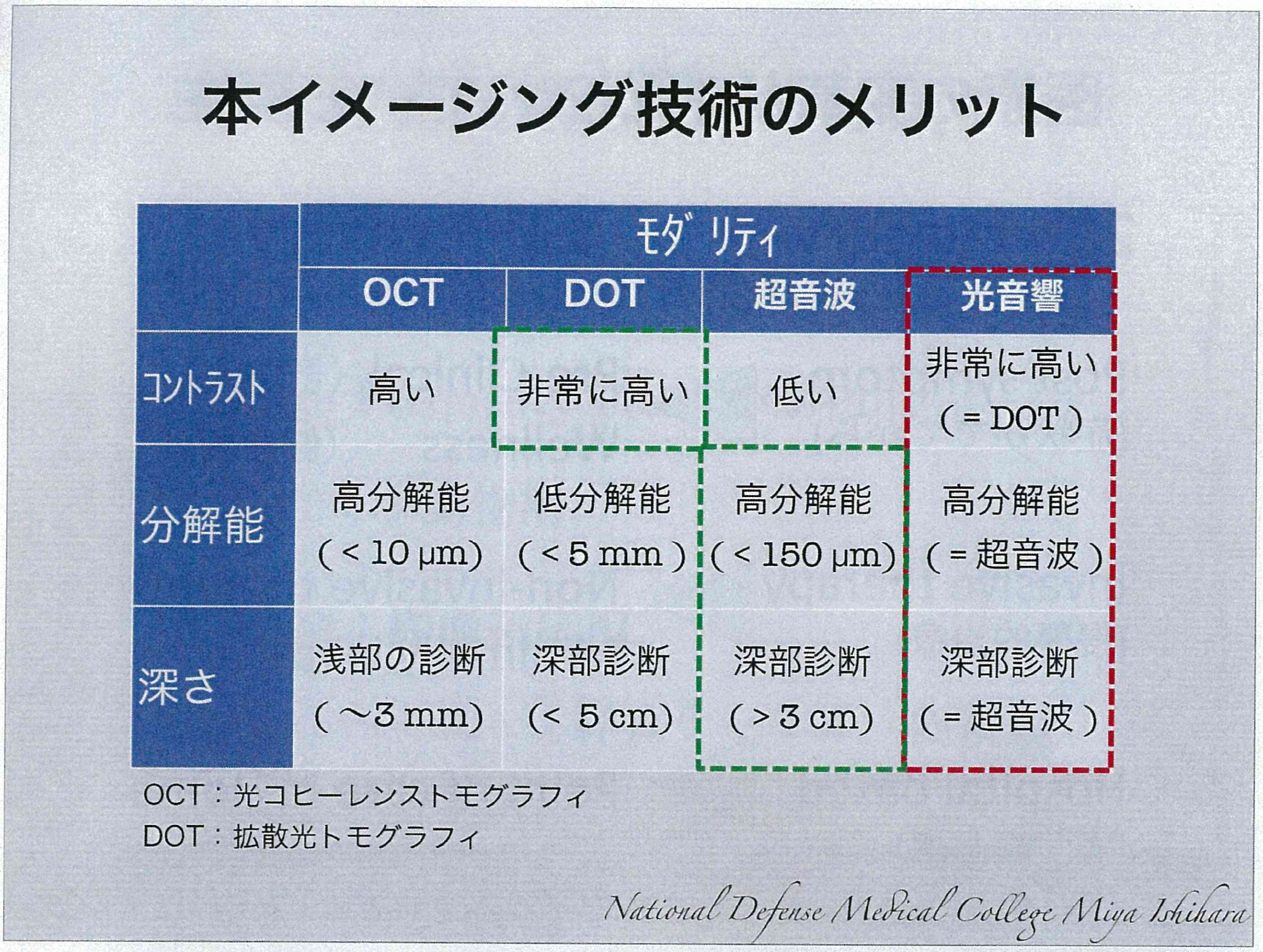
- 拡散光から光吸収分布を推定
- 低分解能だが深部診断が可能

散乱の影響→　深部を高分解能に画像化 することが困難

本イメージングの特徴

- 生きたまま観察できる
  →生体に優しいイメージング
- 高い空間分解能を持つ
  →細胞レベルも可能なイメージング
- 高い時間空間分解能を持つ
  →生体の動きのイメージング
- 大掛かりな設備は不要である

→環境に優しいイメージング



本イメージング技術のメリット

	モダリティ			
	OCT	DOT	超音波	光音響
コントラスト	高い	非常に高い	低い	非常に高い (= DOT)
分解能	高分解能 (< 10 µm)	低分解能 (< 5 mm)	高分解能 (< 150 µm)	高分解能 (= 超音波)
深さ	浅部の診断 (～3 mm)	深部診断 (< 5 cm)	深部診断 (> 3 cm)	深部診断 (= 超音波)

OCT：光コヒーレンストモグラフィ
DOT：拡散光トモグラフィ

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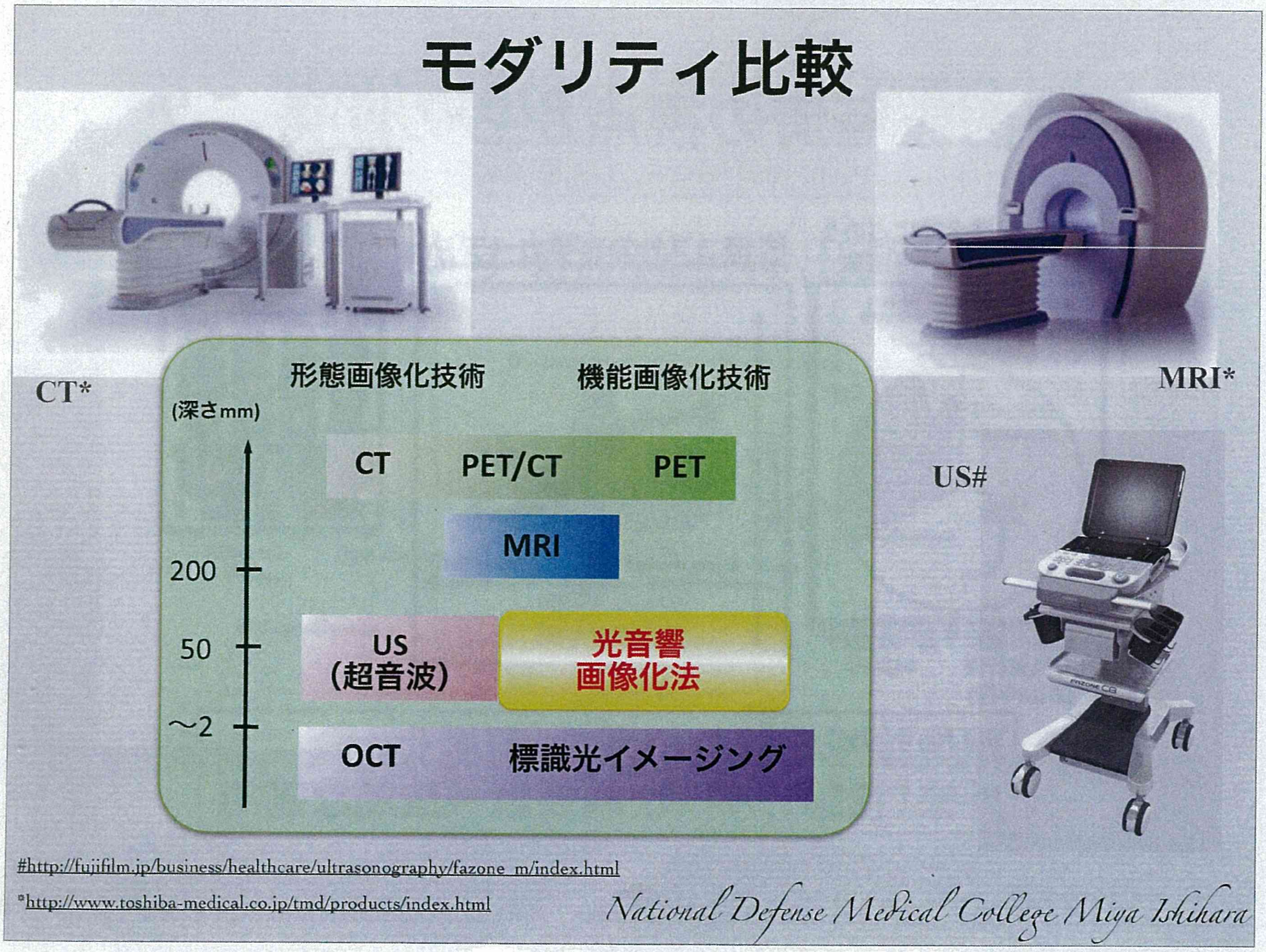

モダリティ比較

#http://fujifilm.jp/business/healthcare/ultrasonography/fazone_m/index.html

*http://www.toshiba-medical.co.jp/tmd/products/index.html

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医療の変革が求められている現在

20th century	21st century
Post symptom (症状がでてから)	Pre-Clinical（予防的） Wellness　（健康管理）
Invasive therapy (侵襲的治療)	Non-invasive therapy Minimally invasive
Hospital based (病院ありき)	Point of care in Home

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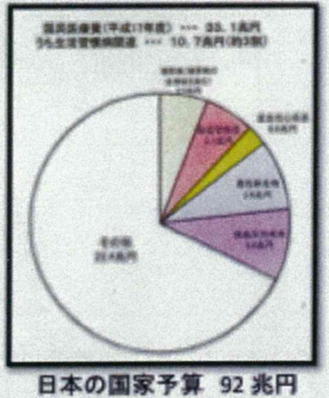
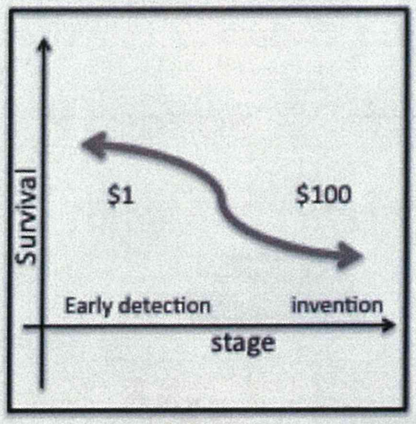
医療経済の視点からの期待

国民医療費全体に占める生活習慣病関連医療費



日本の国家予算　92 兆円
国債発行額　　44兆円
(2010年度)

医療コストのS字カーブ



超高齢社会による保険危機

画像診断機器の小型化・可搬化
外来（検診），術中，内視鏡→広範な適用

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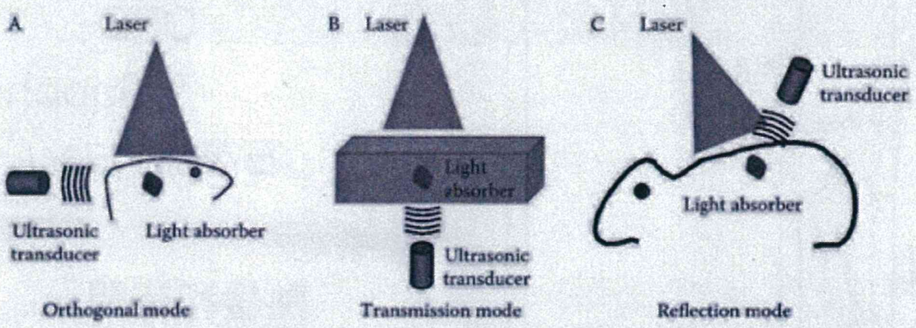
光音響画像化技術の分類１

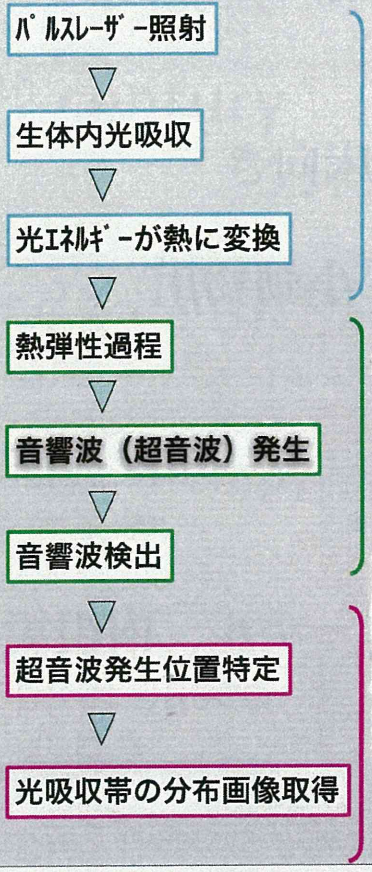
- ✻ **PAI**：汎用的　→　臨床向き
- ✻ **High Frequency PAI**：小動物用
- ✻ **PAT**：小動物用
- ✻ **PAM**：顕微鏡応用
- ✻ **Intravascular**　：経カテーテル、内視鏡

光音響画像化技術の分類２

撮像対象に対する励起と検出の位置関係



光音響画像化の要素技術



パﾞルスレーザﾞー照射

▽

生体内光吸収

▽

光ｴﾈﾙｷﾞーが熱に変換

▽

熱弾性過程

▽

音響波（超音波）発生

▽

音響波検出

▽

超音波発生位置特定

▽

光吸収帯の分布画像取得

要素技術

光技術

- 光源,　導光系

超音波技術

- 超音波検出器

信号処理技術

- 画像再構成処理

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要素技術としての光技術

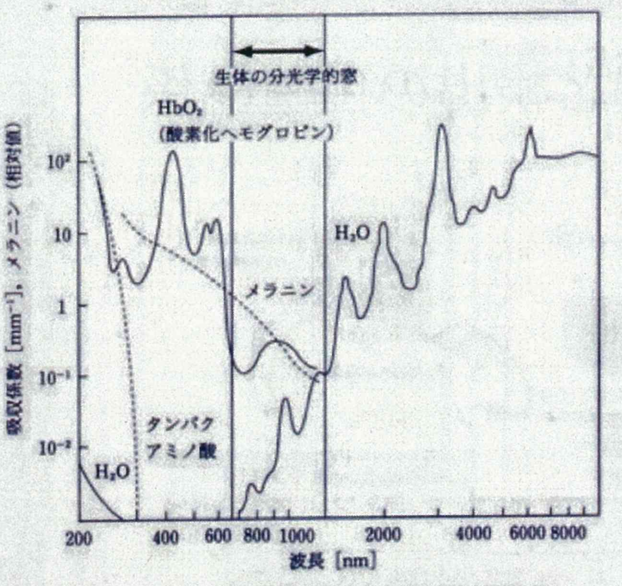

図7.4　軟組織における各種物質の吸収係数の波長依存性2)

波長帯：近赤外領域

レーザー：　Nd:YAG

　　　　　OPO

　　　　　Ti:Sapphire

導光：　石英ｶﾞﾗｽﾌｧｲﾊﾞー

熱緩和時間: τ_{th}

$$\tau_{th} = \frac{L_p^2}{4\chi}$$

L_p:光侵達長、χ:熱伝導率

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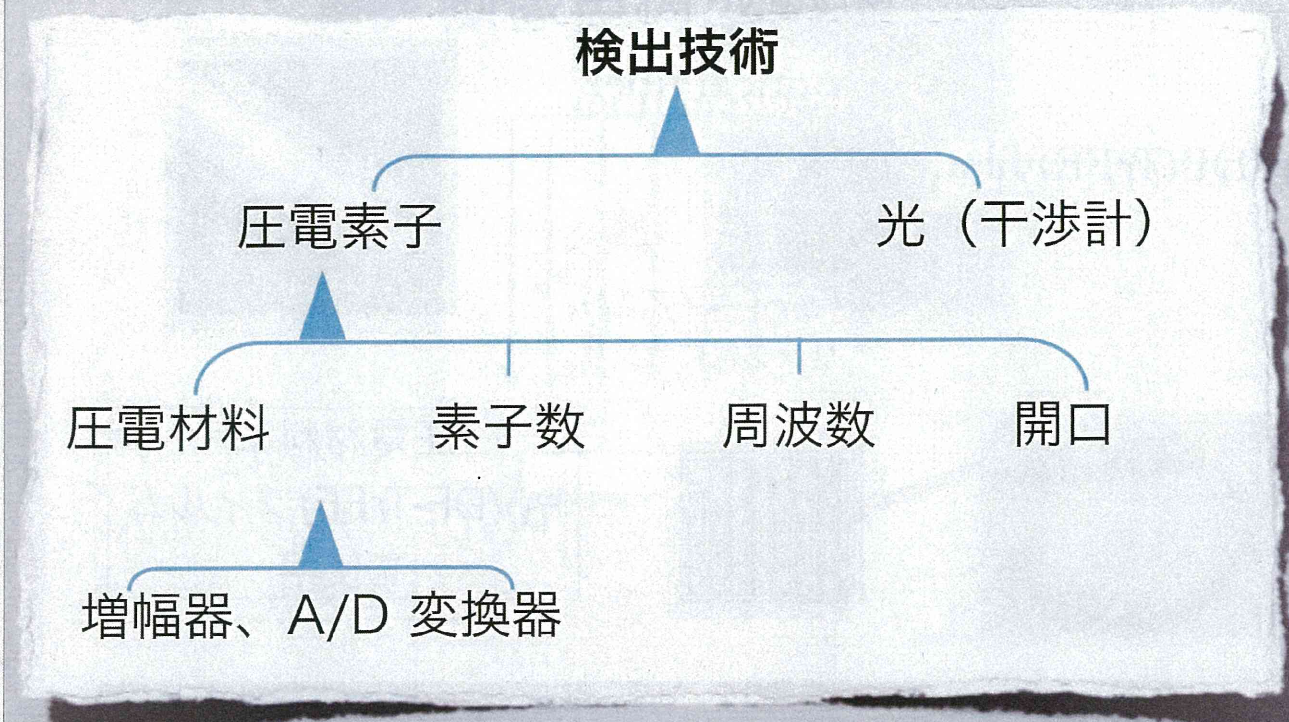
要素技術としての超音波検出技術



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光音響信号計測における圧電材料

	圧電フィルム （P(VDF-TrFE)）	**圧電セラミック** （PZT）	（P(VDF-TrFE)）**の利点**
機械的Q値	3〜10	500	広帯域な周波数特性を有する
音響 **ｲﾝﾋﾟｰﾀﾞﾝｽ**	4.51	34.8	生体との境界面で損失が少ない

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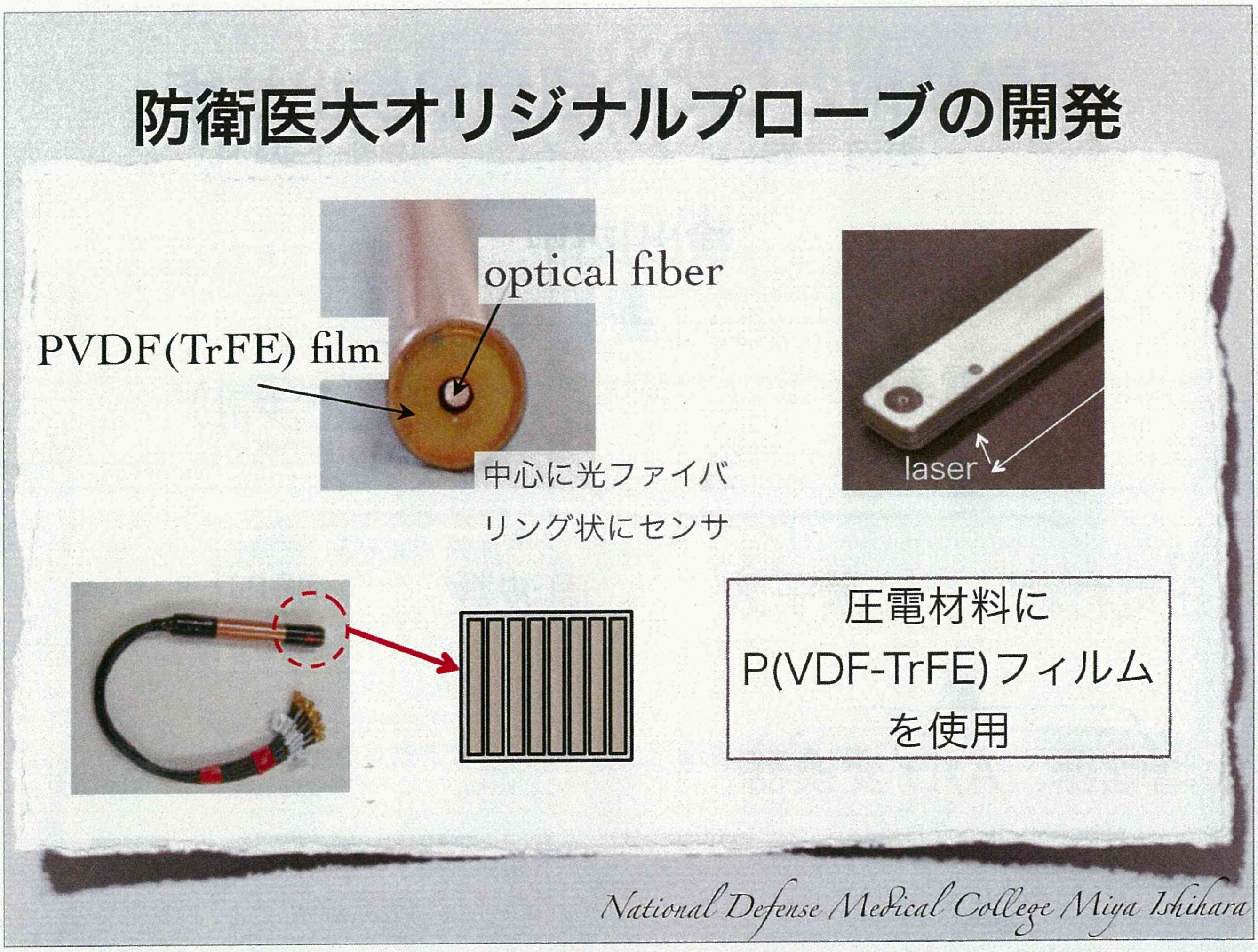

防衛医大オリジナルプローブの開発

optical fiber

PVDF(TrFE) film

中心に光ファイバ
リング状にセンサ

laser

圧電材料に
P(VDF-TrFE)フィルム
を使用

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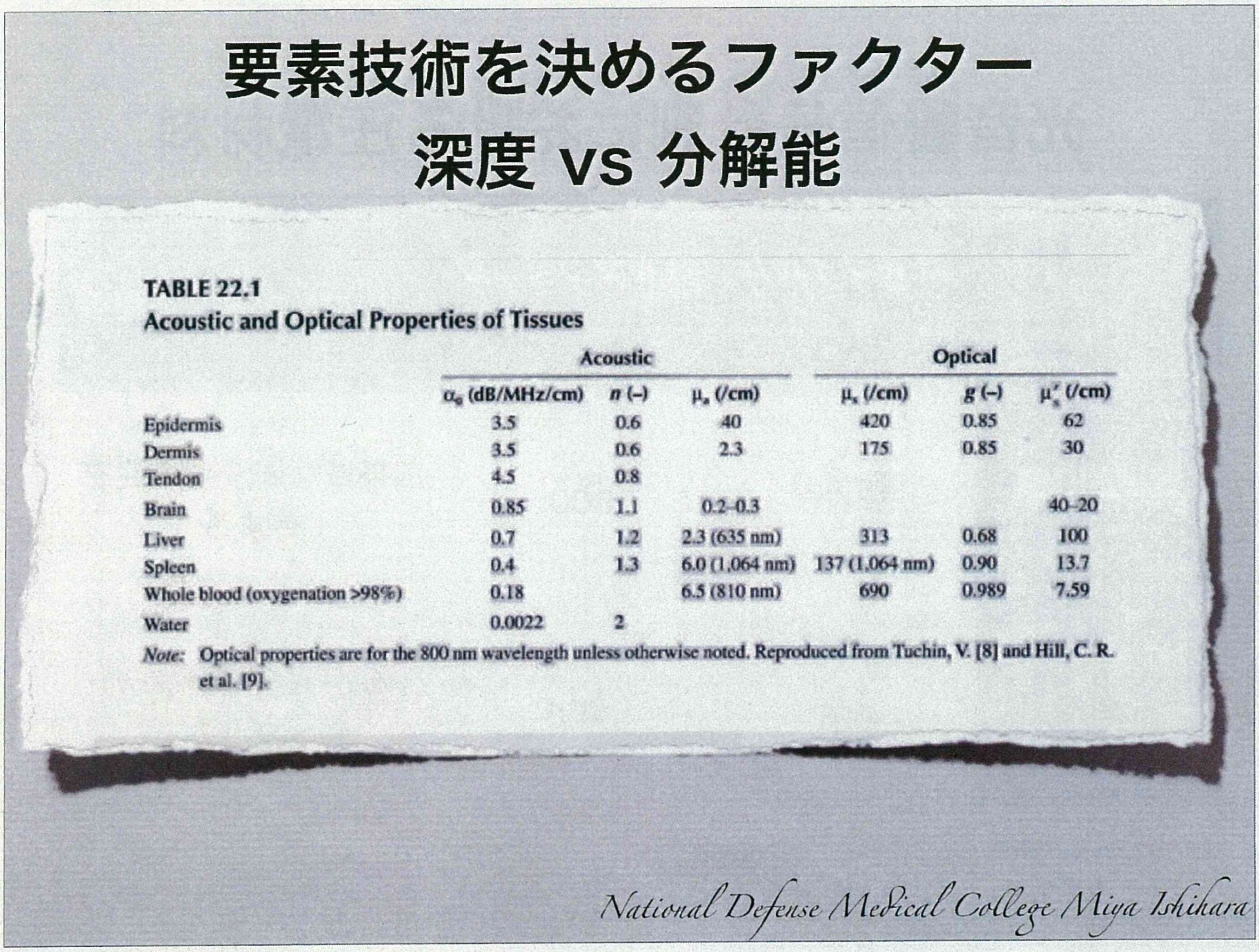

要素技術を決めるファクター
深度 vs 分解能

TABLE 22.1
Acoustic and Optical Properties of Tissues

	Acoustic			Optical		
	α_0 (dB/MHz/cm)	n (–)	μ_a (/cm)	μ_s (/cm)	g (–)	μ_s' (/cm)
Epidermis	3.5	0.6	40	420	0.85	62
Dermis	3.5	0.6	2.3	175	0.85	30
Tendon	4.5	0.8				
Brain	0.85	1.1	0.2–0.3			40–20
Liver	0.7	1.2	2.3 (635 nm)	313	0.68	100
Spleen	0.4	1.3	6.0 (1,064 nm)	137 (1,064 nm)	0.90	13.7
Whole blood (oxygenation >98%)	0.18		6.5 (810 nm)	690	0.989	7.59
Water	0.0022	2				

Note: Optical properties are for the 800 nm wavelength unless otherwise noted. Reproduced from Tuchin, V. [8] and Hill, C. R. et al. [9].

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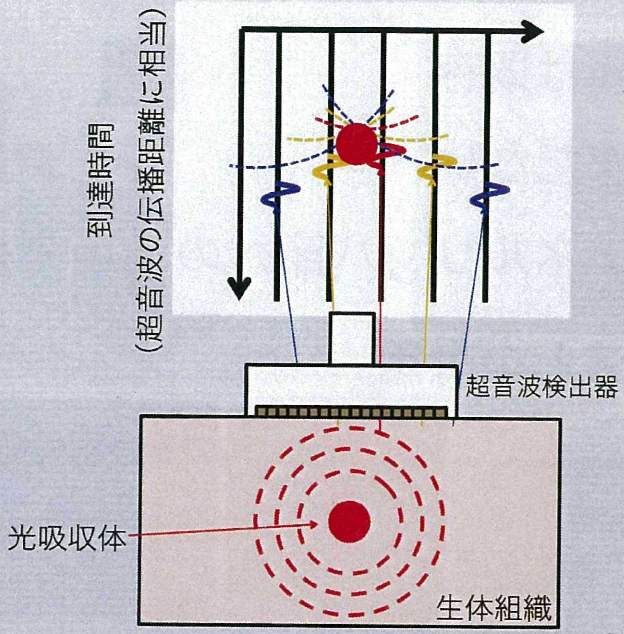
要素技術としての信号処理技術

➡画像再構成処理



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光音響画像化技術（代表例）

リアルタイム処理が可能な手法

Fourier Transform Algorithm　(2005)
：周波数軸での処理

Back Projection Algorithm　(2005)
：時間軸での処理

高精度な画像再構成を目指す処理

Iterative Reconstruction Algorithm　(2002)

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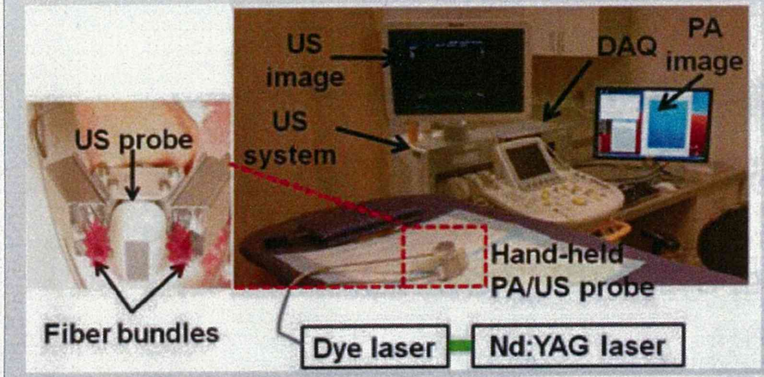
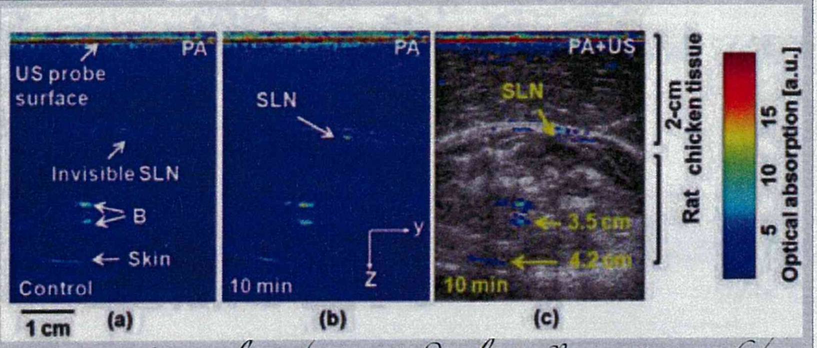
光音響画像化技術の現況

- 小動物用装置は既存
- 医療機器はまだない
- 乳癌、センチネルリンパ節への適用の検討
- 血管内超音波との併用

光音響イメージング例

＊PAI：汎用的　→　臨床用

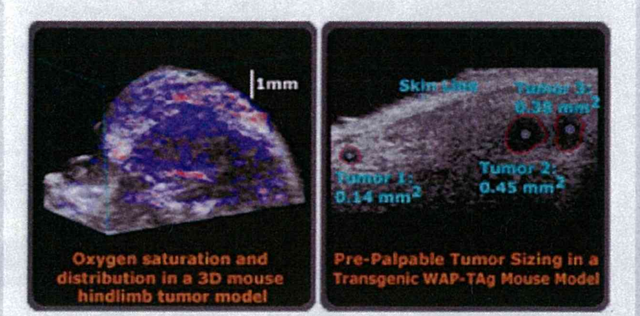




C Kim, T N. Erpelding, L Jankovic, M D. Pashley, L V. Wang, "Deeply penetrating in vivo photoacoustic imaging using a clinical ultrasound array system",Biomedical Optics Express, 1(1), pp278-284, 2010

光音響イメージング例

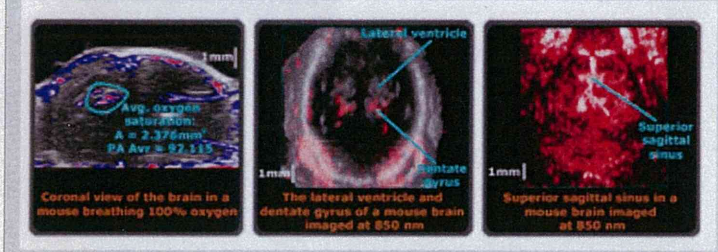
✻ High Frequency PAI：小動物用



Oxygen saturation and distribution in a 3D mouse hindlimb tumor model

Pre-Palpable Tumor Sizing in a Transgenic WAP-TAg Mouse Model

http://www.visualsonics.com/photoacoustics-cancer



Coronal view of the brain in a mouse breathing 100% oxygen

The lateral ventricle and dentate gyrus of a mouse brain imaged at 850 nm

Superior sagittal sinus in a mouse brain imaged at 850 nm

超音波画像との重畳化
分解能　down to 45 µm
深さ　１～２cm

http://www.visualsonics.com/neurobiology-photoacoustics

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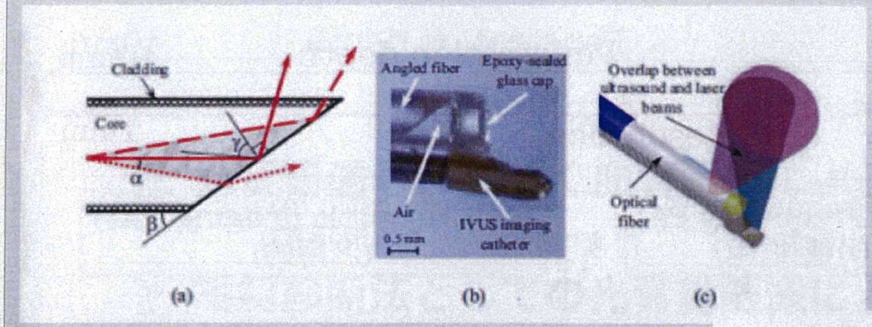
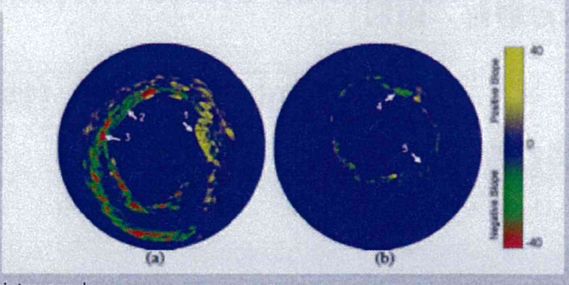
光音響イメージング例

✻ Intravascular： 経カテーテル、内視鏡



(a) (b) (c)



(a) (b)

A B. Karpiouk, B Wang, S Y. Emelianova, "Development of a catheter for combined intravascular ultrasound and photoacoustic imaging", Rev. Sci. Instrum, No.81, 014901, 2010

S Sethuraman, J H. Amirian, S H. Litovsky, R W. Smalling, S Y. Emelianov, "Spectroscopic intravascular photoacoustic imaging to differentiate atherosclerotic plaques", Opt. Exp., 16(5), 3362, 2008

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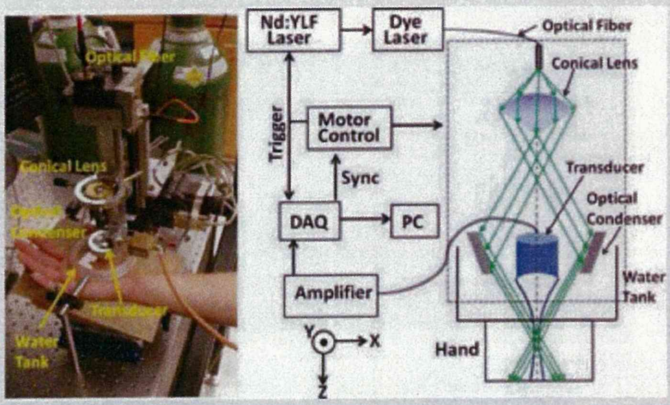
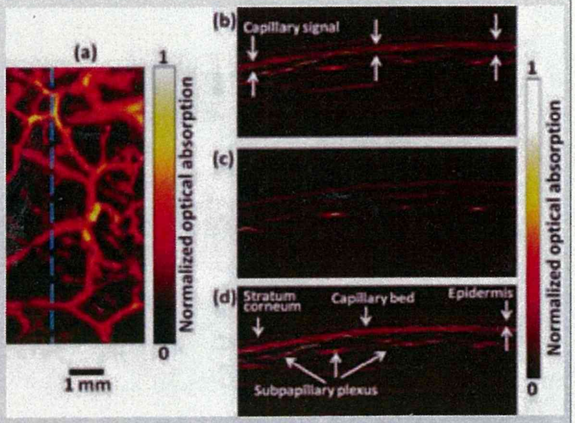
光音響イメージング例

＊ PAM：顕微鏡応用





光の焦点より音の焦点の方が小さい

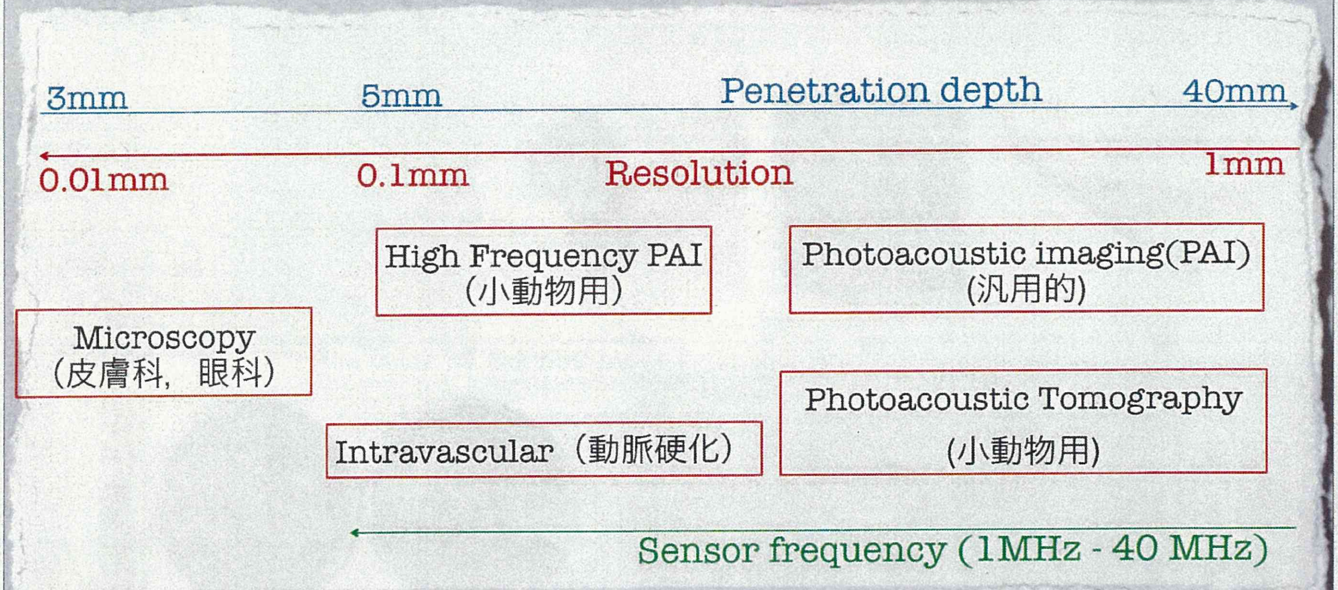
深さ　～3mm

水平分解能　40-120um

深さ分解能　15-30um

C P. Favazza, L A. Cornelius, L V. Wang, "In vivo functional photoacoustic microscopy of cutaneous microvasculature in human skin", Journal of Biomedical Optics, Vol. 16, No. 2, 026004, 2011

光音響イメージングの分類



High Frequency PAI
（小動物用）

Photoacoustic imaging(PAI)
(汎用的)

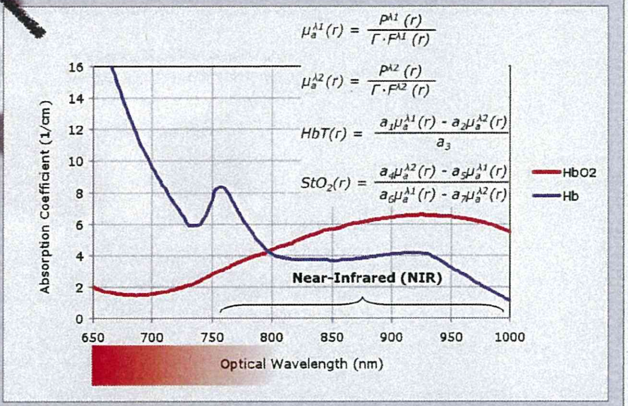
Microscopy
（皮膚科，眼科）

Intravascular（動脈硬化）

Photoacoustic Tomography
(小動物用)

機能画像としての光音響画像

超音波画像との重畳
血中酸素飽和度マッピング
分子特異的なイメージング



$$\mu_a^{\lambda 1}(r) = \frac{P^{\lambda 1}(r)}{\Gamma \cdot F^{\lambda 1}(r)}$$

$$\mu_a^{\lambda 2}(r) = \frac{P^{\lambda 2}(r)}{\Gamma \cdot F^{\lambda 2}(r)}$$

$$HbT(r) = \frac{a_1\mu_a^{\lambda 1}(r) - a_2\mu_a^{\lambda 2}(r)}{a_3}$$

$$StO_2(r) = \frac{a_4\mu_a^{\lambda 2}(r) - a_5\mu_a^{\lambda 1}(r)}{a_6\mu_a^{\lambda 1}(r) - a_7\mu_a^{\lambda 2}(r)}$$

今後の展開

- 光音響信号に基づく血管画像による健康管理
- 機能診断法としての光音響画像による予防的診断

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Lasers in Surgery and Medicine

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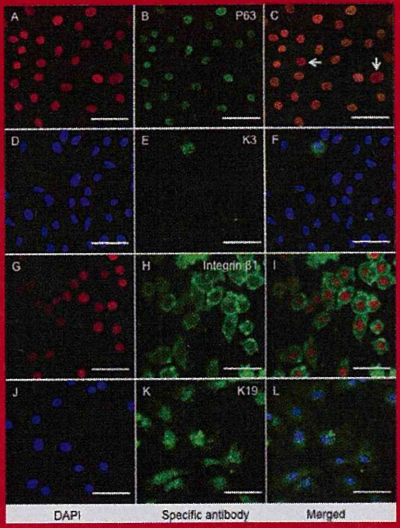
Interstitial PDT for Vascular Anomalies

Sub-Surface, Micrometer-Scale Incisions Produced in Rodent Cortex Using Tightly-Focused Femtosecond Laser Pulses

Photochemical Tissue Bonding: A Potential Strategy for Treating Limbal Stem Cell Deficiency



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Clinical Reports

Pre-Clinical Reports

Basic Research

Cover micrograph: Immunofluorescent staining of LSCs. ***Panels A, D, G,*** *and* ***J*** *are DAPI stained.* ***B:*** *Staining of P63 in nucleus. White arrows indicate P63 negative cells.* ***E:*** *Staining of K3 in cytoplasm.* ***H:*** *Staining of integrin β1 in cell membrane and cytoplasm.* ***K:*** *Staining of K19 in cytoplasm. Panel* ***C, F, I,*** *and* ***L*** *are merged images of the DAPI and specific antibody stained images. Scale bar equals 50 μm.*

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A Diagnostic System for Articular Cartilage Using Non-Destructive Pulsed Laser Irradiation

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Background and Objectives: Osteoarthritis involves dysfunction caused by cartilage degeneration, but objective evaluation methodologies based on the original function of the articular cartilage remain unavailable. Evaluations for osteoarthritis are mostly based simply on patient symptoms or the degree of joint space narrowing on X-ray images. Accurate measurement and quantitative evaluation of the mechanical characteristics of the cartilage is important, and the tissue properties of the original articular cartilage must be clarified to understand the pathological condition in detail and to correctly judge the efficacy of treatment. We have developed new methods to measure some essential properties of cartilage: a photoacoustic measurement method; and time-resolved fluorescence spectroscopy.

Materials and Methods: A nanosecond-pulsed laser, which is completely non-destructive, is focused onto the target cartilage and induces a photoacoustic wave that will propagate with attenuation and is affected by the viscoelasticity of the surrounding cartilage. We also investigated whether pulsed laser irradiation and the measurement of excited autofluorescence allow real-time, non-invasive evaluation of tissue characteristics.

Results: The decay time, during which the amplitude of the photoacoustic wave is reduced by a factor of $1/e$, represents the key numerical value used to characterize and evaluate the viscoelasticity and rheological behavior of the cartilage. Our findings show that time-resolved laser-induced autofluorescence spectroscopy (TR-LIFS) is useful for evaluating tissue-engineered cartilage.

Conclusions: Photoacoustic measurement and TR-LIFS, predicated on the interactions between optics and living organs, is a suitable methodology for diagnosis during arthroscopy, allowing quantitative and multidirectional evaluation of the original function of the cartilage based on a variety of parameters. Lasers Surg. Med. 43:421–432, 2011. © 2011 Wiley-Liss, Inc.

Key words: osteoarthritis; photoacoustic measurement; time-resolved autofluorescence spectroscopy; tissue-engineered cartilage

INTRODUCTION

Osteoarthritis is thought to affect about 30 million people in Japan [1], but is not a direct threat to life. However, this condition both affects activities of daily living and diminishes quality of life among sufferers, so the associated human and social loss is difficult to estimate. The disease involves dysfunction caused by cartilage degeneration, but objective methodologies of evaluation based on the original function of the articular cartilage are currently unavailable. Evaluations that are currently used to establish conservative therapies or the prognosis of surgery as a treatment for osteoarthritis are merely based on patient symptoms or the degree of joint space narrowing on X-ray images. Accurate measurement and quantitative evaluation of the mechanical characteristics of cartilage (viscosity, elasticity, and lubrication) are important, and the tissue properties of the original articular cartilage need to be recognized if the pathological condition is to be understood in detail and treatment effects judged accurately. The development of such evaluation technologies is thus required to facilitate a functional diagnosis of osteoarthritis. If these evaluations can be achieved non-invasively, an accurate understanding of the pathologies should be possible, allowing the planning and performance of treatments for locomotor apparatus diseases that accompany the degeneration of cartilage, such as osteoarthritis. Such evaluations would also be useful as objective tools in situations such as the clinical

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