Standardization in

Biological and Medical Imaging
Optoacoustics meets Ionoacoustics

Vasilis Ntziachristos

IBMI

Institute for Biological and Medical Imaging

Chair for Biological Imaging

Technische Universität München & Helmholtz Zentrum München

HelmholtzZentrum münchen
German Research Center for Environmental Health

TECHNOLOGY

MSOT combines high-resolution real-time ultrasound detection with the specificity of optical contrast

APPLICATIONS

MSOT impacts many areas in biological, pharma-cological, medical and materials-related research

EVENTS

Meet us personally and learn more about MSOT at one of the upcoming conferences or MSOT webinars

ABOUT US

All the news and contact data...and an invitation to join our team!

PARTICIPATE IN AN IMAGING REVOLUTION.

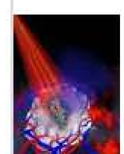
iThera Medical offers the next generation in molecular imaging. Introducing MSOT - Multispectral Optoacoustic Tomography.

With its unique ability to accurately visualize and quantify tissue molecules, nanoparticles, biomarkers and optical agents, *in vivo* and in real time, through several centimeters of tissue, MSOT stands at the forefront of the next era in biomedical imaging.

Launch of Hybrid OA / US Technology

iThera Medical proudly announces the launch of its

NEWS



University of Leeds publishes using MSOT: "Gold nanotubes launch a three-pronged attack on cancer cells"

MSOT selected as "one of

SurgVision

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Products

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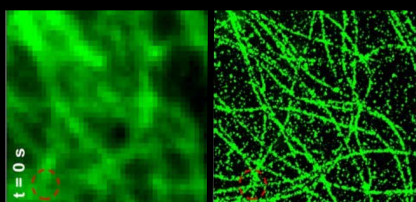
News

Company

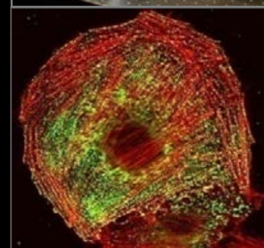
Resolution 0.1μm 1μm 100μm 1mm

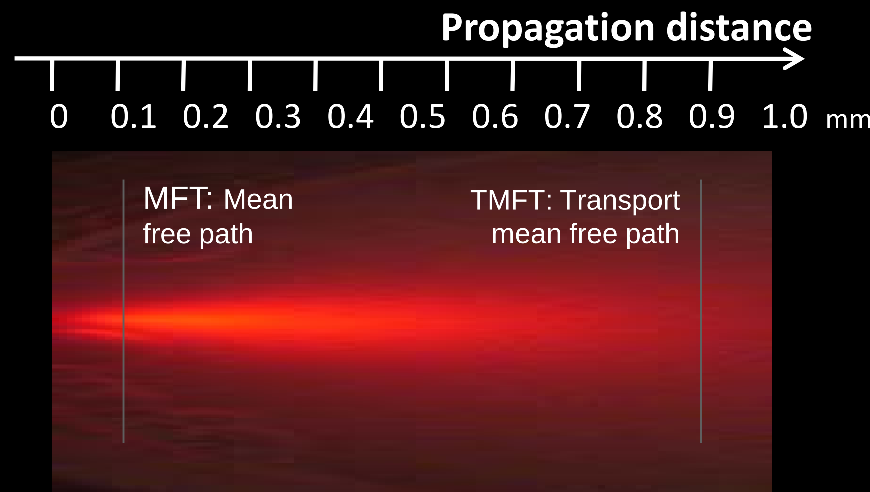
Imaging depth 0.1mm 1mm 1cm 10cm

Super-resolution
(Nobel Prize 2014)



Confocal / Multi-photon
Optical Microscopy





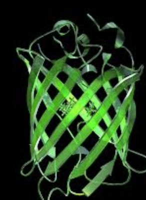
At least one scattering event

Increasing photon -scattering

Random walk

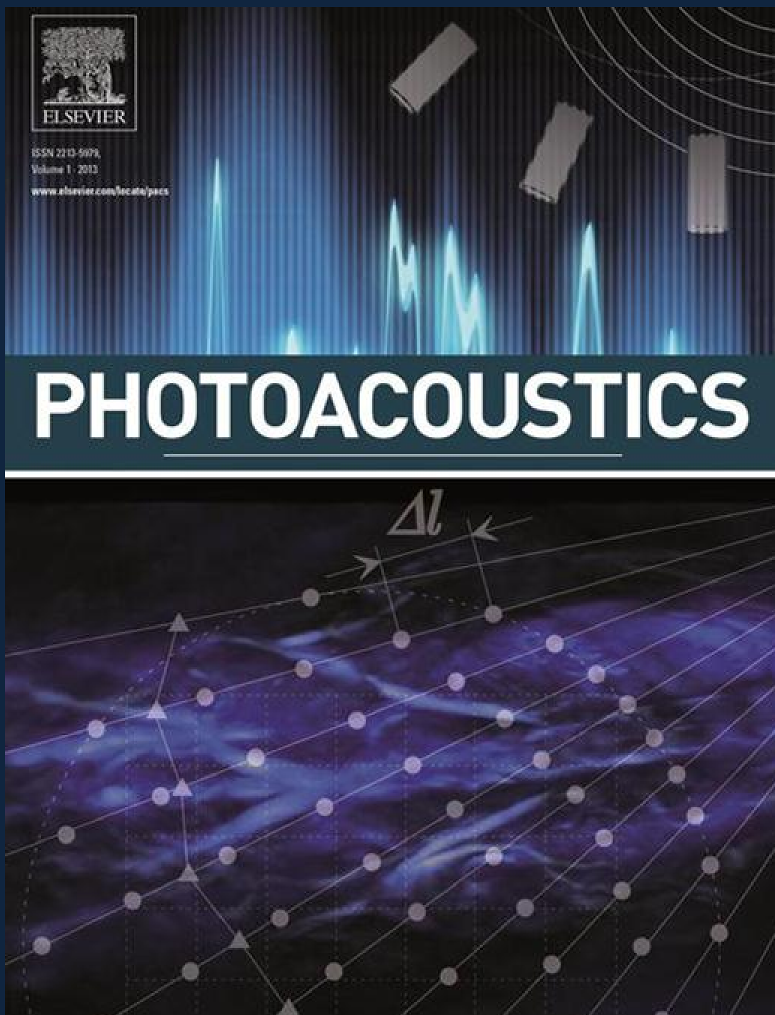
Ntziachristos V., Nature Methods 7(8); 603 (2010)

Fluorescence Proteins
(Nobel Prize 2008)



Promote the Photoacoustics community

http://ees.elsevier.com/pacs/



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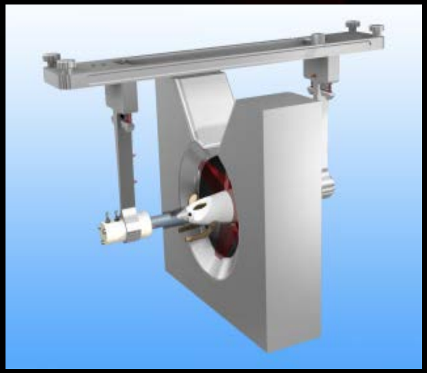
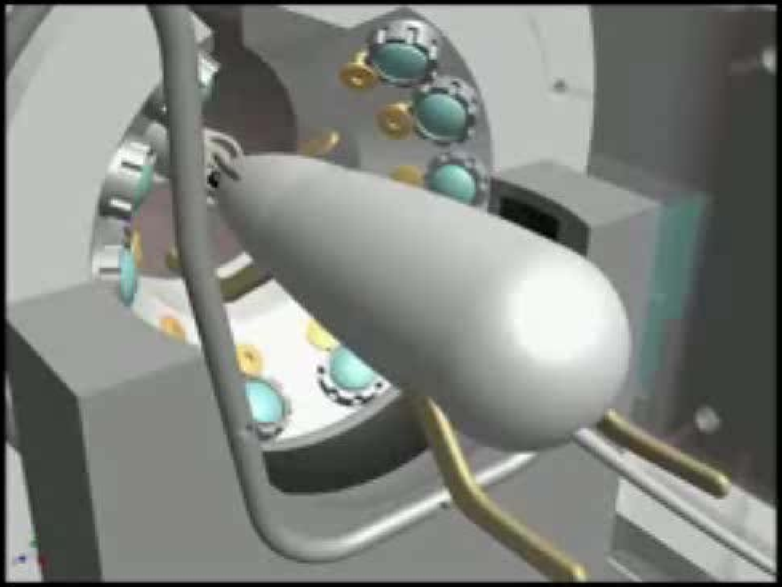
Multi-spectral opto-acoustic tomography (MSOT)



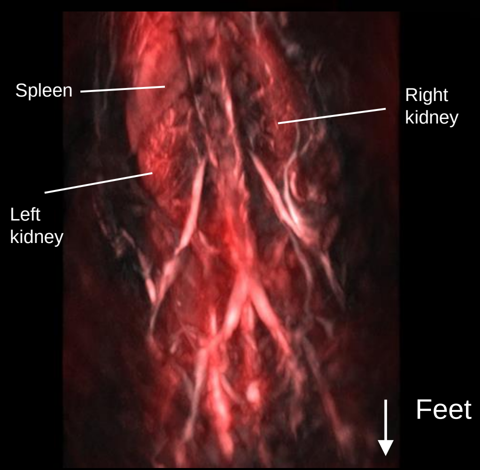
3D imaging by scanning along z-axis



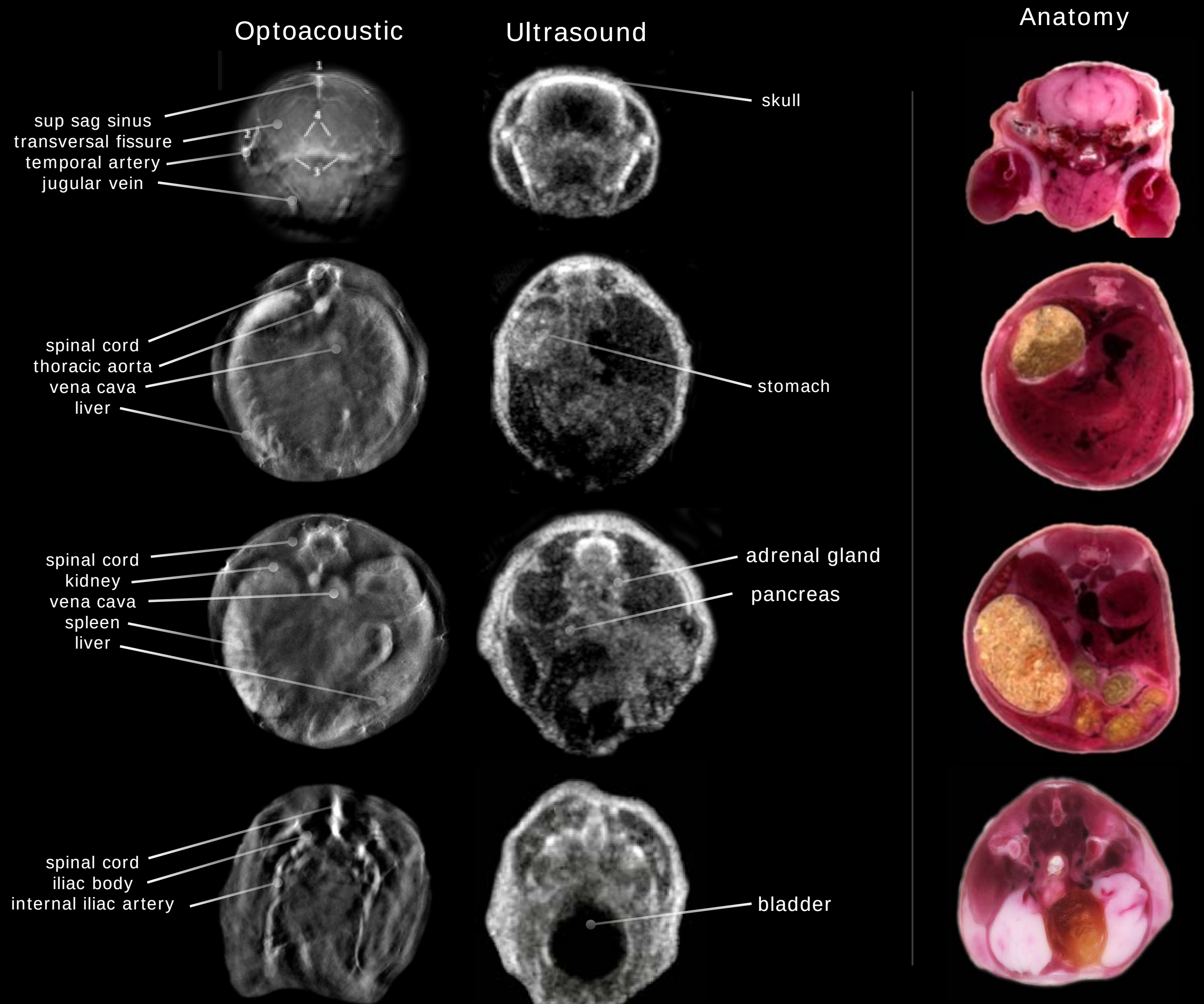
Nature Photonics 3, 412-417 (2009)
ACR Chemical Review, 110(5); 2783-2794 (2010)
Nature Methods 7(8); 603-614, (2010)
Nature Protocols 6(8):1121-9 (2011).
Nature Photonics 9, 219–227 (2015)

Multi-spectral opto-acoustic tomography (MSOT)

3D Tomography in sagittal scan

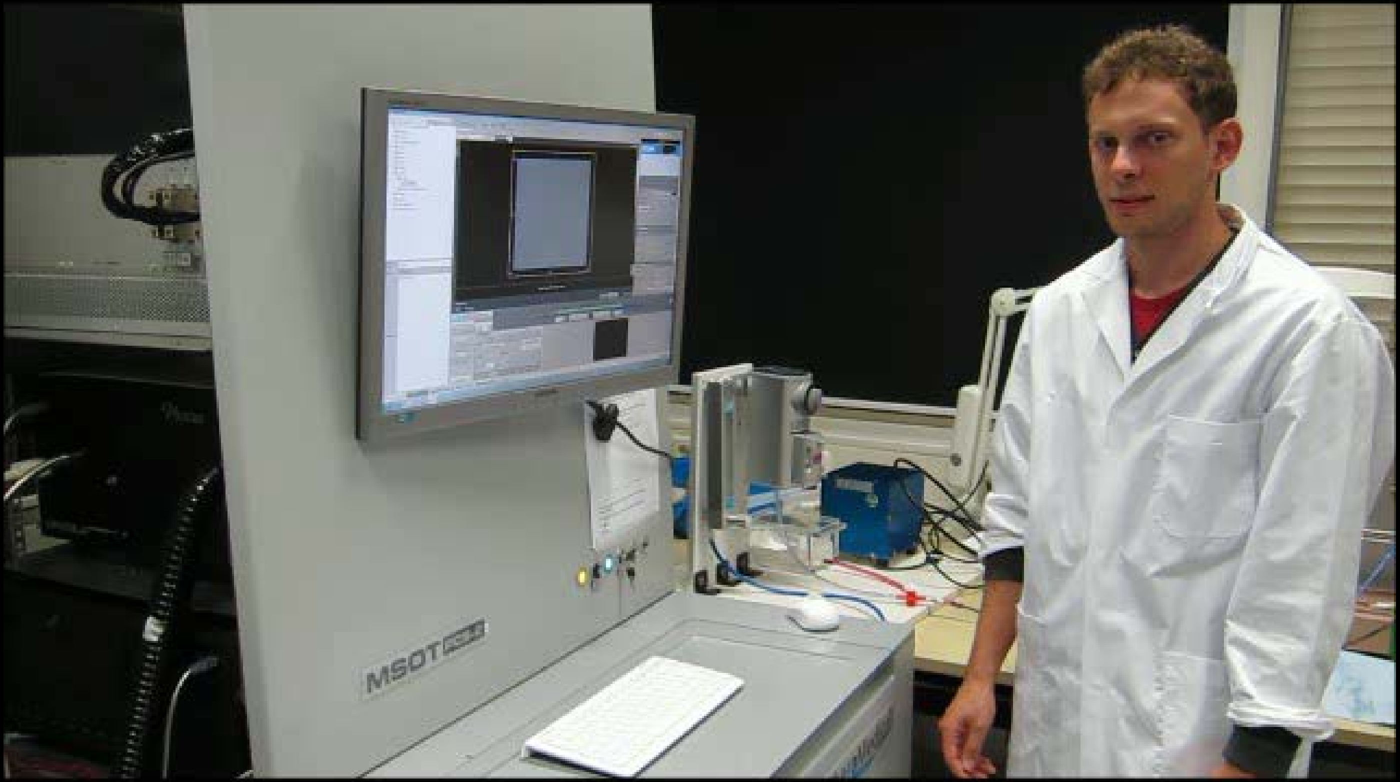


Gateau J., et. al. IEEE TMI 2013



Nature Photonics 9; 219–227 (2015).), ***ACR Chemical Review***, 110(5); 2783-2794 (2010)
Nature Methods 7(8); 603-614, (2010), ***Nature Protocols*** 6(8):1121-9 (2011).

“Real-time” imaging



Nature Photonics 3, 412-417 (2009)
ACR Chemical Review, 110(5); 2783-2794 (2010)
Nature Methods 7(8); 603-614, (2010)
Nature Protocols 6(8):1121-9 (2011).

nature photonics

REVIEW ARTICLE

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Advances in real-time multispectral optoacoustic imaging and its applications

Adrian Taruttis[1] and Vasilis Ntziachristos[2,3]*

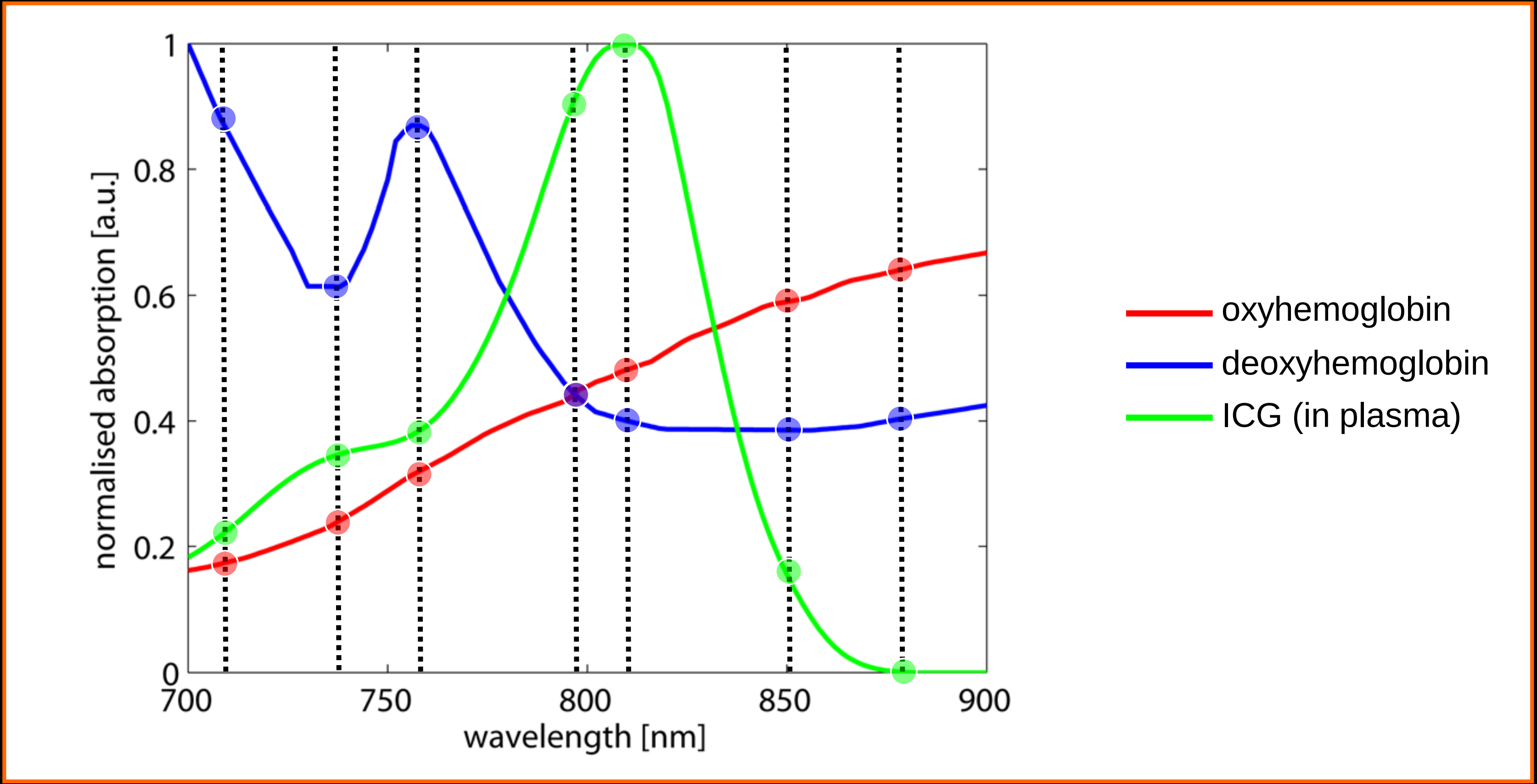
Optoacoustic imaging, or photoacoustic imaging, is insensitive to photon scattering within biological tissue and, unlike conventional optical imaging methods, makes high-resolution optical visualization deep within tissue possible. Recent advances in laser technology, detection strategies and inversion techniques have led to significant improvements in the capabilities of optoacoustic systems. A key empowering feature is the development of video-rate multispectral imaging in two and three dimensions, which offers fast, spectral differentiation of distinct photoabsorbing moieties. We review recent advances and capabilities in the technology and its corresponding emerging biological and clinical applications.

Despite its attractive features for optical imaging and multidimensional sensing, optoacoustic (photoacoustic) imaging had a slow start. Already in the 1970s and early 80s, optoacoustics was considered a modality for absorption spectroscopy and for subsurface visualization[1], including biological applications[2]. It took at least until the mid-90s, with the advent of high-energy pulsed lasers, before it became clear that optoacoustic imaging could be a valuable biomedical imaging modality[3–5]. Several milestones in optoacoustic imaging were reached in the years that followed, including imaging of structural, functional and molecular parameters[6–9]. Of particular importance in the progress of optoacoustic imaging in biomedical applications has been the sequential illumination of tissue at multiple wavelengths and subsequent processing in the form of spectral unmixing algorithms. Spectral imaging enables physiological and molecular imaging by retrieving signals from multiple tissue chromophores and exogenous agents[10,11] (Box 1). We refer to this method as

the technological advances in the context of the novel features they enable. We use the term dimension in the imaging sense to extend the three geometrical dimensions to also include the time axis, the optical wavelength axis and the ultrasound frequency axis—the latter potentially providing an additional axis so that images can be analysed over multiple scales[28,29].

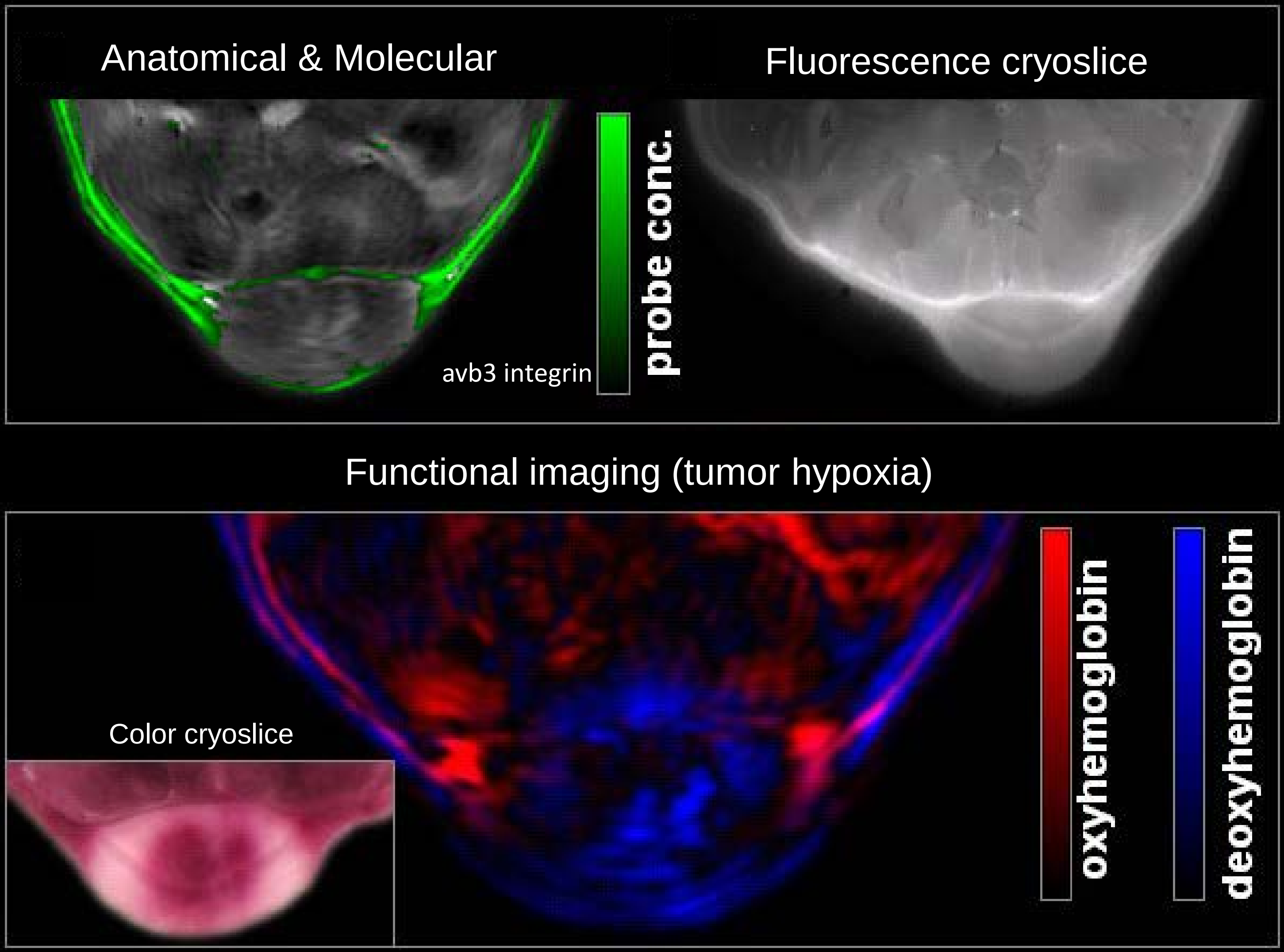
Volumetric imaging. Optoacoustic imaging is fundamentally a three-dimensional imaging method. Tissue illumination, using light pulses or other forms of transient intensity, is afforded by light that generally creates a diffusive pattern within tissue and generates optoacoustic signals from the illuminated volume. Imaging systems must then record time-resolved pressure signals around the boundary of that volume so that the initial pressure distribution, resulting from optical absorption and subsequent thermal expansion, can be reconstructed. Two-dimensional imaging by focusing

Multi-spectral opto-acoustic tomography (MSOT)



ACR Chemical Review, 110(5); 2783-2794 (2010)
Nature Methods 7(8); 603-614, (2010)
Nature Photonics 3, 412-417 (2009)

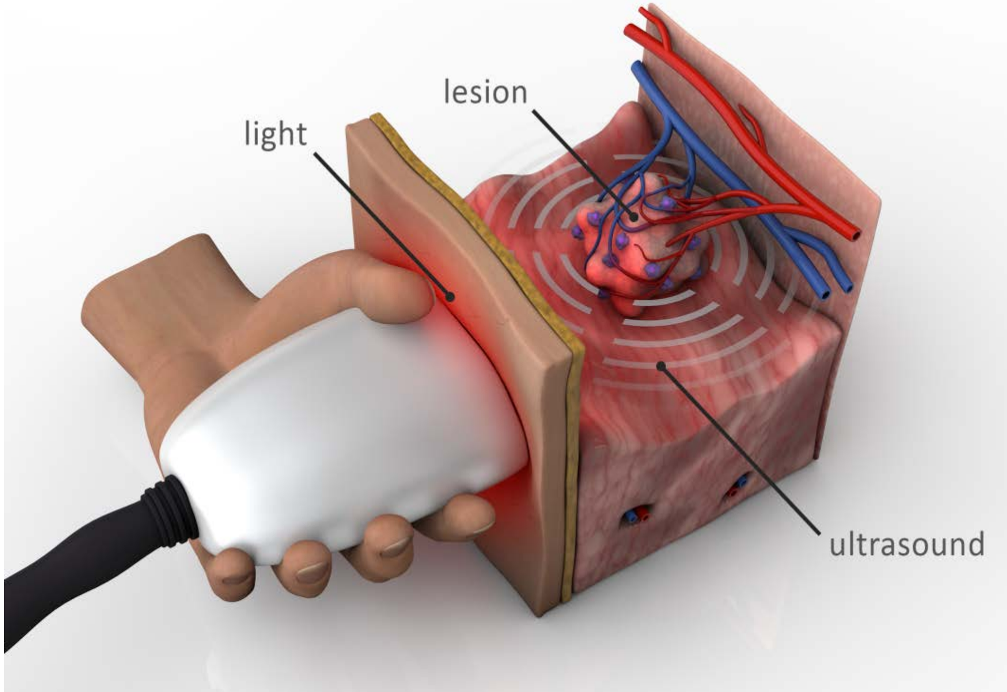
Anatomical functional and molecular imaging



Herzog E, et.al Radiology. **263**(2):461-8. (2012).

Multispectral Optoacoustic Tomography

Handheld MSOT for clinical translation



erc

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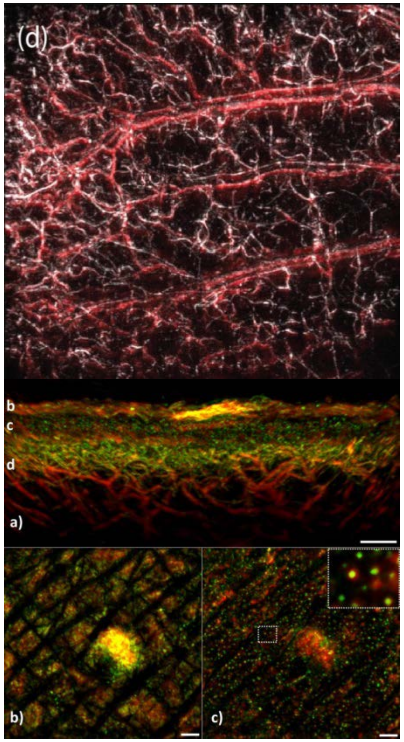
und Forschung

DFG



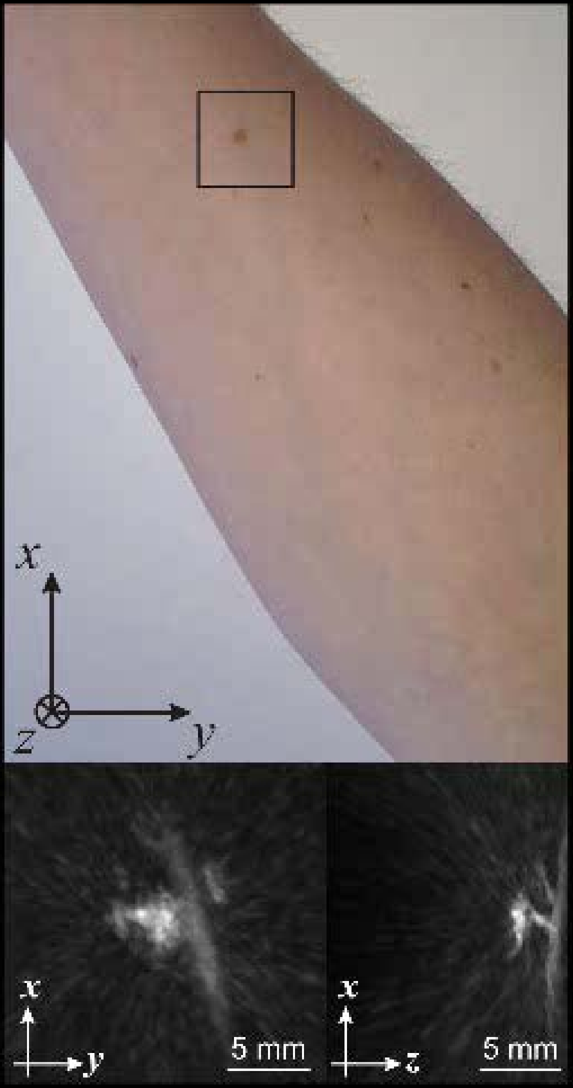
NEW LABEL-FREE Imaging

- Oxygenation / Hypoxia
- Microvasculature, rarefaction
- Metabolism (rate of oxygen consumption)
- Inflammation (dilation, Hb concentration)
- Perfusion / Flow

Phenotypic measurements for accelerating discovery / drug efficacy studies

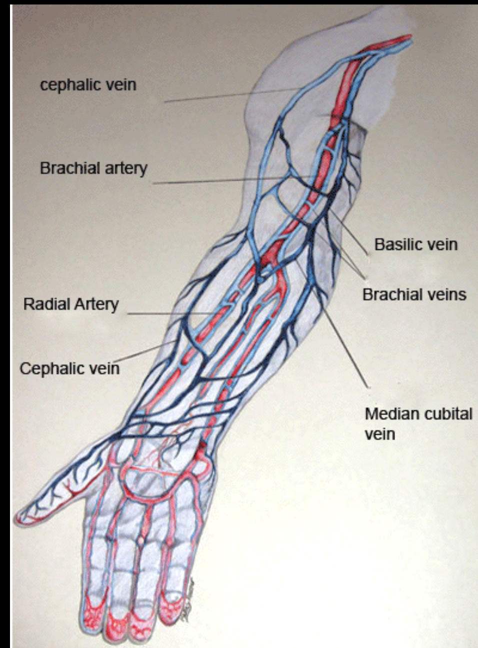
Applications in dermatology, PAD/diabetes angioplasty, endoscopy/surgery, wound healing

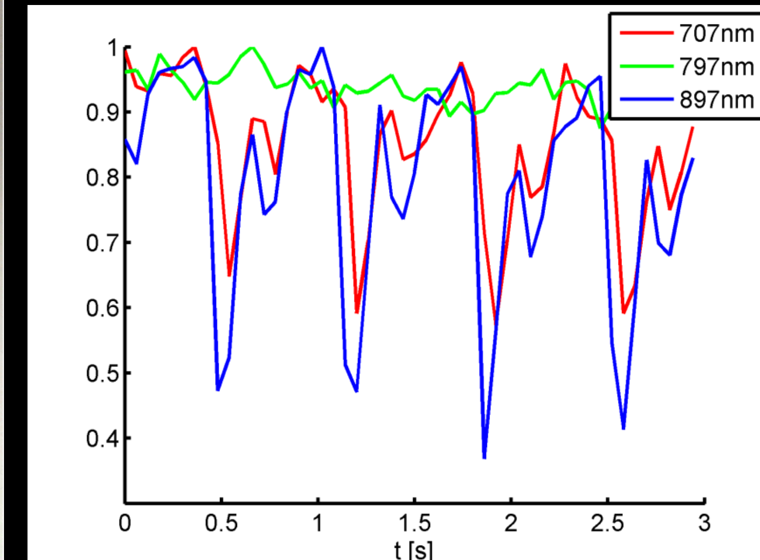
Video imaging of arm/hand vasculature

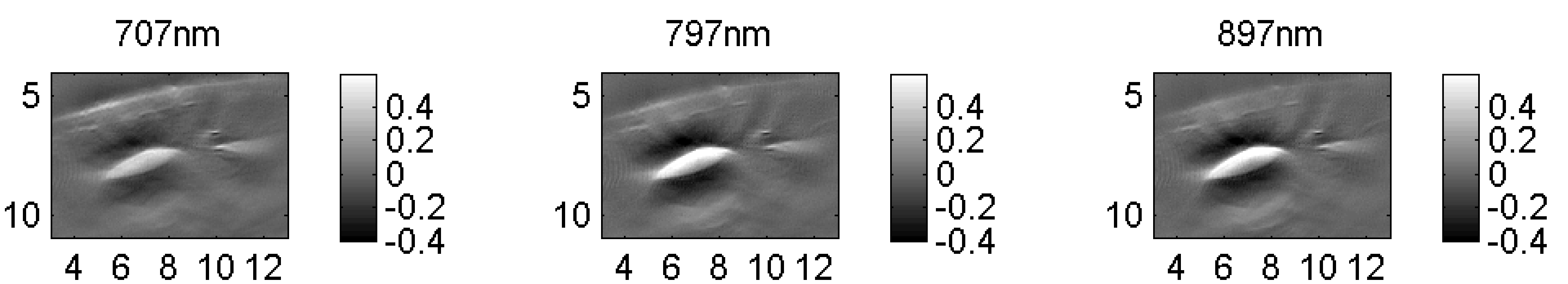


Luis Dean, Daniel Razansky

Imaging the wrist area







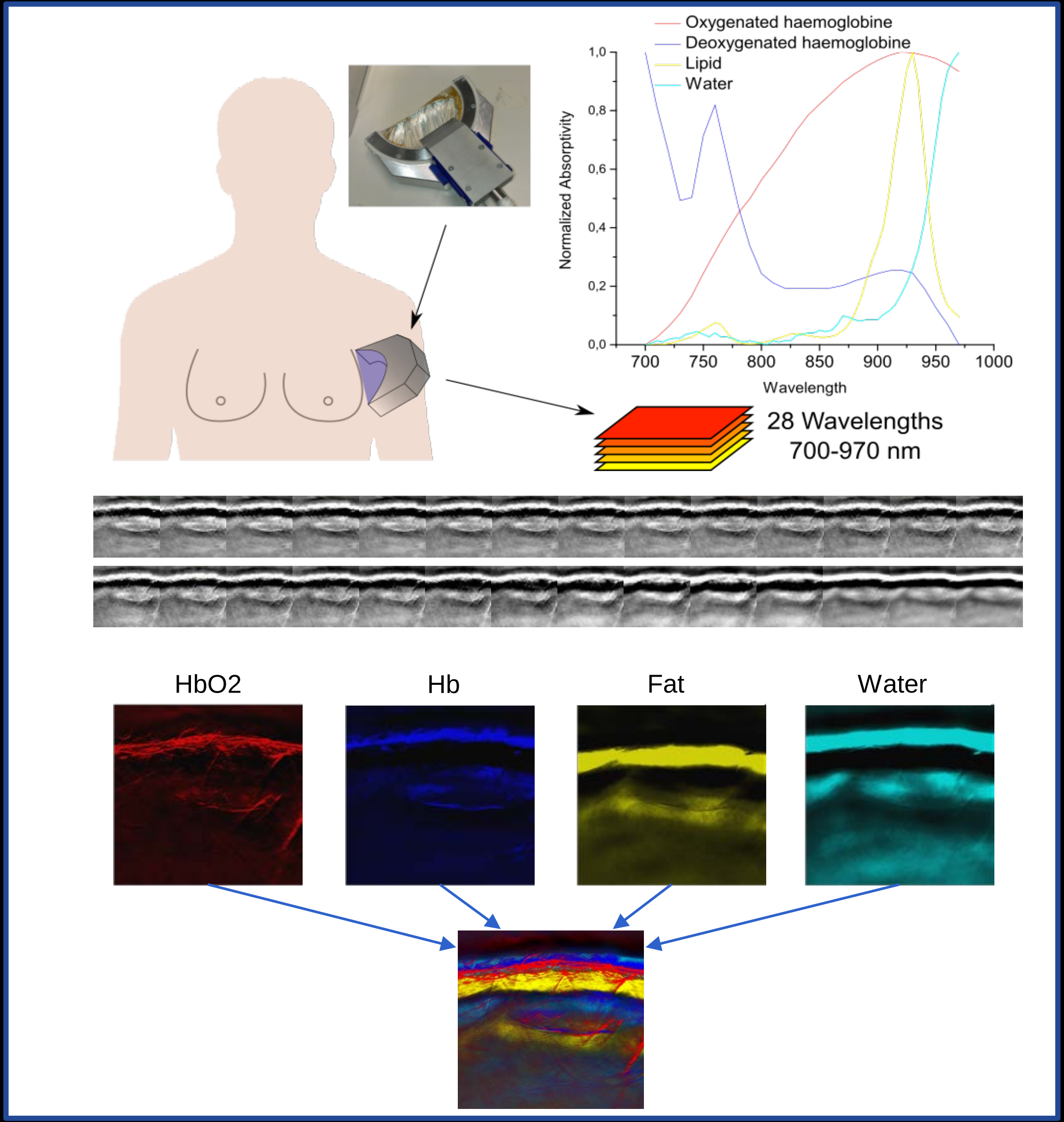
3 wavelength imaging at a multispectral framerate of 17 Hz

Breast Cancer Imaging

Imaging Protocol

28 Wavelength
Data Collection

Spectral Unmixing



Breast Cancer Imaging

Imaging Protocol

28 Wavelength
Data Collection

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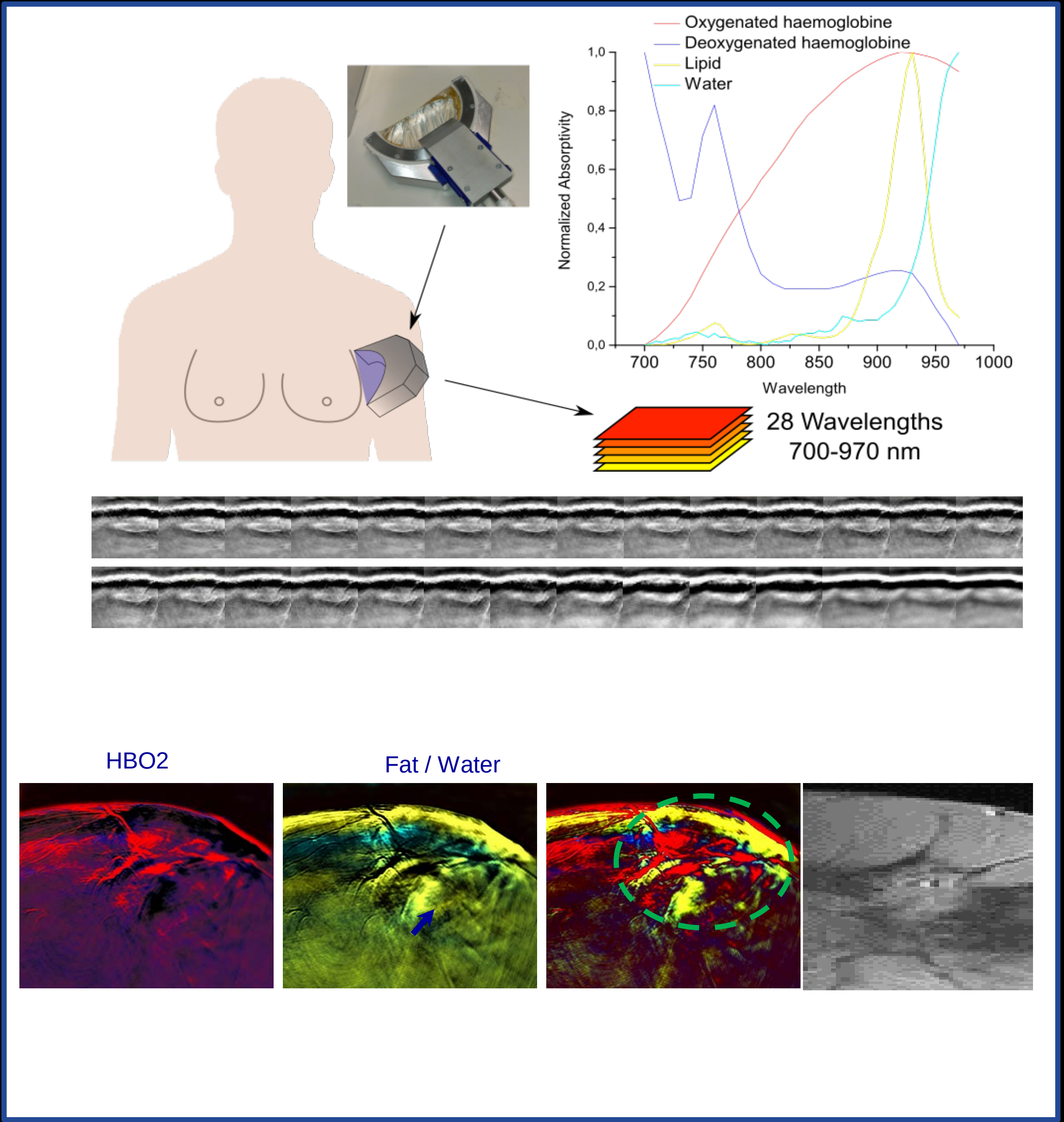
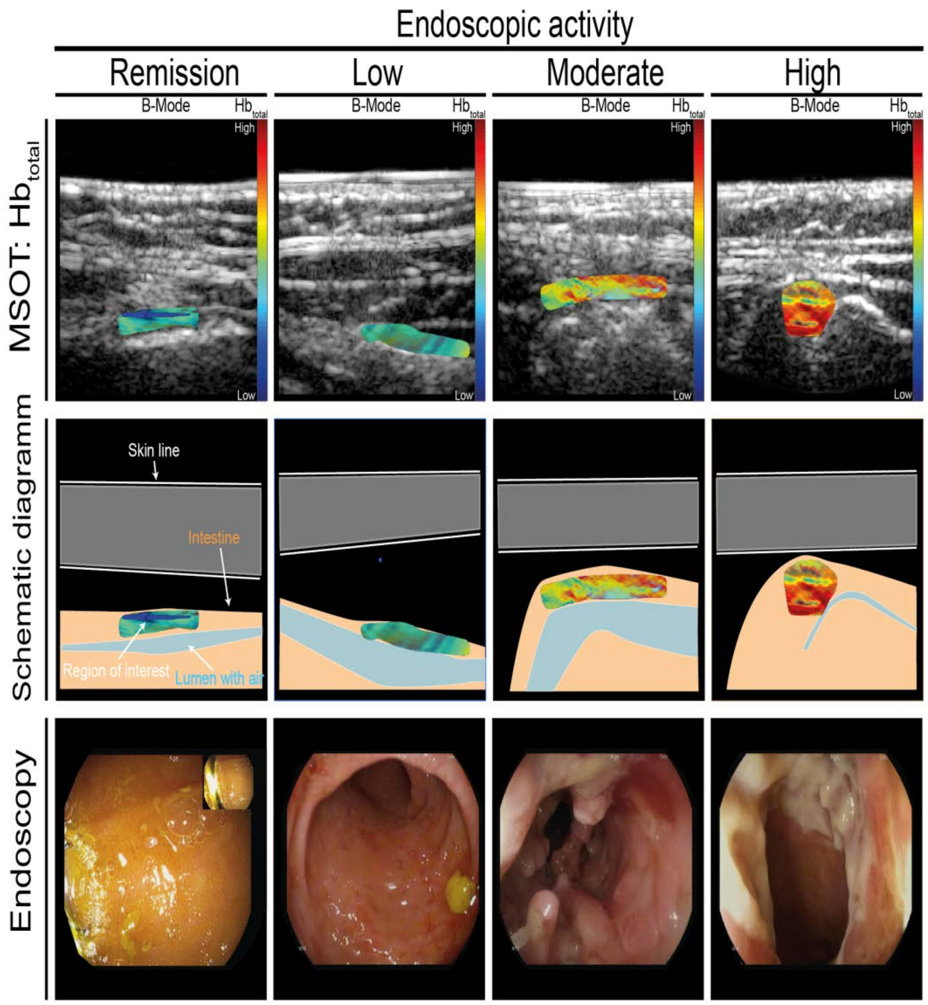
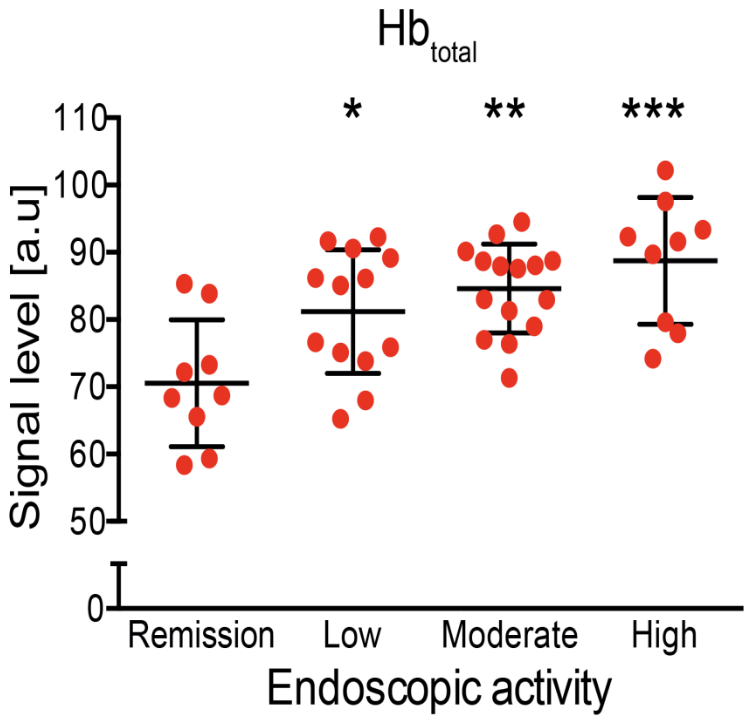


MSOT of endoscopic mucosal healing in Crohn's disease patients

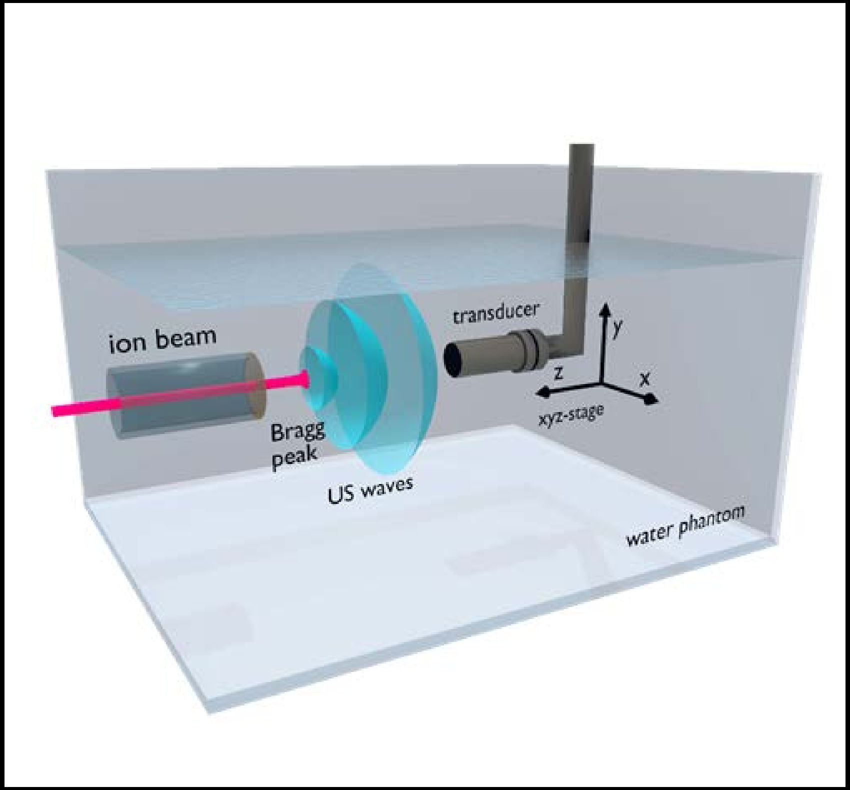


Courtesy Max Waldner, Erlangen



Knieling et al.,
New England Journal of Medicine *in press*

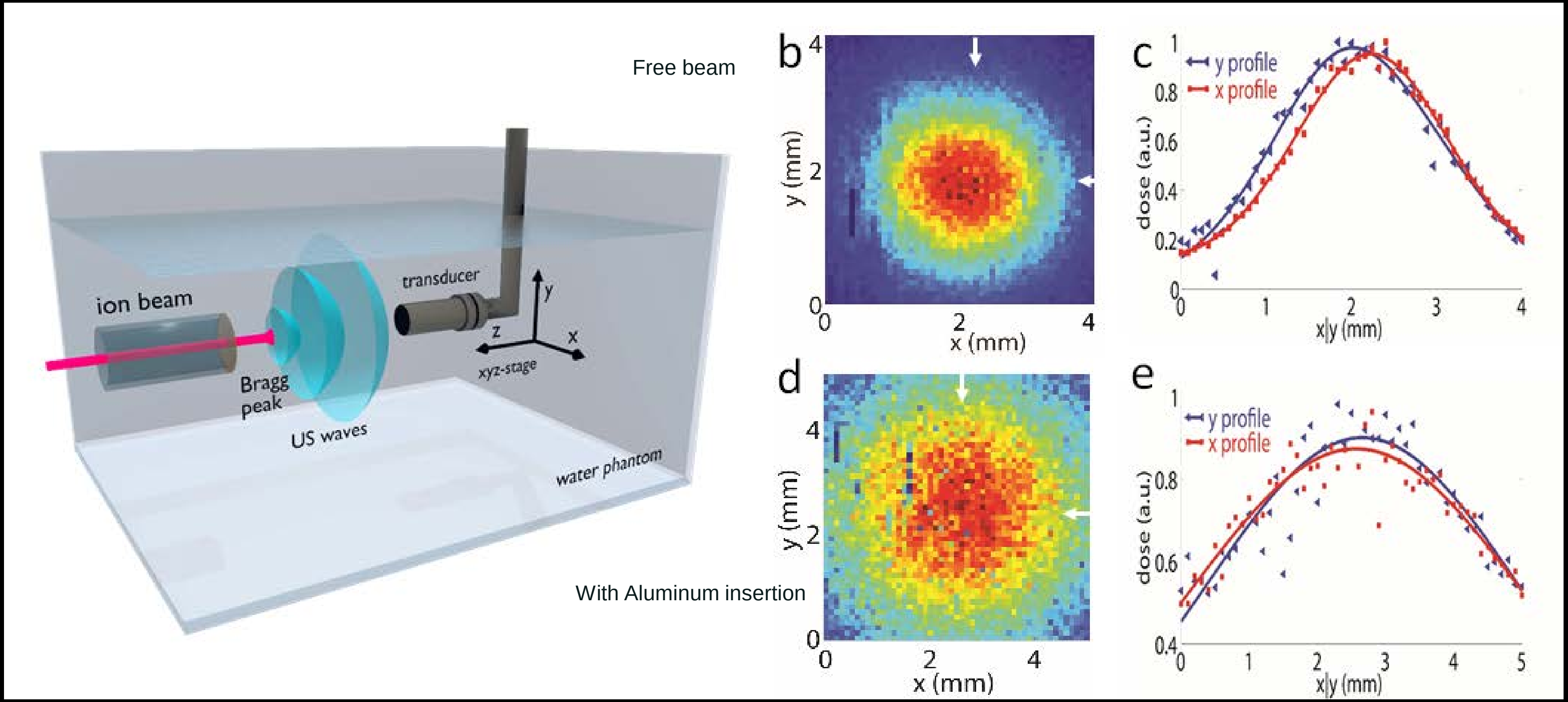
2D imaging of the Proton Bragg Peak



20 MeV protons

Collaboration with Parodi, Assmann LMU

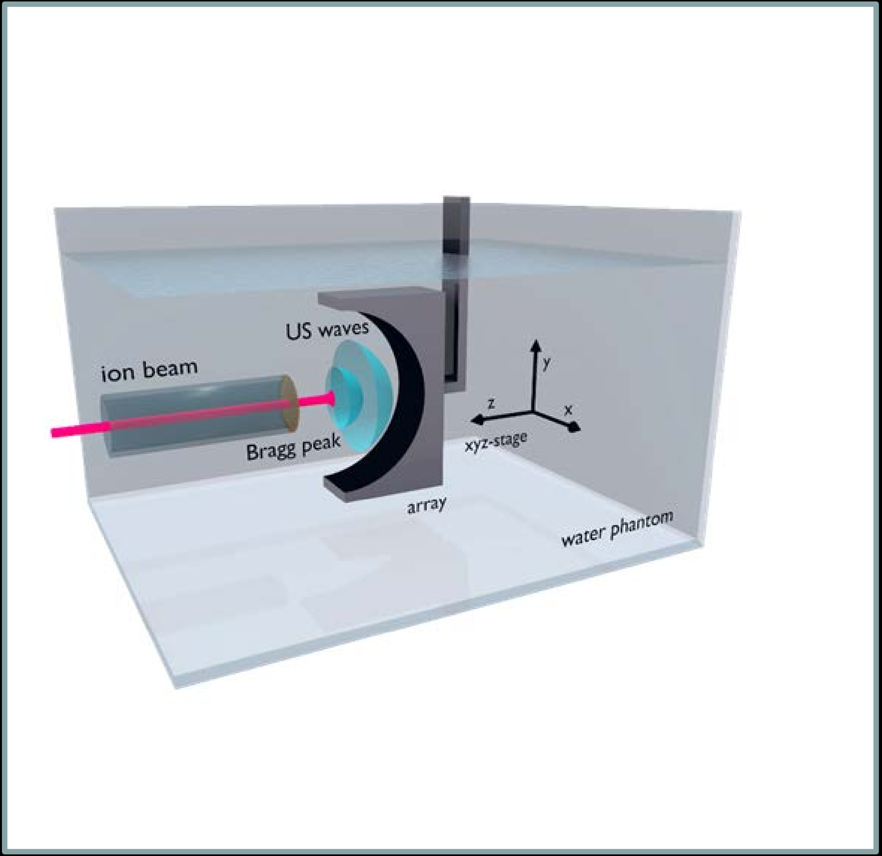
2D imaging of the Proton Bragg Peak



20 MeV protons

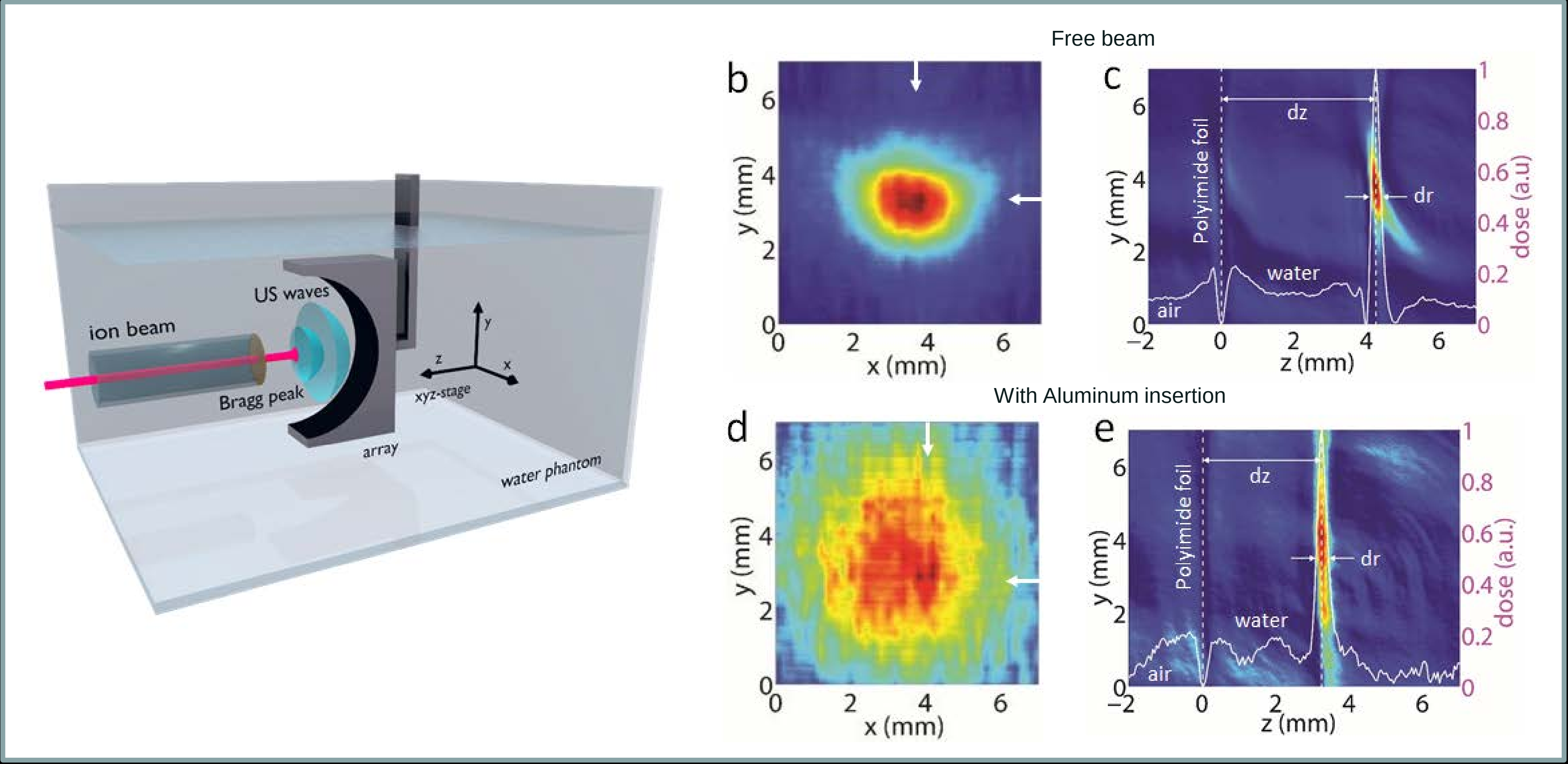
Collaboration with Parodi, Assmann LMU

3D imaging of the Proton Bragg Peak



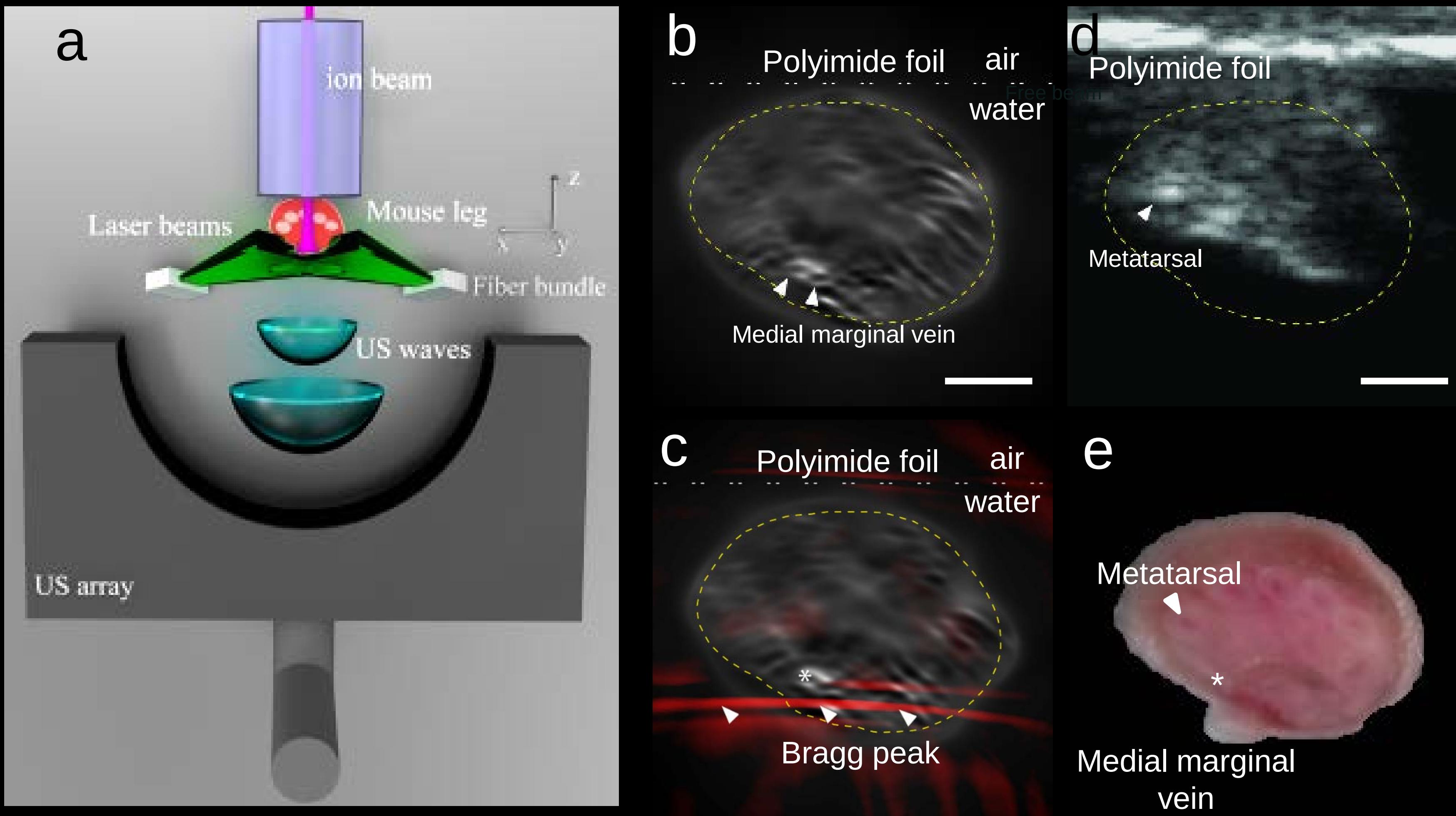
20 MeV protons

3D imaging of the Proton Bragg Peak

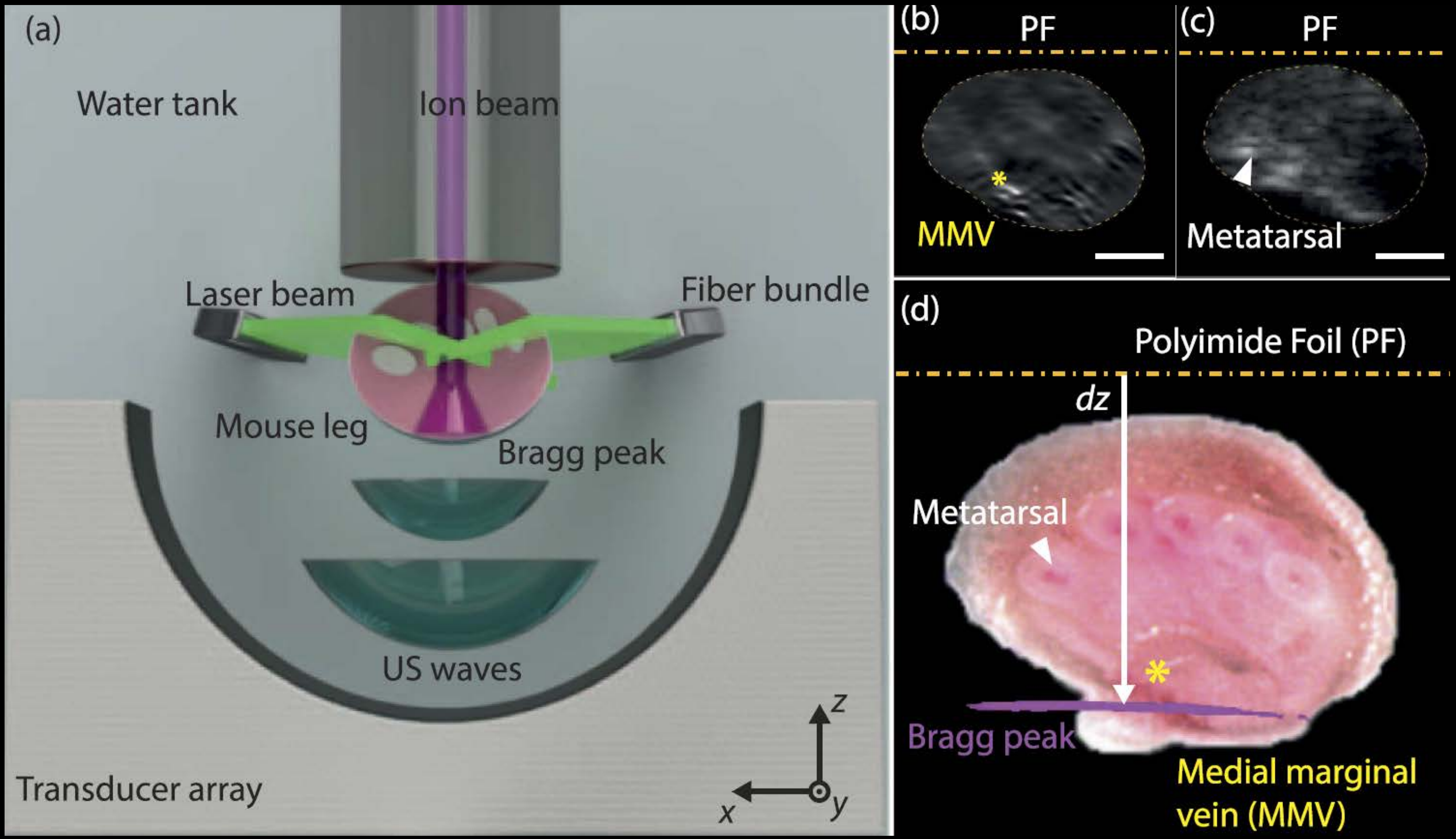


20 MeV protons

3D imaging of the Proton Bragg Peak



3D imaging of the Proton Bragg Peak



3D imaging of the Proton Bragg Peak

- Real time imaging of therapy
- Source characterization
- Interaction with materials

A new standardization problem

The most common medical imaging modality

Radiological imaging

Intra-operative imaging

Difficulty to achieve R0 resection
Limitations in accurate staging

Concept

THE AMERICAN JOURNAL OF ROENTGENOLOGY AND RADIUM THERAPY

VOL. 66 JULY, 1951 No. 1

CLINICAL AND EXPERIMENTAL STUDIES OF INTRACRANIAL TUMORS WITH FLUORESCEIN DYES

WITH AN ADDITIONAL NOTE CONCERNING THE POSSIBLE USE OF K^{42} AND IODINE 131 TAGGED HUMAN ALBUMIN*†

By G. E. MOORE, C. M. CAUDILL, J. F. MARVIN, J. B. AUST, S. N. CHOU, *and* G. A. SMITH

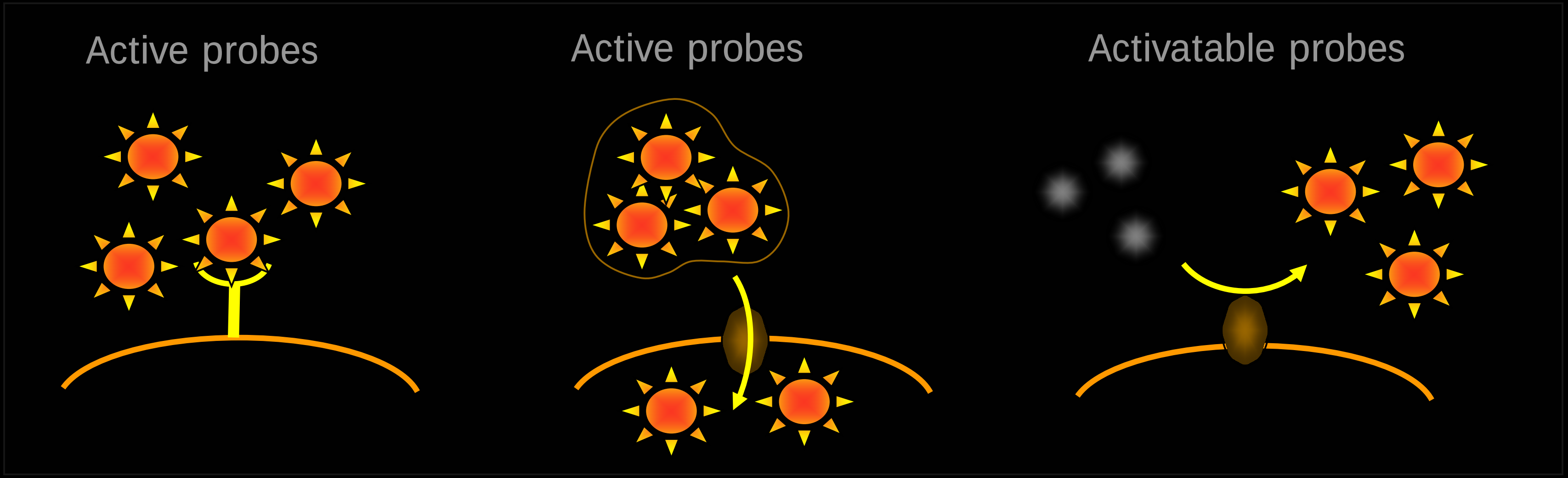
MINNEAPOLIS, MINNESOTA

WITH the introduction of asepsis and of anesthetic agents the horizons of general surgery were rapidly extended. Neurosurgery, on the other hand, lagged behind. Its growth was dependent not only upon more rigid conditions of asepsis and the development of unique technical procedures, but also upon the evolution of diagnostic methods for accurately localizing intracerebral lesions. Although improved neurological knowledge and the advent of roentgenology allowed an increased scope of operative intervention, fuller realization of surgical technique been made to utilize a unique property of central nervous system vessels (blood-brain barrier) for the diagnosis and localization of brain tumors.[2]

It has been found that most positively charged (basic) dyes are readily able to penetrate into the central nervous system, while negatively charged dyes (acidic) are generally incapable of passing into the brain tissue. Under many pathological conditions, this differentially permeable barrier is broken down locally. In the presence of a tumor or abscess an acid dye will easily penetrate into the area of the lesion

Fluorescent probes for engineering contrast *in-vivo*

Optical Imaging for *in-vivo* pathology

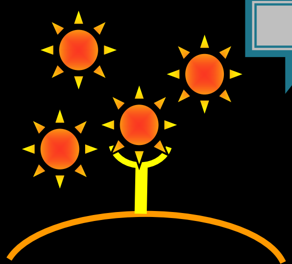


Weissleder & Ntziachristos, *Nat. Med.* 9(1): 123-8 (2003)

Clinical translation pipeline

INPUT

Fluorescence agent



Toxicity → GMP Production → Clinical studies

Small Animal Imaging Validation

Real-time MSN imaging Data standardization

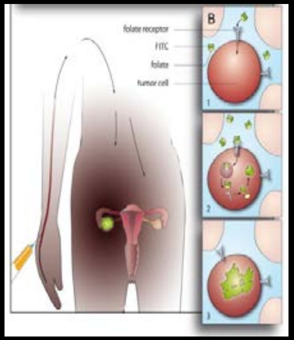
Collaboration with E. De Vries, van Dam UMCG

OUTPUT

REGULATIONS TRACK

Standardized fluorescence data portfolio

CLINICAL TRACK



- Explore known molecules and drugs
- Microdosing
- Image accuracy (fidelity)
- Standardization

Scheuer W. et. al. Science Trans. Med. **4**(134):11 (2012).
Koch M., et. al. Annual Review of Medicine **67**:153-64 (2016).

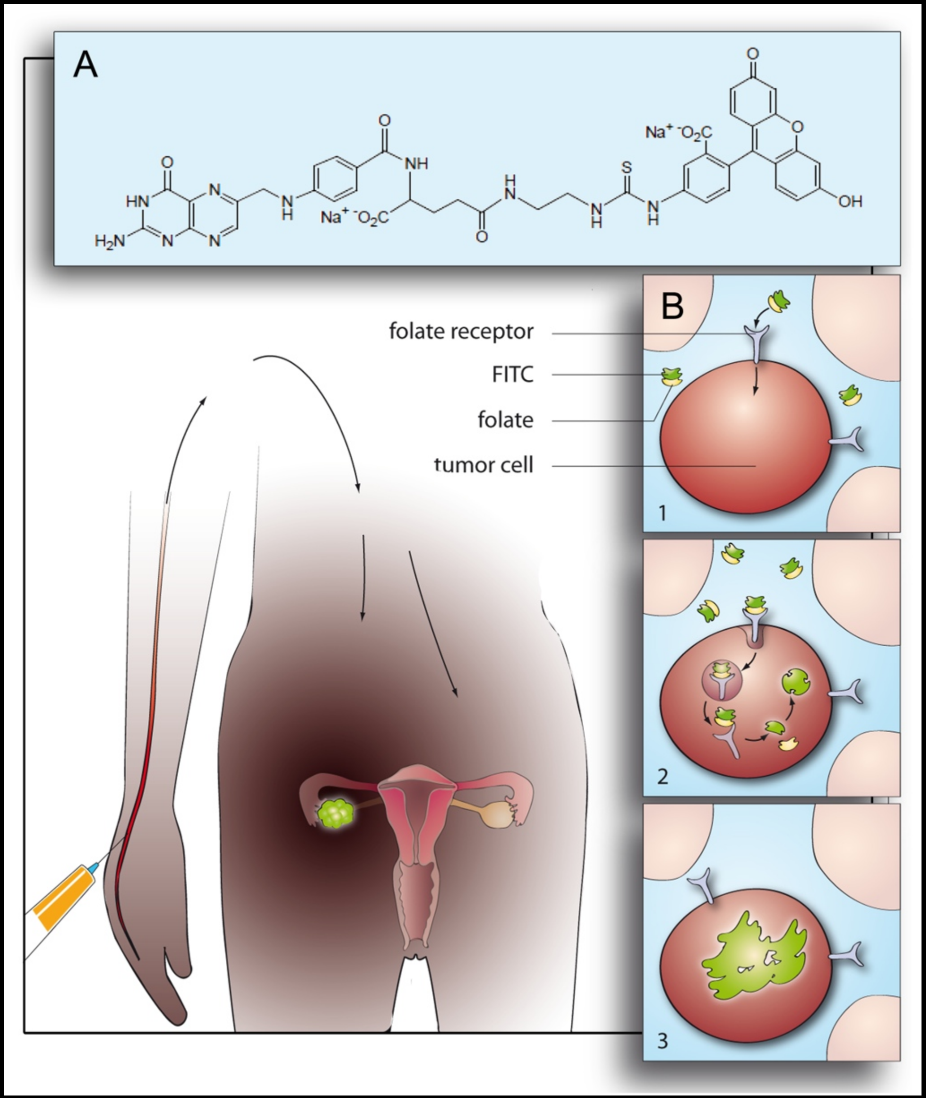
Multi-spectral normalized imaging (MSNI)

Collaboration with UMCG; Prof. van Dam, Prof. De Vries

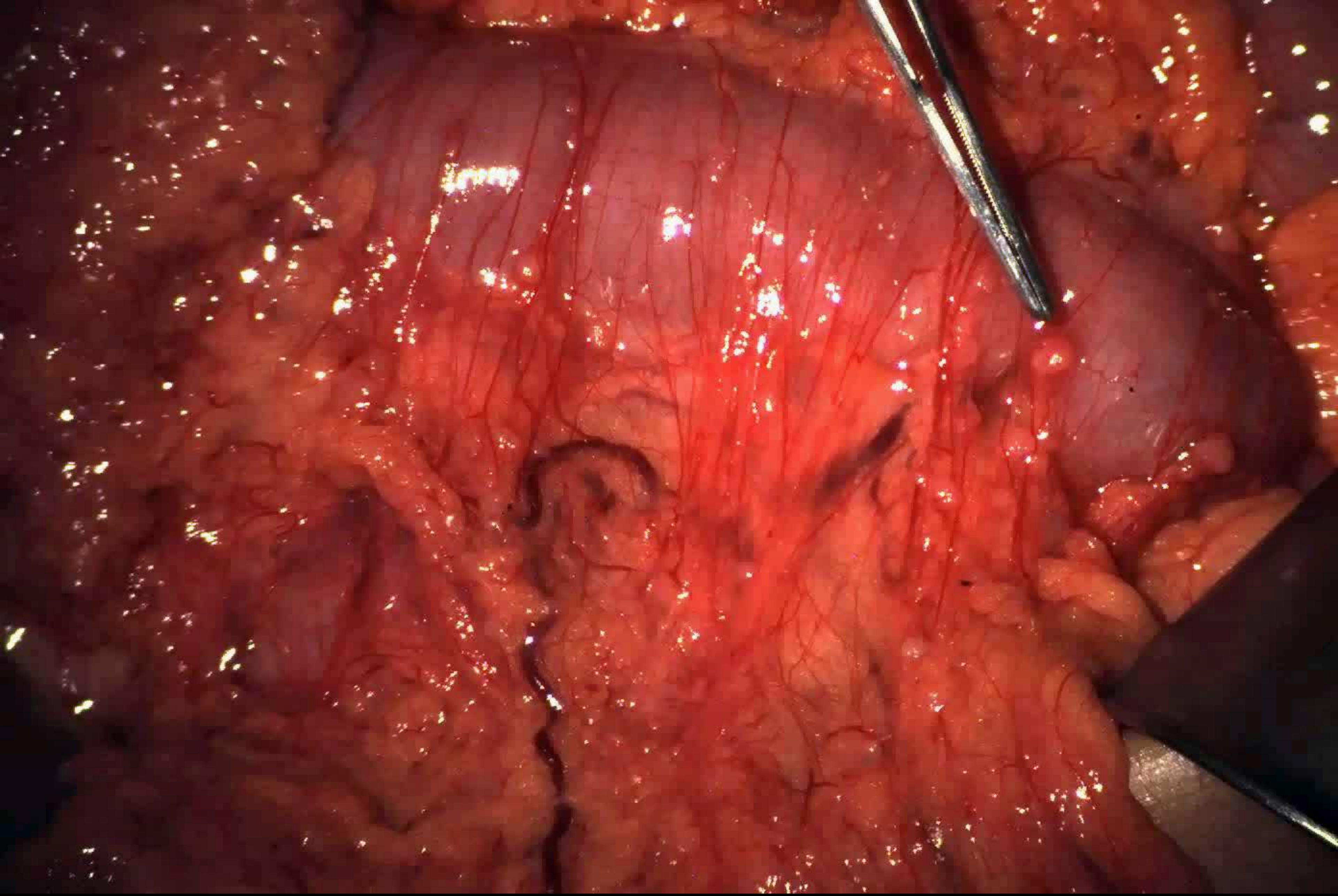
Nature Medicine 17, 1315-1319 (2011)
J Surg. Onc. 18(12):3506-13 (2011(2011).
Gynecol. Oncol. 120(2):291-5 (2011)

Mol Imaging Biol. DOI: 10.1007/s11307-010-0425-7 (2010)
J. Biomed Opt. 15(6):066024. (2010).
J. Biomed. Opt. 14(6):064012 (2009).

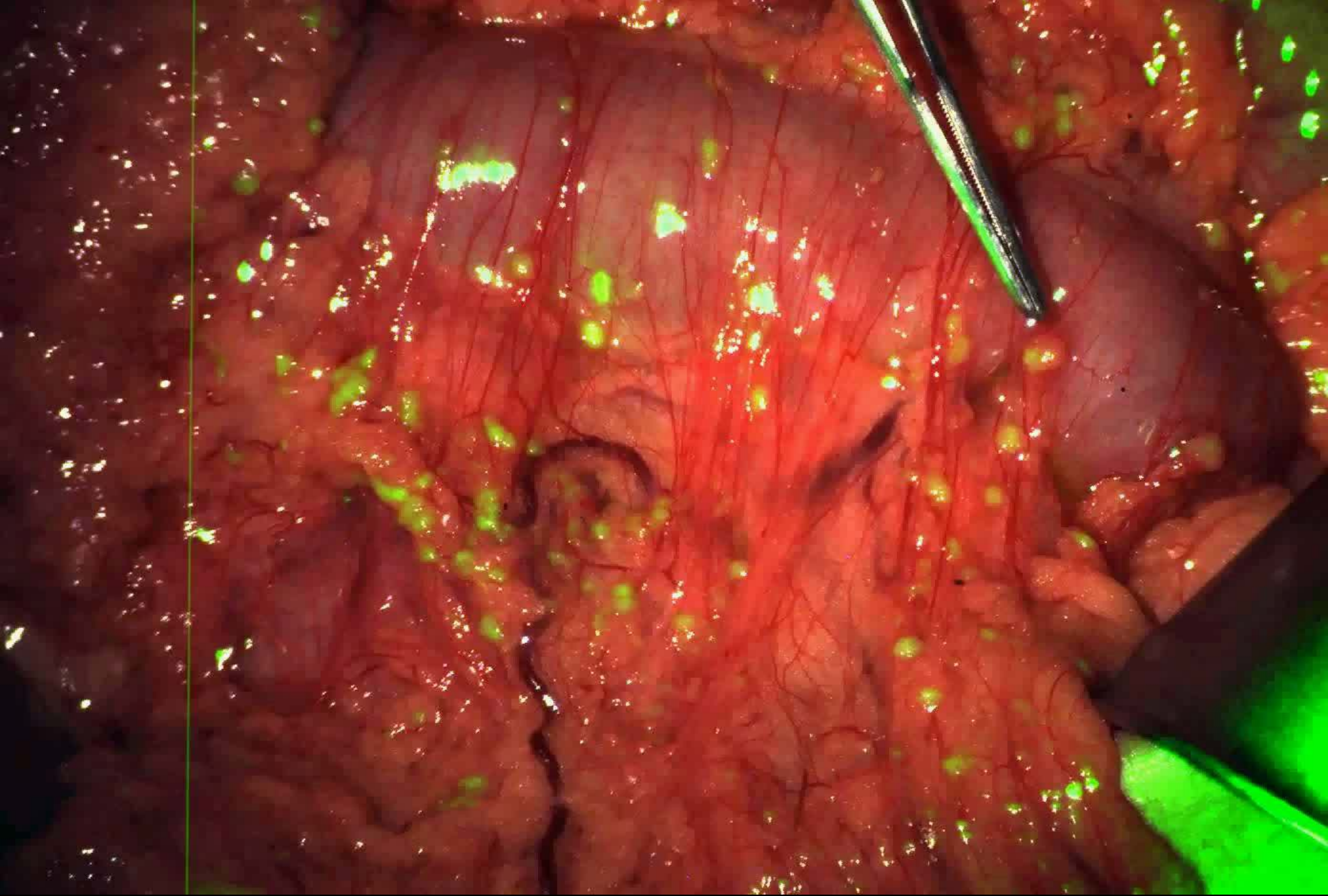
Intra-operative Tumor-Specific Fluorescent Imaging in Ovarian Cancer by Folate Receptor-α Targeting: First In-Human Results



Nature Medicine 17, 1315-1319 (2011)



Nature Medicine 17, 1315-1319 (2011)

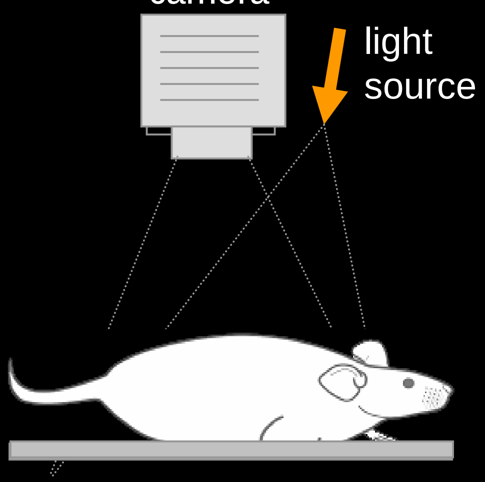


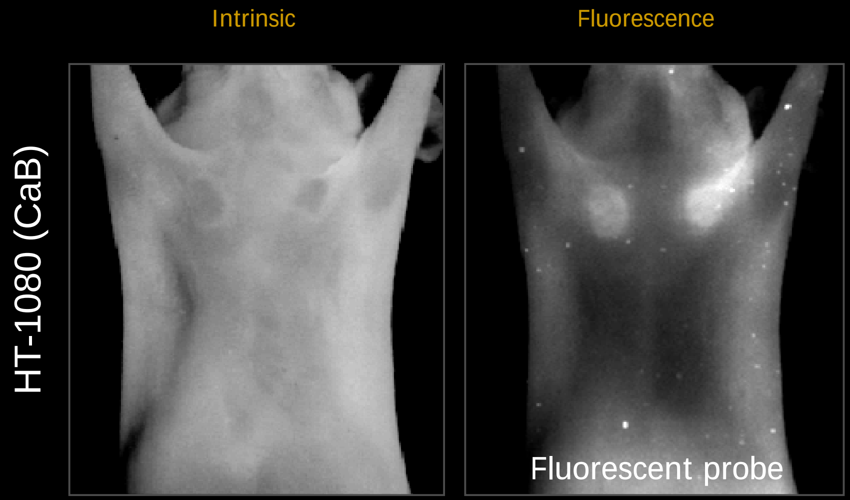
Nature Medicine 17, 1315-1319 (2011)

Challenges for clinical propagation:

1. **Specificity** : Which molecular agent?

2. Scattering : Which imaging approach / system?





This is not a fluorescence image!!!!

Scheuer W. et. al. Science Trans. Med. 4(134):11 (2012).
Koch M., et. al. Annual Review of Medicine 67:153-64 (2016).

Camera Selection

Technical Simplicity **High-end Performance**

Camera Specifications ?

High-Fidelity Fluorescence Imaging

HiFFI

HI FI

High-Fidelity Fluorescence Imaging

HiFFI

High-Fidelity Fluorescence Imaging (HiFFI) is defined as:

the accurate representation of fluorochrome bio-distribution in tissues, independently of the particular system, experimental and tissue conditions used. HiFFI implies that the fluorescence image recorded does not change when experimental parameters change.

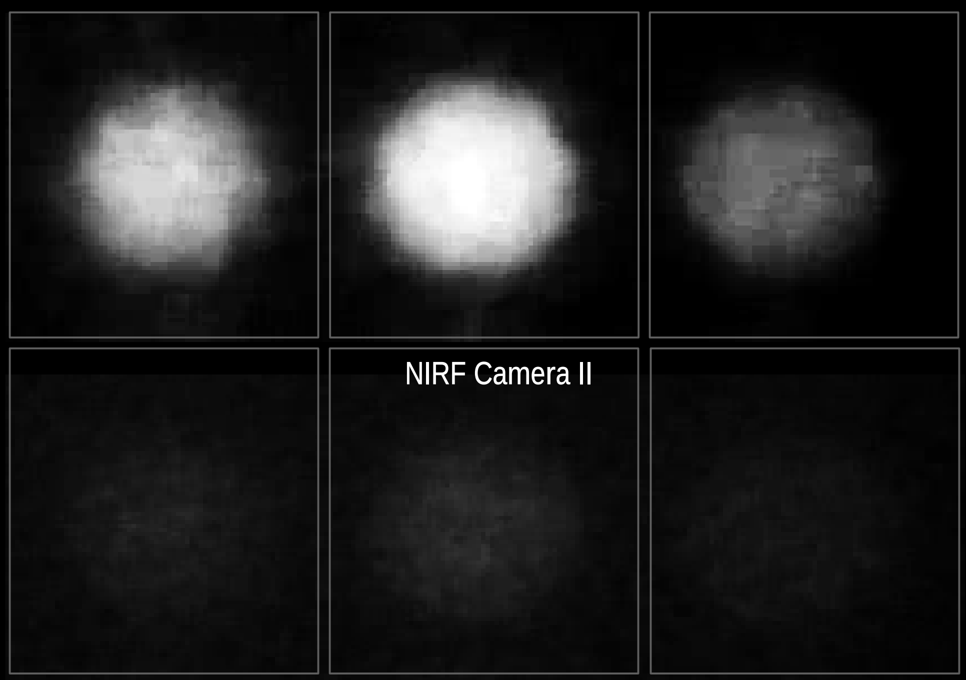
TABLE I:

Parameters affecting FMI performance

INVARIABLE PARAMETERS

PARAMETER	TYPICAL RANGE	EFFECT ON FMI PERFORMANCE	CALIBRATION	REMEDY
Camera Sensitivity Electrical / read noise	nM - pM $2e^-$ - $20e^-$ per read operation	▪ Dose of agent required ▪ Frame rate achieved ▪ Minimum fluorescence activity detected ▪ Phase 0 / Micro-dosing operation ▪ Sensitivity and specificity of clinical findings	Measure sensitivity with standard	Use highly sensitive CCD technology, current amplification methods, low noise electronics, cooling technology to reduce noise.
Resolution	10 – 500 micrometers	Minimum lesion size visible on white light images	Register white-light and apparent diffusive resolution with standard	Match the number of CCD pixels and field of view to the desired resolution.
Dynamic range and dark current	10^4-10^6	▪ Ability to differentiate different amounts of distributed agent ▪ Saturation effects	Measure with standard	Select CCD sensors with high full well capacity
Frame capture Speed	1 – 100 Hz		N/A	Select camera with fast read electronics and data transfer
Spectral coverage	400 – 1700nm	▪ Resolution achieved ▪ Sensitivity achieved ▪ Depth achieved	Use fluorochromes (quantum dots) of known spectral responses	Select CCD material with sufficient sensitivity in spectral range covered
Cross-talk & ambient light	0.1-50% of excitation light	▪ Reduction of sensitivity ▪ Increase background noise ▪ Increase image artifacts	Measure cross-talk and ambient light under control conditions	Select proper filters Condition light source Subtract reference light / time-share measurement
Illumination homogeneity	Varies with system design	▪ Shadowing effects on the images collected ▪ Accuracy (quantification) variations of different lesions ▪ Sensitivity and specificity of clinical findings	Measure the illumination pattern (see also BOX 1)..	Multi-angle illumination Normalize image with captured illumination pattern

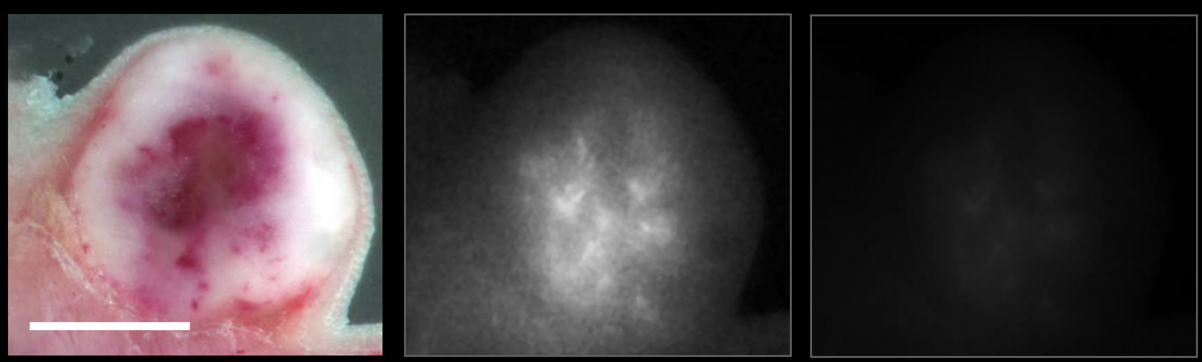
Effects of sensitivity



Phantom

Sensitivity / Specificity
Dose required

In-vivo



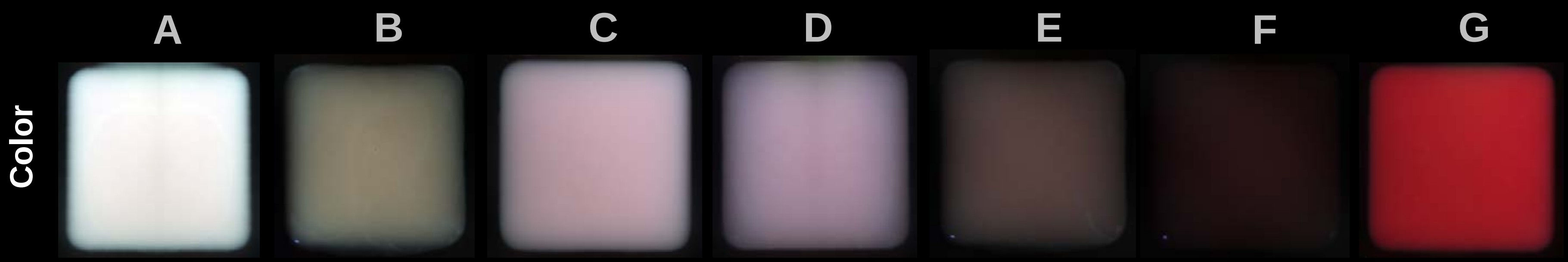
Variable parameters

VARIABLE PARAMETERS

PARAMETER	TYPICAL RANGE	EFFECT ON FMI PERFORMANCE	CALIBRATION	REMEDY
Camera –tissue distance and field of view	15 - 100 cm	▪ Variations of fluorescence intensity recorded. ▪ Changes in focus. ▪ Sensitivity	Record the for changes in field of view and distance	Real-time distance and FOV sensors or estimators
Depth of focus	1-10cm	Reduced resolution with changes in tissue elevation and camera-tissue distance.	Record iris setting, and depth of focus settings	Use high depth of focus to avoid out of focus images Use autofocus mechanism
Variation of optical properties	Scatter : 5 – 30 cm^{-1} Absorption : 0.05 – 0.5 cm^{-1}	▪ Variations on fluorescence signal intensity ▪ Variations of apparent fluorescence distribution ▪ Variations in resolution and diffusion on the image	Record system performance as a function of optical property change	Record the absorption and scattering tissue variations in real time.
Auto-fluorescence	Varies with spectral region (See Fig.1c)	▪ Reducing detection sensitivity ▪ Possibly leading to false positives	Record system performance as a function of background fluorescence	Use spectral differentiation of target fluorescence over background fluorescence
Lesion depth	0 – 2 cm	▪ Attenuation of fluorescence intensity ▪ Variable diffusion and loss of resolution ▪ Spectral changes	Record system performance as a function of fluorescence depth	Tomography Depth reconstruction based on spectral changes

Effect of optical properties:

Is epi-illumination accurate for clinical use?

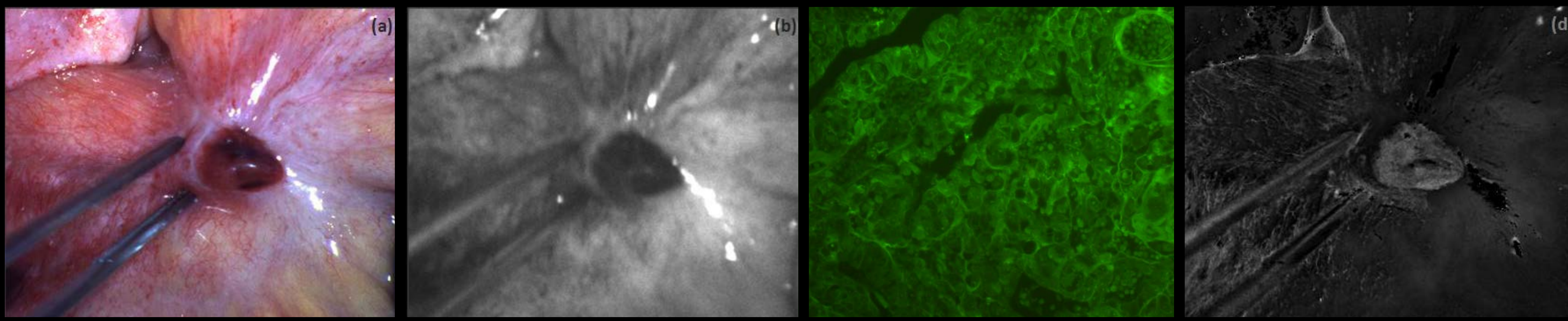


Variation of optical properties leads to fluorescence intensity variations

Variation of fluorescence intensity leads to false positives and false negatives

Pilot clinical trials : Targeted agents

Color | Fluorescence | Immunohist. | Corrected Fluorescence

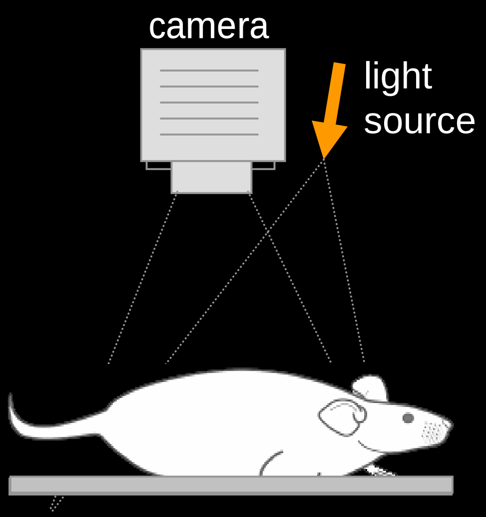


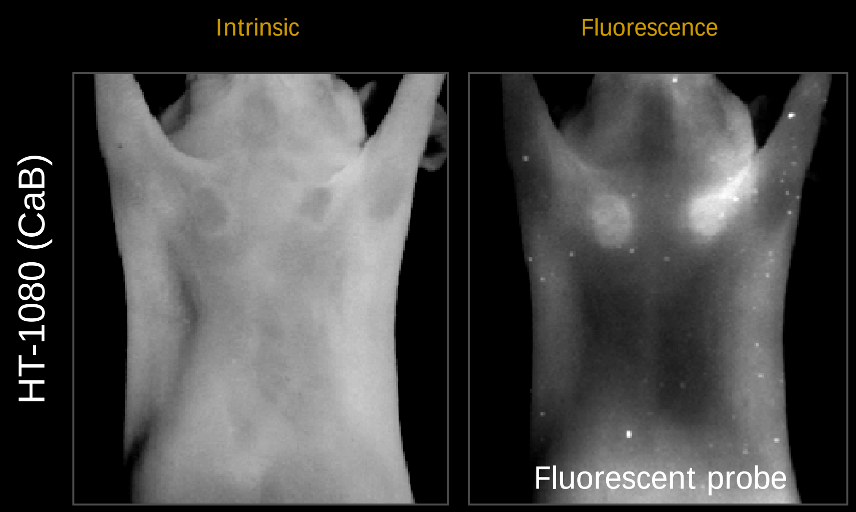
Camera and Experimental Parameters Modify the Fluorescence Image

1. **Invariable parameters (hardware)**:
   System characteristics (Which camera?)

2. **Variable parameters** :
   How accurate is fluorescence imaging?

→ HiFFI



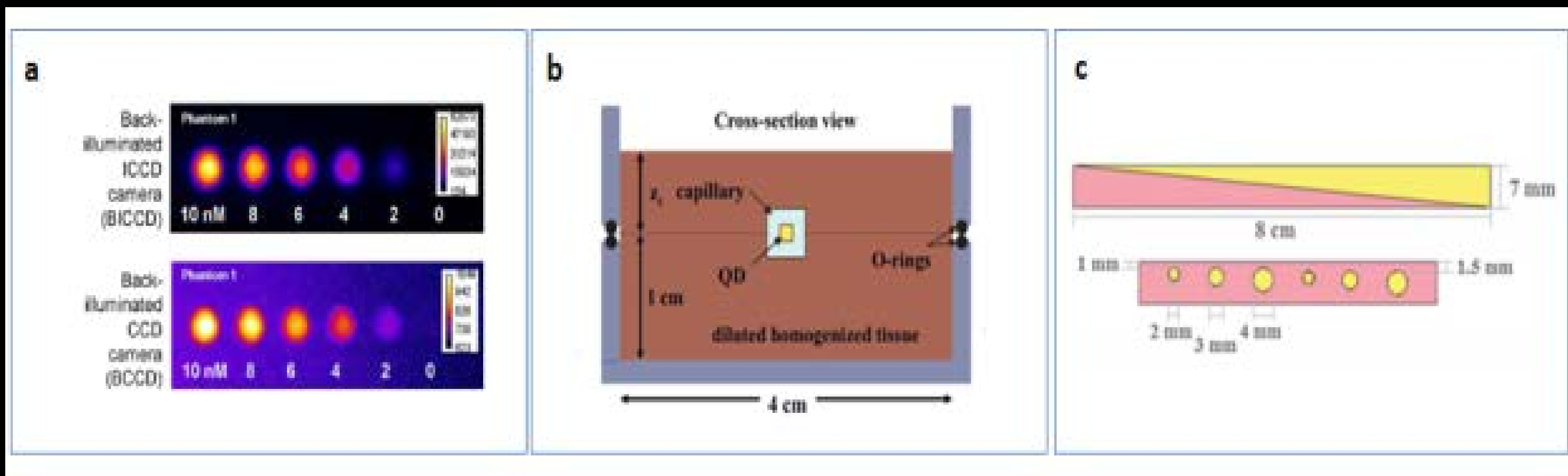


***Scheuer W. et. al. Science Trans. Med.* 4**(134):11 (2012).
***Koch M., et. al. Annual Review of Medicine* 67**:153-64 (2016).

STANDARDIZATION

Composite Phantoms

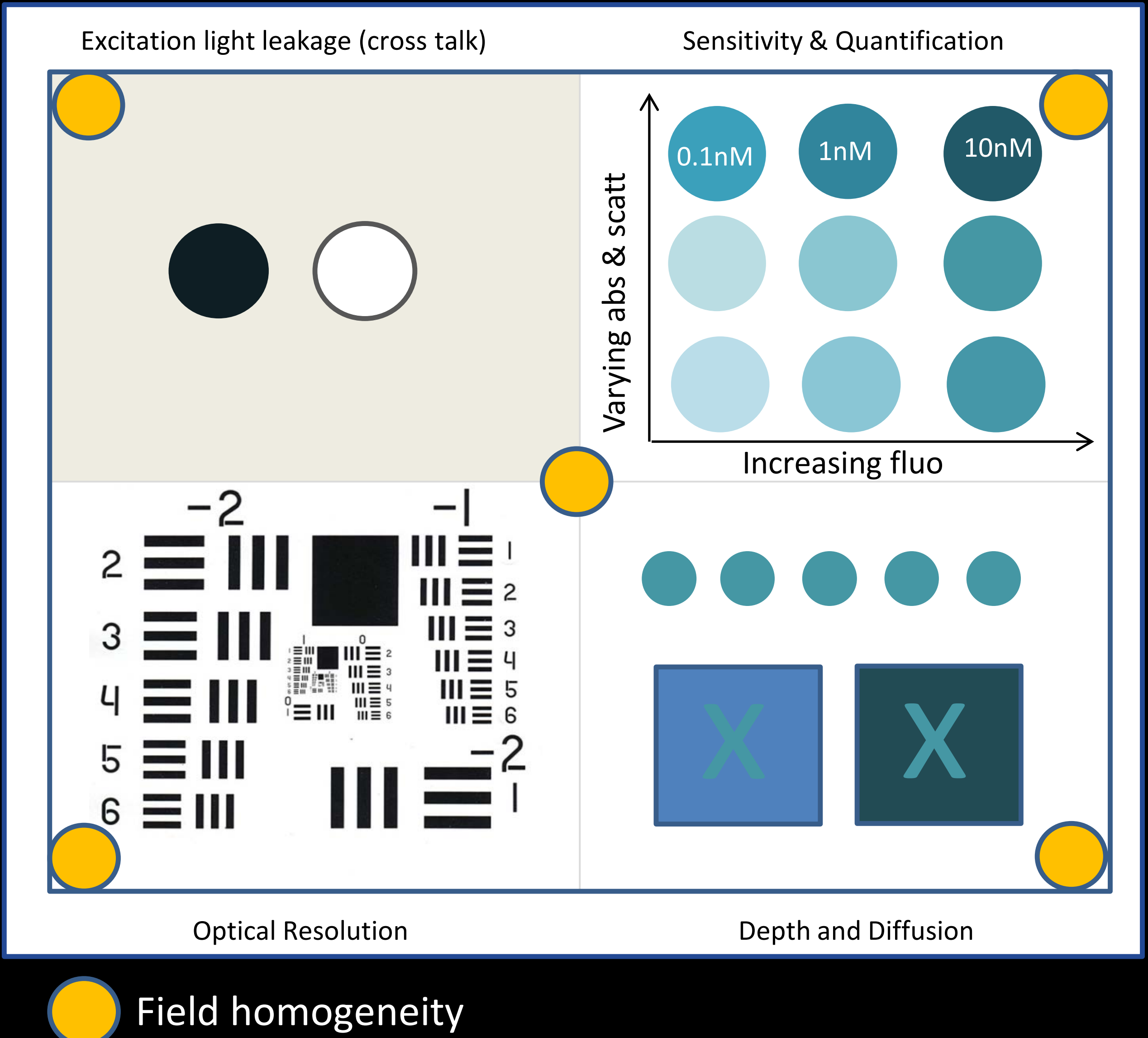
Fluorescence imaging standard



Anastasopoulou M, Koch M, Gorpas D, Karlas A, Klemm U, Garcia-Allende PB, **Ntziachristos V**.
J Biomed Opt. 2016 Sep;21(9):091309. doi: 10.1117/1.JBO.21.9.091309.

COMPOSITE fluorescence imaging standard

Brian Pogue
Timothy Zhu
Brian Wilson
Keith Paulsen
Sylvain Gioux
Josh Pfefer
Bruce Tromberg
Heidrun Wabnitz
Arjun Yodh
Yu chen
L. Maritoni
R. McDonald
D. Grosenik
Yu Chen
Beatriz Garcia



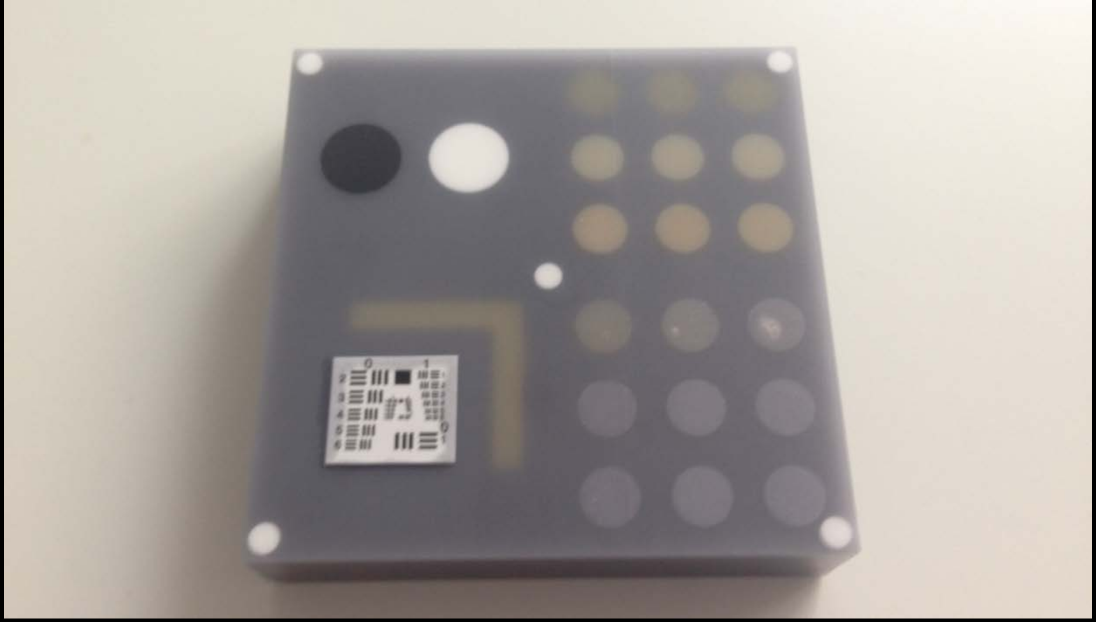
3x mua

3x mus

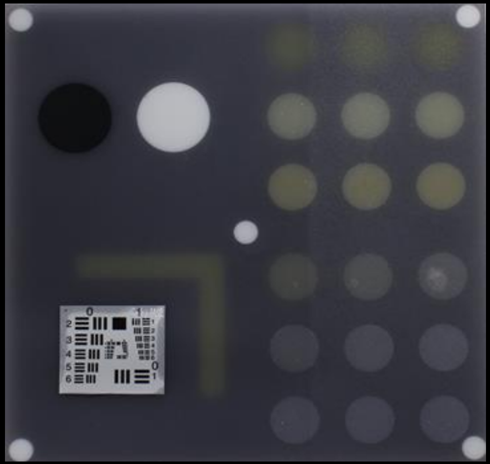
Varying depth

Varying background properties to test "diffusive resolution"

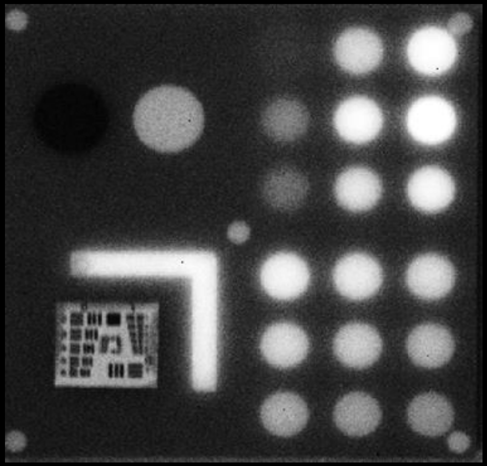
COMPOSITE fluorescence imaging standard - visible



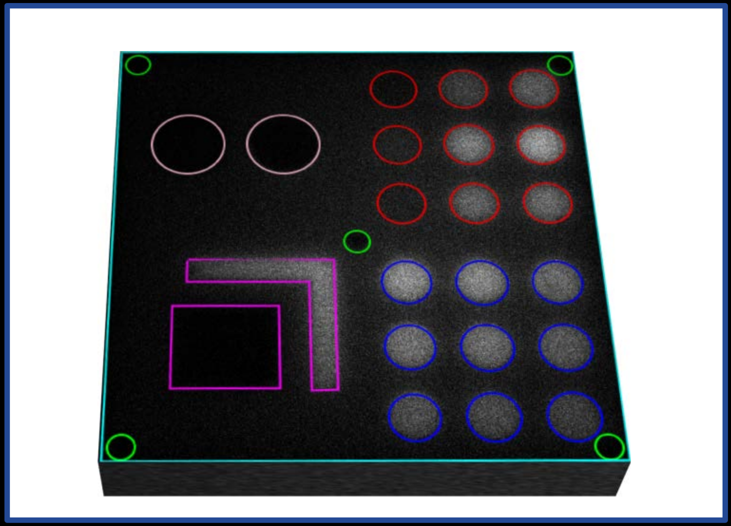
Color image (top view)



Fluorescence image (top view)



Automated
feature extraction



Anastasopoulou M, et.al.
J Biomed Opt. 2016 21(9)

COMPOSITE fluorescence imaging standard - visible

Anastasopoulou et al.: Comprehensive phantom for interventional fluorescence molecular imaging

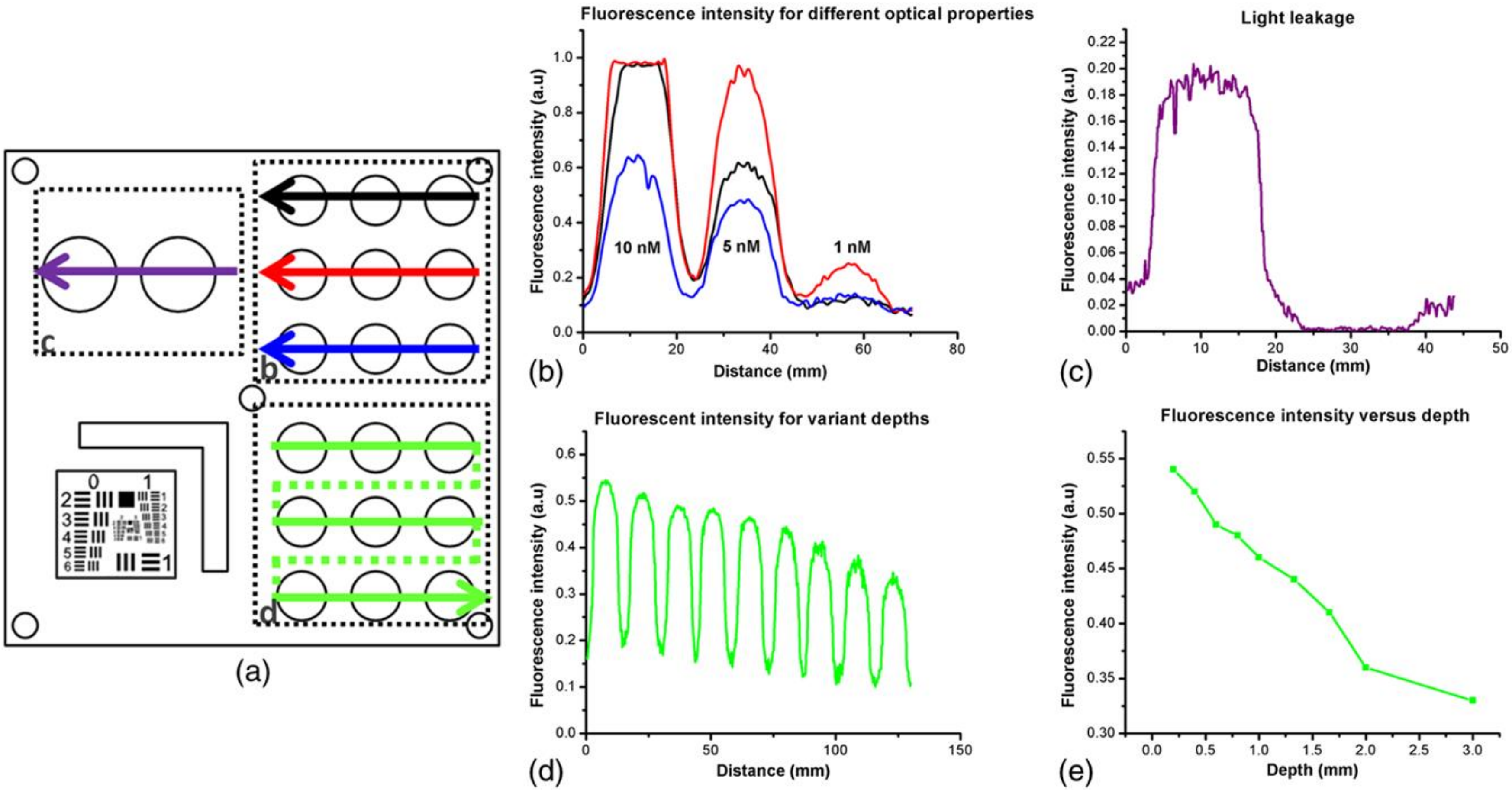


Fig. 4 Cross sections of the fluorescent image of the phantom. (a) Phantom schematic with arrows painted with colors corresponding to the cross sections. (b) Fluorescence intensity across each column (different fluorophore concentration). (c) Intensity across the highly reflecting and absorbing area. (d) Fluorescence intensity for different depths. (e) Fluorescence intensity versus the depth distance.

COMPOSITE fluorescence imaging standard - visible

Anastasopoulou et.al.
J Biomed Opt. 2016 21(9):091309.

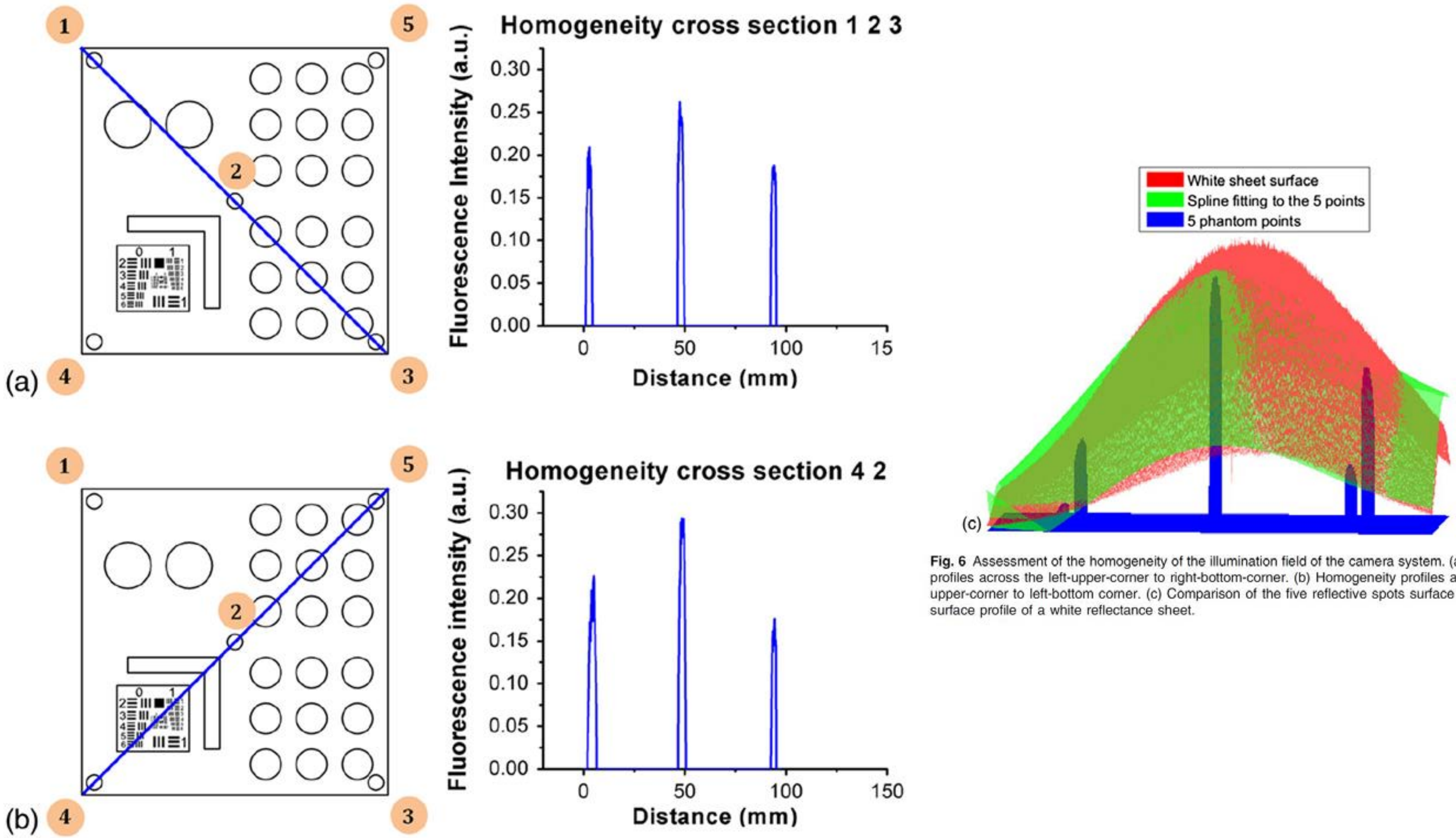
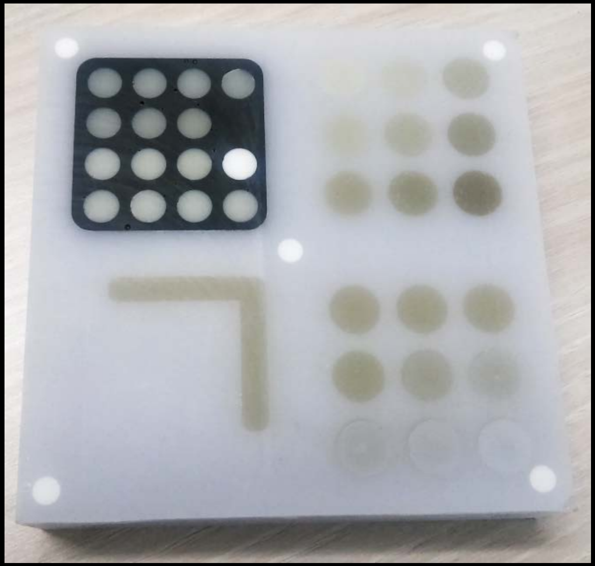
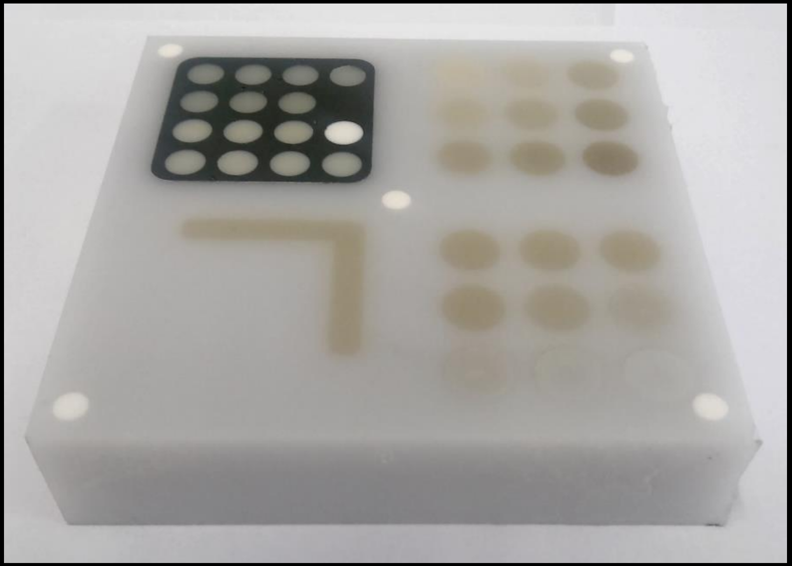


Fig. 6 Assessment of the homogeneity of the illumination field of the camera system. (a) Homogeneity profiles across the left-upper-corner to right-bottom-corner. (b) Homogeneity profiles across the right-upper-corner to left-bottom corner. (c) Comparison of the five reflective spots surface profile with the surface profile of a white reflectance sheet.

Fluorescence imaging standard – near infrared





Distribute a phantom to different labs

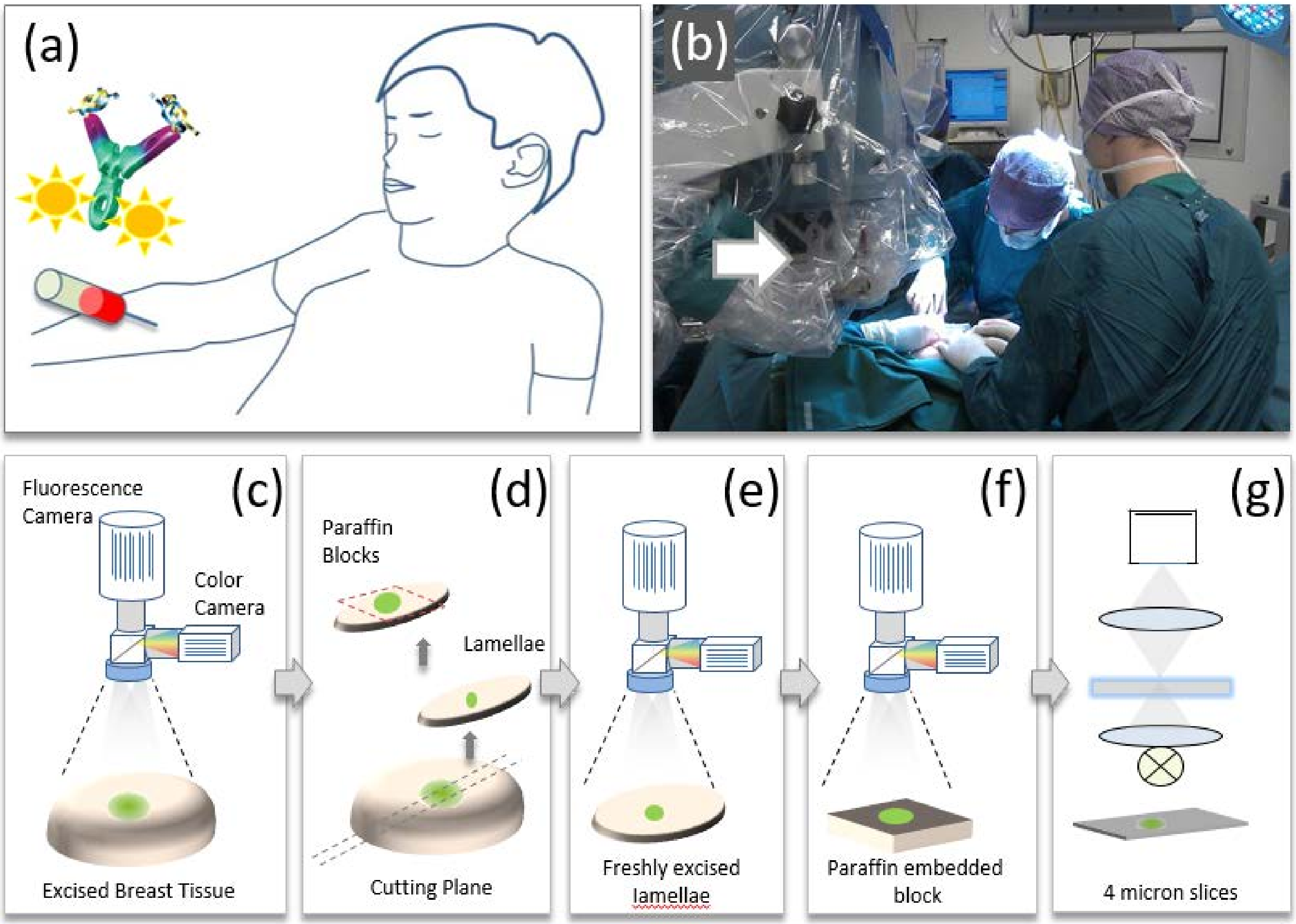
Standardization – what to do with it?

The use of composite phantoms can be applied in regard to at least one of the following actions:

- **Guidelines:** Ensure a minimum performance specification for all systems / cameras employed in clinical studies in regard to system and experimental parameters.
- **System calibration:** Measure and adjust system parameters in order to reach a desired performance.
- **Referencing:** Compare different *systems* to each-other.
- **Data-consistency**: Register camera parameters that *data* produced by different systems can be referenced to each-other or "converted" to one standard.
- **Quality control:** Ensure optimal operation of an imaging system prior to a study and over time.
- **H/W & Algorithmic validation.** Examining the performance of algorithms implemented in a system for improving an aspect of the system or data collected (see reversion).
- **Absolute quantification.** Providing reference signals of known fluorochrome amounts.

THRESHOLDS and HiFFI

Fluorescence Molecular Imaging – bevaCW800

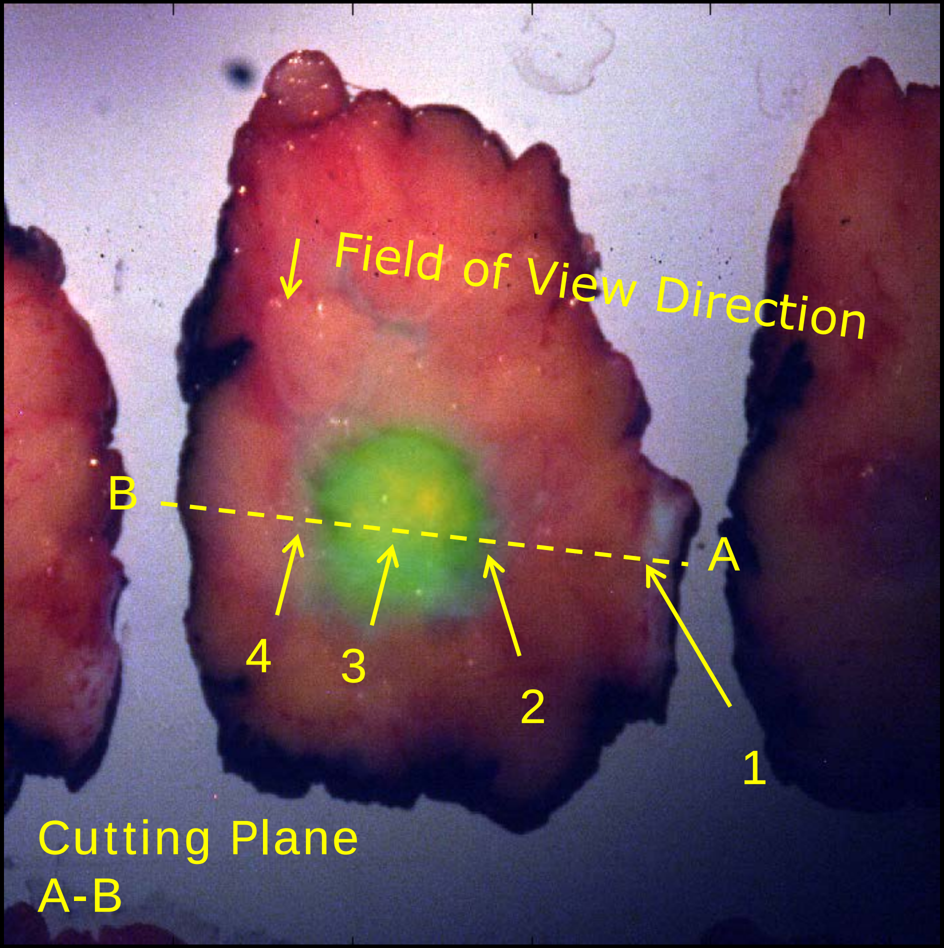


Time	5 min	1h	24h	28h
Resolution	150 µm	150 µm	20µm	0.5µm
FoV	15c15 cm²	15x15 cm²	2x2 cm²	1x1 cm²

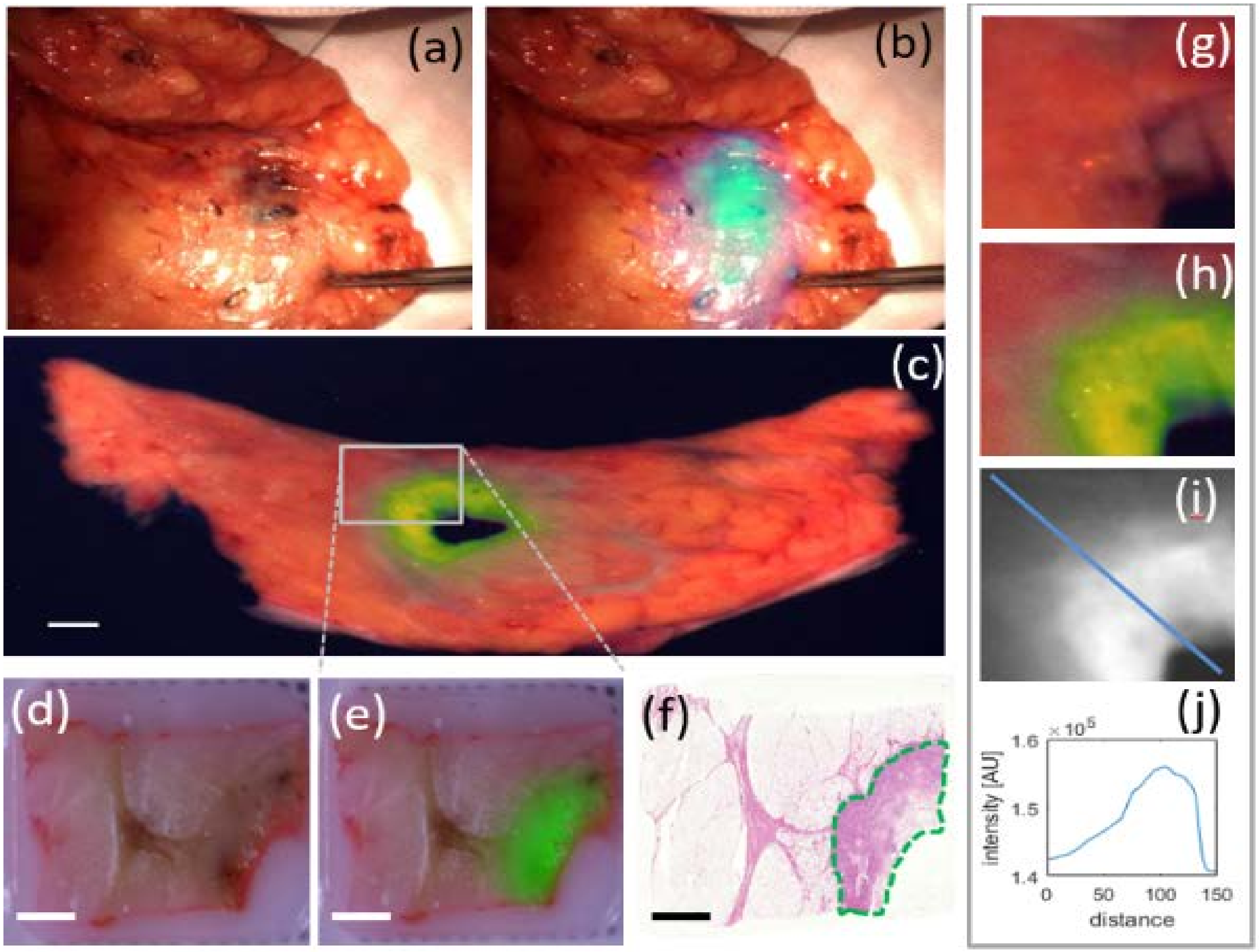
Licor, UMCG, SurgVision

Koch M., et. al. Cancer Research 2016
Lamberts LE et. al. Clinical Cancer Research 2016

Slices of Interest: (~ 3mm thickness)



fSTREAM: Streamlined analysis of fluorescent specimen

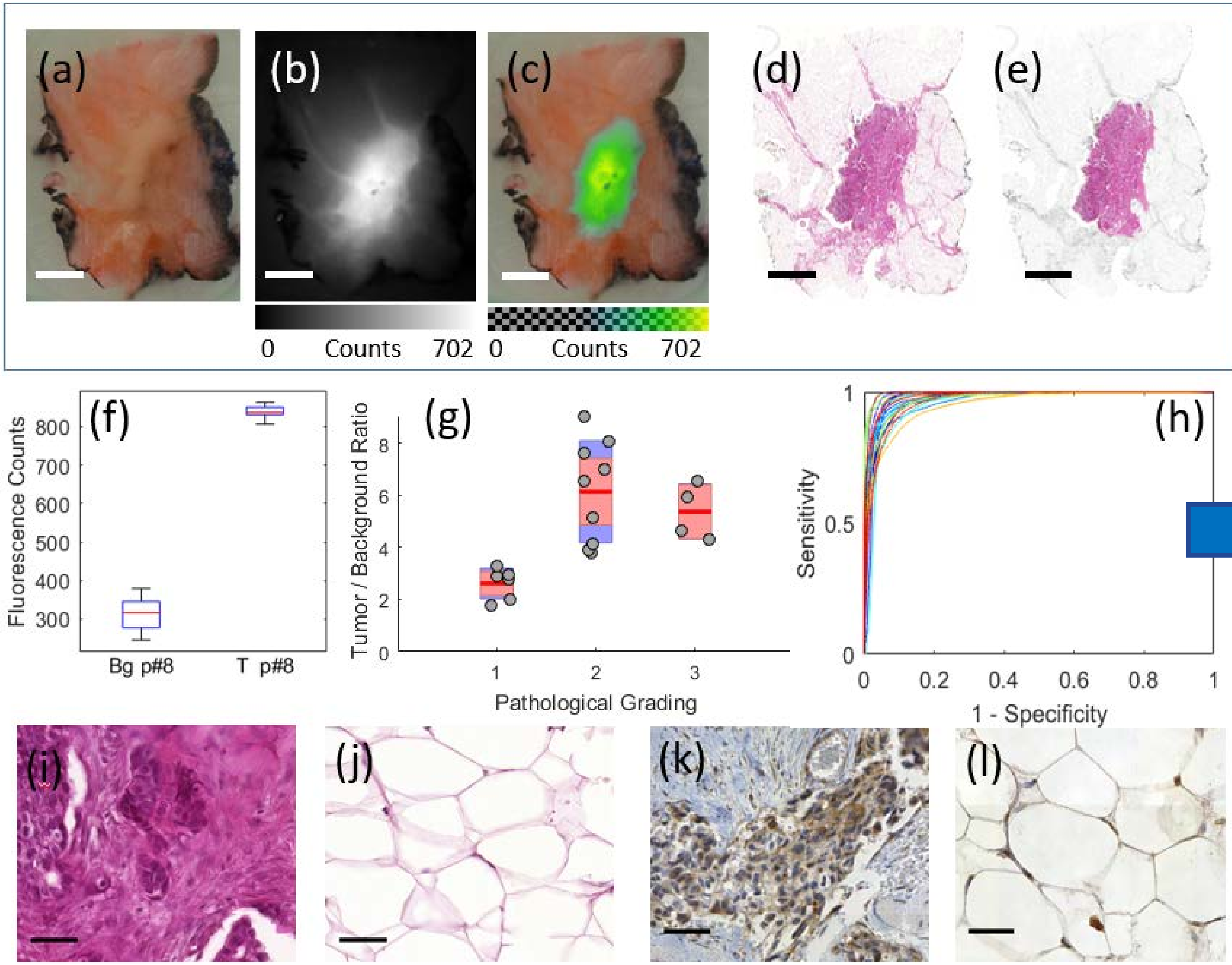


Koch M., et. al. Cancer Research 2016

fSTREAM:
Streamlined analysis of fluorescent specimen

Koch M., et. al. Cancer Research 2016

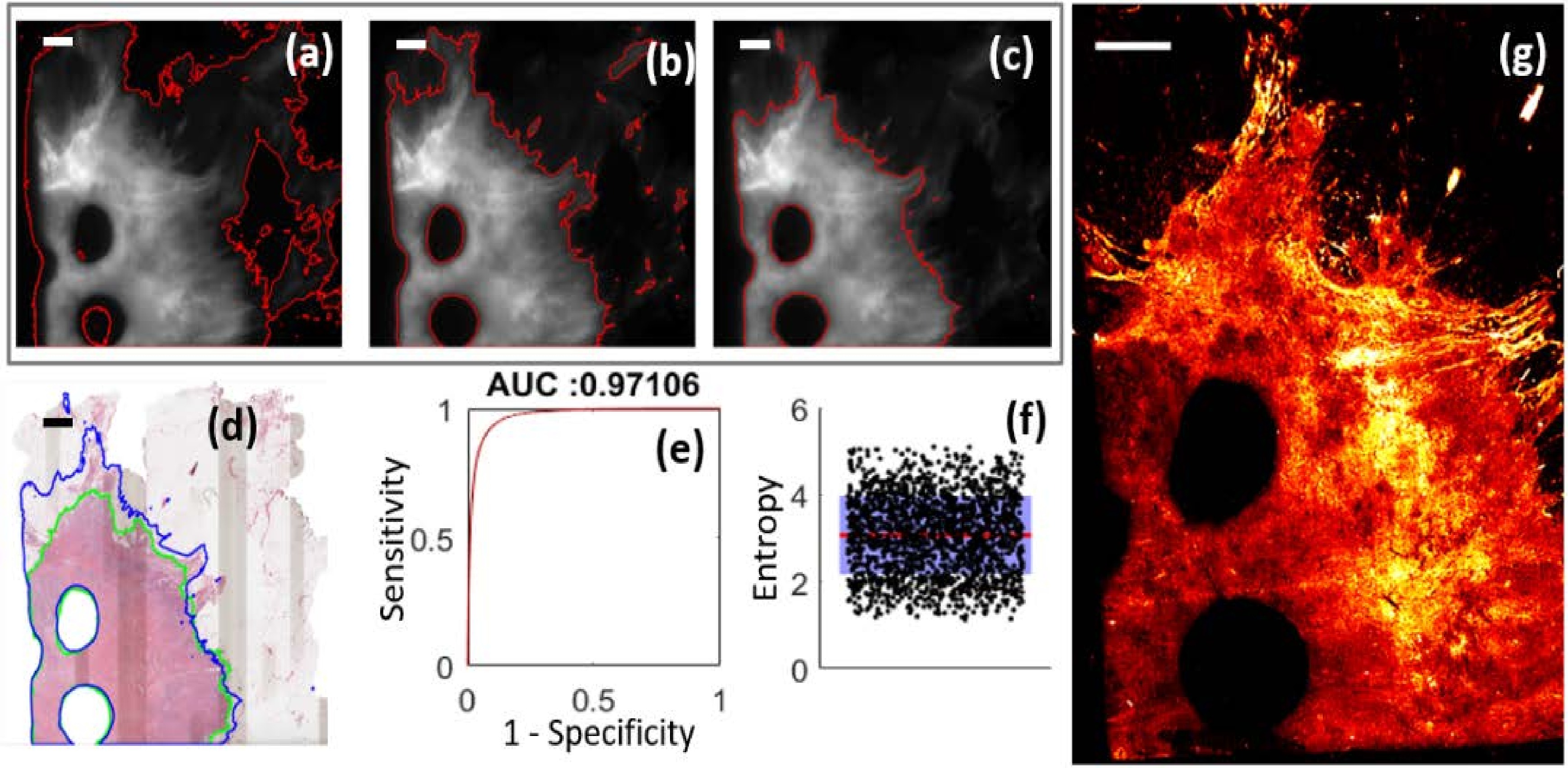
fSTREAM: Streamlined analysis of fluorescent specimen



How do we apply one threshold for the entire surgical procedure?

Koch M., et. al. Cancer Research 2016

fSTREAM: Global Threshold



$$C(\alpha, \beta, \gamma) = \left(1 - AUC(S([\alpha, \beta, \gamma]), G)\right)$$

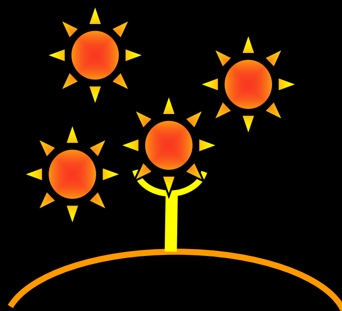
S: Normalized image
G: Binary image of tumor vs. background
AUC: Area under the curve
α, β, γ: Normalization parameters fitted to minimize function C

Sensitivity 98%
Specificity 79%

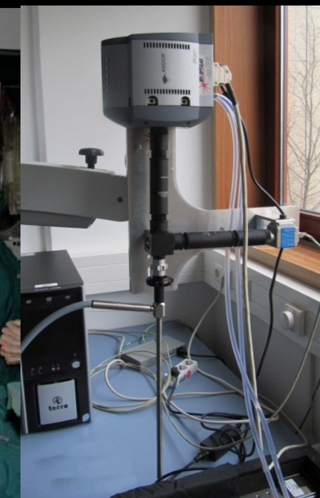
Koch M., et. al. Cancer Research 2016

Clinical translation of Fluorescence Molecular Imaging

Clinical translation of fluorescence agents



Clinical translation of systems



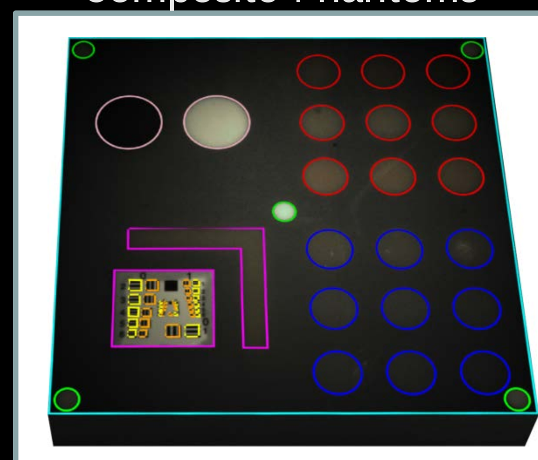
Targets & Agents

TABLE I: Prioritized list of common breast and colorectal biomarkers

Colon Cancer Biomarkers	Breast cancer Biomarkers
EGFR	CXCR4
CXCR4	VEGF-A
EpCAM	EGFR
CEA	Mammoglobin-A
Muc1	CA-IX
MMPs	CA-XII
VEGF-A	Her2/neu

Target
CEA
CXCR4
EGFR
EpCAM
Folate receptor-a
Integrin
Muc1
TAG-72
VEGF

Composite Phantoms



HiFFI

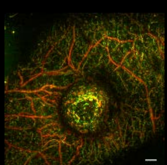
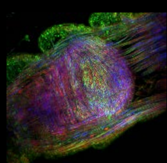
Standardization

IBMI is recruiting!

group leaders, post-docs, and PhD students (f/m)

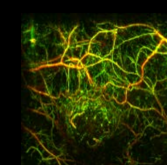
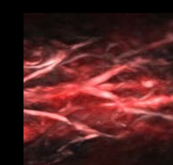
Munich is a hotspot of scientific excellence and famous for its high quality of life.

Moving into TranslaTUM, a brand-new research center at TUM, in summer 2017

Contact IBMI and join the team now!

andreas.brandstaetter@tum.de

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Daniel Razansky Associate Prof.
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Claudia Hildebrand Senior Scientist

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Andreas Bühler	Yihong Yan	Amy Lin	Sven Gottschalk	George Tseverelakis
Nicolas Beziere	Moritz Kneipp	Yong Hong	Till Grandinger	Christian Lutzweiler
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UNIVERSITY MEDICAL CENTER GRONINGEN (Prof. van Dam)

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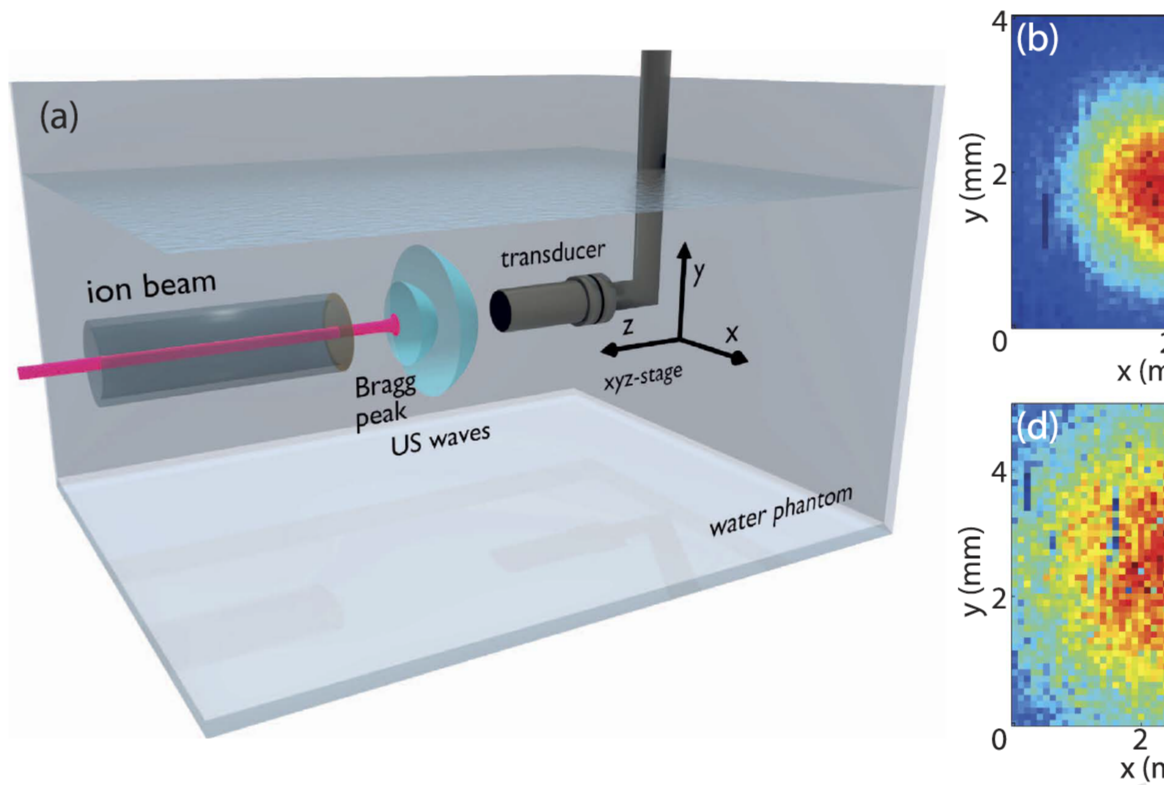

Figure 1. Experimental setup for 2D ionoacoustic imaging of prot
scan system using a focused high resolution acoustic wave sensor to c
in water. Increased energy losses could be induced by means of an alu
path. (**b**) Maximum intensity projection after raster scanning the pro
of the maximum. (**c**) Line profile of the Bragg peak in *x* and *y* directio
(triangle and squares) and Gaussian fits to calculate the full width hal
we determined the FWHM to be 2.4 ± 0.3 mm (red line) and in *y*-dire
beak characterization with Al absorber. Maximum intensity projectio