SFB 824
Project A1

Vasilis Ntziachristos

Chair for Biological Imaging
Institute for Biological and Medical Imaging

HelmholtzZentrum münchen
German Research Center for Environmental Health

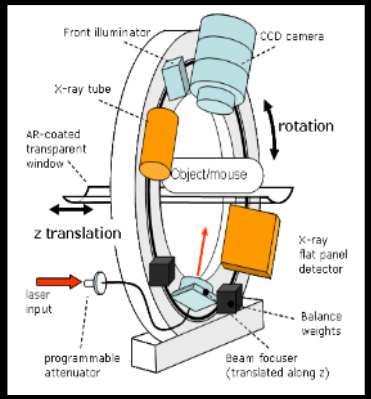
WORKSHOP ON

FMT-XCT

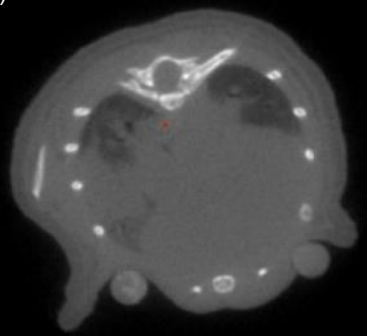
Hybrid Fluorescence
Molecular Tomography –
X-ray Computed Tomography System

introduction & reception

Thursday 24th November, 13:00
Lecture Hall Pavillon
Klinikum rechts der Isar
Ismaninger Str. 22, 81675 Munich



(b)



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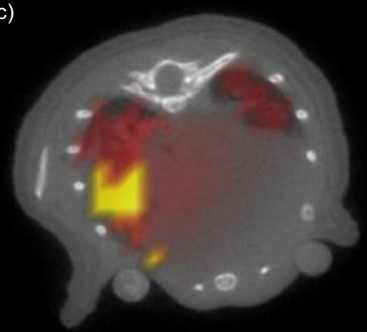


Ale et. al. **Nature Methods** 9: 615–620 (2012)
Ntziachristos V., **Nature Methods** 7(8); 603 (2010)
Schulz et. al. IEEE TMI 29(2):465-73 (2010).

J. Cell. Mol. Med. Vol 15, No 4, 2011 pp. 874-887

In vivo imaging of CT26 mouse tumours by using cmHsp70.1 monoclonal antibody

Stefan Stangl [a], Mathias Gehrmann [a], Ralf Dressel [b], Frauke Alves [c], Christian Dullin [d], George Themelis [e], Vasilis Ntziachristos [e], Eva Staeblein [a], Axel Walch [f], Isabel Winkelmann [f], Gabriele Multhoff [a, *]

Radiotherapy and Oncology 99 (2011) 313–316

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Molecular radiobiology

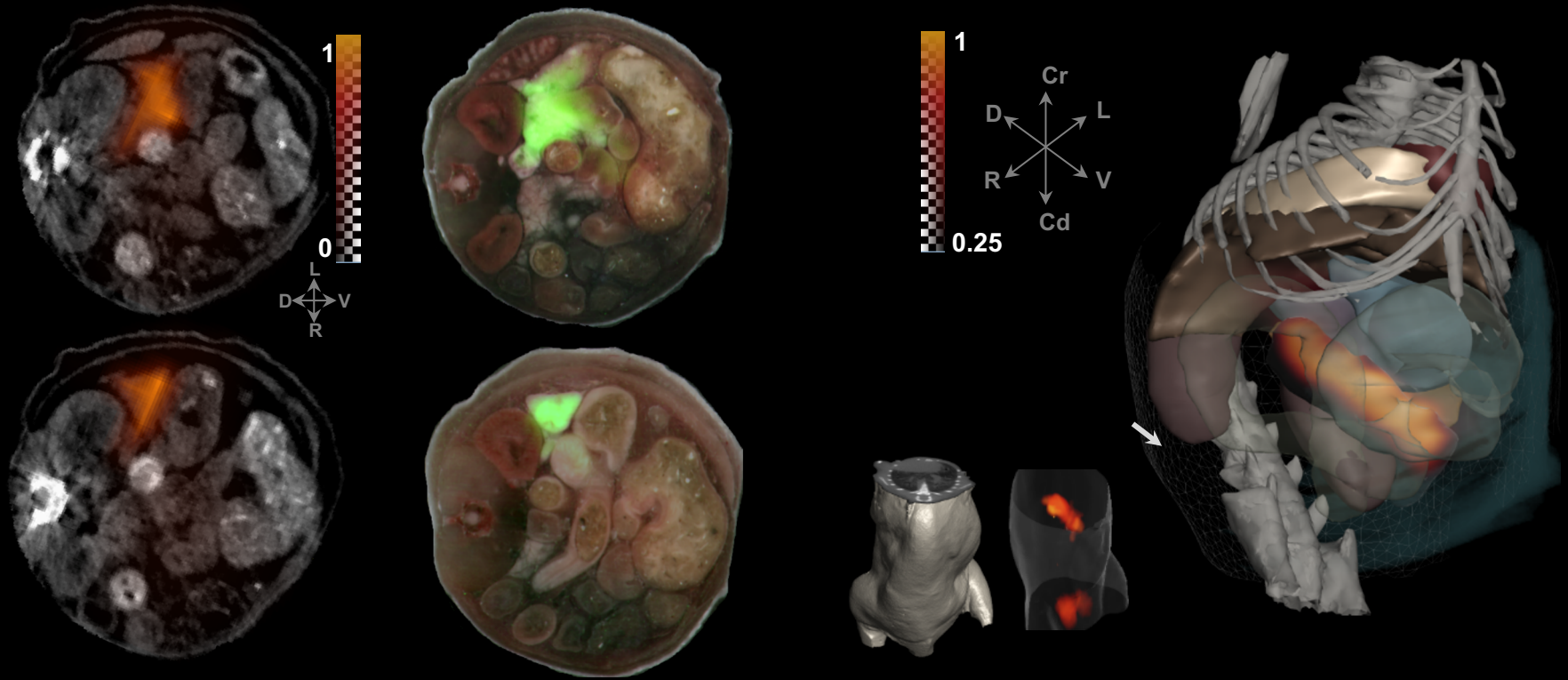
Detection of irradiation-induced, membrane heat shock protein 70 (Hsp70) in mouse tumors using Hsp70 Fab fragment

Stefan Stangl [a], George Themelis [b], Lars Friedrich [c], Vasilis Ntziachristos [b], Athanasios Sarantopoulos [b], Michael Molls [a], Arne Skerra [c], Gabriele Multhoff [a,*]

[a] Dept. of Radiation Oncology, TU München and Helmholtz Zentrum München (HMGU), CCG-Innate Immunity in Tumor Biology, Germany; [b] HMGU, Institute of Biological and Medical Imaging, Munich, Germany; [c] Munich Center for Integrated Protein Science, Technische Universität München, Freising-Weihenstephan, Germany

FMT-PCCT imaging of the PDAC model

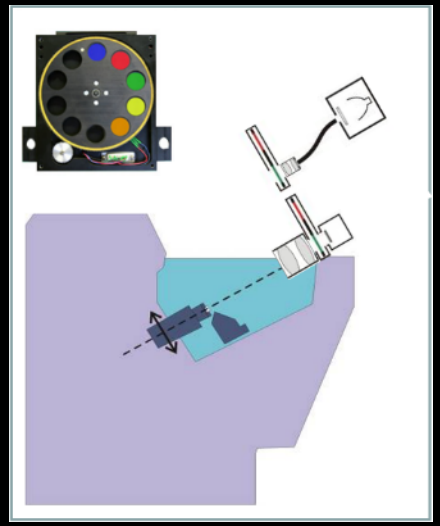
IntegriSense 680



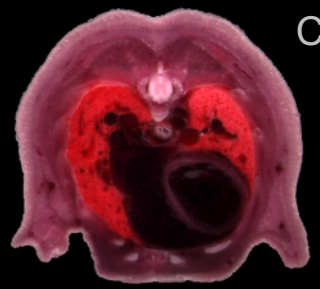
FMT-PCCT **Validation**

P. Mohajerani , et al. IEEE TMI 2013

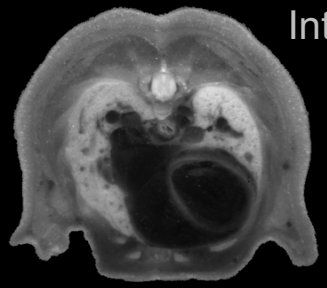
Automatic cryoslicer imaging



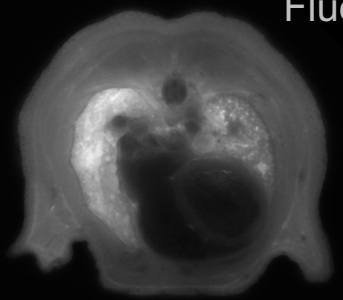
Sarantopoulos et. al. Mol. Imag. Biol. 2010



Color

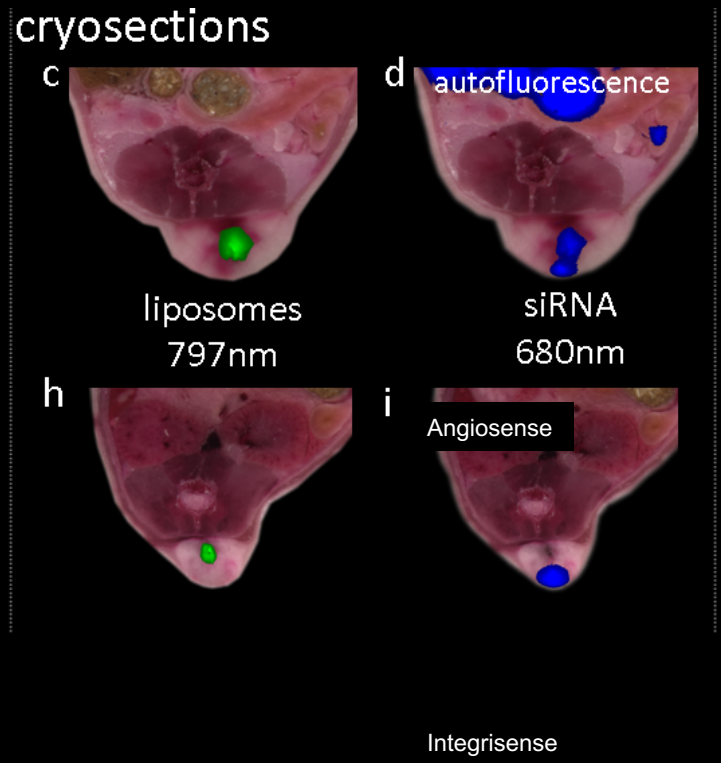


Intrinsic



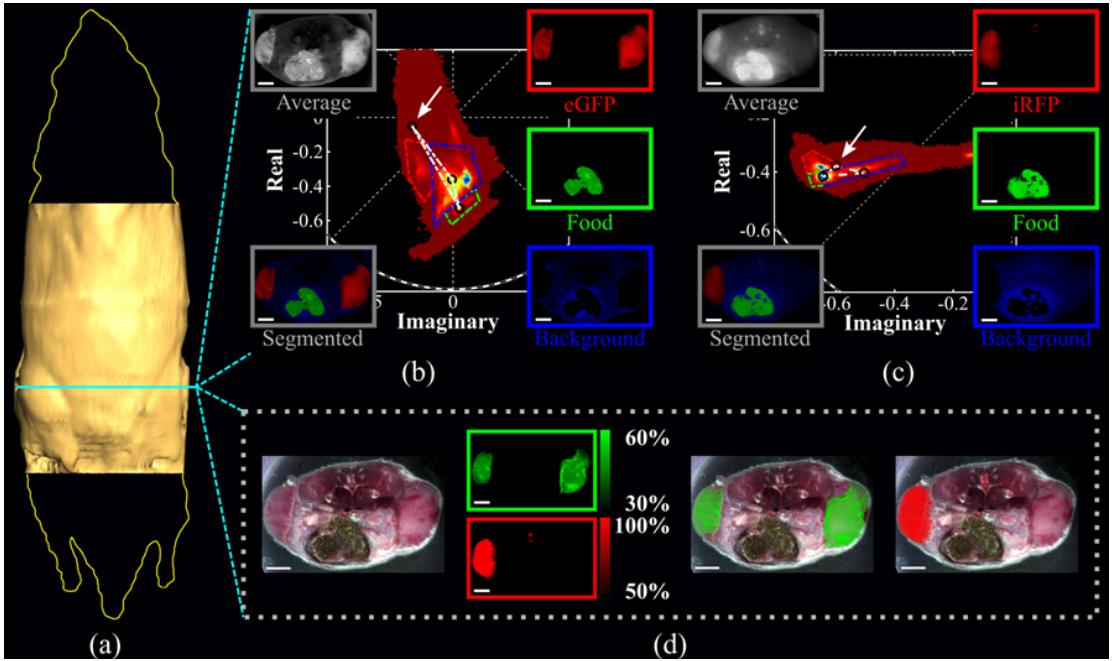
Fluorescence

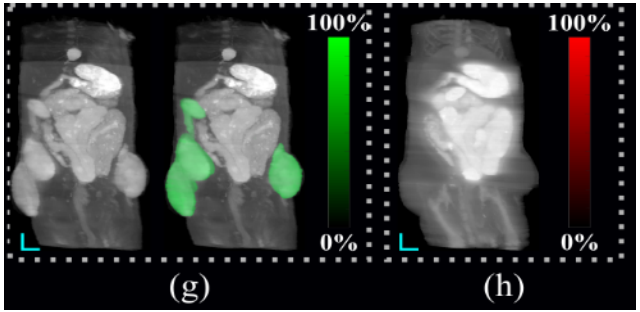
Bio-distribution

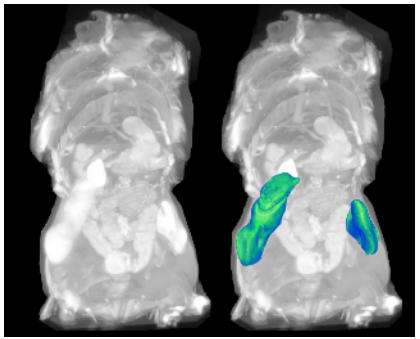


C10 - Development of imaging approaches to monitor tumor-reactive T cells

Spectral unmixing



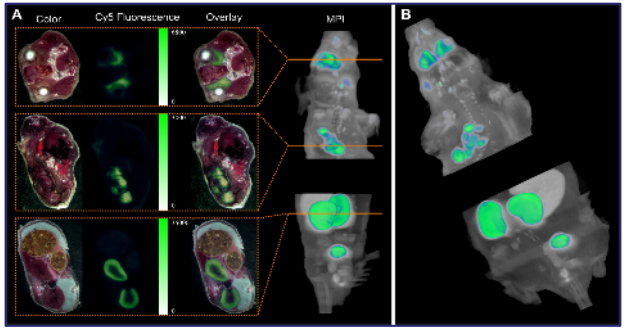




Prof. Dr. Angela Krackhardt
Dr. Calogero D'Alessandria

Fluorescence Cryostat as Core Facility

Cy5 Observation



SMA-targeted hybrid probe PSMA-I&F for nuclear and fluorescence imaging of prostate cancer

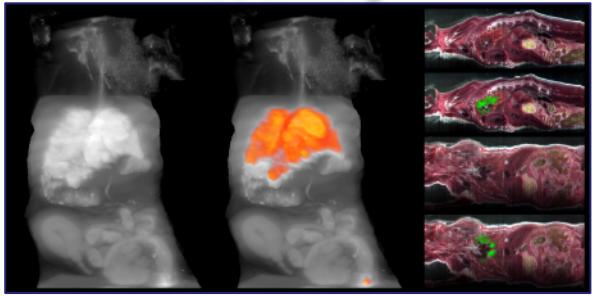
J. Nucl. Med. 60(1):71-78, 2019

Brown Fat

A dual Ucp1 reporter mouse model for imaging and quantification of brown and brite fat recruitment

Mol. Metab. 20:14-27, 2019

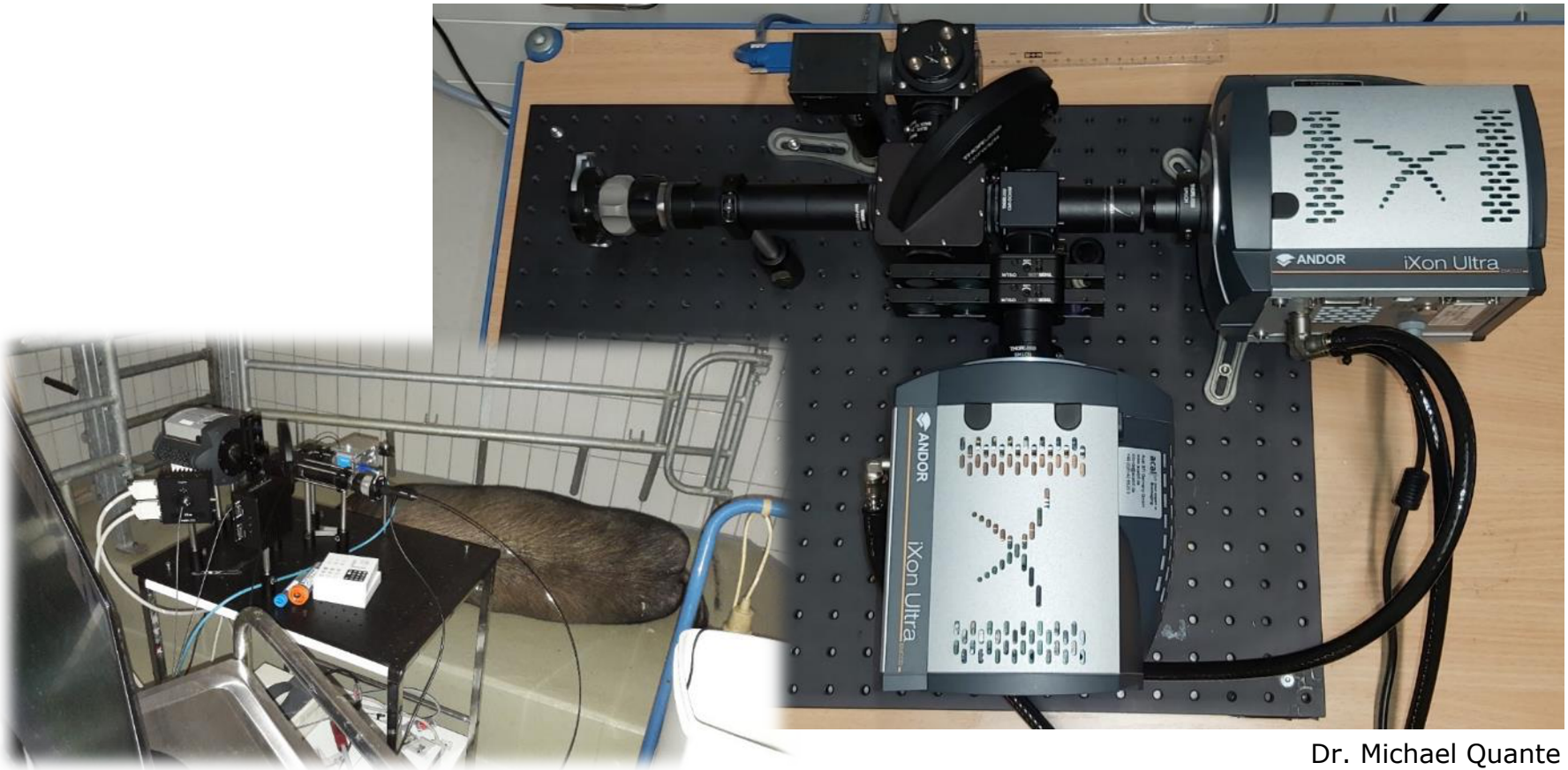
ICG Unmixing



Therapeutic Fluorescent Hybrid Nanoparticles for Traceable Delivery of Glucocorticoids to Inflammatory Sites

Theranostics 8(22):6367-6383, 2018

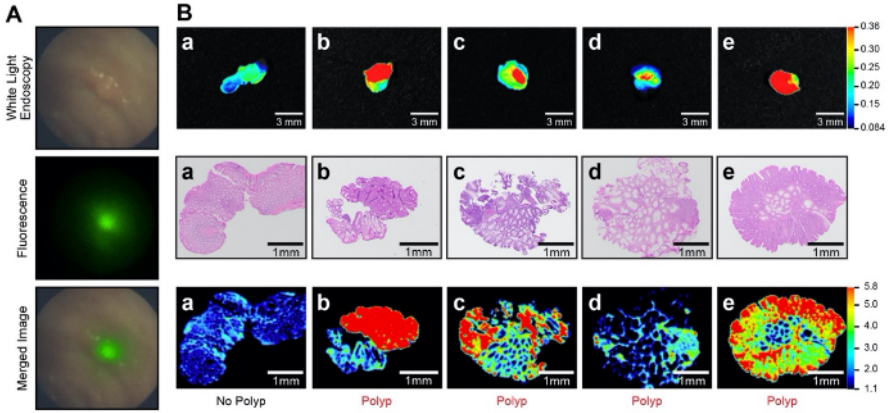
B5 - CXCR4-imaging in esophageal cancer - diagnosis and prognosis - *Dual wavelength FME system*



Dr. Michael Quante

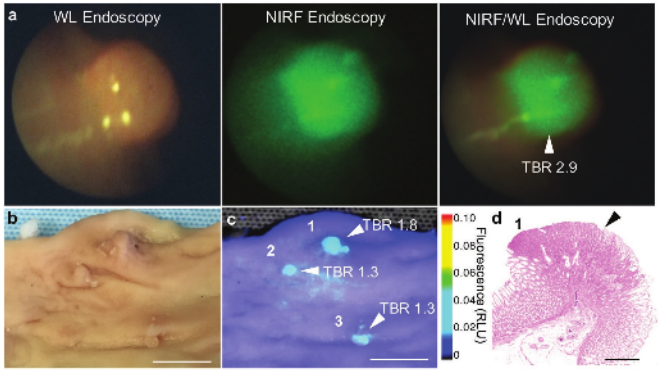
FME in Z3 / Swine Colonoscopy

A protease-activated, near-infrared fluorescent probe for early endoscopic detection of premalignant gastrointestinal lesions



Proc Natl Acad Sci USA 2021 118(1):e2008072118

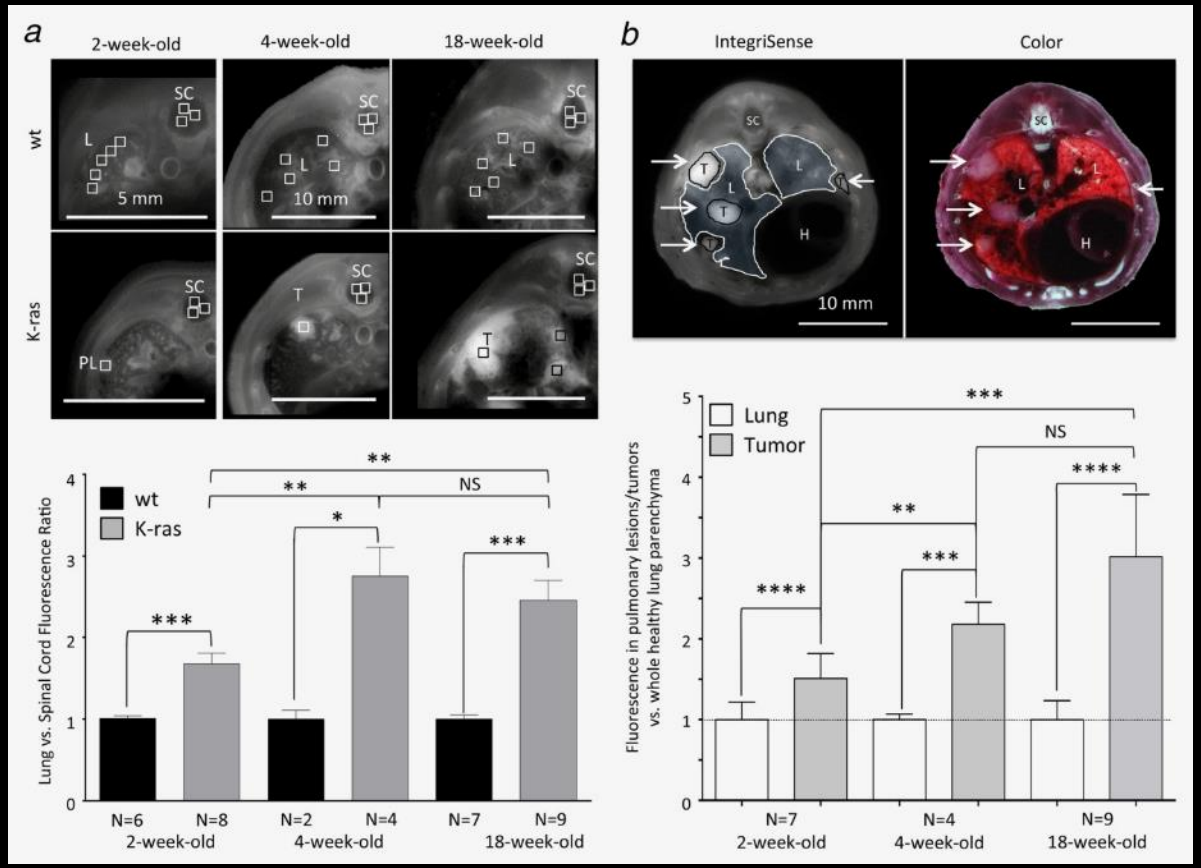
Biodegradable Fluorescent Nanoparticles for Endoscopic Detection of Colorectal Carcinogenesis

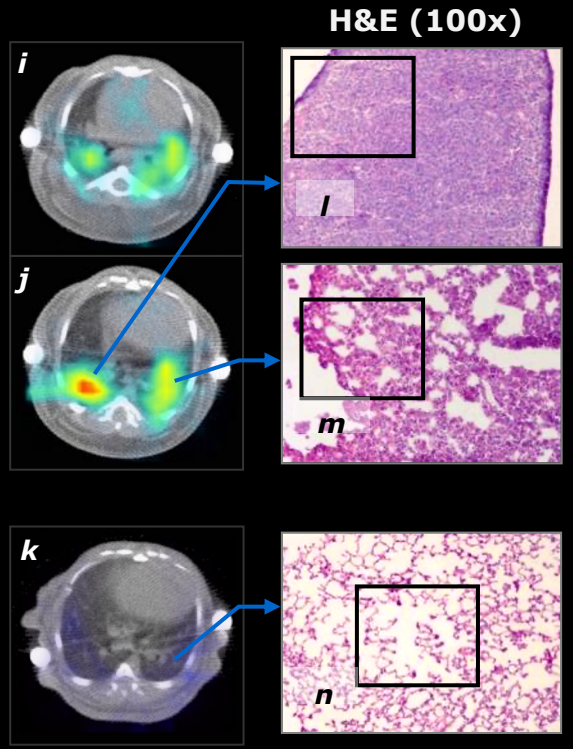


Adv Funct Mater 2019 29(51):1904992 (IF 16.8)

Gorpas, Saur, Ntziachristos, Schnieke,
Rogalla, Contag, Gambhir, Harmsen, Bogyo

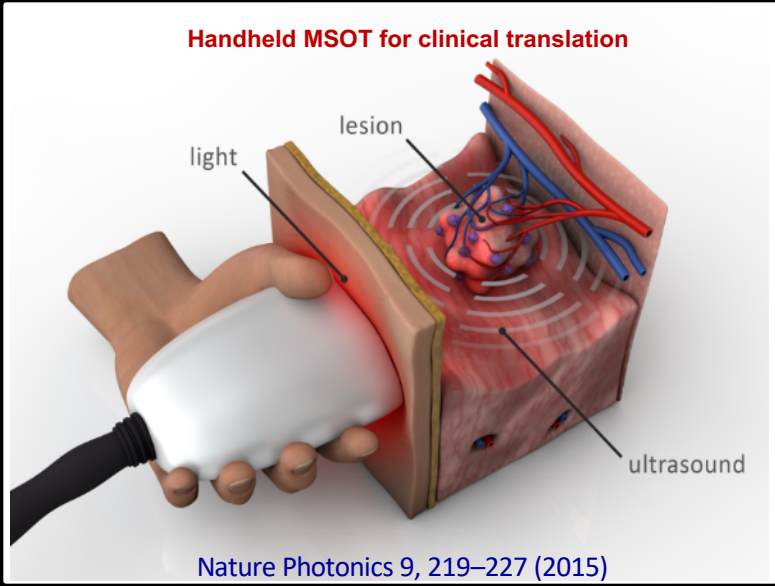
Early Detection of Lung Cancer

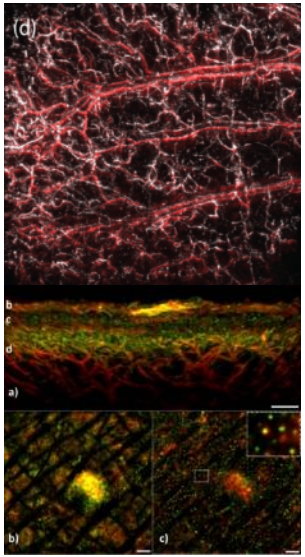




Niedre PNAS 2008
Ermolayev Int. J. Cancer 2013

Multispectral Optoacoustic Tomography

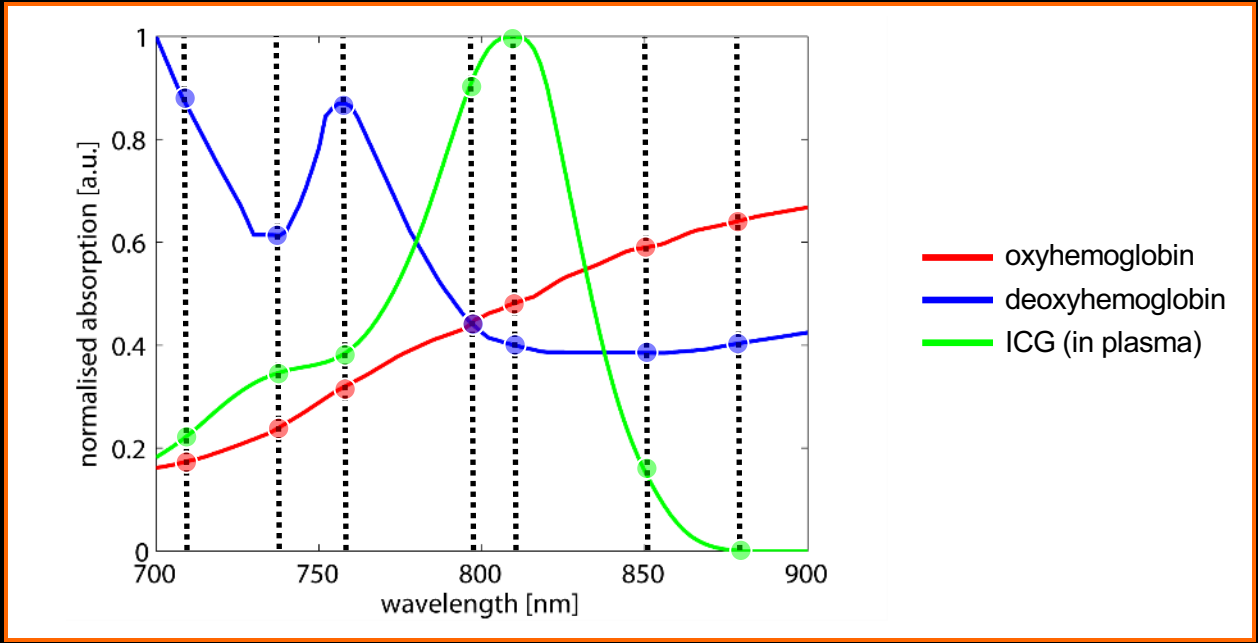




NEW LABEL-FREE Imaging

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

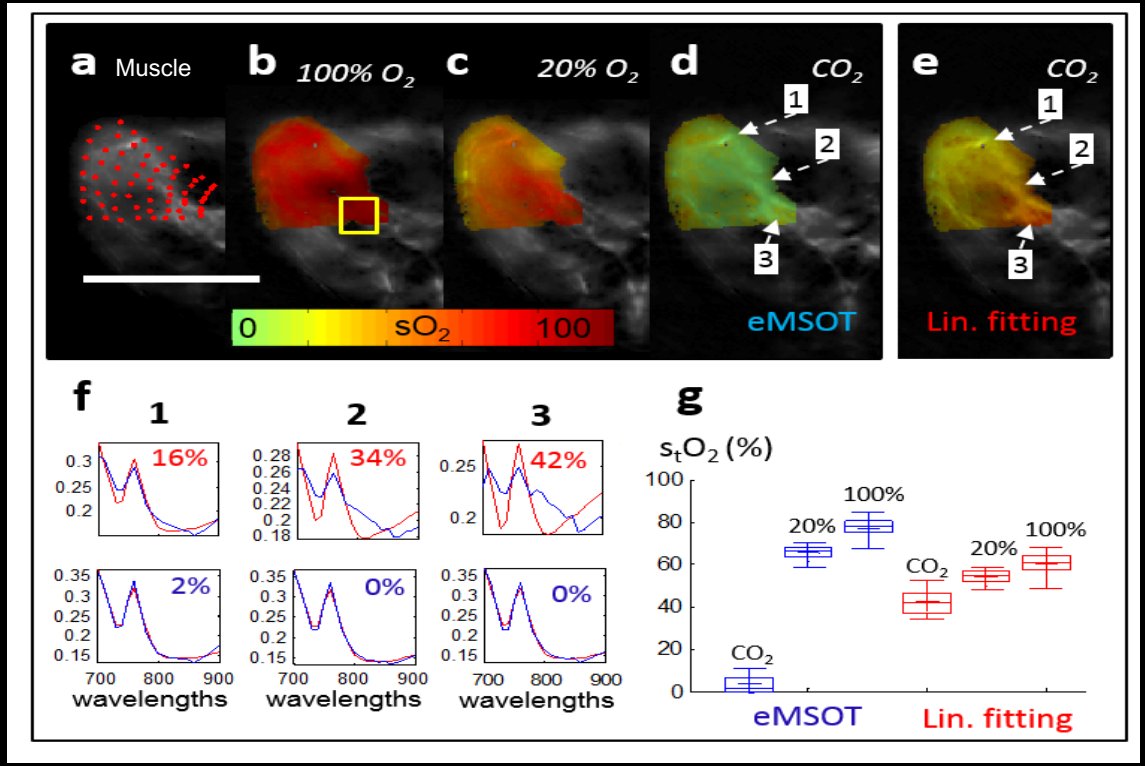
Multi-spectral opto-acoustic tomography (MSOT)



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

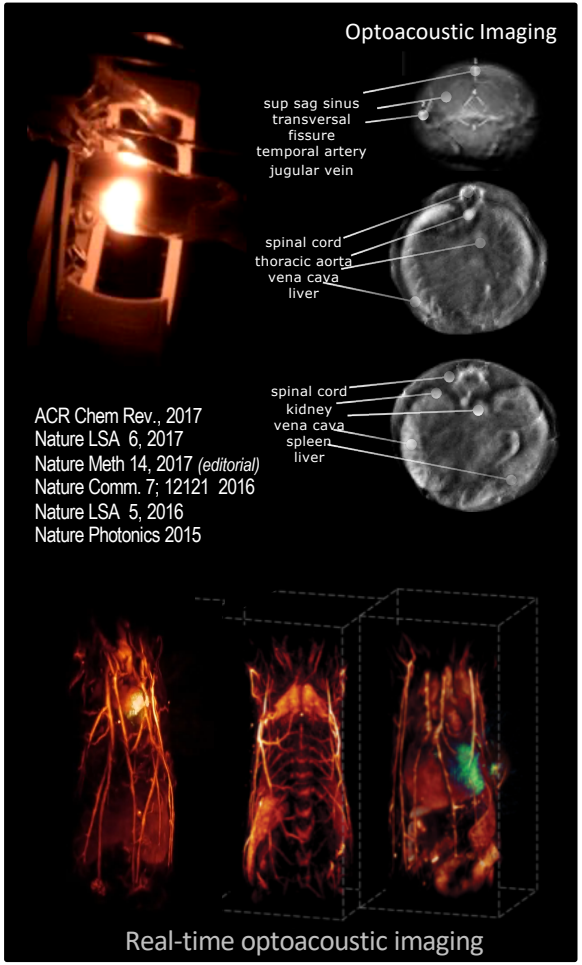
Oxygenation quantification - eMSOT

Description of light fluence in the spectral domain

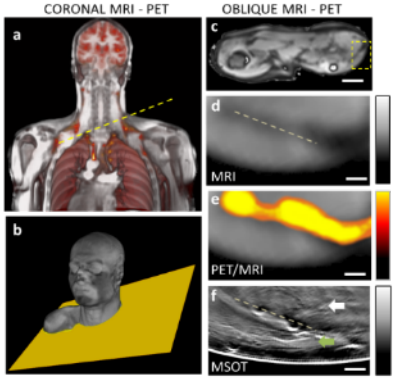


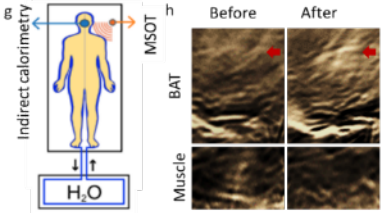
Tzoumas S., et. al Nature Comm. 2016

SMALL ANIMAL IMAGING

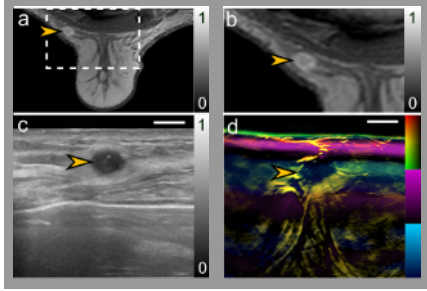


IMAGING METABOLISM

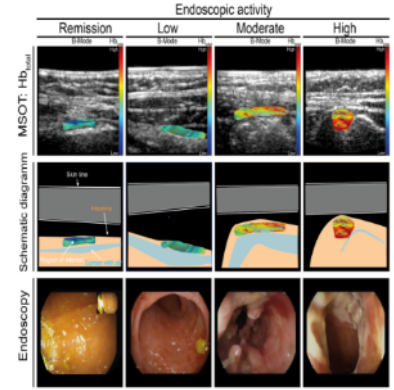




Cell Metabolism 27(3):689-701 2018
Cell doi: j.cell.2018.10.016 2018



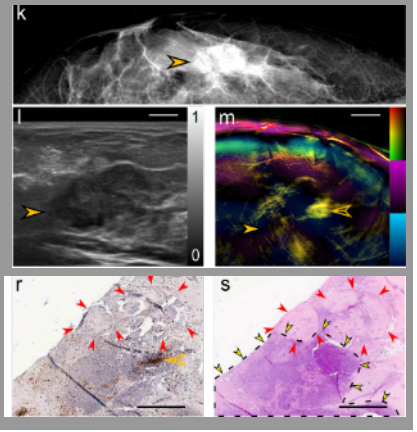
IMAGING INFLAMMATION



New England J. of Medicine 376:129 2017
Nature Medicine 25, 1905–1915 (2019)

BREAST CANCER IMAGING

Clin Cancer Res 23:6912 (2017)

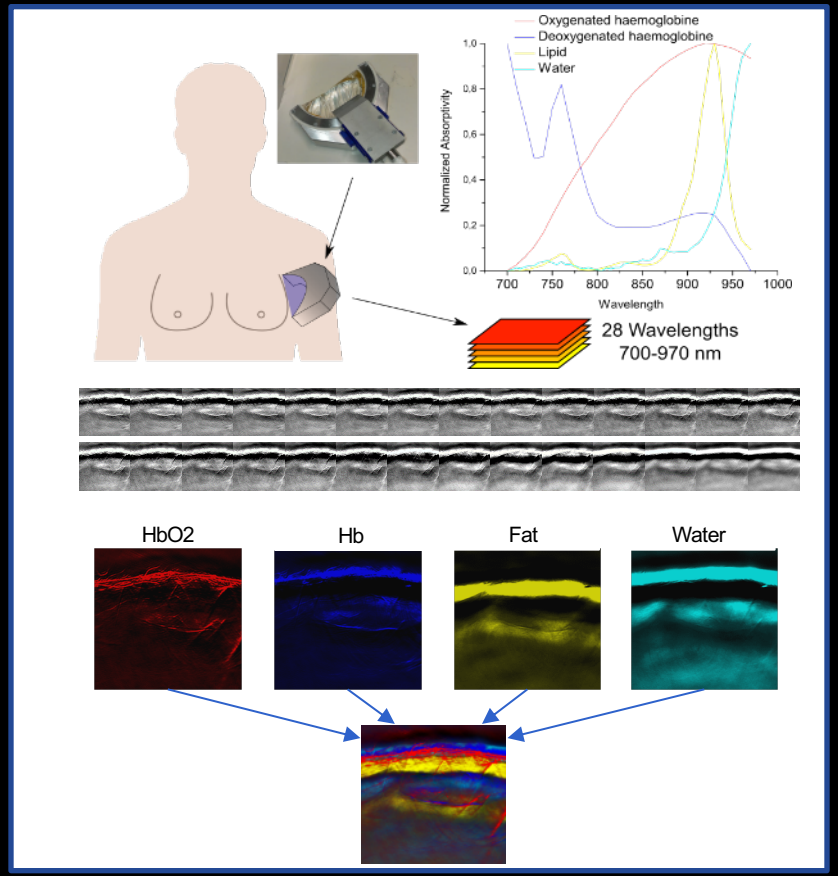


Breast Cancer Imaging

Imaging Protocol

28 Wavelength
Data Collection

Spectral Unmixing



Diot G., et. al. Clinical Cancer Research (2017)

Breast Cancer Imaging

Imaging Protocol

28 Wavelength
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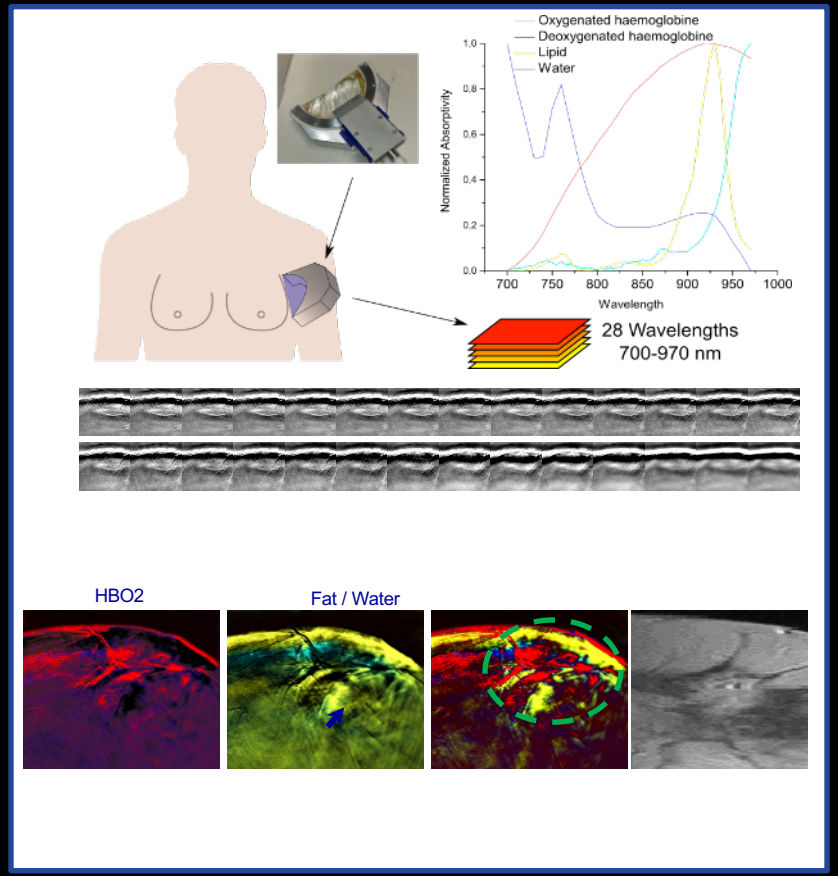
Spectral Unmixing



Diot G., et. al. Clinical Cancer Research (2017)

cancers

MDPI

Article

Mutation of the Cell Cycle Regulator p27kip1 Drives Pseudohypoxic Pheochromocytoma Development

Hermine Mohr [1,2], Simone Ballke [3], Nicole Bechmann [4,5], Sebastian Gulde [1,2], Jaber Malekzadeh-Najafabadi [6], Mirko Peitzsch [5], Vasilis Ntziachristos [6,7], Katja Steiger [3], Tobias Wiedemann [1,2] and Natalia S. Pellegata [1,2,*]

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[2] Joint Heidelberg-IDC Translational Diabetes Program, Heidelberg University Hospital, 69120 Heidelberg, Germany
[3] Institute of Pathology, School of Medicine, Technical University Munich, Trogerstr. 18, 81675 Munich, Germany; simone.ballke@tum.de (S.B.); katja.steiger@tum.de (K.S.)
[4] Department of Medicine III, University Hospital Carl Gustav Carus, Technical University Dresden, Fetscherstrasse 74, 01307 Dresden, Germany; Nicole.Bechmann@uniklinikum-dresden.de
[5] Institute of Clinical Chemistry and Laboratory, University Hospital Carl Gustav Carus, Technical University Dresden, Fetscherstrasse 74, 01307 Dresden, Germany; Mirko.Peitzsch@uniklinikum-dresden.de
[6] Chair of Biological Imaging, Technical University of Munich, Ismaninger Straße 22, 81675 Munich, Germany; jaber.malekzadeh@helmholtz-muenchen.de (J.M.-N.); v.ntziachristos@helmholtz-muenchen.de (V.N.)
[7] Institute for Biomedical Imaging, Helmholtz Centre Munich, Ingolstaedter Landstr.1, 85764 Neuherberg, Germany
* Correspondence: natalia.pellegata@helmholtz-muenchen.de; Tel.: +49-(0)89-3187-2633

check for updates

Citation: Mohr, H.; Ballke, S.; Bechmann, N.; Gulde, S.; Malekzadeh-Najafabadi, J.; Peitzsch, M.; Ntziachristos, V.; Steiger, K.; Wiedemann, T.; Pellegata, N.S.et al. Mutation of the Cell Cycle Regulator p27kip1 Drives Pseudohypoxic Pheochromocytoma Development. *Cancers* **2021**, *13*, 126. https://doi.org/10.3390/cancers13010126

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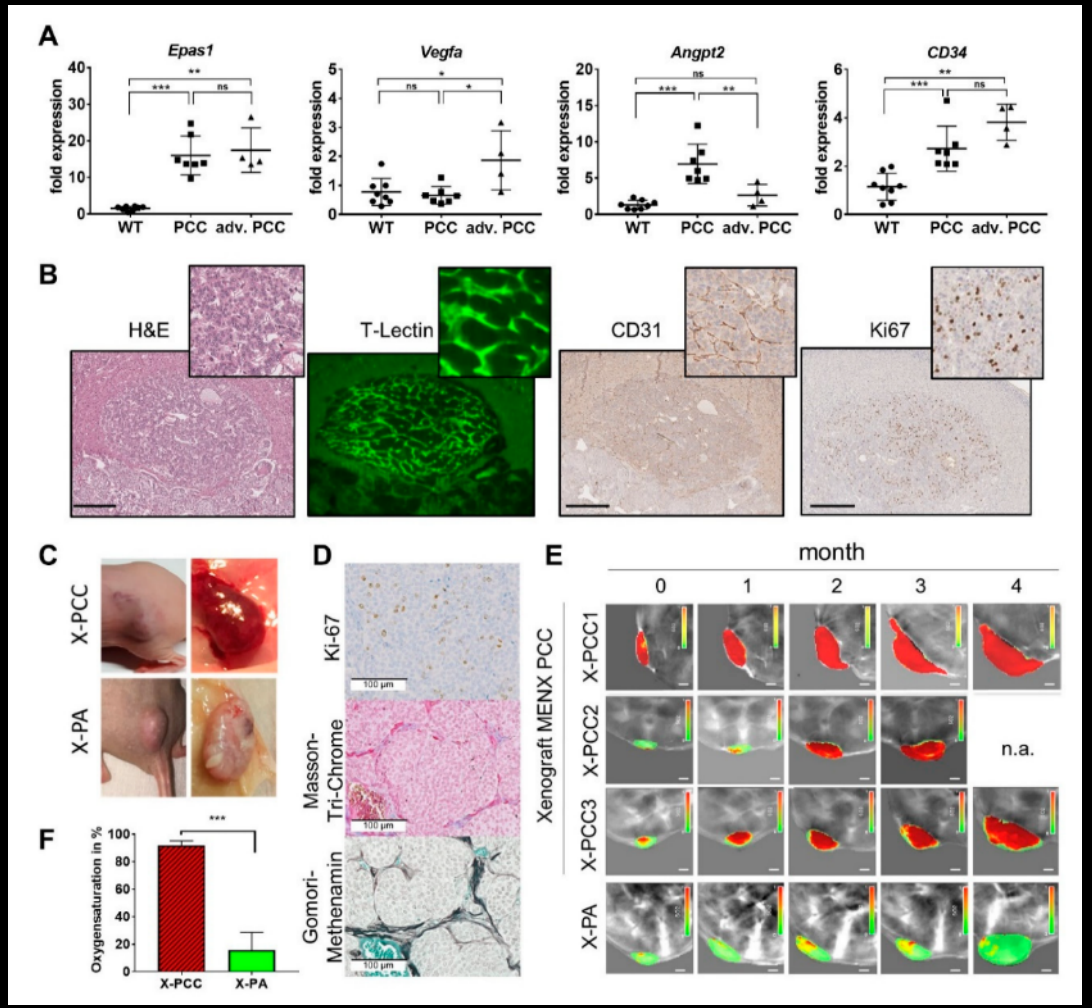
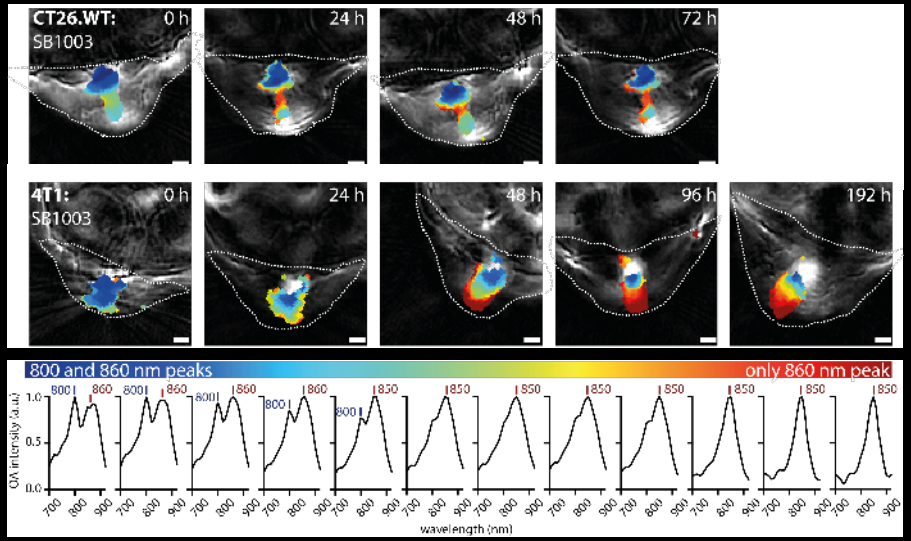
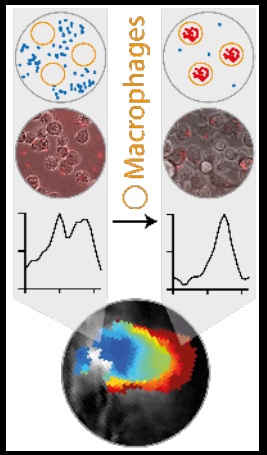
Simple Summary: Pheochromocytomas and paragangliomas (PPGLs) can be subdivided into at least three different subgroups associated with different clinical manifestations and depending on the risk to metastasize. A shortage in human tumor material, the lack of a functional human cell line and very limited animal models were major drawbacks for PPGL research and consequently for the development of patient-tailored targeted therapies. We have previously reported that the MENX rat model develops pheochromocytoma with a full penetrance at the age of 8–10 months, however, it was unclear which human group the rat tumors modeled best. In order to characterize the rat pheochromocytomas, we analyzed gene expression, the catecholamine profile, TCA-cycle metabolism, methylation, angiogenesis, histology and mitochondrial ultrastructure. In all aspects, rat MENX pheochromocytomas resemble the features of the human pseudohypoxia group, the most aggressive one and in need of effective therapeutic approaches.

Abstract: Background: Pseudohypoxic tumors activate pro-oncogenic pathways typically associated with severe hypoxia even when sufficient oxygen is present, leading to highly aggressive tumors. Prime examples are pseudohypoxic pheochromocytomas and paragangliomas (p-PPGLs), neuroendendocrine tumors currently lacking effective therapy. Previous attempts to generate mouse models for p-PPGLs all failed. Here, we describe that the rat MENX line, carrying a *Cdkn1b* (p27) frameshift-mutation, spontaneously develops pseudohypoxic pheochromocytoma (p-PCC). Methods: We compared rat p-PCCs with their cognate human tumors at different levels: histology, immunohistochemistry, catecholamine profiling, electron microscopy, transcriptome and metabolome. The vessel architecture and angiogenic potential of pheochromocytomas (PCCs) was analyzed by light-sheet fluorescence microscopy ex vivo and multi-spectral optoacoustic tomography (MSOT) in vivo. Results: The analysis of tissues at various stages, from hyperplasia to advanced grades, allowed us to correlate tumor characteristics with progression. Pathological changes affecting the mitochrondrial ultrastructure where present already in hyperplasias. Rat PCCs secreted high levels of norepinephrine and dopamine. Transcriptomic and metabolomic analysis revealed changes in oxidative phosphorylation that aggravated over time, leading to an accumulation of the oncometabolite 2-hydroxyglutarate, and to hypermethylation, evident by the loss of the epigenetic mark 5-hmC. While rat PCC xenografts showed high oxygenation, induced by massive neoangiogenesis, rat primary PCC transcriptomes



Rhodobacter *(purple bacteria) as a marker for Macrophage activity* in vivo



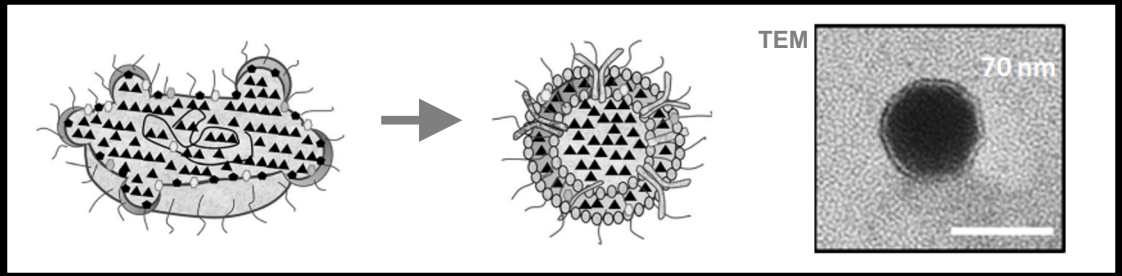


Peters L, et. L. *Nature Communications.* 2019. 10(1):1191.

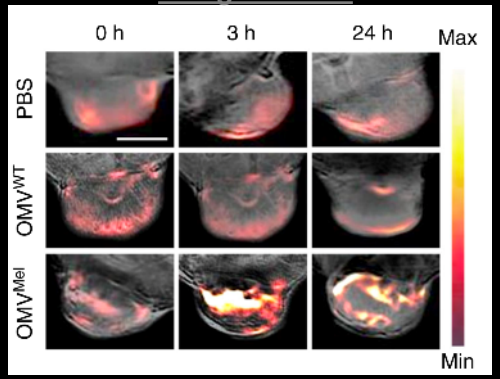
Bacteria derived vesicles – agents with diagnostic and therapeutic perspective:

E. Coli producing vesicles containing melanin (▲)

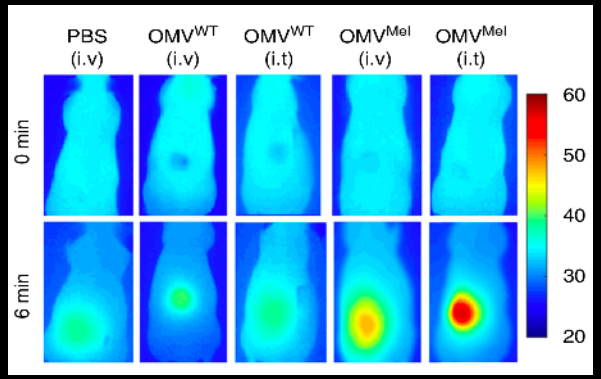
Melanin vesicle (OMV^{Mel})



Optoacoustic tumor imaging using OMV^{Mel}



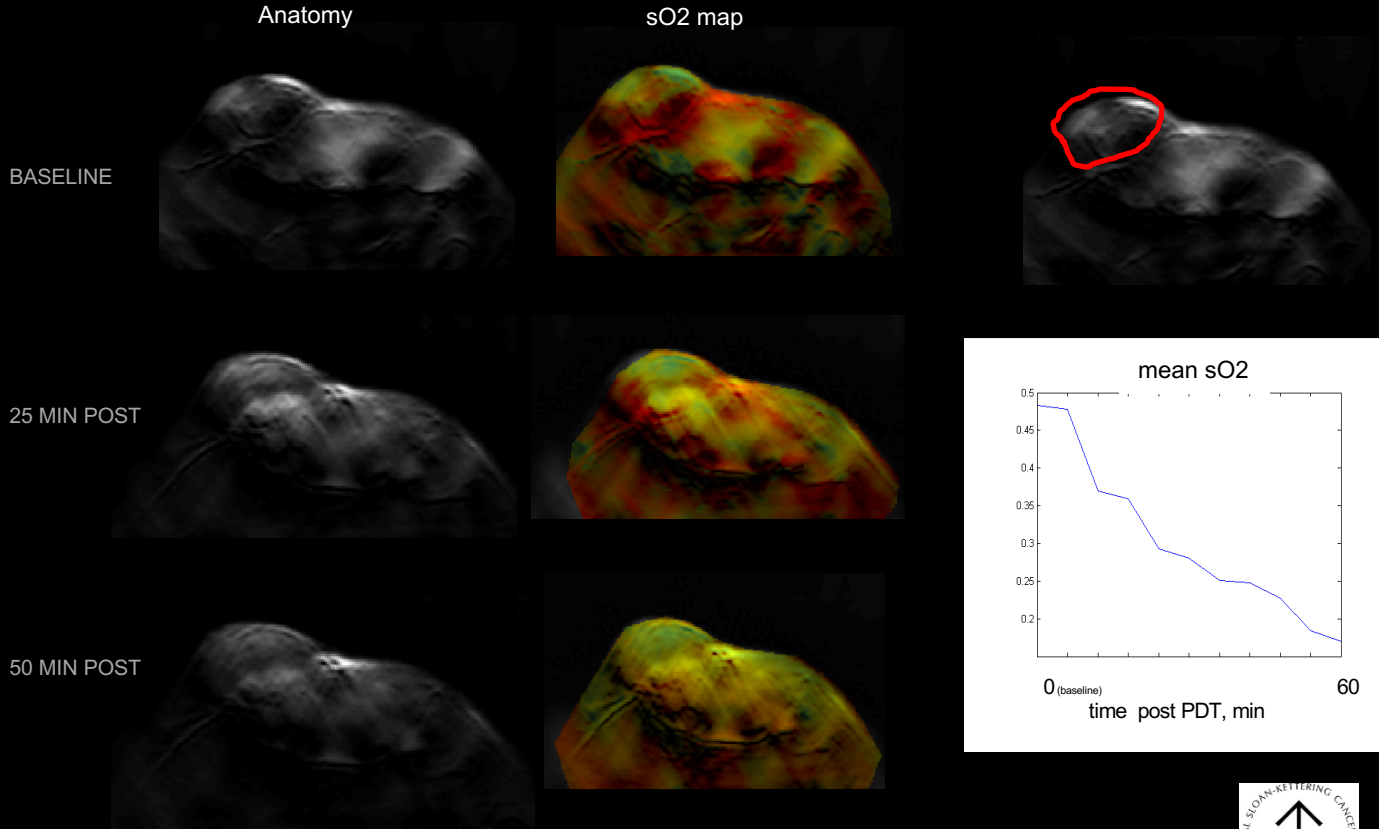
Photothermal effect of OMV^{Mel}



Gujrati V, et. al. *Nature Communications*. 2019. 10(1):1114.

Imaging of PDT effects

Coleman Group, Grimm, Kircher groups - MSKCC
Avigdor Scherz – Weizmann Institute



Volker Neuschmelting, Kwanghee Kim, Jaber Malekzadeh

ORGANIZATION & STEERING COMMITTEE

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medical director
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Fax: +49 89 4140-7709
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Clinic on the right of the Isar TU Munich

Prof. Dr. Gabriele Multhoff
Clinic and Polyclinic for Radiation Therapy and Radiological Oncology
Clinic on the right of the Isar TU Munich

Prof. Dr. Vasilis Ntziachristos
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Technical University of Munich

Prof. Dr. Hans-Jürgen Wester
Chair of Radiopharmaceutical Chemistry

Prof. Dr. med. Wilko Weichert
Institute for General Pathology and Pathological Anatomy
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Prof. Dr. Wolfgang Weber
Clinic and Polyclinic for Nuclear Medicine
Clinic on the right of the Isar TU Munich

EVENTS

04/02/2020 09:00
IN VIVO MAGNETIC RESONANCE - RECENT METHODS AND ADVANCES
MORE INFORMATION

04/01/2020 3:30 p.m.
"RADIOTHERAGNOSTICS IN CANCER RESEARCH - TERBIUM SISTERS AND BEYOND"
MORE INFORMATION

03/28/2019 00:00
GIRLS' DAY OFFER IN THE TRANSLATUM
MORE INFORMATION

06.03.2019 11:30
HSP110 AS A THERAPEUTIC TARGET IN COLORECTAL CANCER: FROM CRYSTALS TO DRUG SELECTION
MORE INFORMATION

Future SFB