

Optical imaging

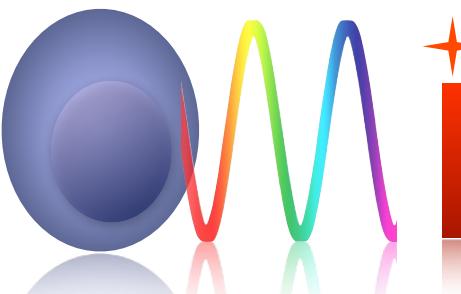
Jan Grimm, MD, PhD

FAIMBE, FWMIC

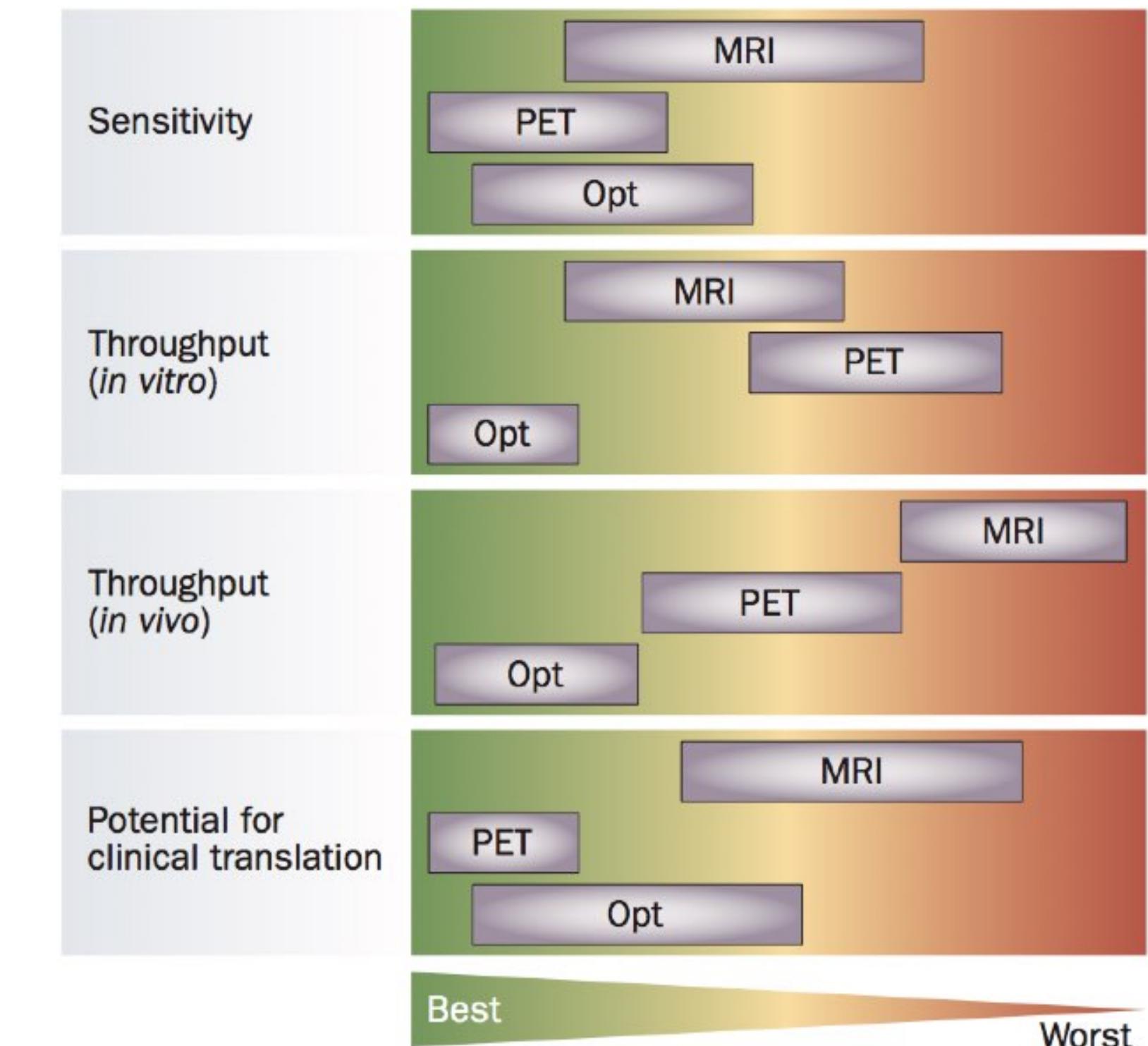
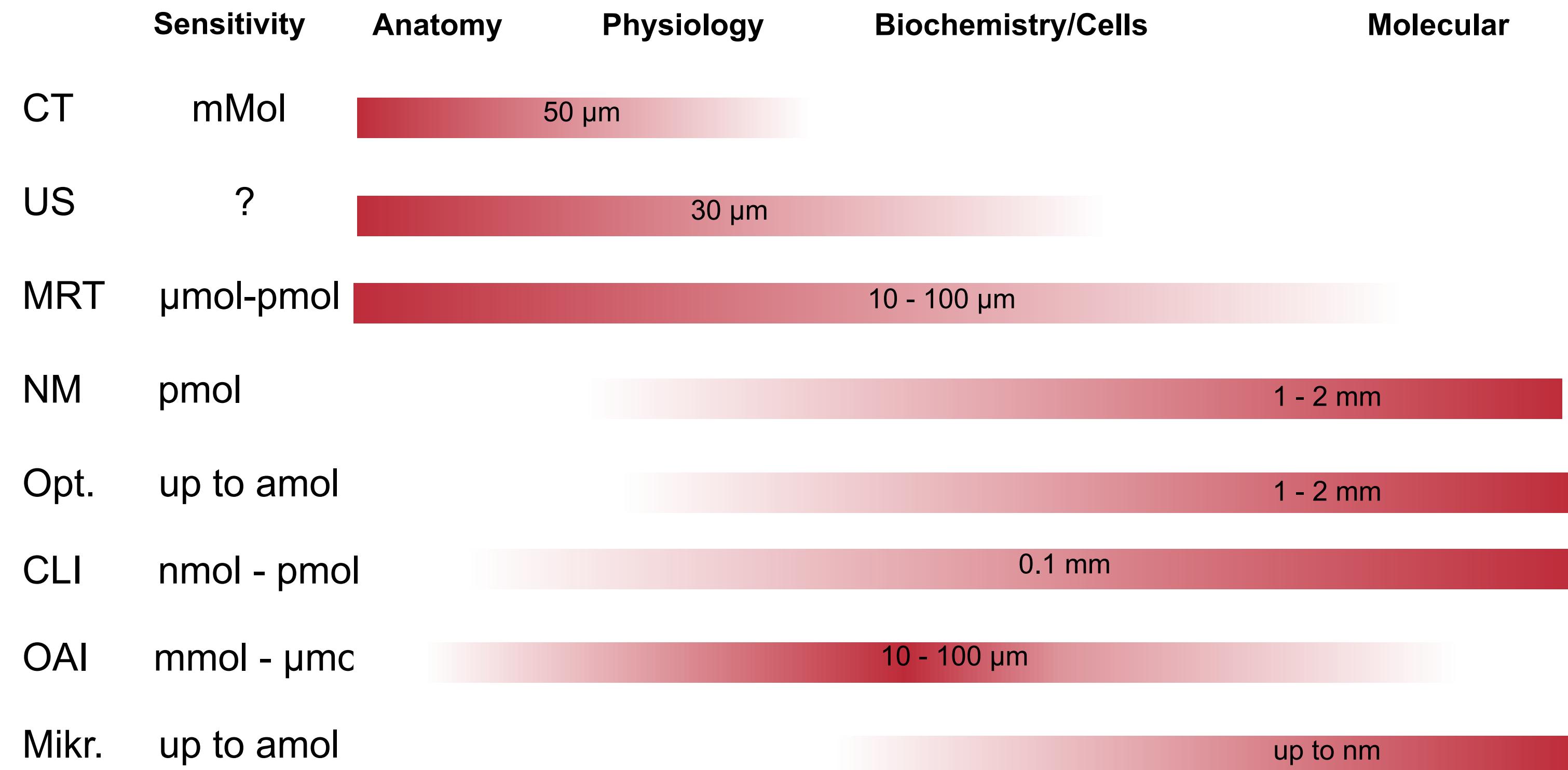
Professor / Lab Head / Attending

Memorial Sloan Kettering Cancer Center & Cornell University

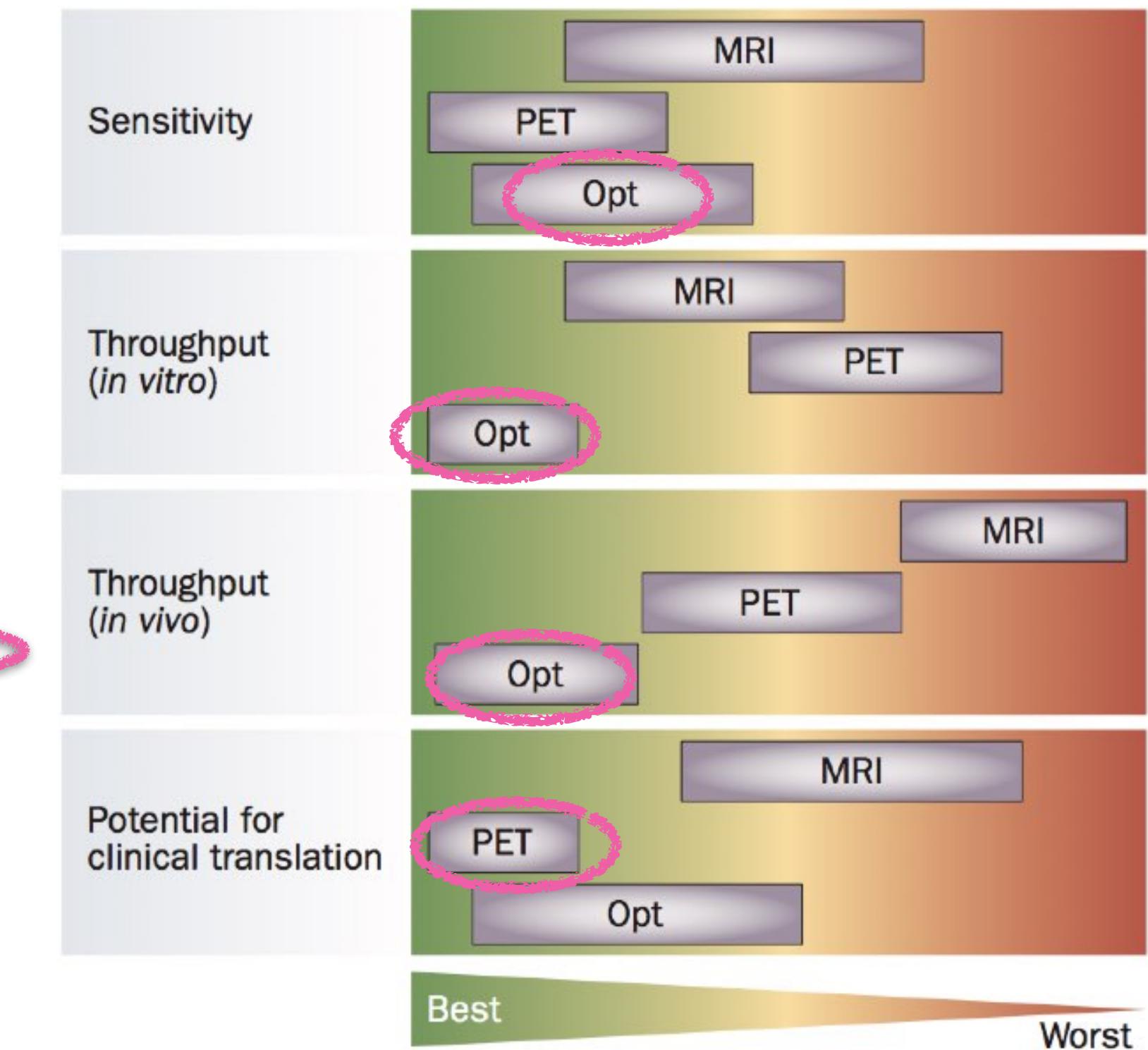
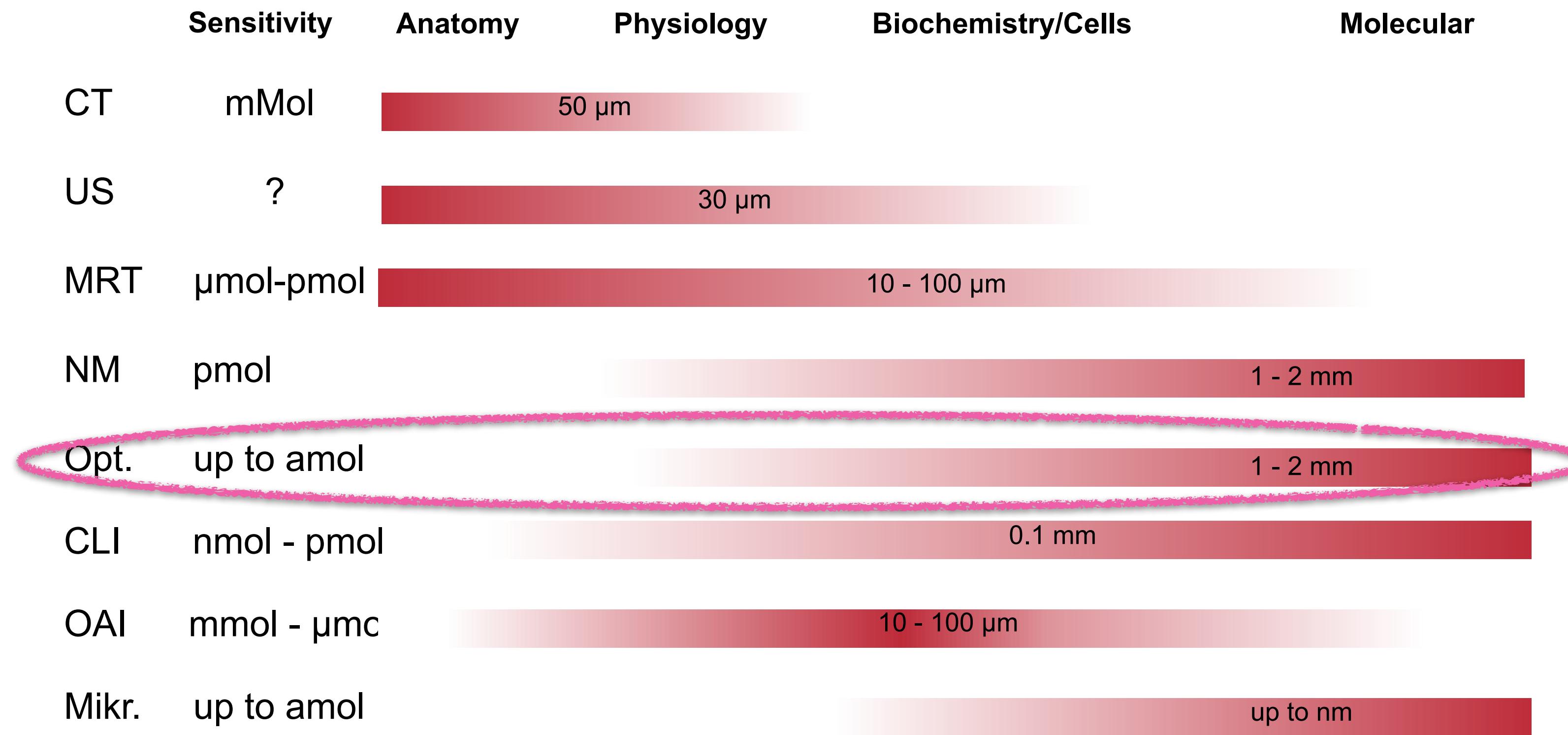
New York, NY, USA



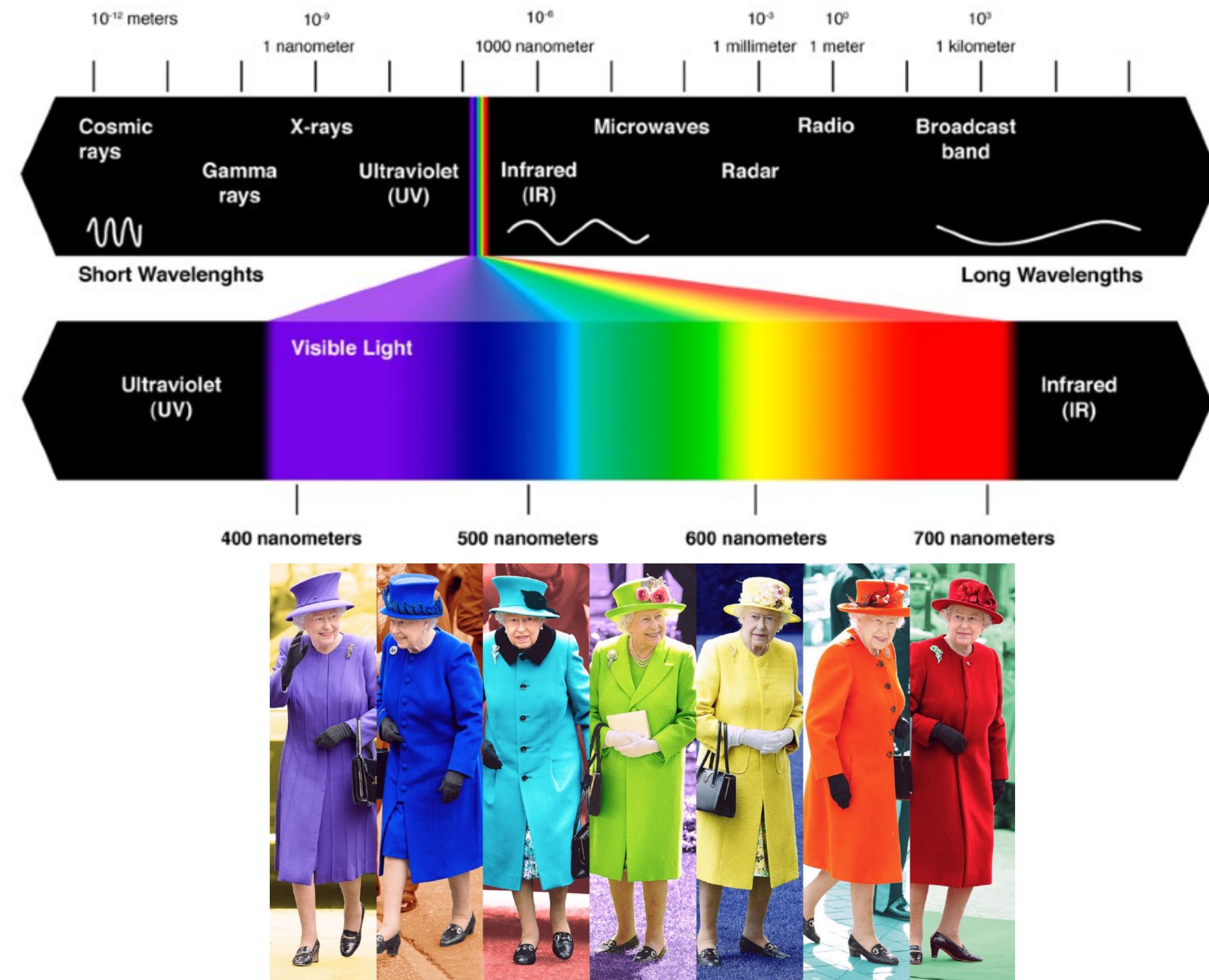
Optical imaging in context



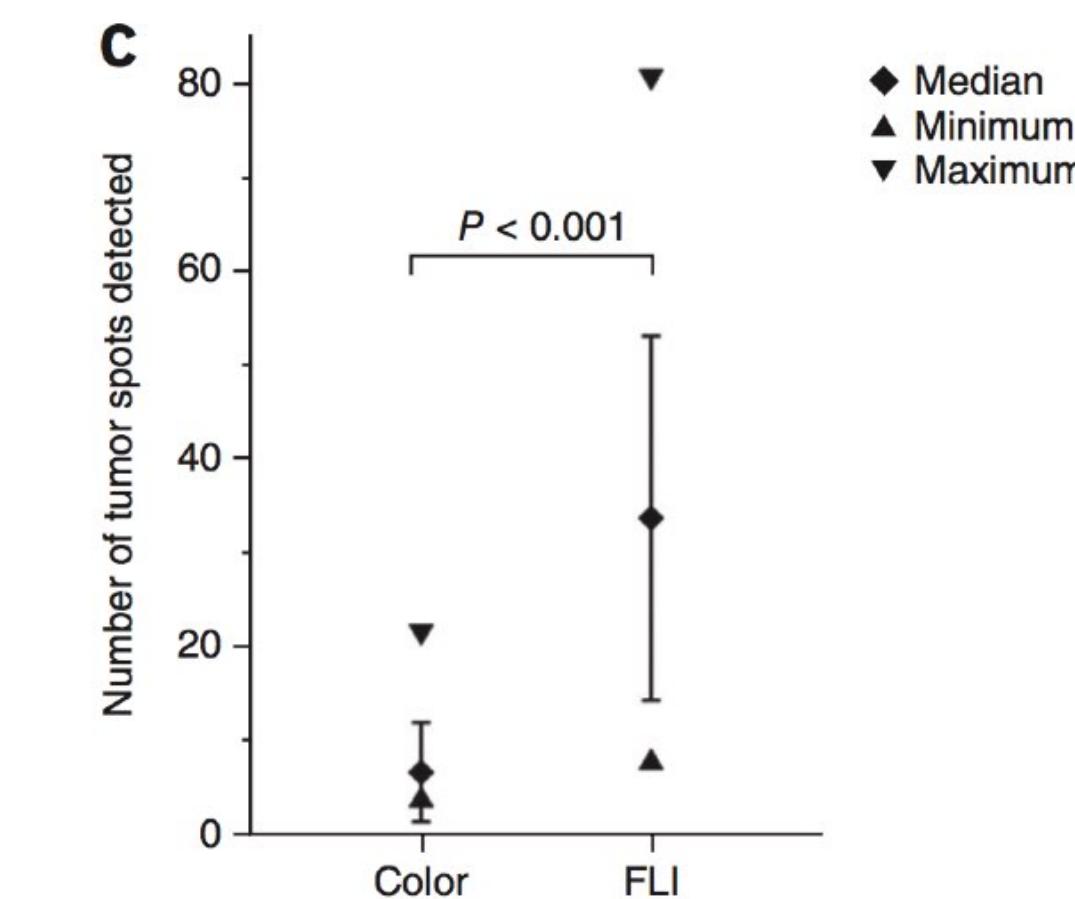
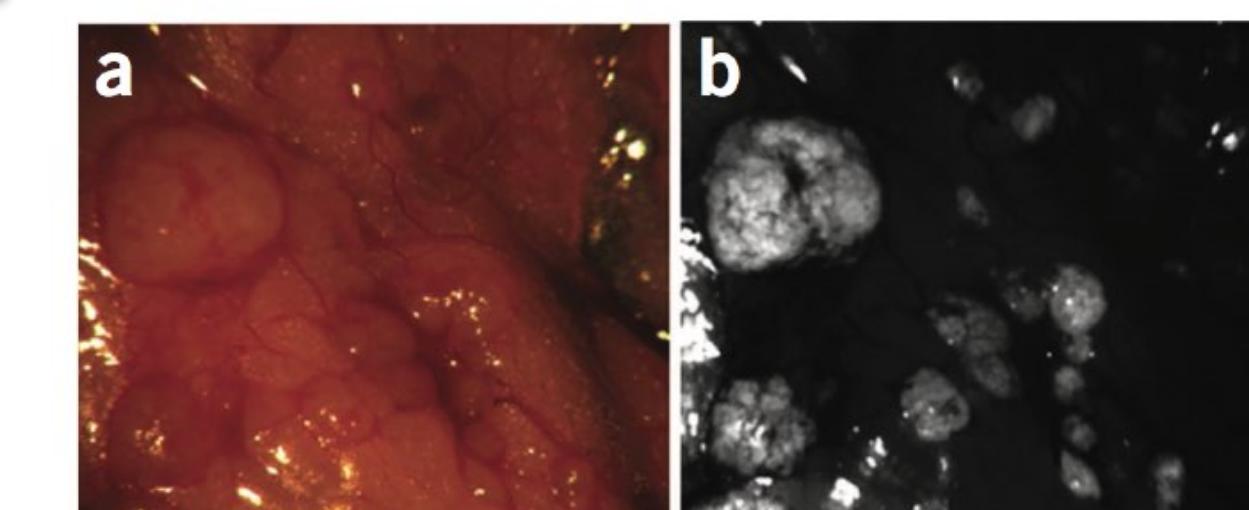
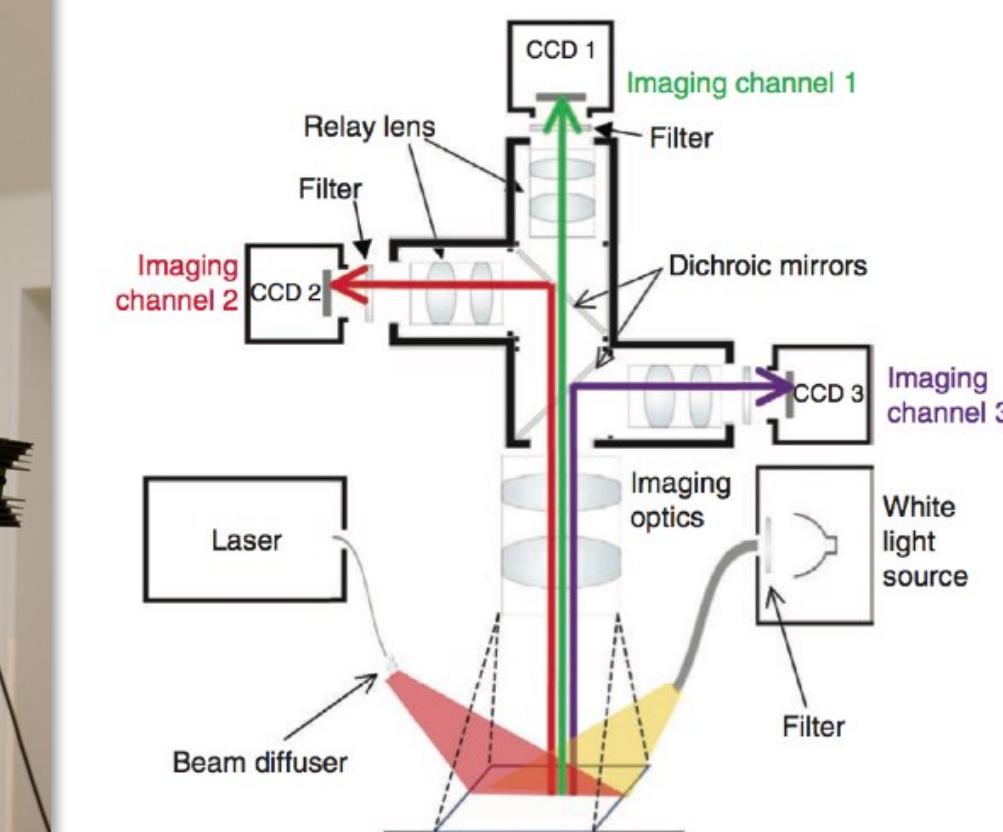
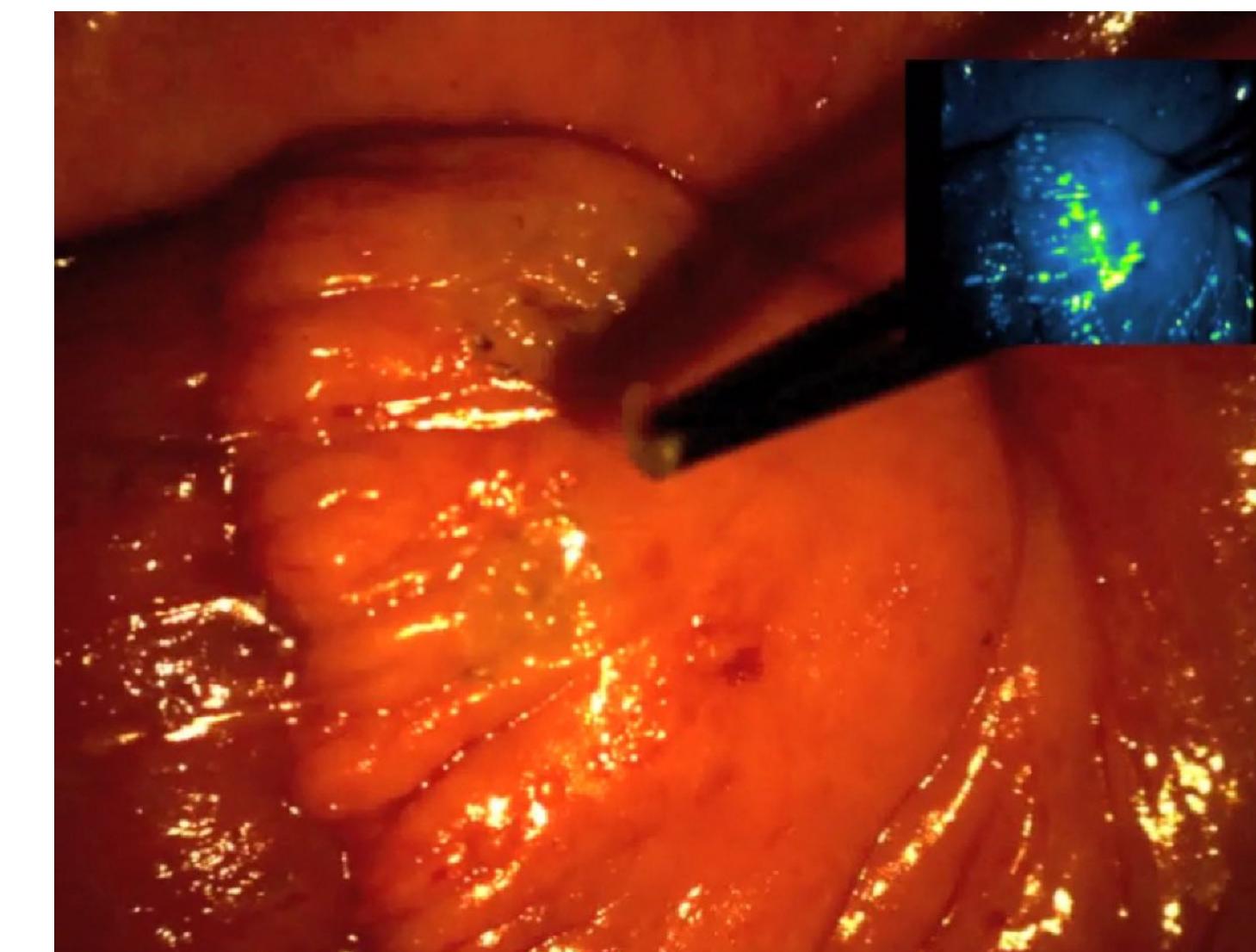
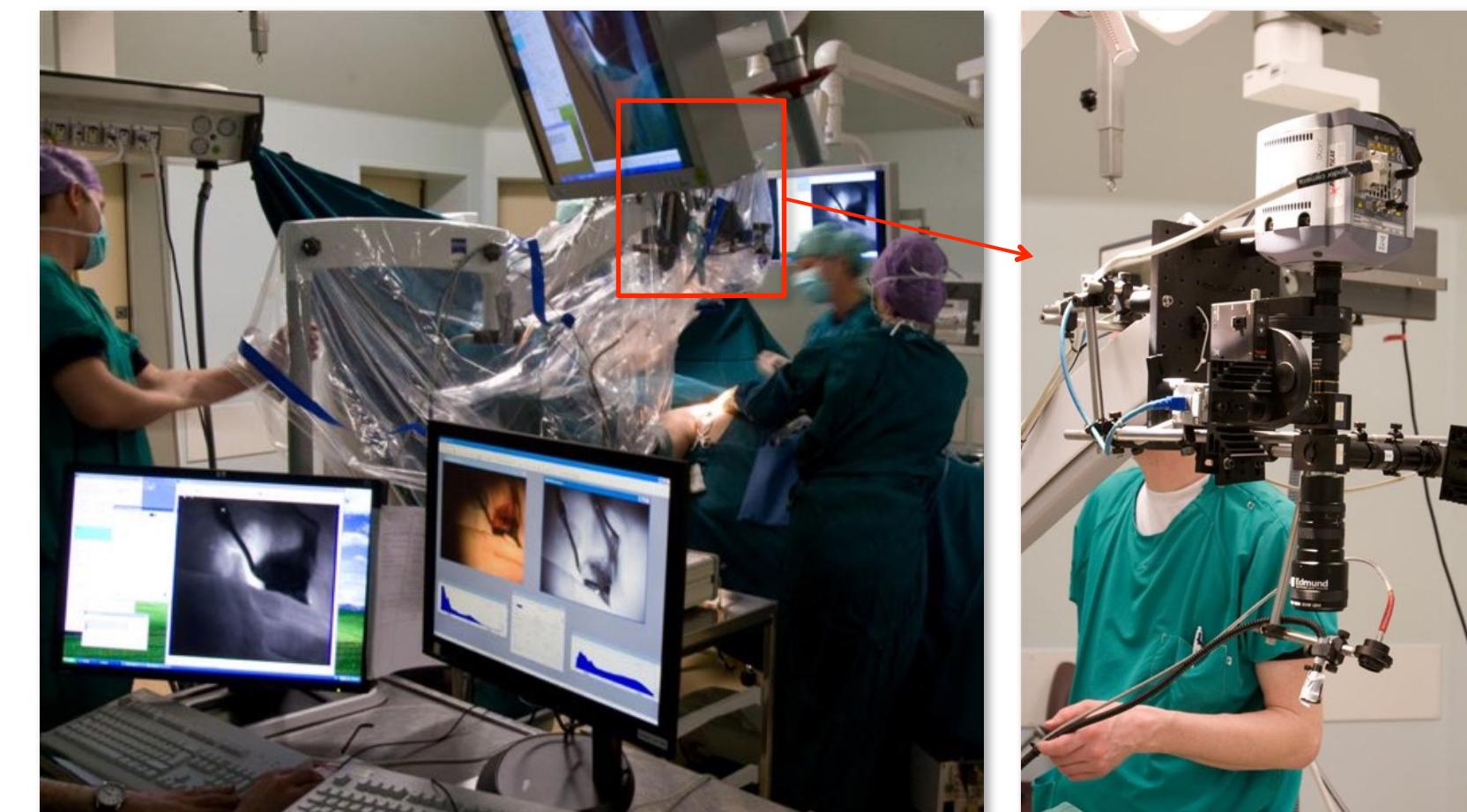
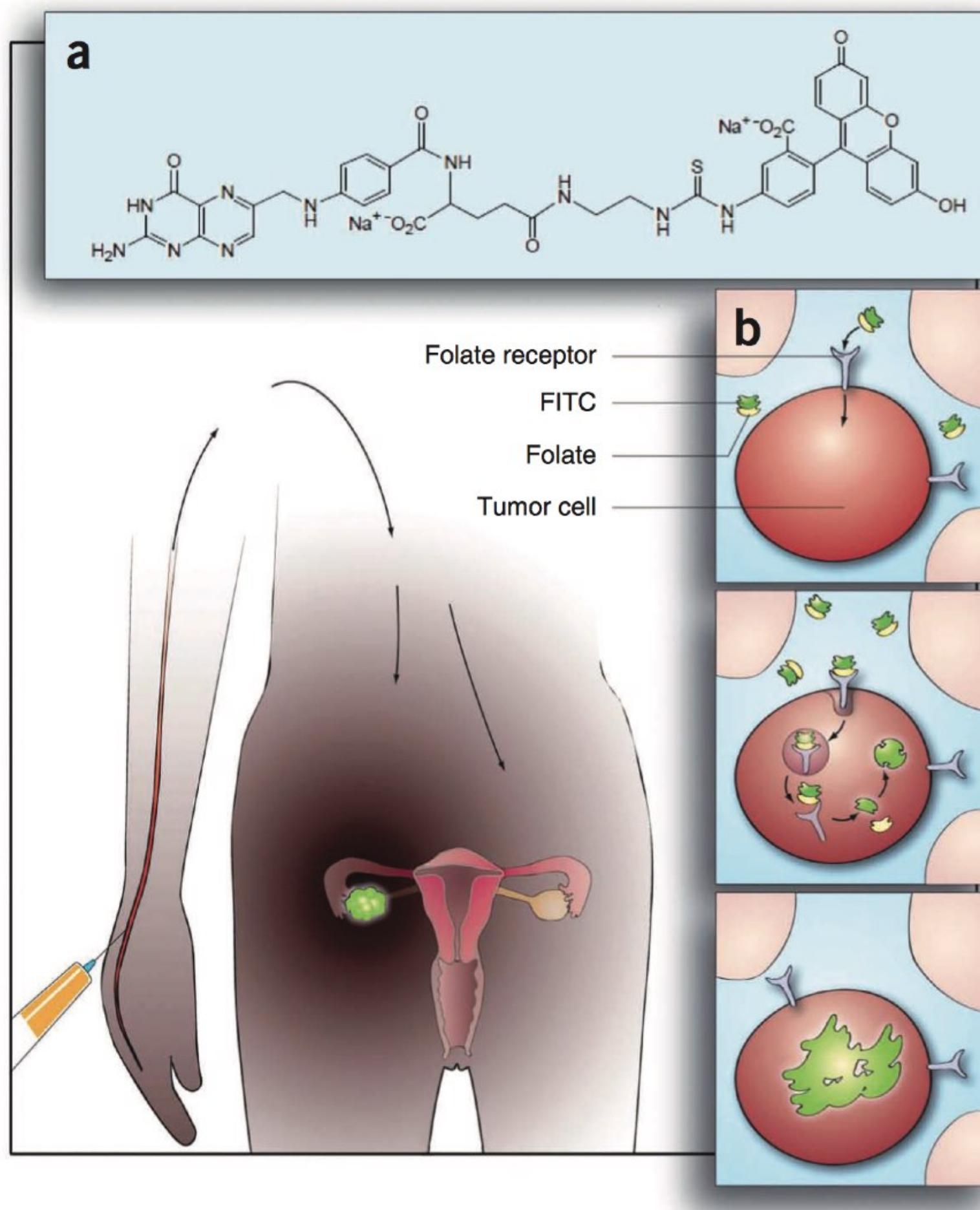
Optical imaging in context



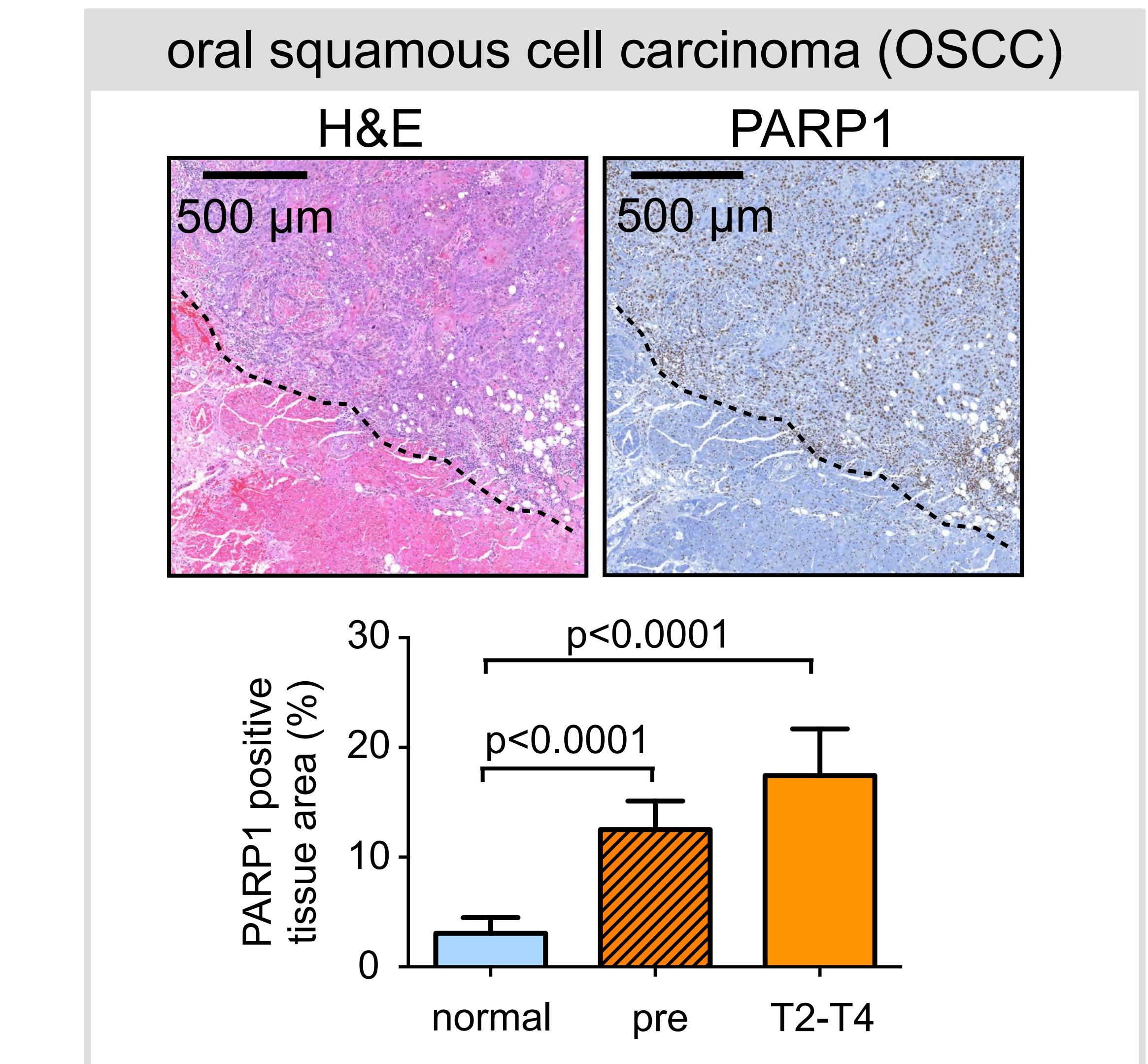
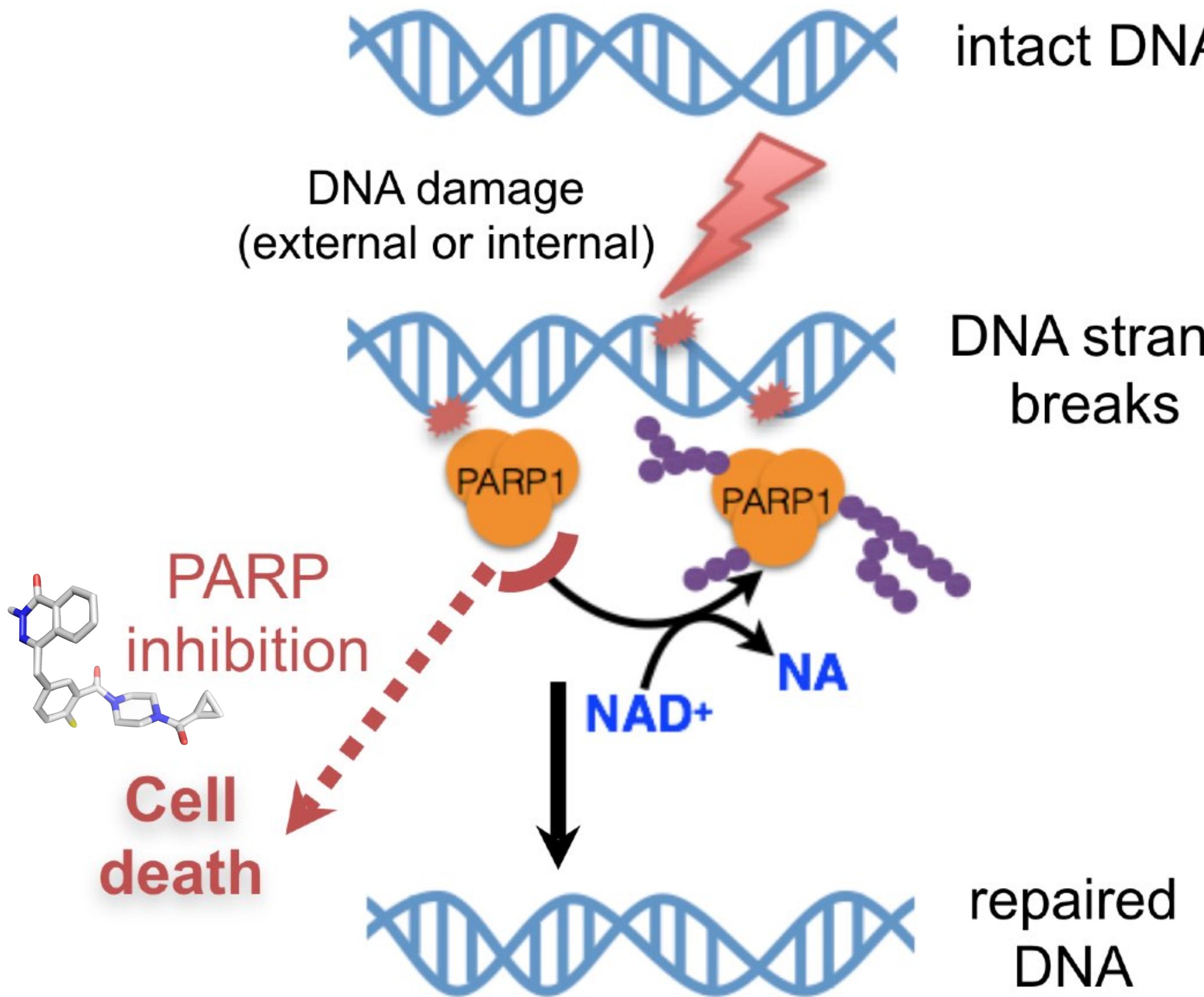
Optical imaging



Intraoperative optical imaging



PARP-1 Molecular Imaging



Kossatz et al. Scientific Reports 2016

Oral cancer detection phase I/II clinical trial



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NCT03085147

increasing dose levels

100 nM - 1000 nM (currently lowest dose level)

1 min PARPi-FL swish and spit

1 min clearing solution swish and spit

phase I: imaging pre-surgery

phase II: imaging in the OR, followed by biopsy confirmation

Oral cancer detection phase I/II clinical trial



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NCT03085147

increasing dose levels

100 nM - 1000 nM (currently lowest dose level)

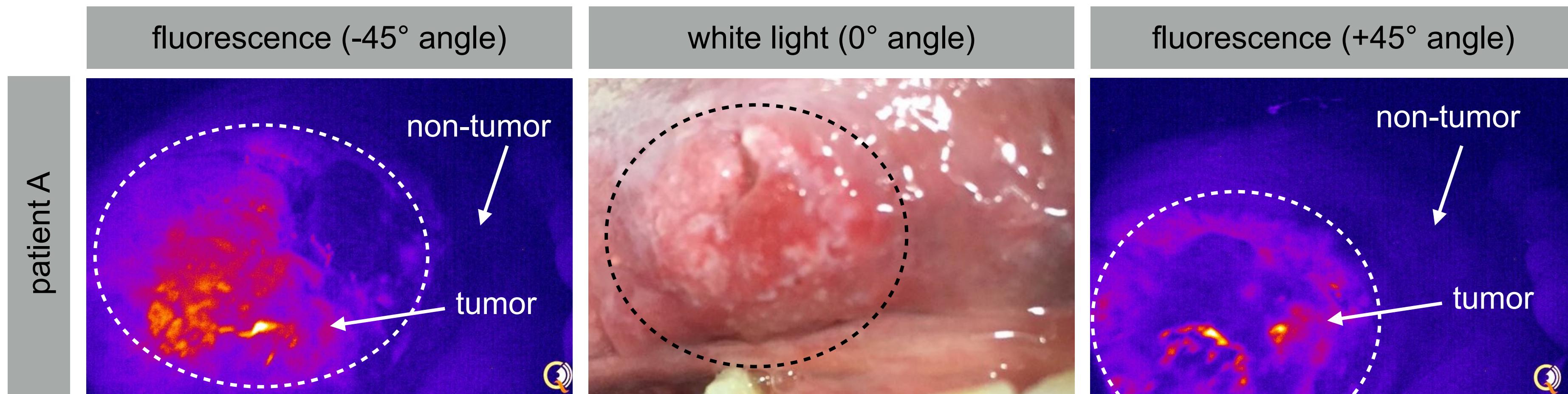
1 min PARPi-FL swish and spit

1 min clearing solution swish and spit

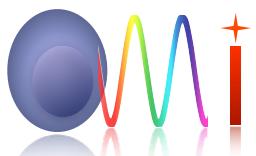
phase I: imaging pre-surgery

phase II: imaging in the OR, followed by biopsy confirmation

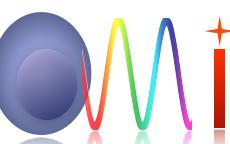
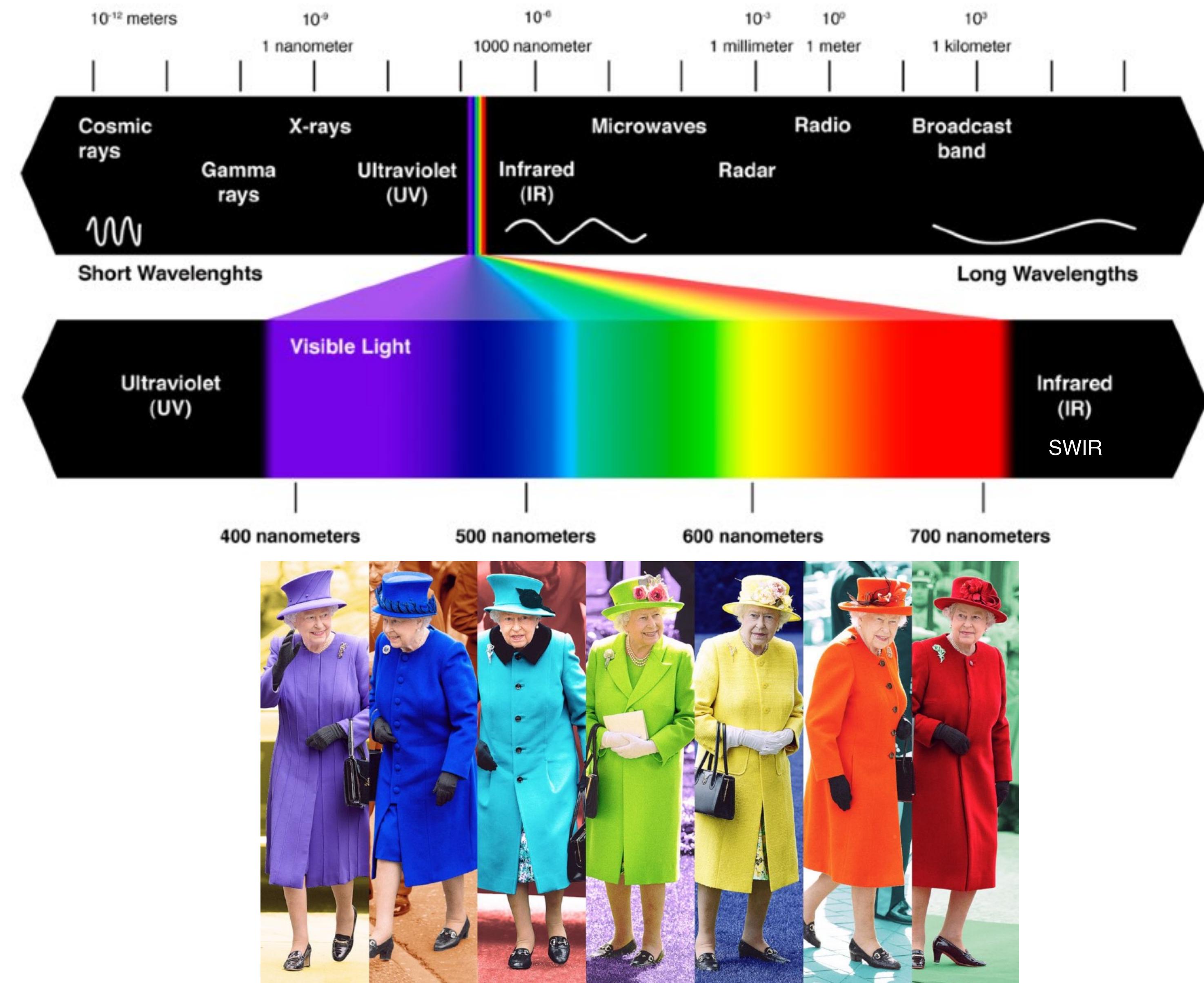
Human Phase I - In Vivo Imaging



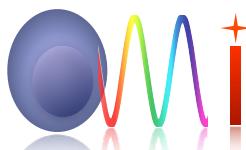
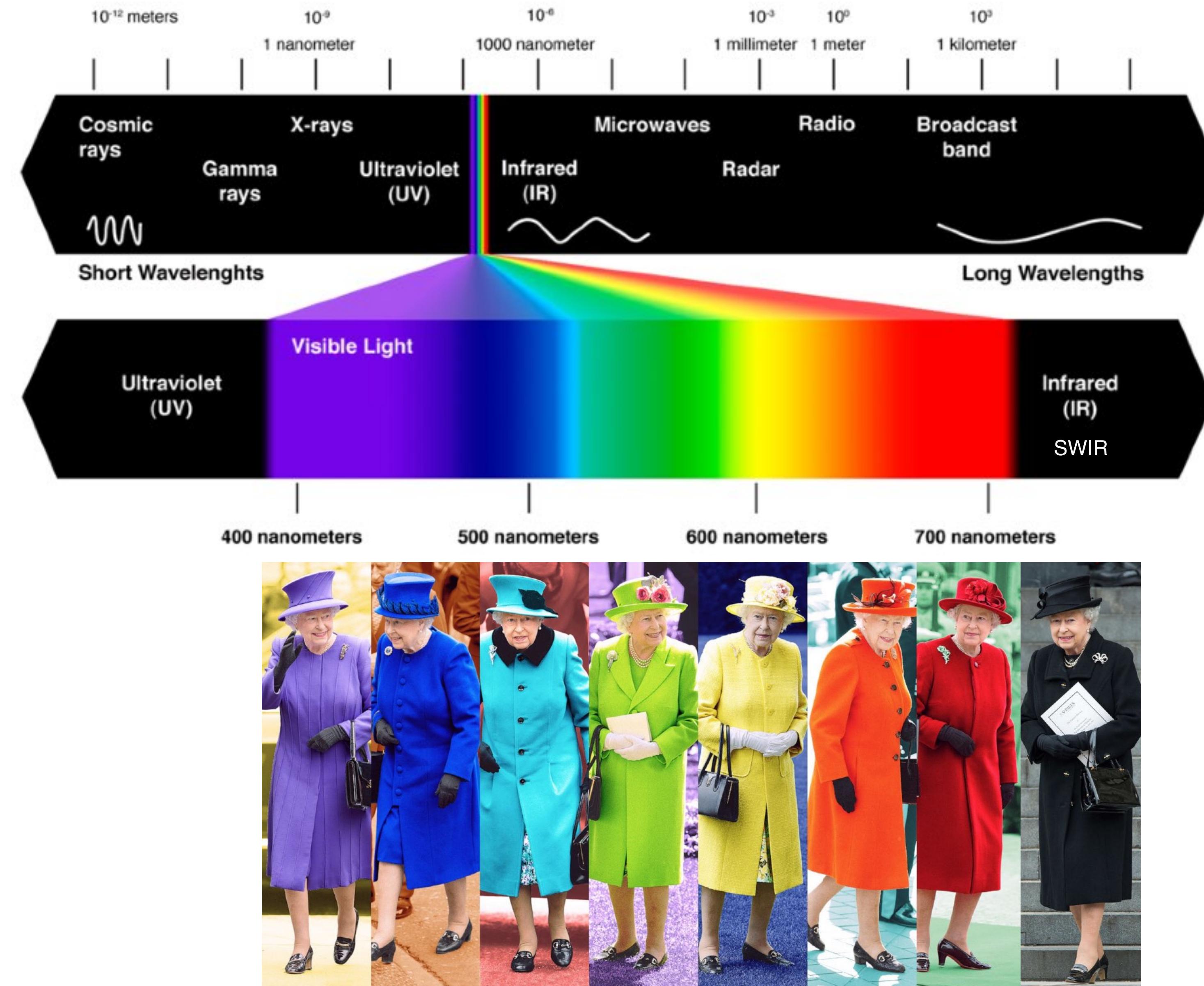
PARP slides courtesy of Thomas Reiner Lab, MSKCC



Spectrum to use

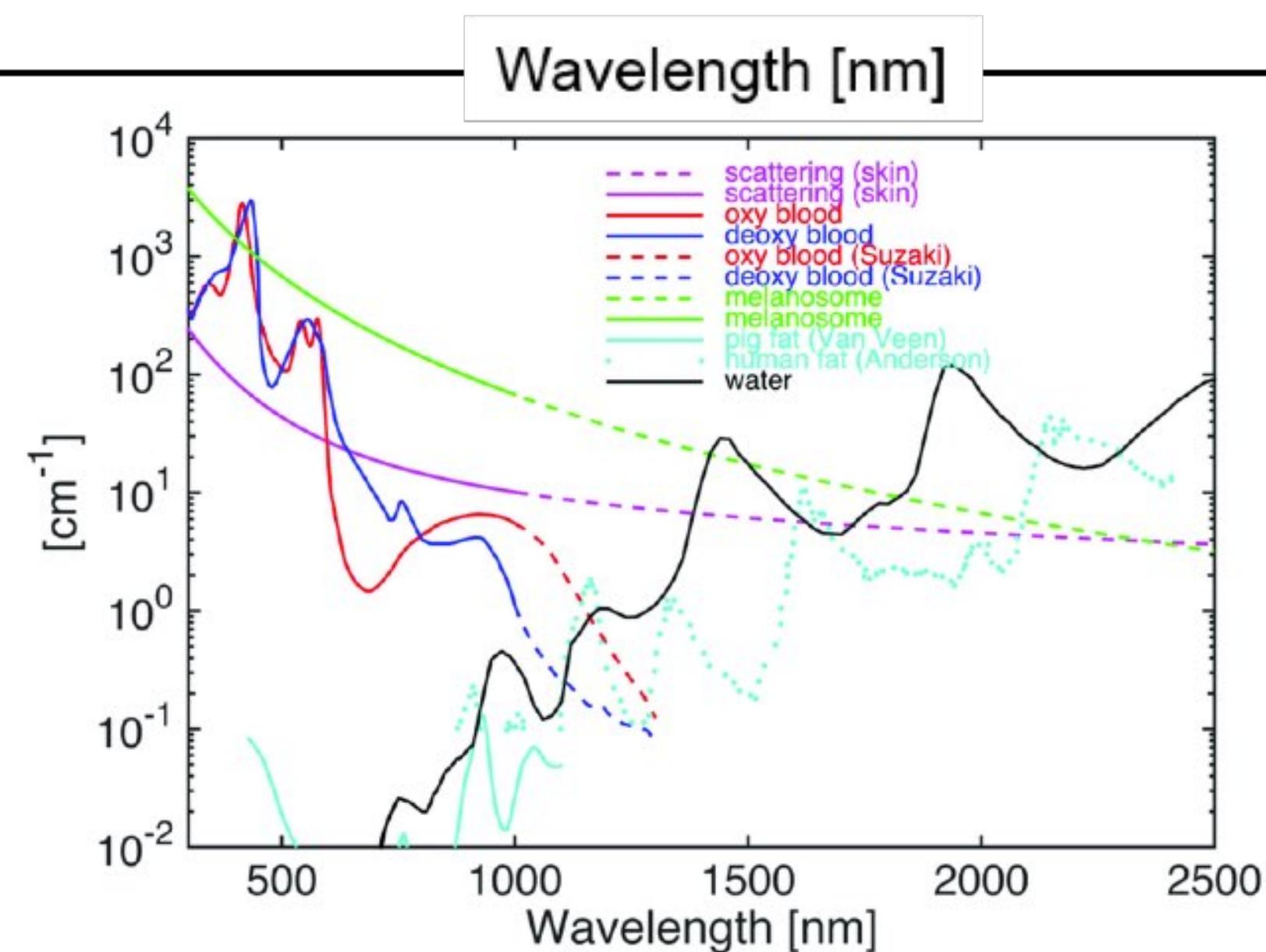
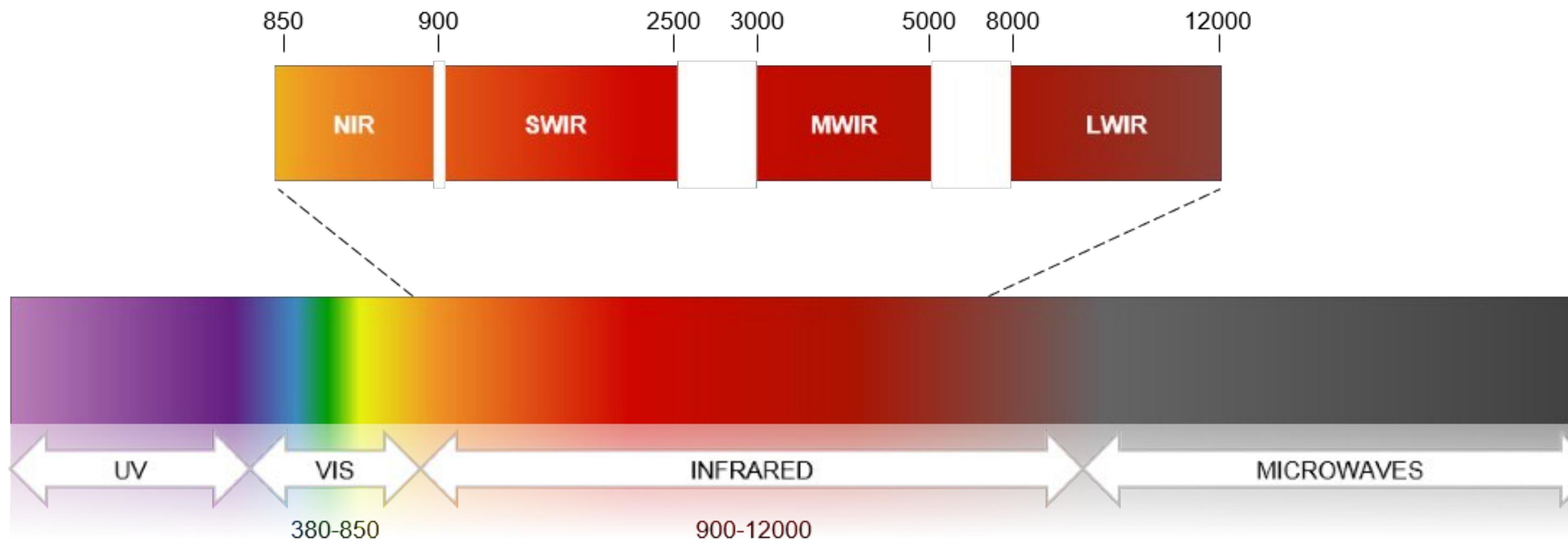


Spectrum to use



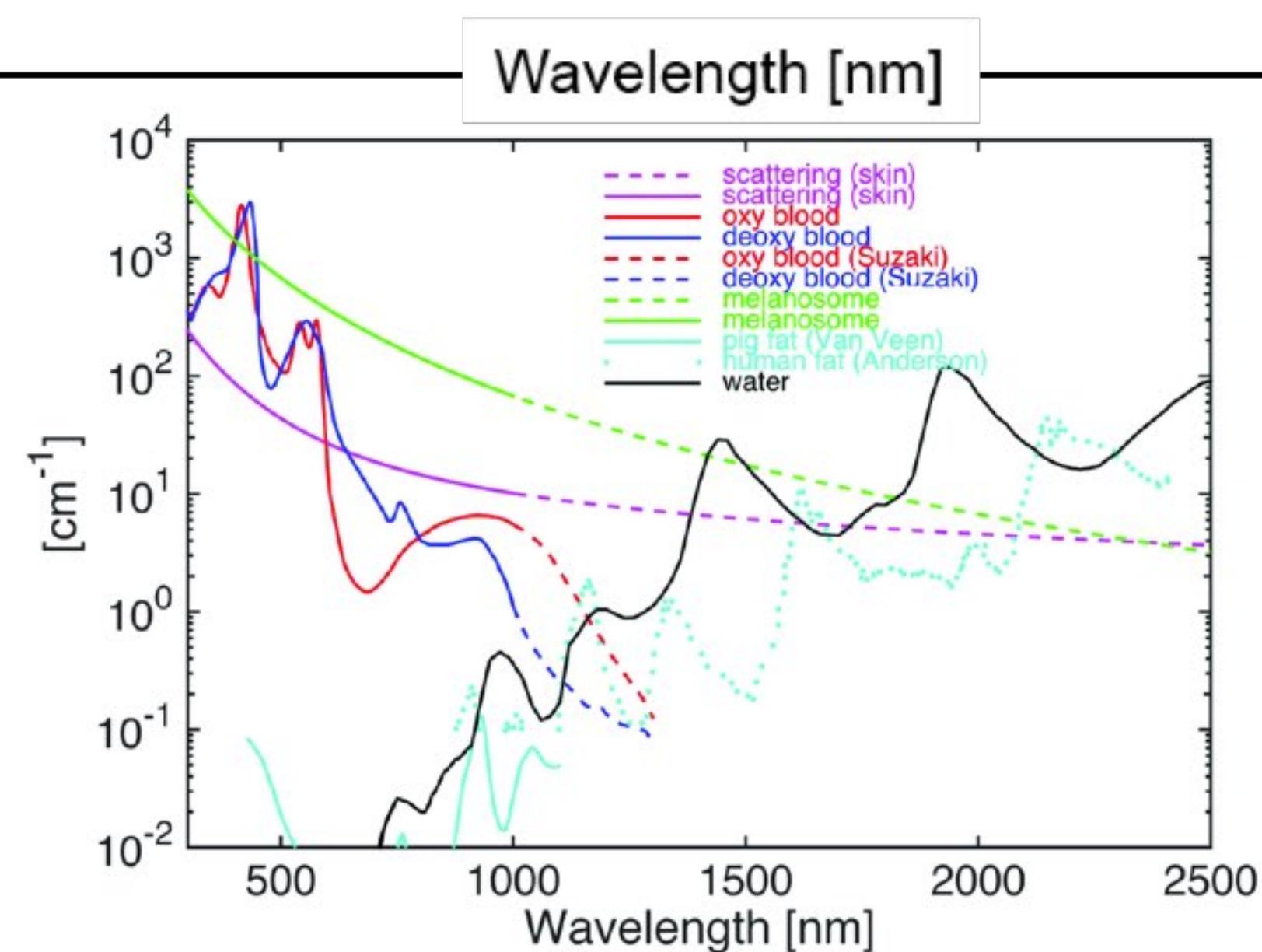
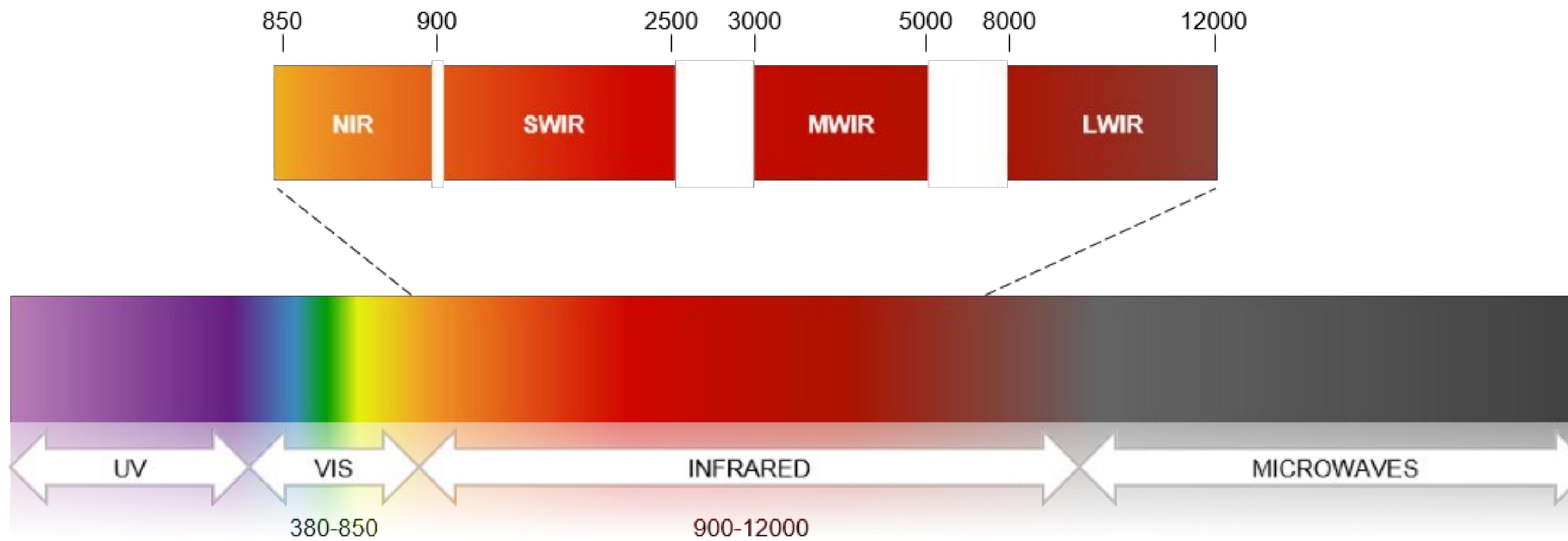
SWIR imaging

Short-wave infrared

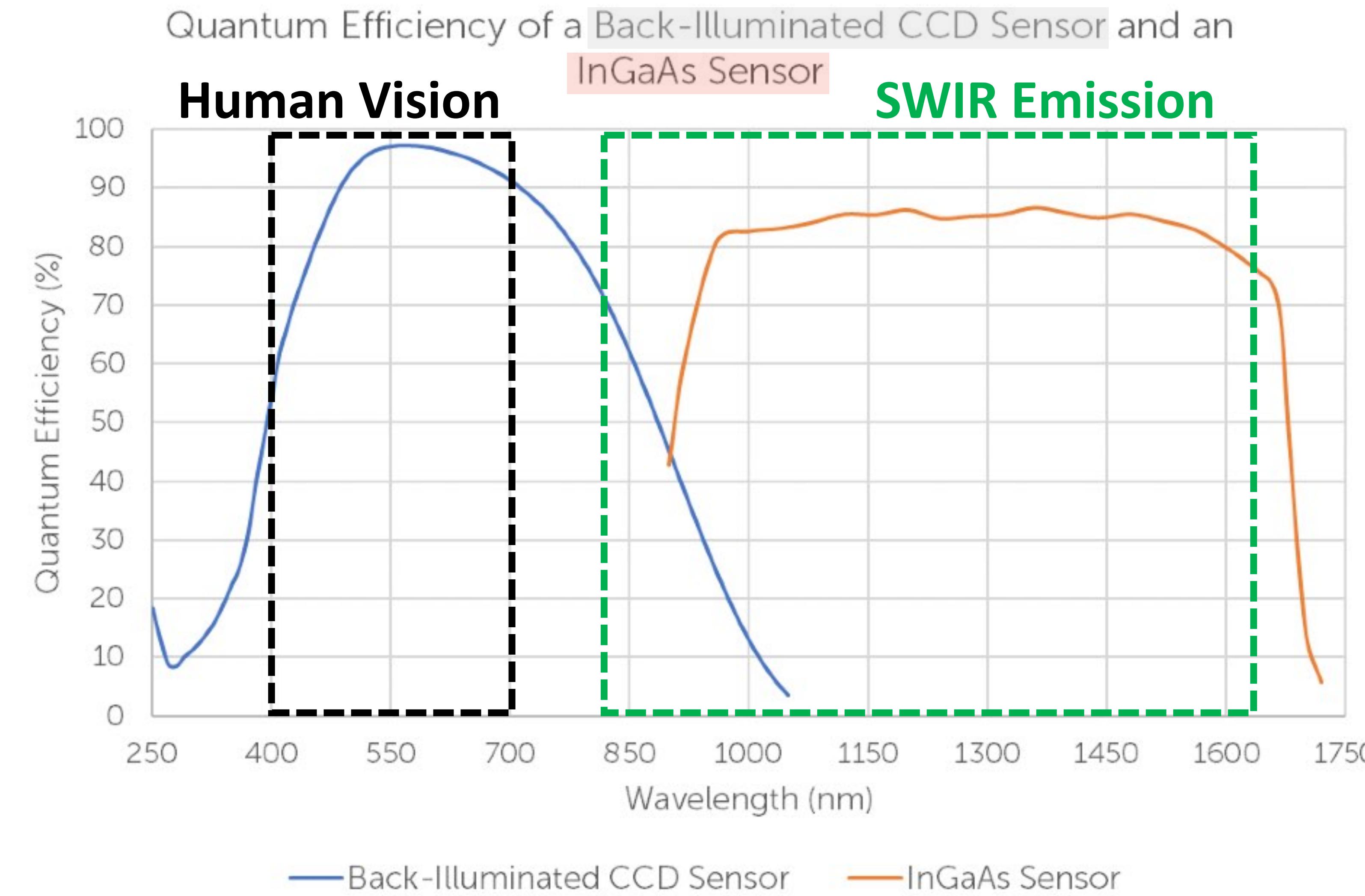


SWIR imaging

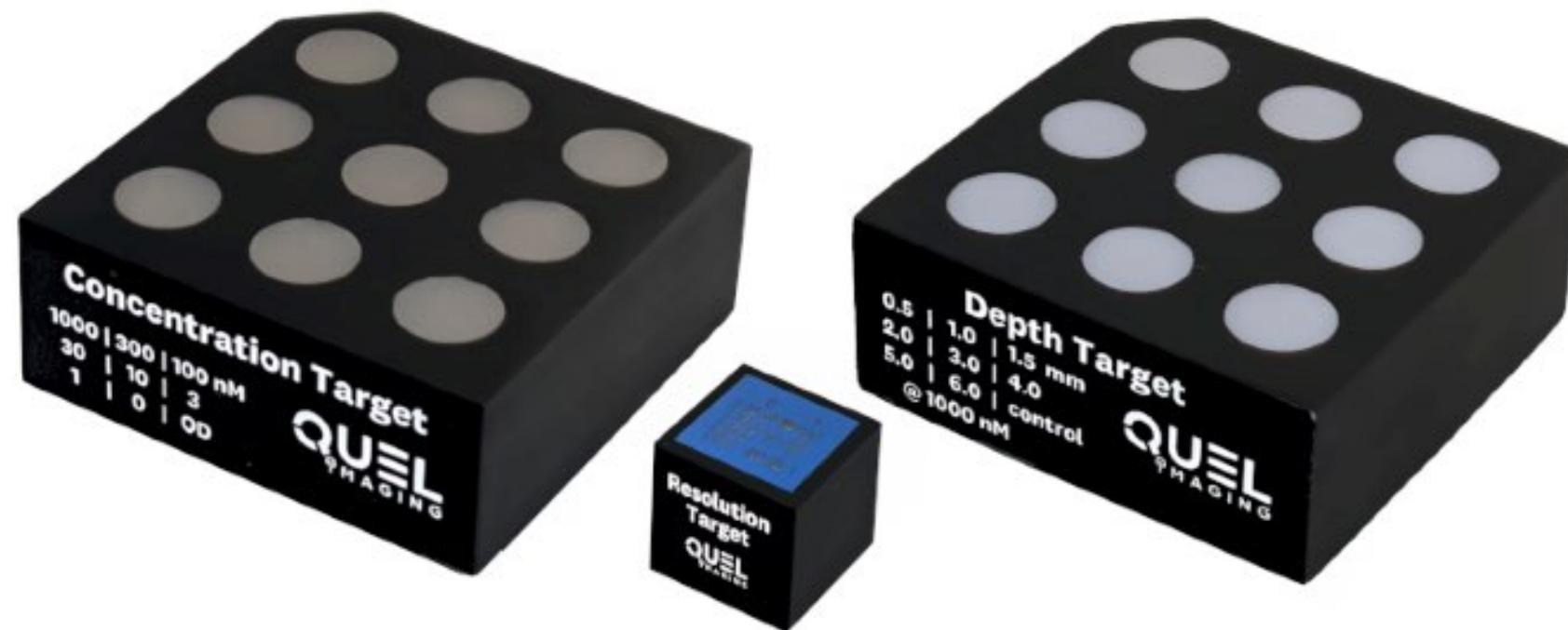
Short-wave infrared



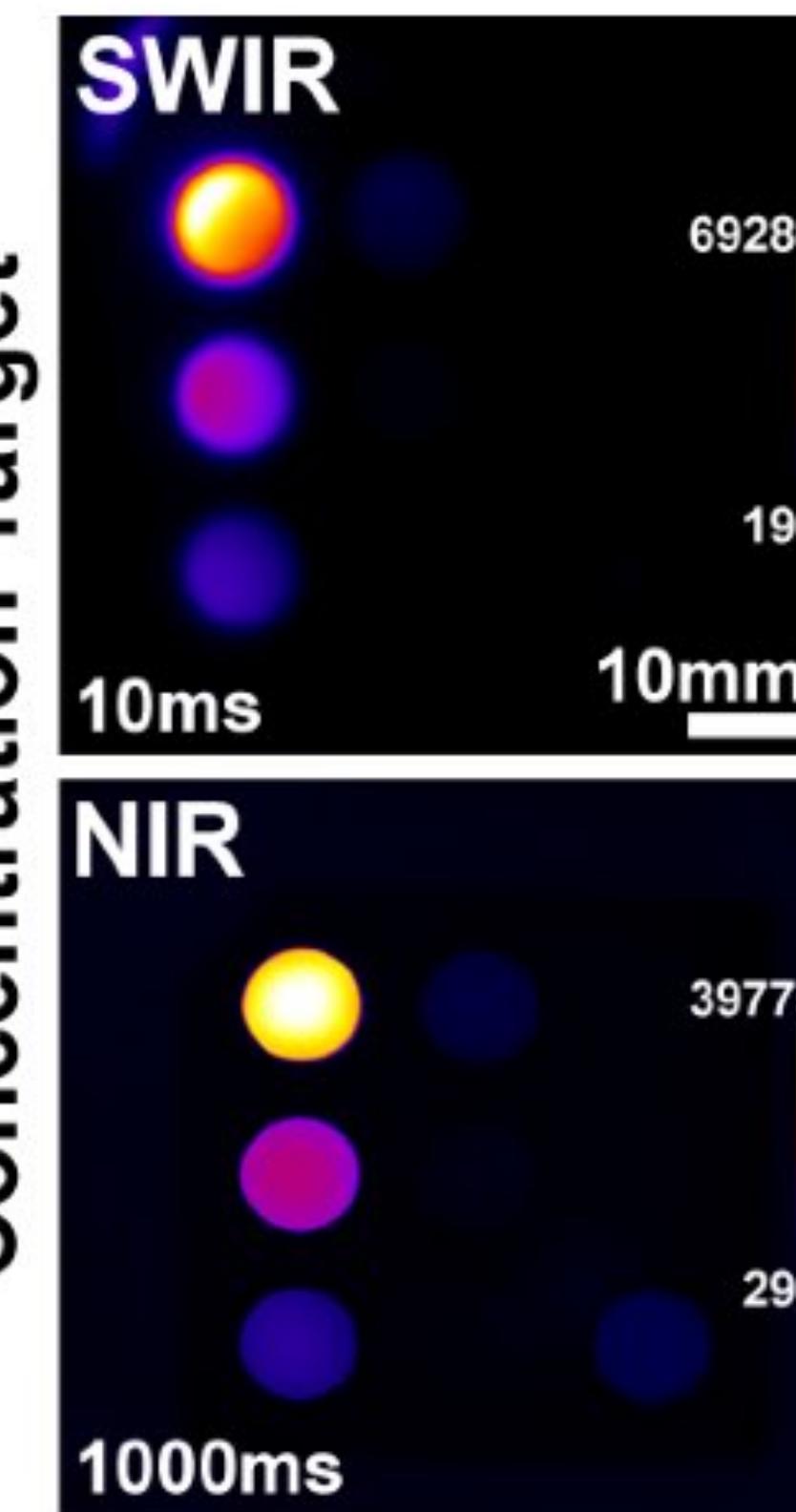
SWIR cameras



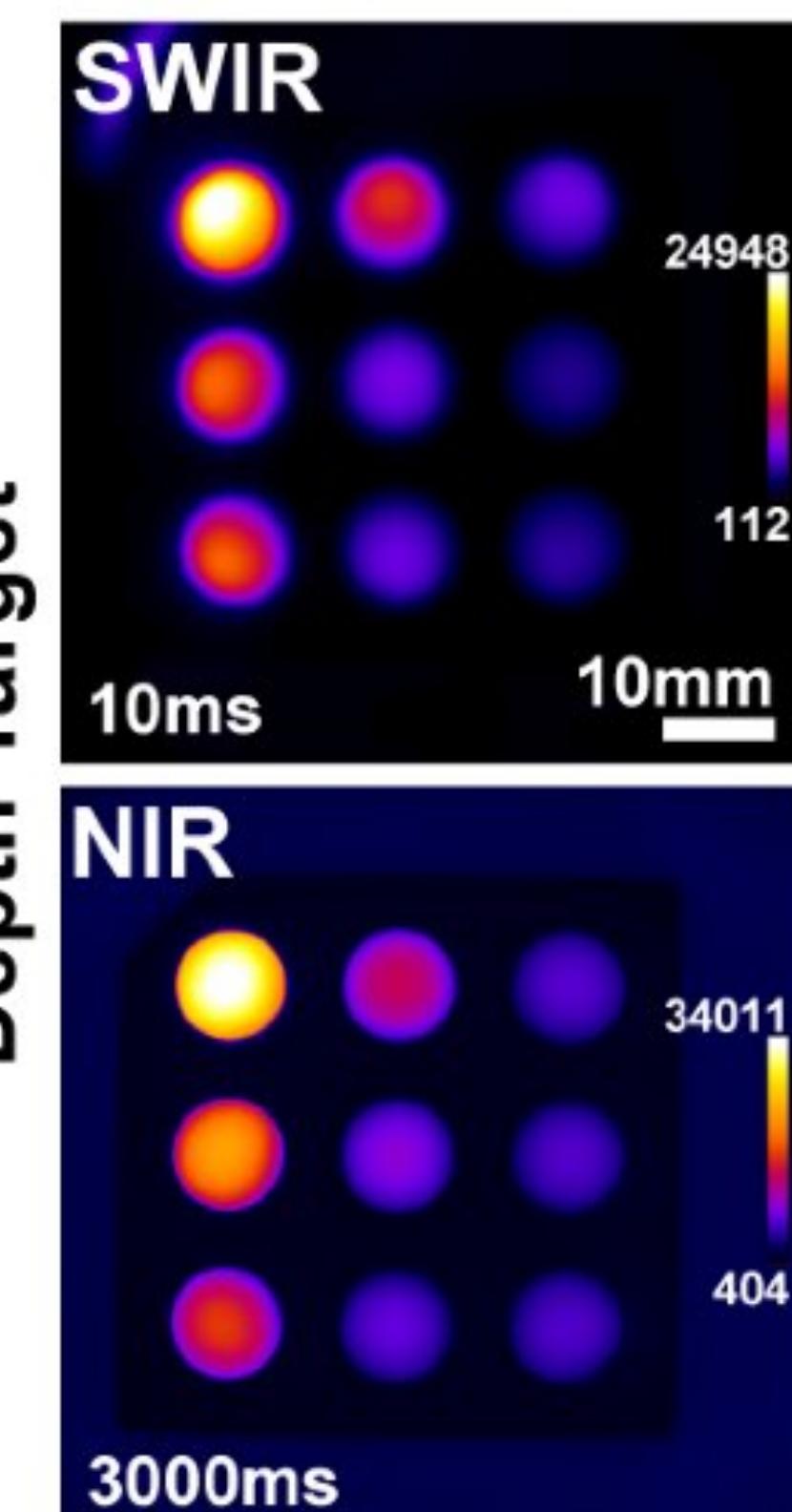
SWIR outperforms NIR



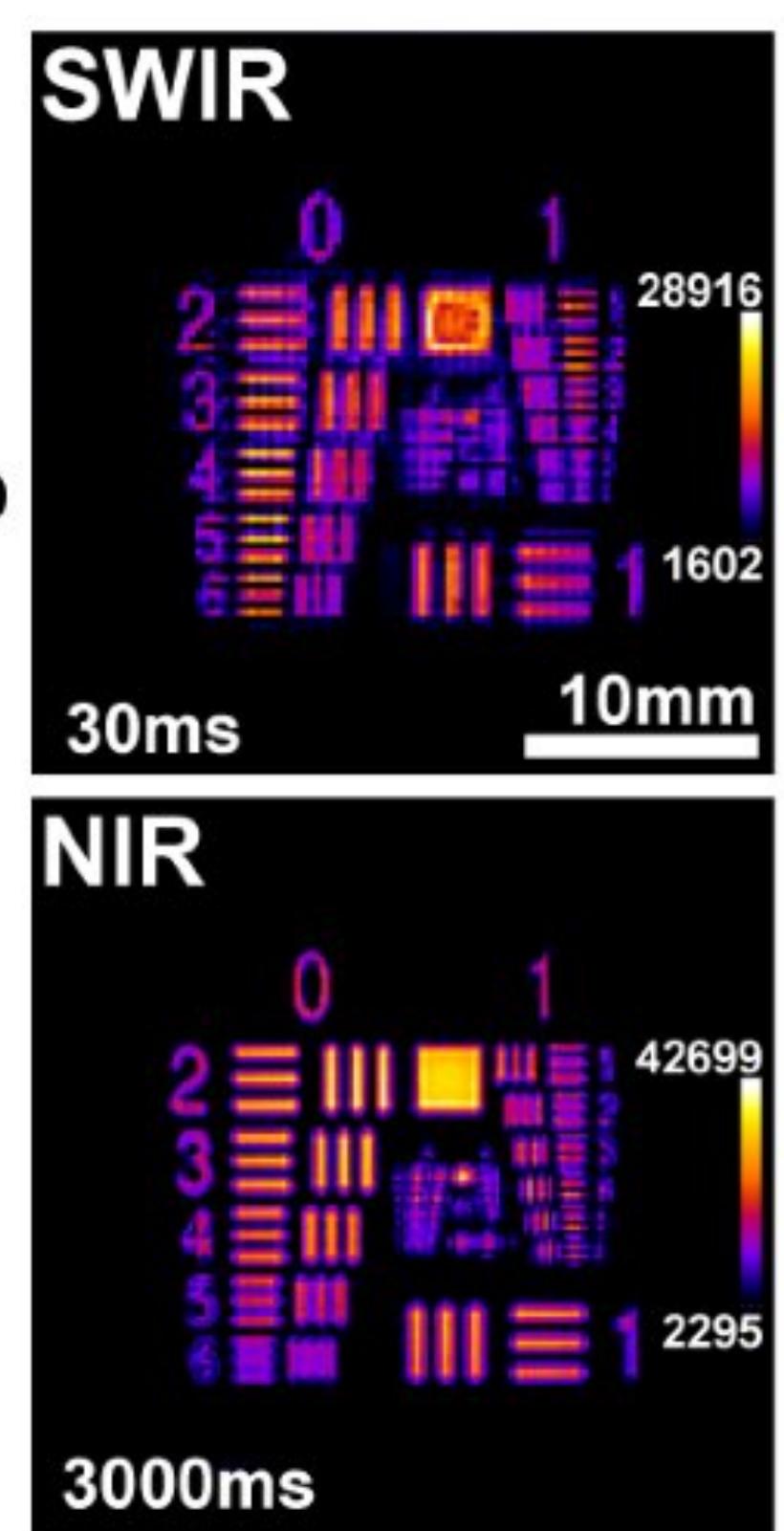
Concentration Target



Depth Target

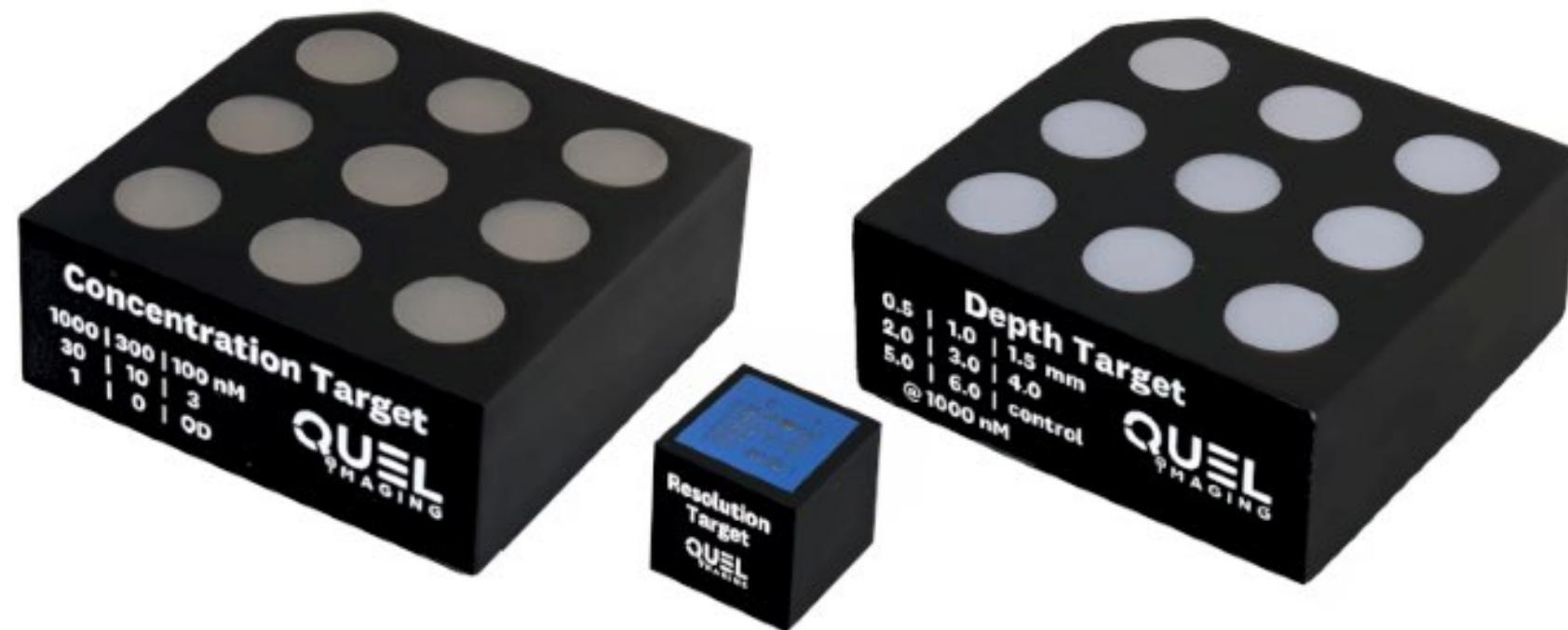


Resolution Target

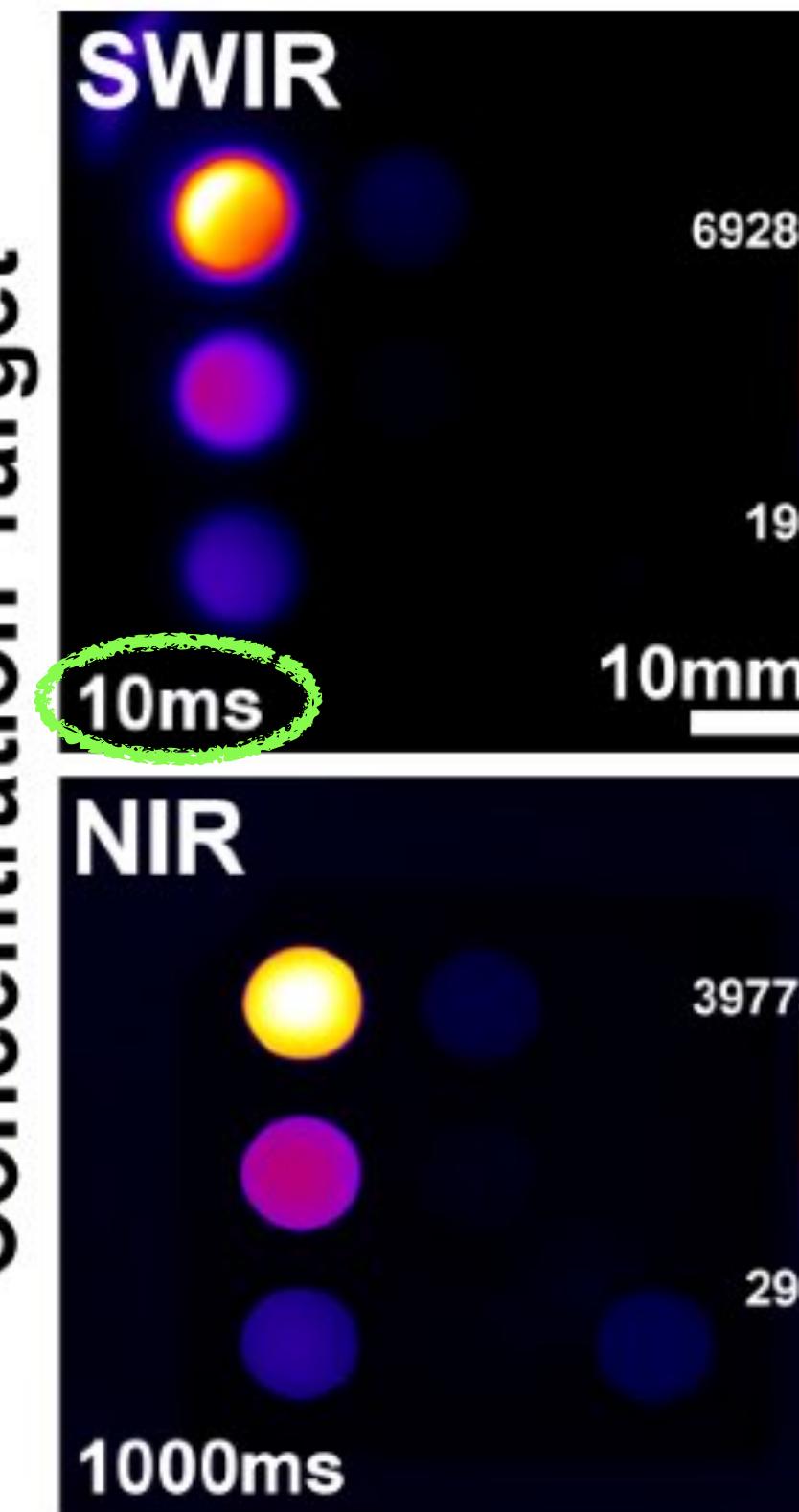


900-1700nm, 100-fold higher sensitivity

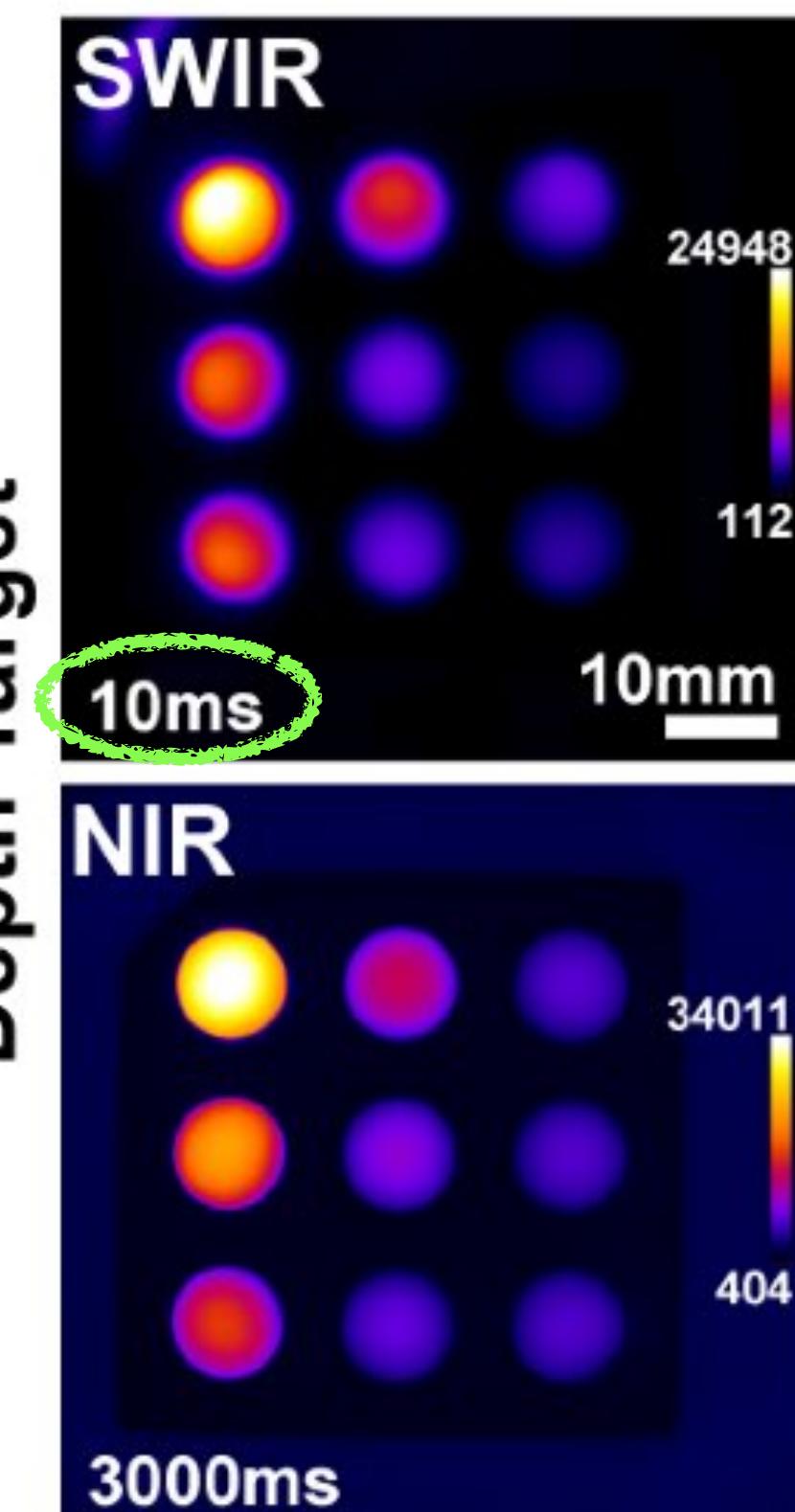
SWIR outperforms NIR



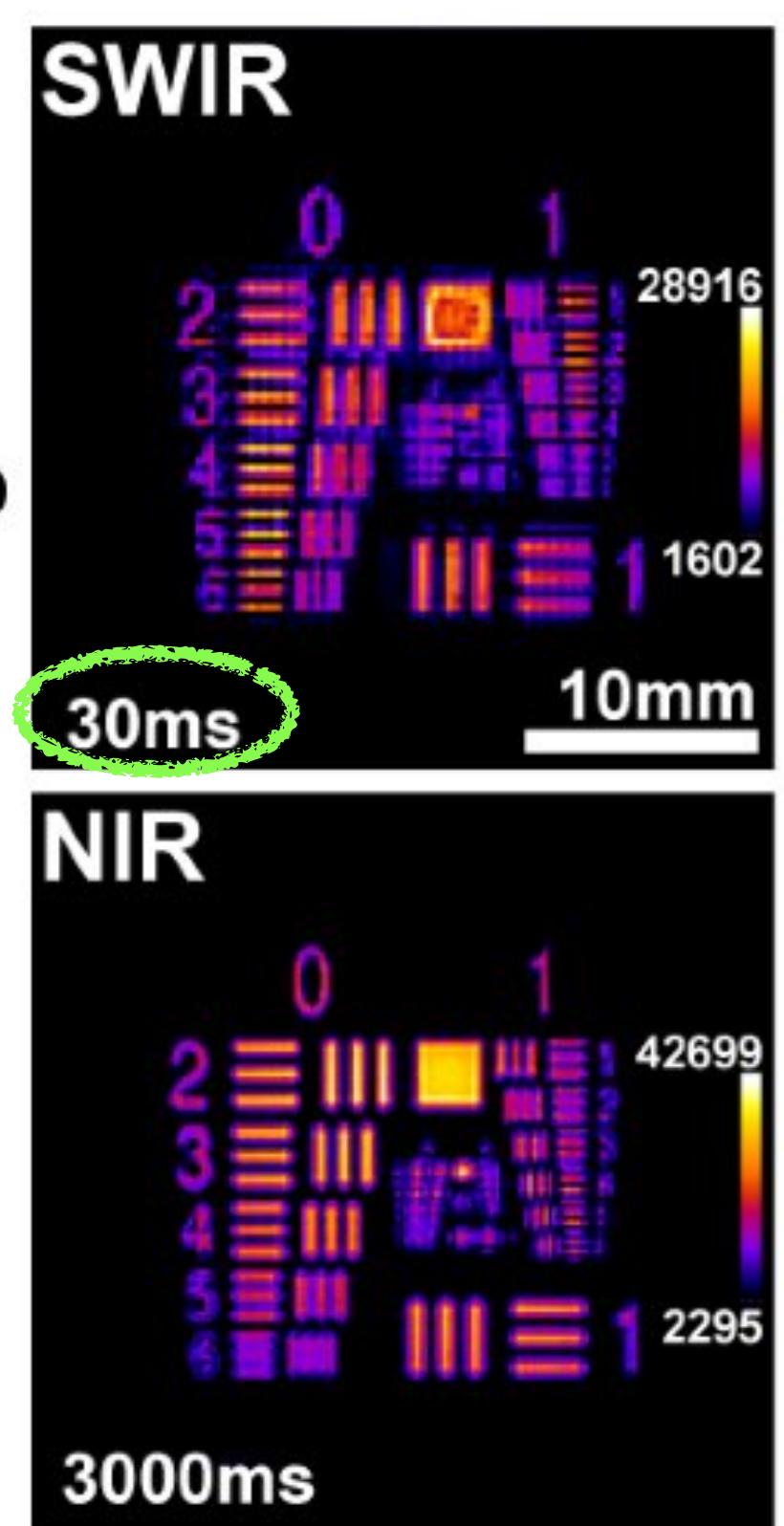
Concentration Target



Depth Target

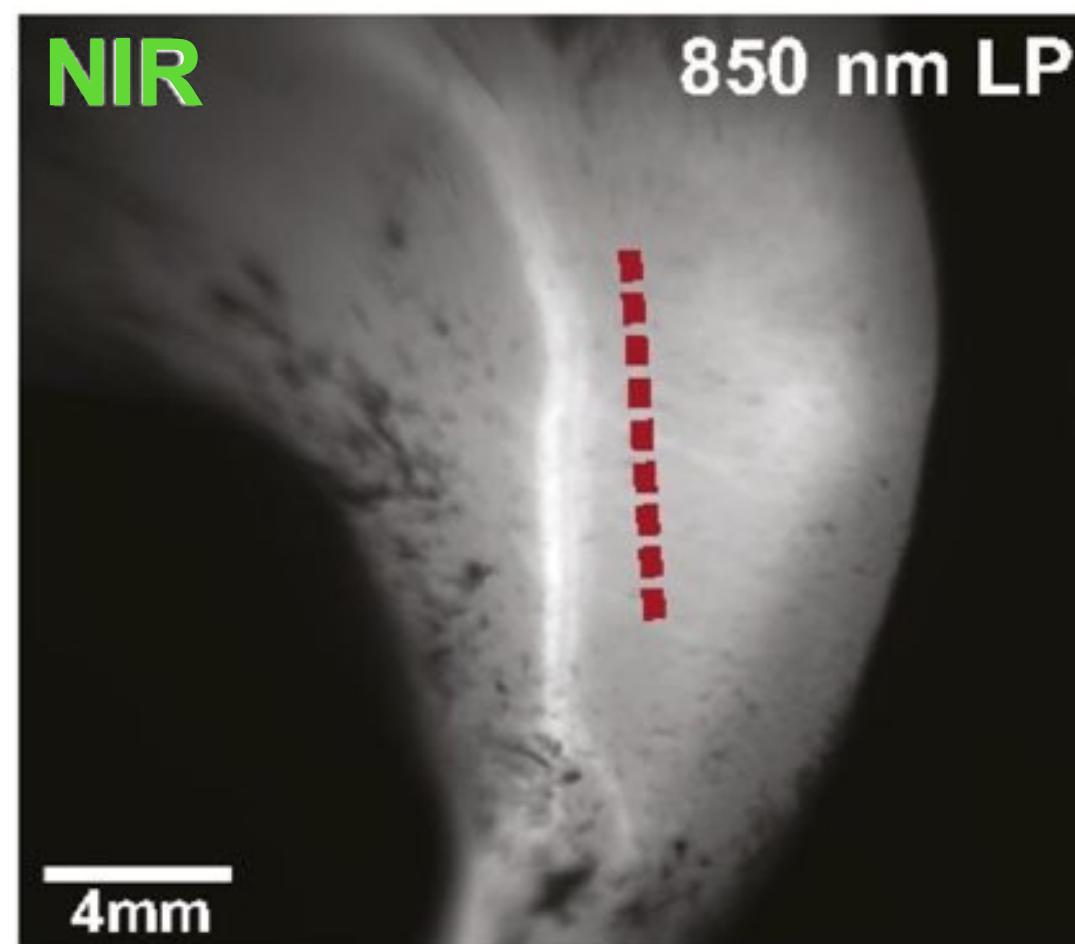
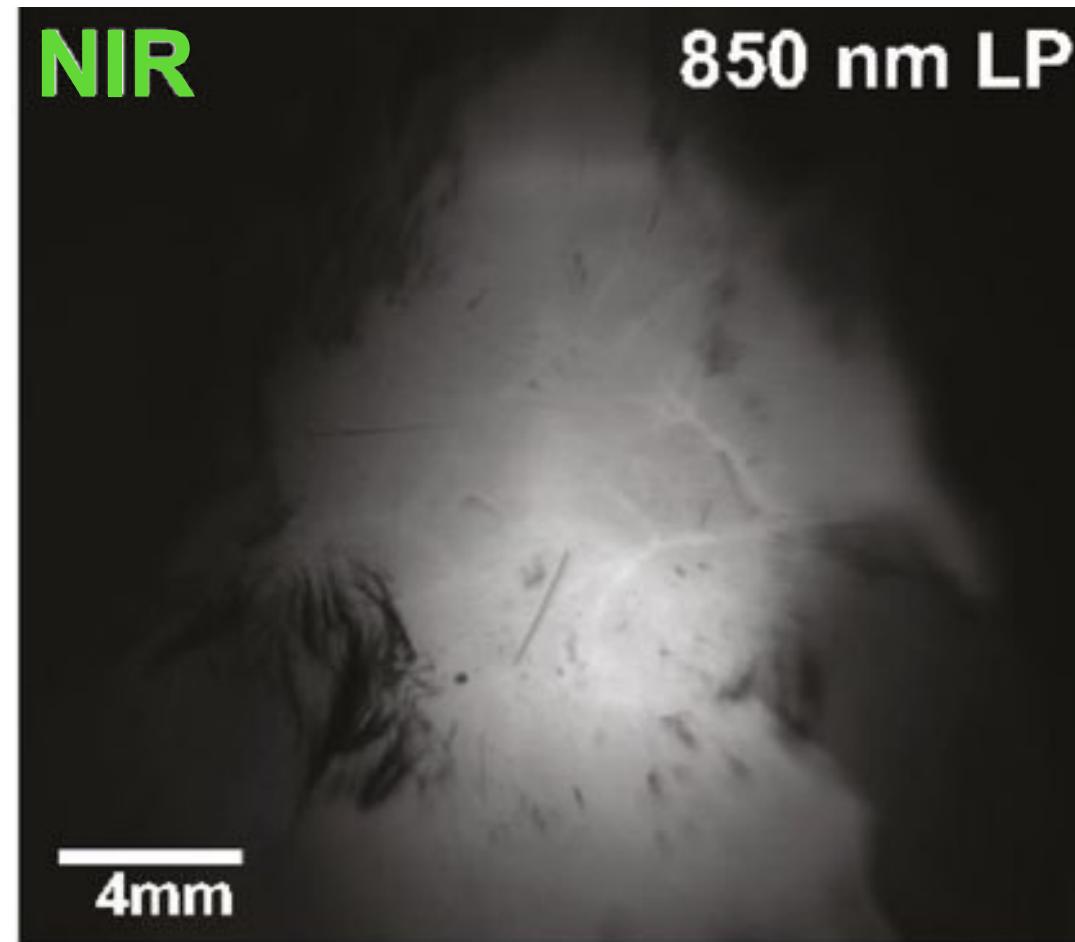


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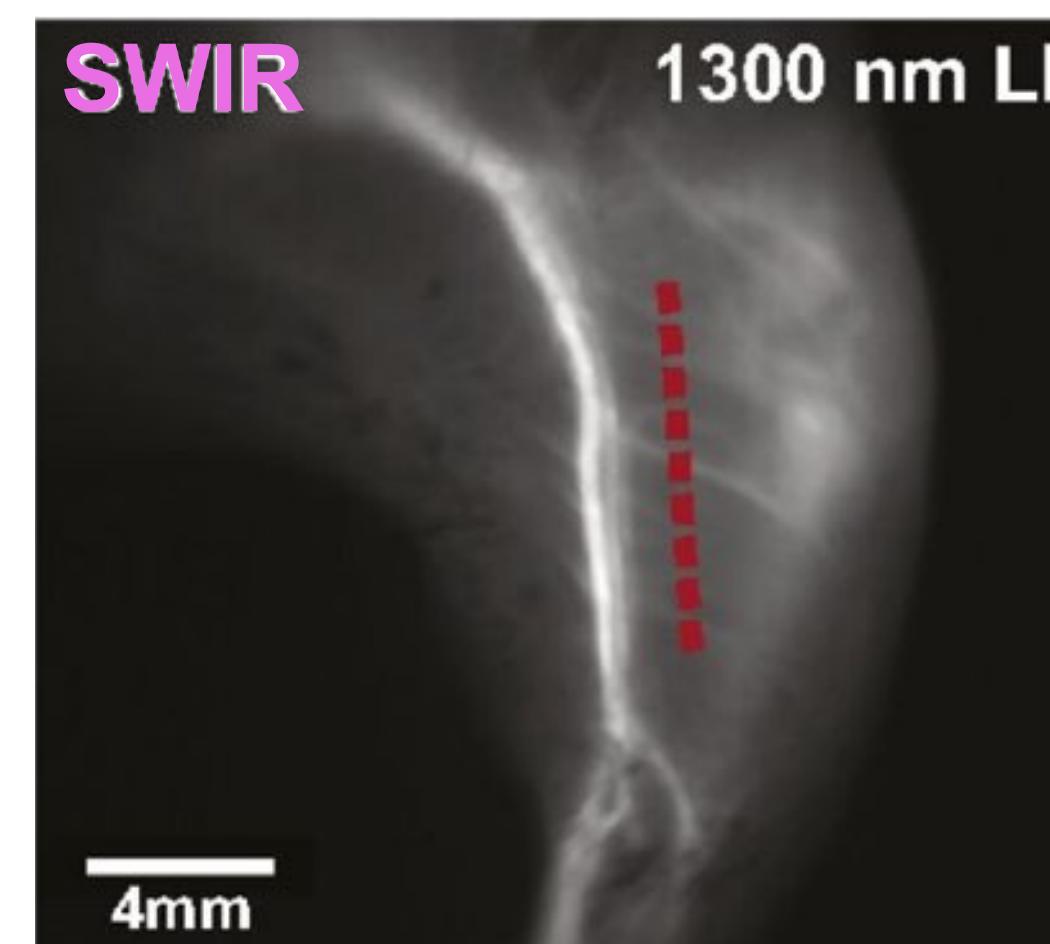
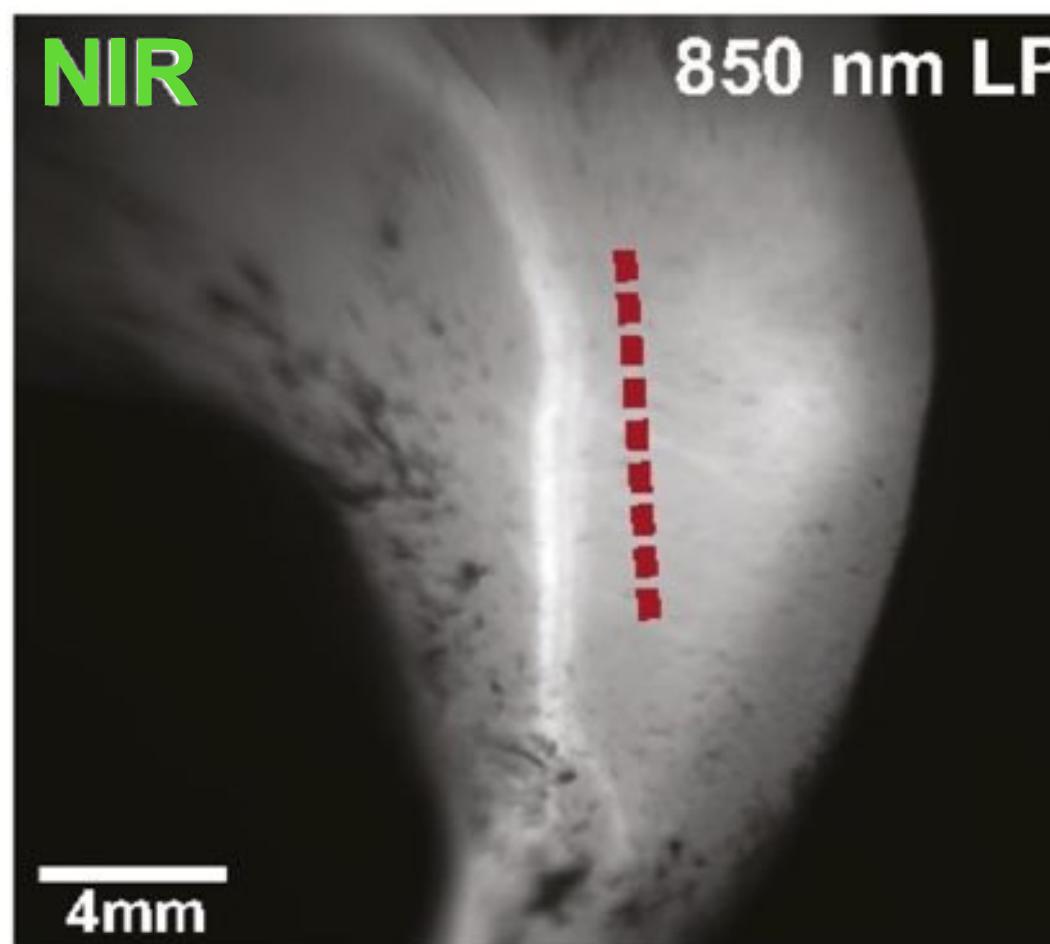
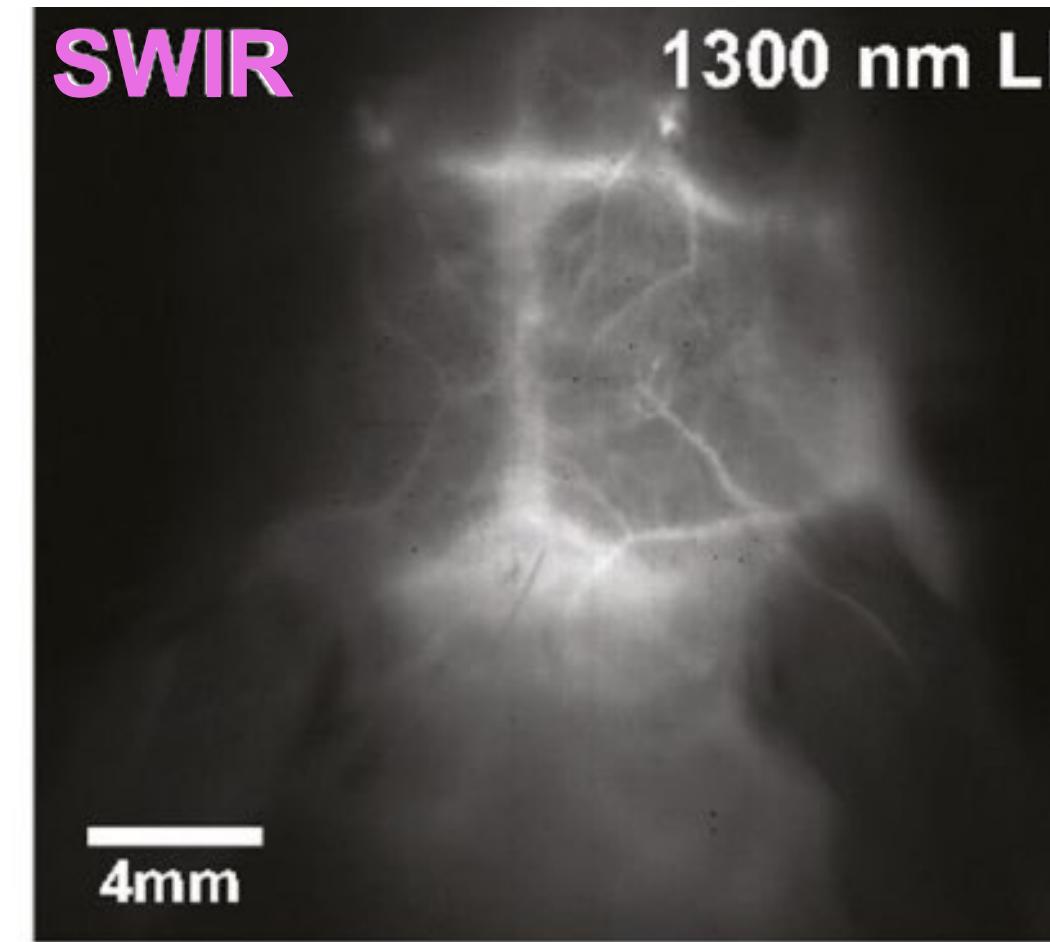
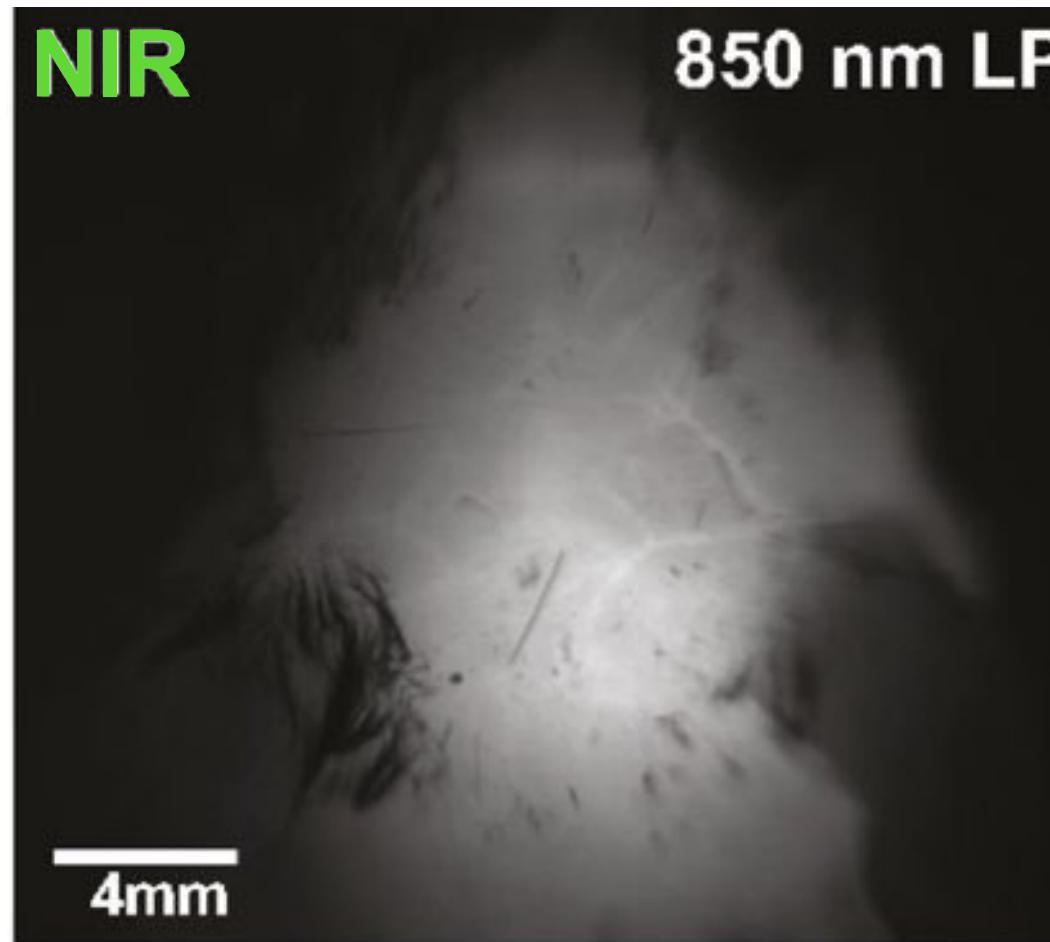


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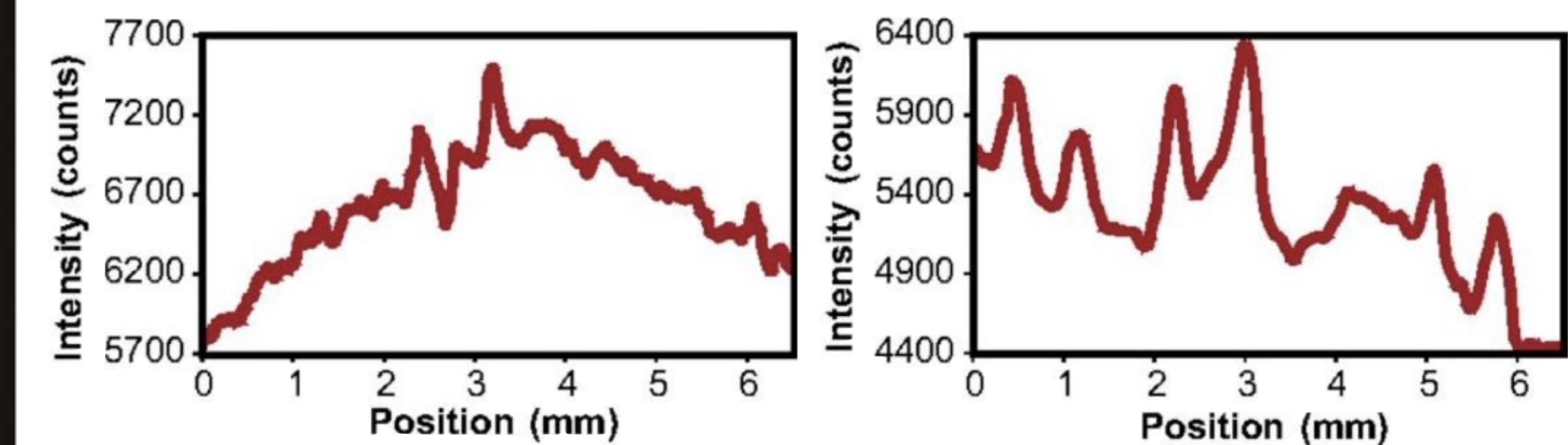
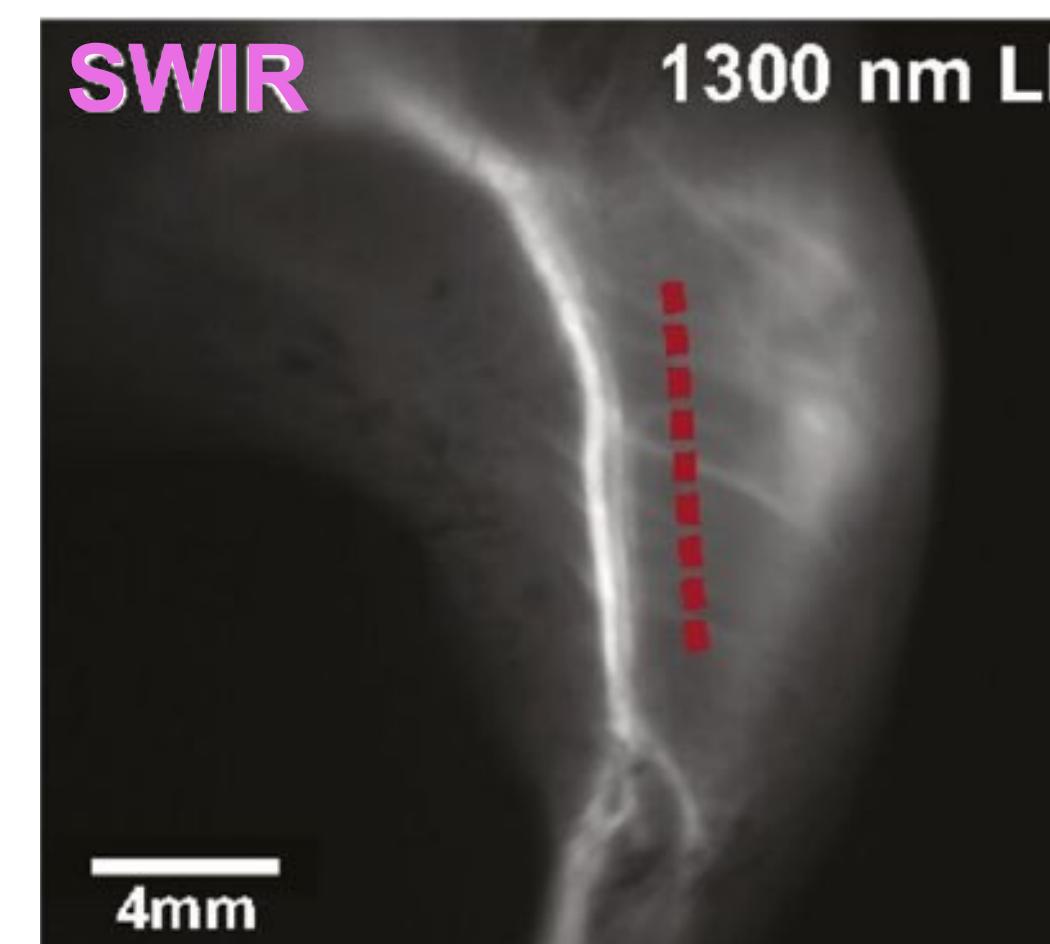
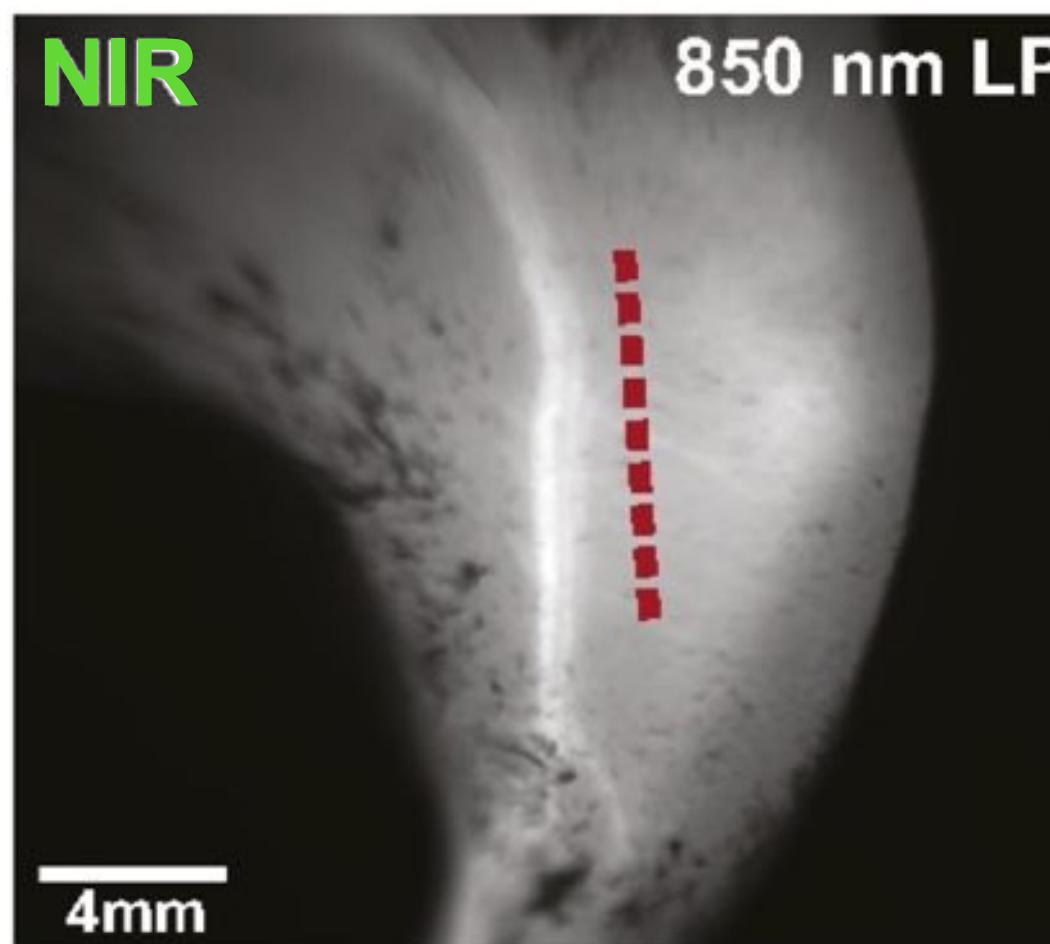
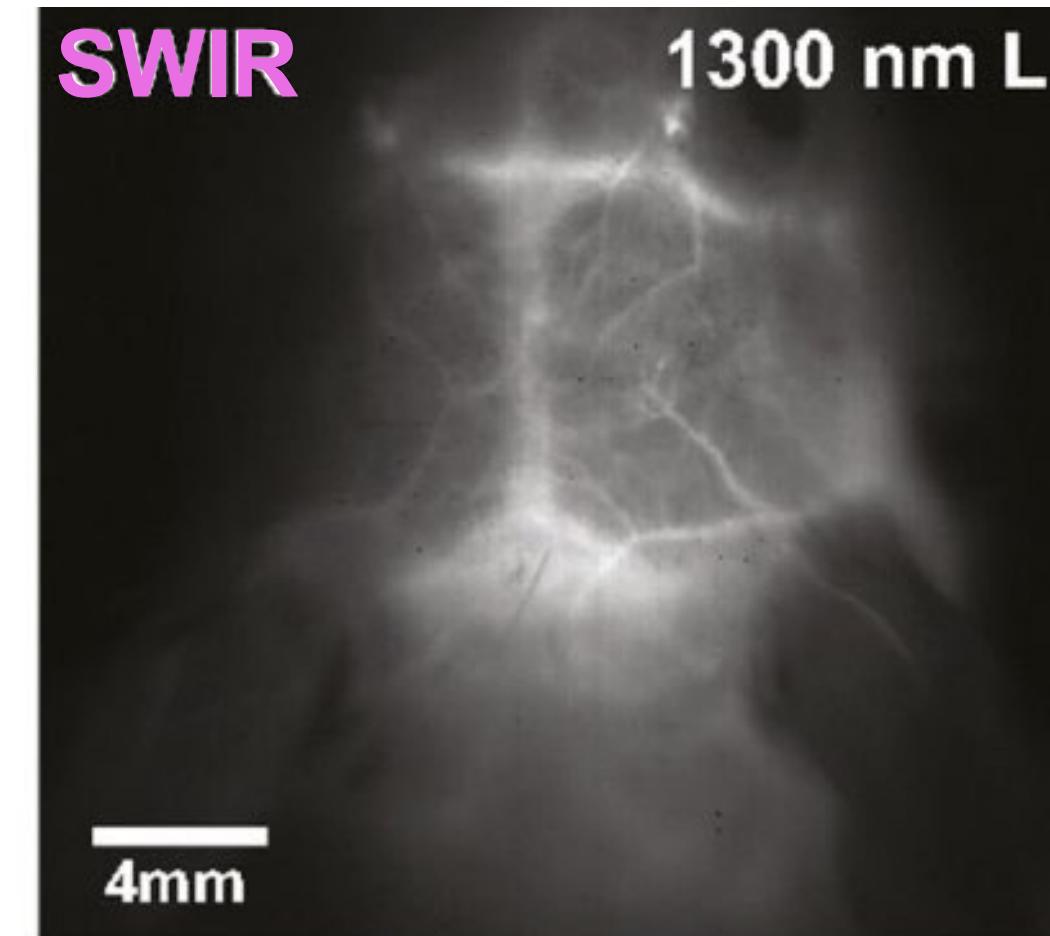
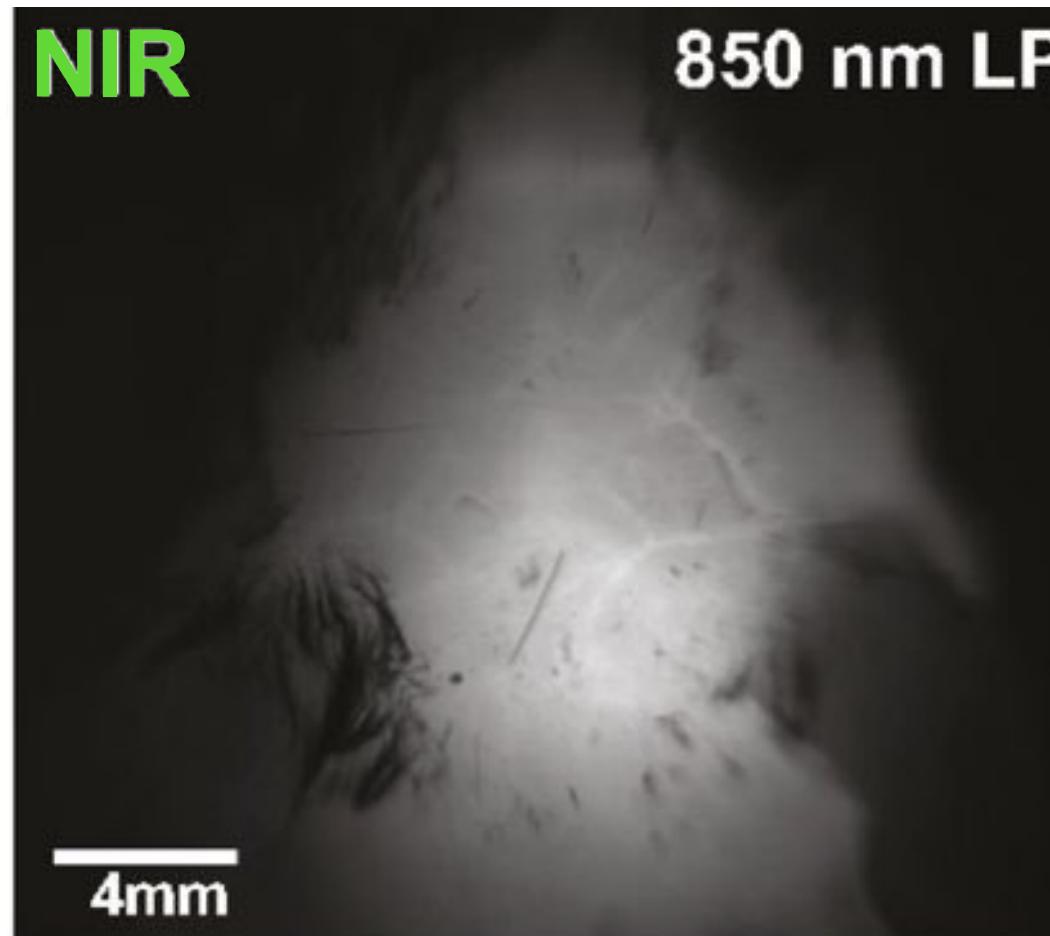
SWIR outperforms NIR (and VIS)



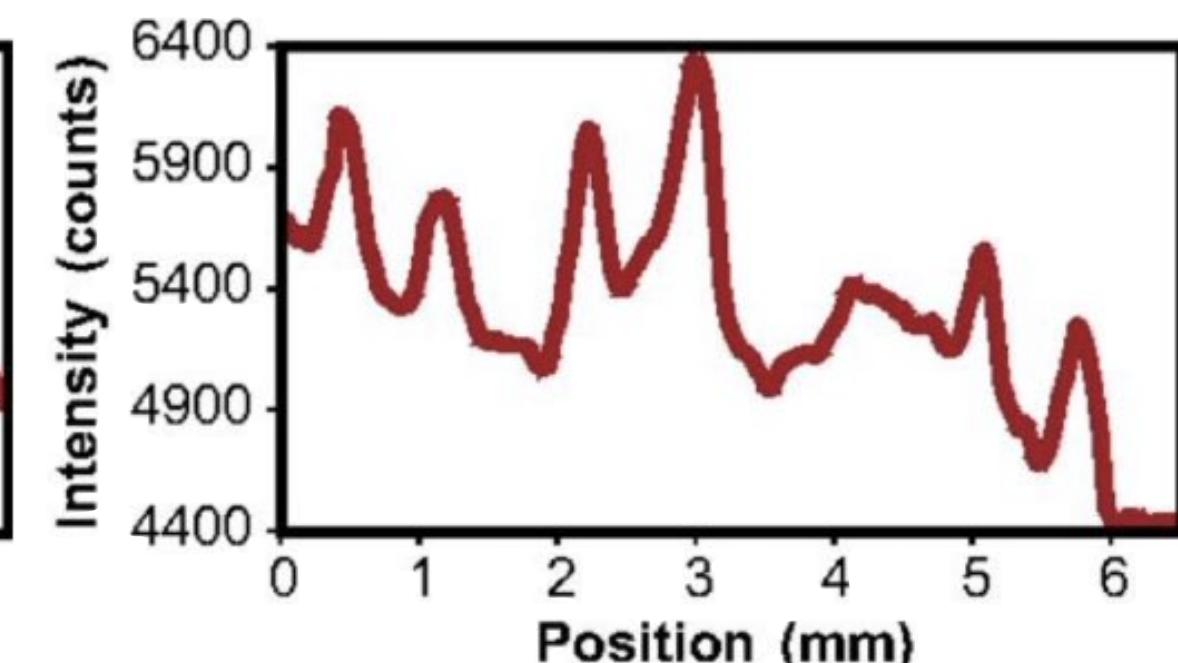
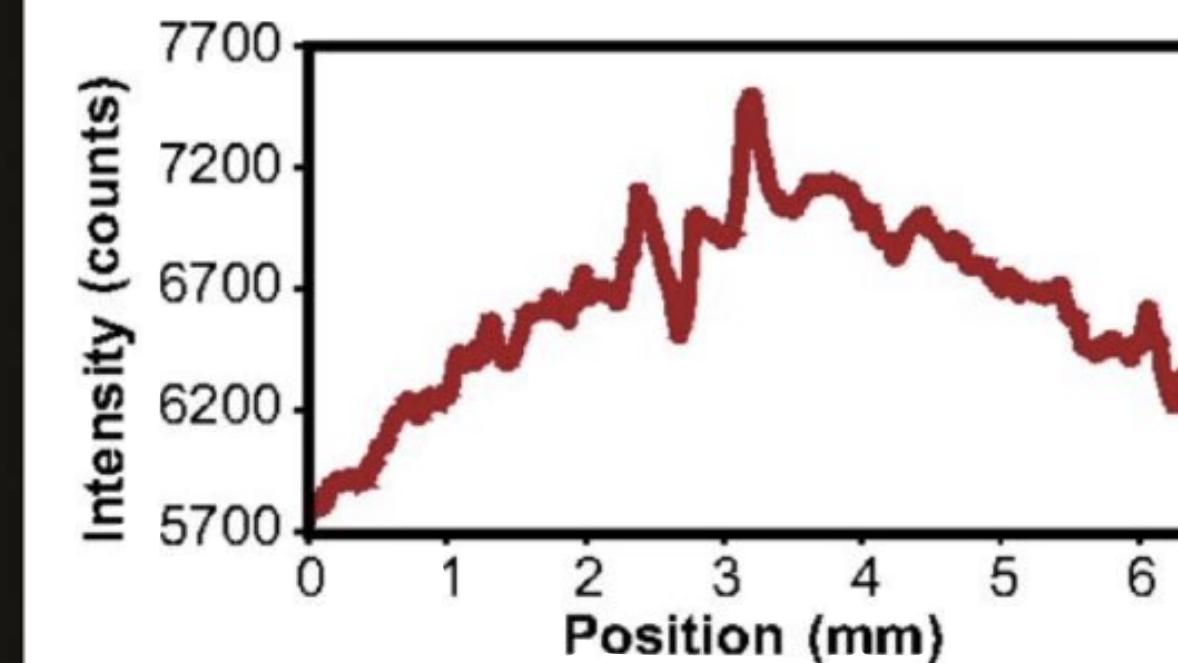
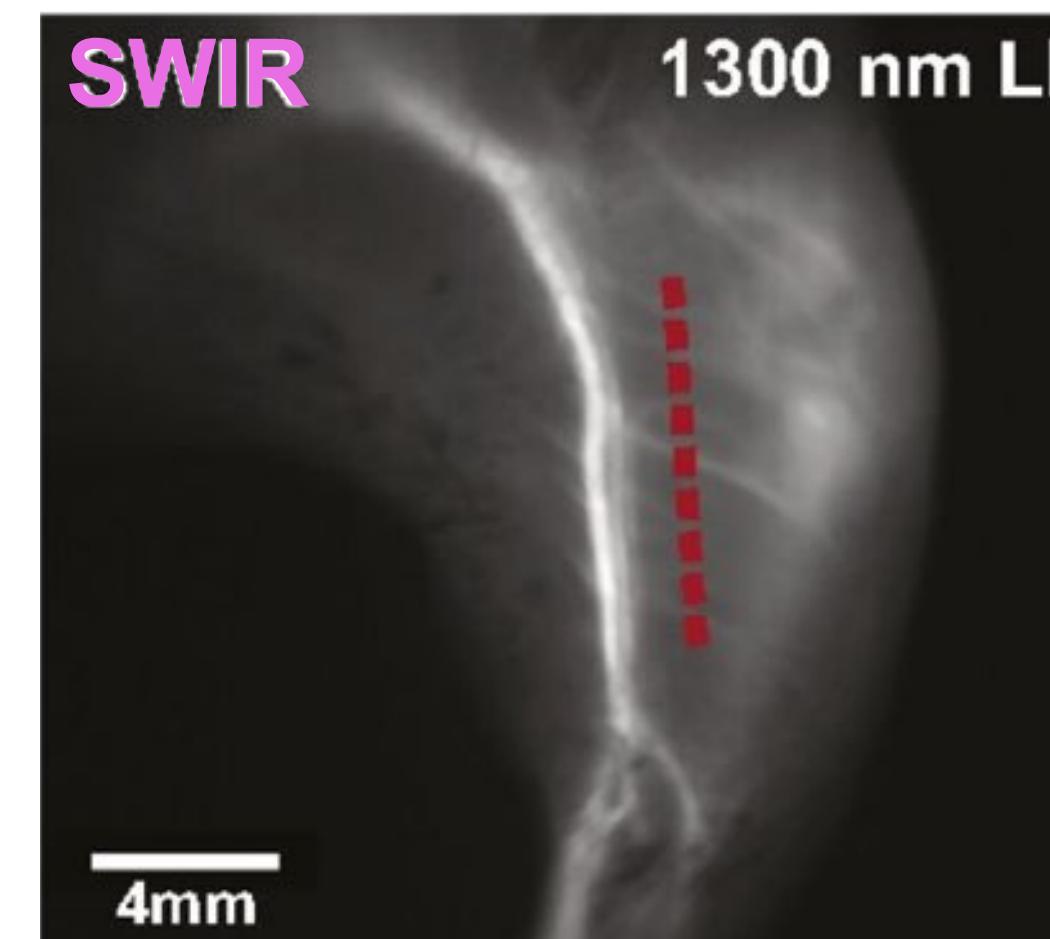
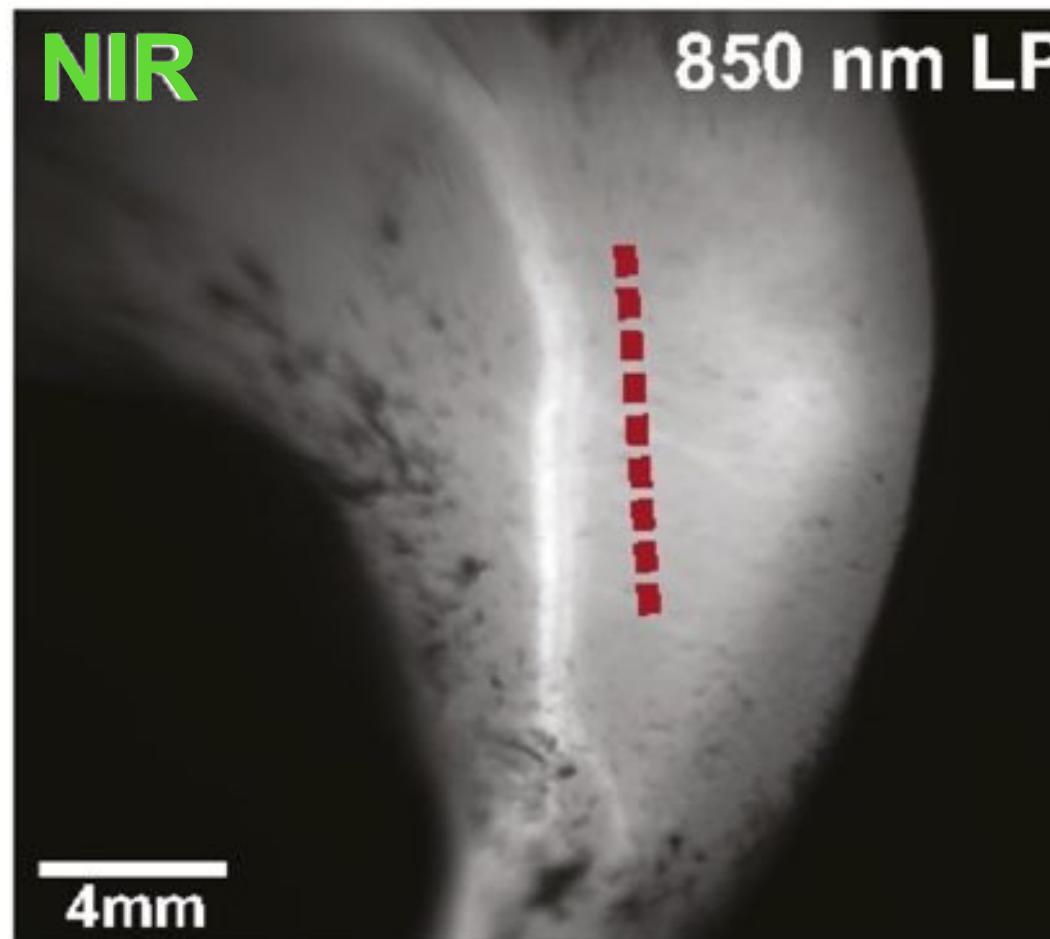
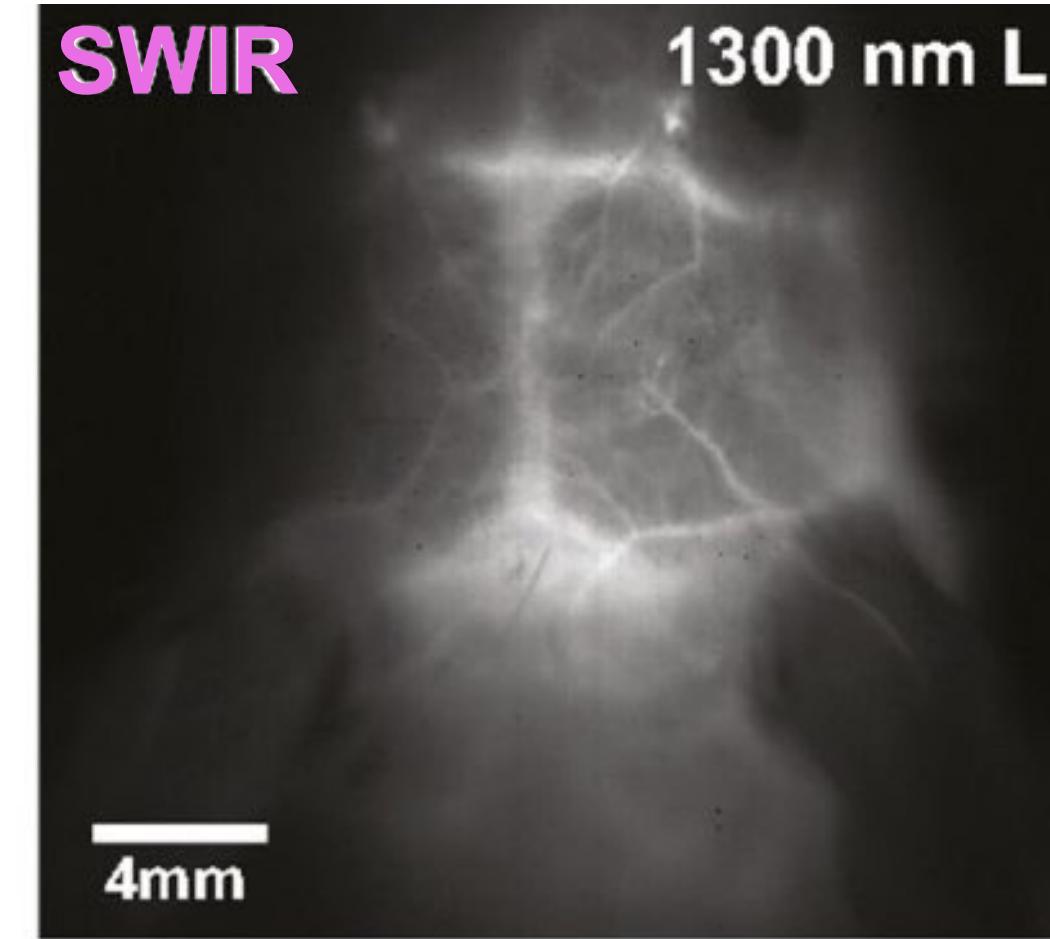
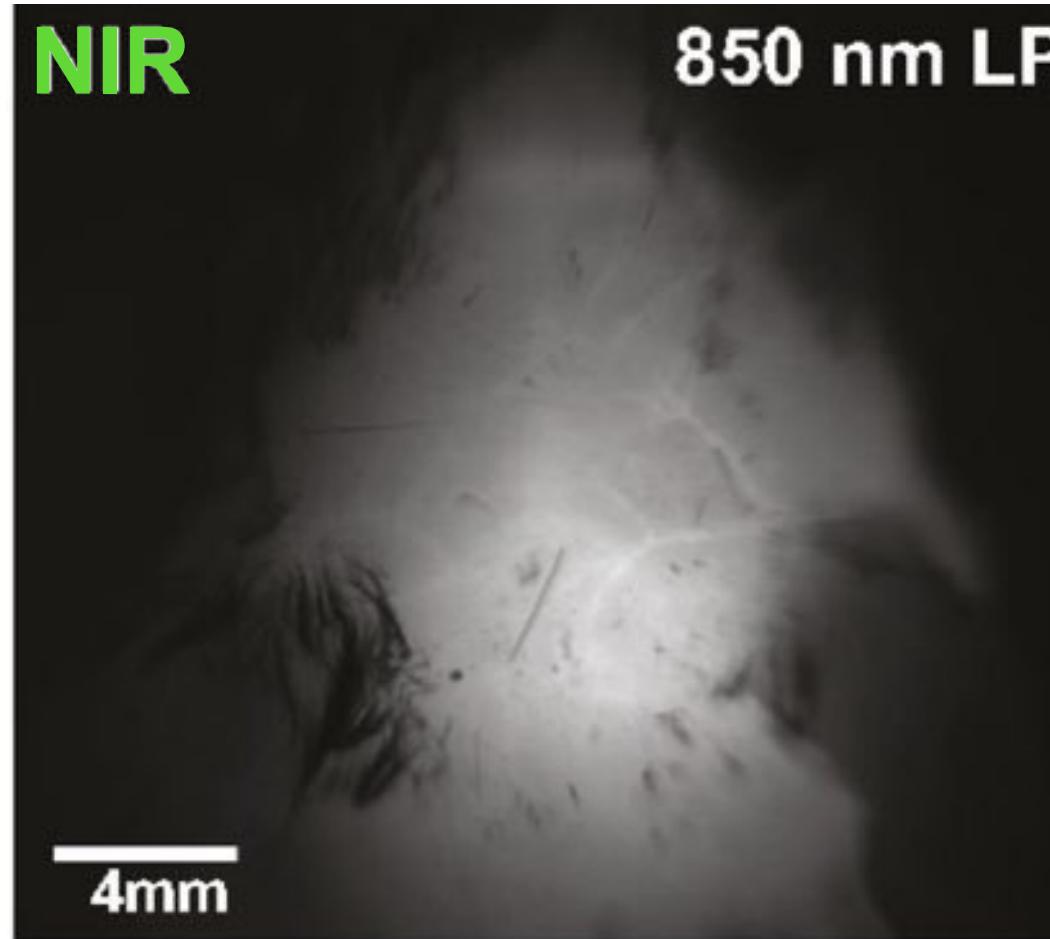
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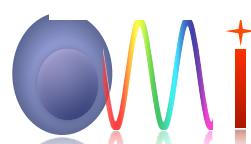
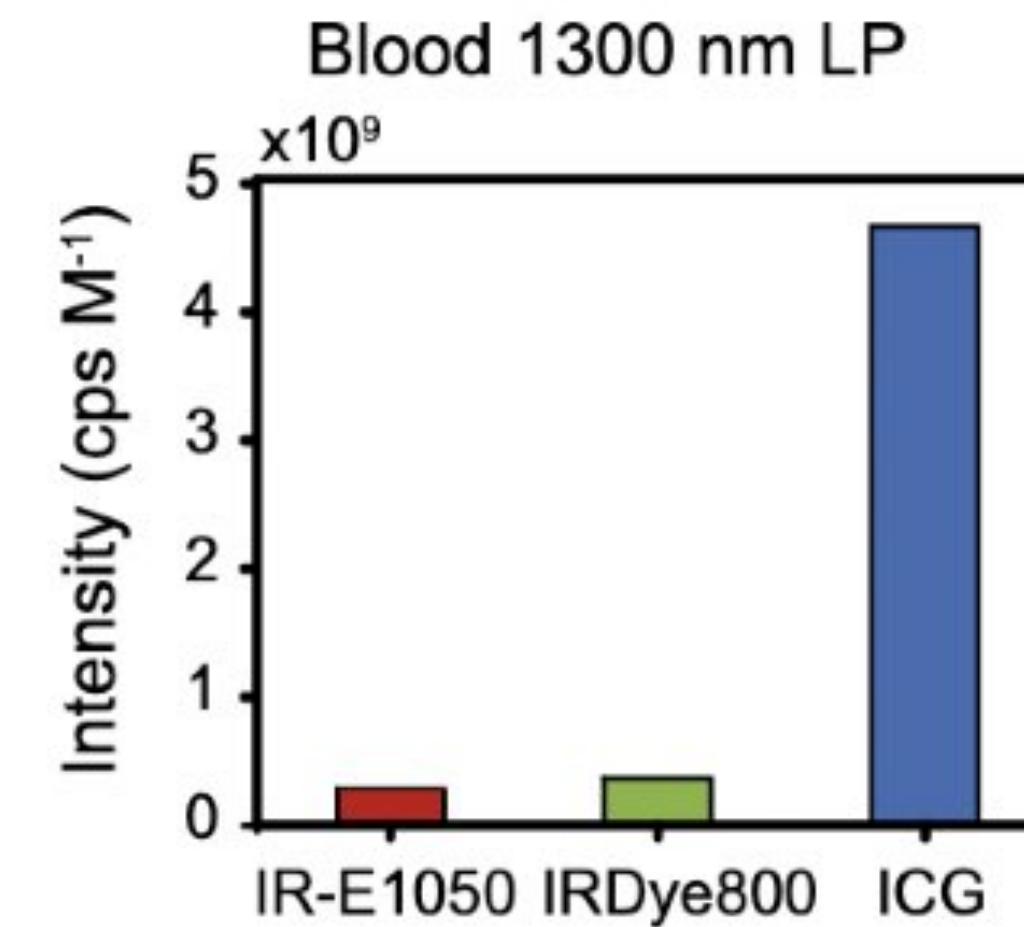
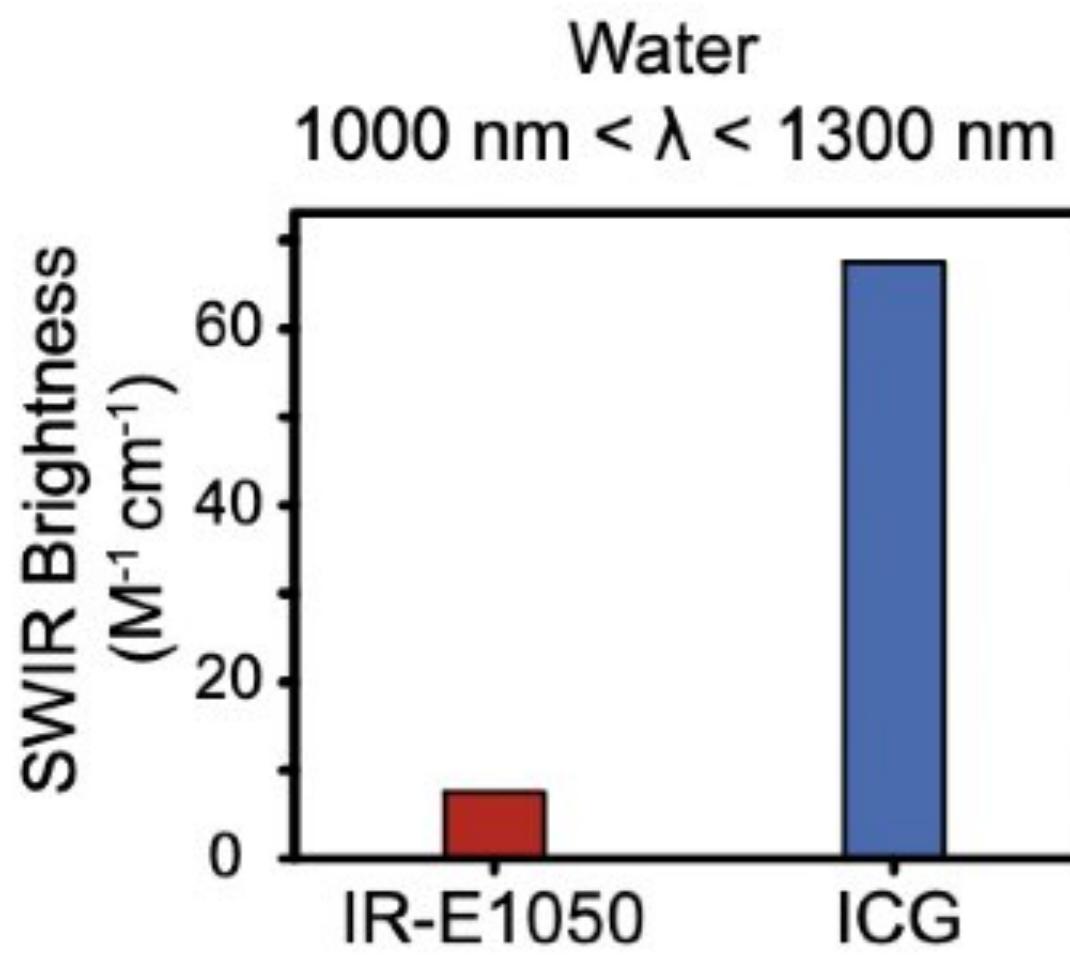
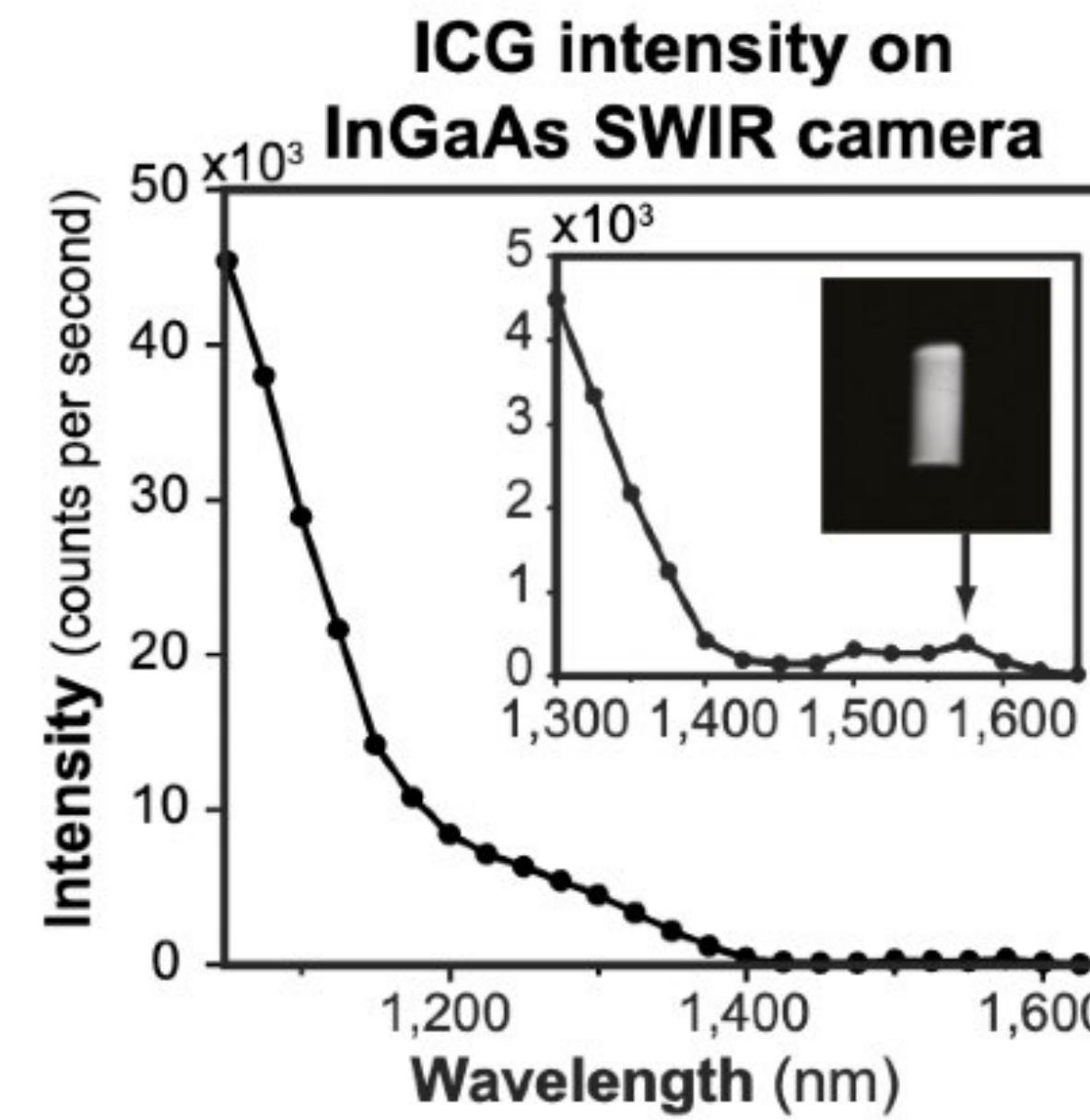
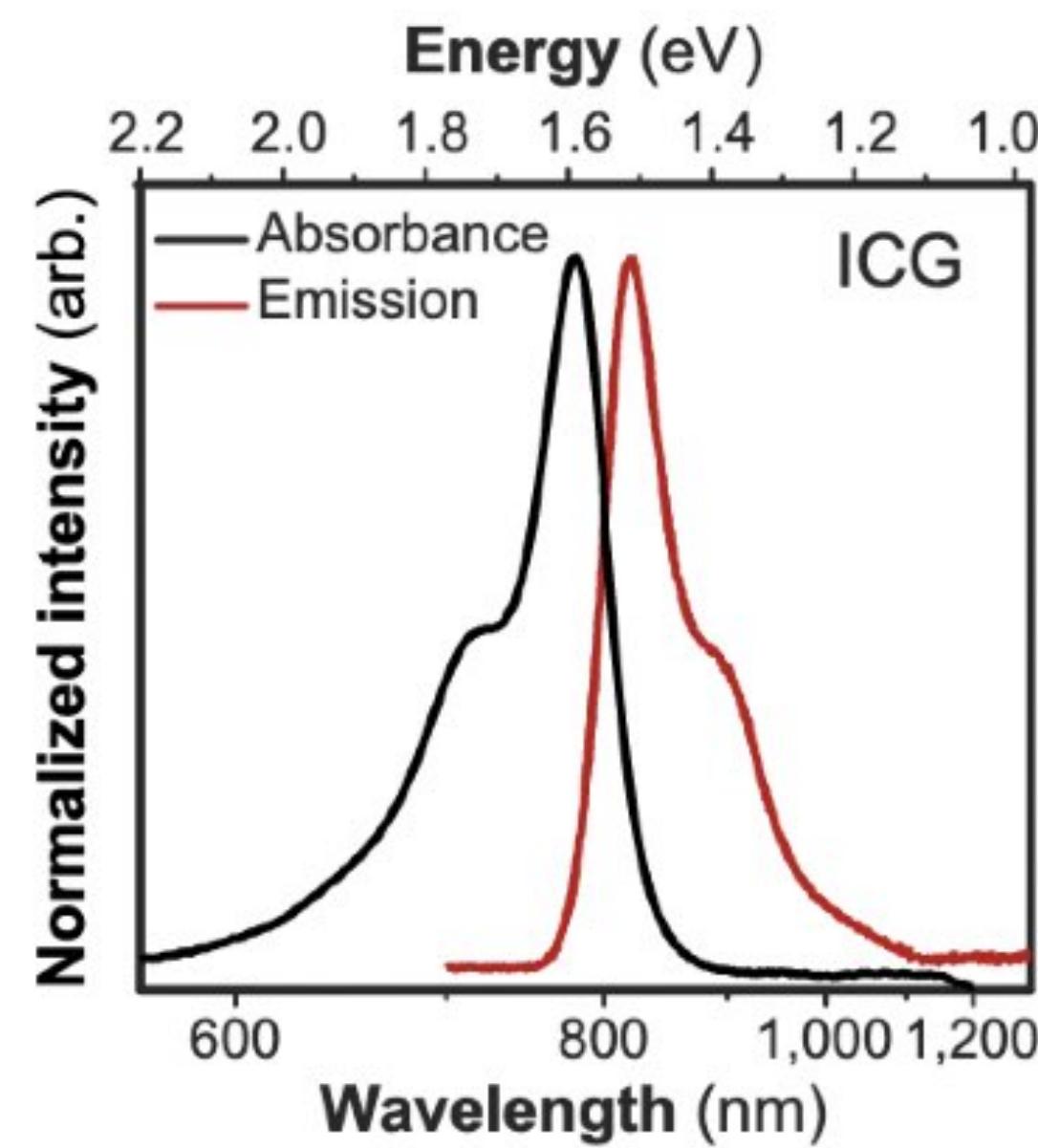
SWIR outperforms NIR (and VIS)



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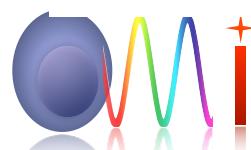
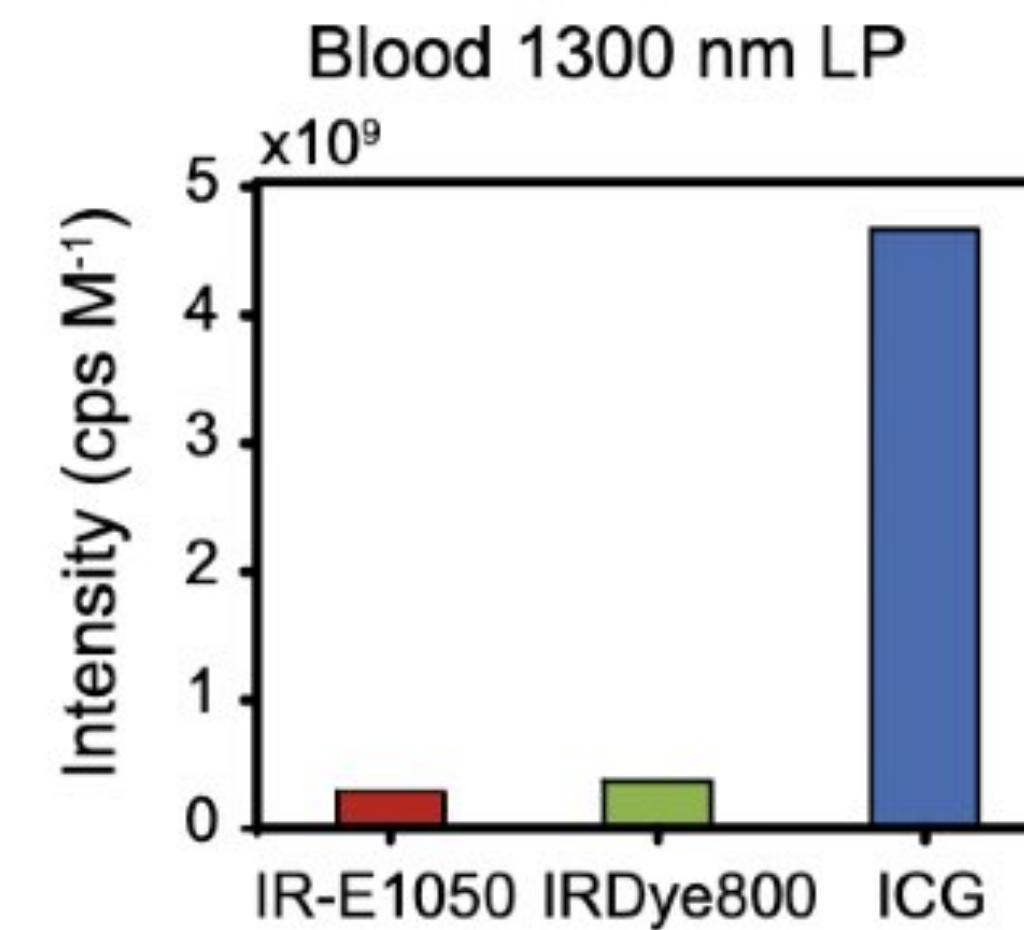
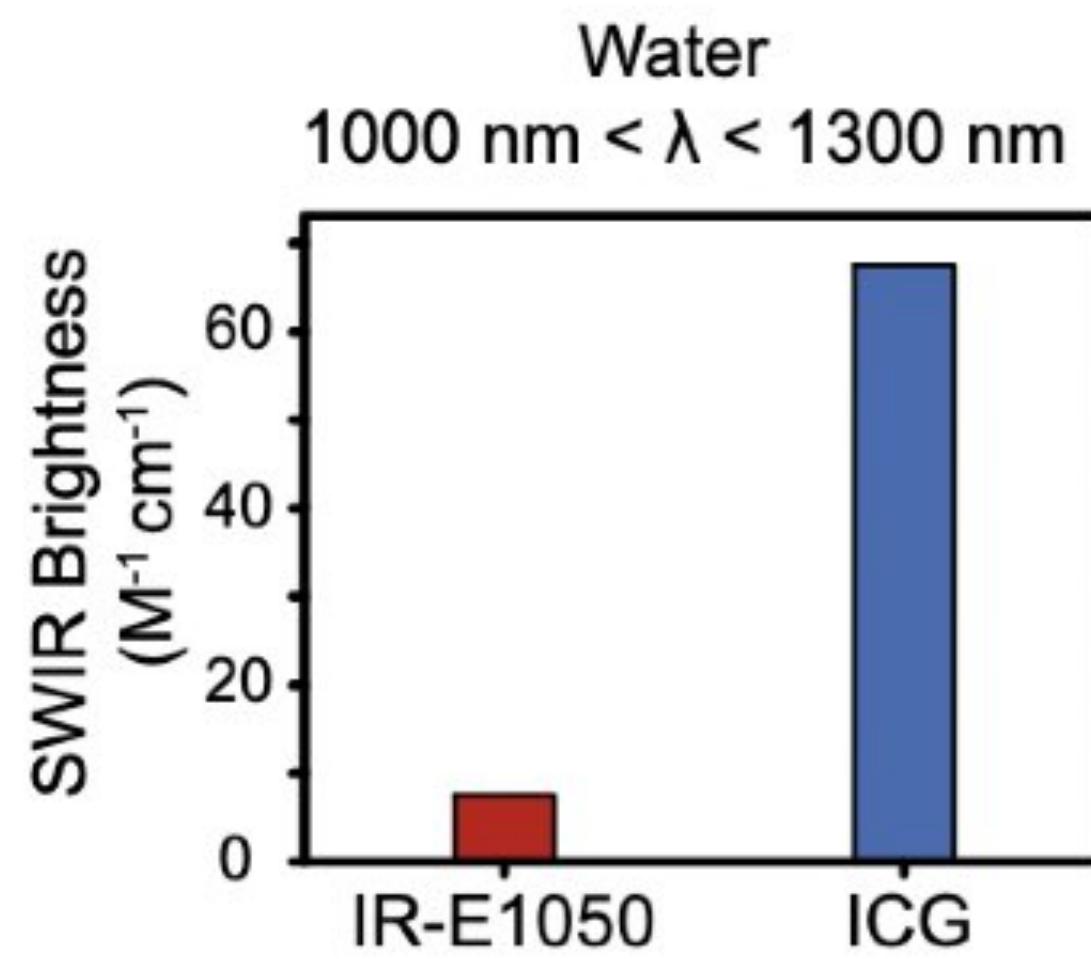
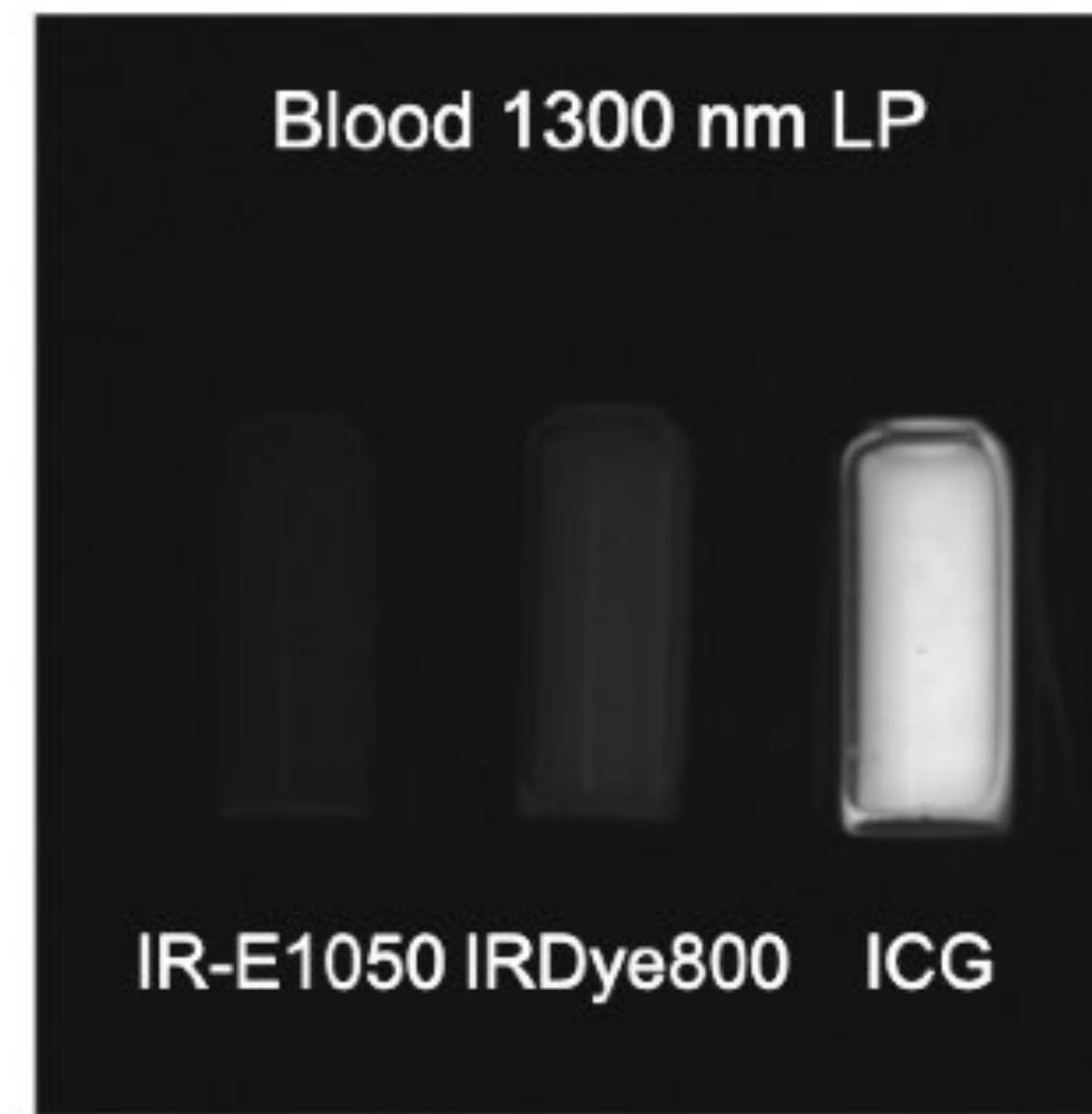
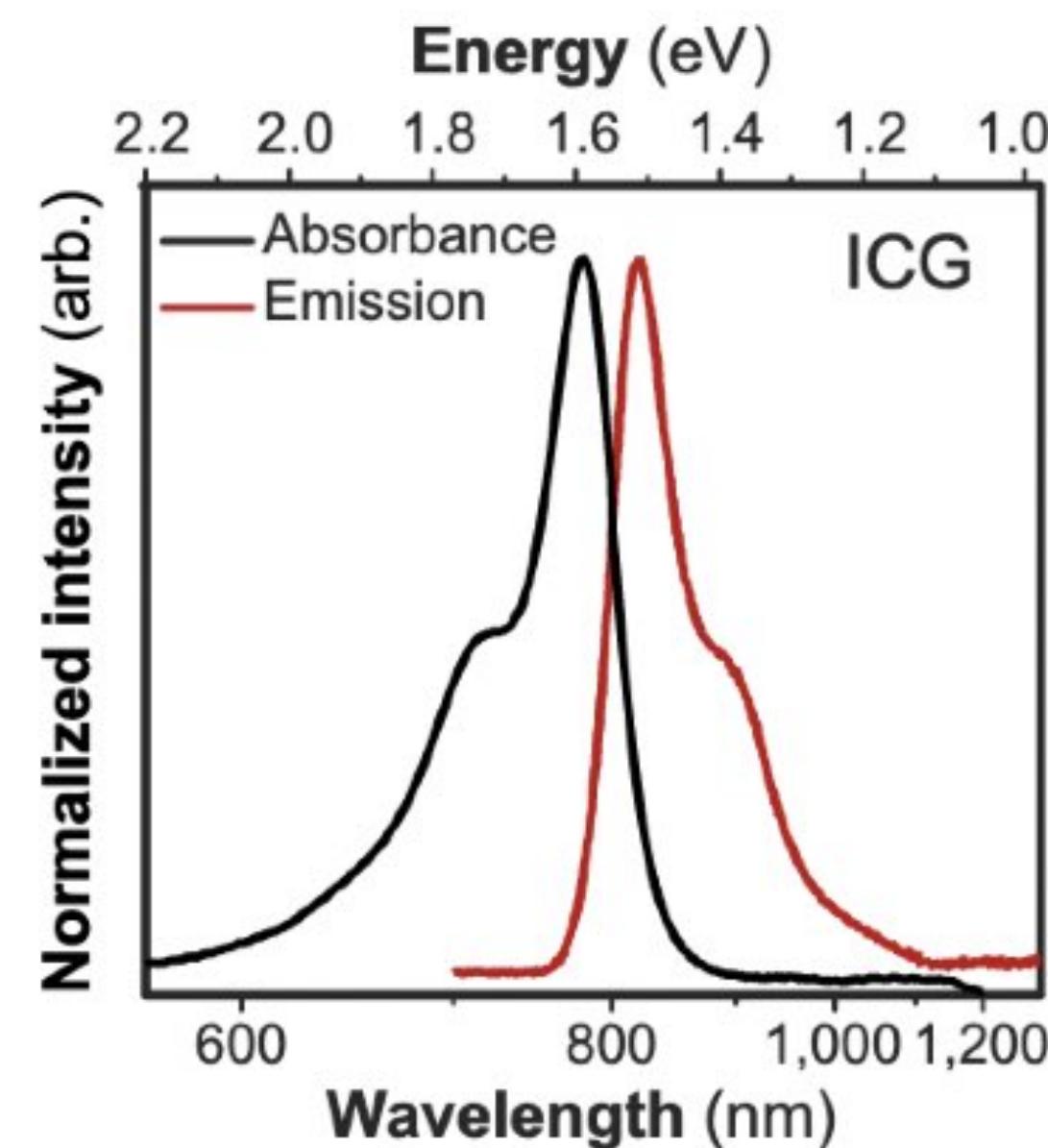
ICG imaging of SWIR



ICG is well detectable with suitable cameras up to 1400nm

Carr JA et al. (2018) PNAS 115(17):4465

ICG imaging of SWIR

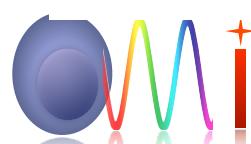
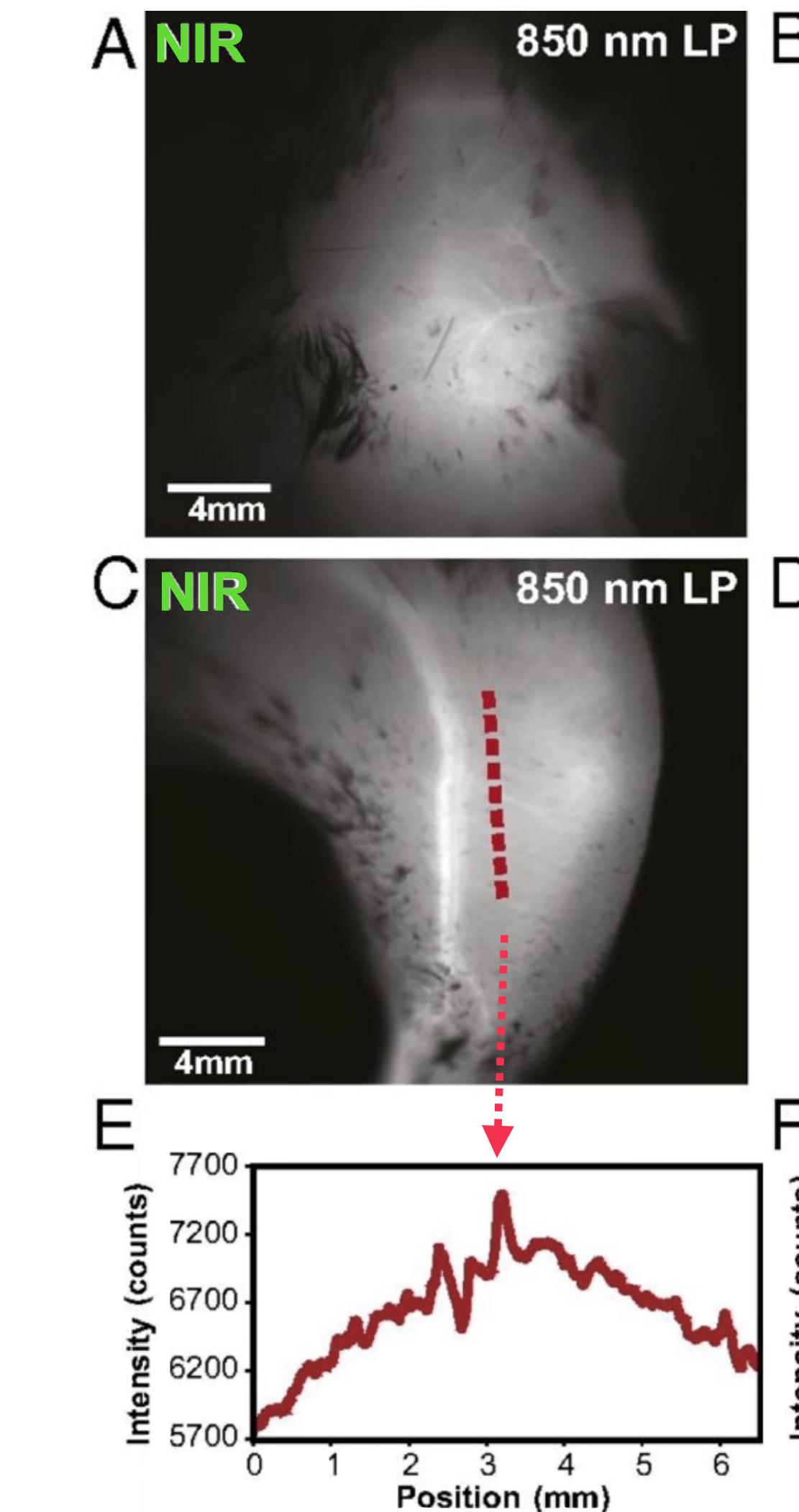
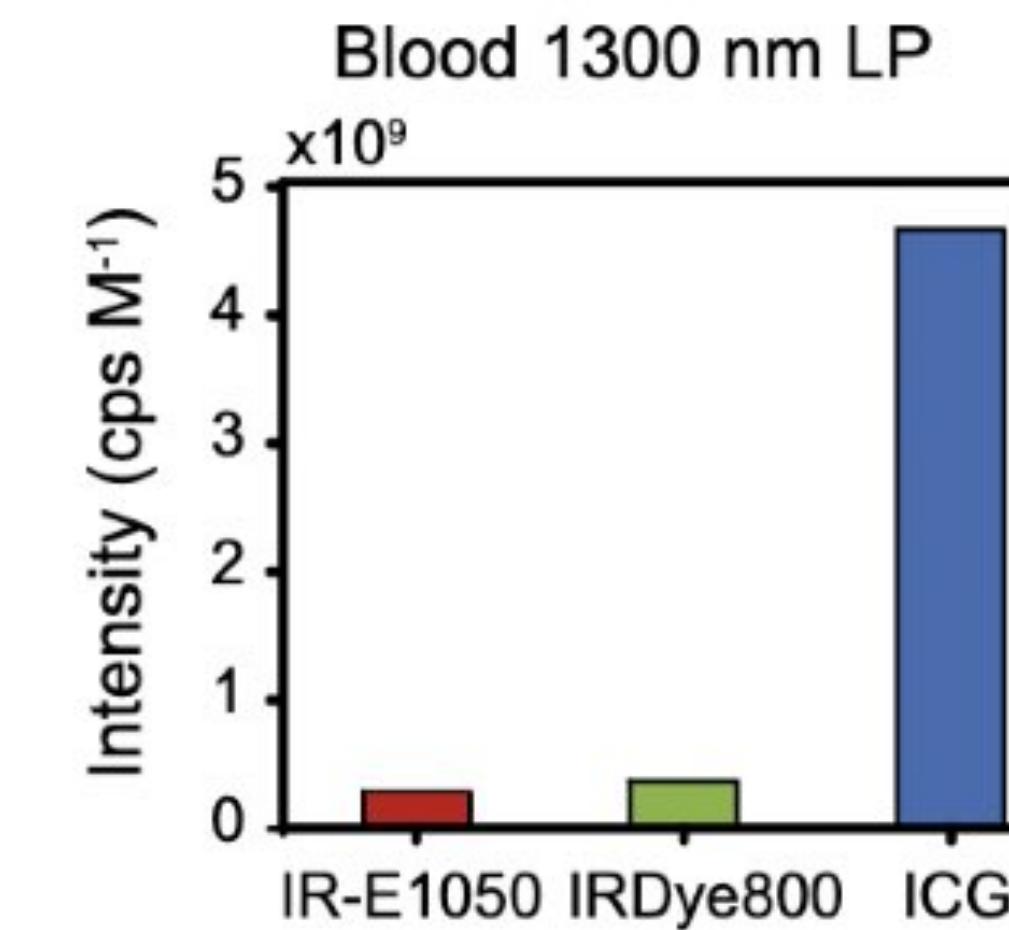
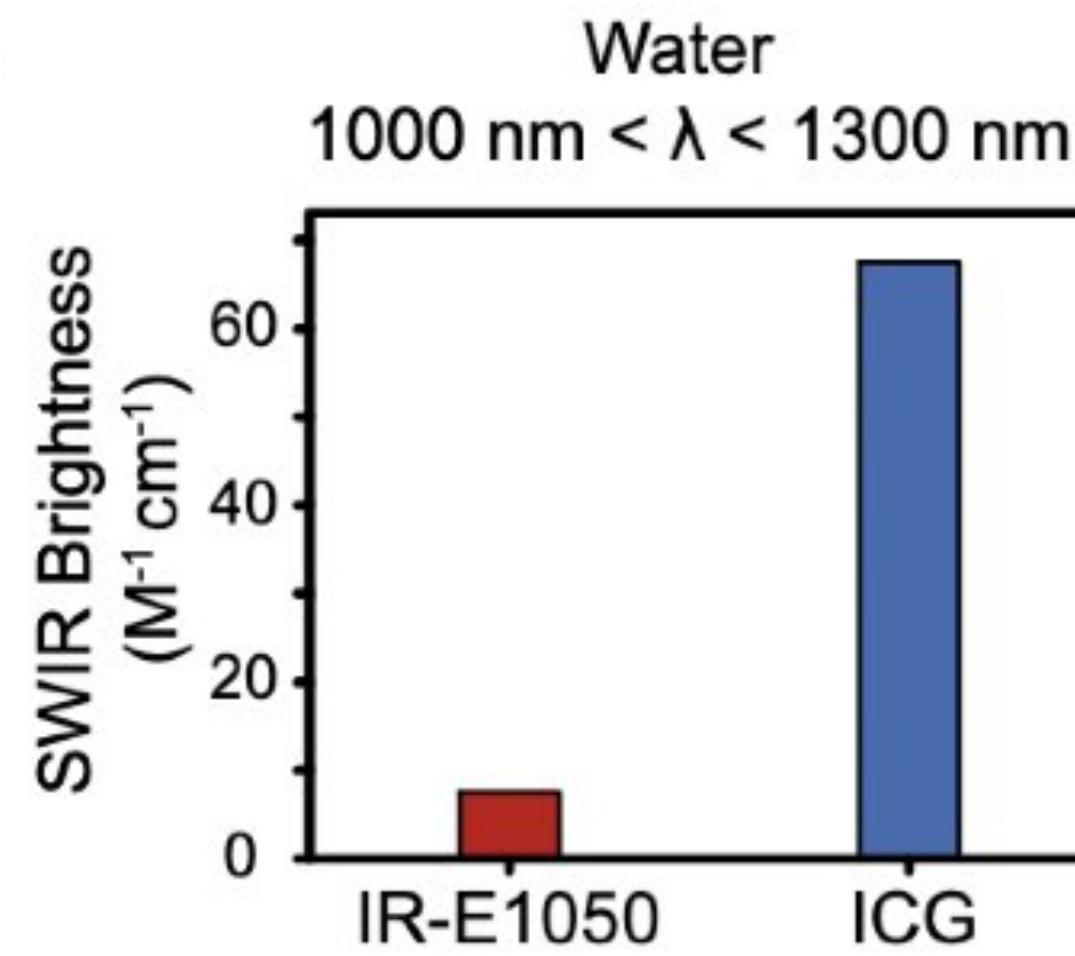
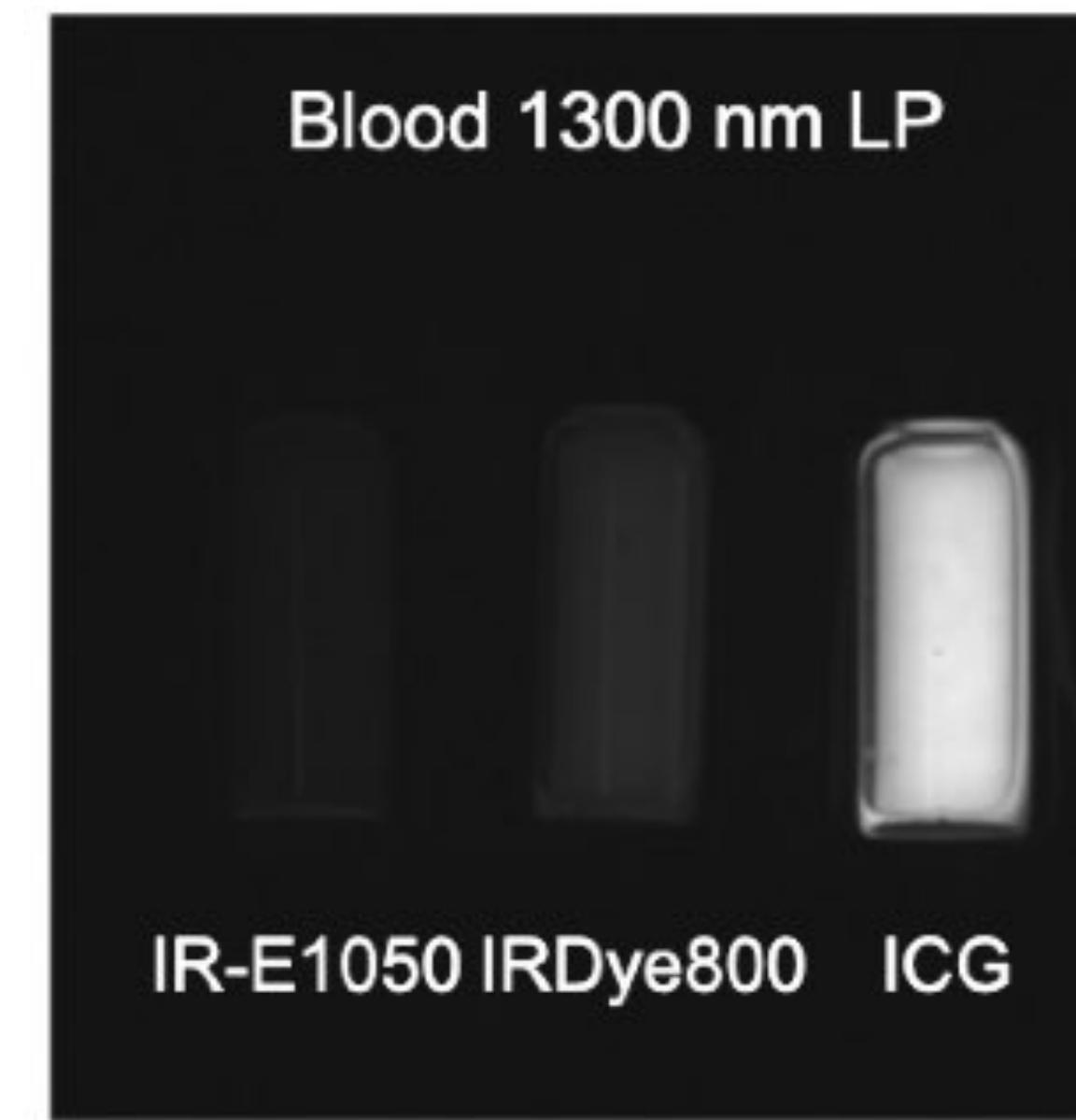
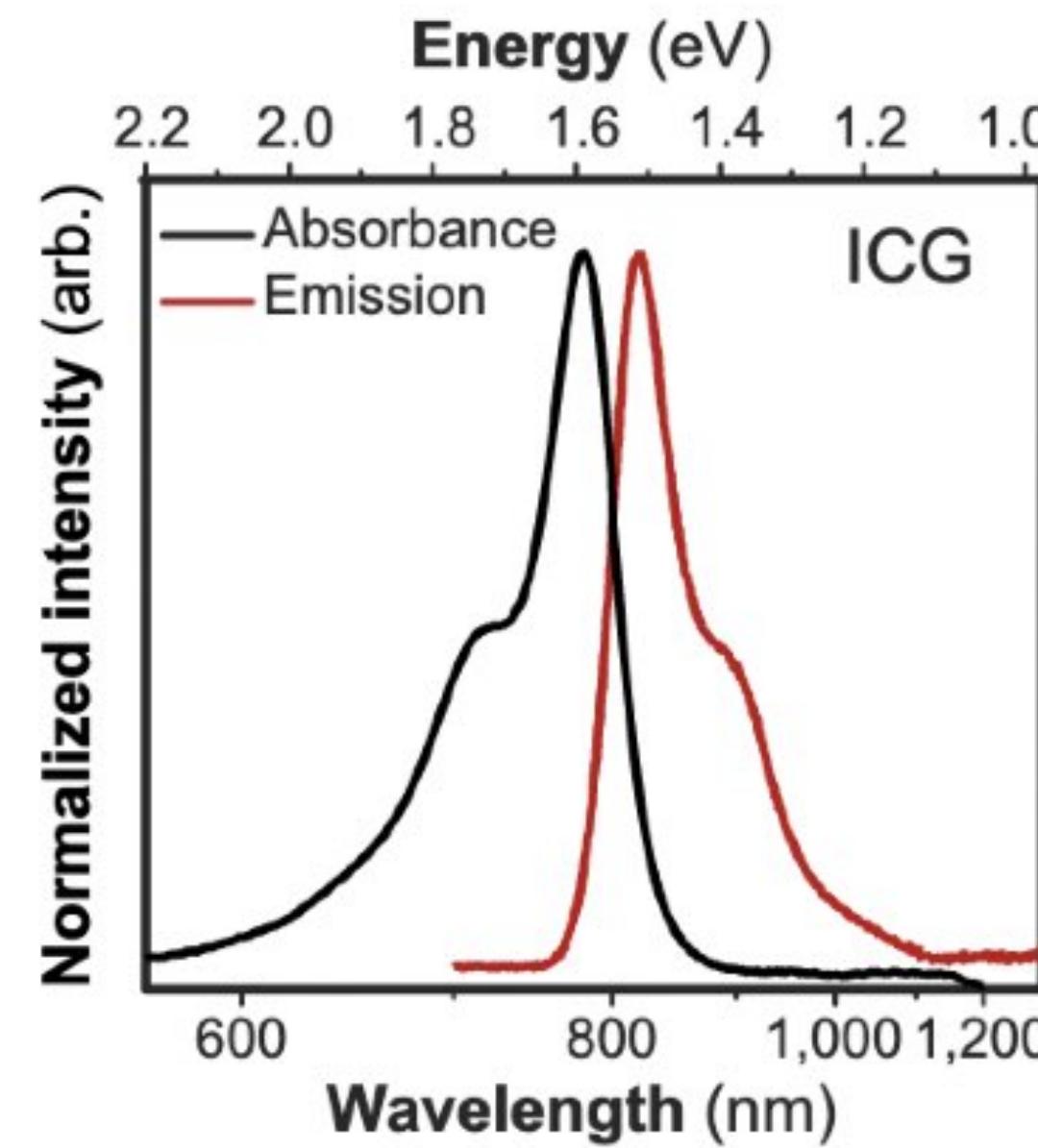


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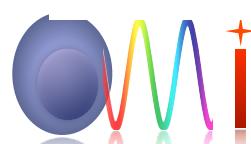
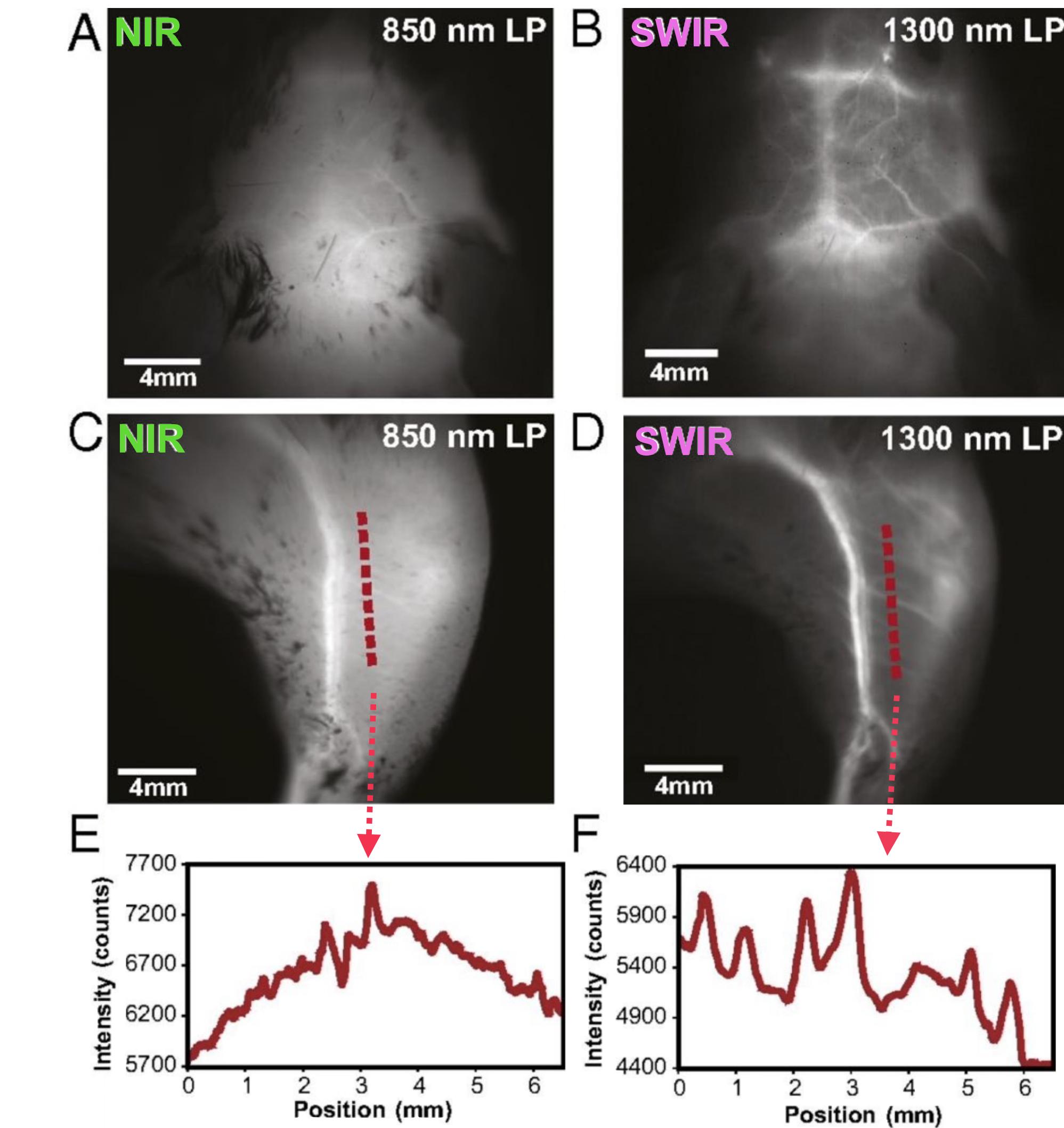
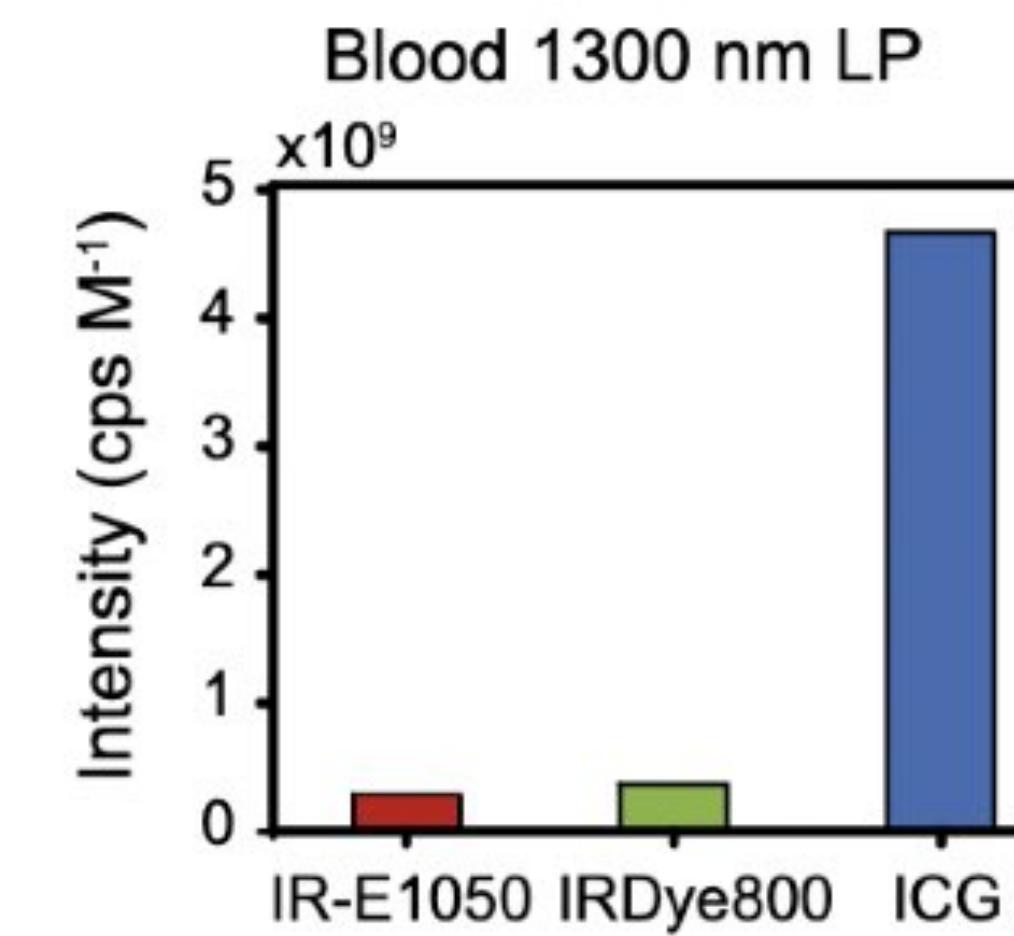
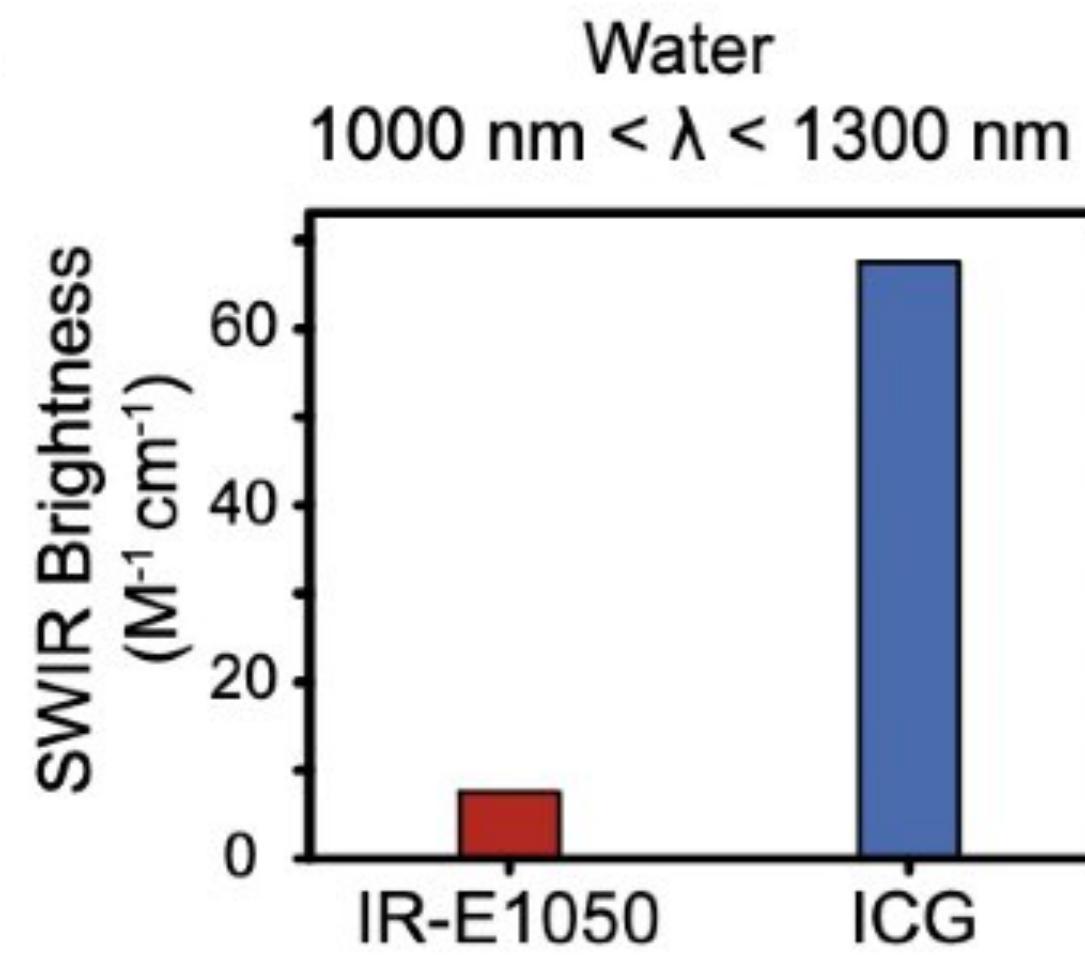
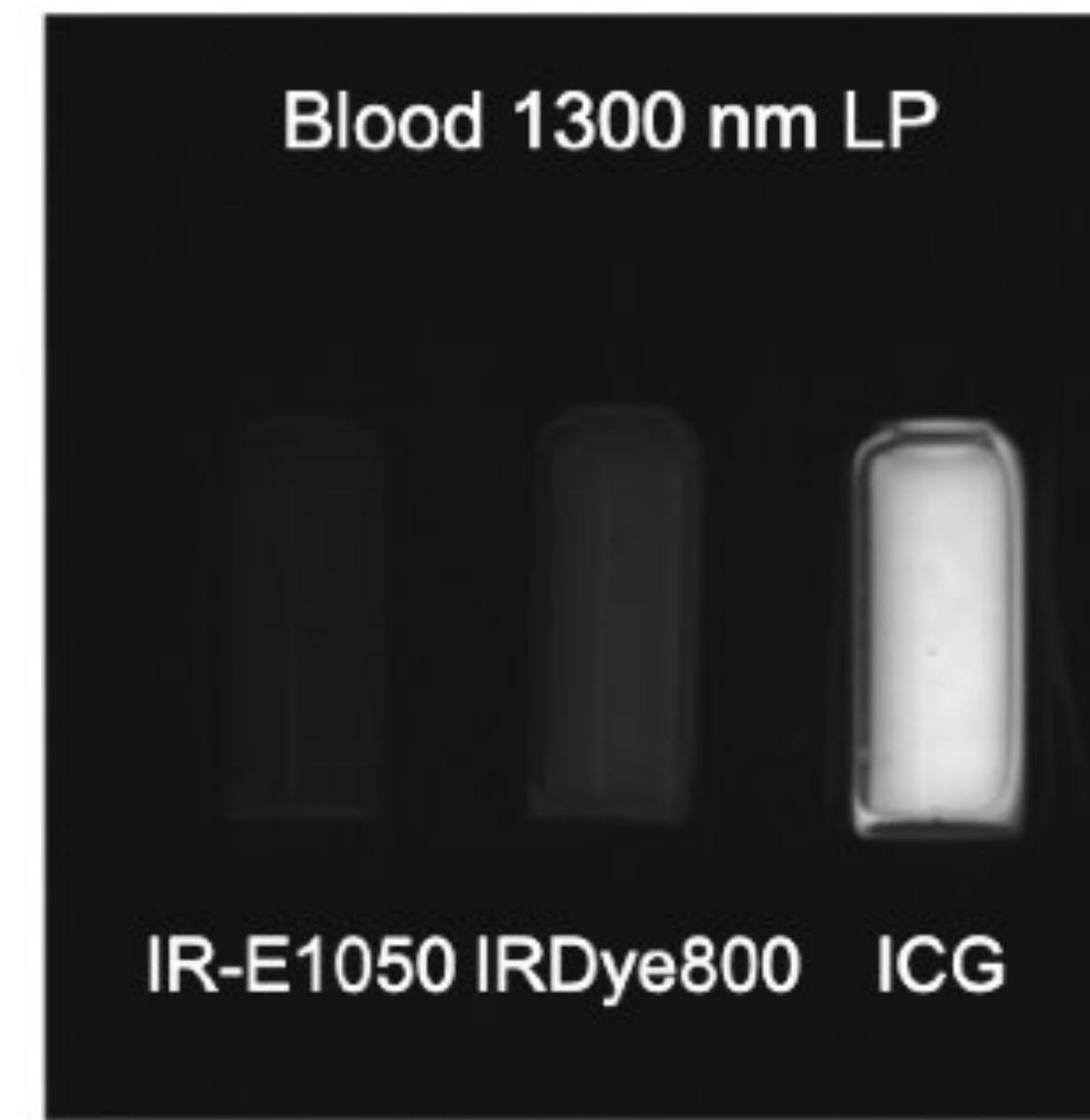
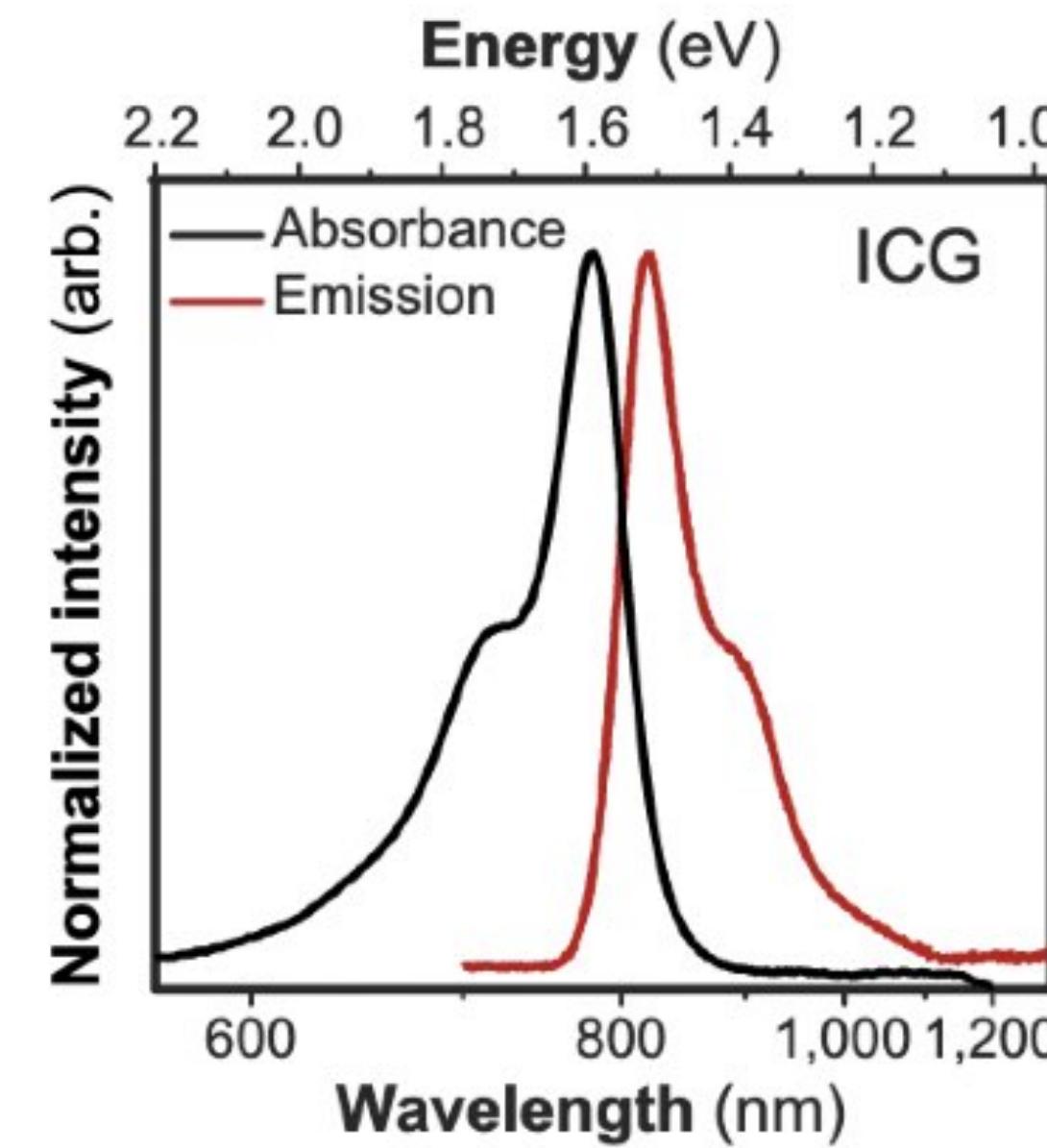


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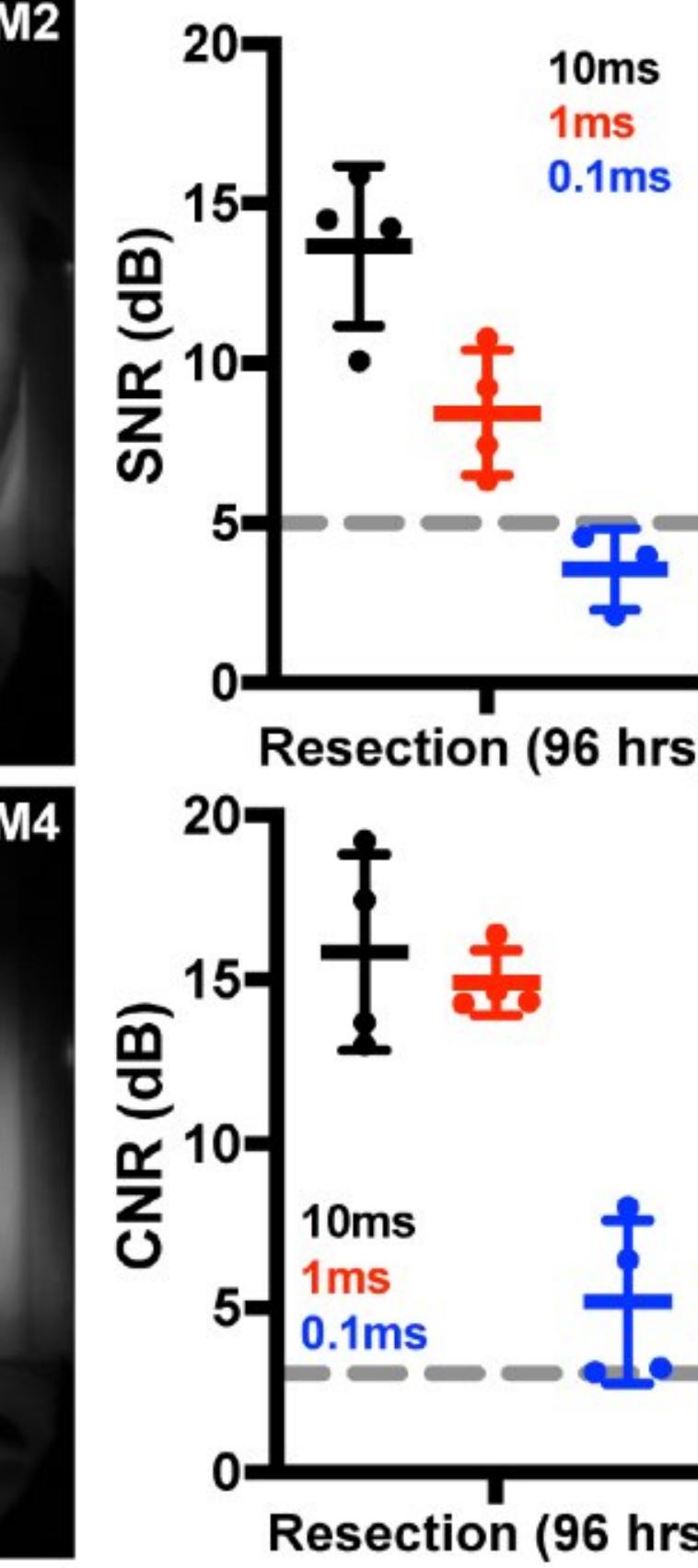
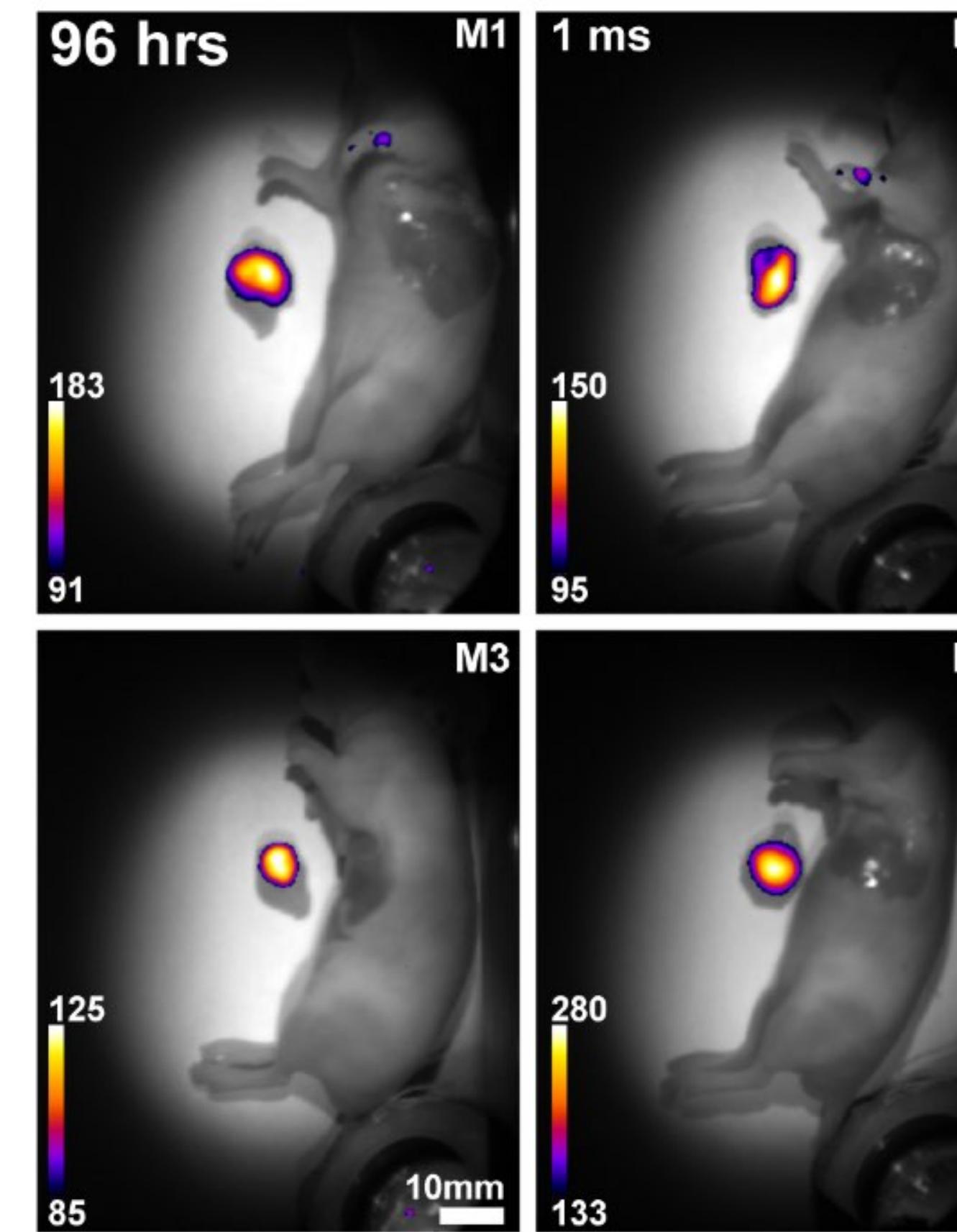
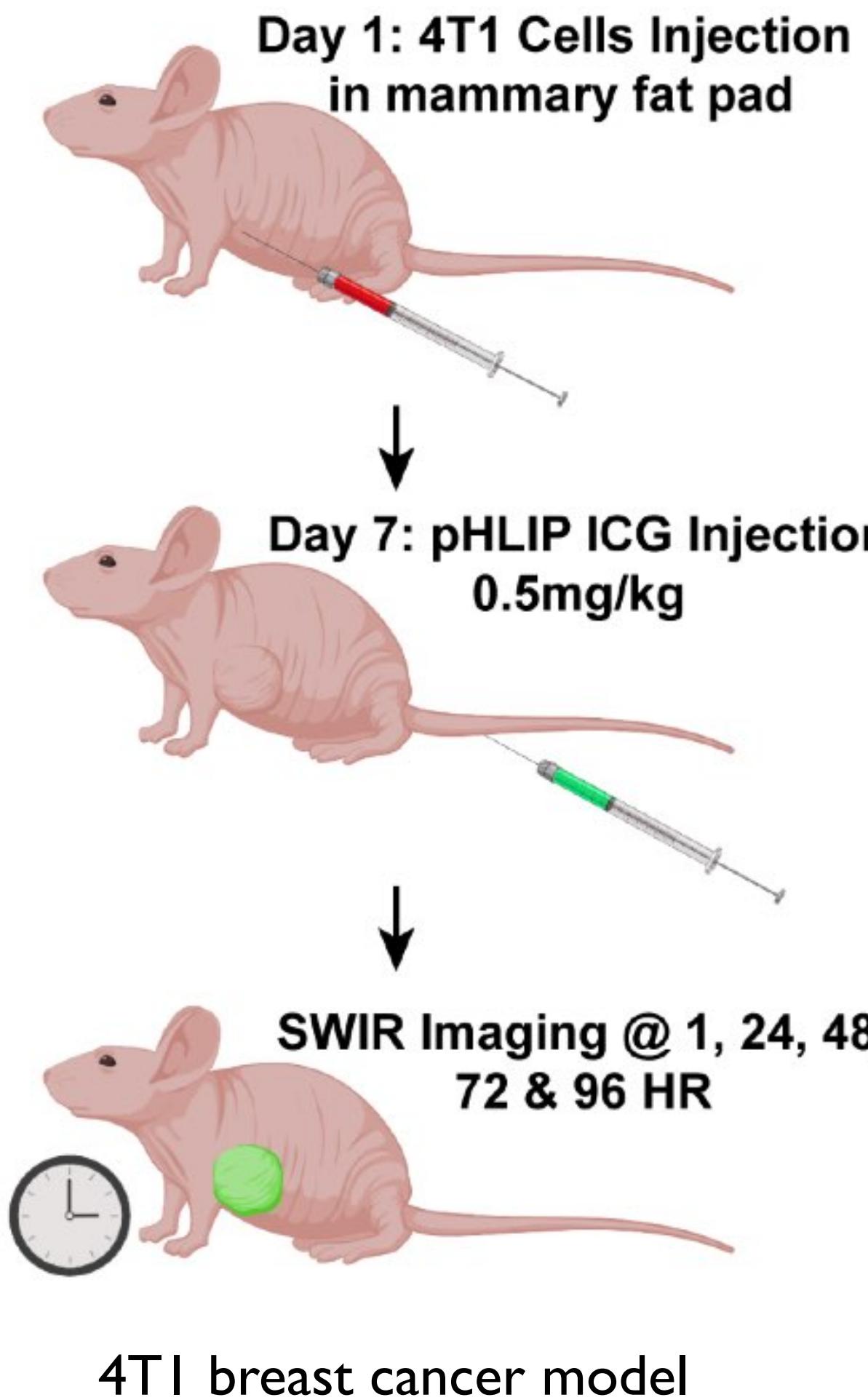


ICG is well detectable with suitable cameras up to 1400nm

Carr JA et al. (2018) PNAS 115(17):4465



SWIR pHILIP ICG Tumor Screening



WL=1300nm LED

McLarney B E et al. (2023) J Nuc Med 64(10):1647

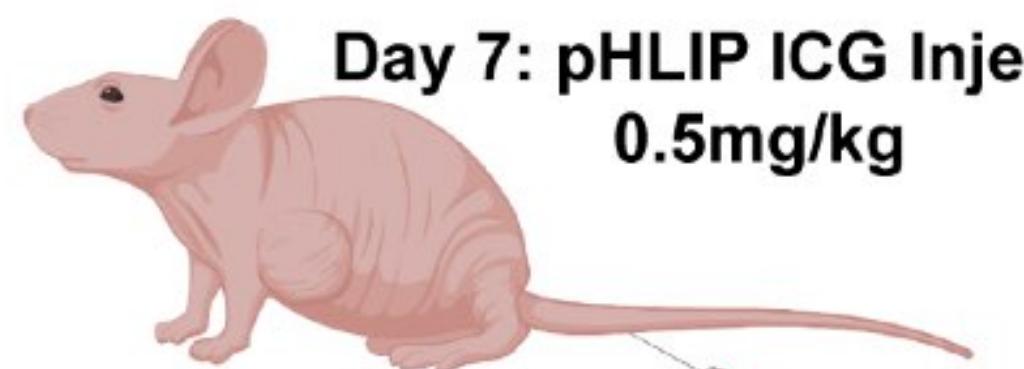


SWIR pHLIP ICG Tumor Screening

Day 1: 4T1 Cells Injection in mammary fat pad



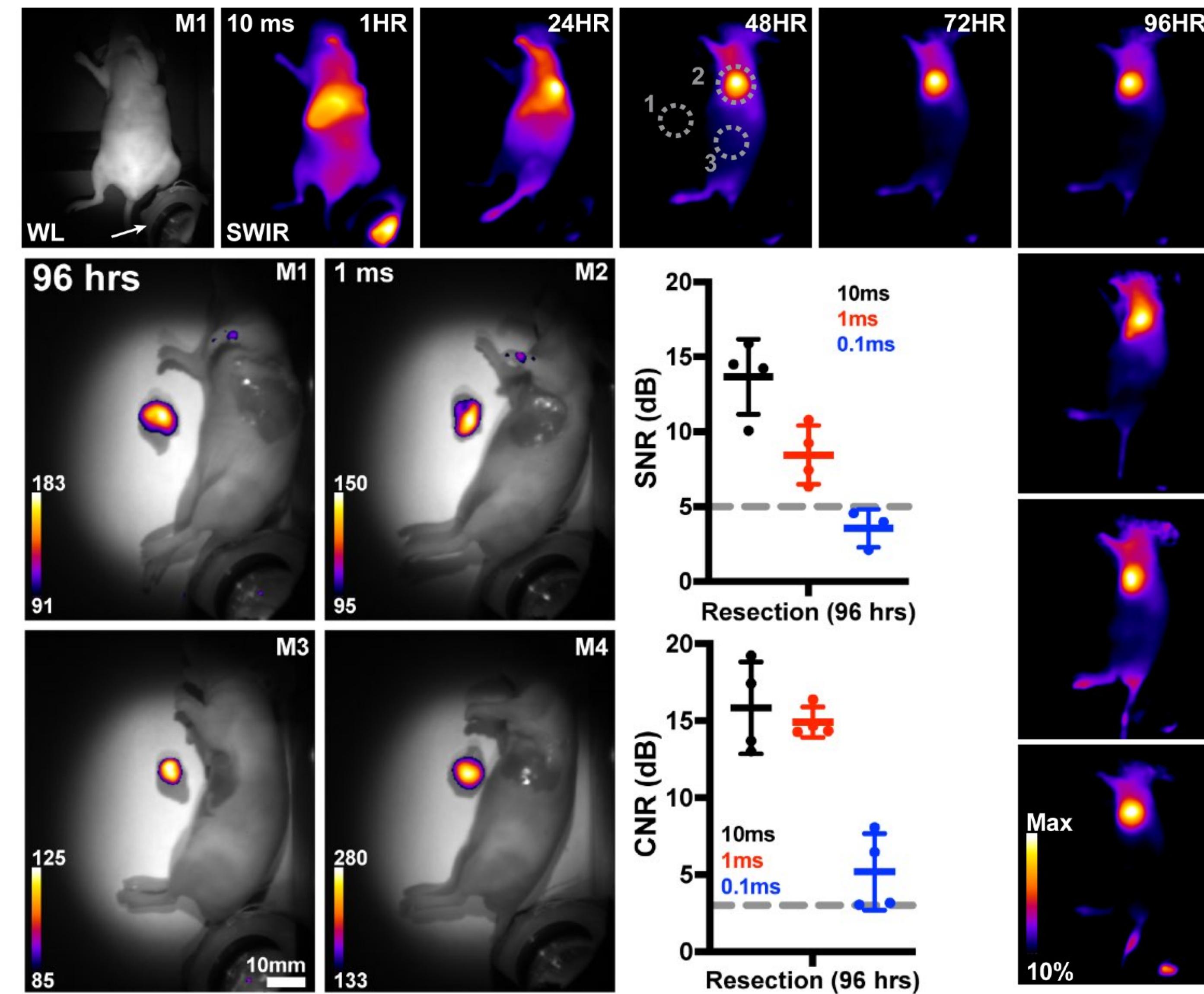
Day 7: pHIP ICG Injection 0.5mg/kg



SWIR Imaging @ 1, 24, 48 72 & 96 HR



4T1 breast cancer model



WL=1300nm LED

McLarney B E et al. (2023) J Nuc Med 64(10):1647



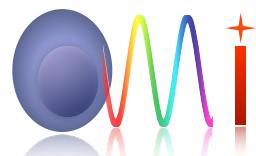
Video rate tumor screening!

**pHLIP ICG & SWIRFI can provide non-invasive
human safe high contrast video rate
tumor imaging, unaffected by LED room lighting**

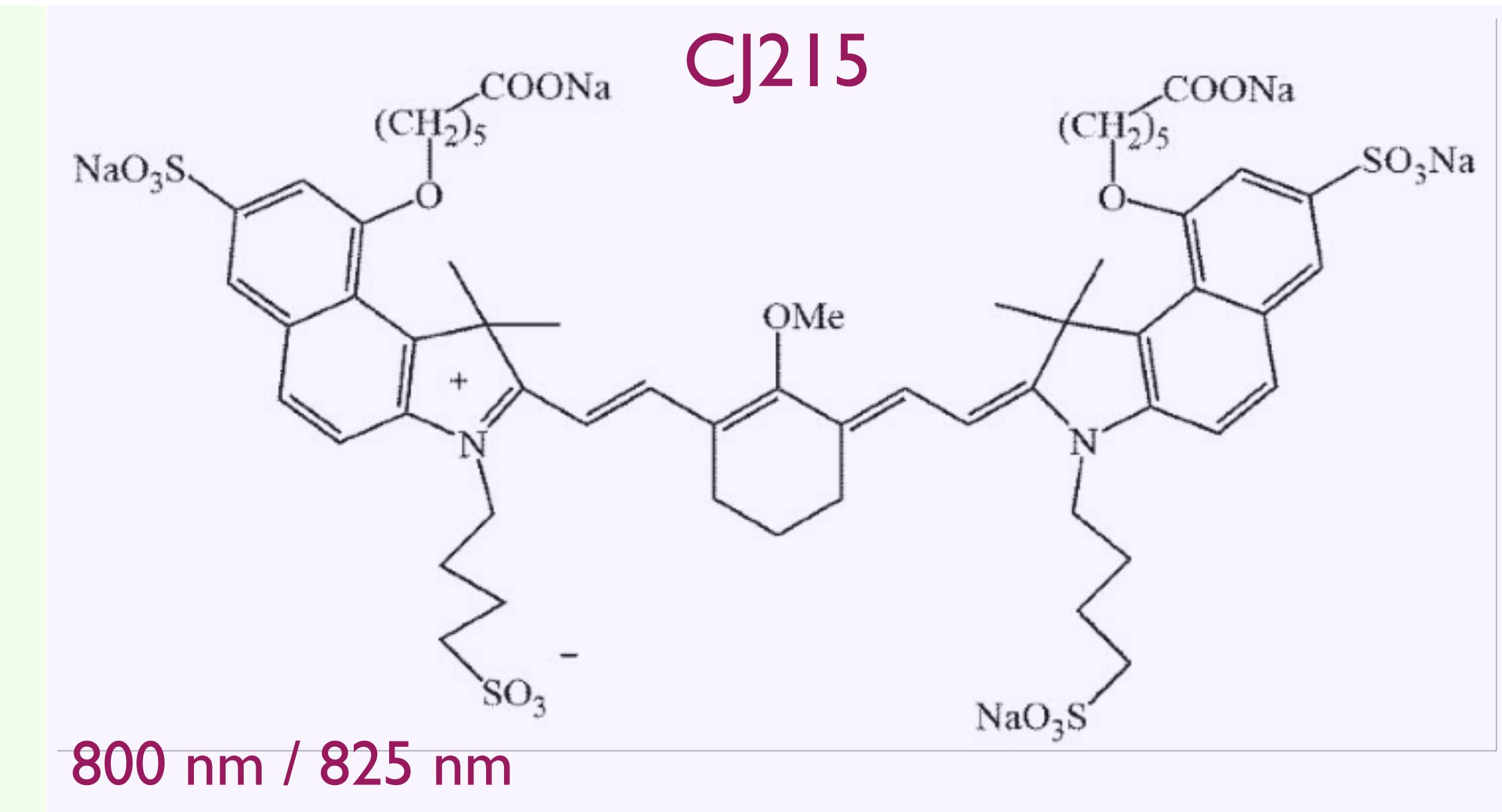
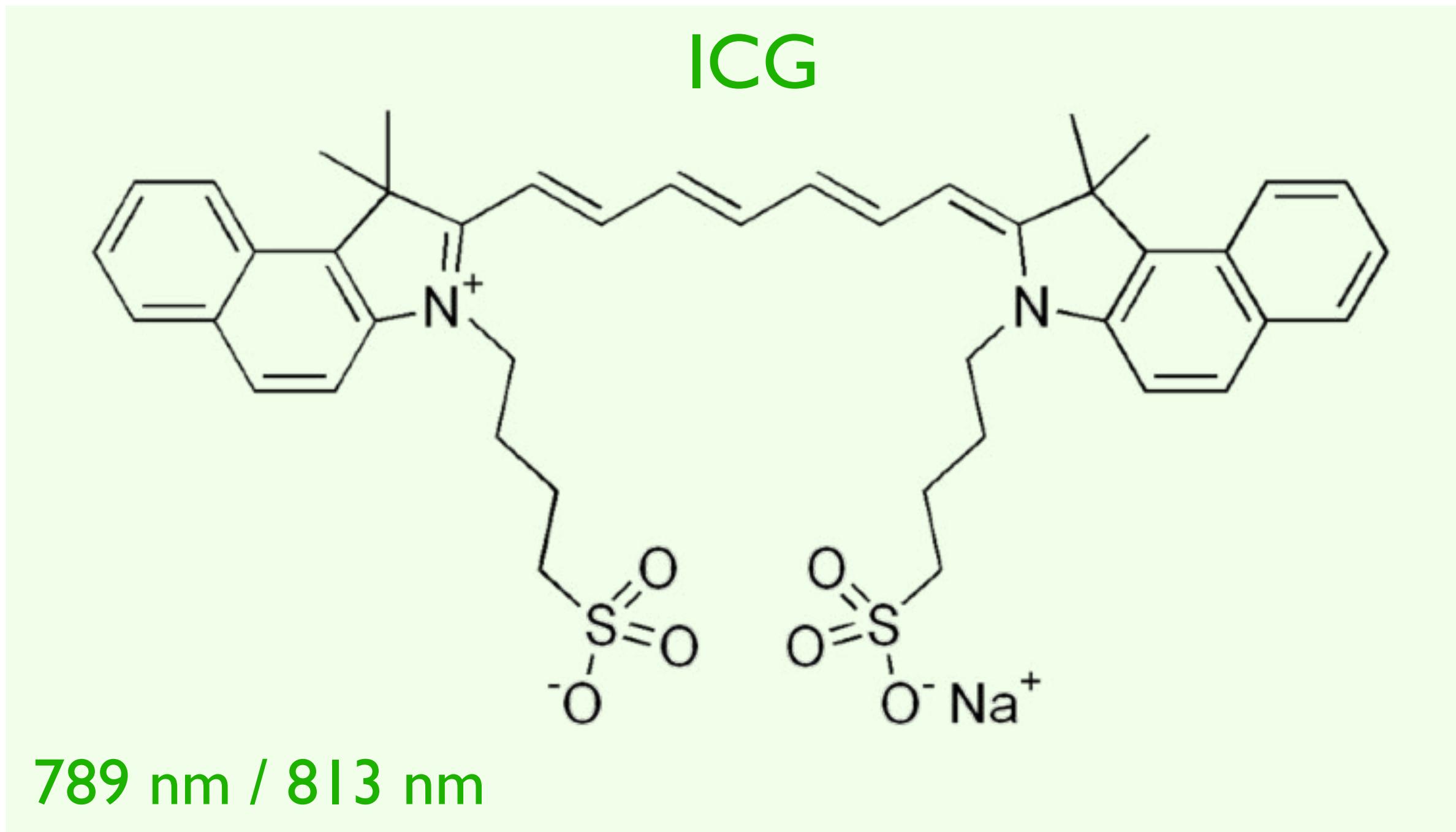


Video rate tumor screening!

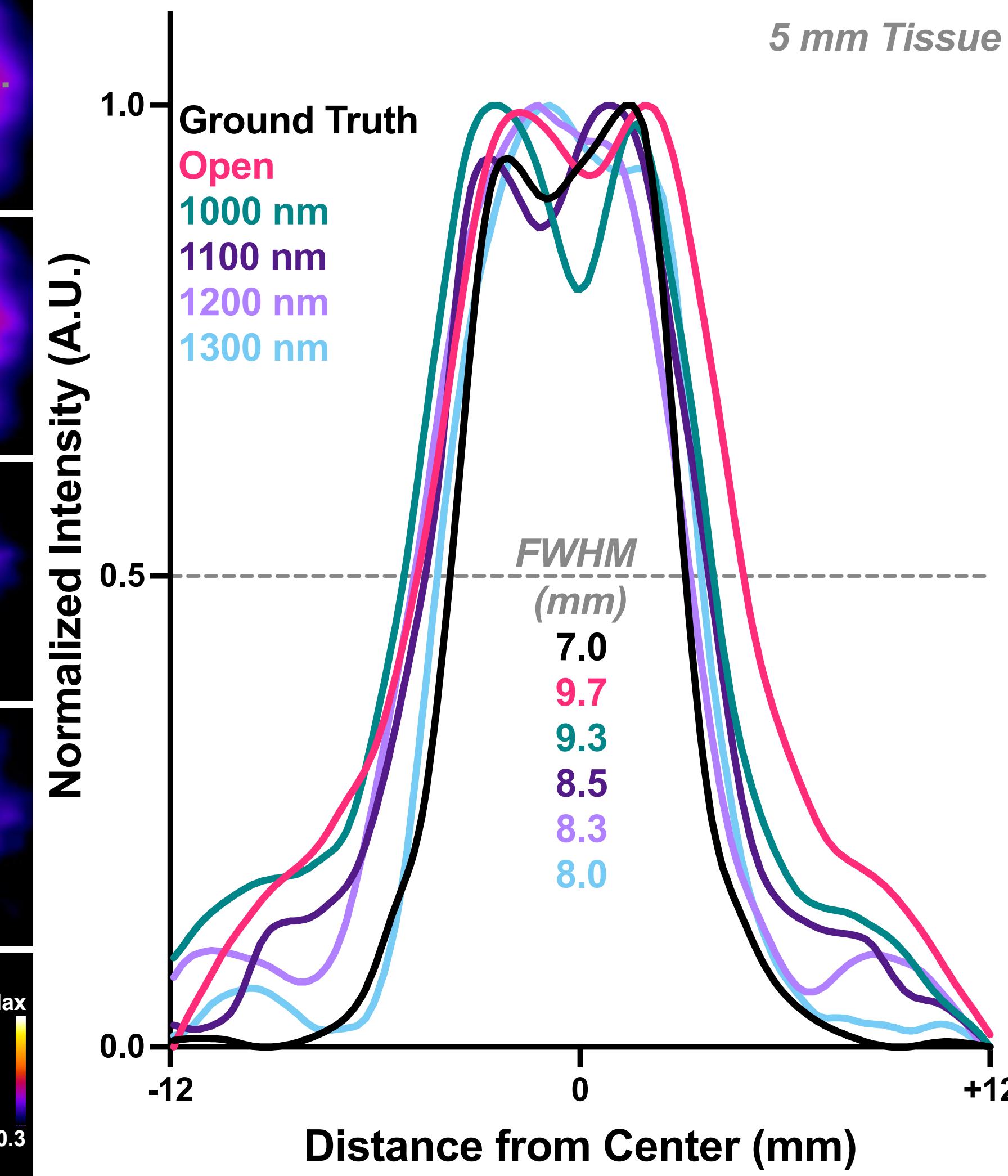
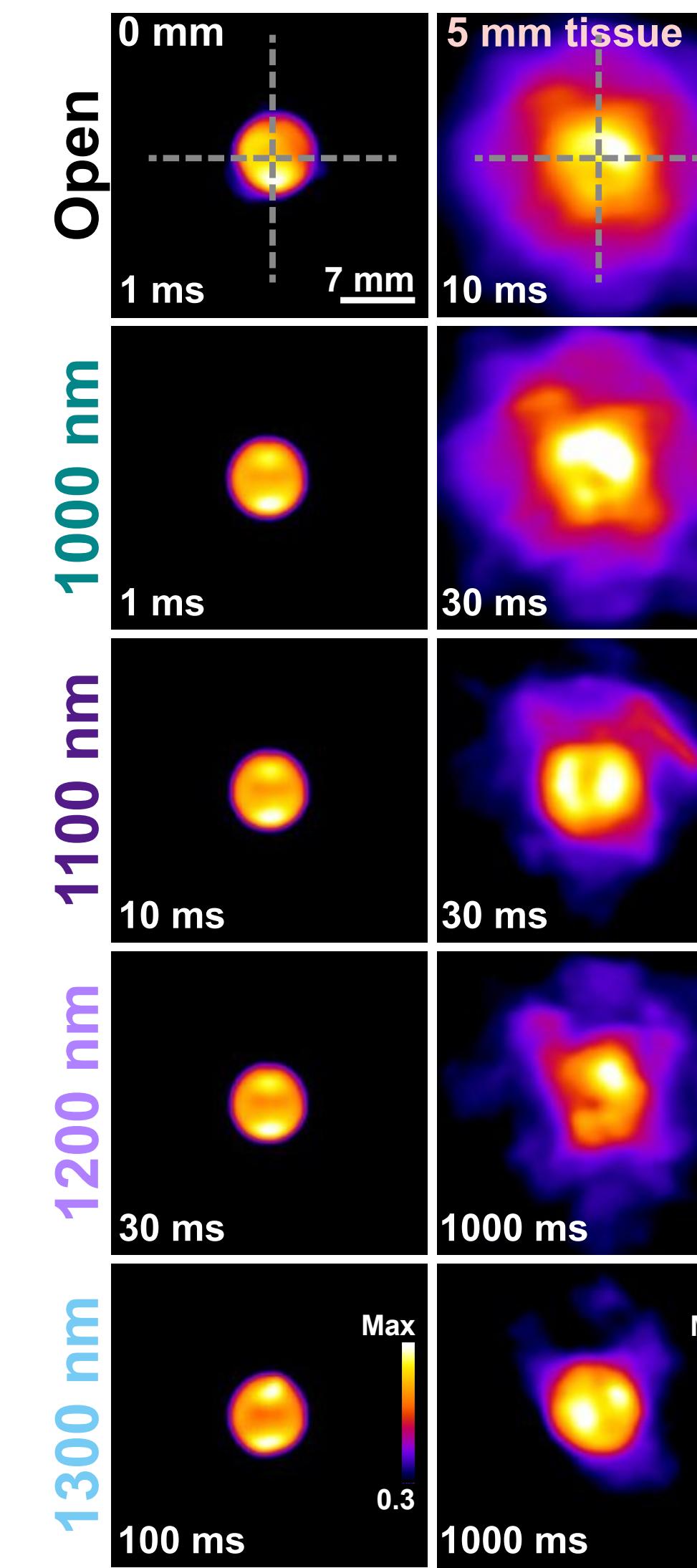
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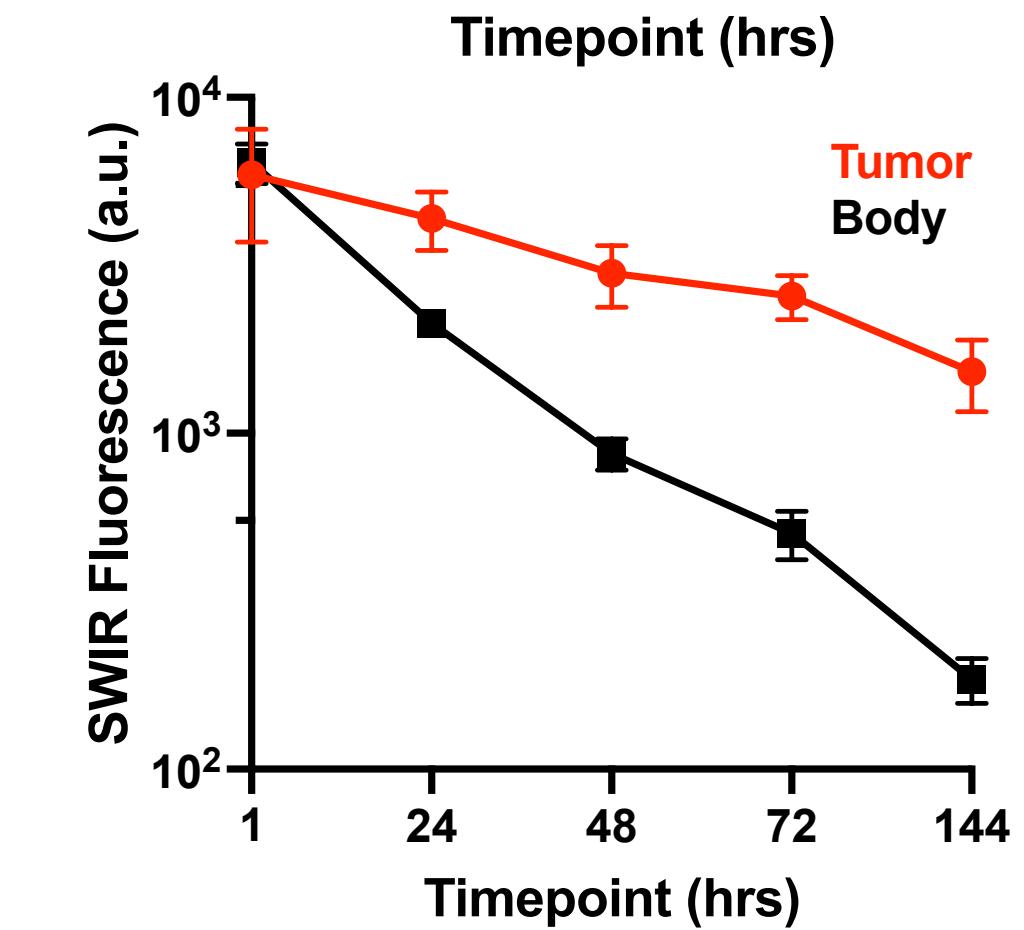
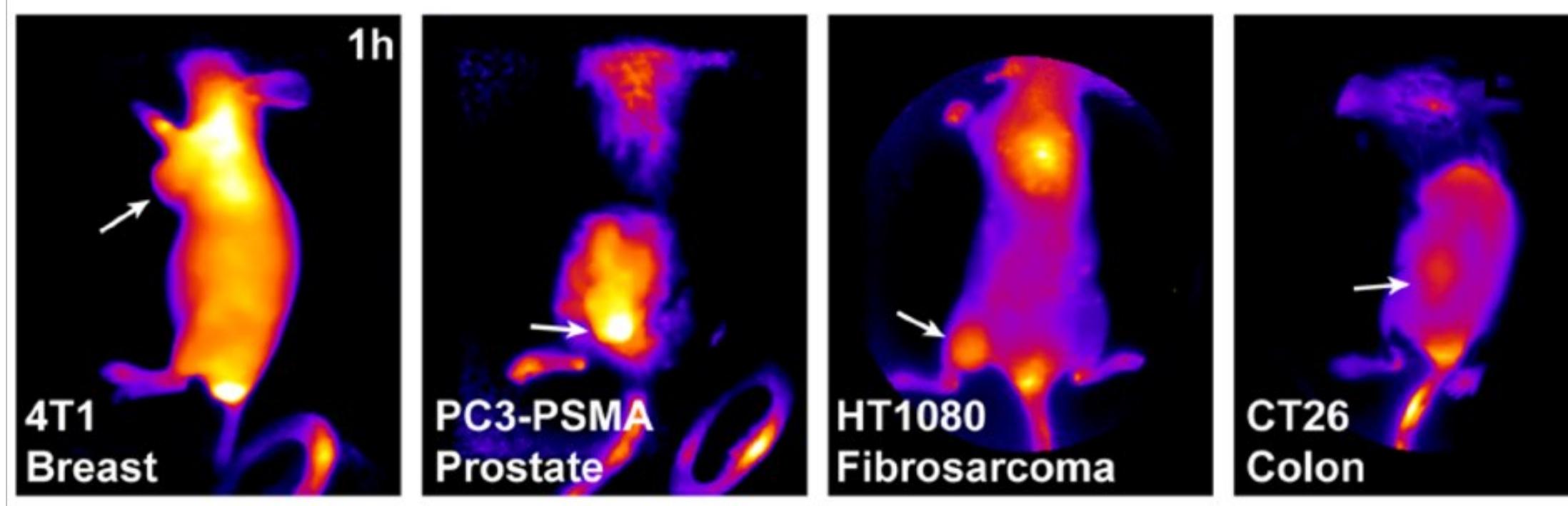
Pan-cancer seeking NIR/SWIR agent



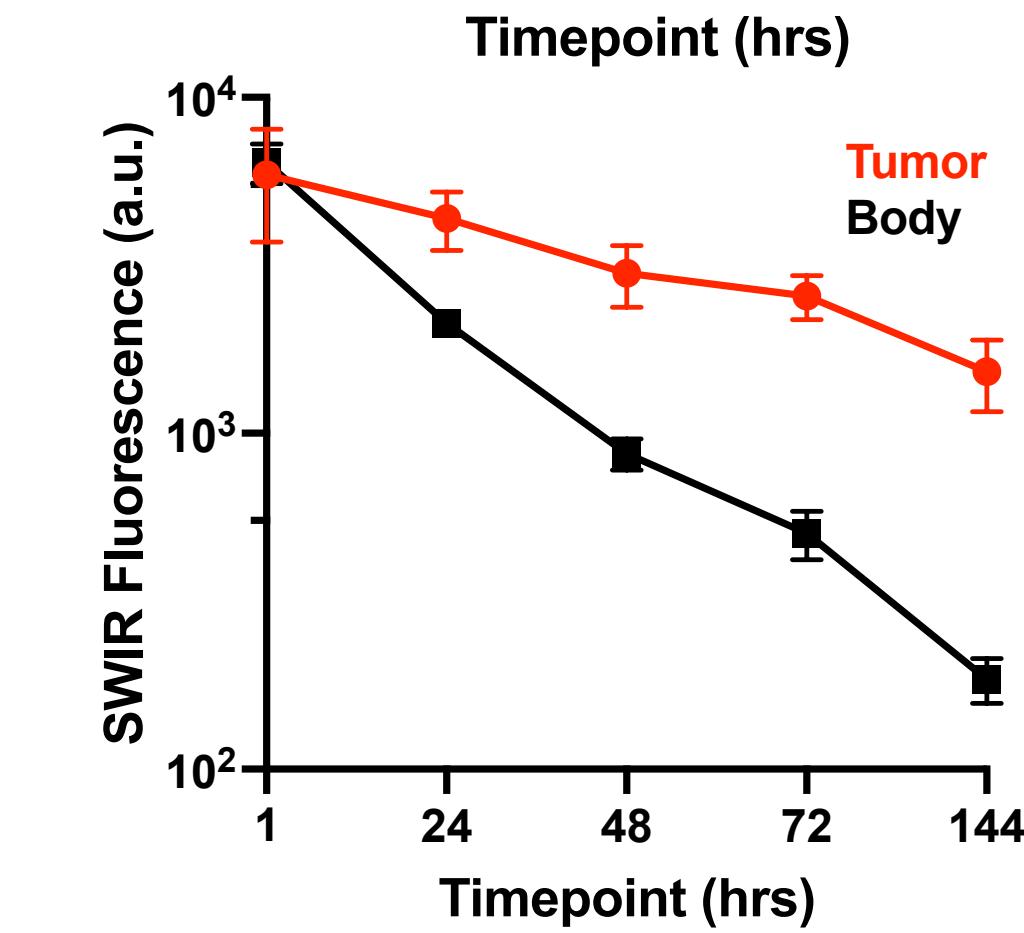
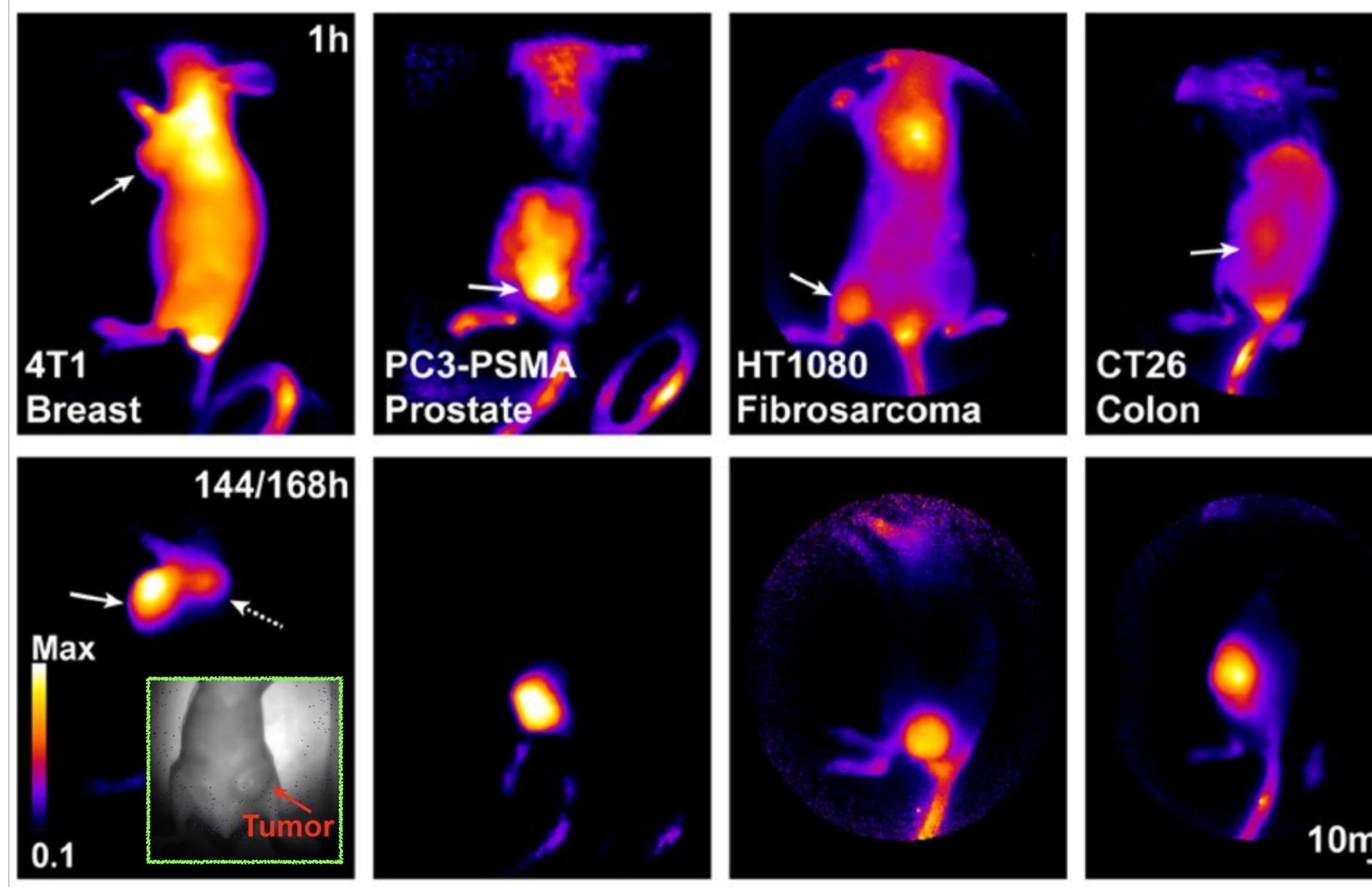
SWIR imaging is closer to the ground truth



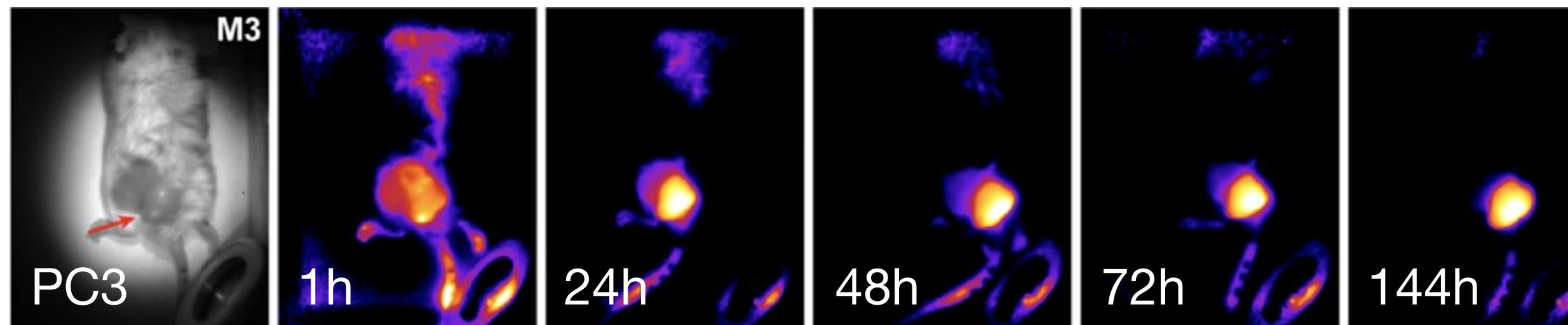
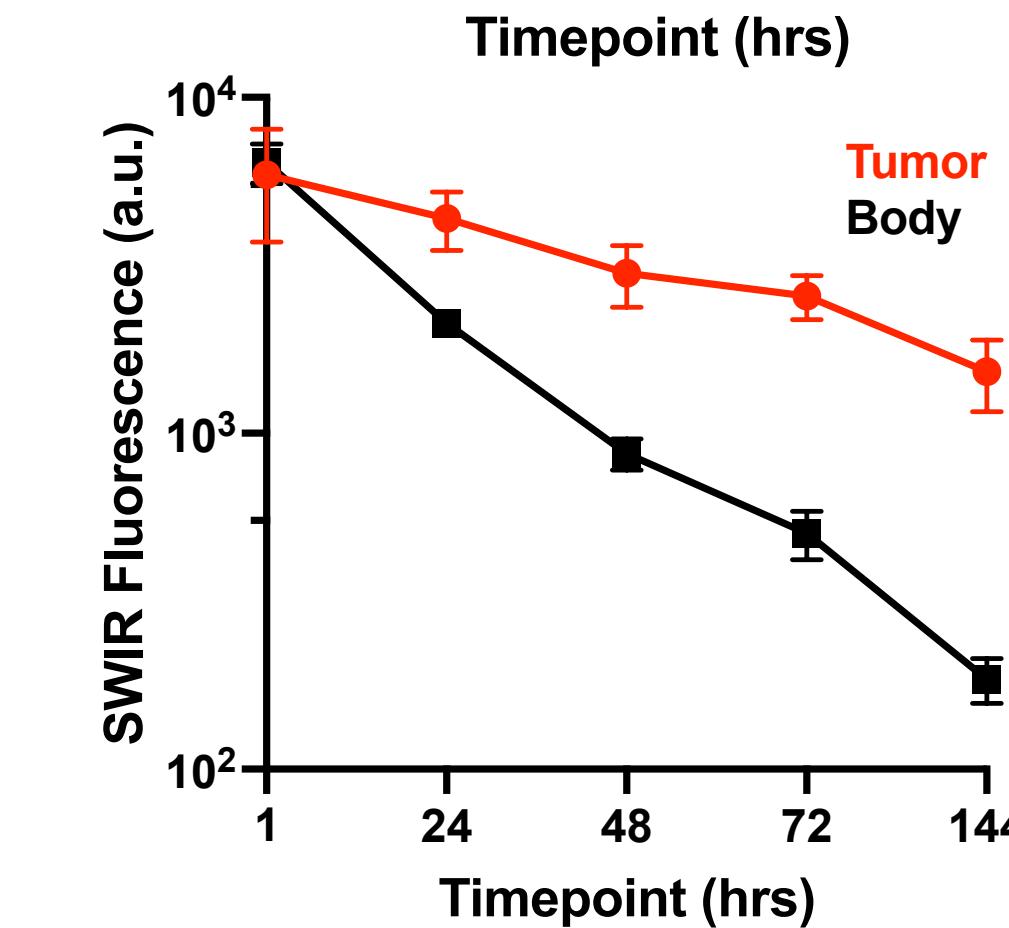
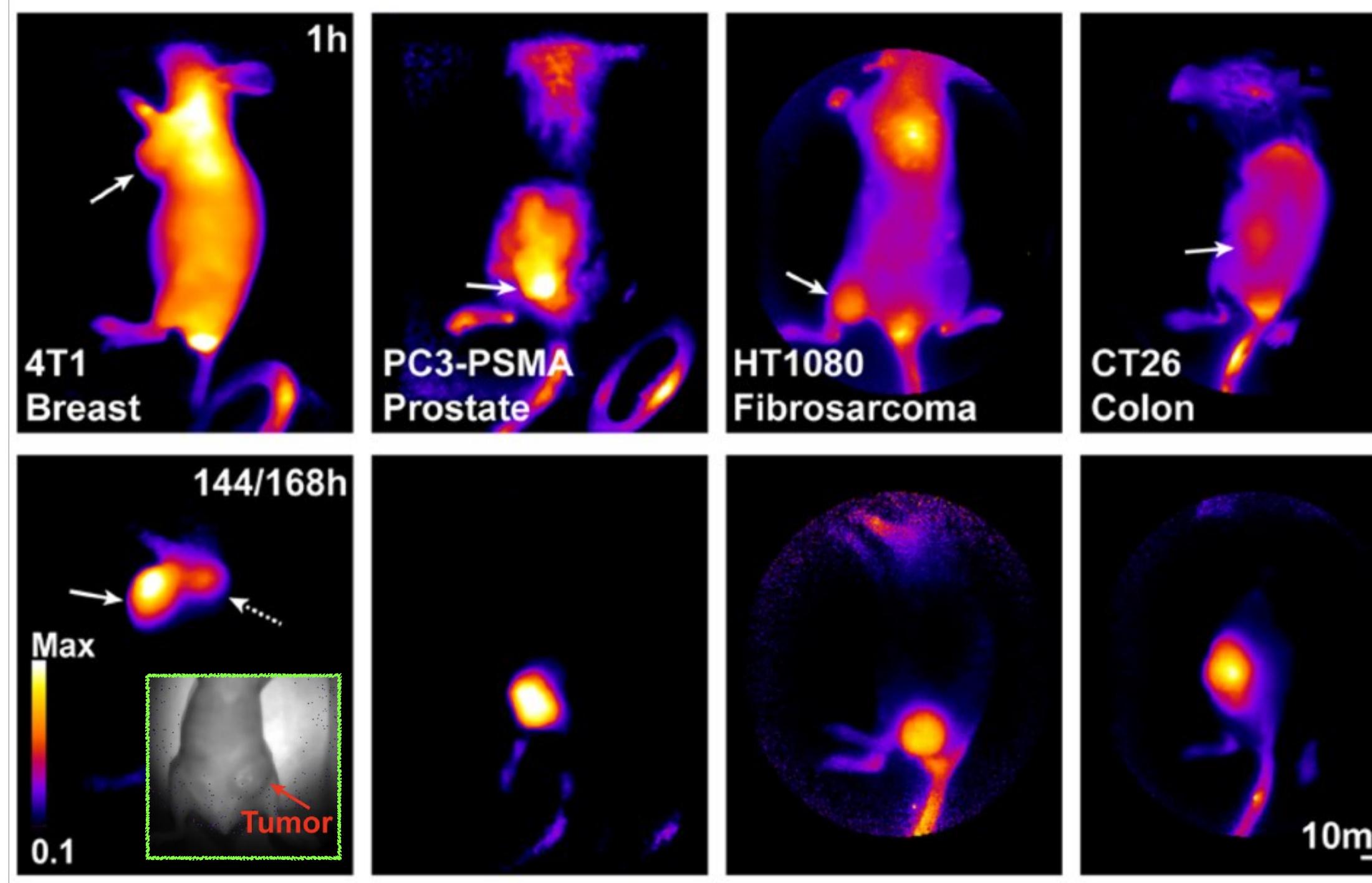
Pan-cancer seeking NIR/SWIR agent



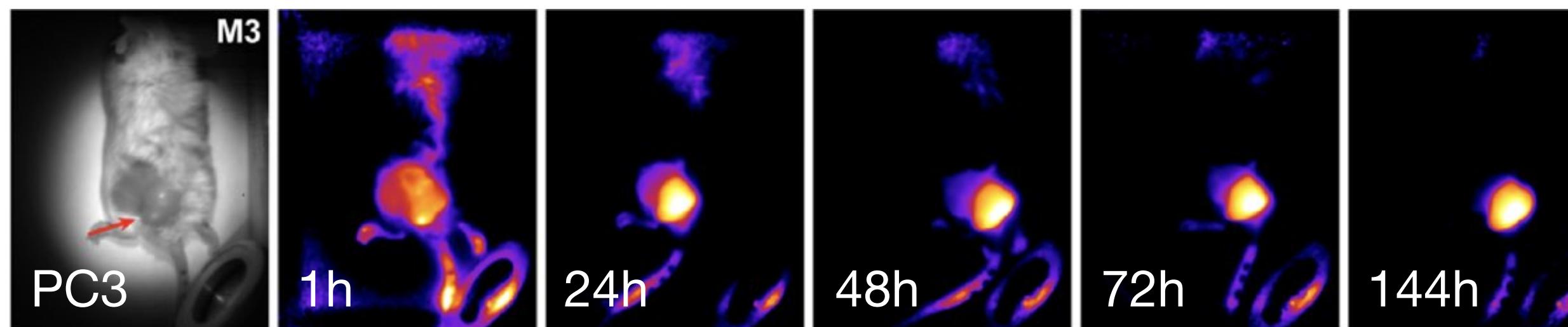
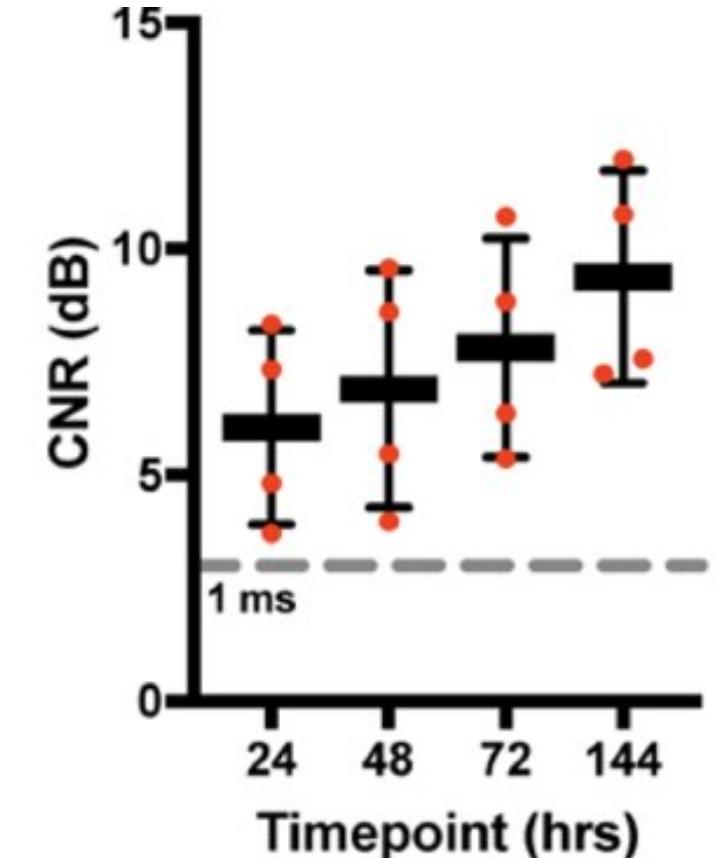
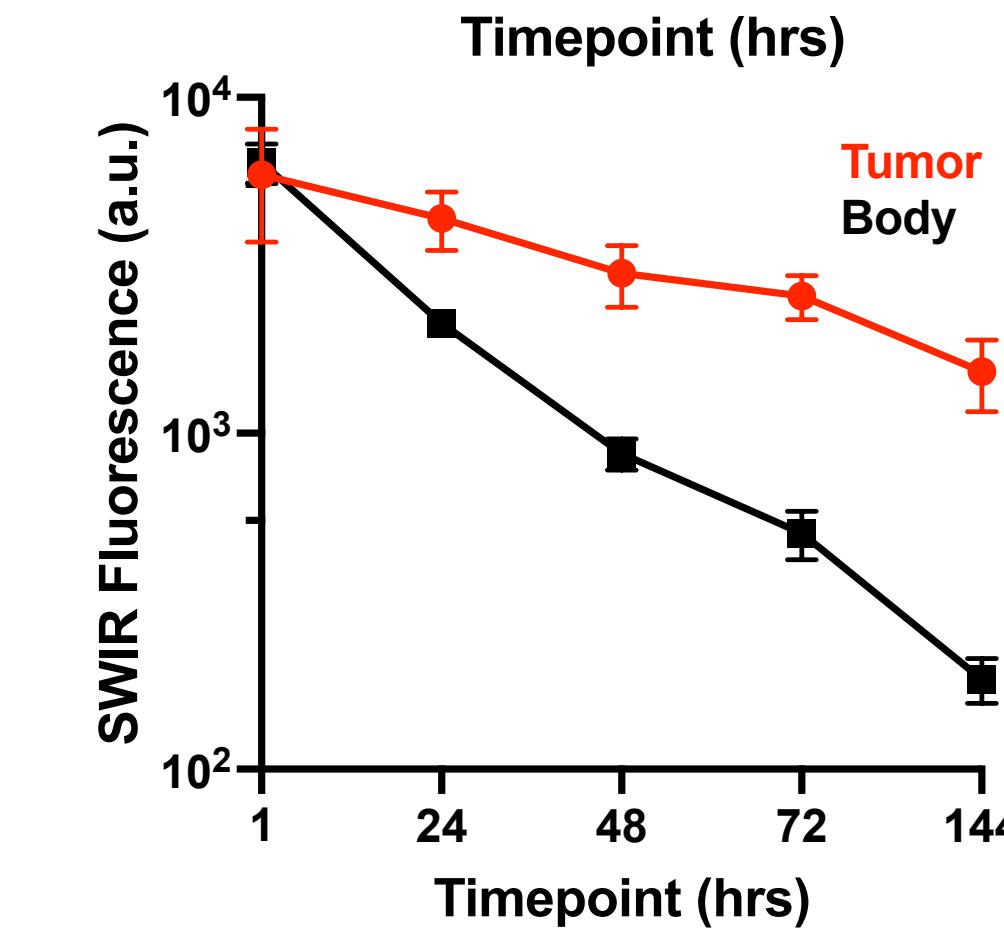
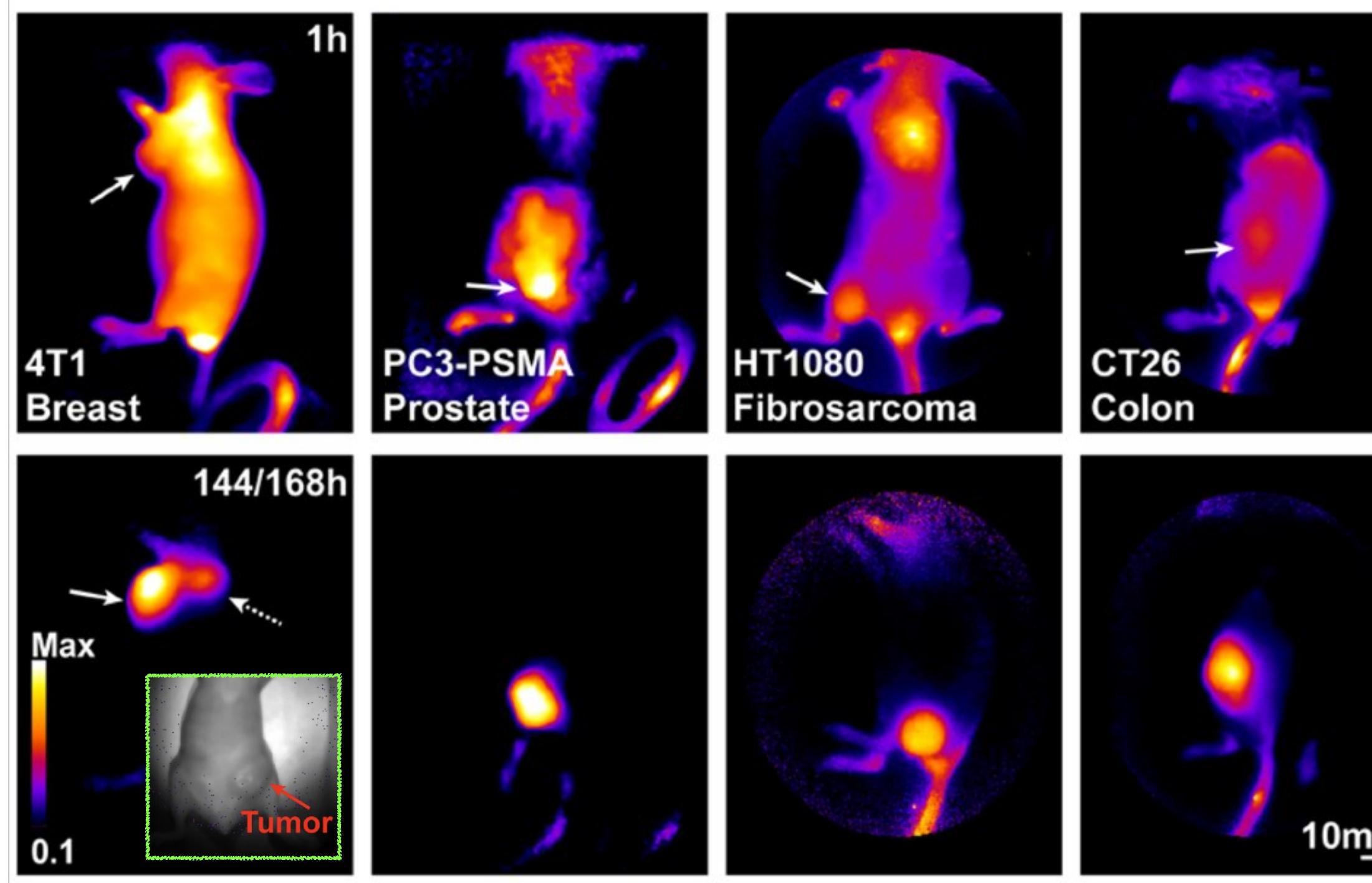
Pan-cancer seeking NIR/SWIR agent



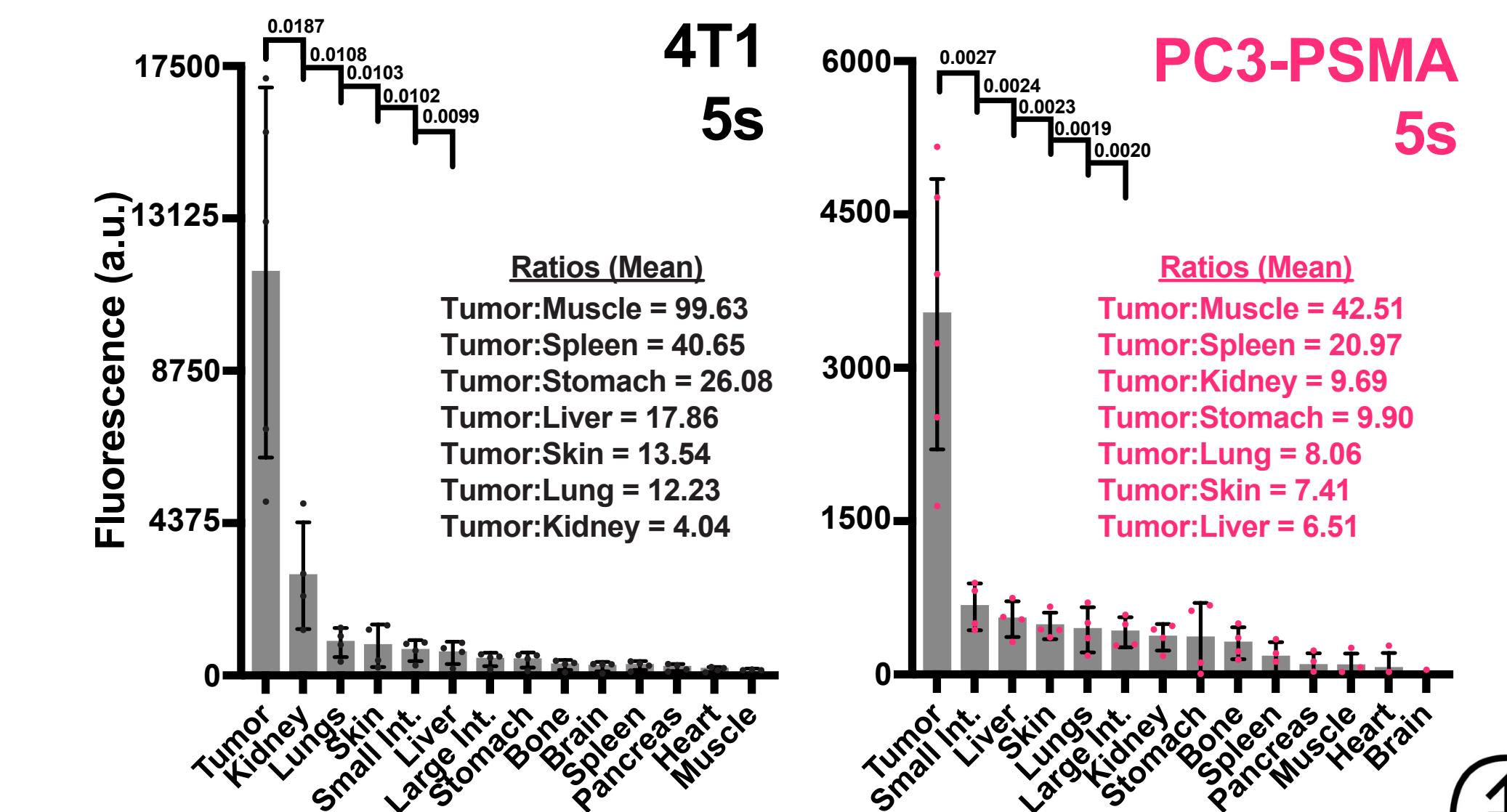
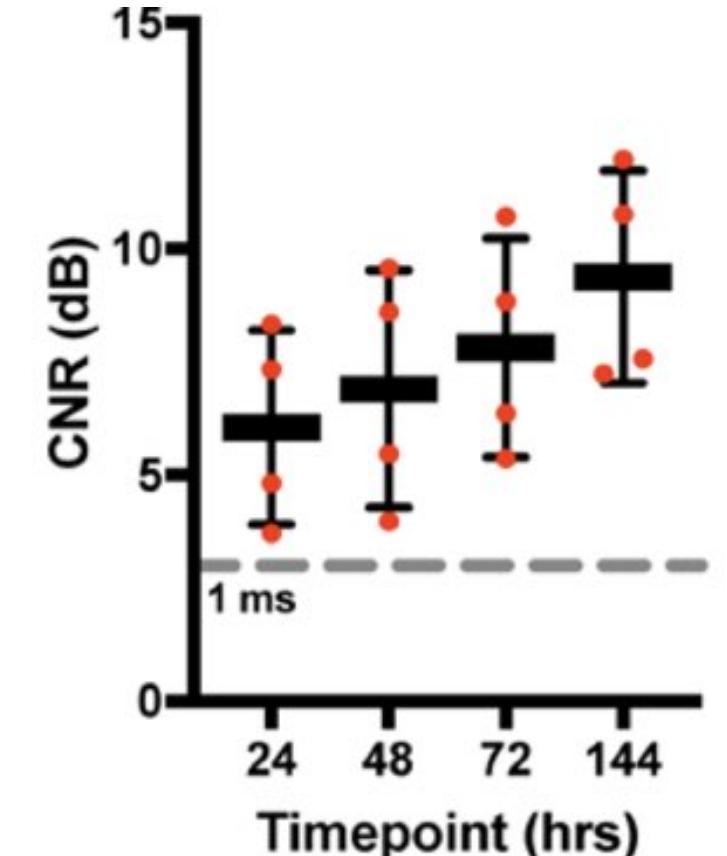
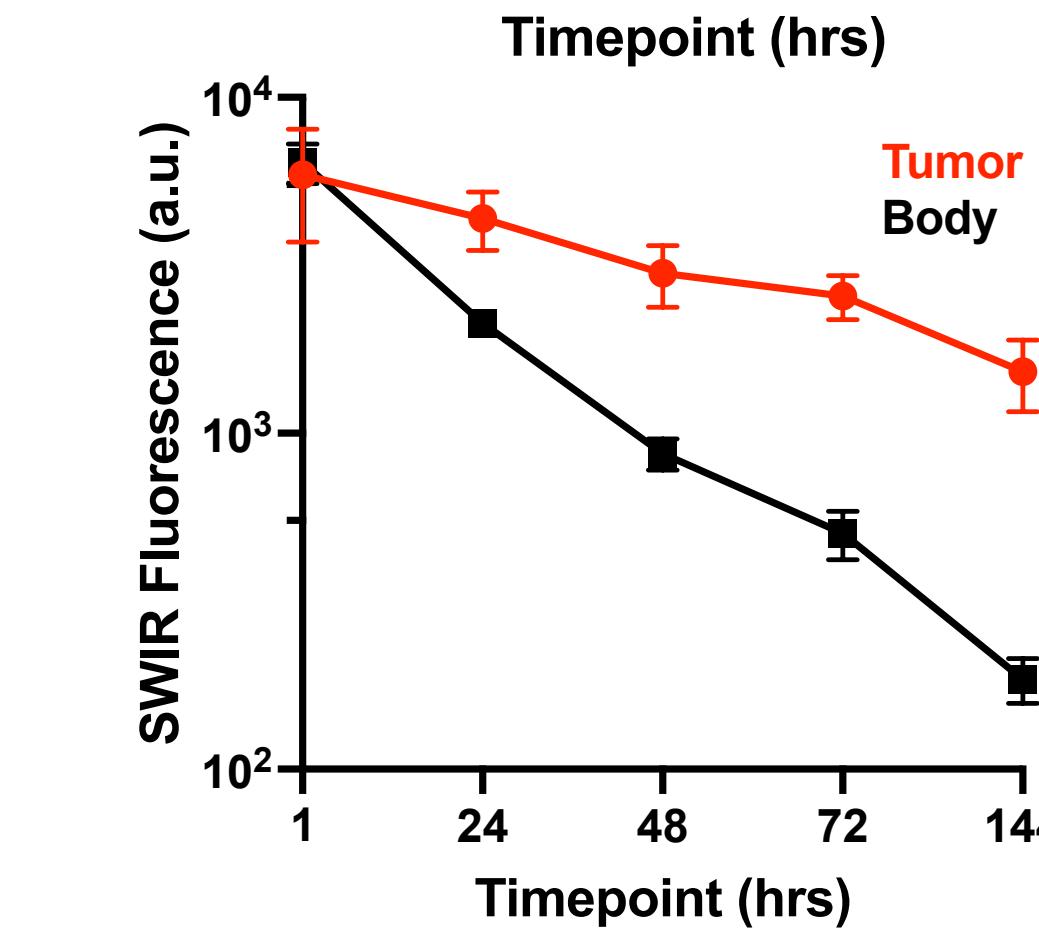
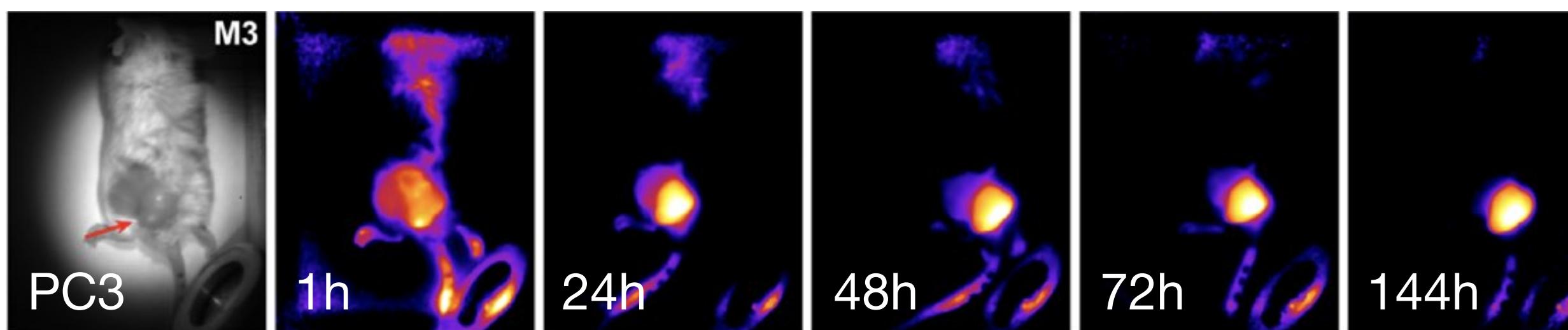
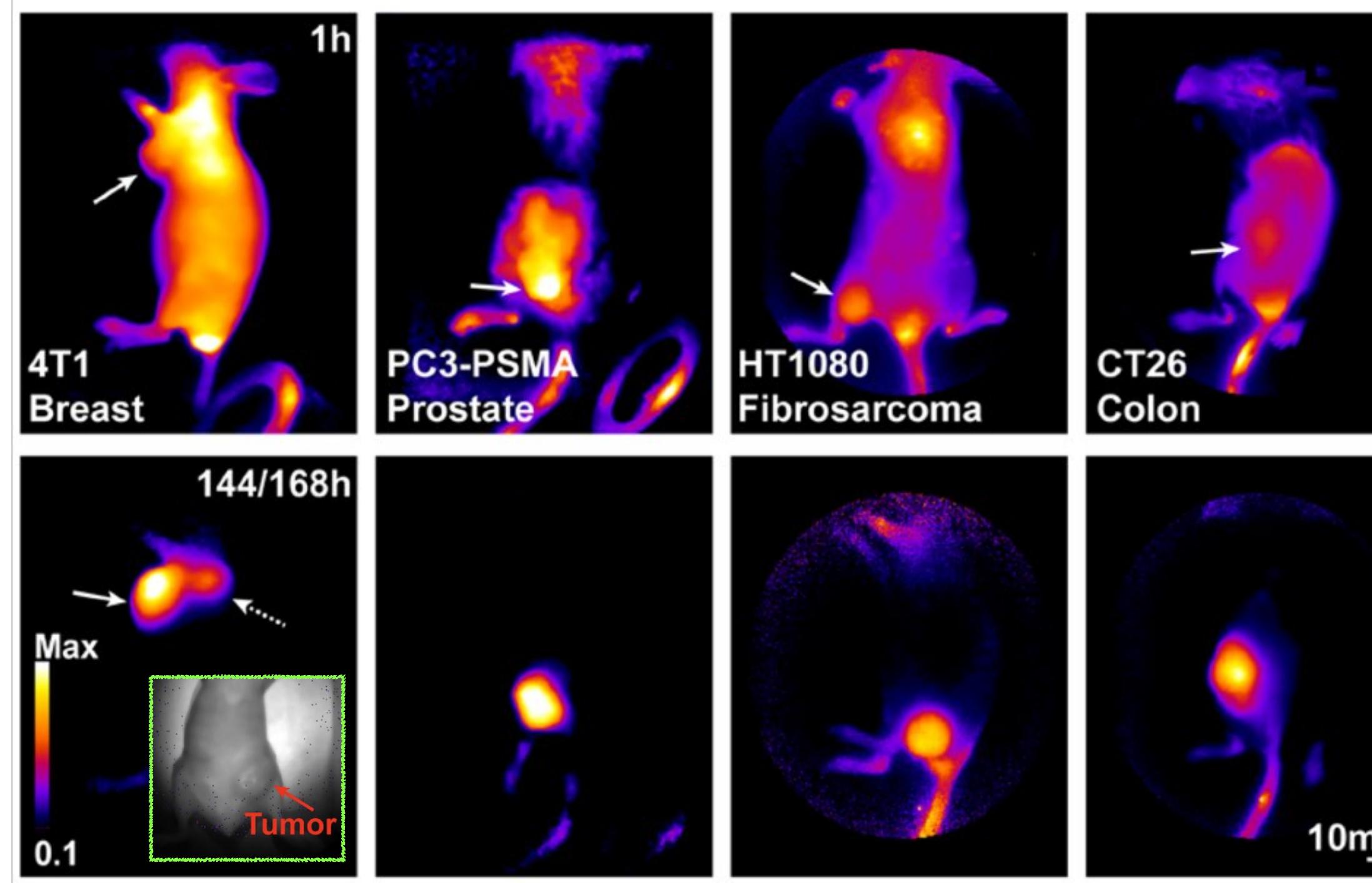
Pan-cancer seeking NIR/SWIR agent



Pan-cancer seeking NIR/SWIR agent

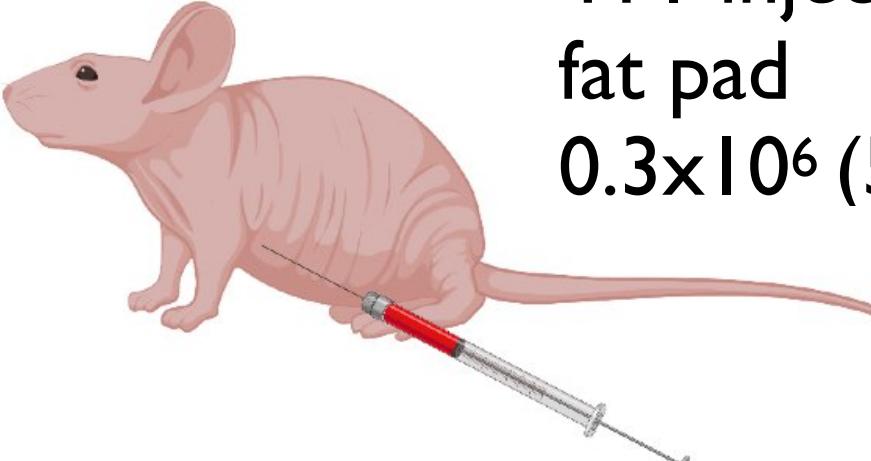


Pan-cancer seeking NIR/SWIR agent



Novel SWIR agent CJ215

4T1 injection into a mammary fat pad
 0.3×10^6 (5, FoxN1^{nu} mice)



I week later
CJ215 I.V. injection, 2 mg/kg
(4 mice, 1 cntrl)

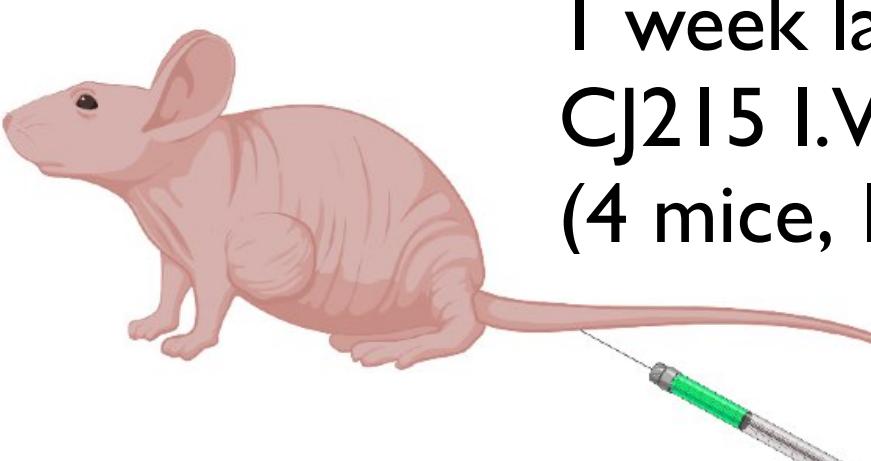
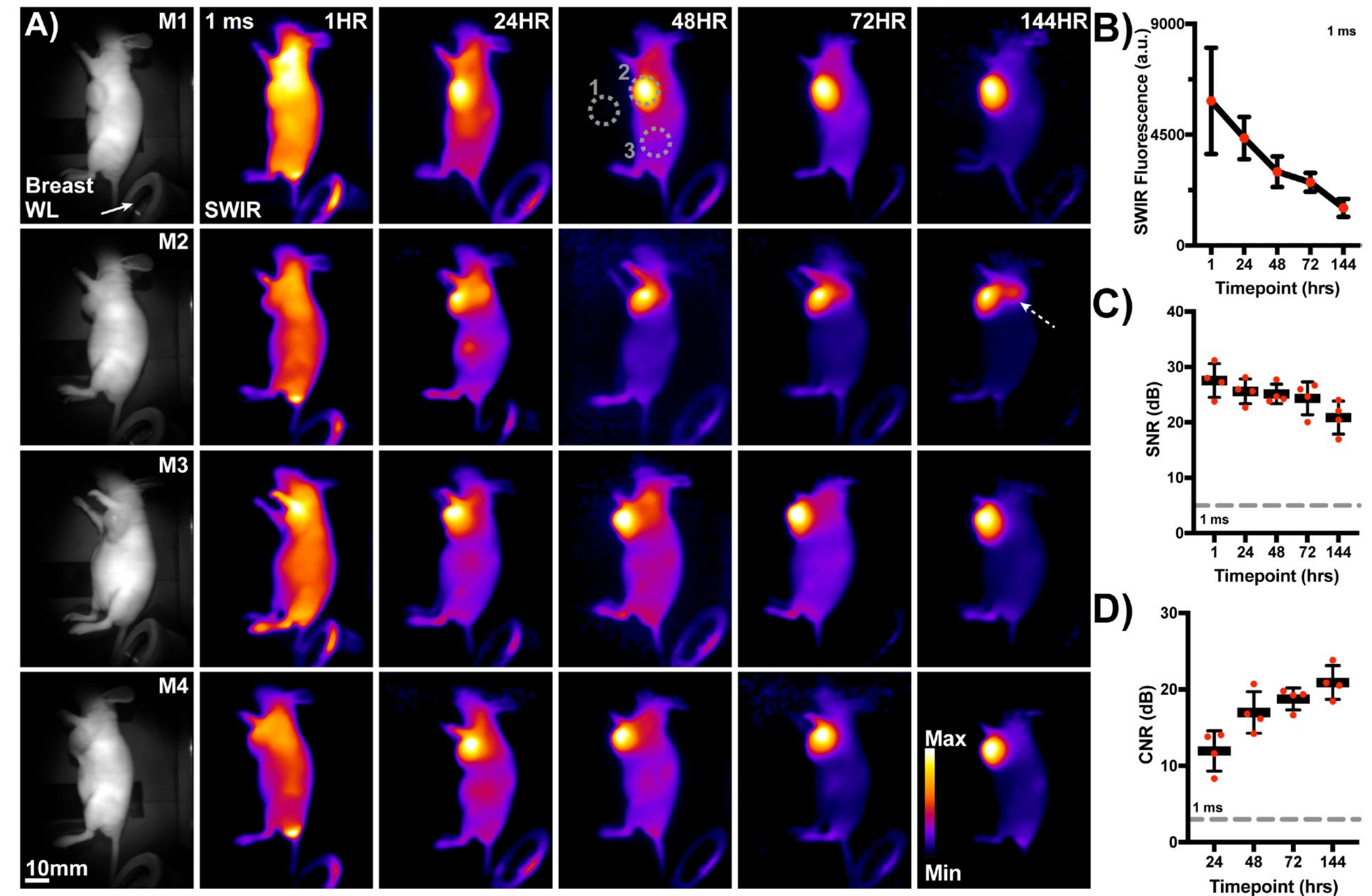
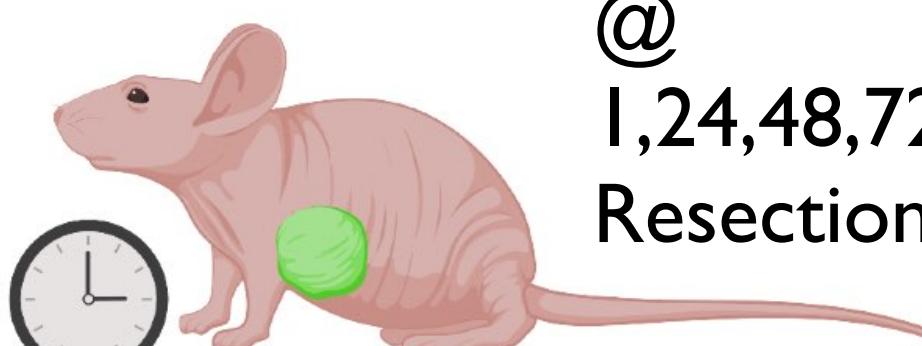
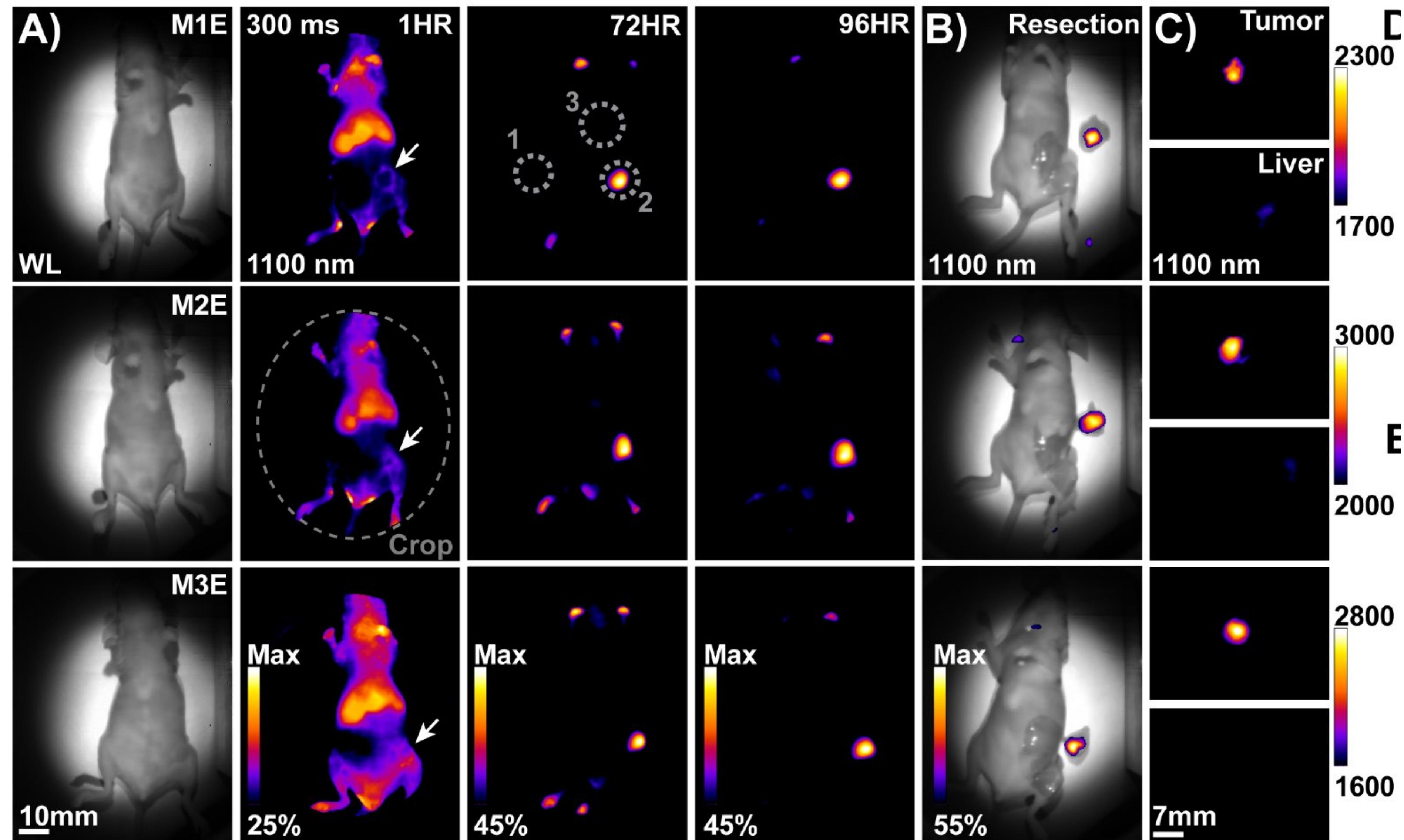


Image dye distribution & targeting
@
1,24,48,72 & 144 hrs
Resection @ 144 hrs

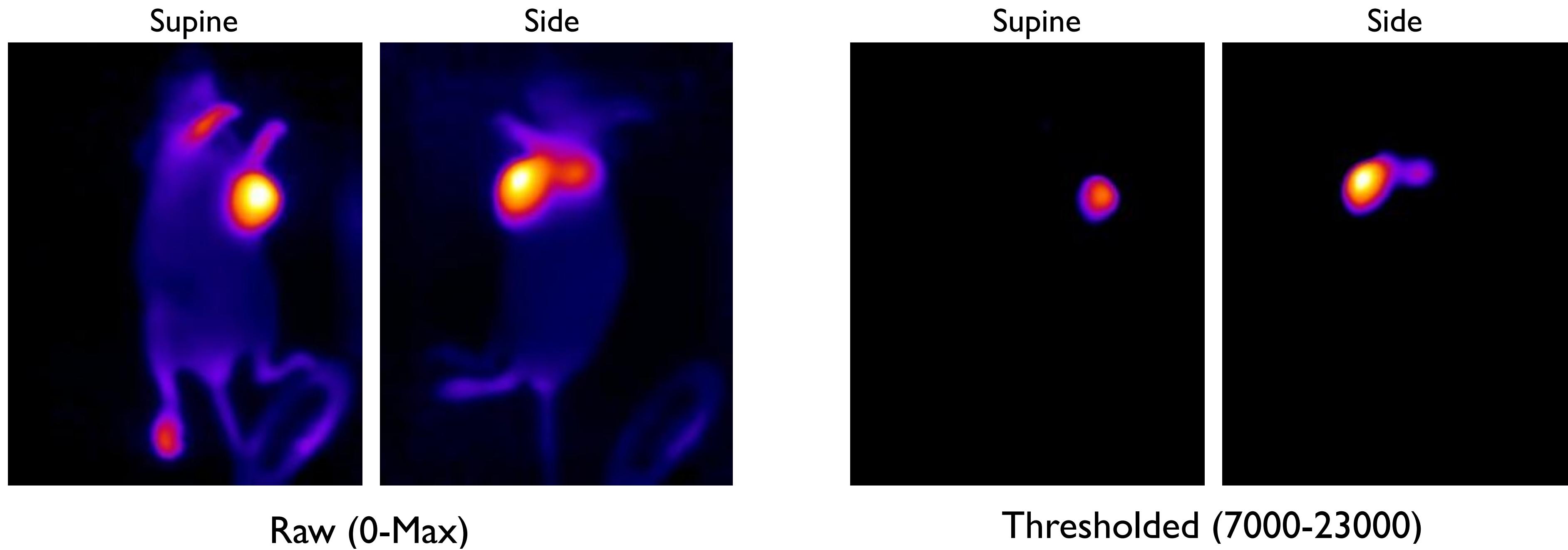


SWIR imaging in vivo

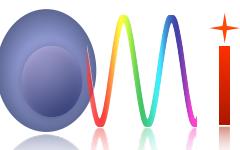


Video rate tumor screening in Contrast Mode

Video-rate images with 10 ms frame rate

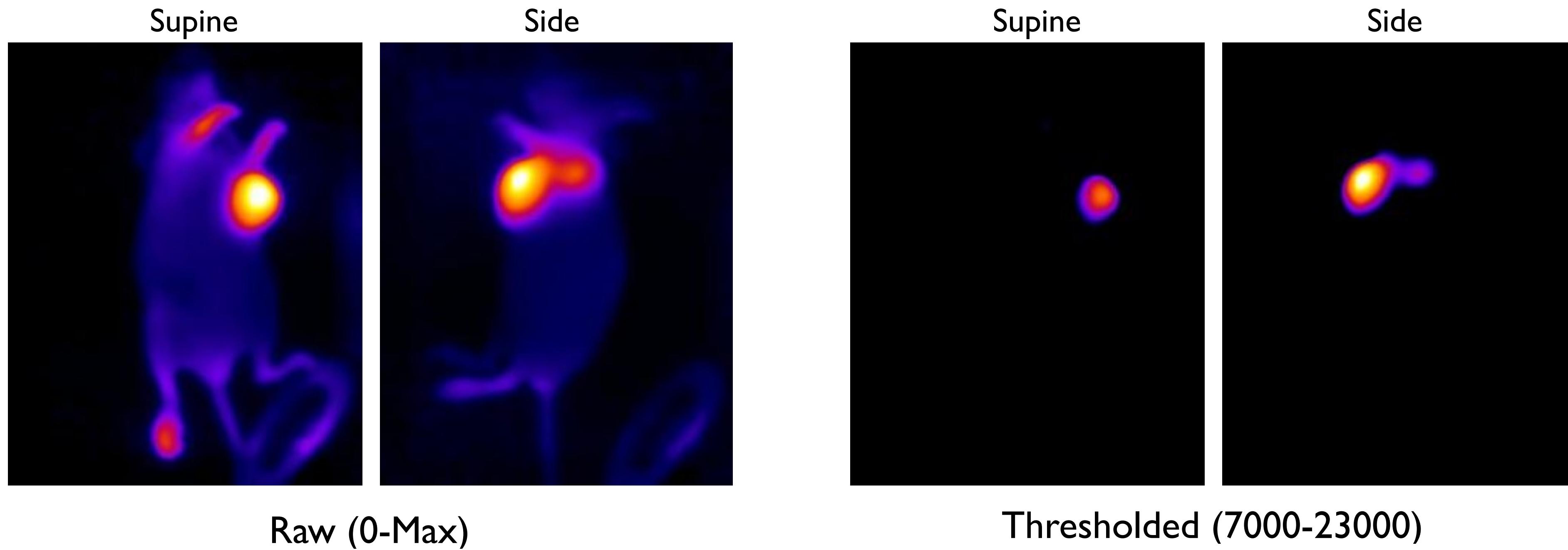


144h post injection (6 days)

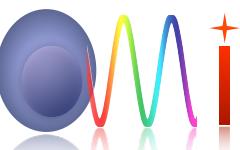


Video rate tumor screening in Contrast Mode

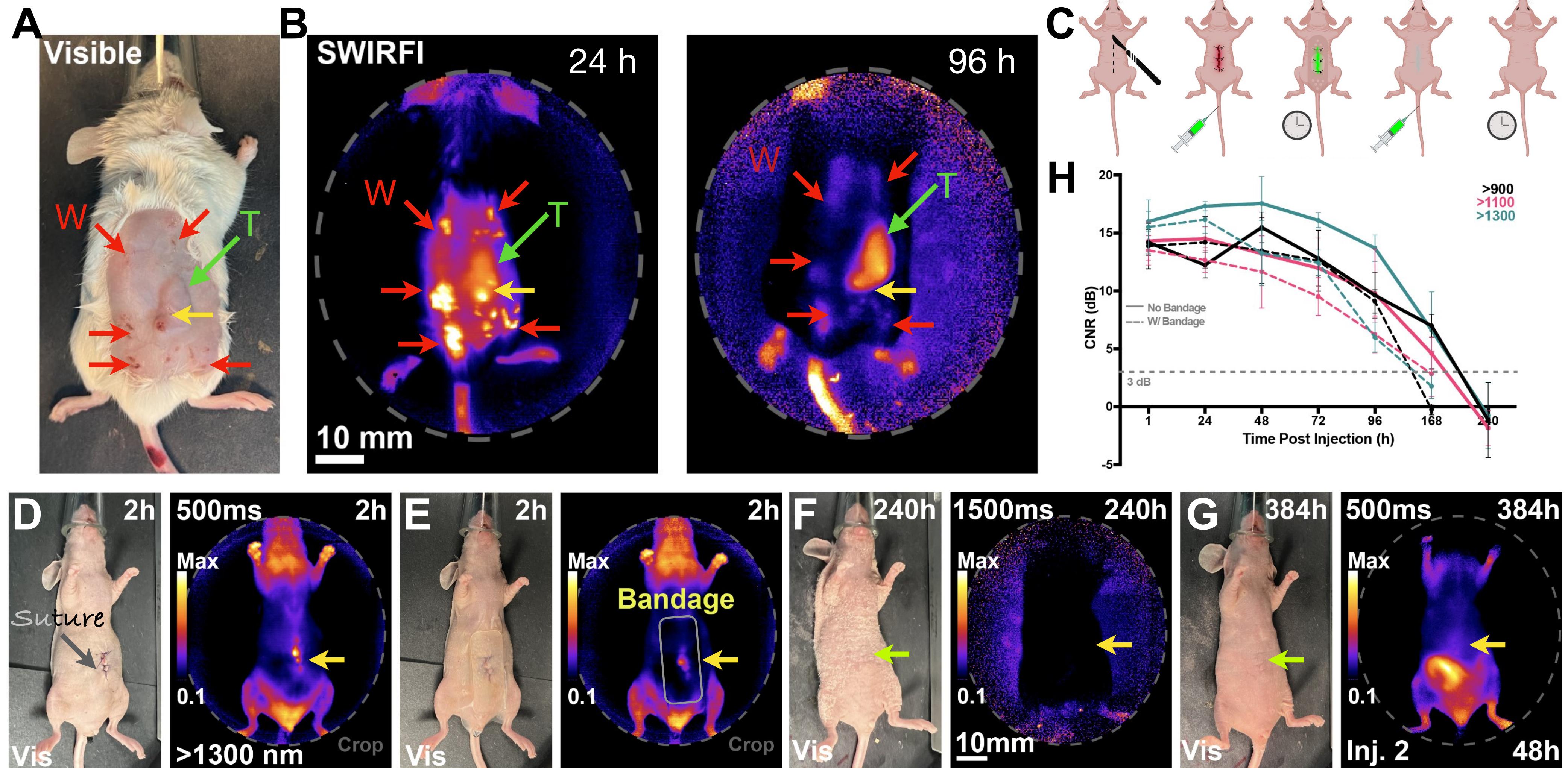
Video-rate images with 10 ms frame rate



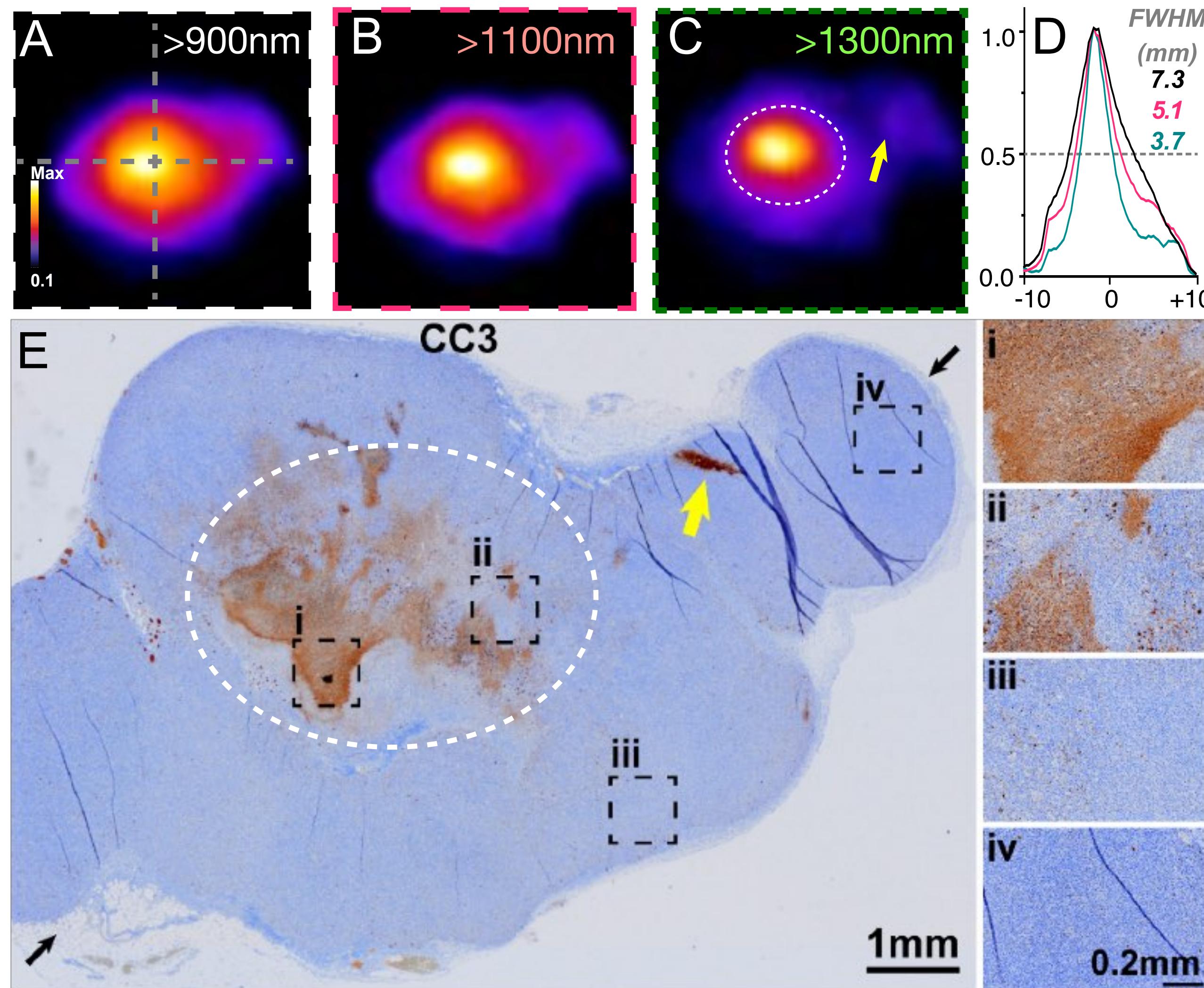
144h post injection (6 days)



Wound monitoring

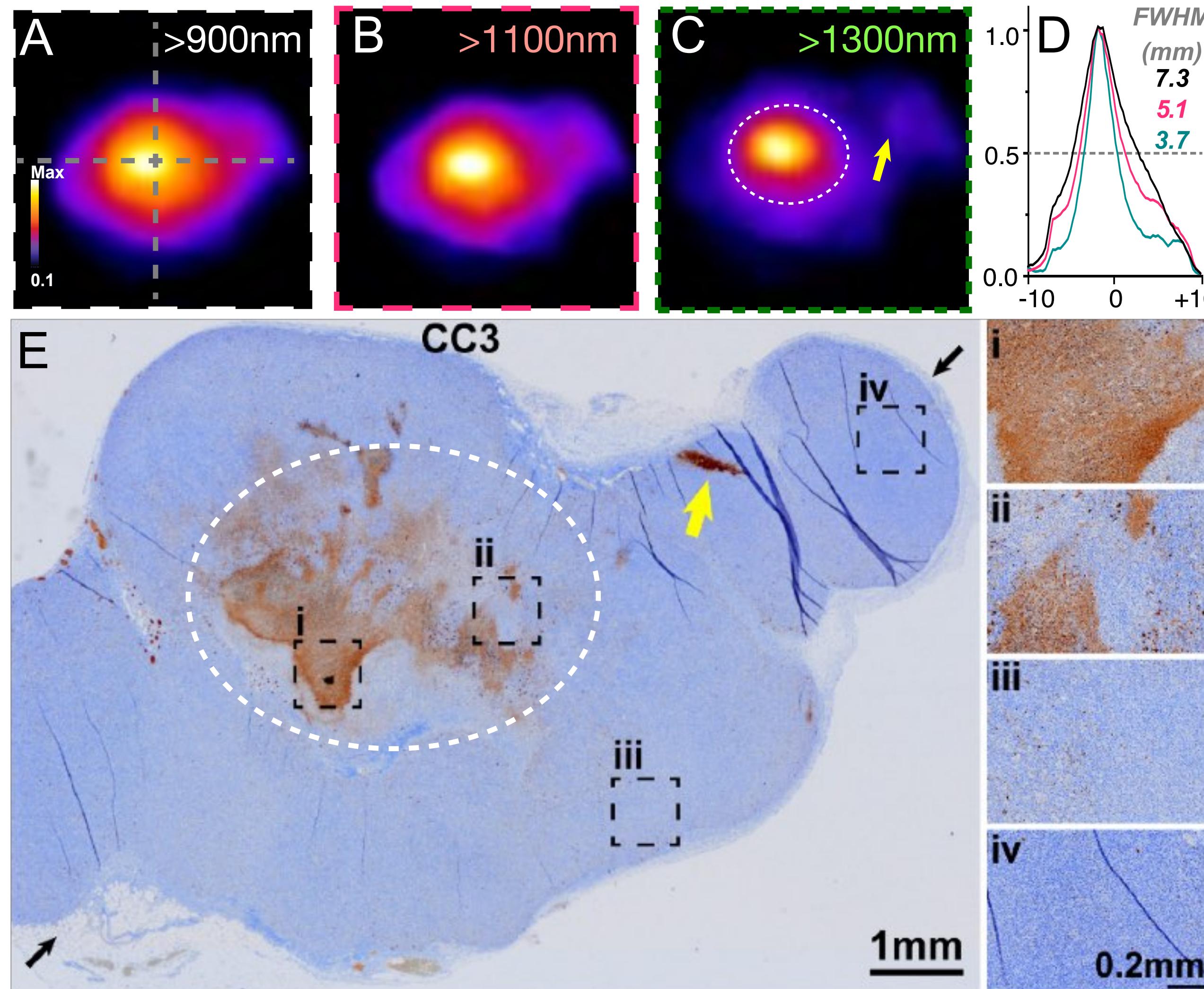


Mechanism?



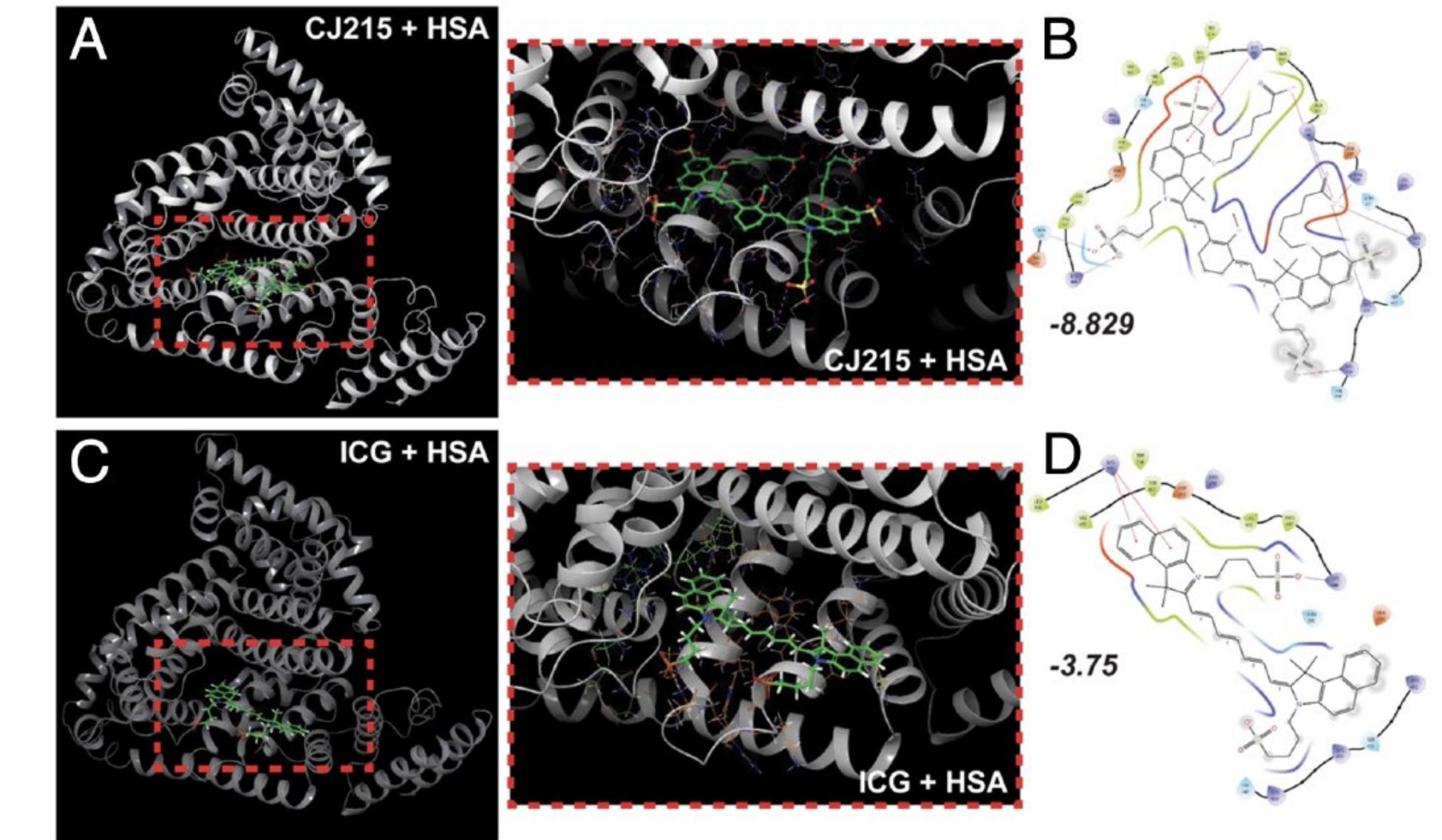
activated CathB

Mechanism?

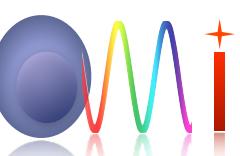
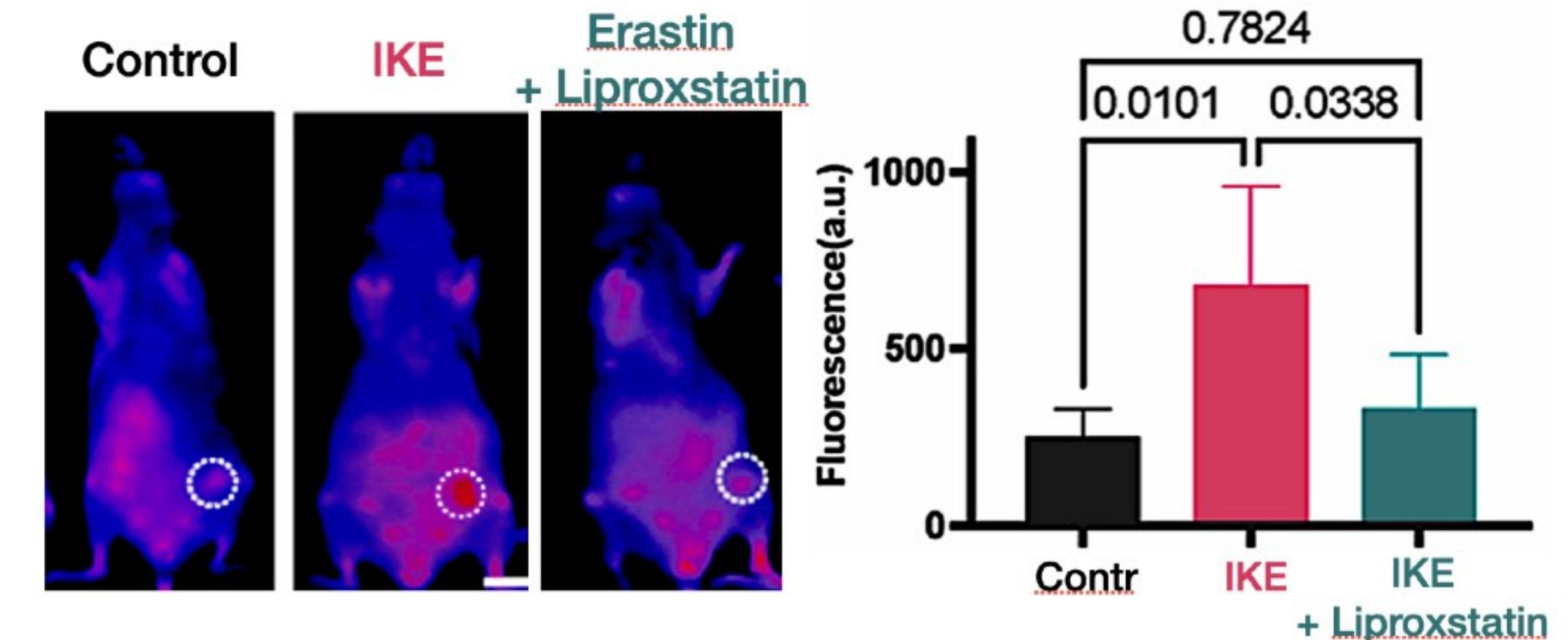
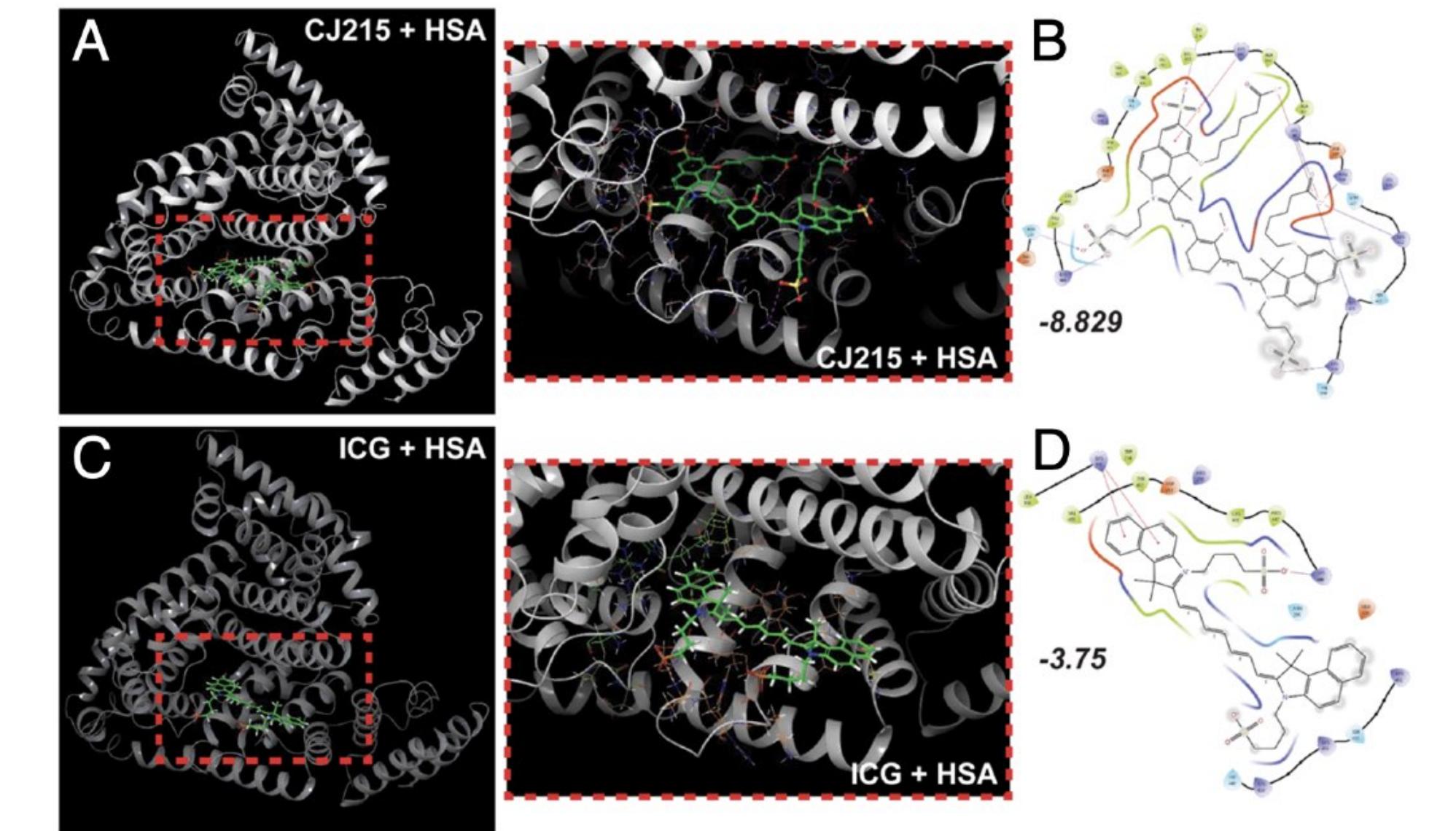
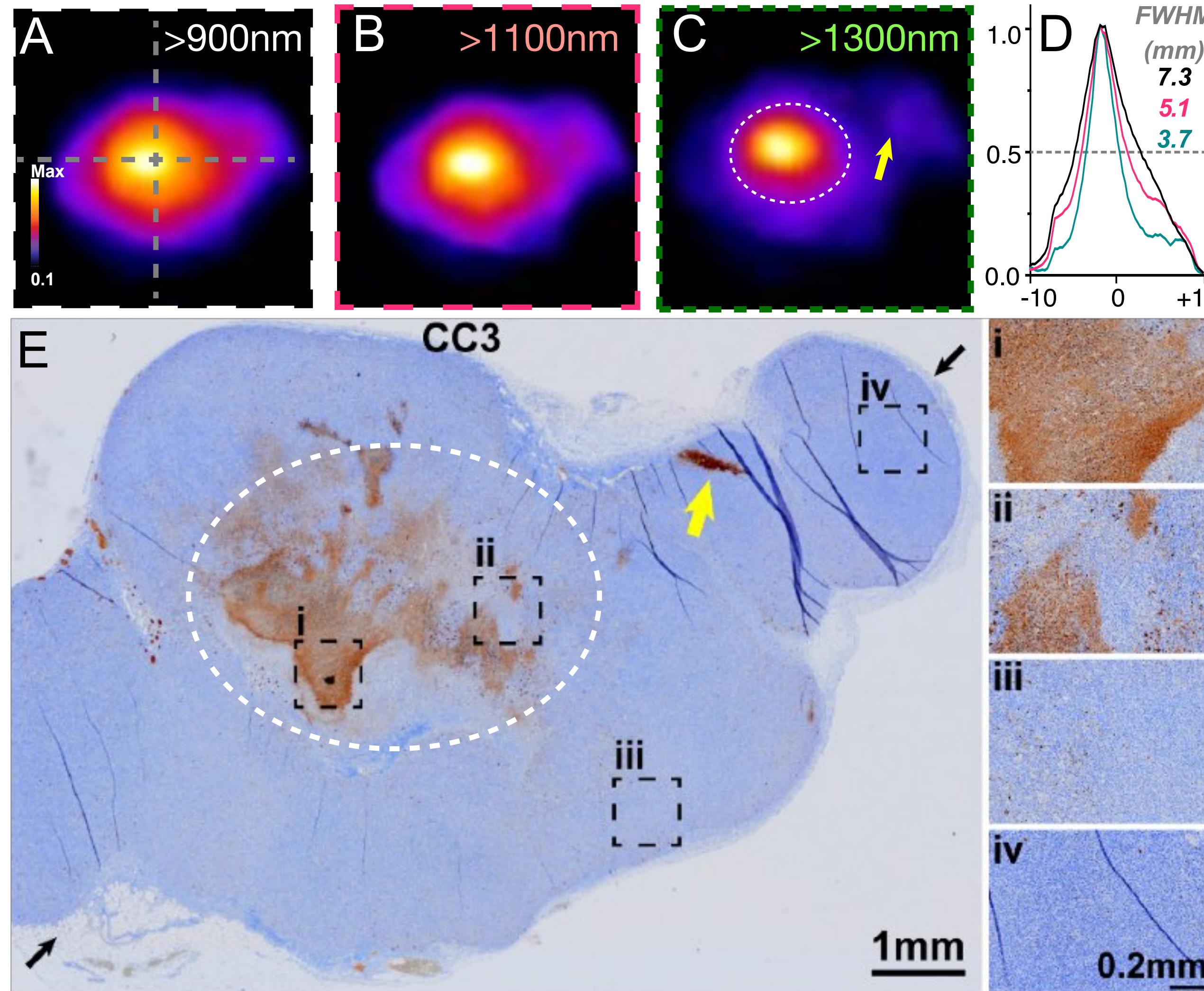


activated CathB

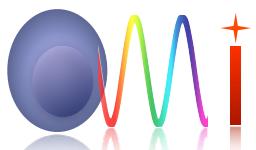
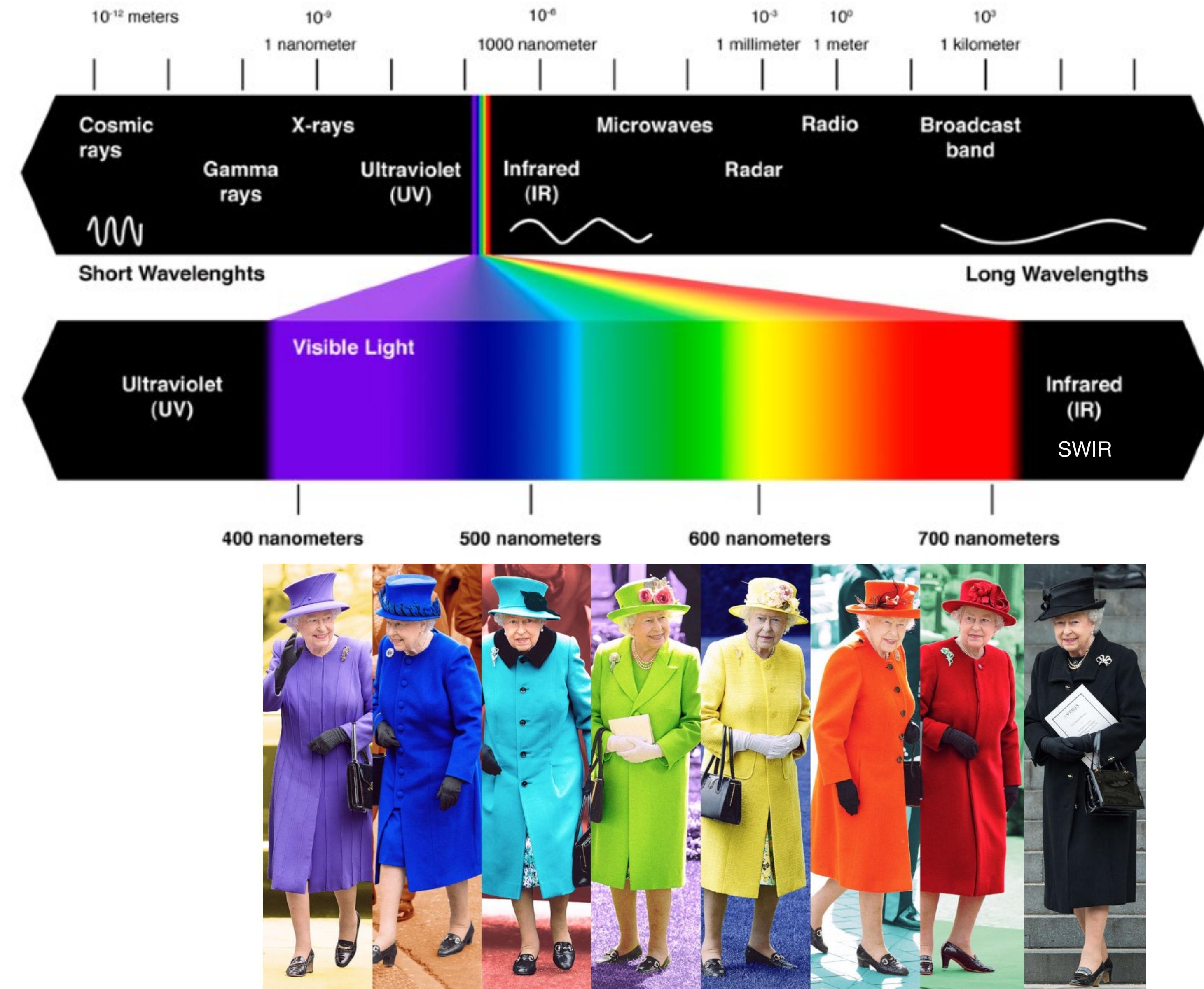
McLarney B et al (2024) Nature Biomedical Engineering 8(9):1092



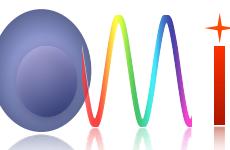
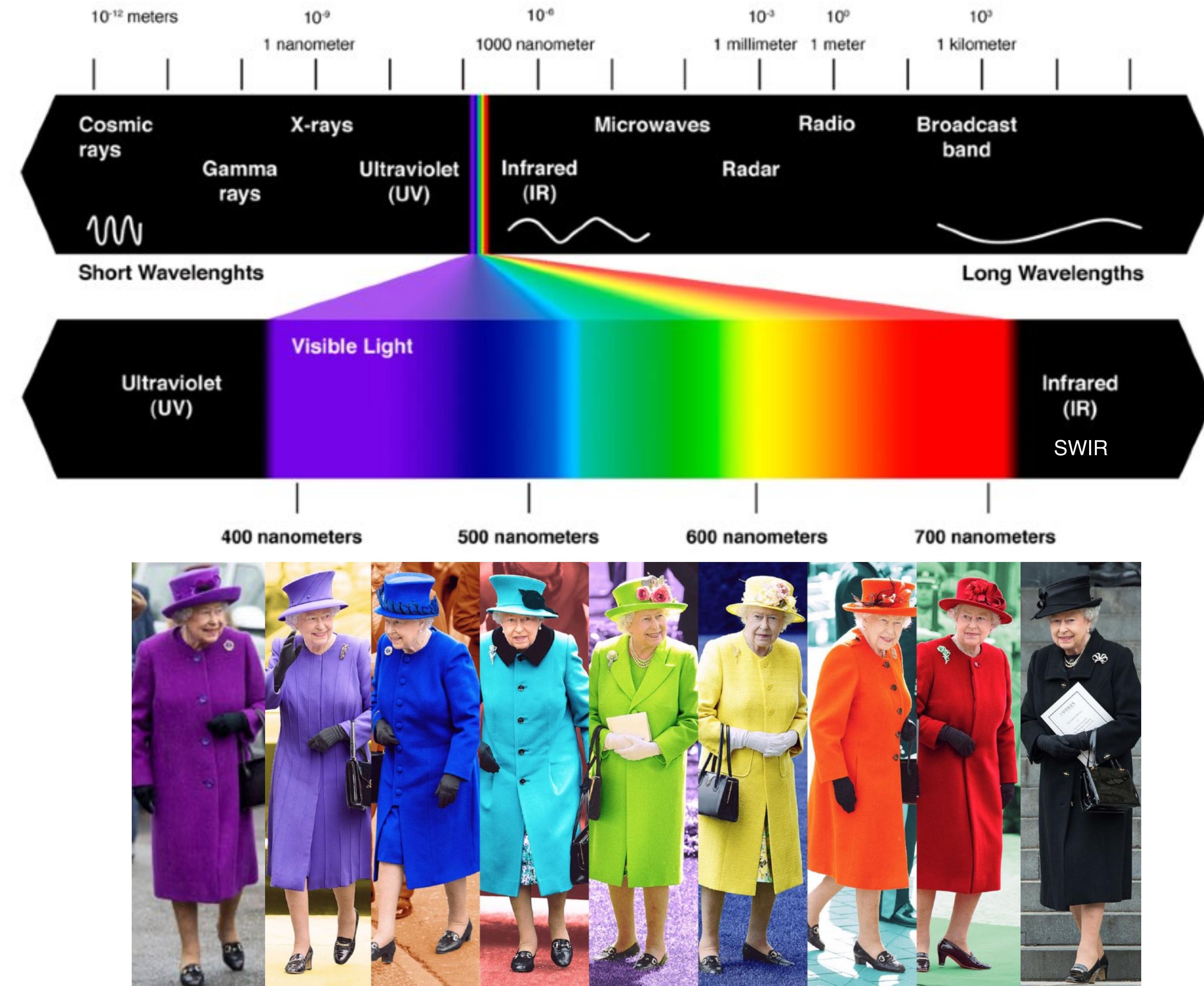
Mechanism?



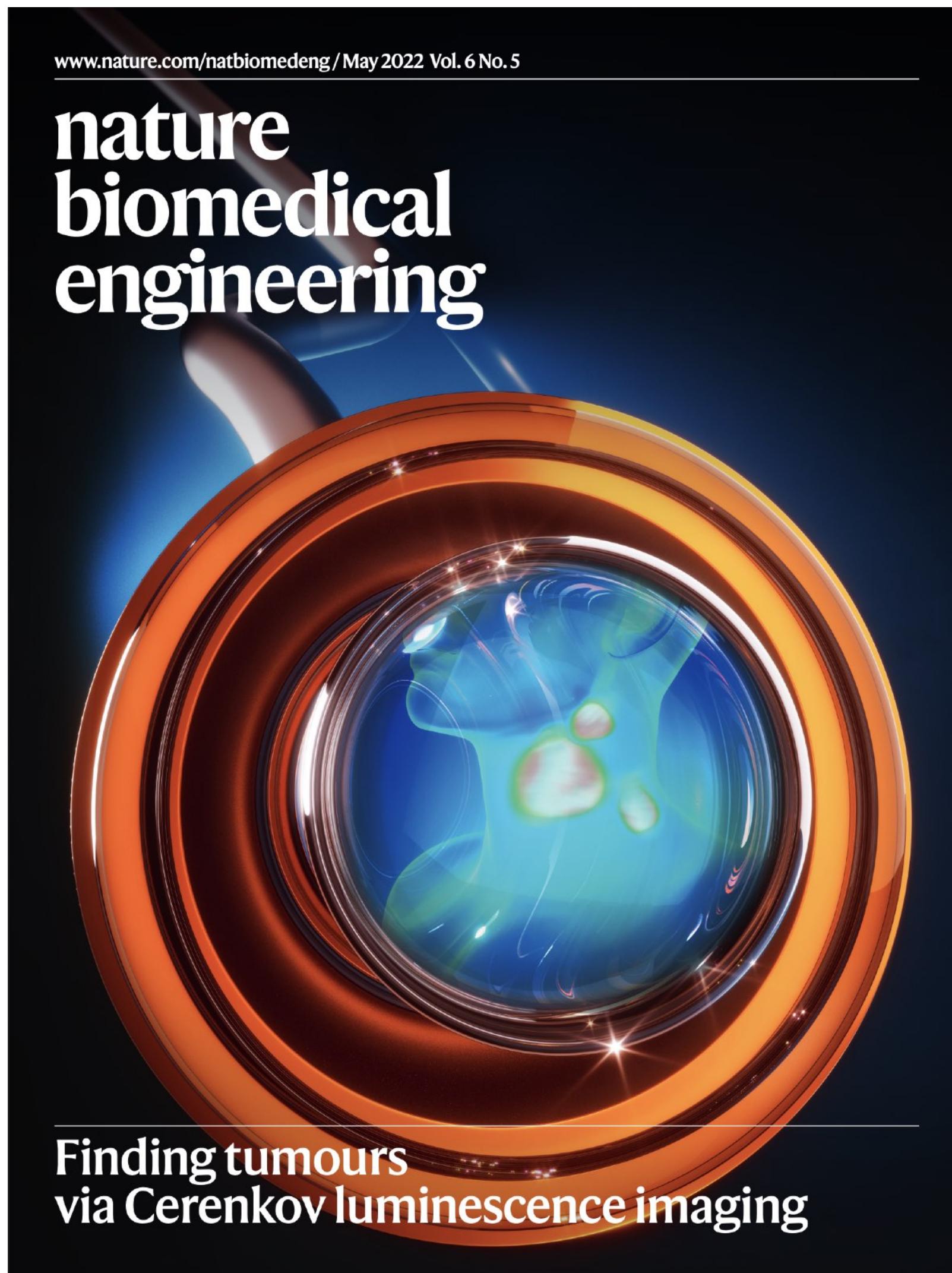
The other end of the spectrum



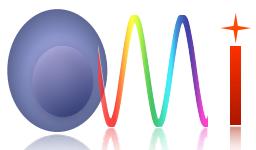
The other end of the spectrum



Overview



Cerenkov luminescence imaging - huh?

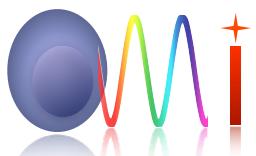


Overview



Cerenkov luminescence imaging - huh?

Preclinical concepts



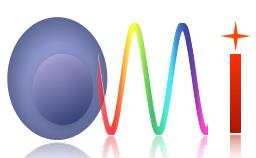
Overview



Cerenkov luminescence imaging - huh?

Preclinical concepts

Clinical translation



Overview

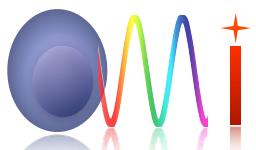


Cerenkov luminescence imaging - huh?

Preclinical concepts

Clinical translation

Theranostics



Overview



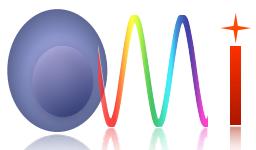
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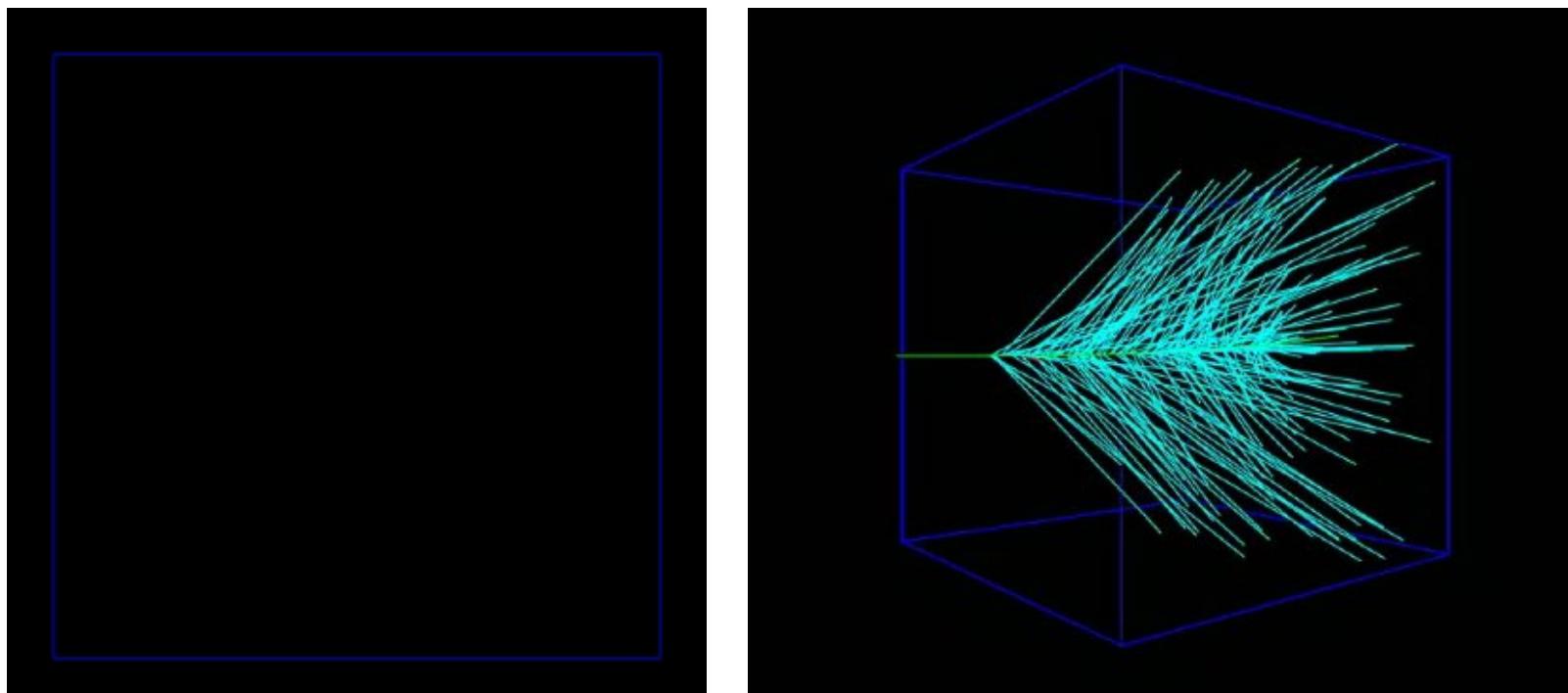
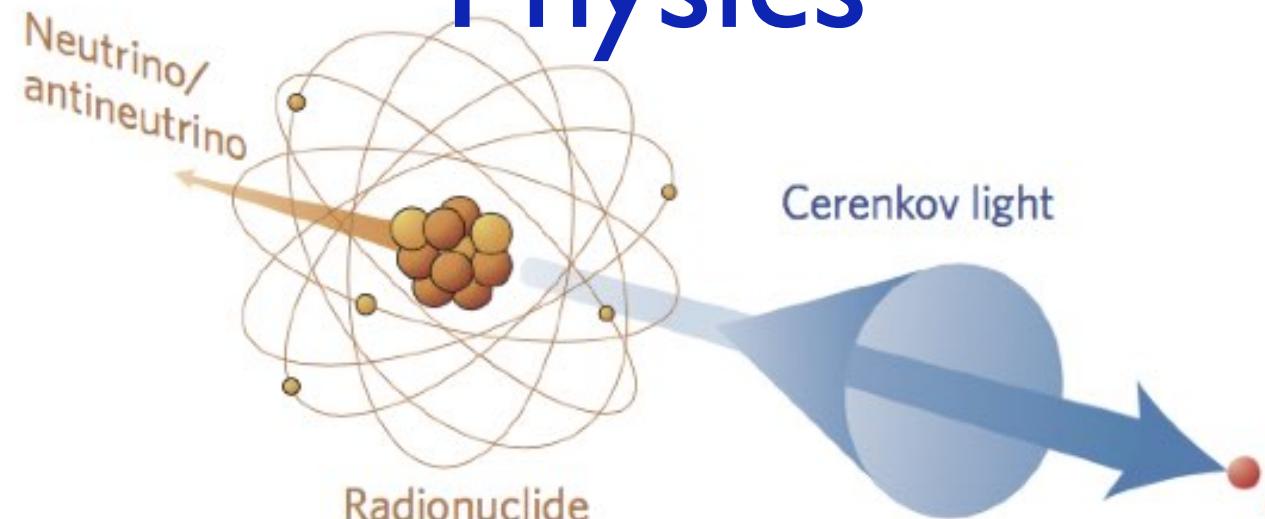
Theranostics

Outlook - and then some

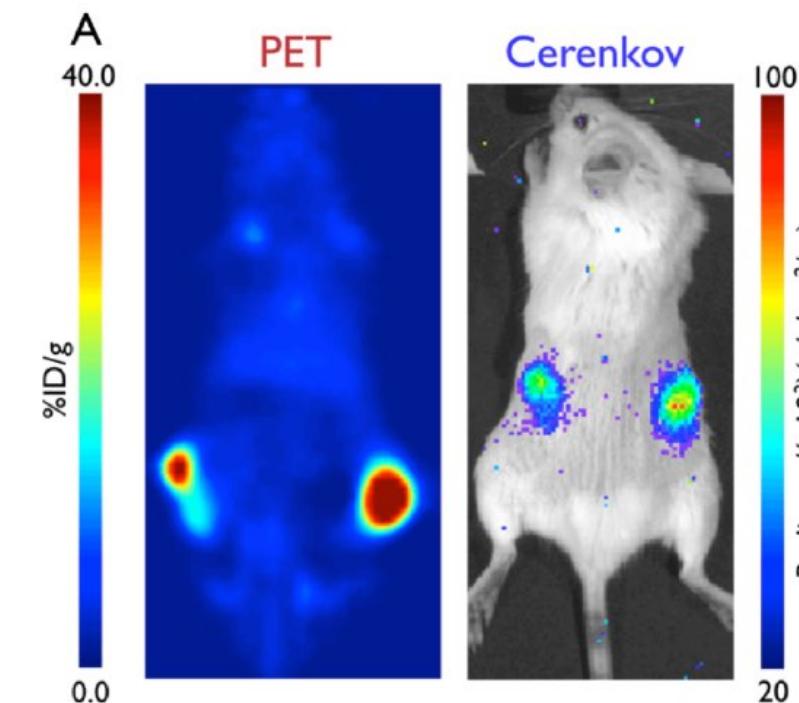
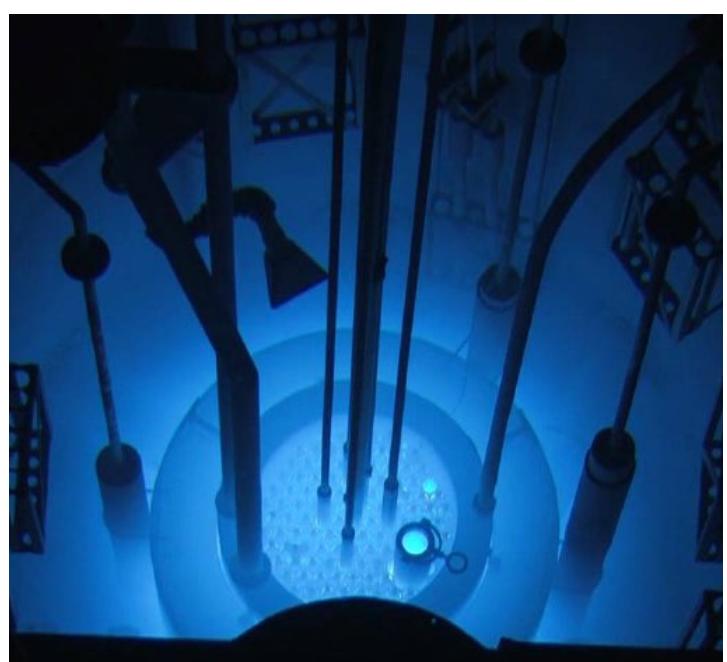


Cerenkov Luminescence Imaging

Physics



courtesy of Brian Pogue, Dartmouth College, NH



Ruggiero A et al. (2010) J Nucl Med 51(7): 1123

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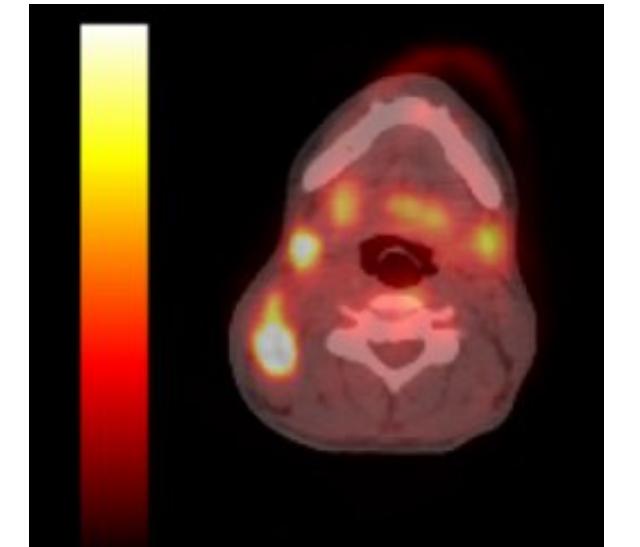
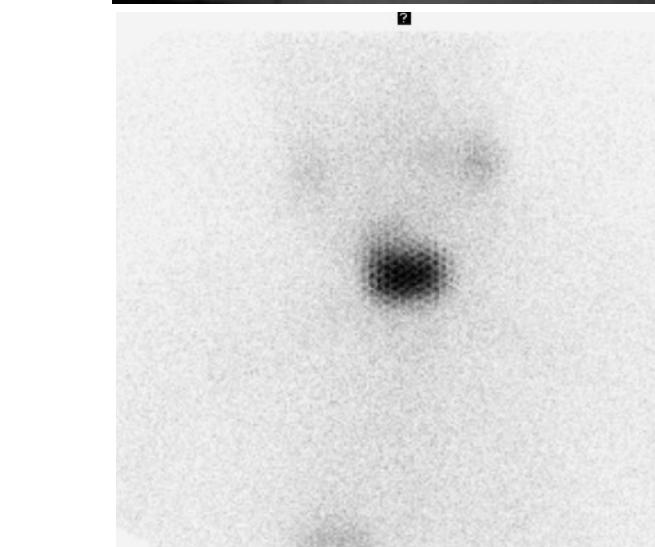
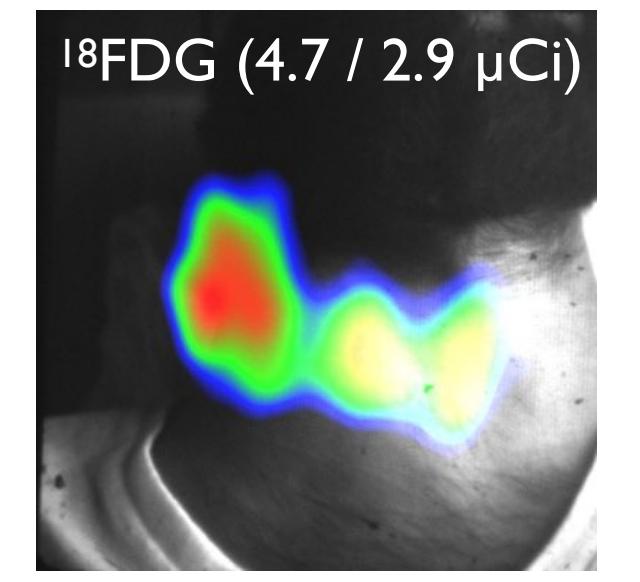
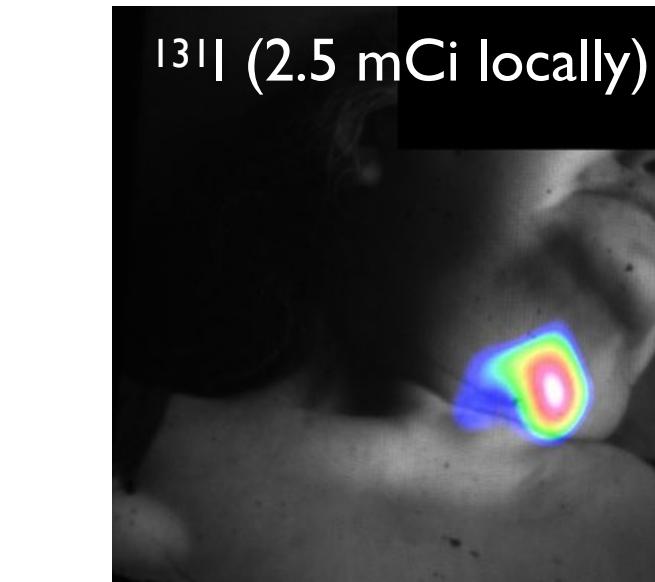
Thorek D et al. (2013) Nature Medicine 19(10):1345

Thorek D et al. (2014) J Nucl Med 55(1):95

Shaffer, Pratt and Grimm (2016) Nature Nanotechnology 12(2):106

Lockau H et al. (2018) J Nucl Med 59(2): 210

Clinical CLI



Das S et al. (2018) J Nucl Med 59(1):58

Grimm J (2018) Nature Biomedical Engineering (2): 205

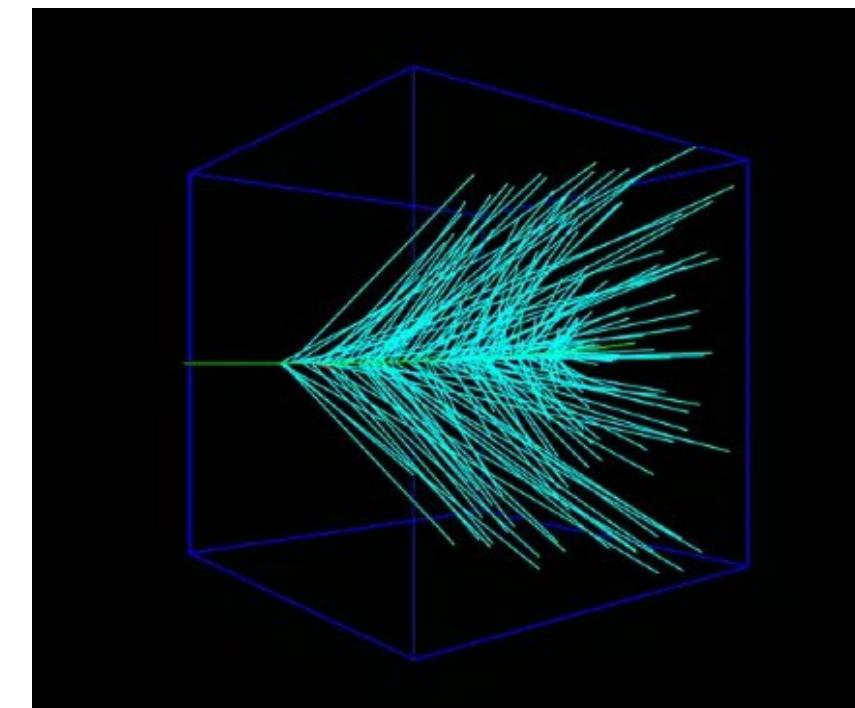
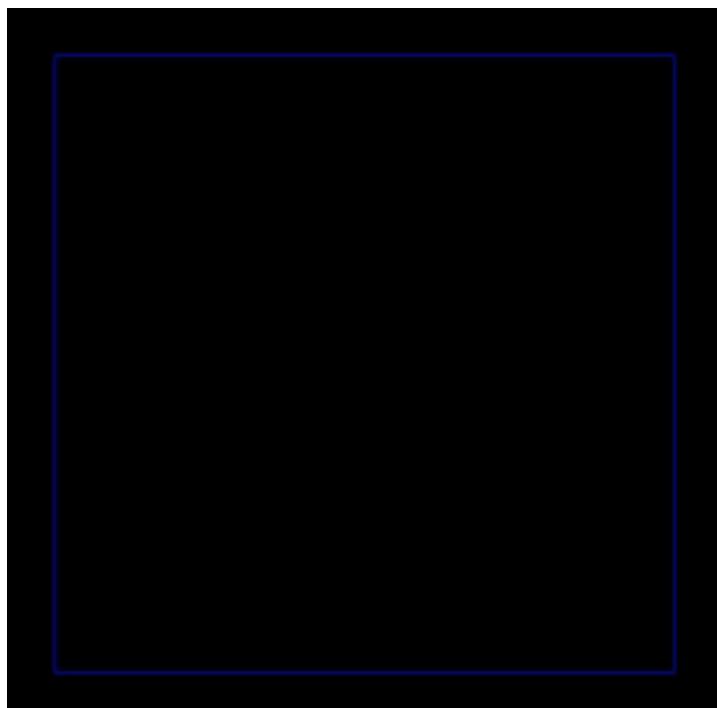
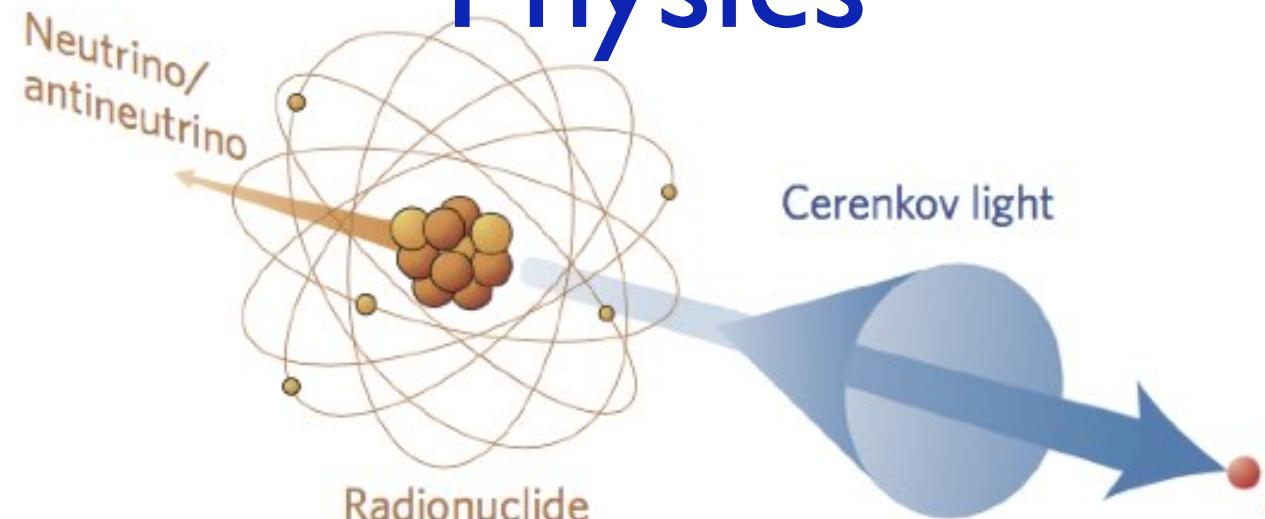
Pratt et al. (2018) Nature Nanotechnology 13(5): 418

Pratt et al. (2022) Nature Biomedical Engineering 6(5):559

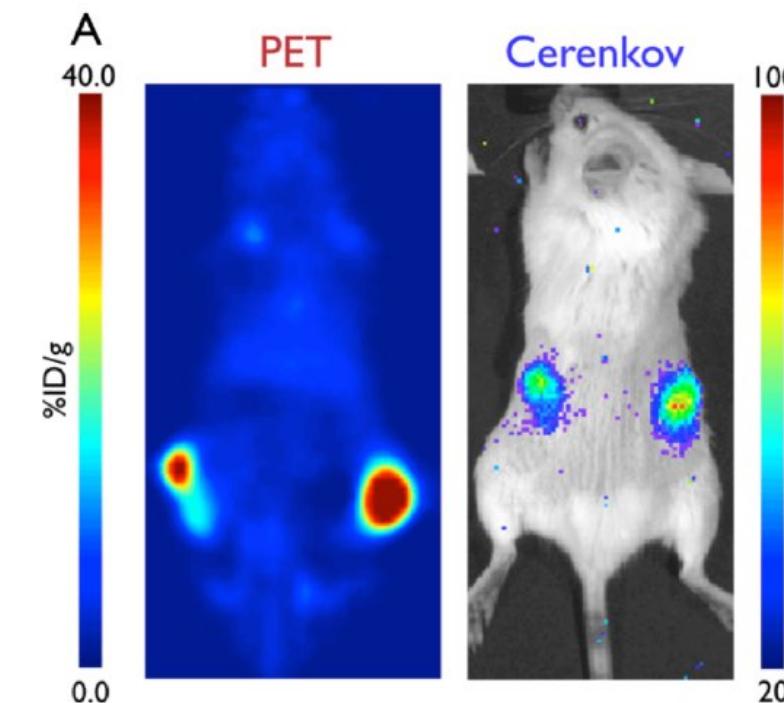
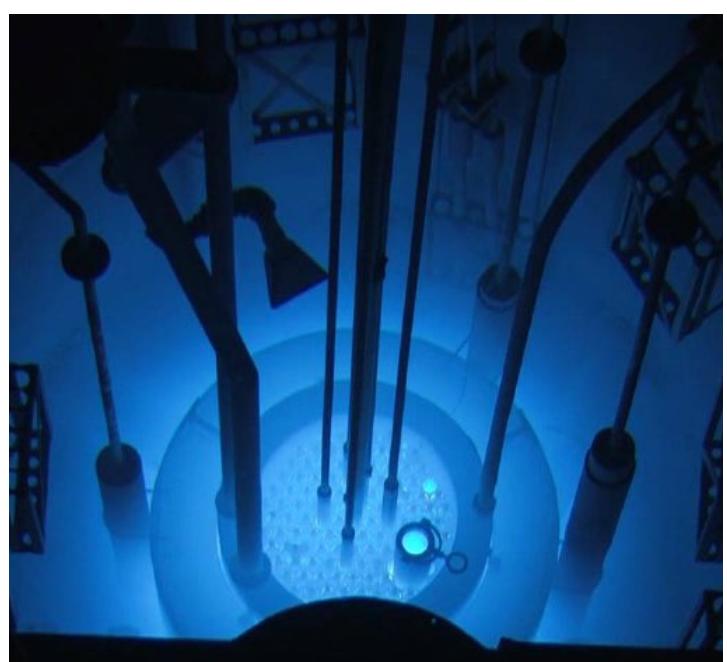


Cerenkov Luminescence Imaging

Physics

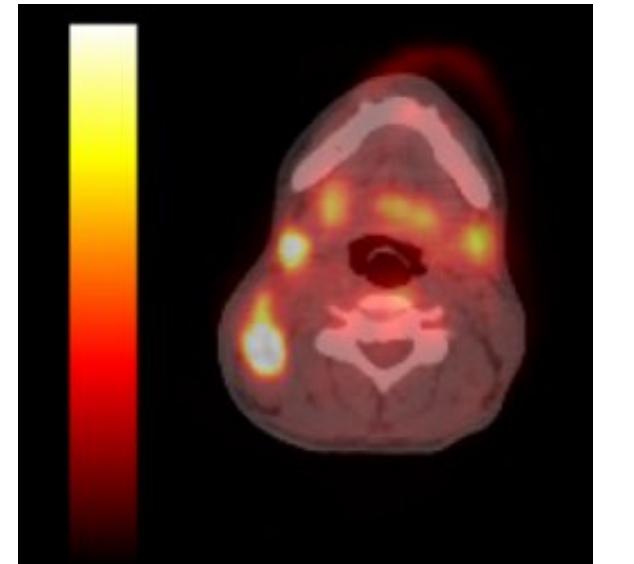
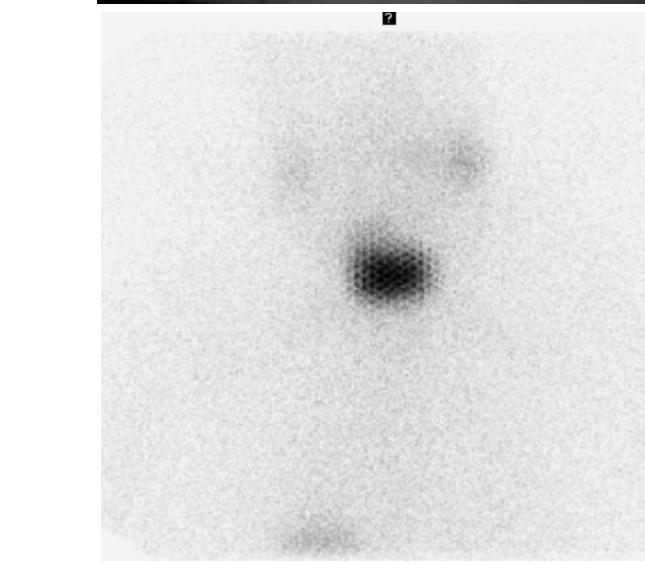
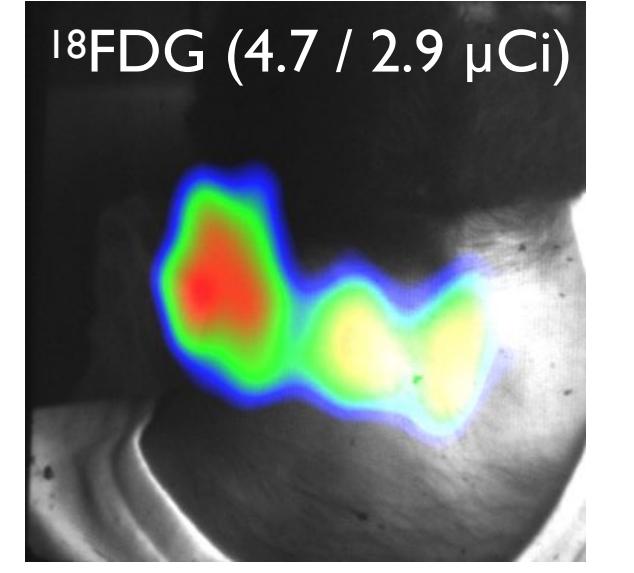
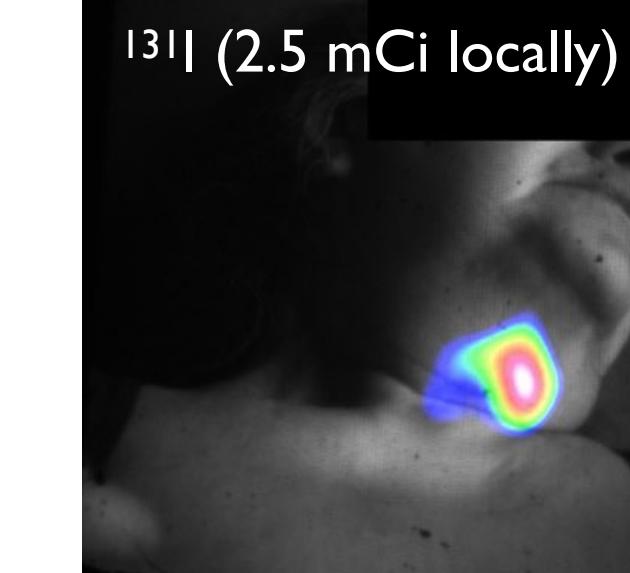


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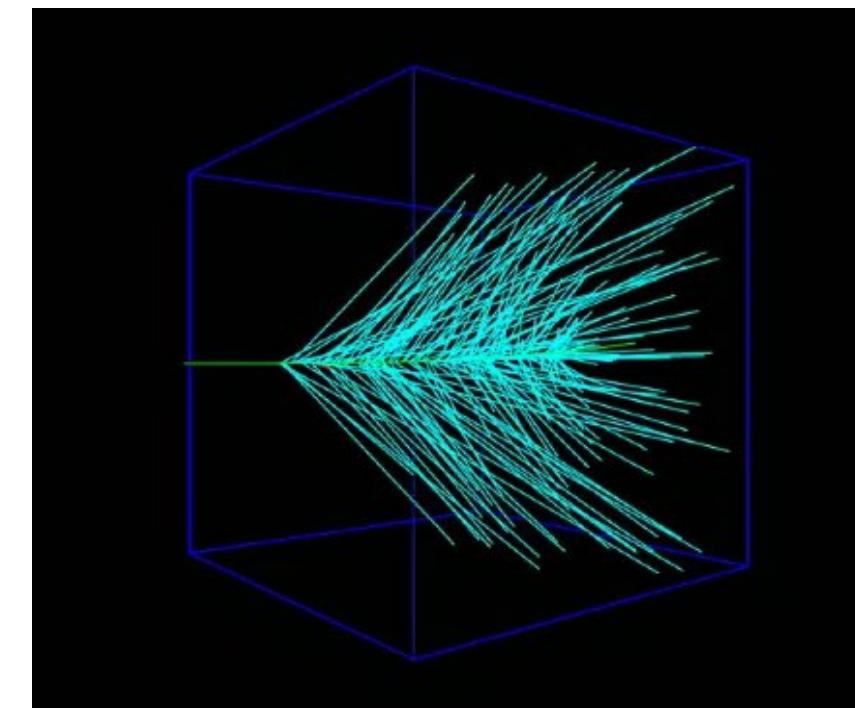
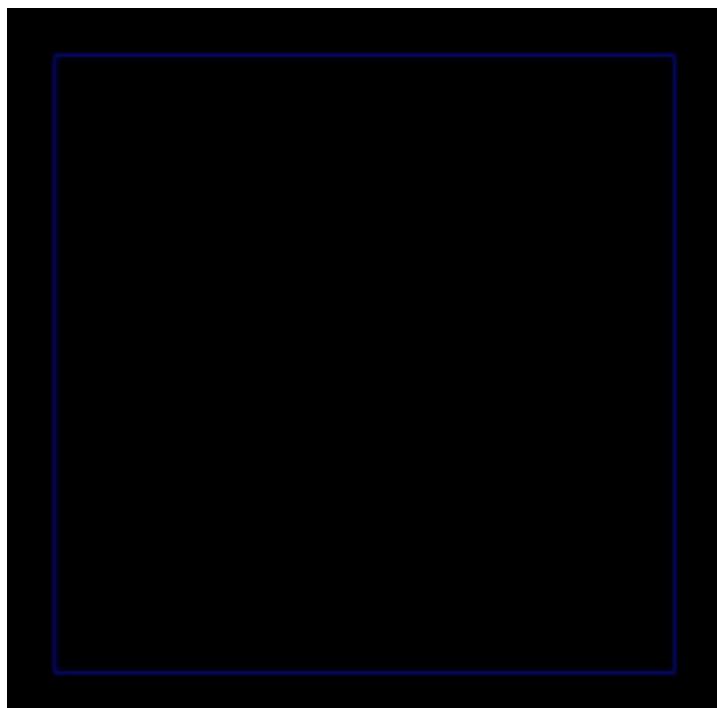
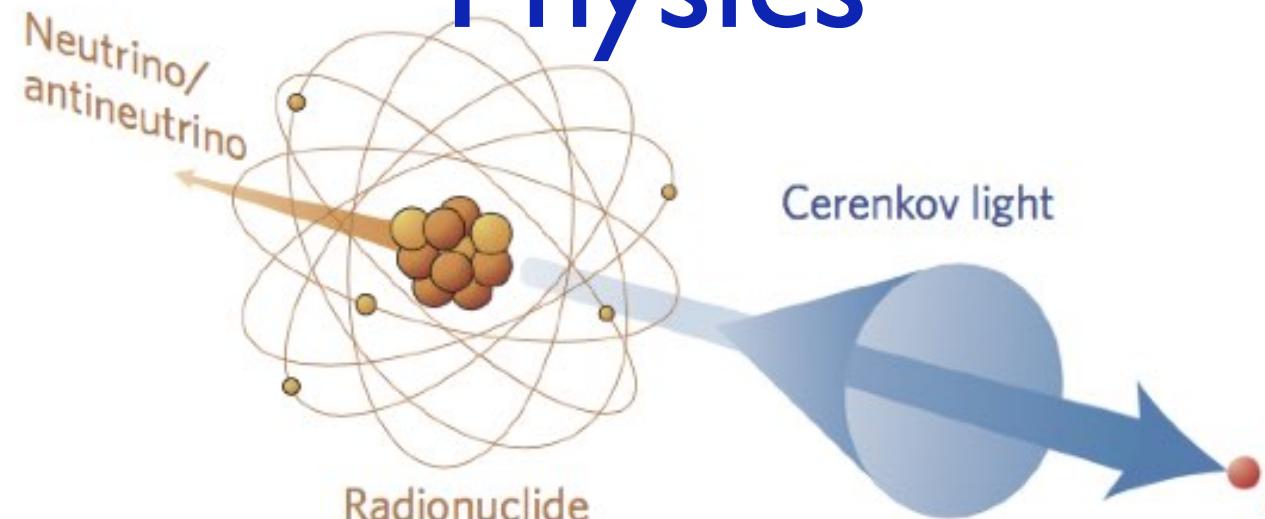
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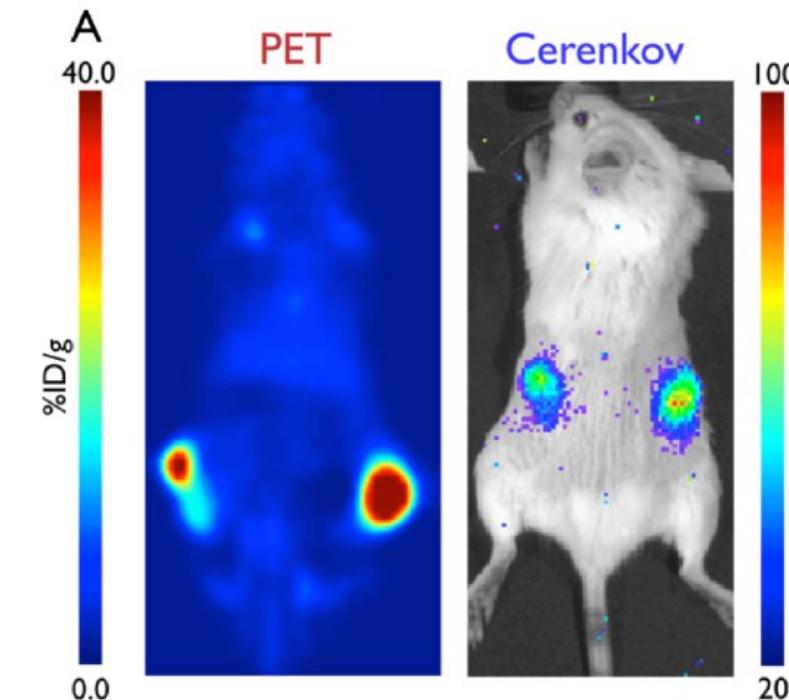
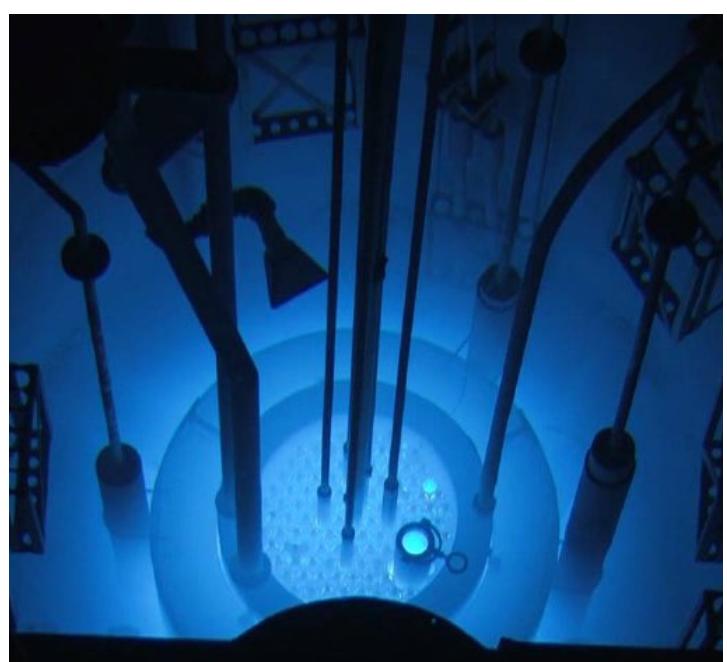


Cerenkov Luminescence Imaging

Physics



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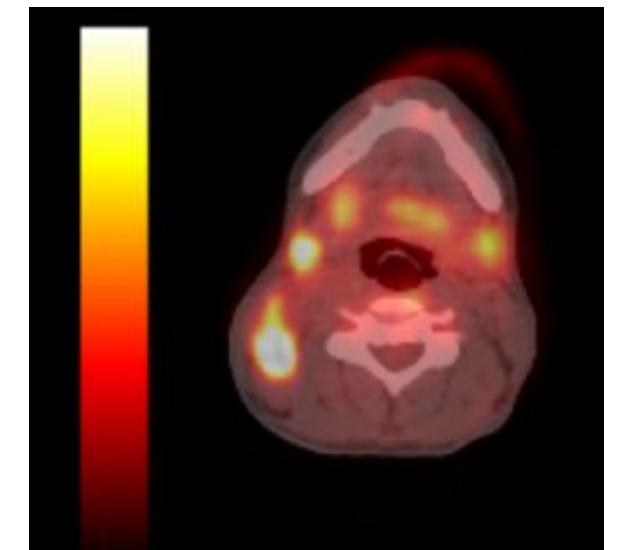
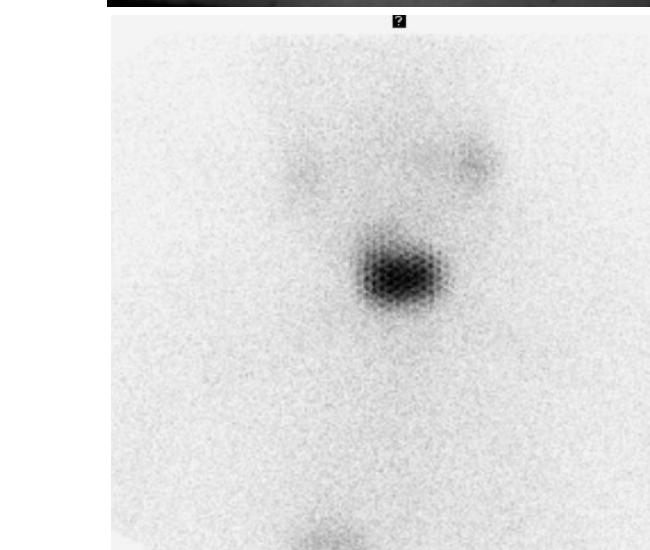
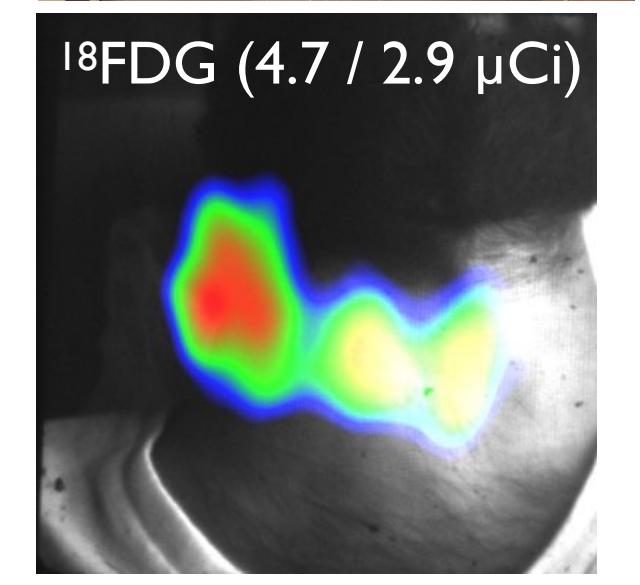
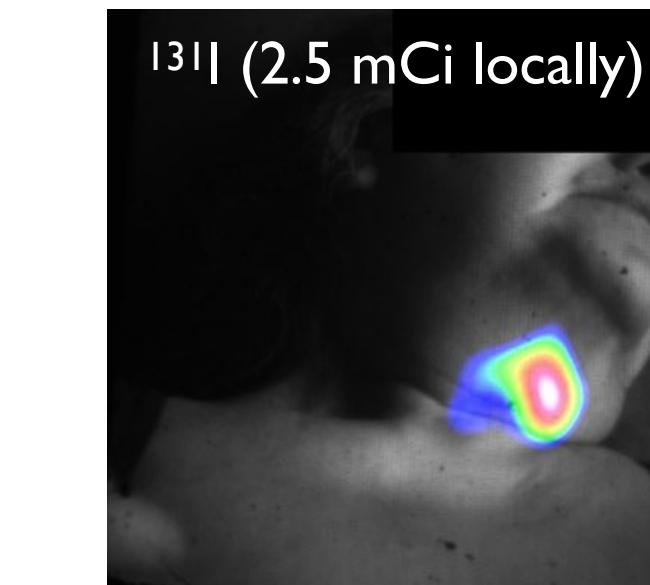
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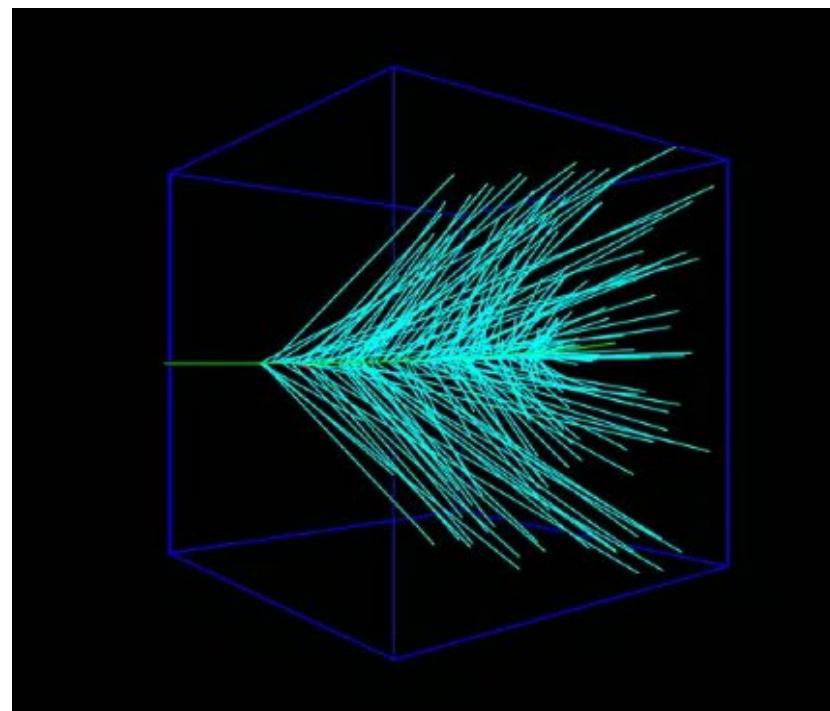
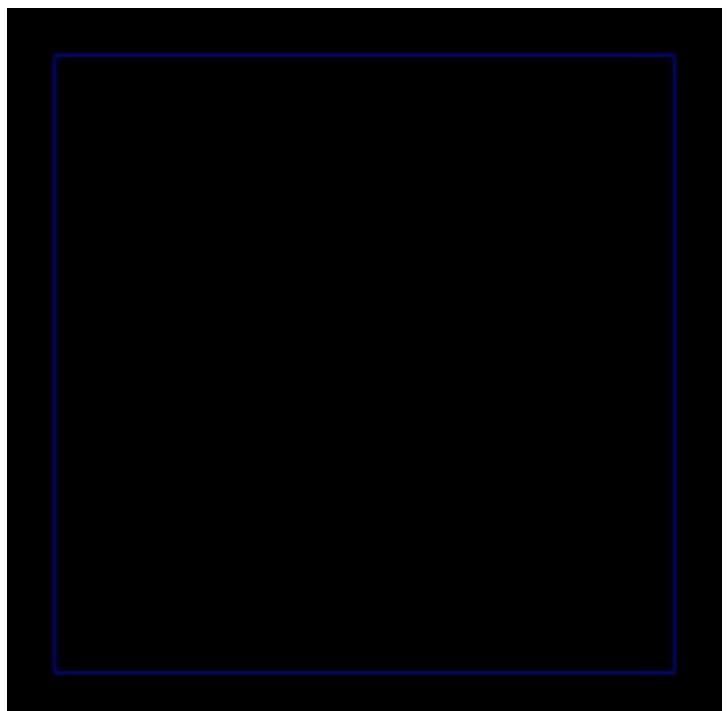
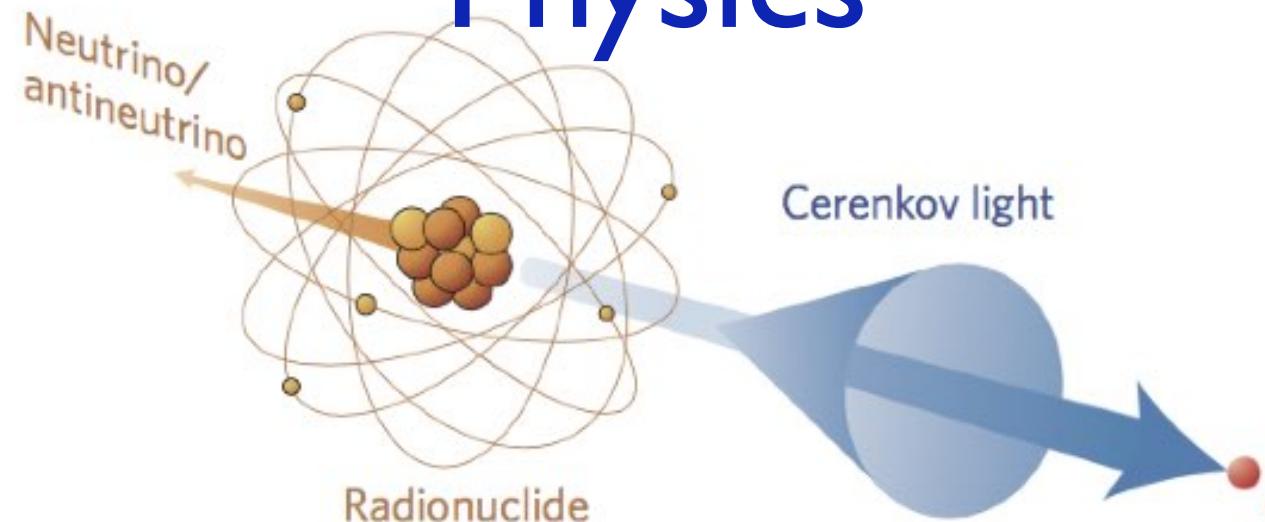
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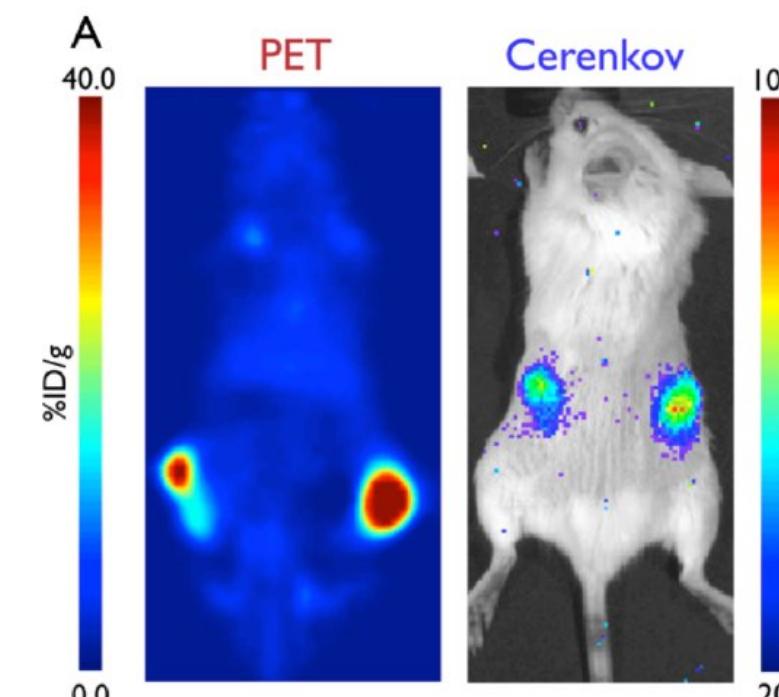
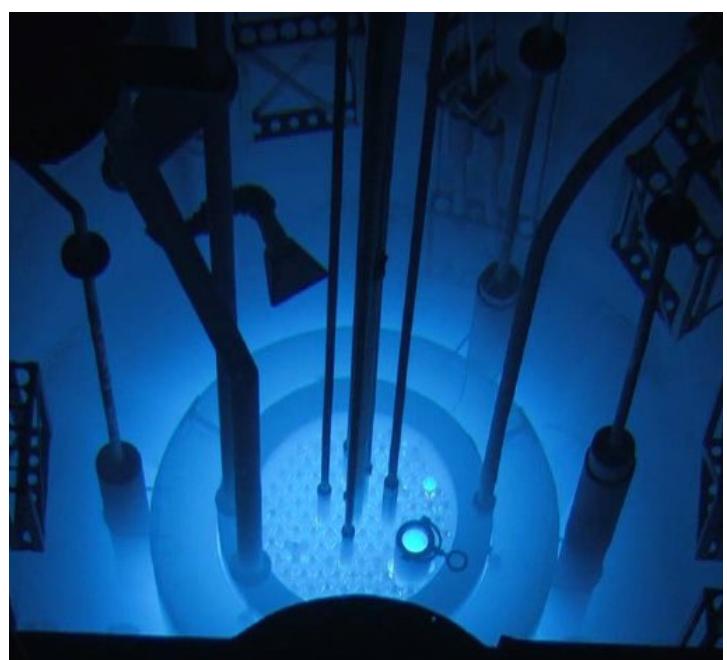


Cerenkov Luminescence Imaging

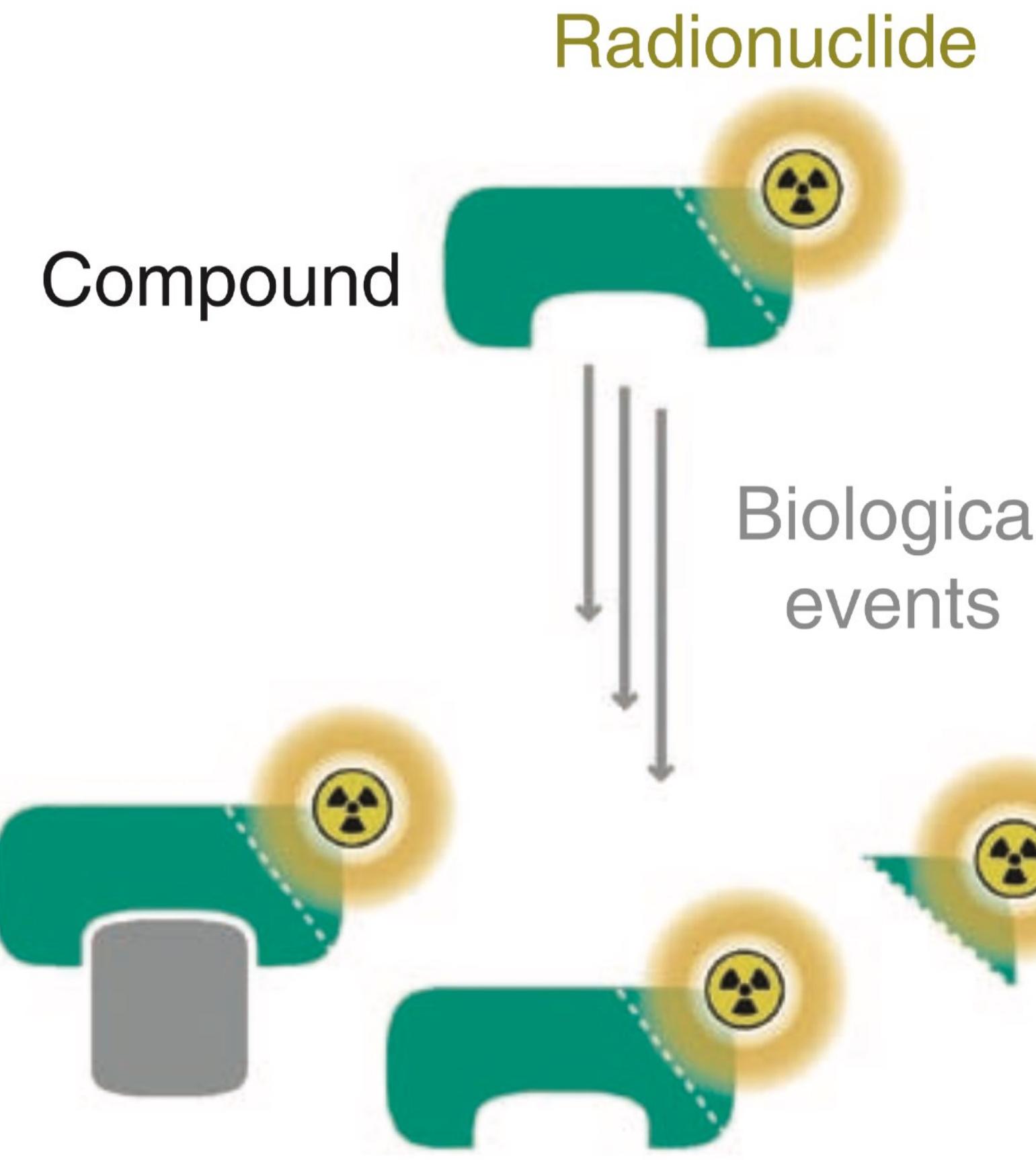
Physics



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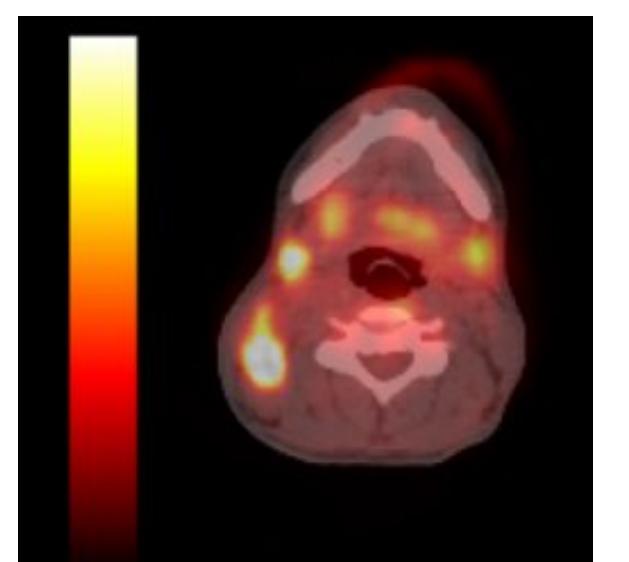
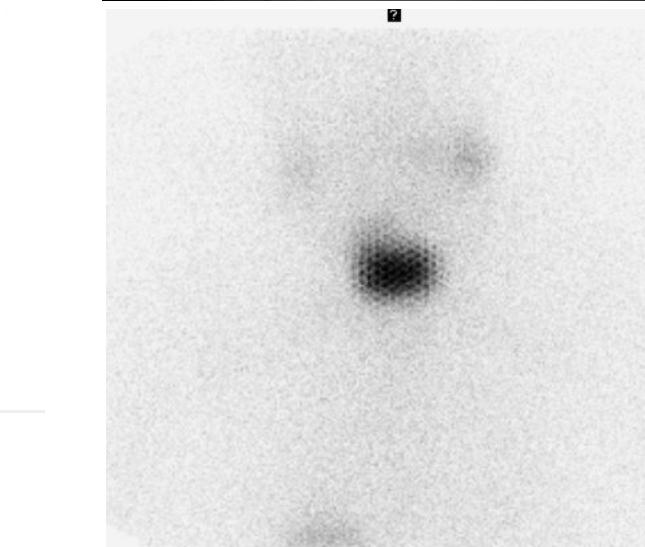
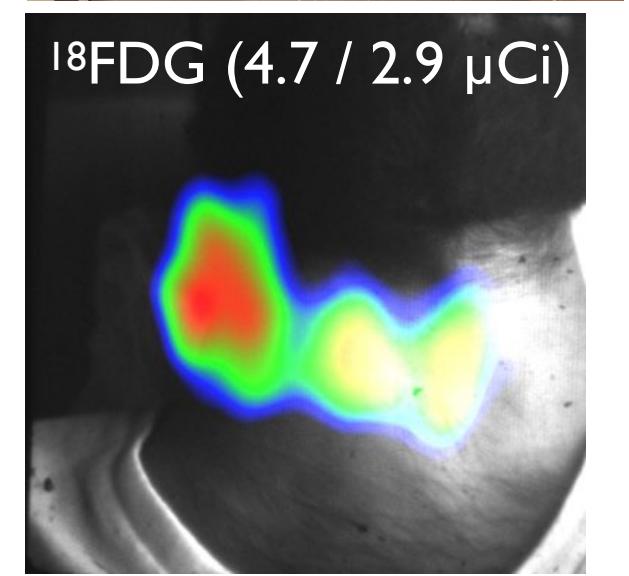
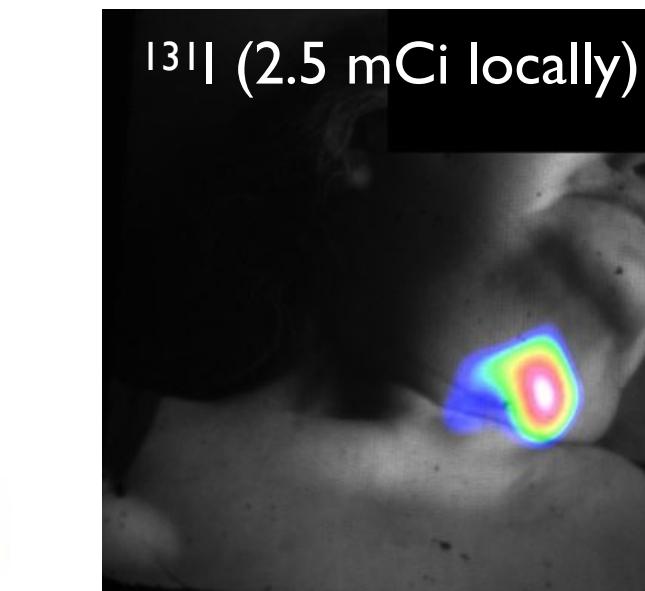


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Clinical CLI

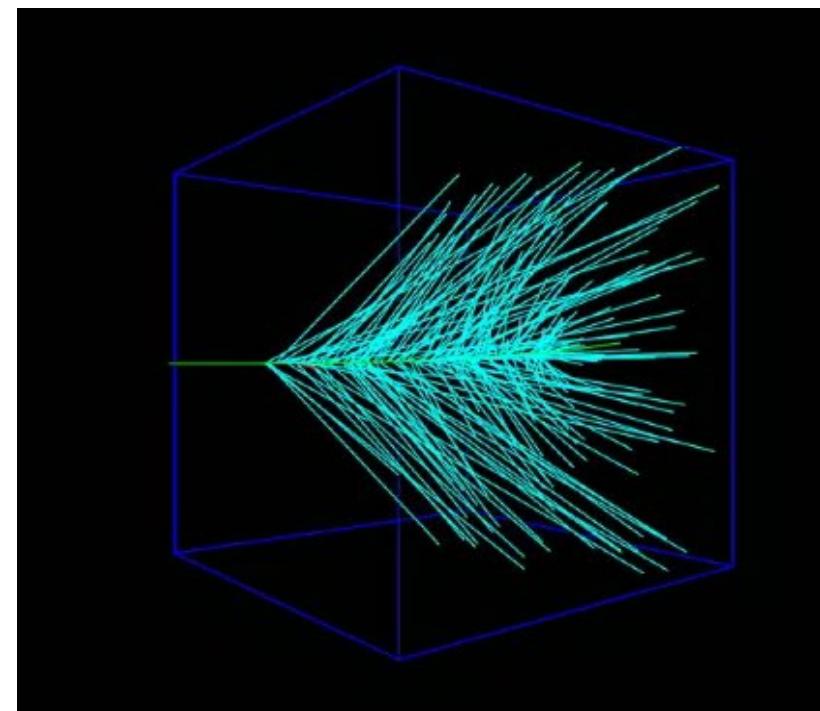
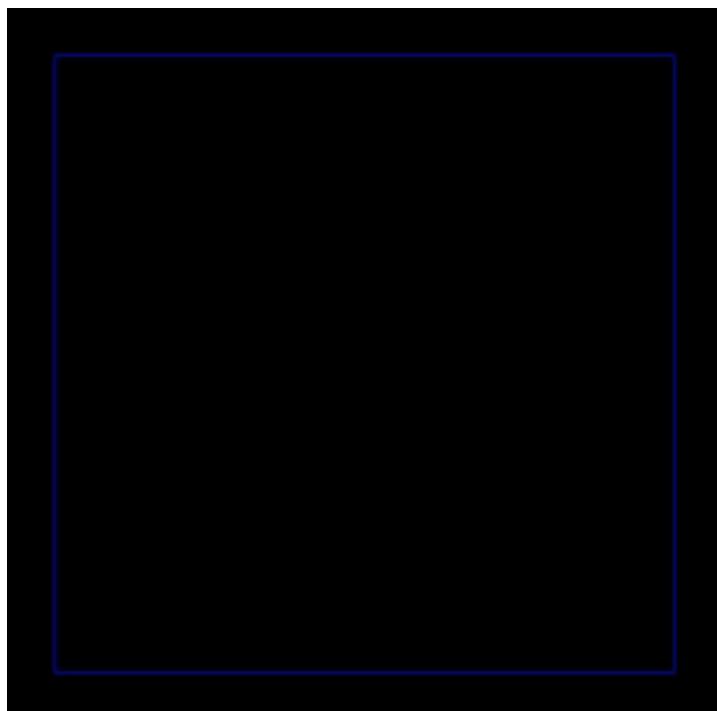
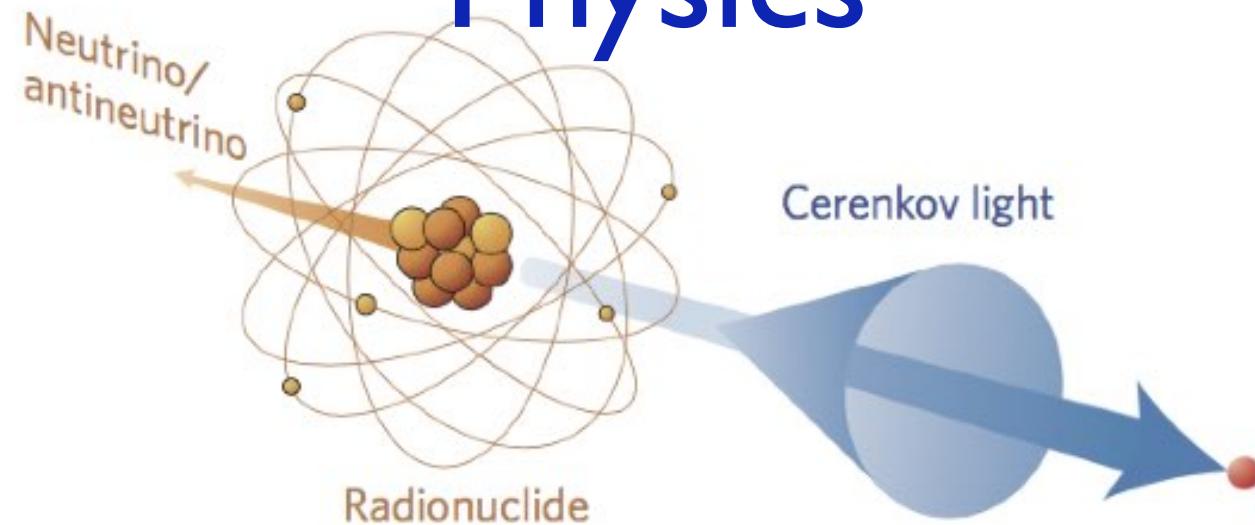


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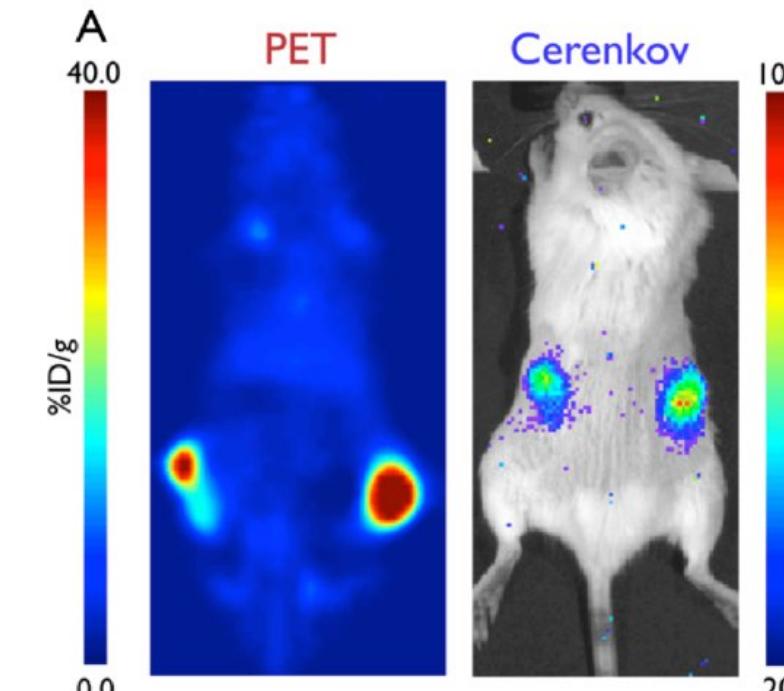
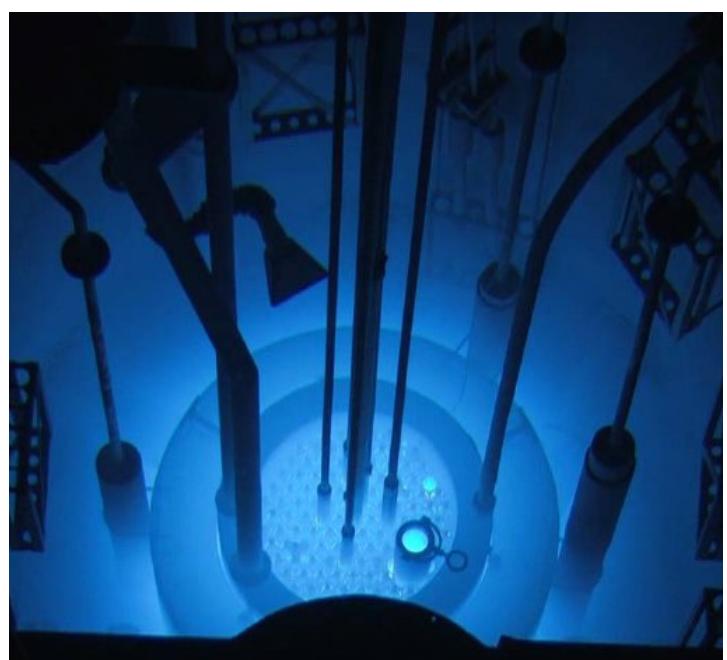


Cerenkov Luminescence Imaging

Physics

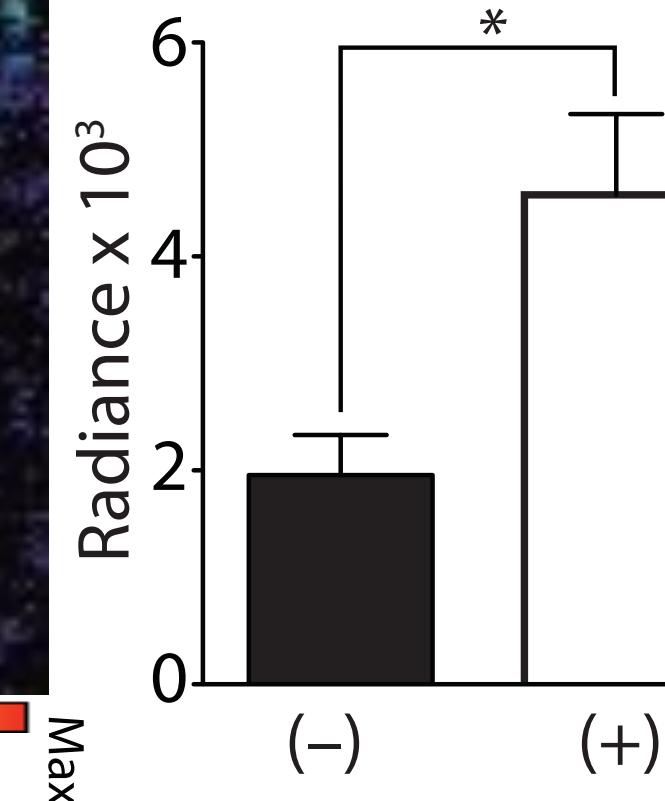
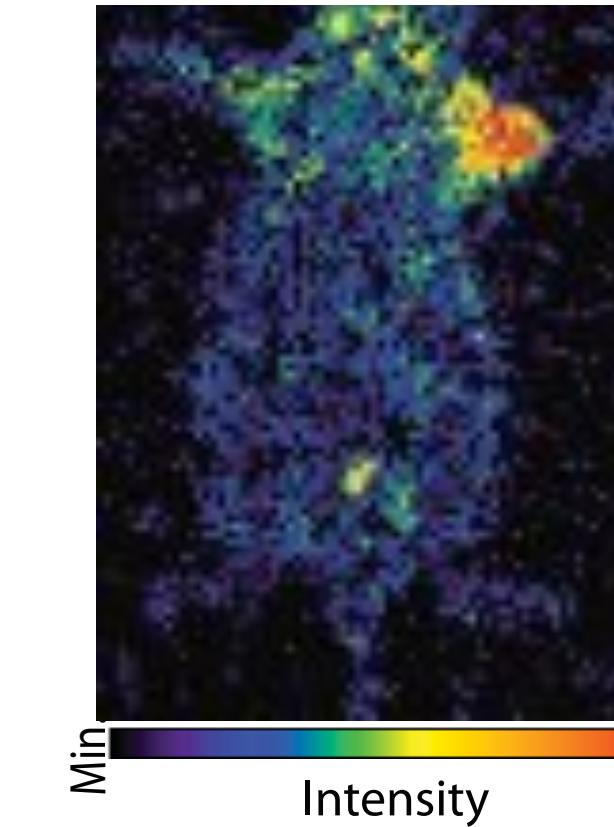
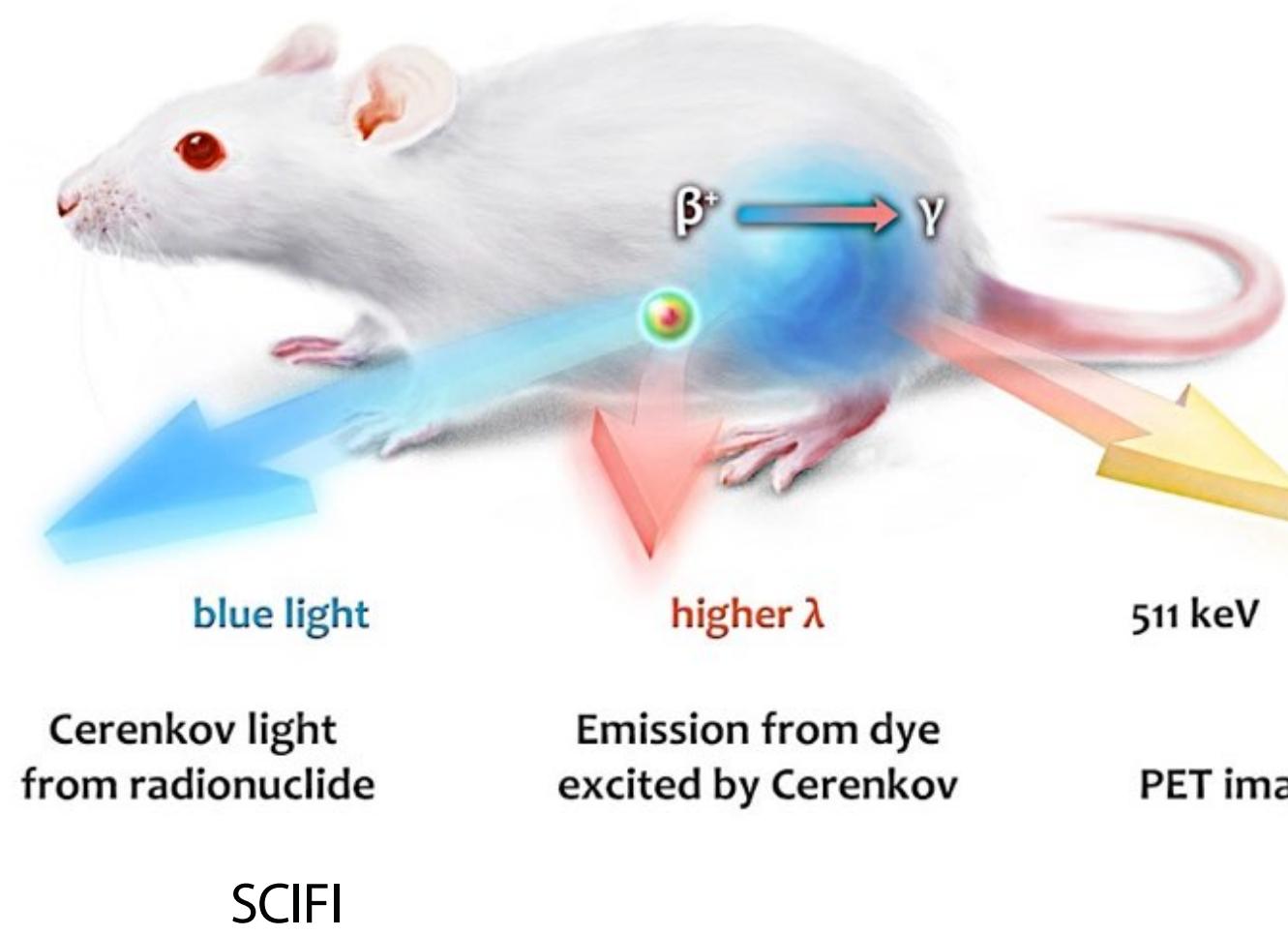


courtesy of Brian Pogue, Dartmouth College, NH



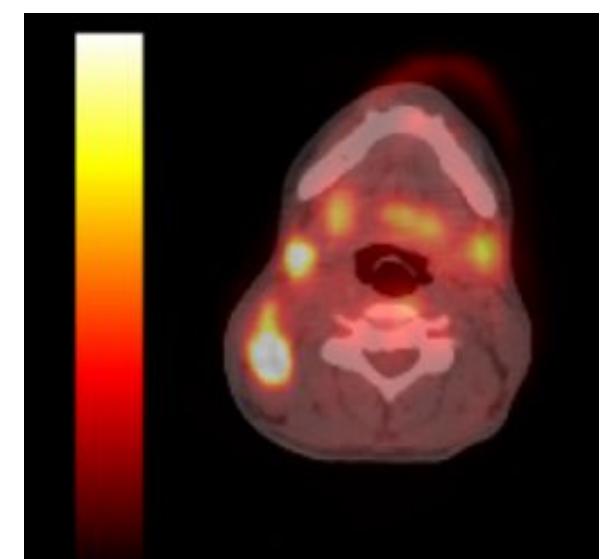
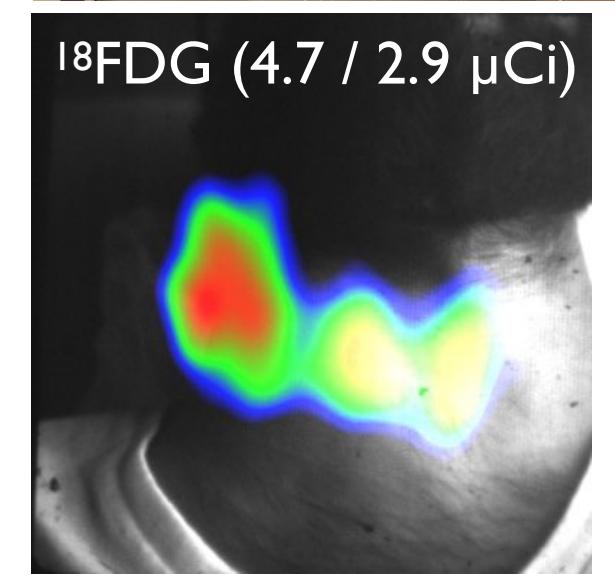
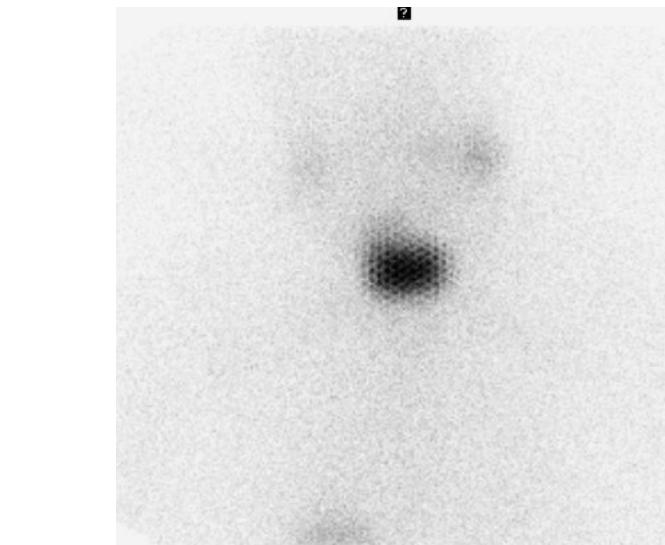
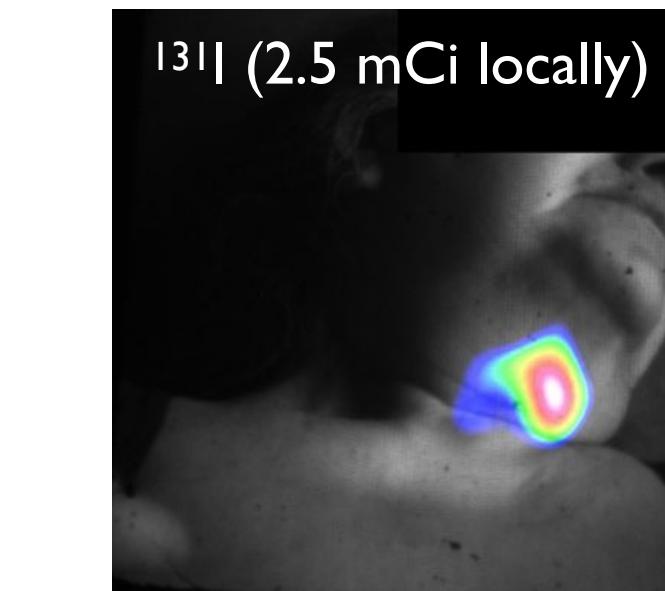
Ruggiero A et al. (2010) J Nucl Med 51(7): 1123
Holland J et al. (2011) Molecular Imaging 10(3):177
Thorek D et al. (2012) J Nucl Med 53(9):1348

Agents



Thorek D et al. (2013) Nature Medicine 19(10):1345
Thorek D et al. (2014) J Nucl Med 55(1):95
Shaffer, Pratt and Grimm (2016) Nature Nanotechnology 12(2):106
Lockau H et al. (2018) J Nucl Med 59(2): 210

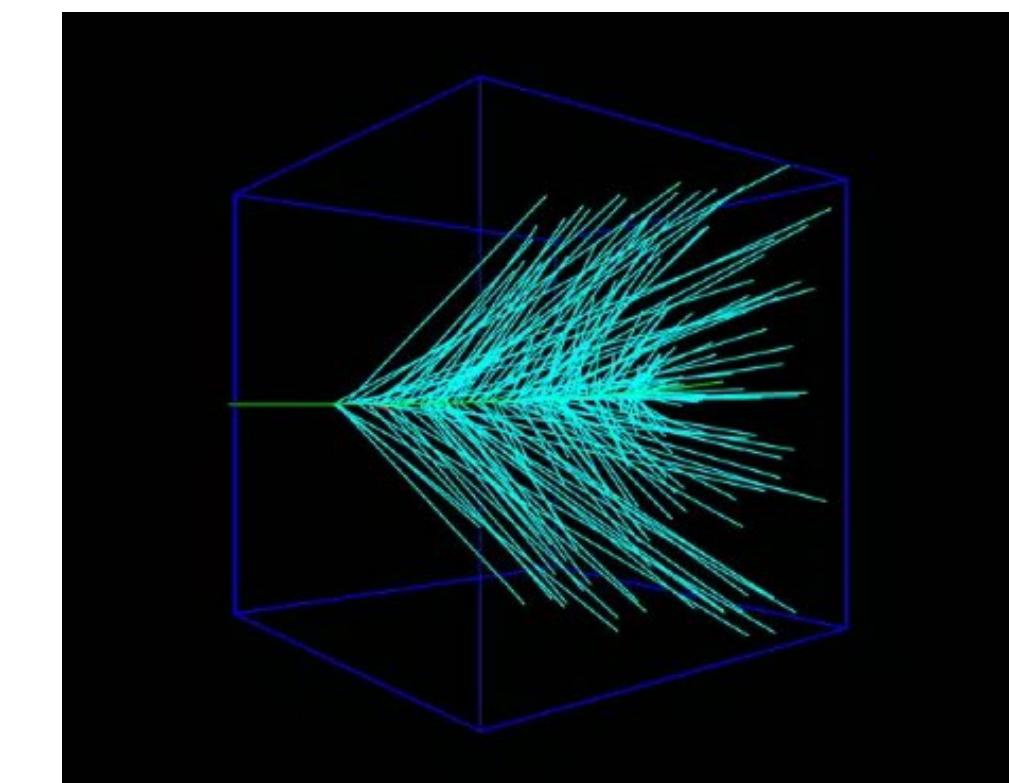
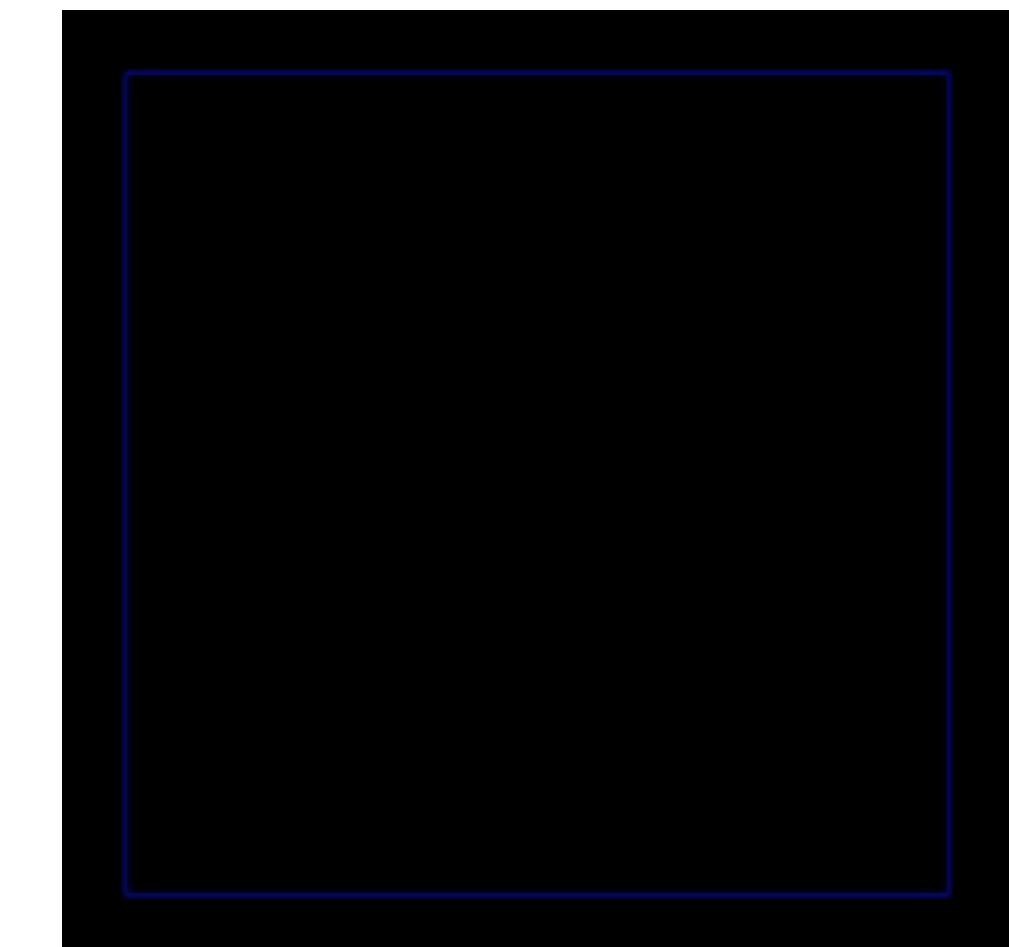
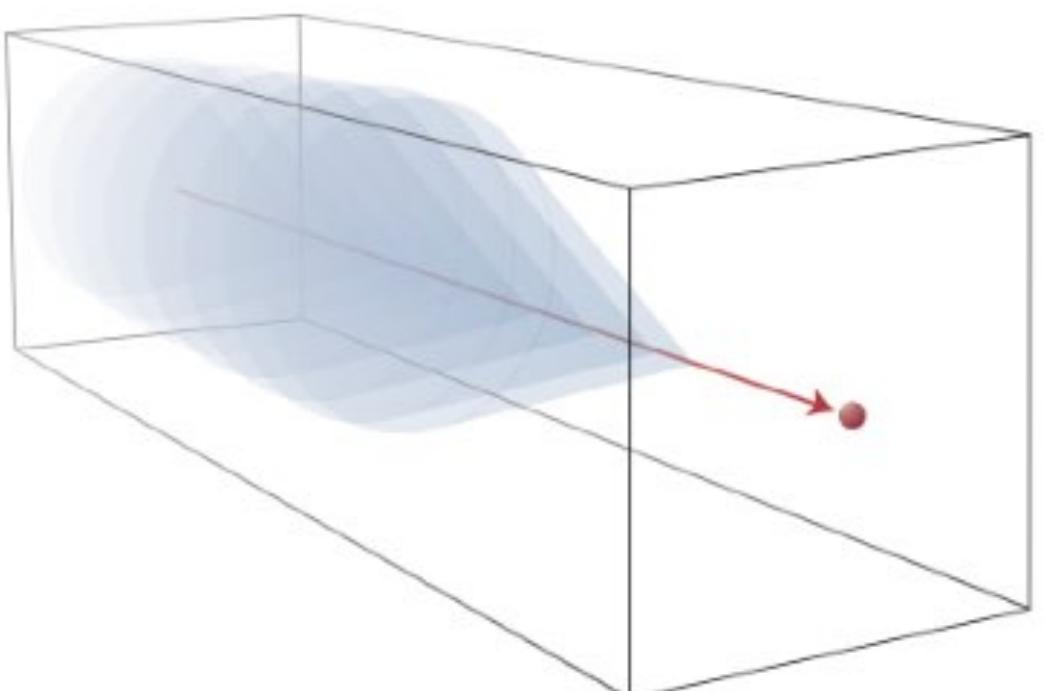
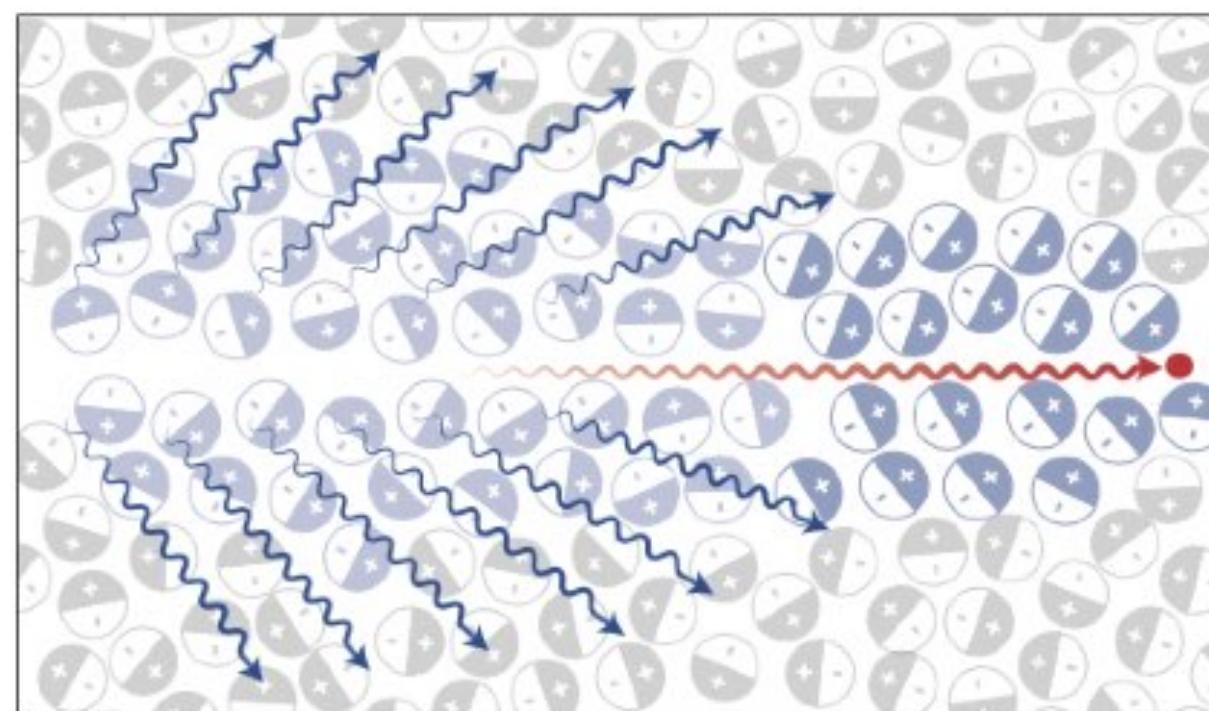
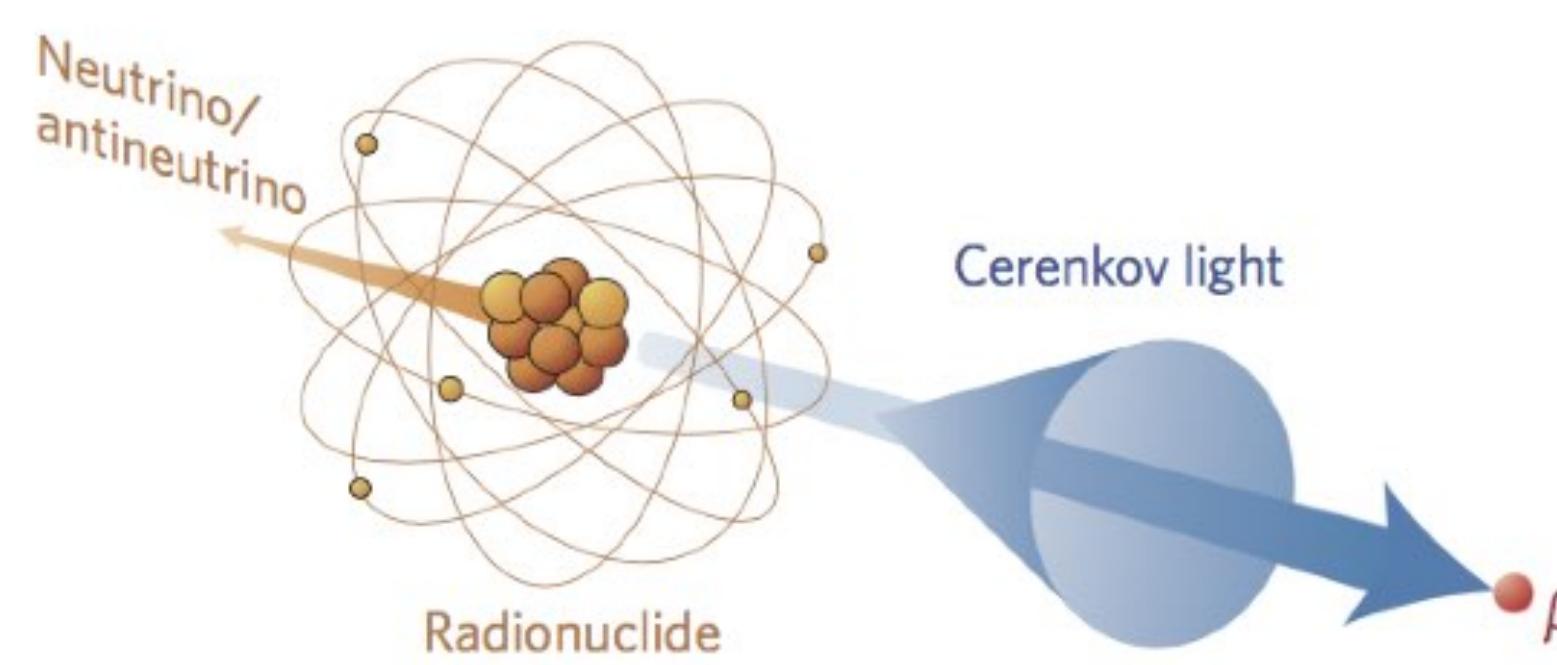
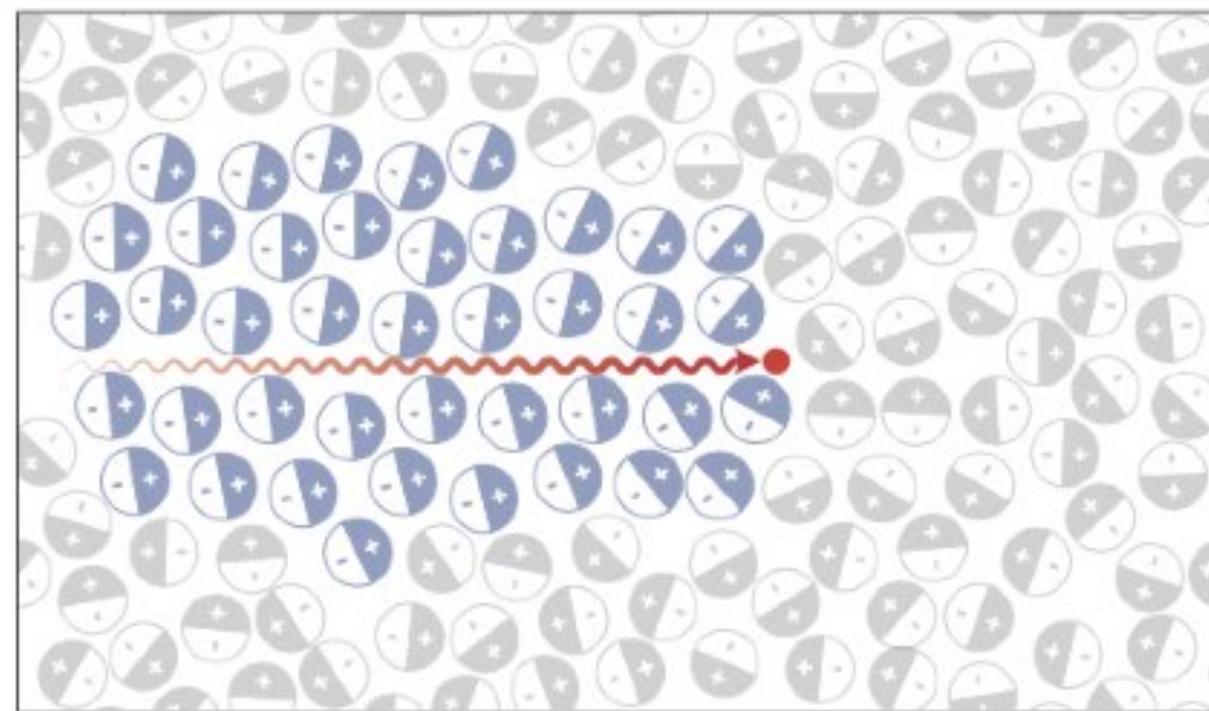
Clinical CLI



Das S et al. (2018) J Nucl Med 59(1):58
Grimm J (2018) Nature Biomedical Engineering (2): 205
Pratt et al. (2018) Nature Nanotechnology 13(5): 418
Pratt et al. (2022) Nature Biomedical Engineering 6(5):559



Cerenkov Luminescence (CL)

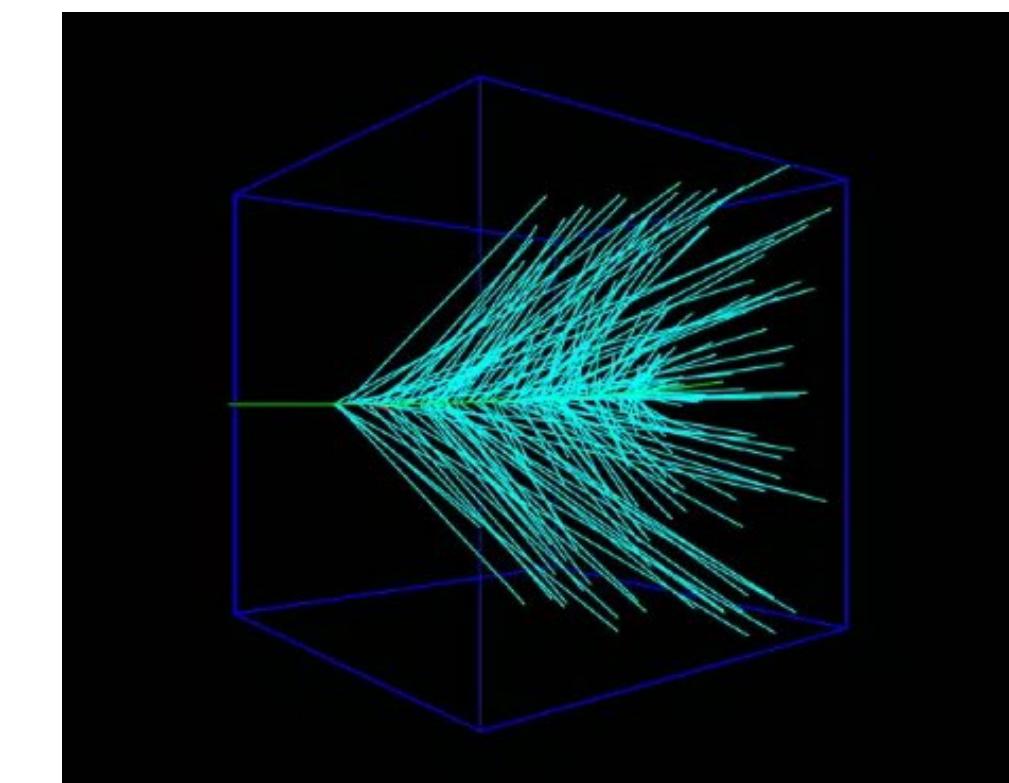
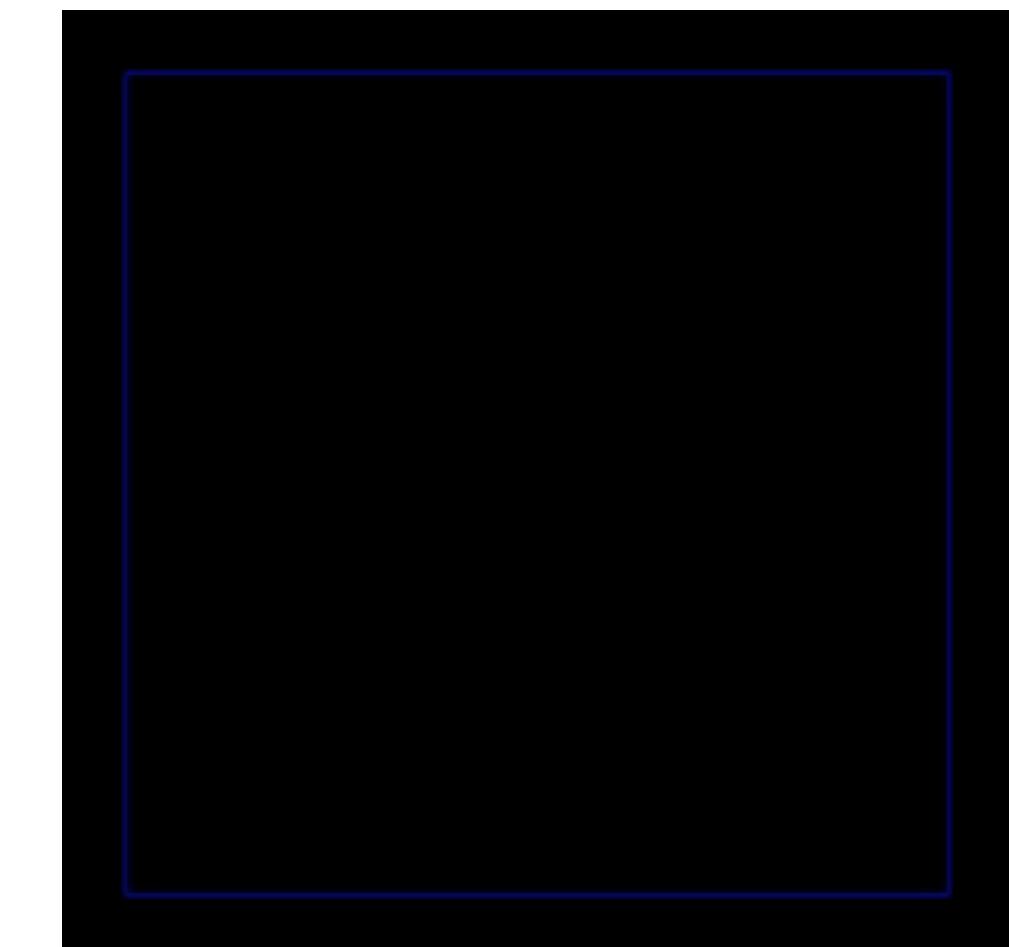
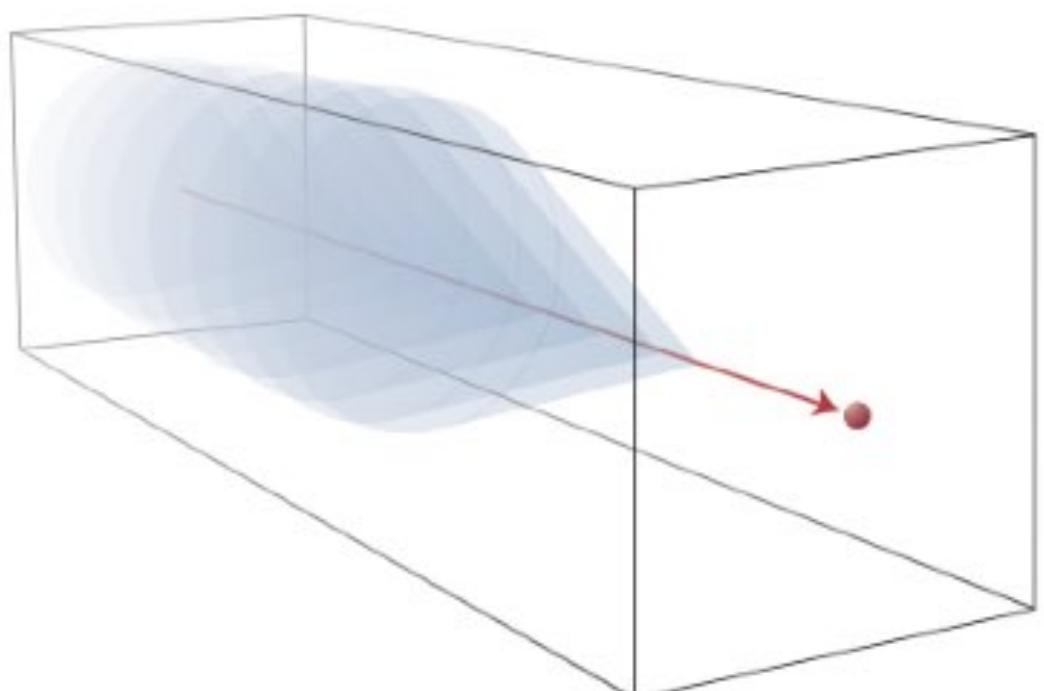
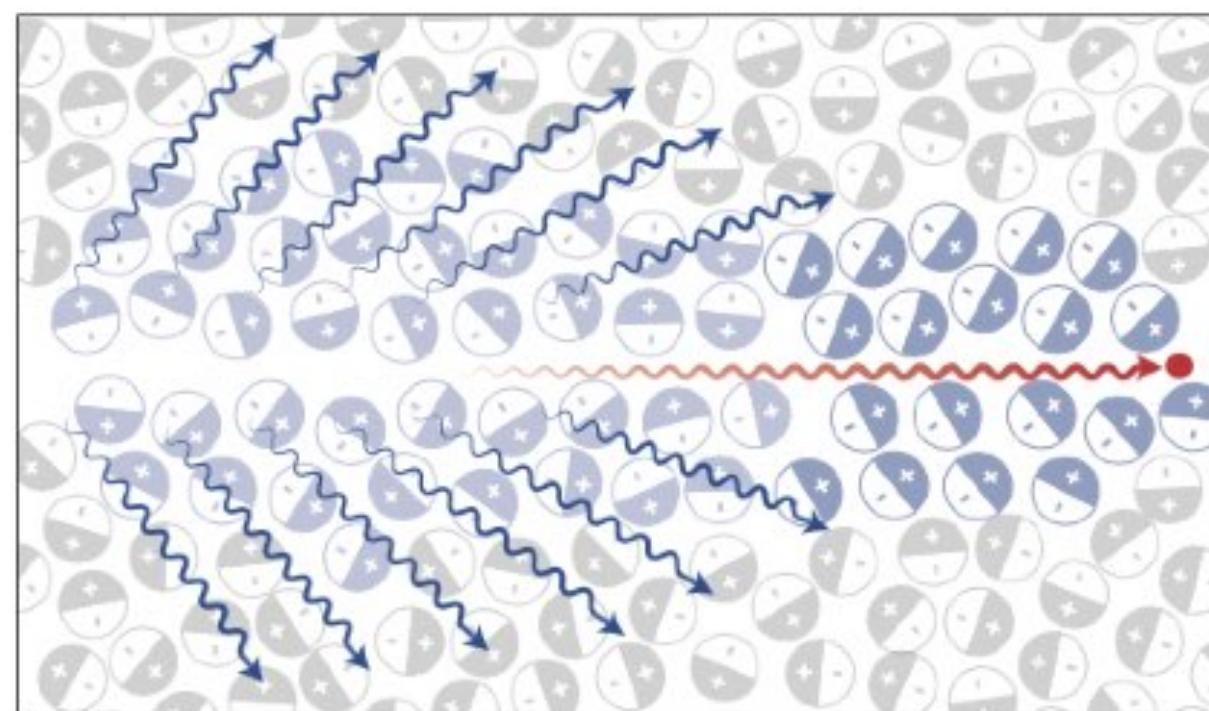
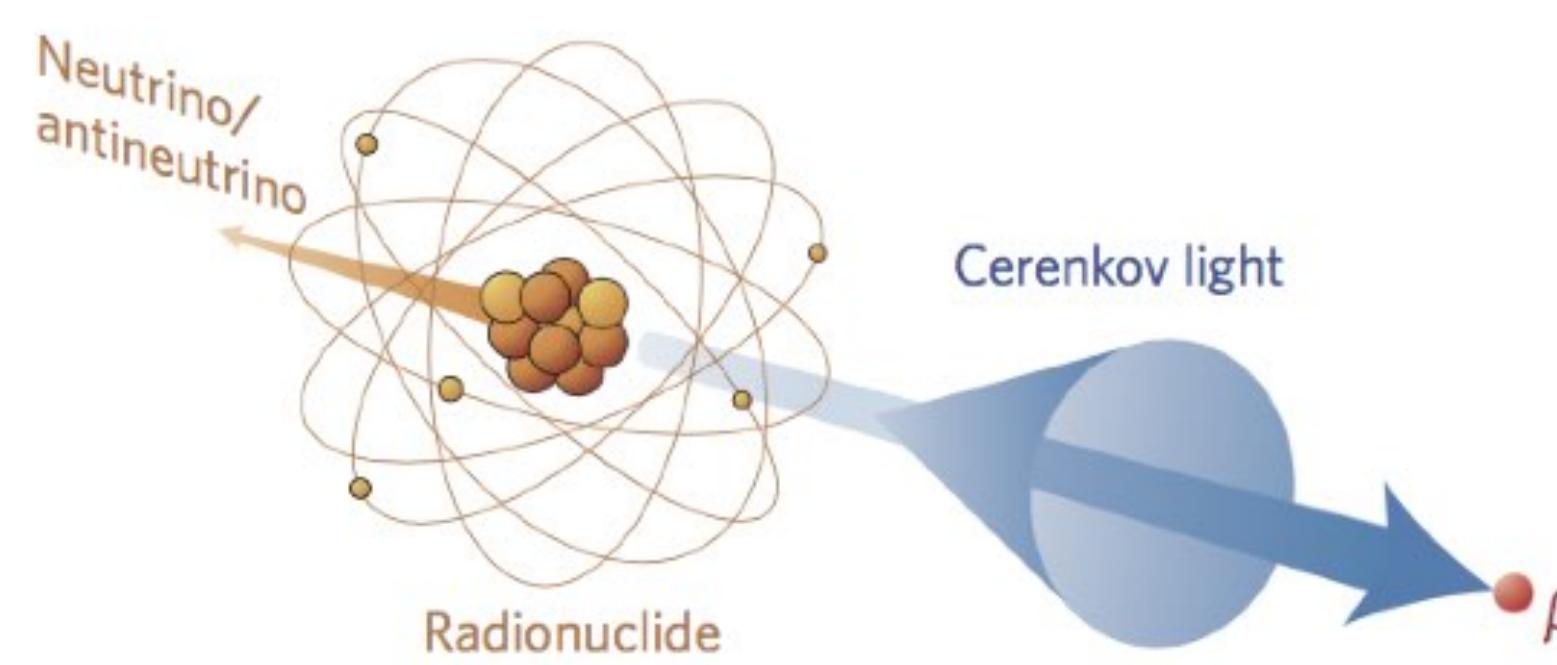
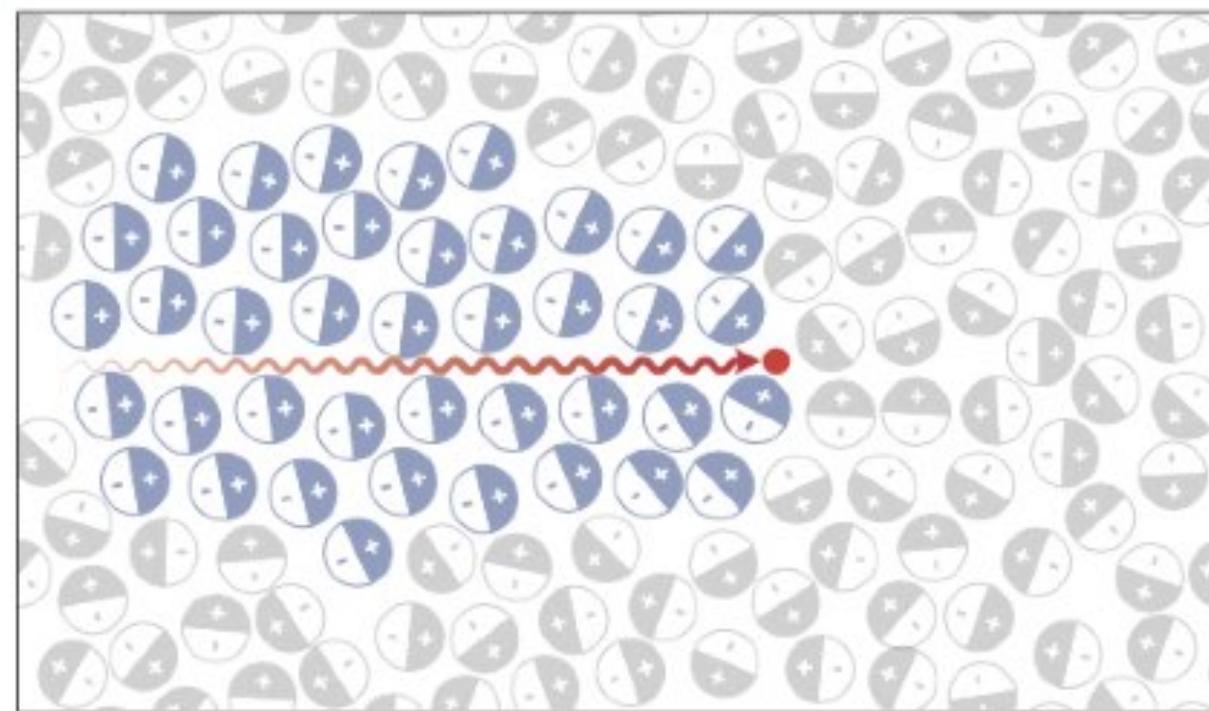


Shaffer, Pratt and Grimm (2016) Nature Nanotech 12(2):106

curtesy of B Pogue, U Wisconsin-Madison

When a charged particle travels through a dielectric medium **faster than the speed of light** in that medium it emits a continuous spectrum of polarized **blue** light.

Cerenkov Luminescence (CL)

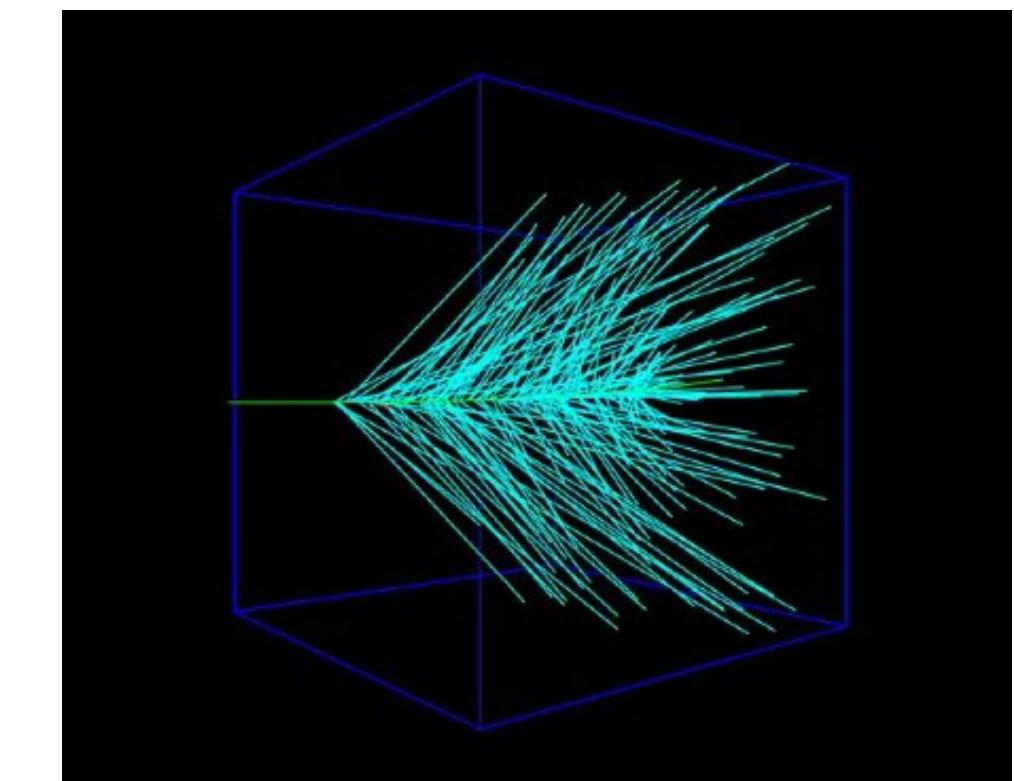
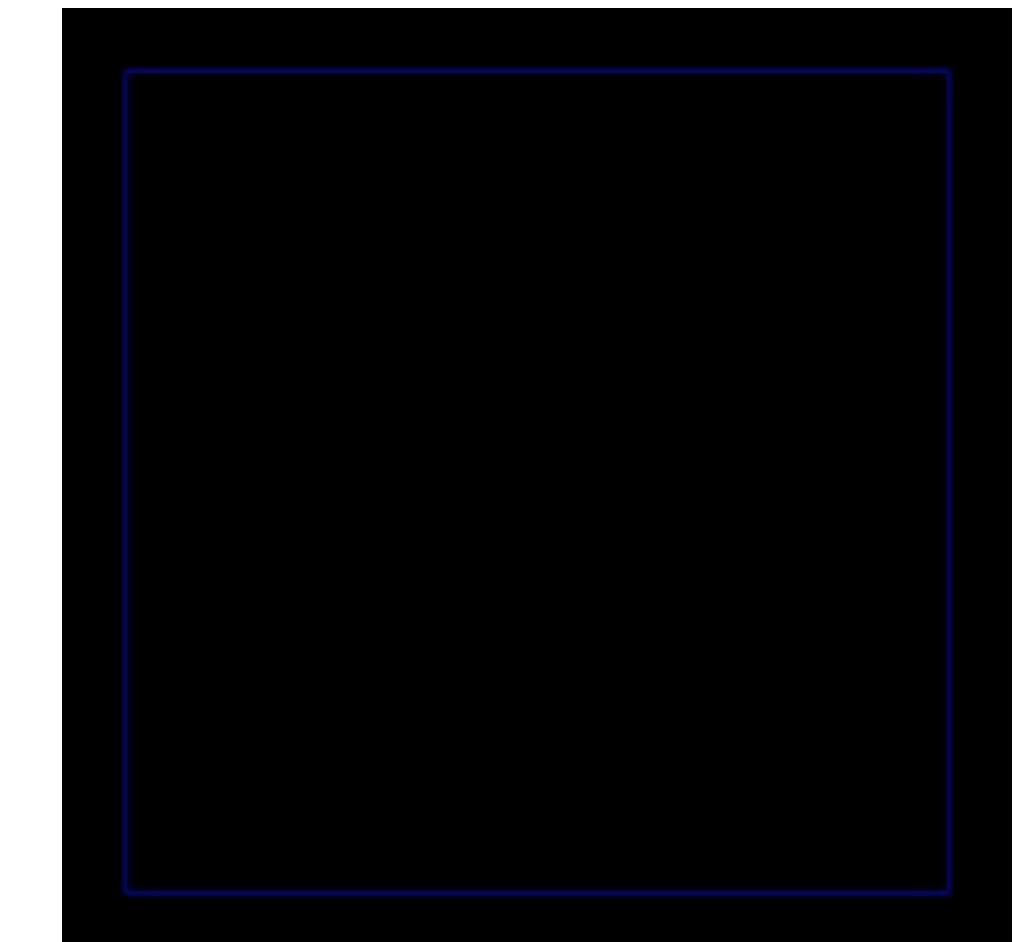
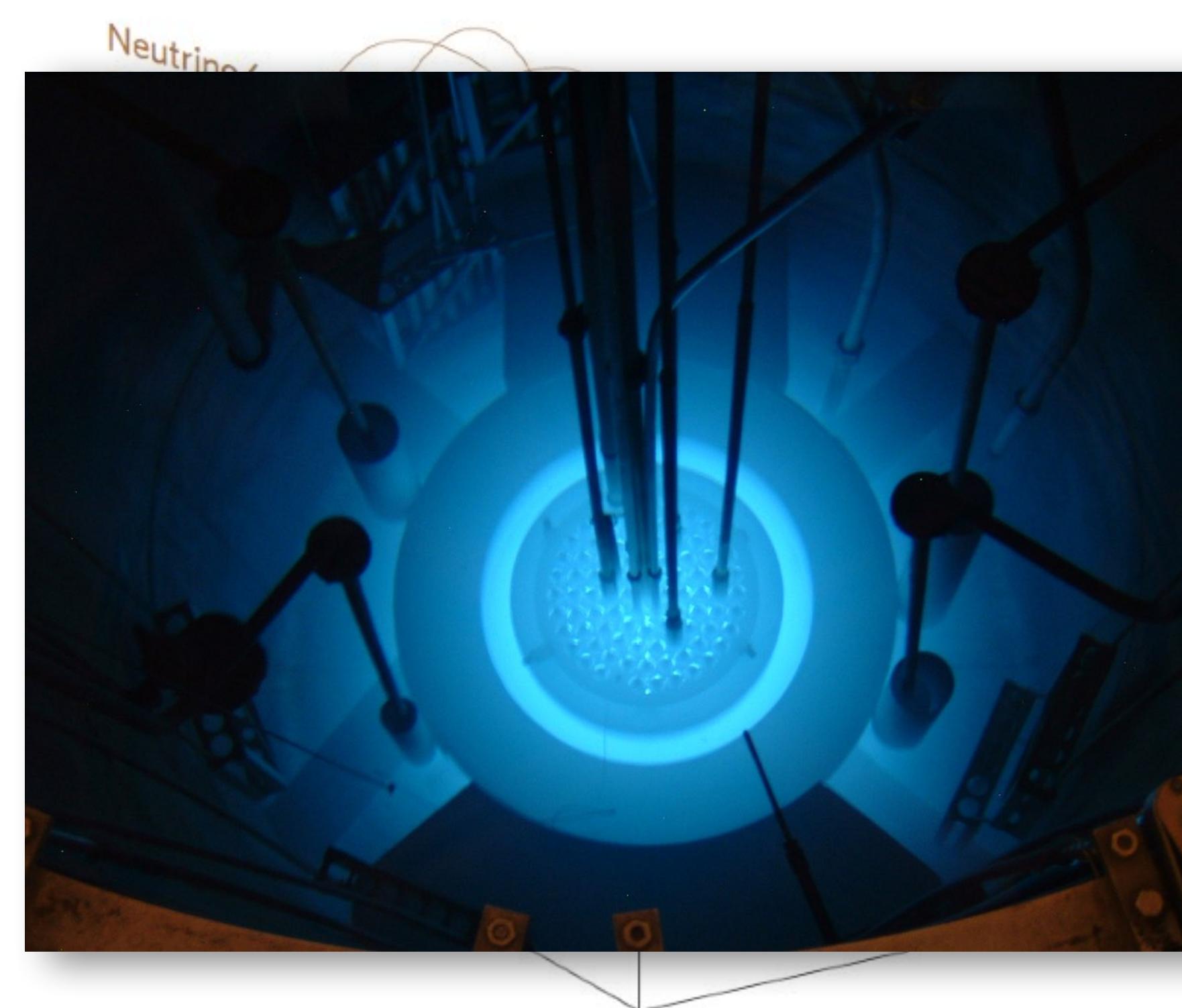
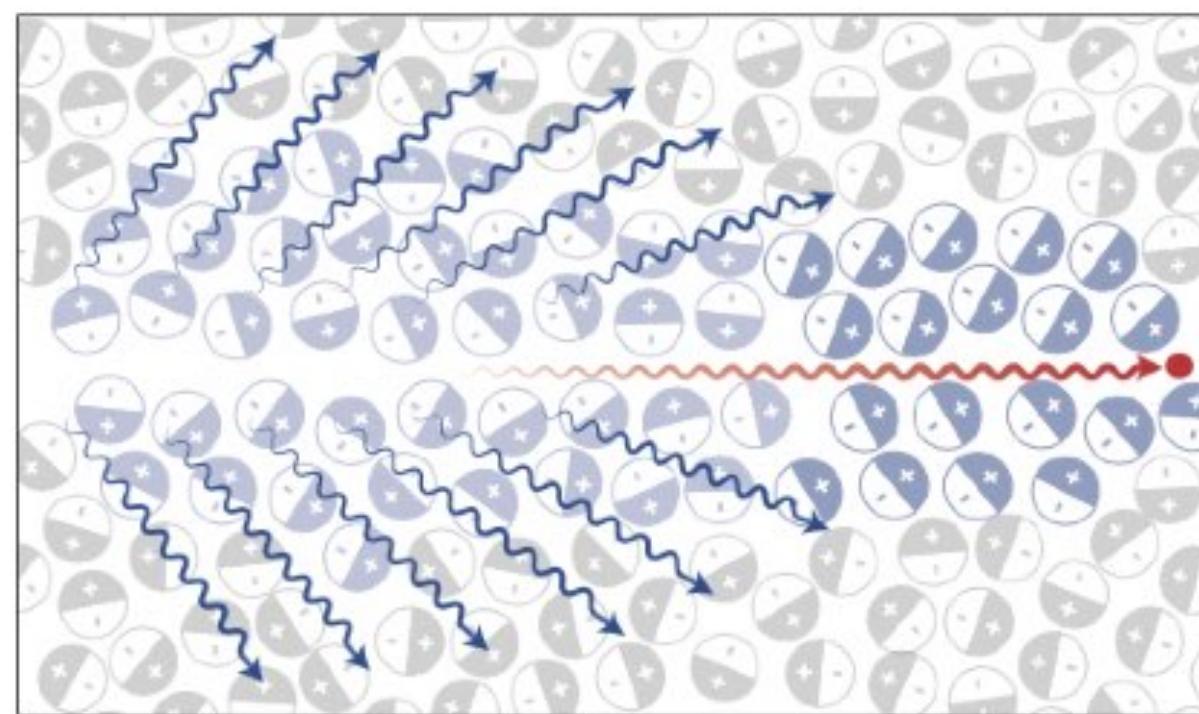
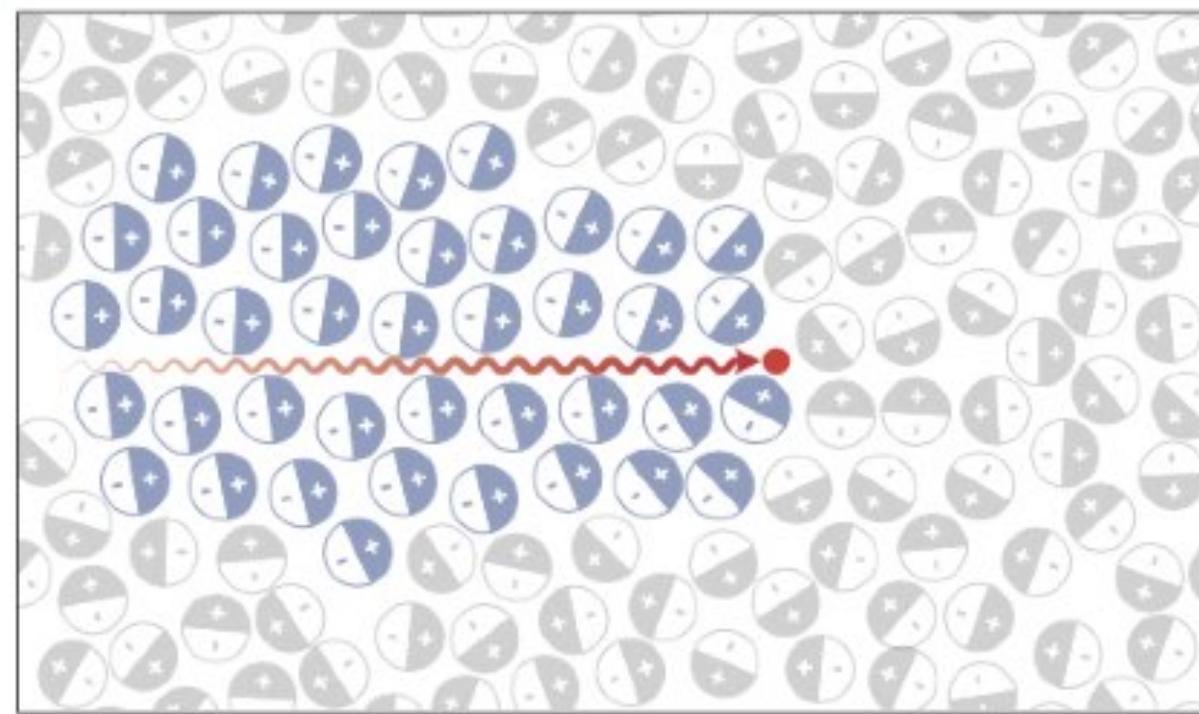


Shaffer, Pratt and Grimm (2016) Nature Nanotech 12(2):106

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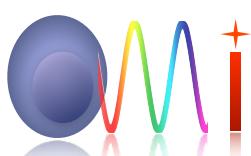
Cerenkov Luminescence (CL)



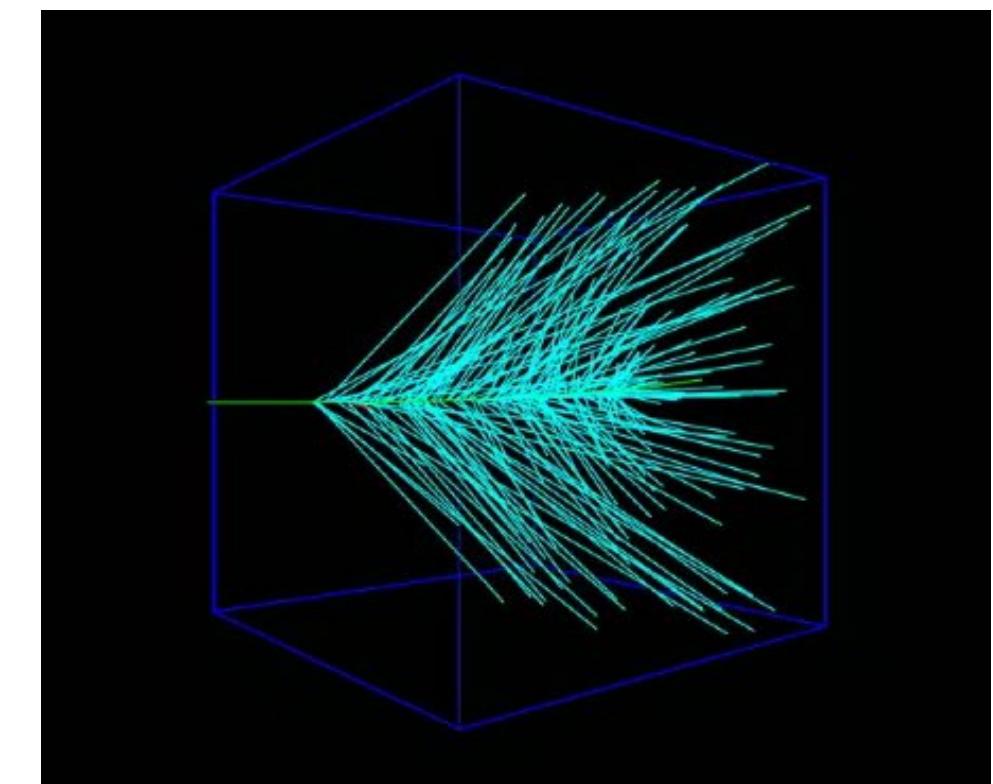
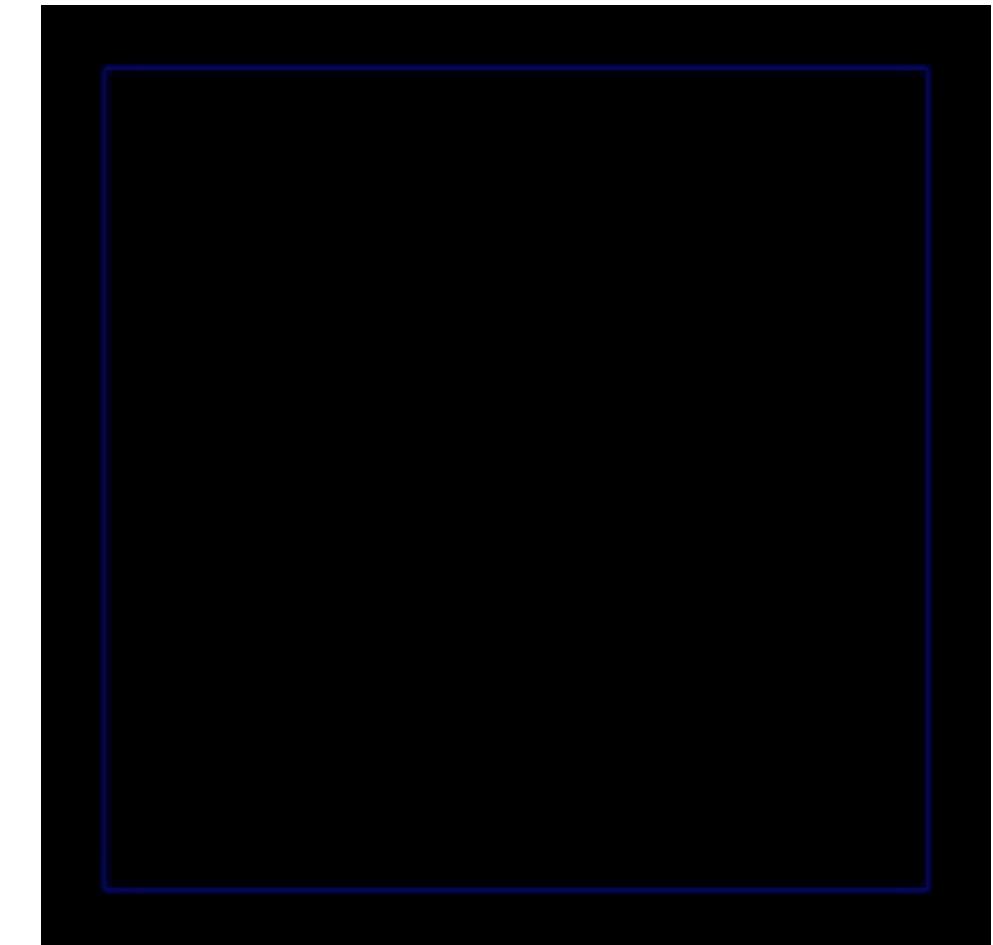
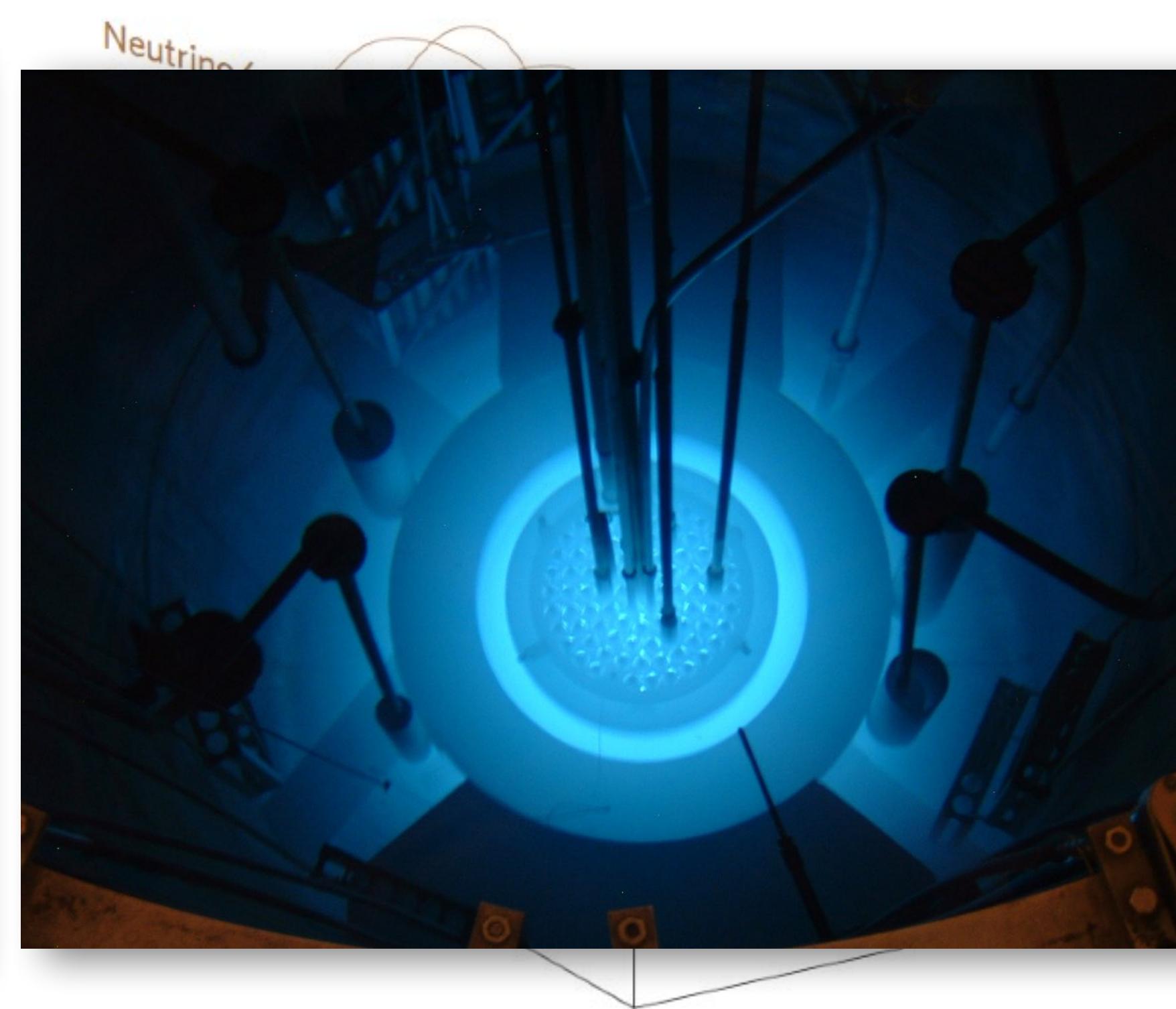
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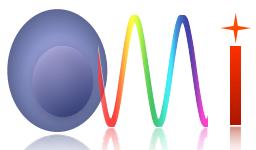
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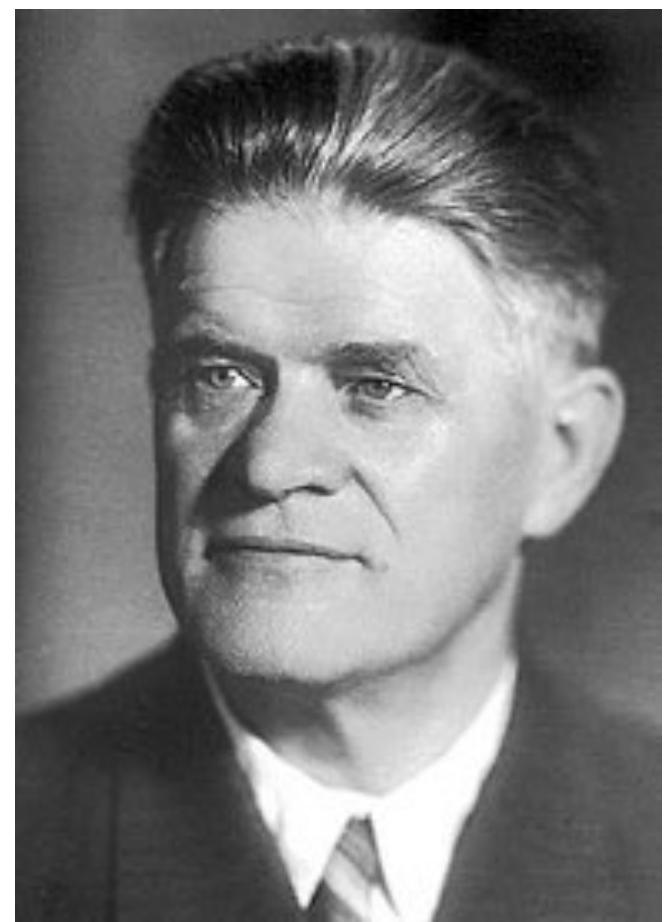
Shaffer, Pratt and Grimm (2016) Nature Nanotech 12(2):106

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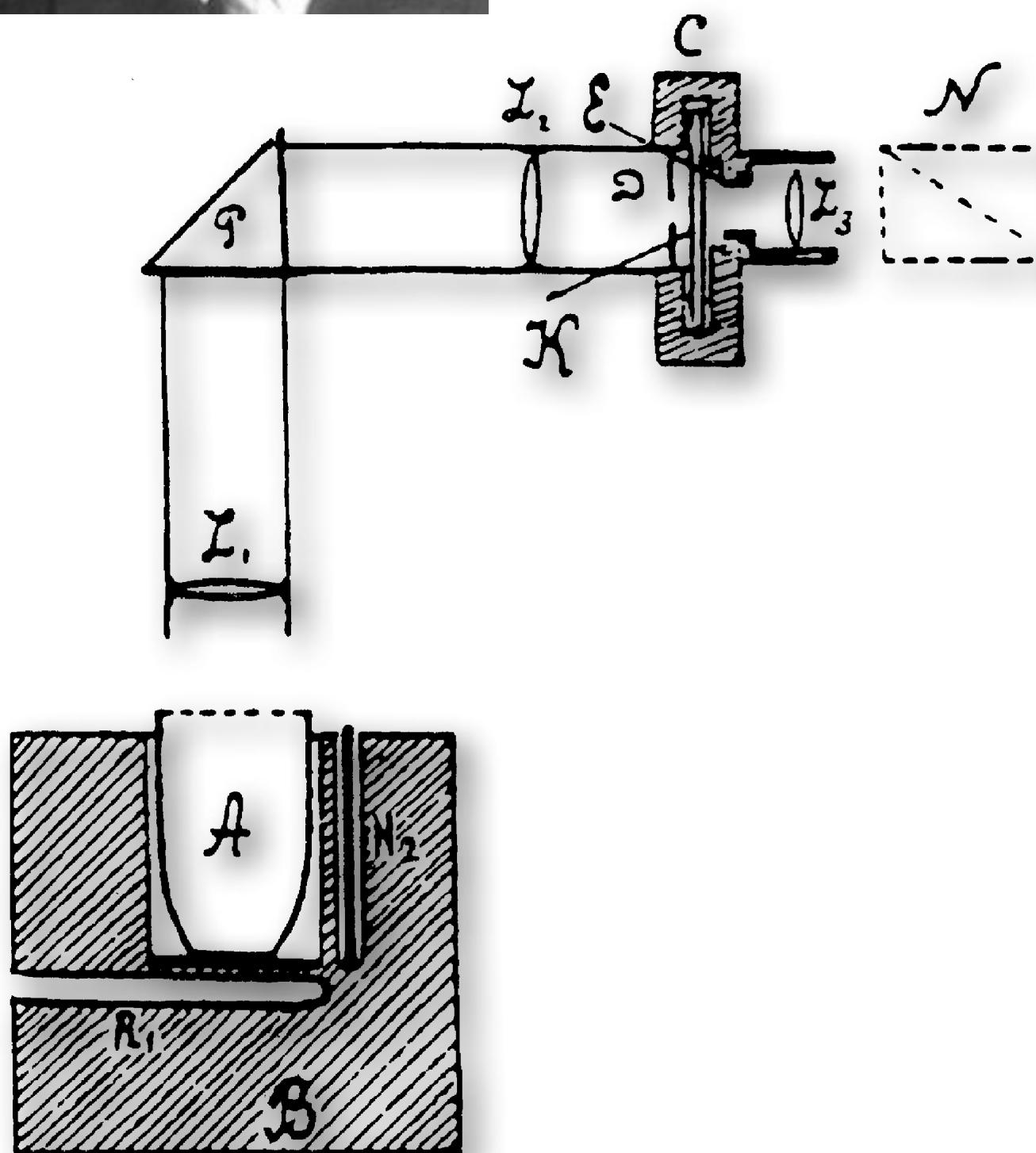
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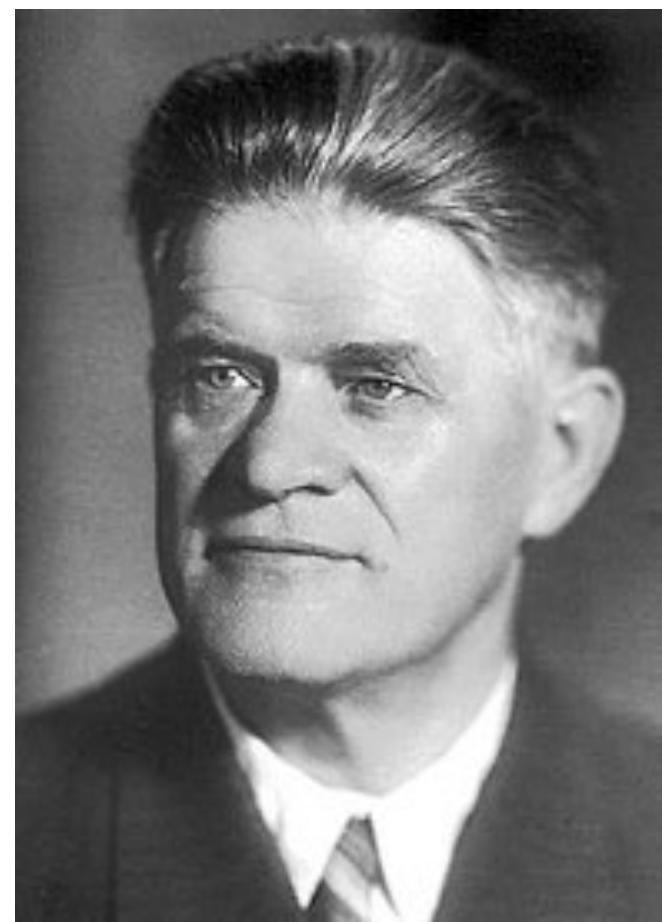
Pavel Cerenkov's lucky mistake



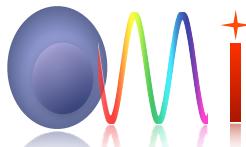
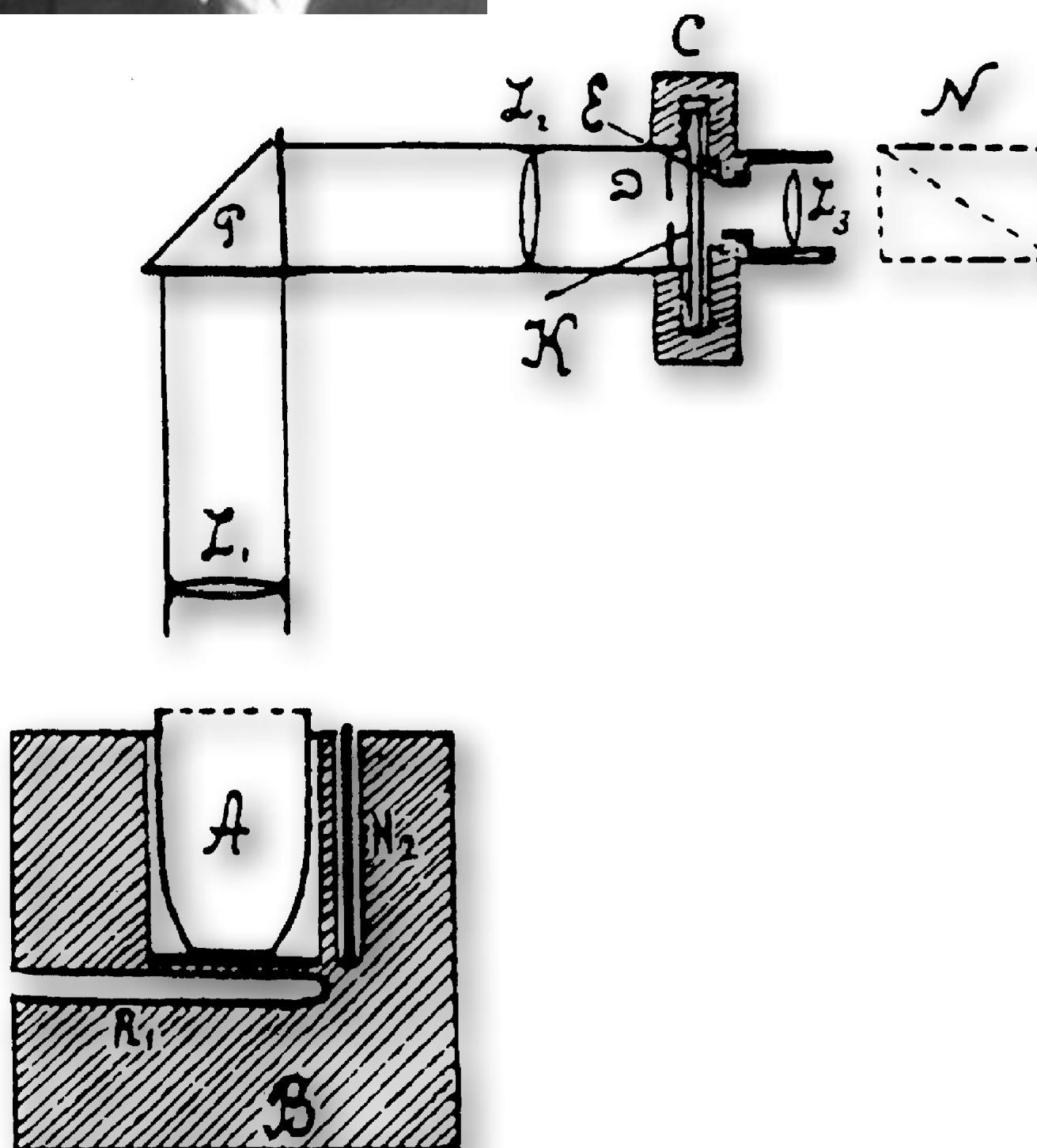
- Cerenkov studied the luminescence of uranyl salt solutions under the gamma-ray radiation of radium.



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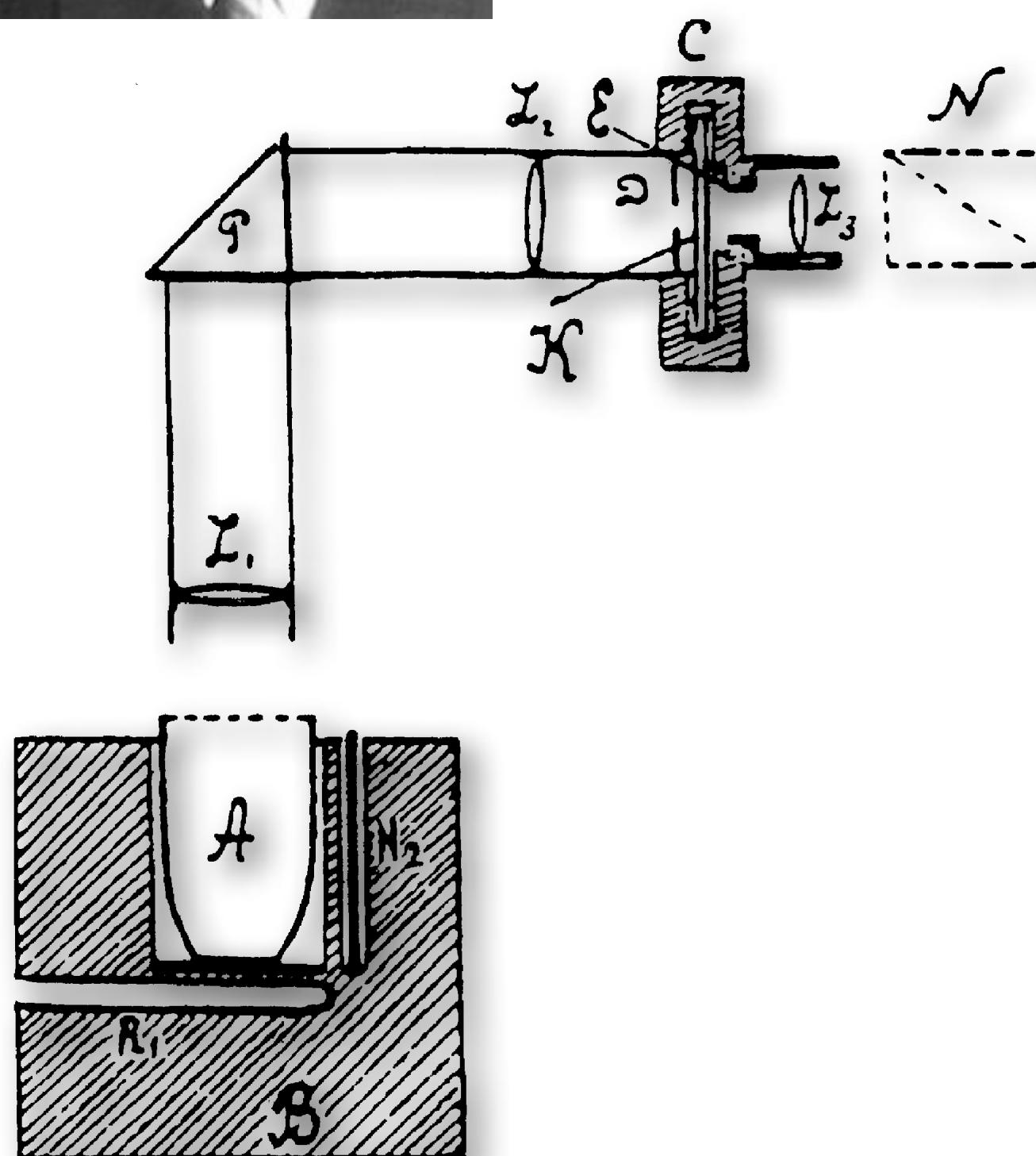
- Cerenkov studied the luminescence of uranyl salt solutions under the gamma-ray radiation of radium.
- Prior to measurement Cerenkov sat in a dark room for 90' to increase his eyes' sensitivity to the weak signal.



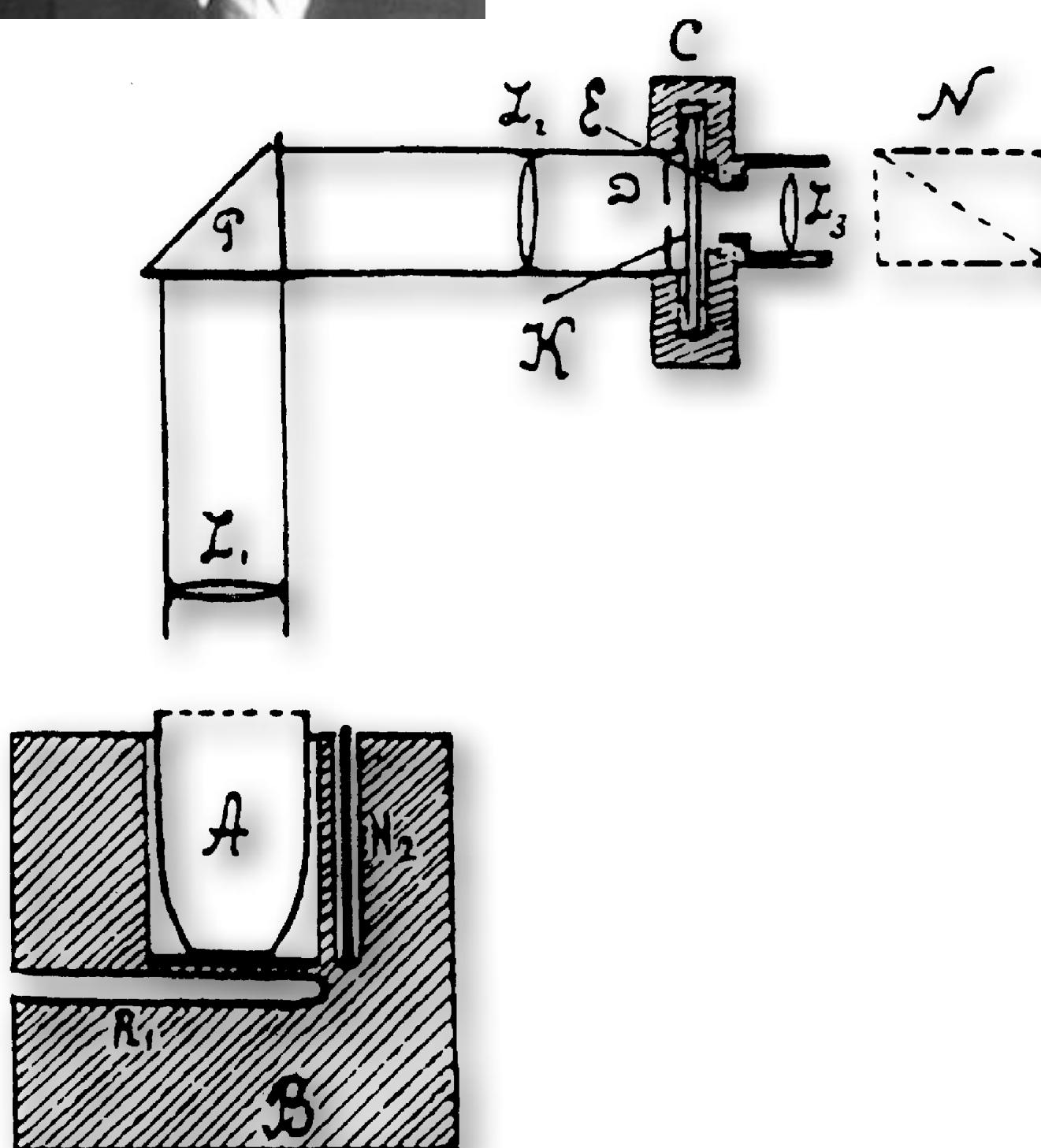
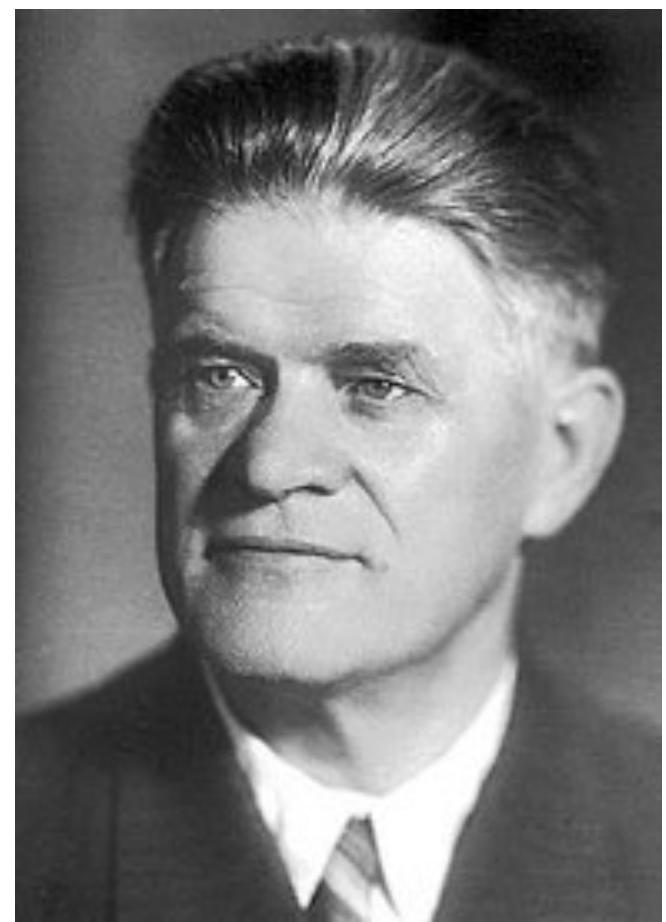
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- Cerenkov studied the luminescence of uranyl salt solutions under the gamma-ray radiation of radium.
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- In 1933, glass A was accidentally filled only with solvent, but it also glowed under radium irradiation.

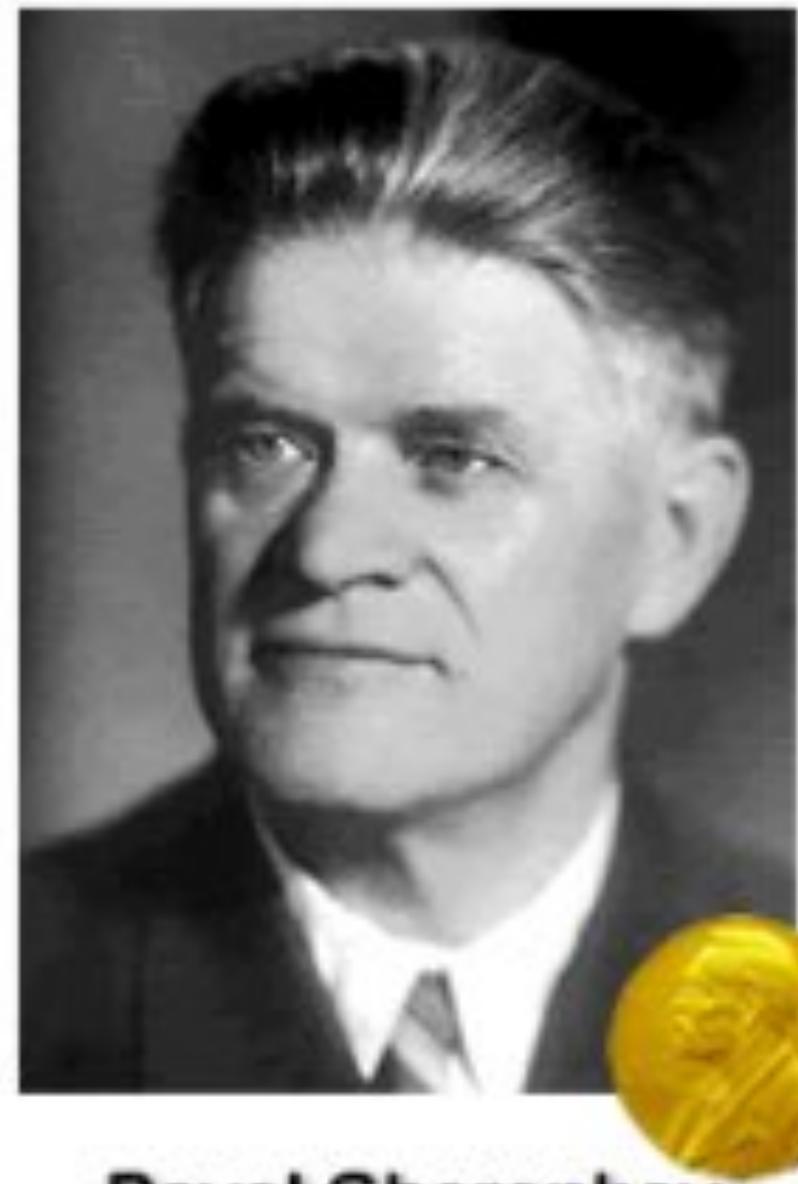


Pavel Cerenkov's lucky mistake



- Cerenkov studied the luminescence of uranyl salt solutions under the gamma-ray radiation of radium.
- Prior to measurement Cerenkov sat in a dark room for 90' to increase his eyes' sensitivity to the weak signal.
- In 1933, glass A was accidentally filled only with solvent, but it also glowed under radium irradiation.
- The intensity was of the same order of magnitude as the glow of the uranyl salt solution in the same solvent (sulfuric acid).

Frank & Tamm



Pavel Cherenkov



Ilya Frank



Igor Tamm

$$\frac{dN}{dx} = 2\pi\alpha \left(1 - \frac{1}{\beta^2 n^2}\right) \int_{\lambda_1}^{\lambda_2} \frac{1}{\lambda^2} d\lambda \quad (1)$$

The Frank-Tamm formula defines photon output over a distance (dN/dx), where α is the fine structure constant, β is the velocity of the particle relative to the speed of light in a vacuum, n is the refractive index of the medium, and λ is the wavelength of interest in the ultraviolet-visible region.

“However, a more detailed quantitative investigation of this light process enabled us to find a range of properties so remarkable as to afford incontrovertible proof that here we were dealing with no ordinary everyday luminescence, but with a phenomenon of an entirely new kind; and one of extraordinary interest not only on account of its significance in principle but also in regard to the many practical possibilities for its use.”

(Cerenkov's Nobel Lecture, Dec. 11 1958; with Frank and Tamm)

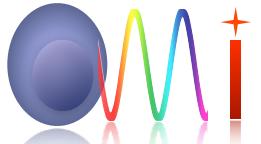
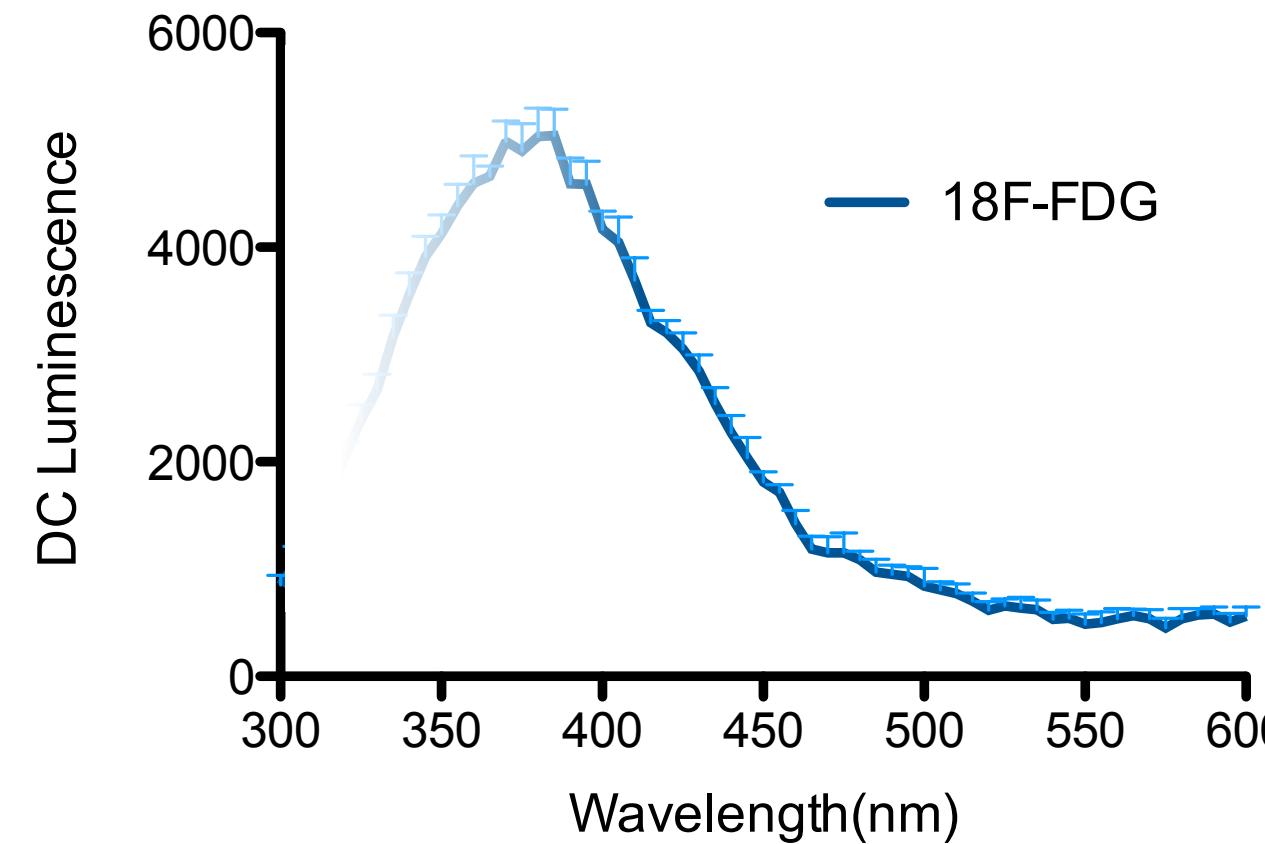


Medical CLI



A Ruggiero

Medical radionuclides emitting energetic charged particles can be used to **generate light** and imaged with sufficiently sensitive cameras.

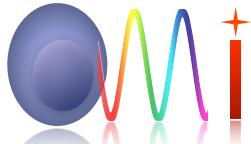
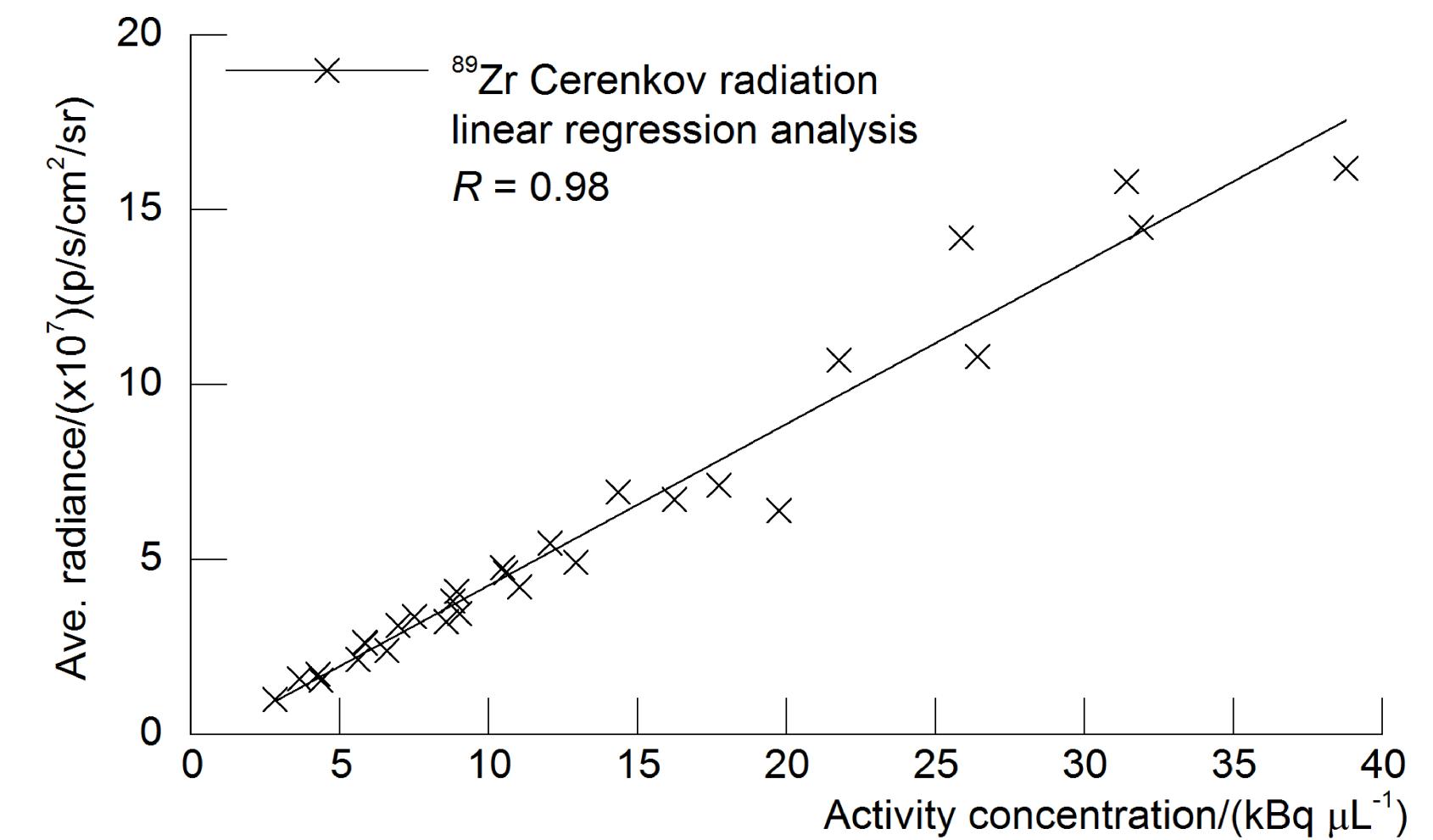
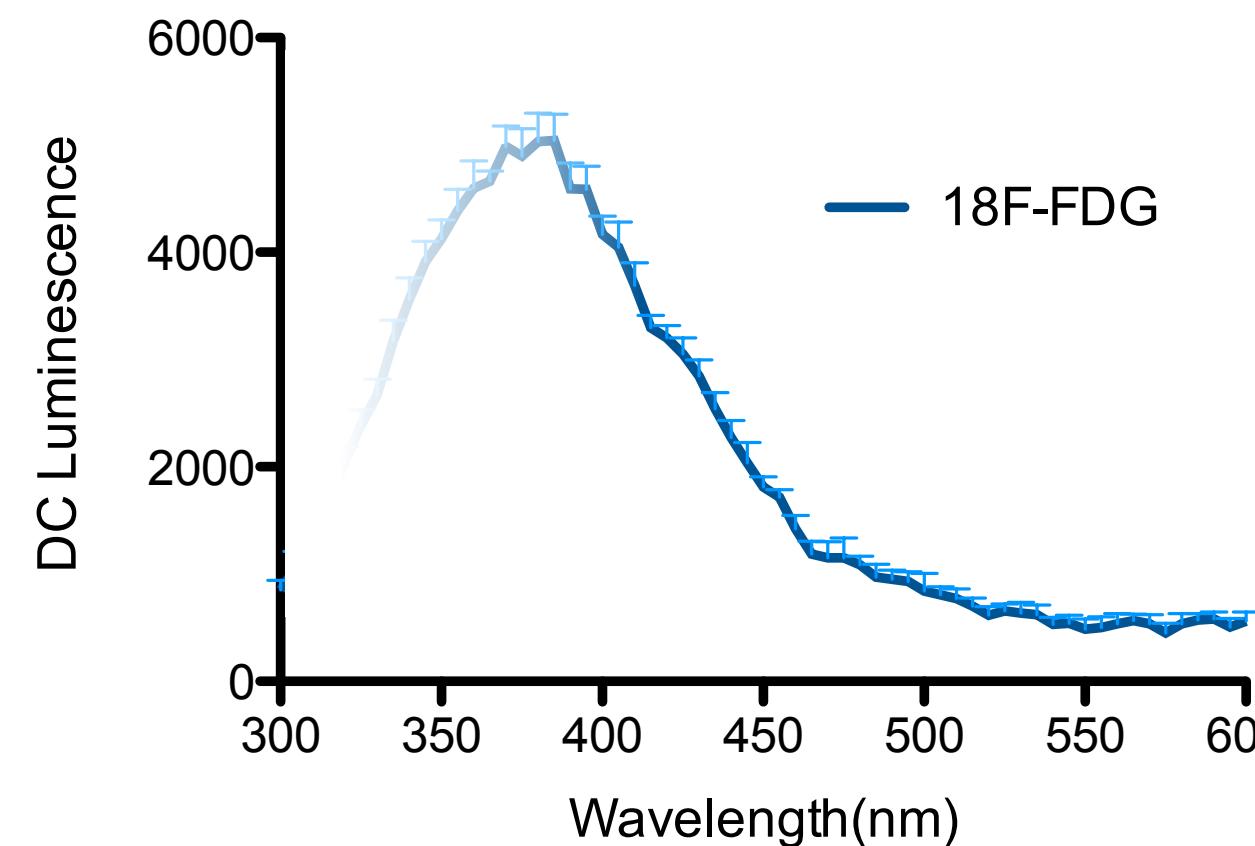


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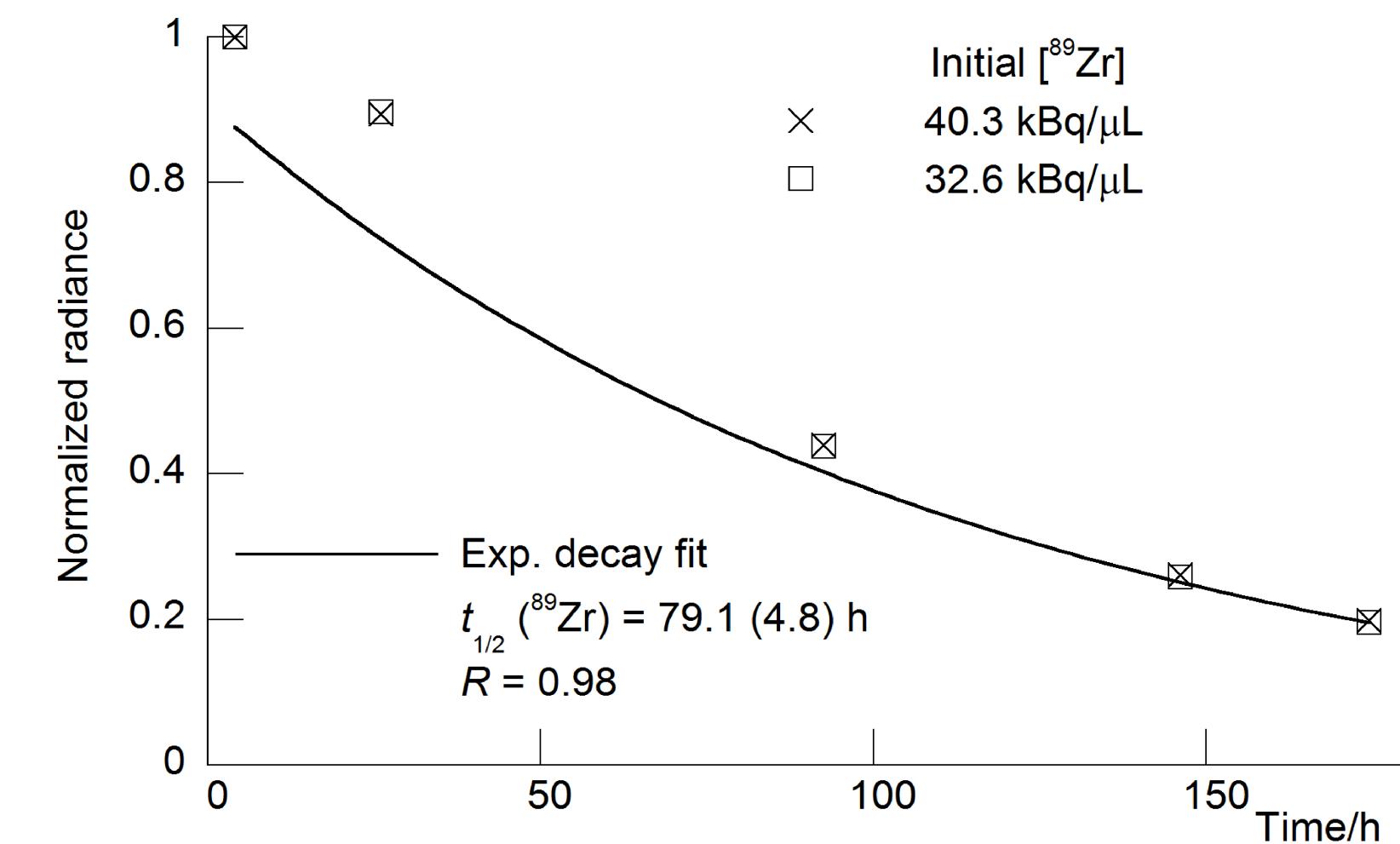
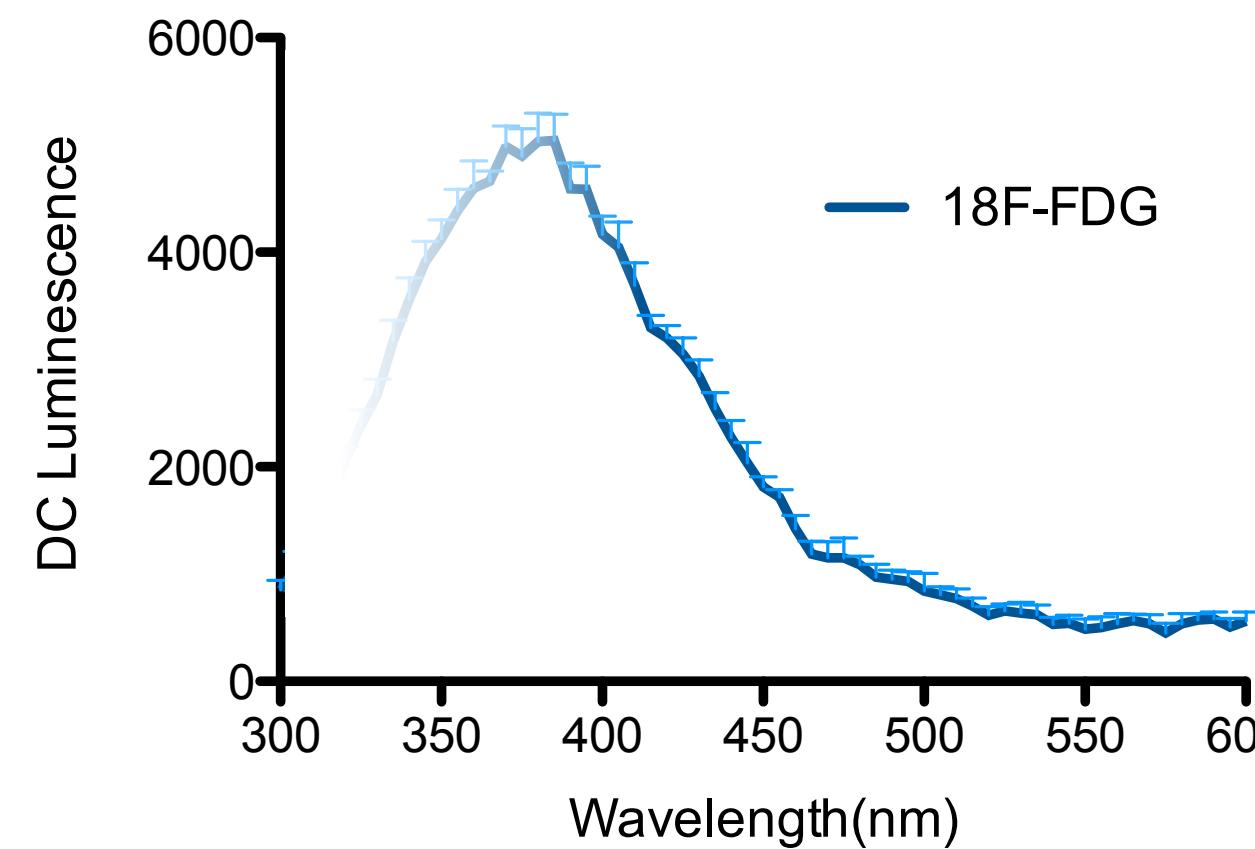


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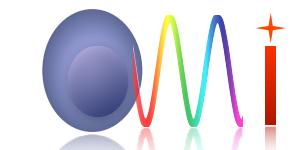
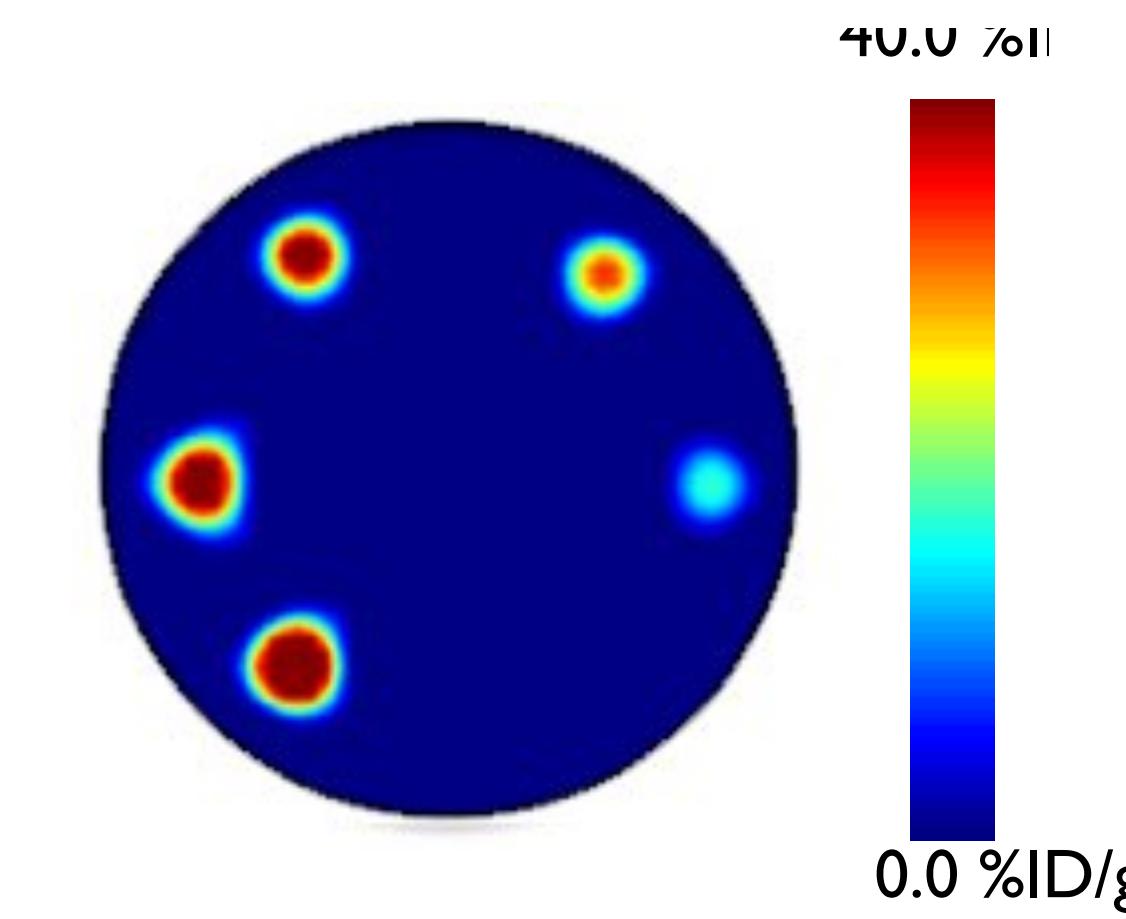
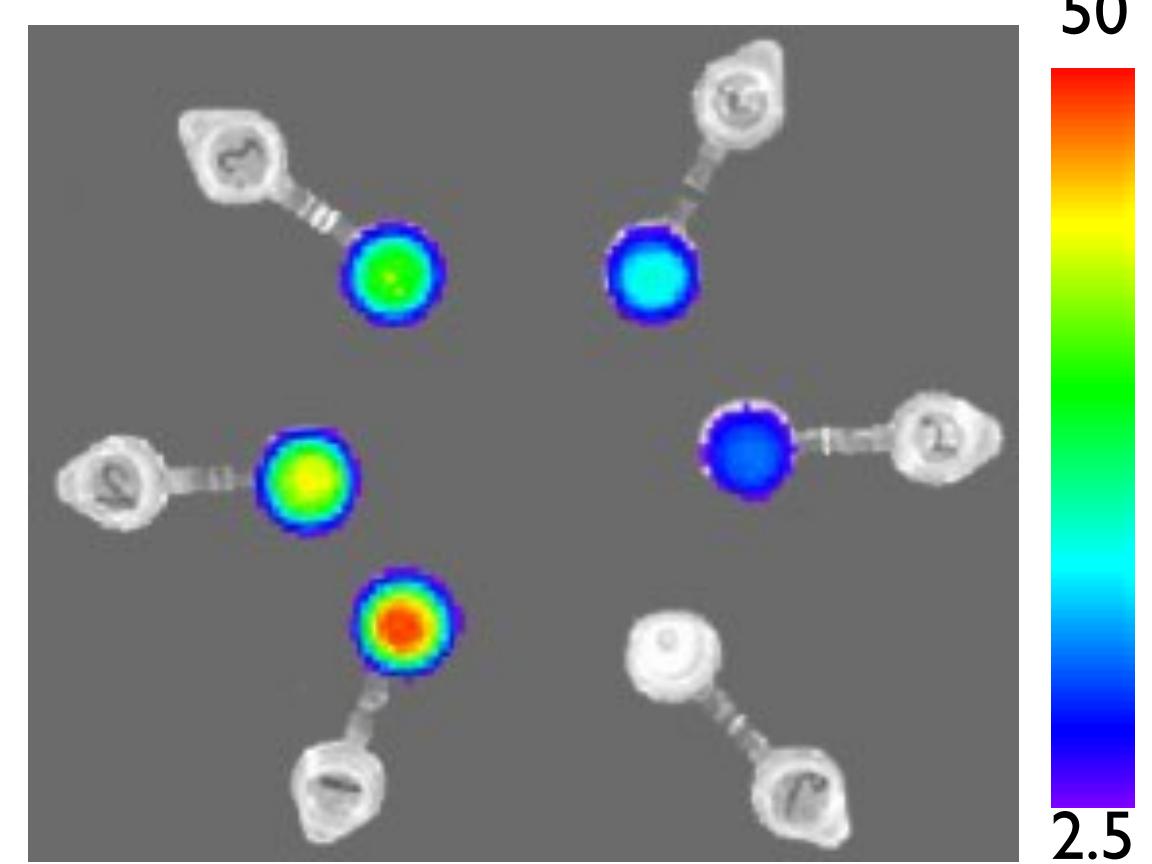
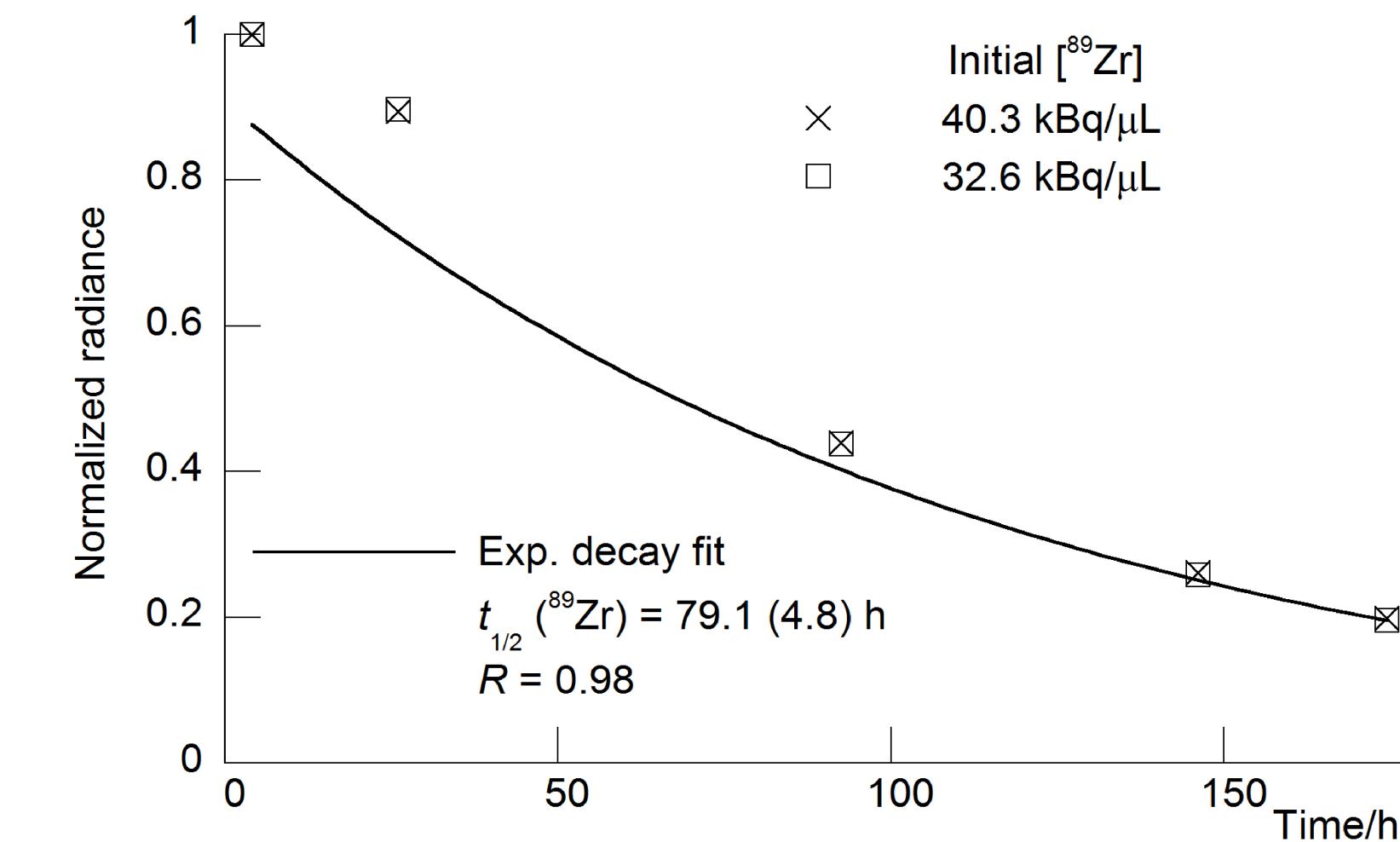
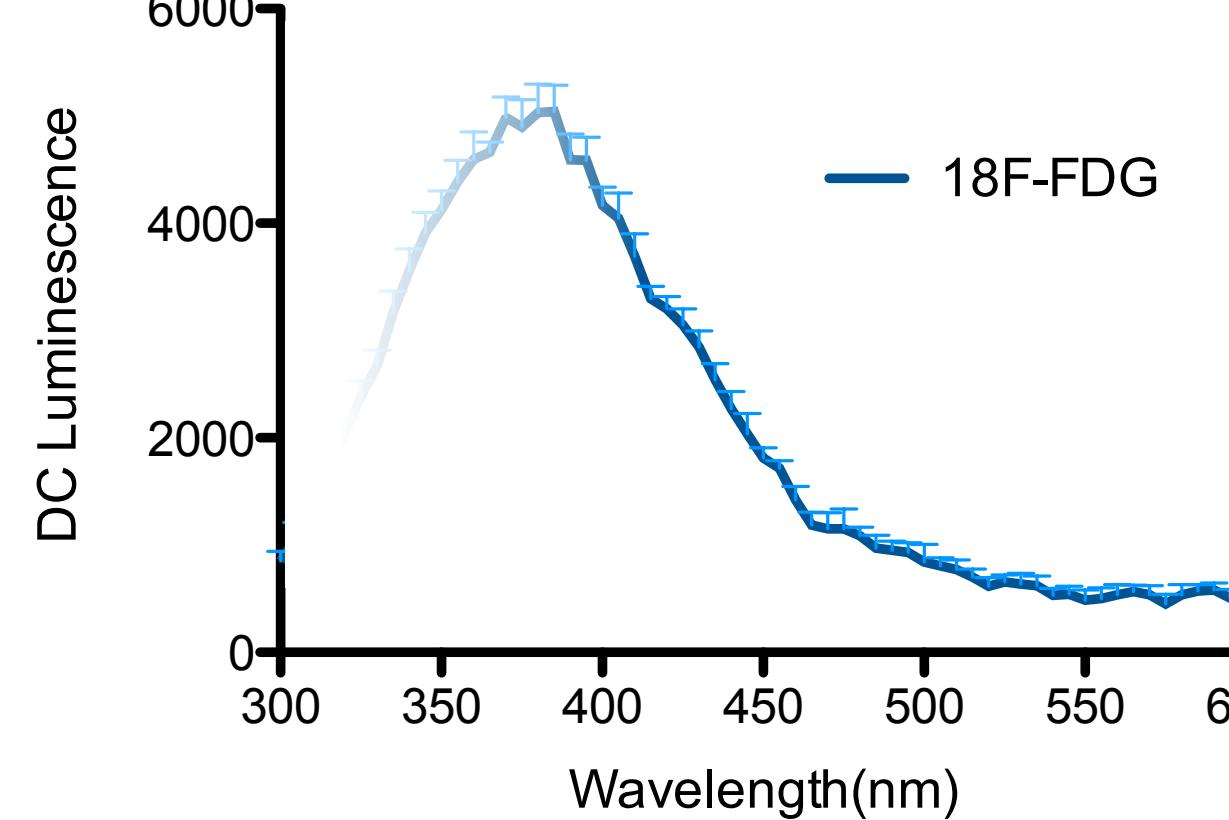


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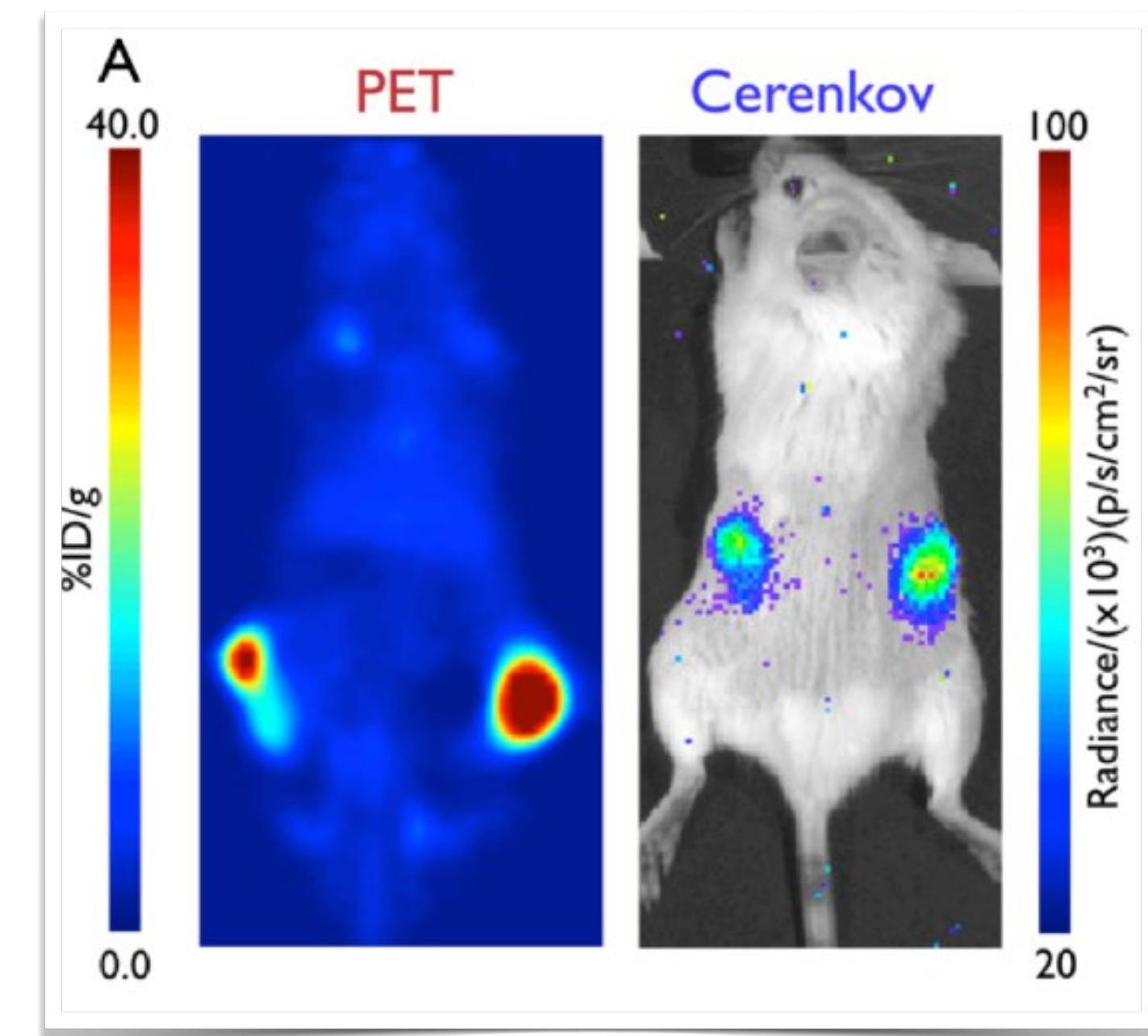
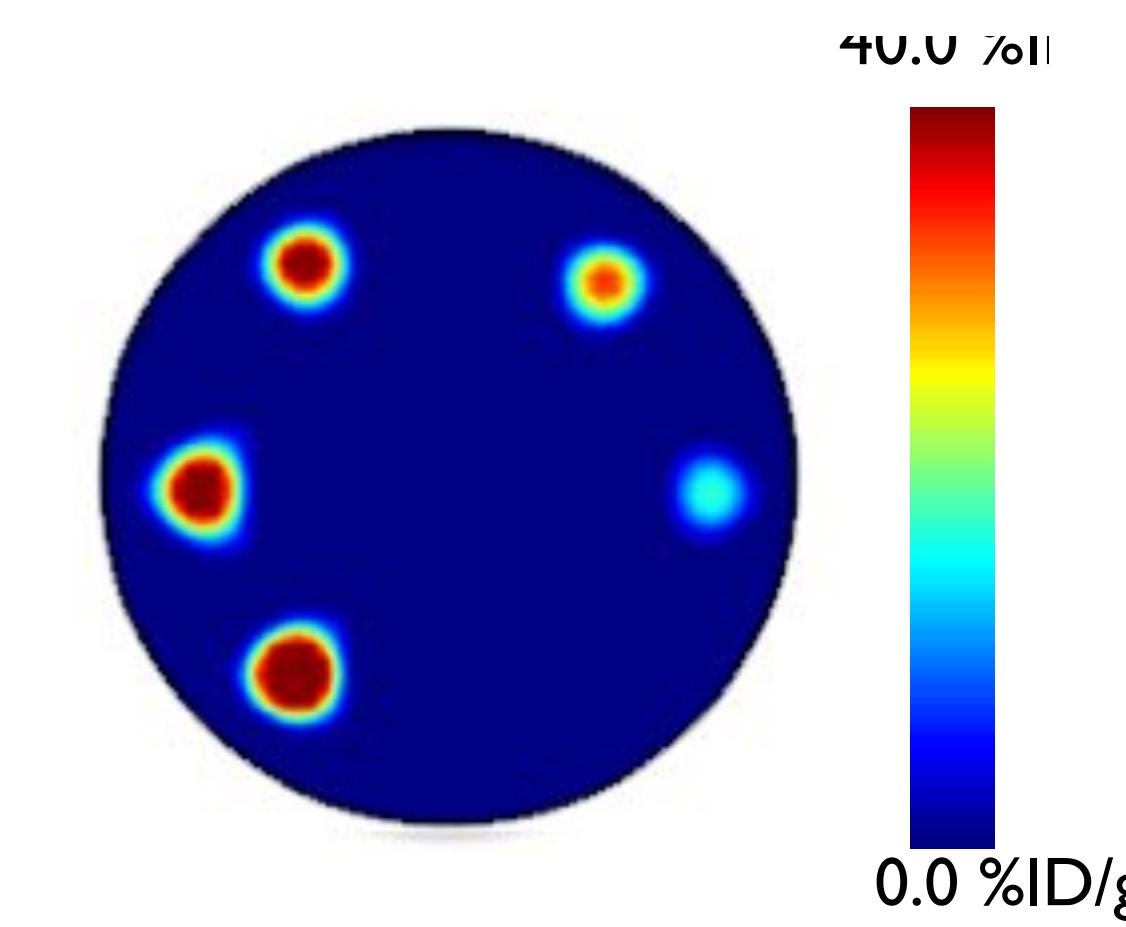
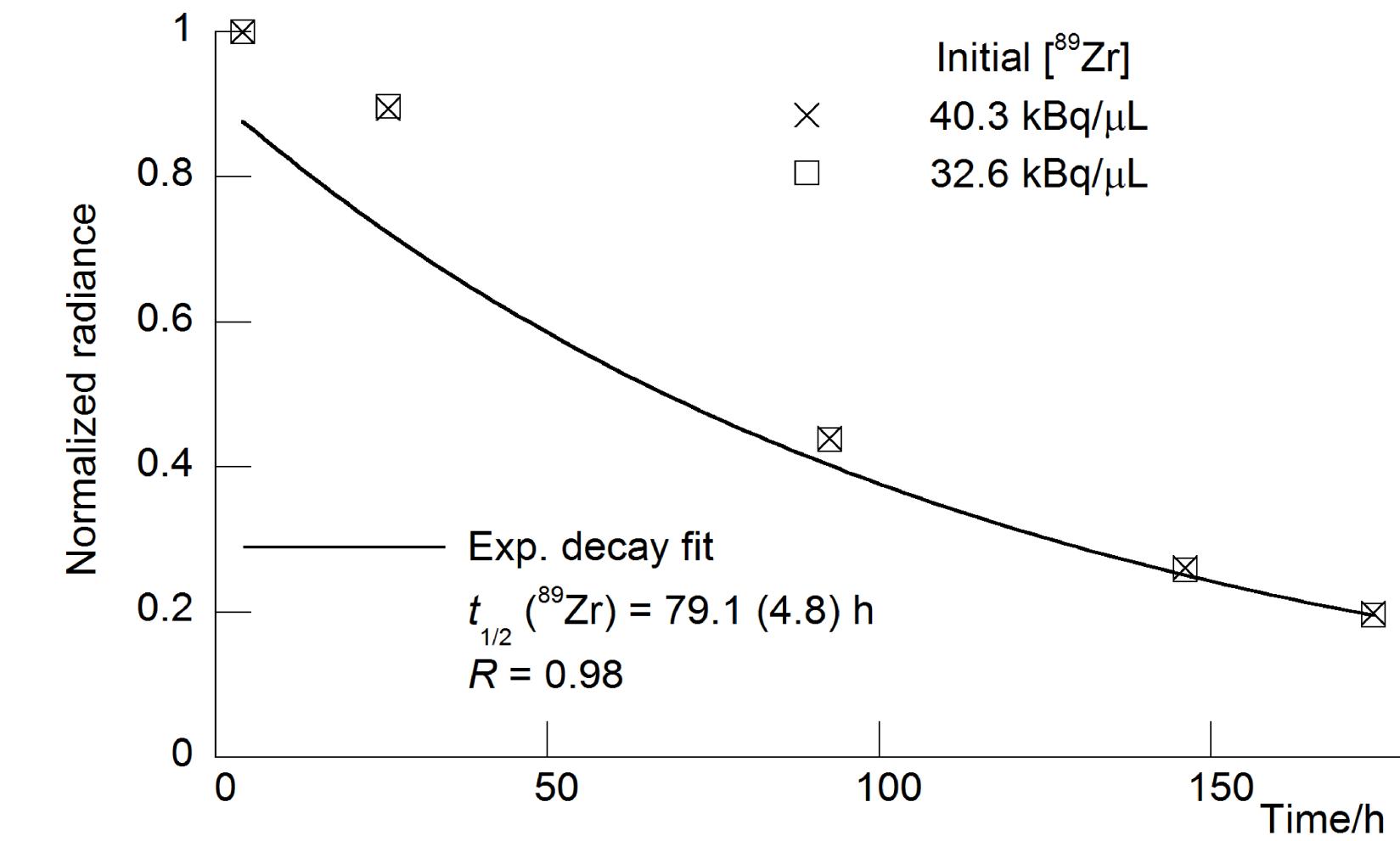
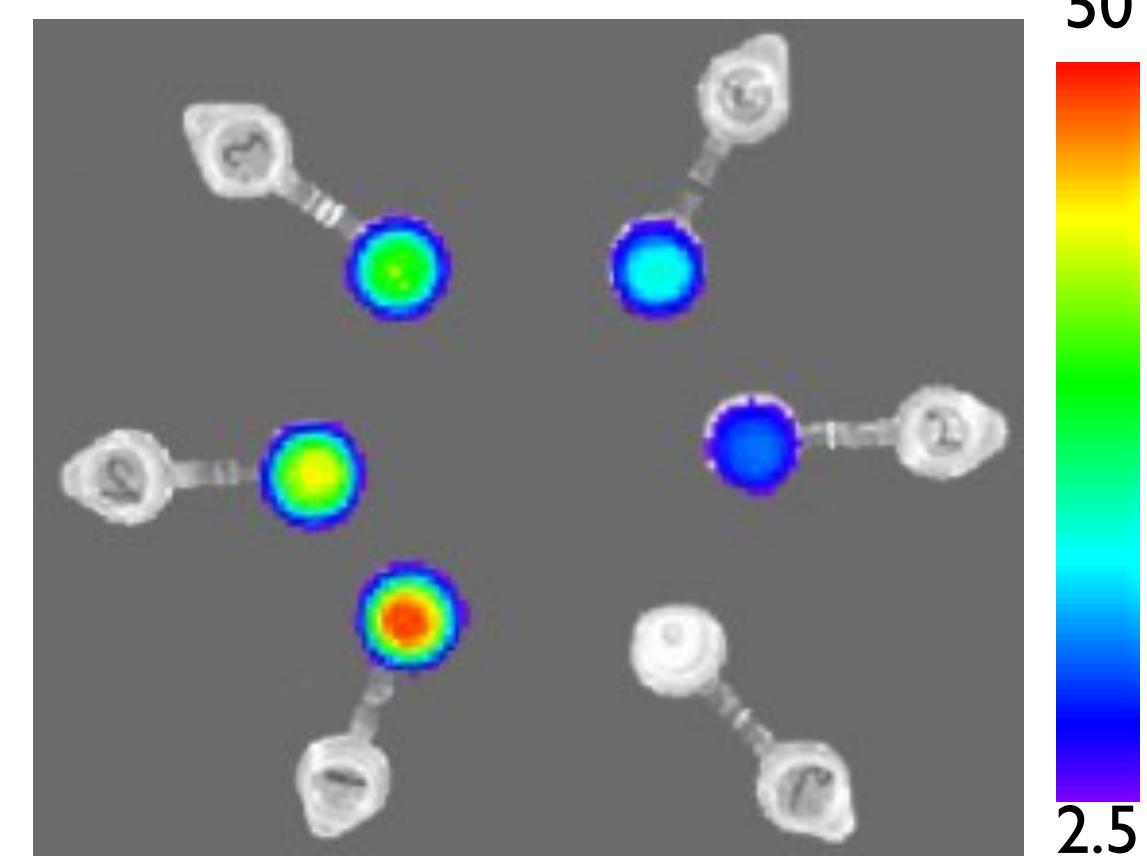
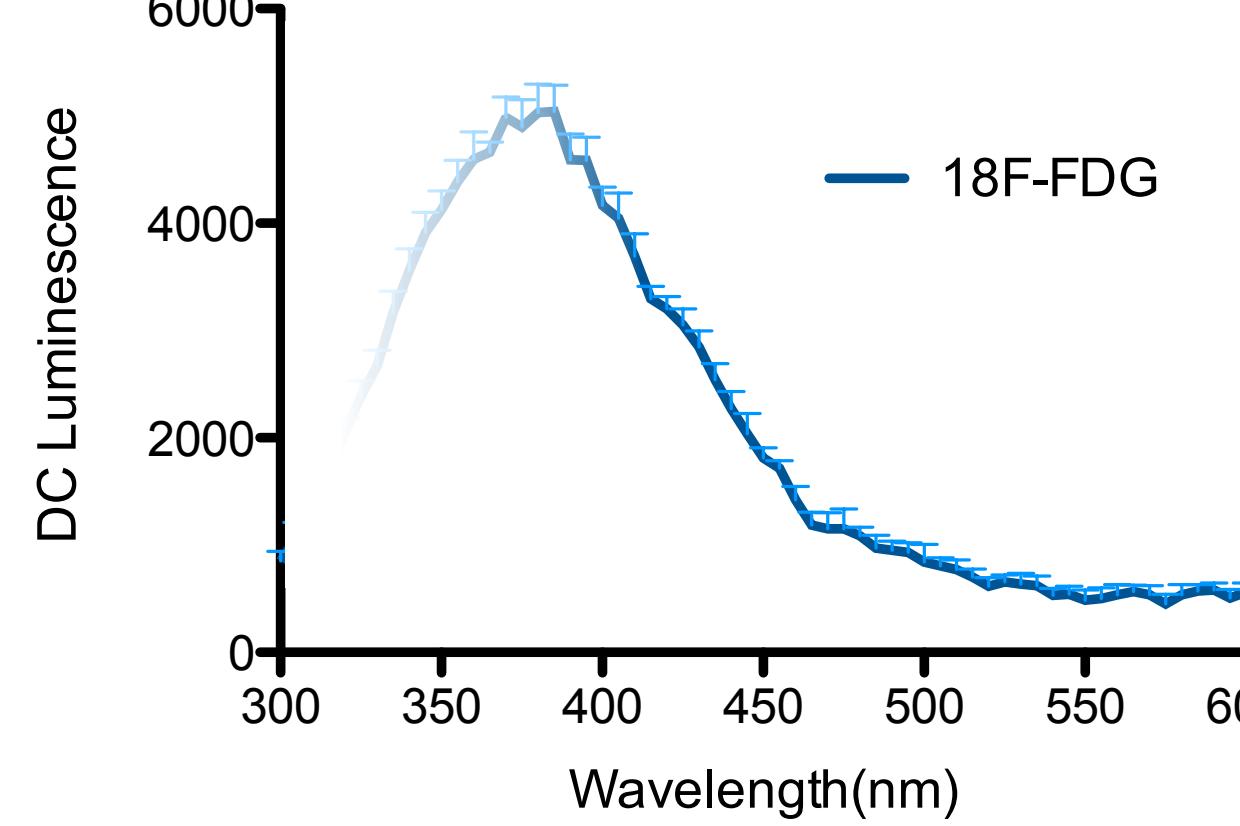


Medical CLI



A Ruggiero

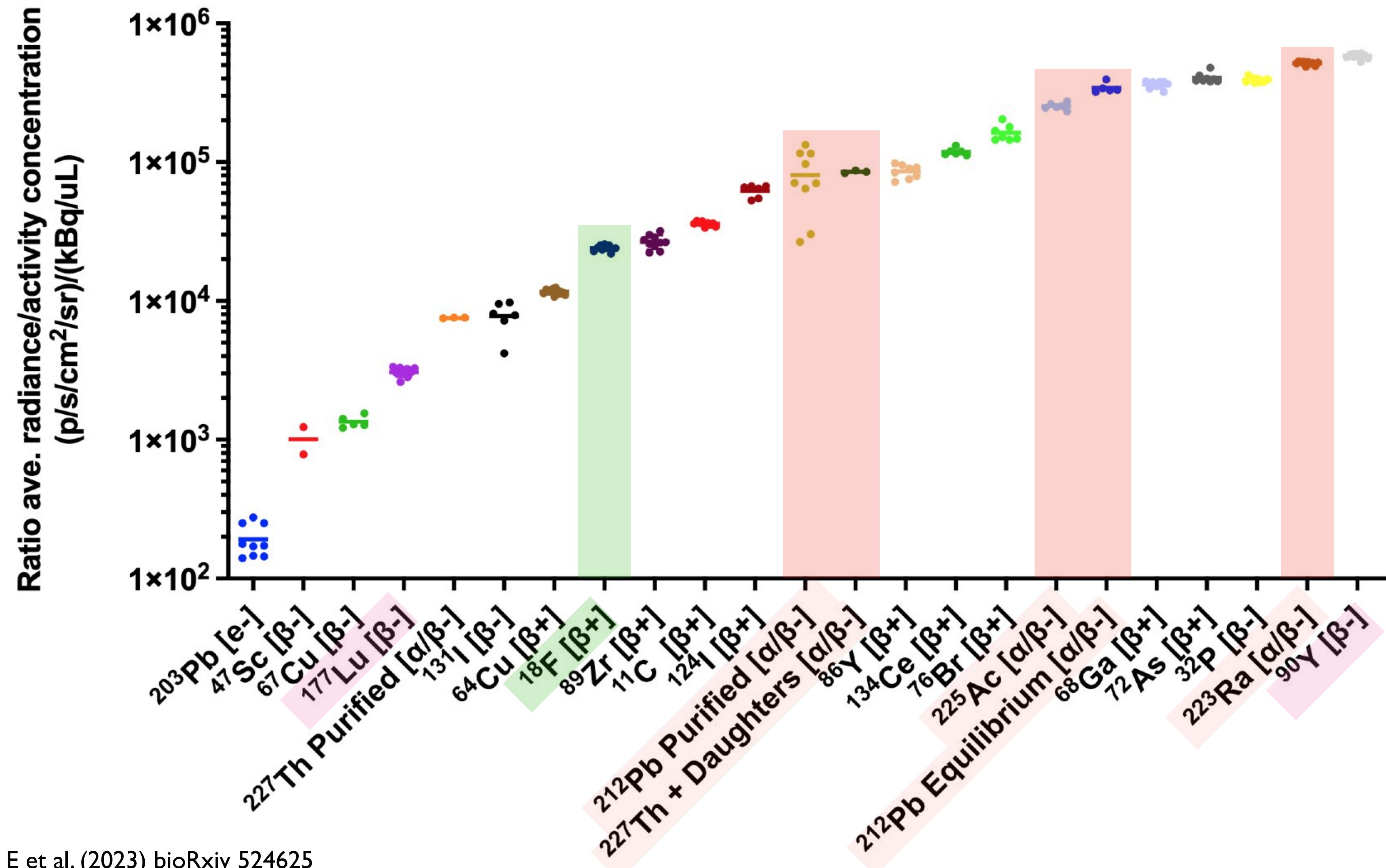
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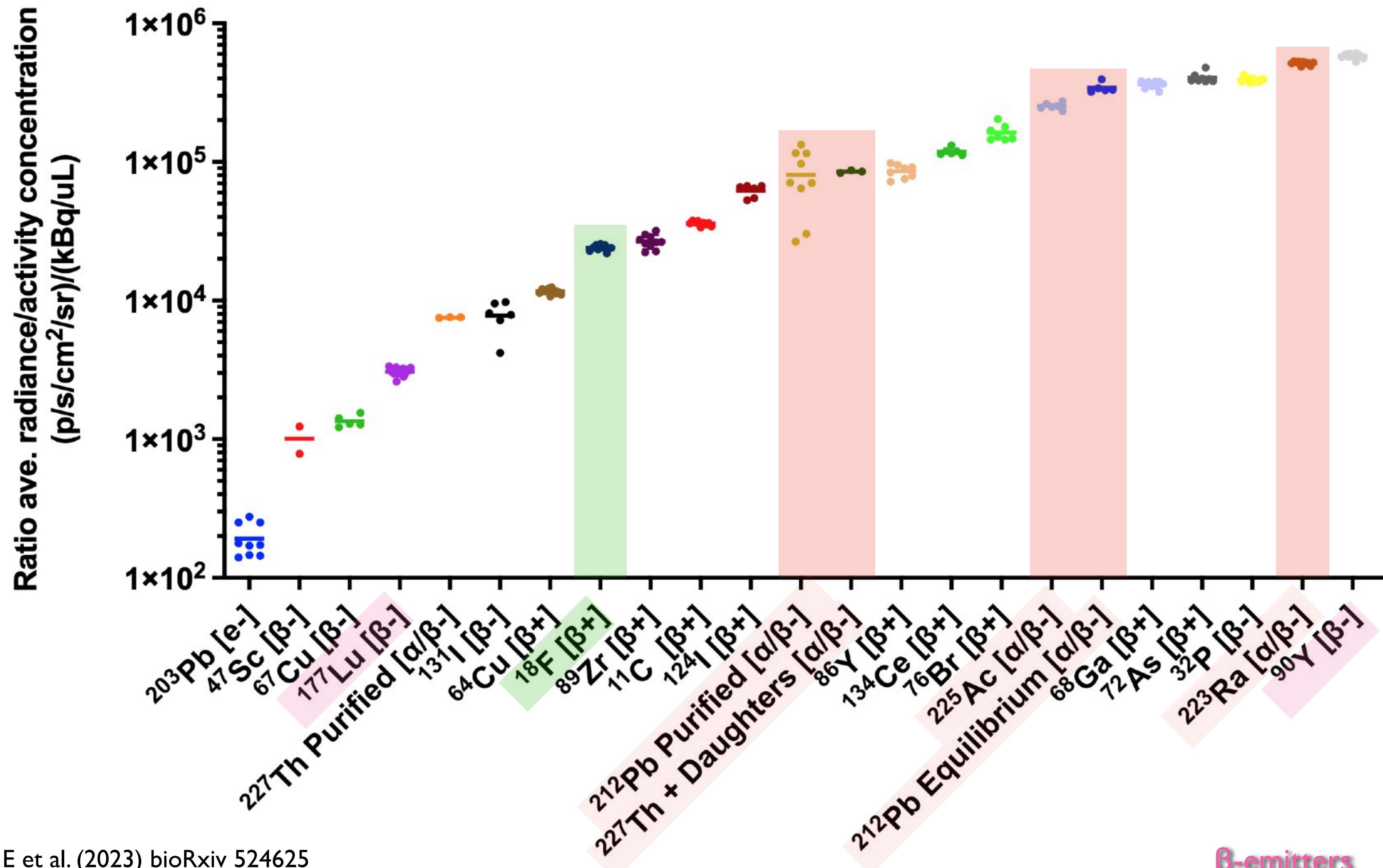
acquisition time of
several minutes



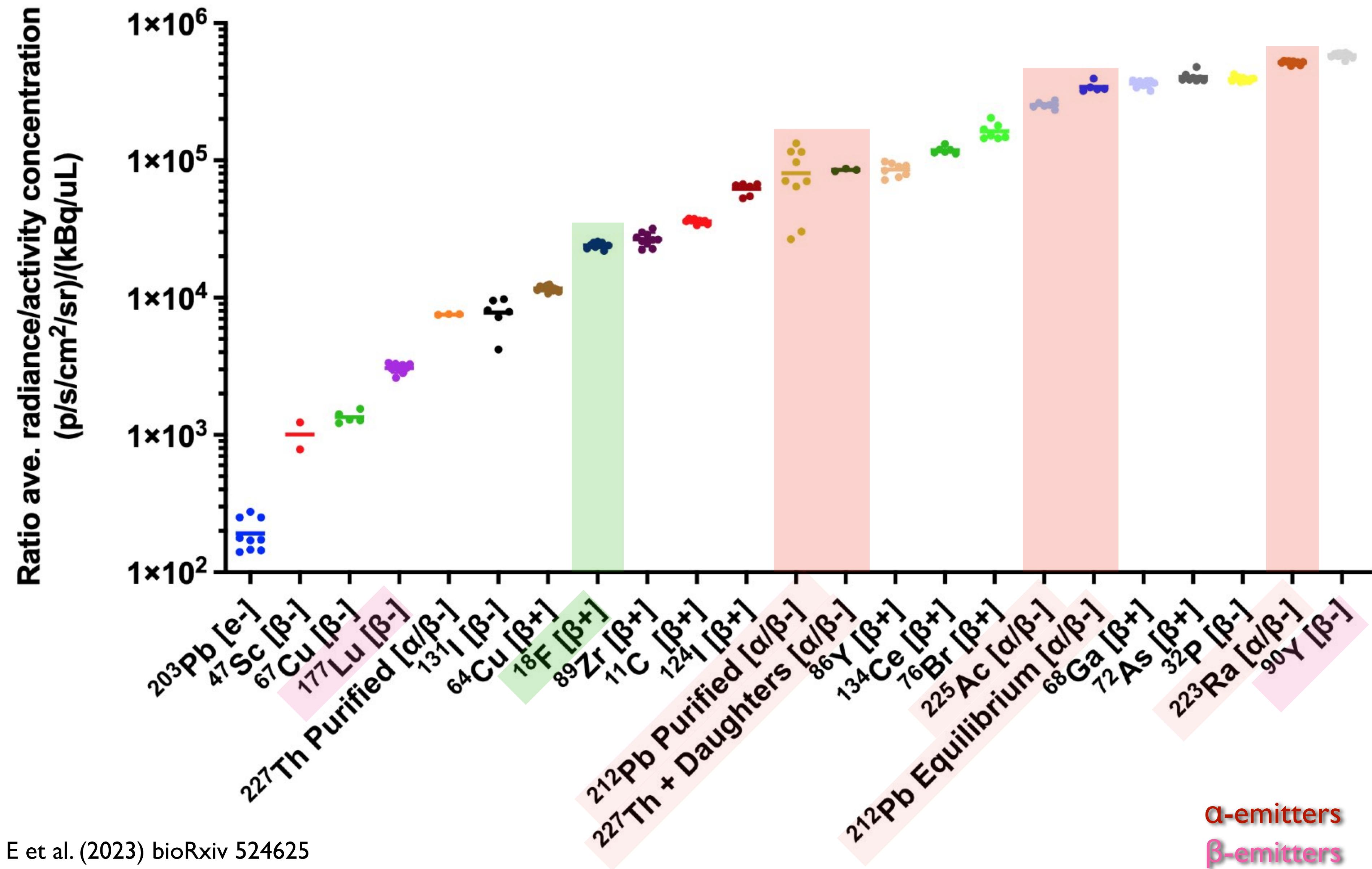
Medical CLI



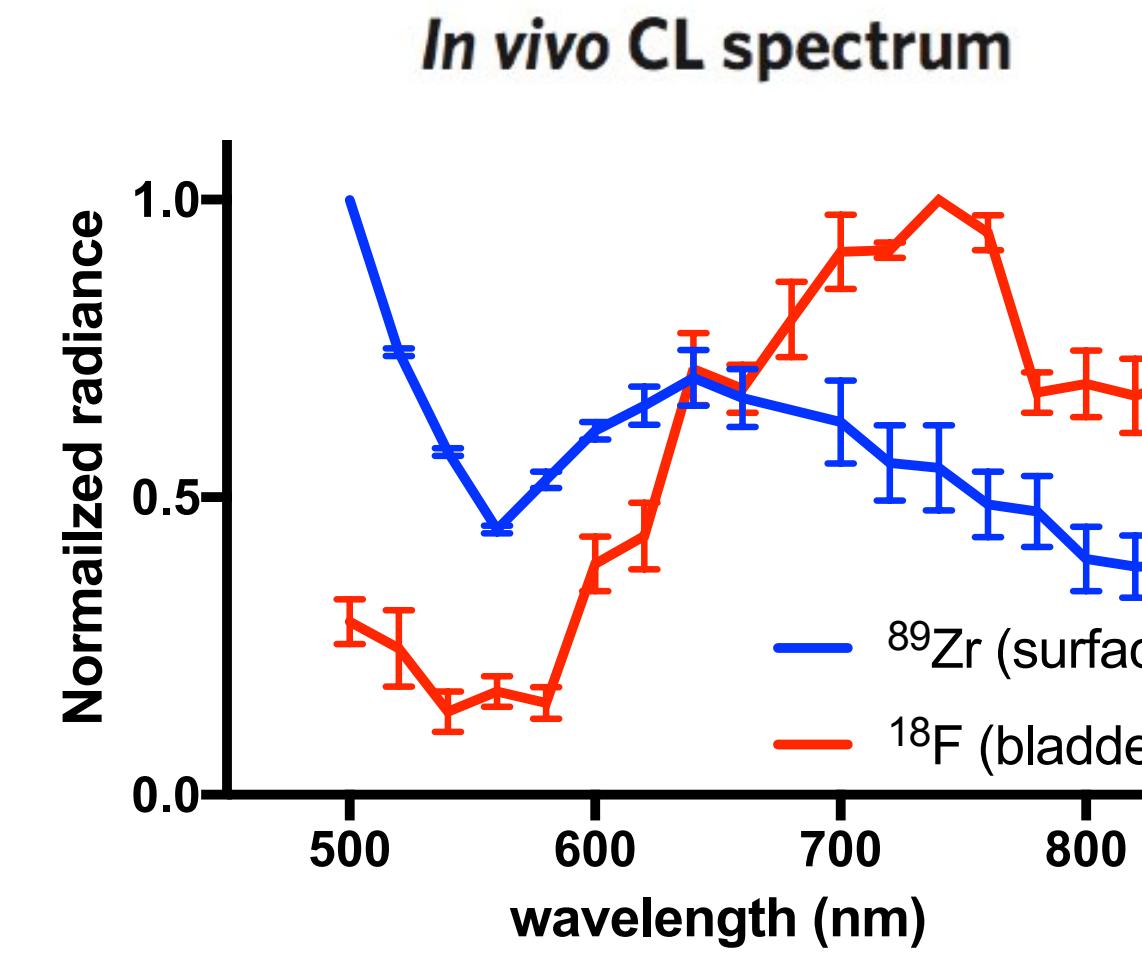
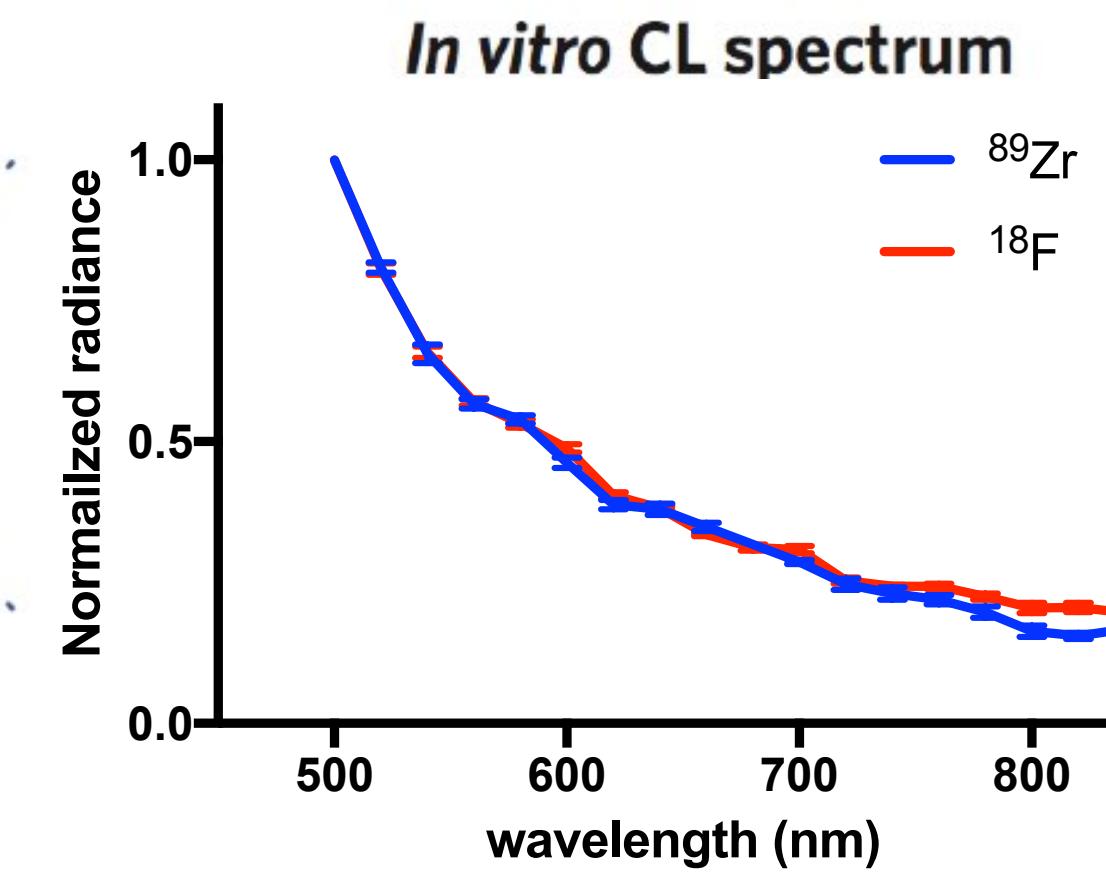
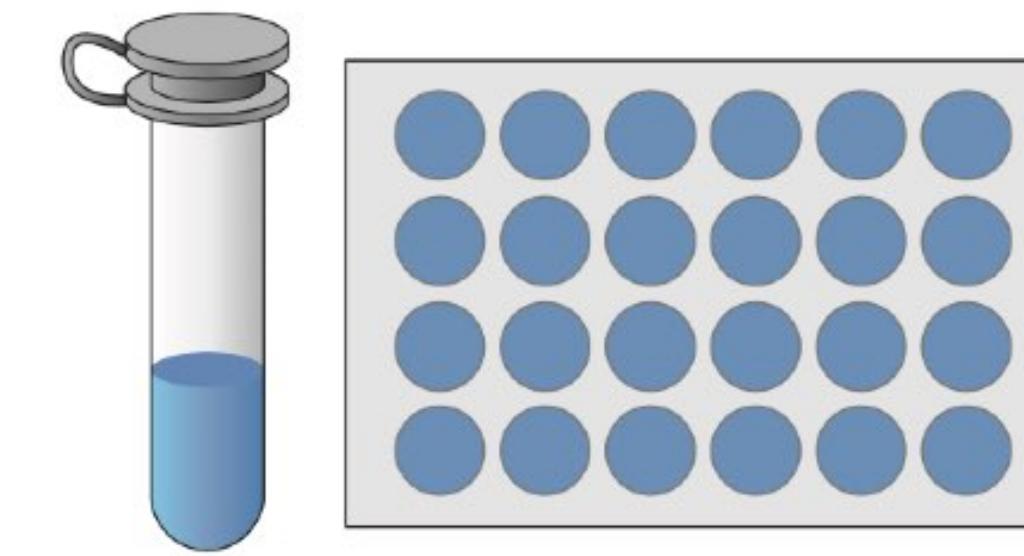
Medical CLI



Medical CLI



Path length & resolution



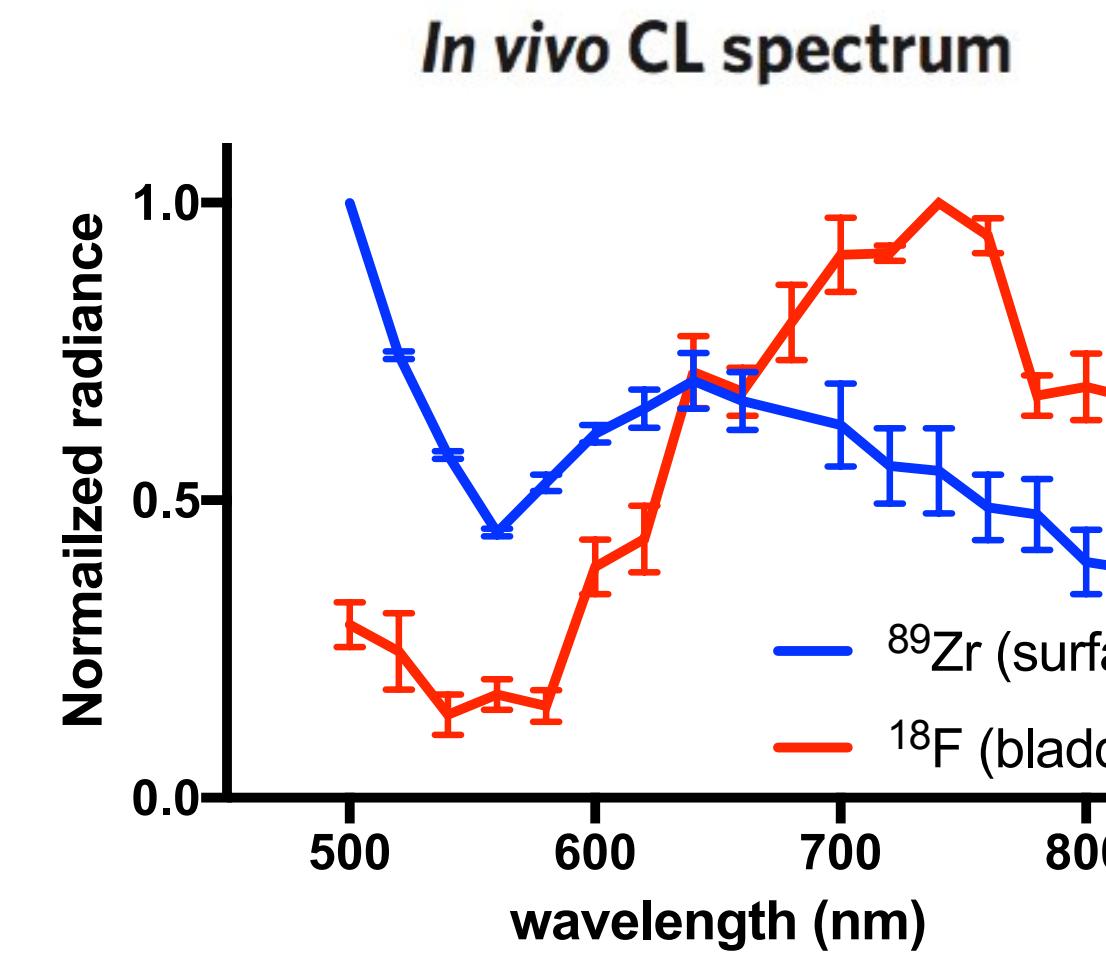
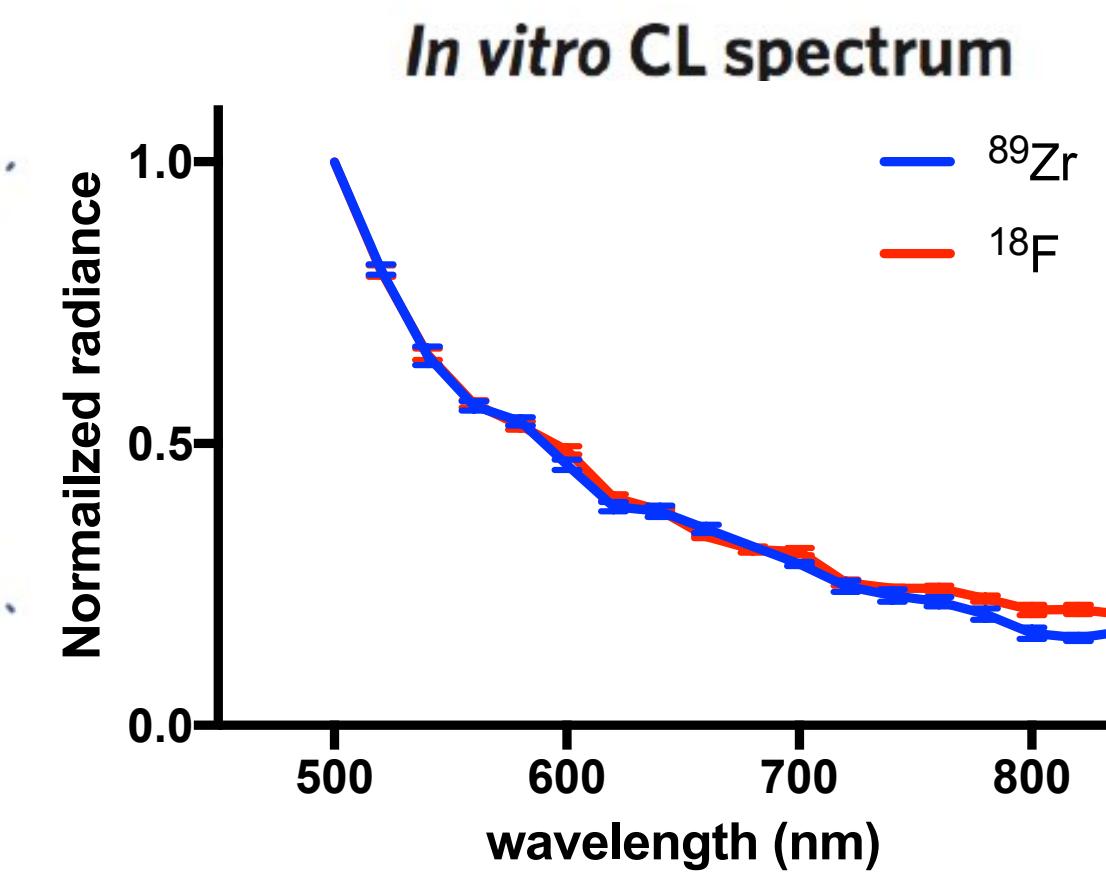
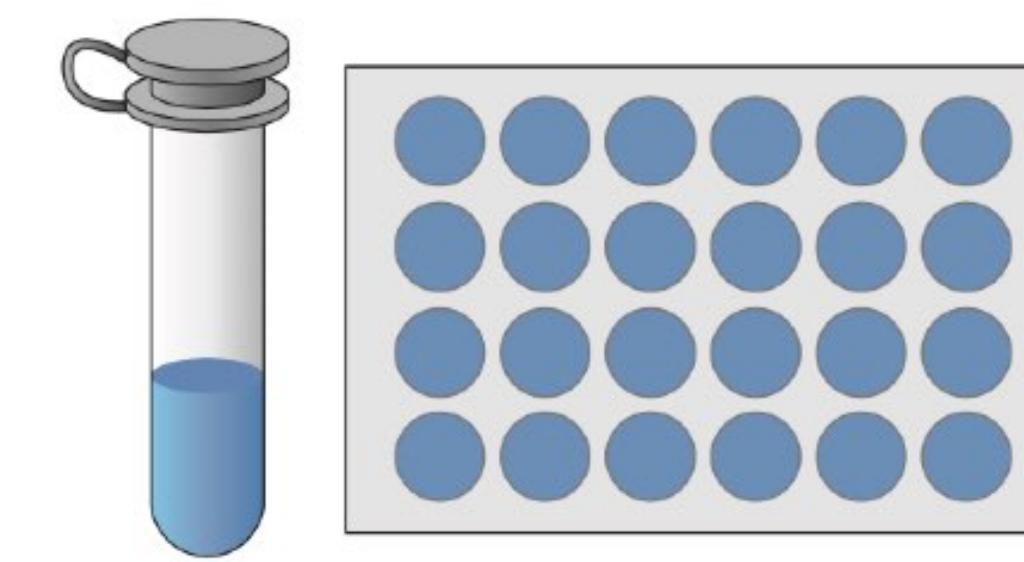
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Shaffer, Pratt and Grimm (2016) Nature Nanotechnology 12(2):106

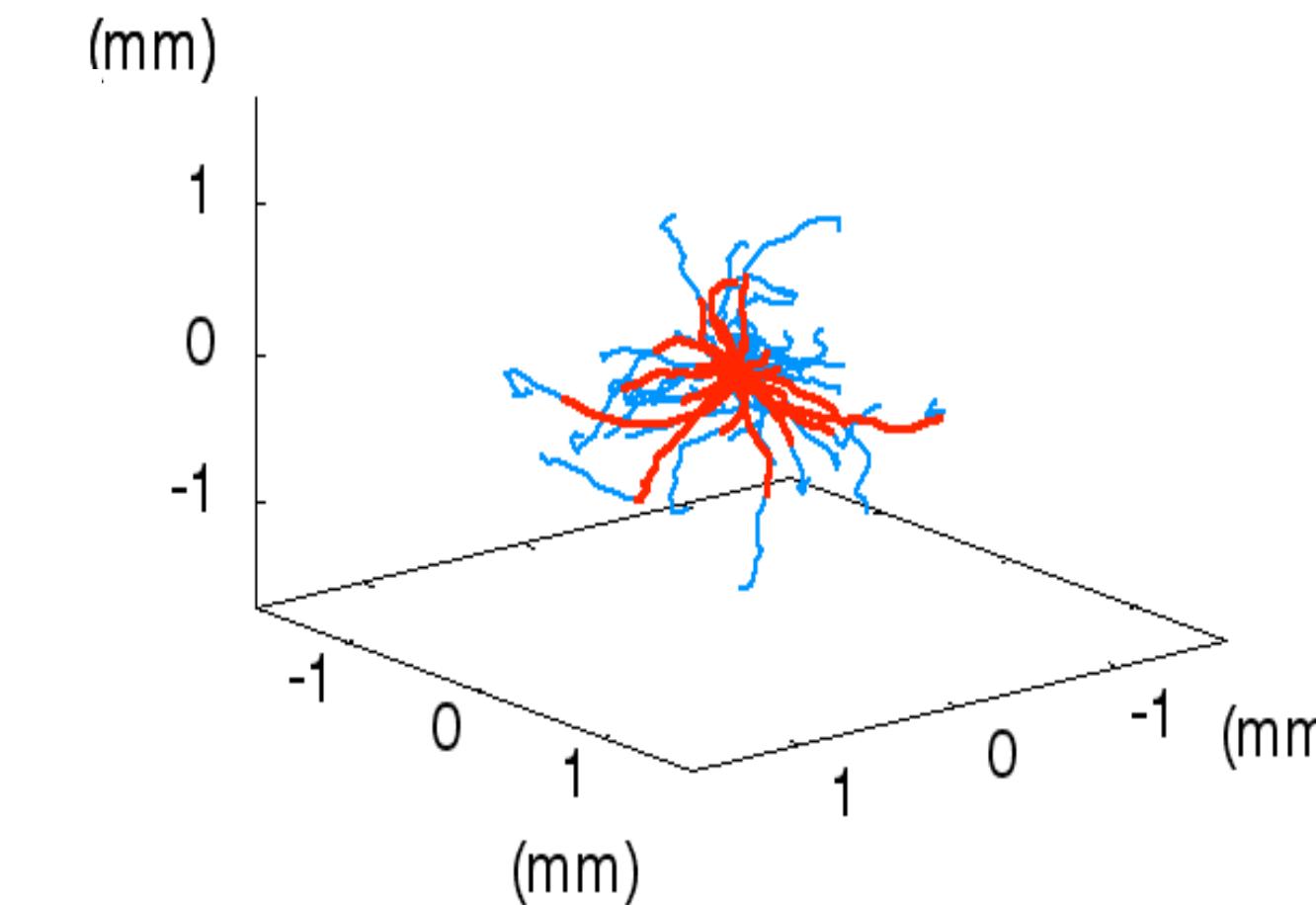
Ciarrocchi E & Belcari N (2017) EJNMMI Physics 4:14



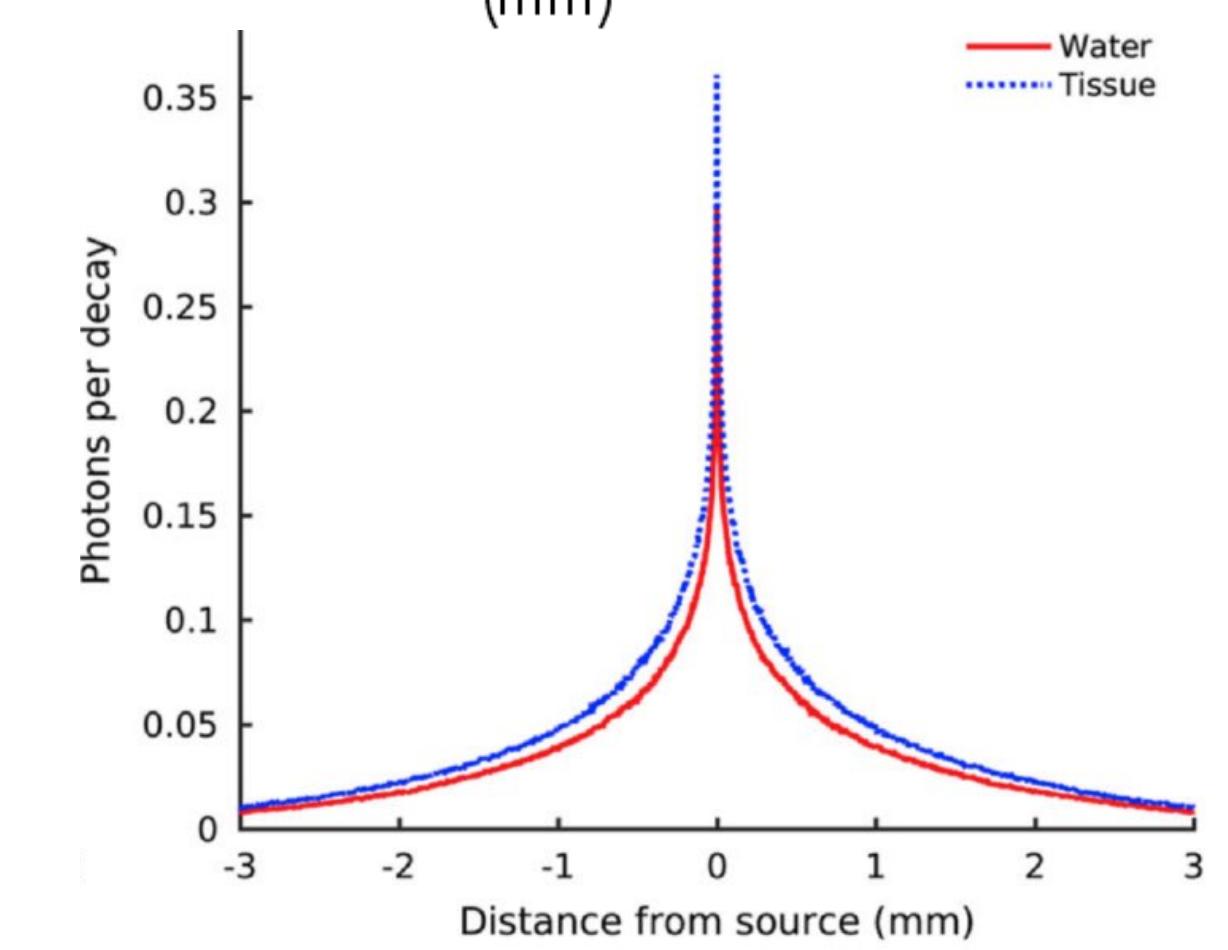
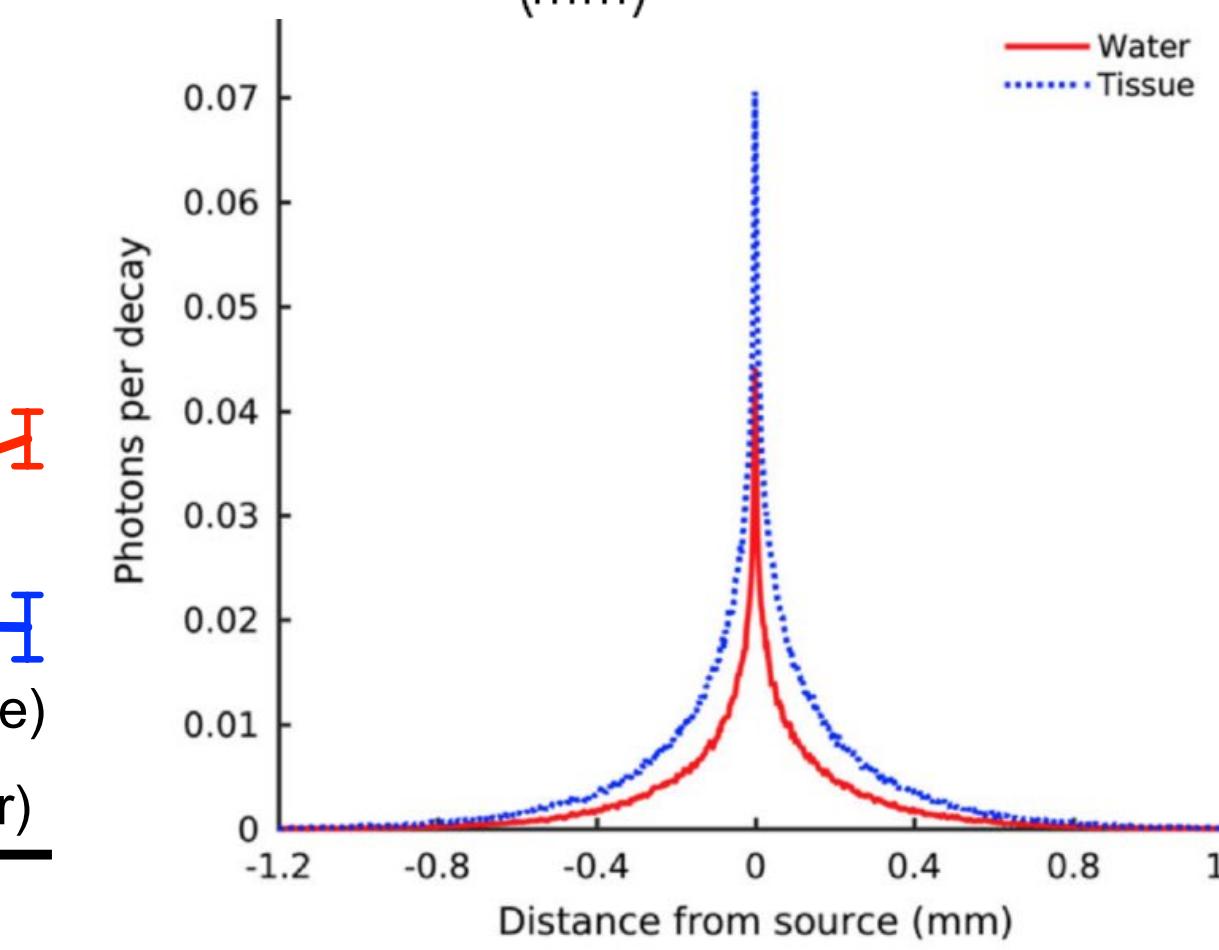
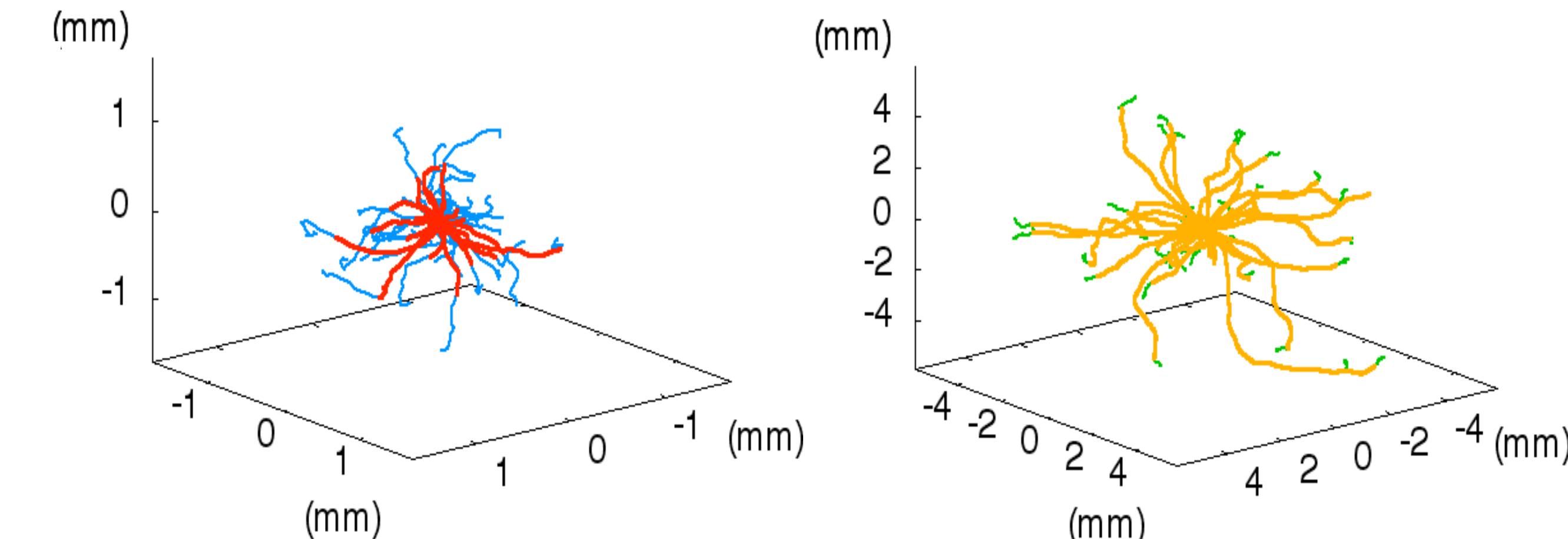
Path length & resolution



¹⁸F $\beta^+ > c, \beta^+ < c$



⁹⁰Y $\beta^+ > c, \beta^+ < c$



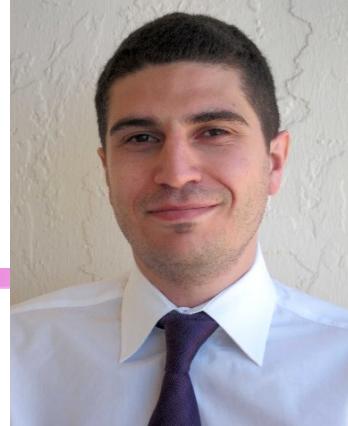
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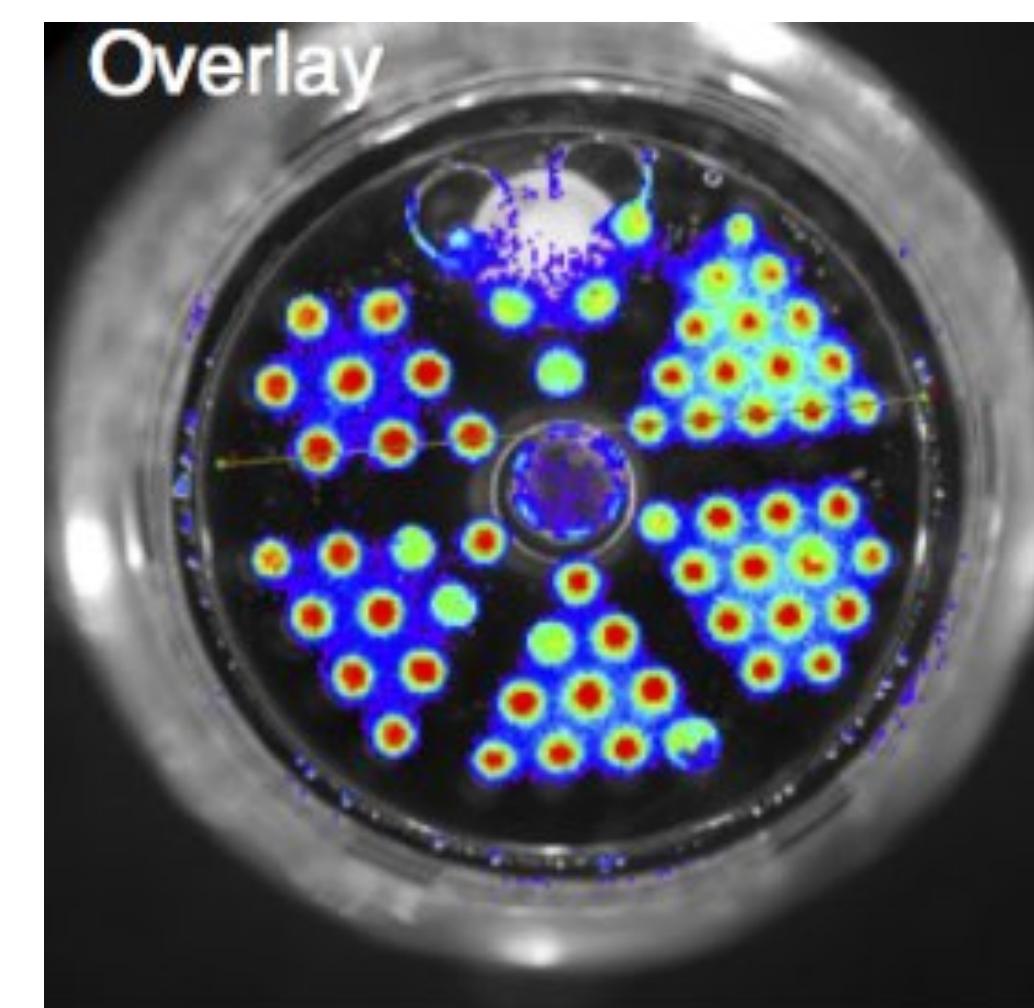
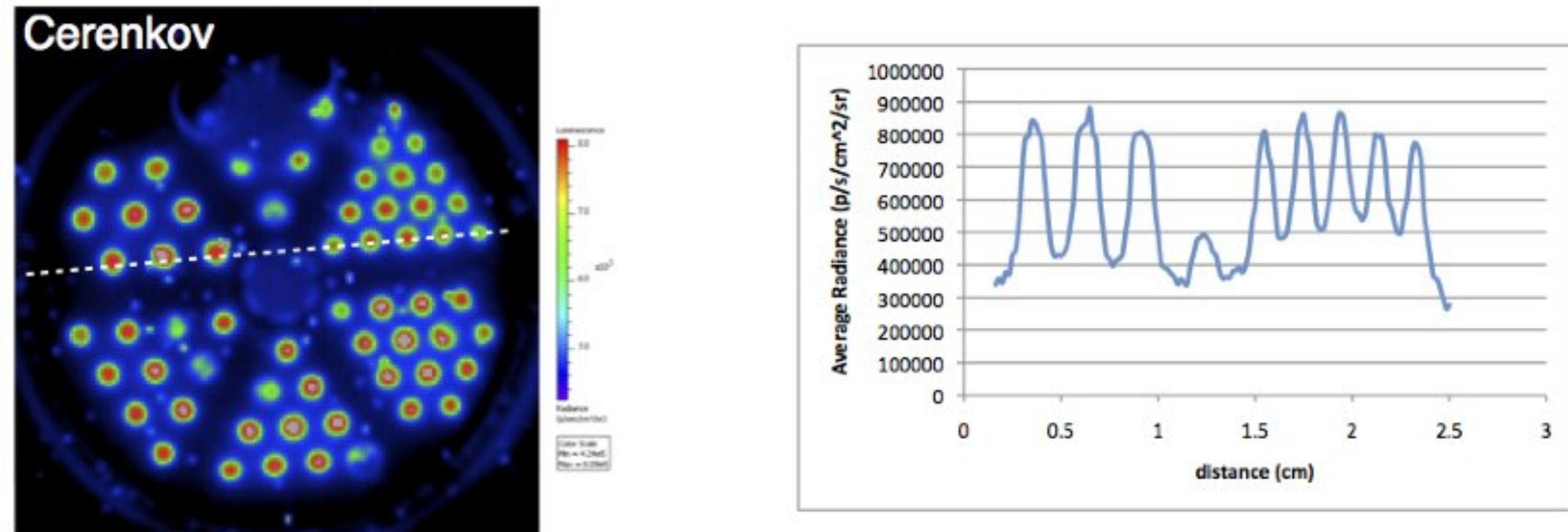
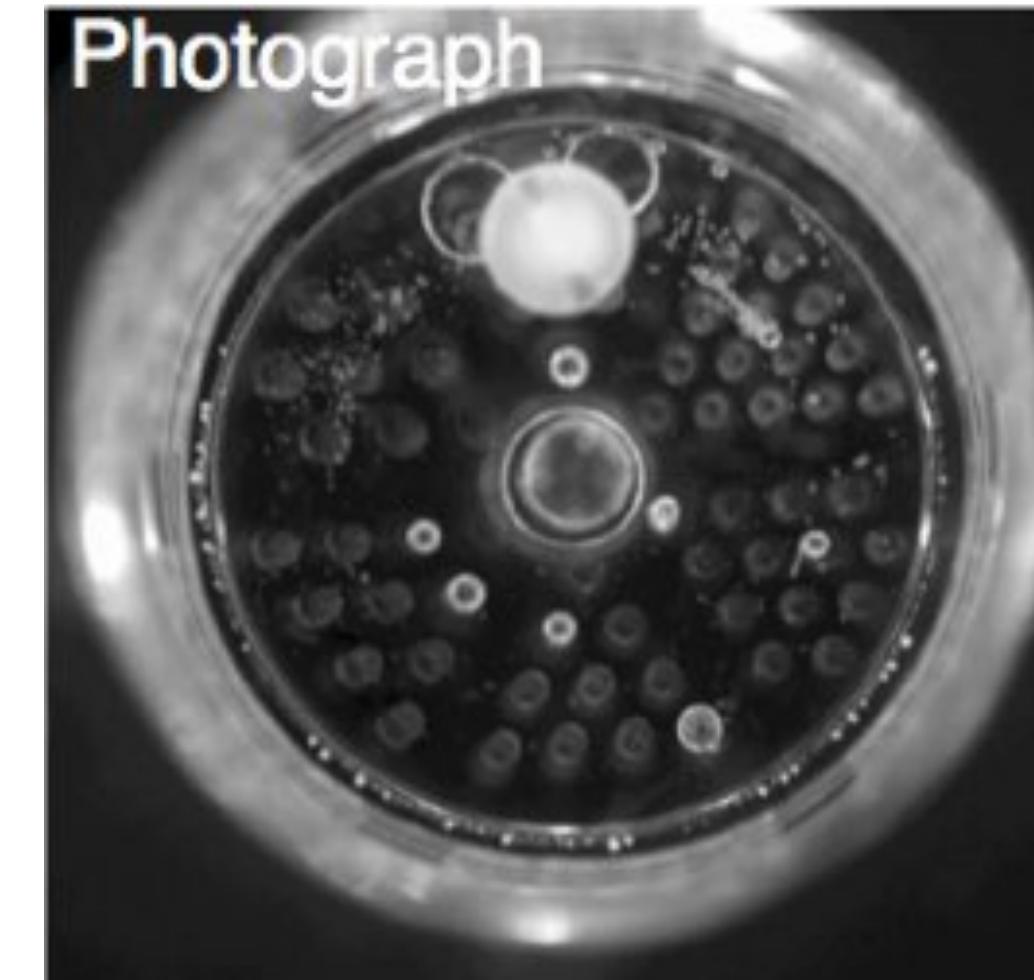
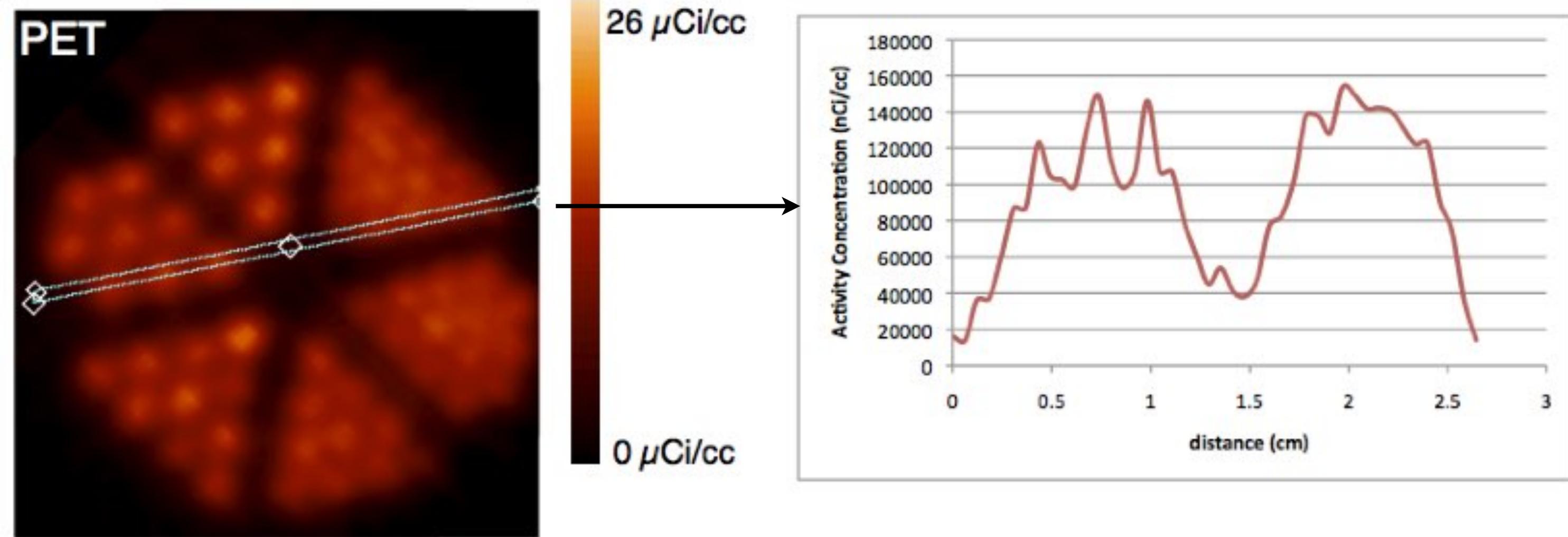


Resolution



D Thorek

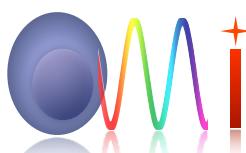
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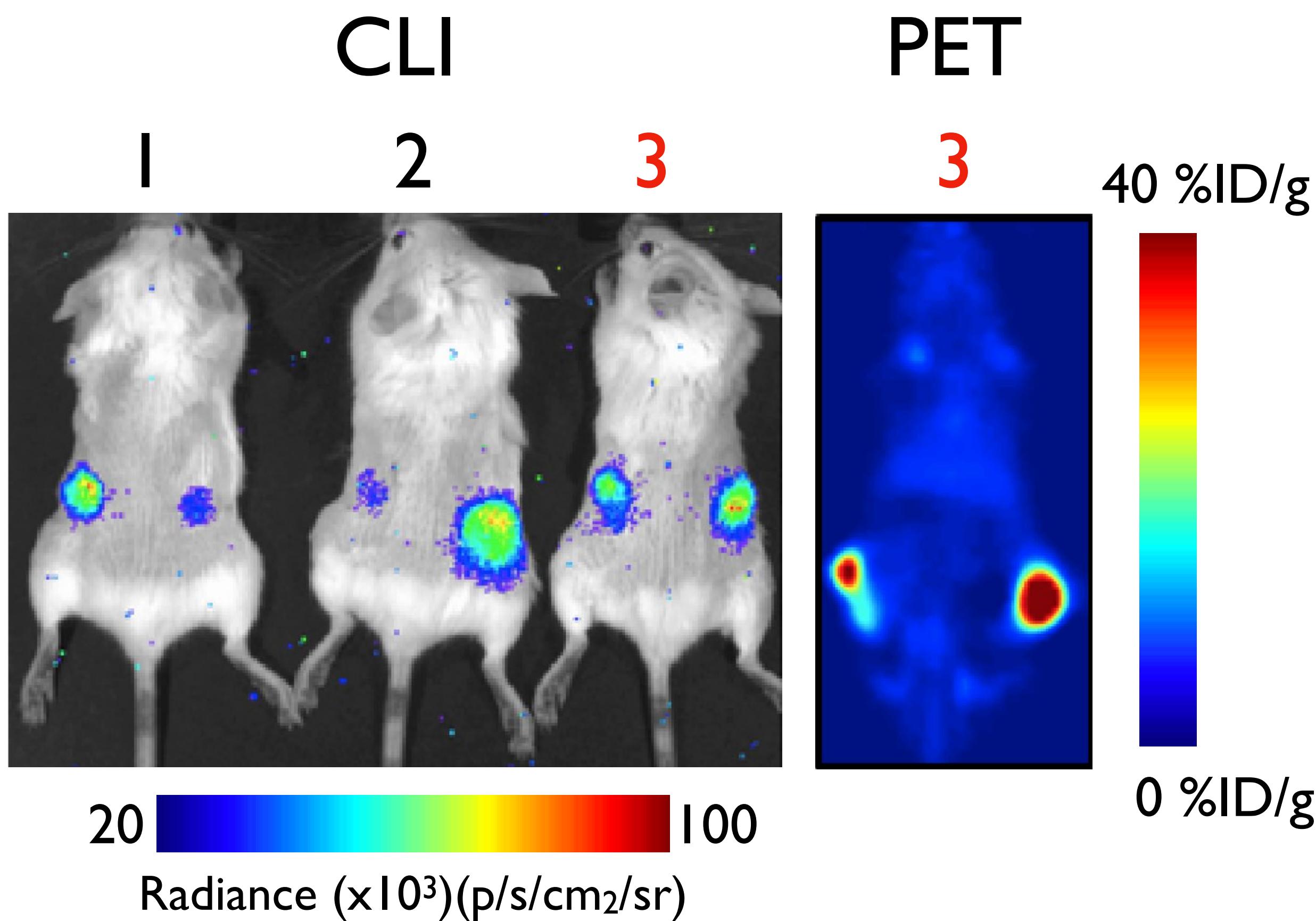
Thorek D et al. (2013) Nature Medicine 19(10):1345-50



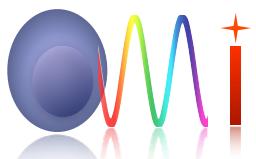
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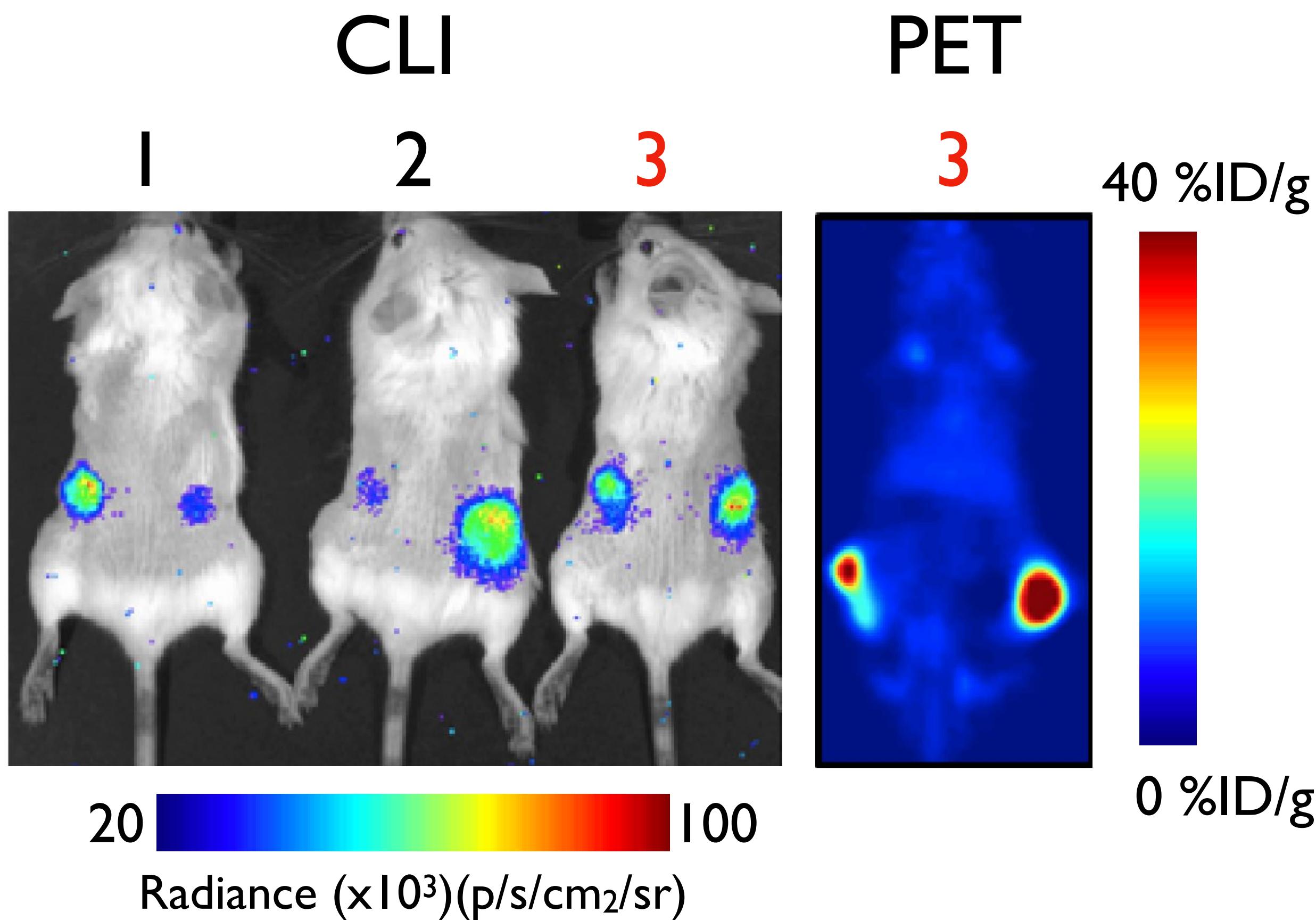
Cerenkov Imaging



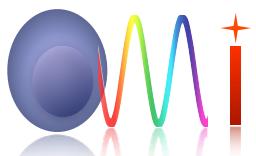
- Optical imaging cheaper than PET



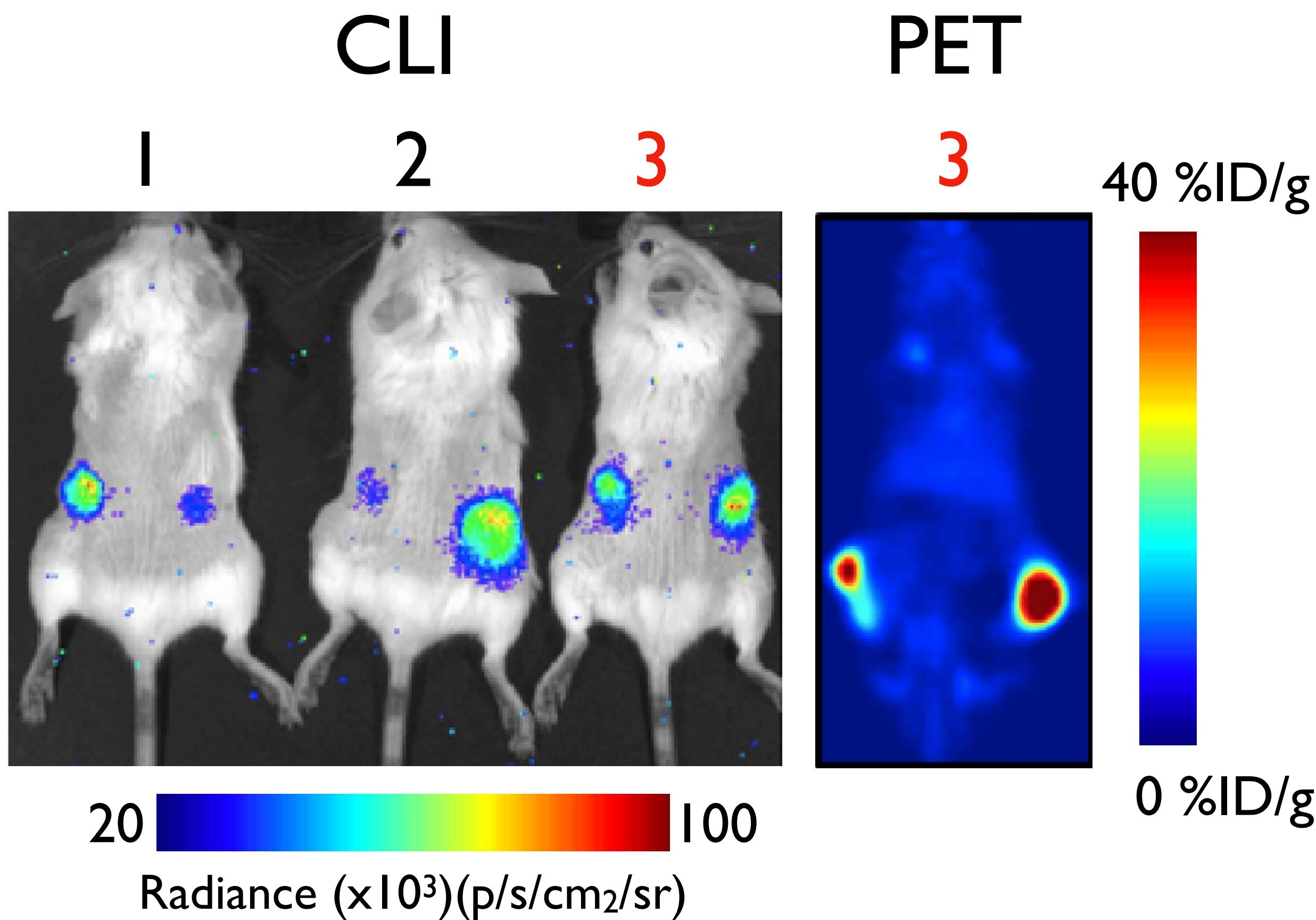
Cerenkov Imaging



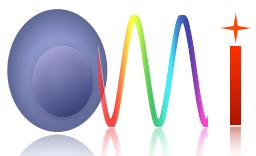
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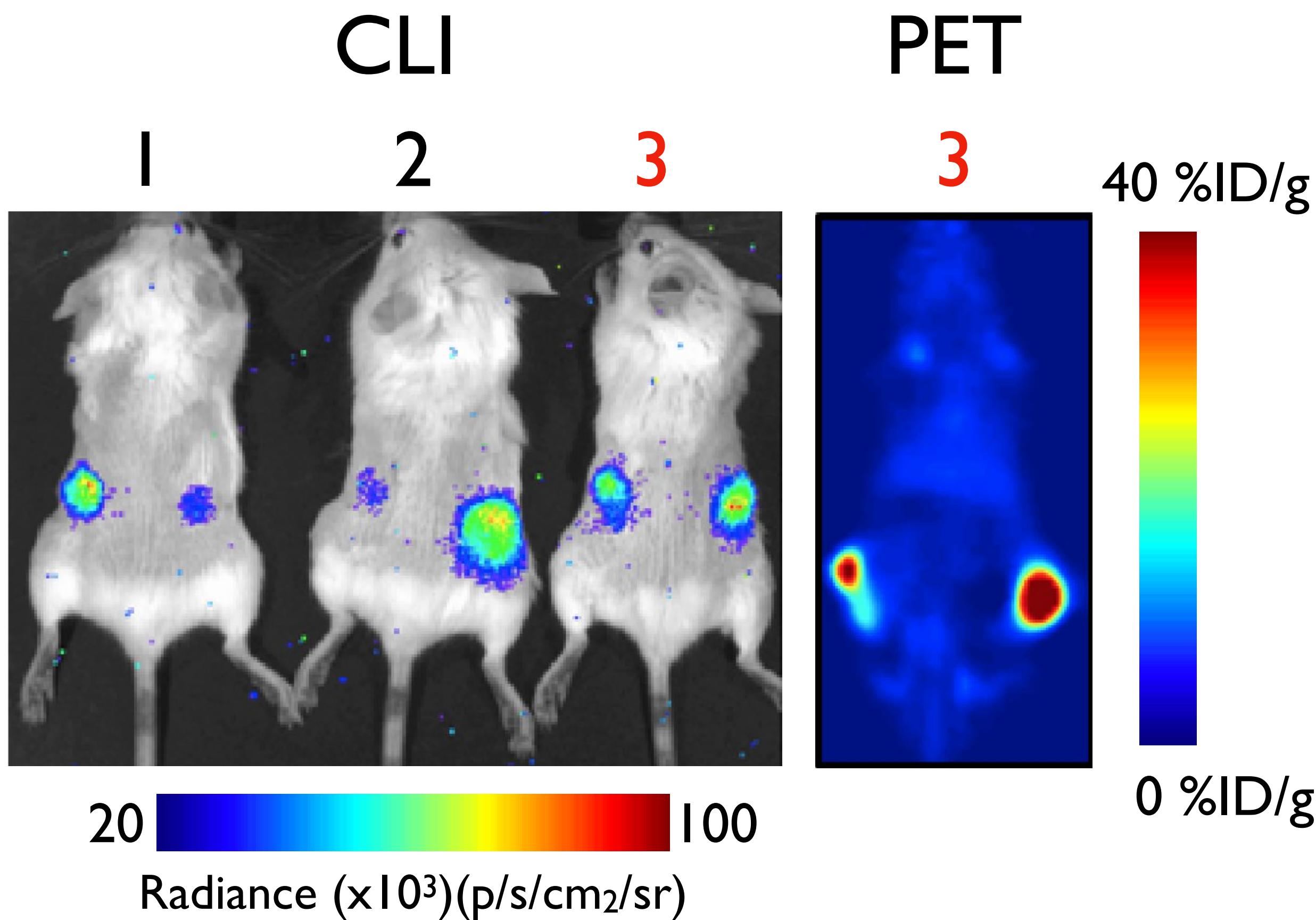
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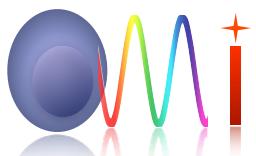
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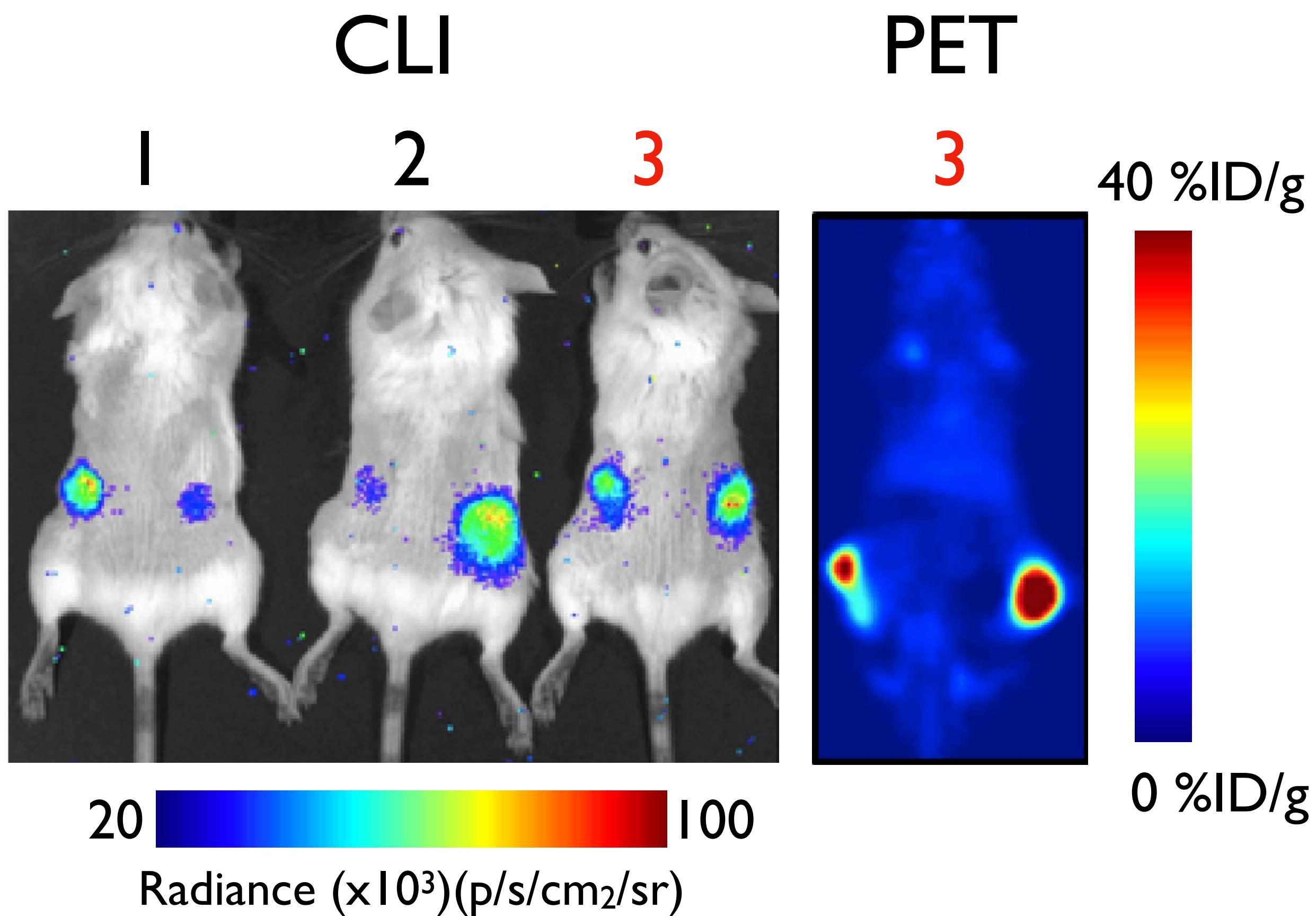
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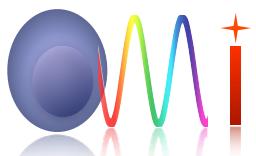
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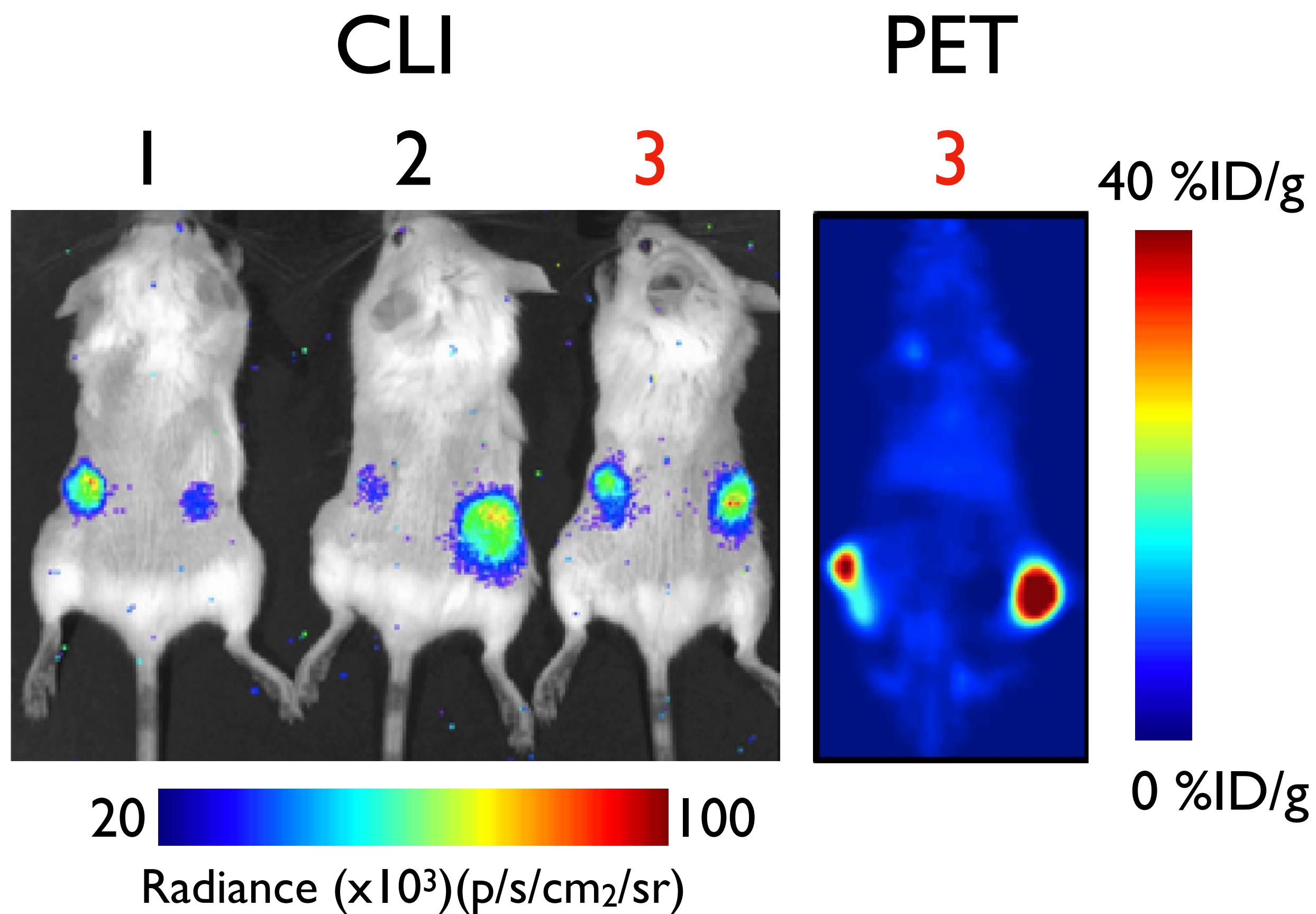
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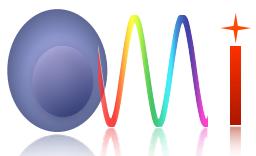
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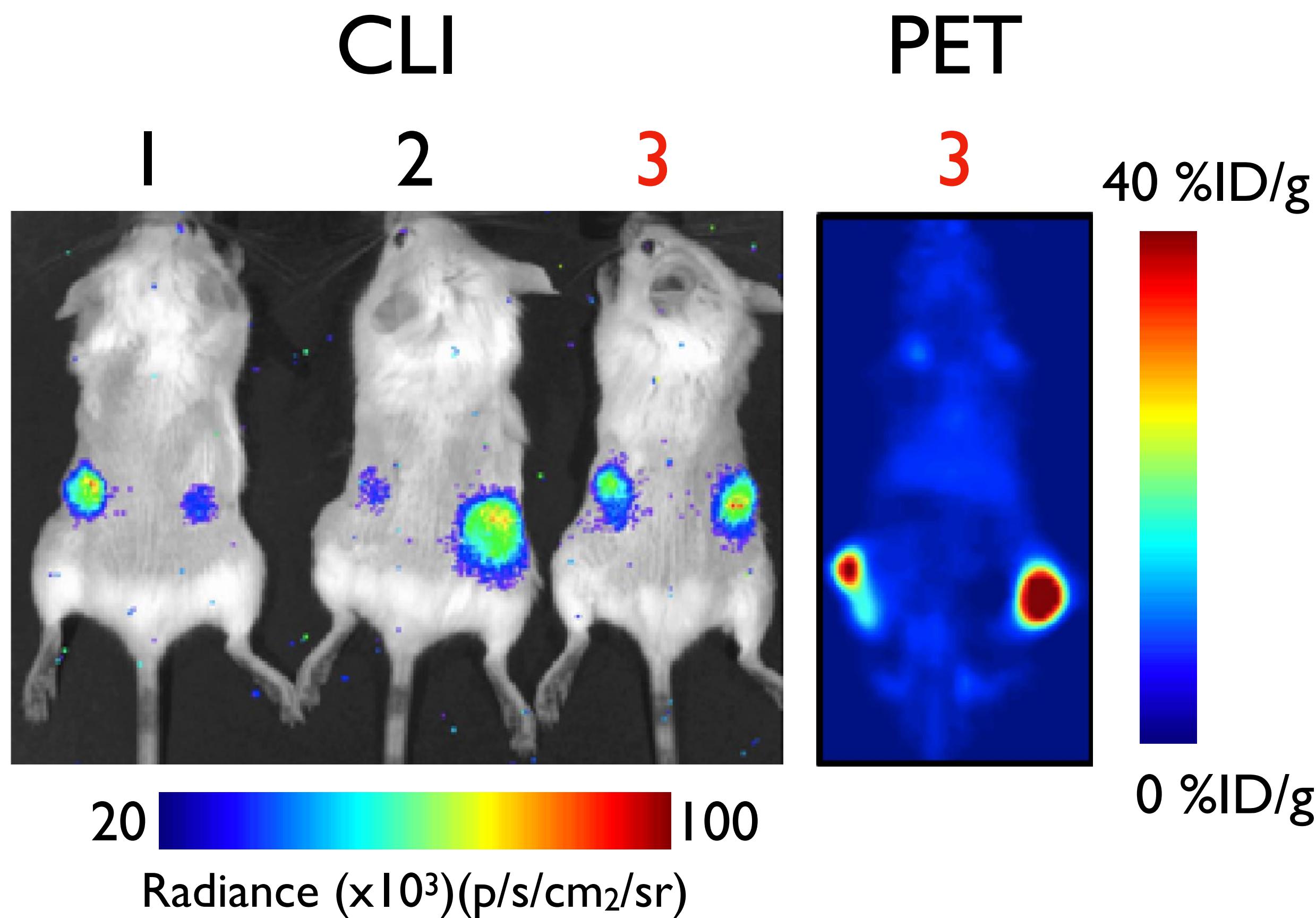
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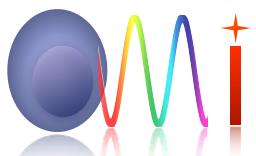
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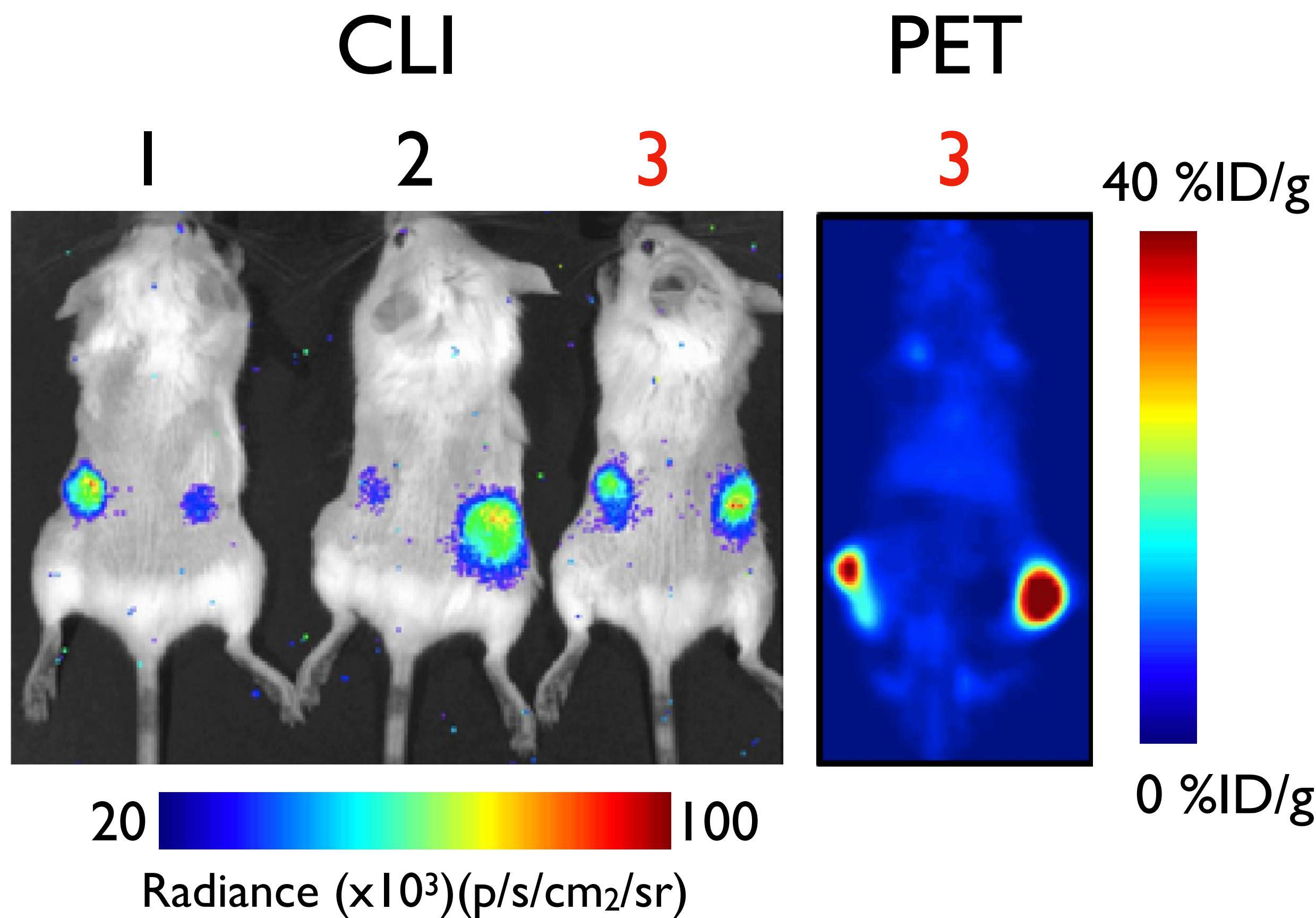
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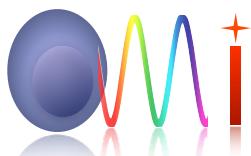
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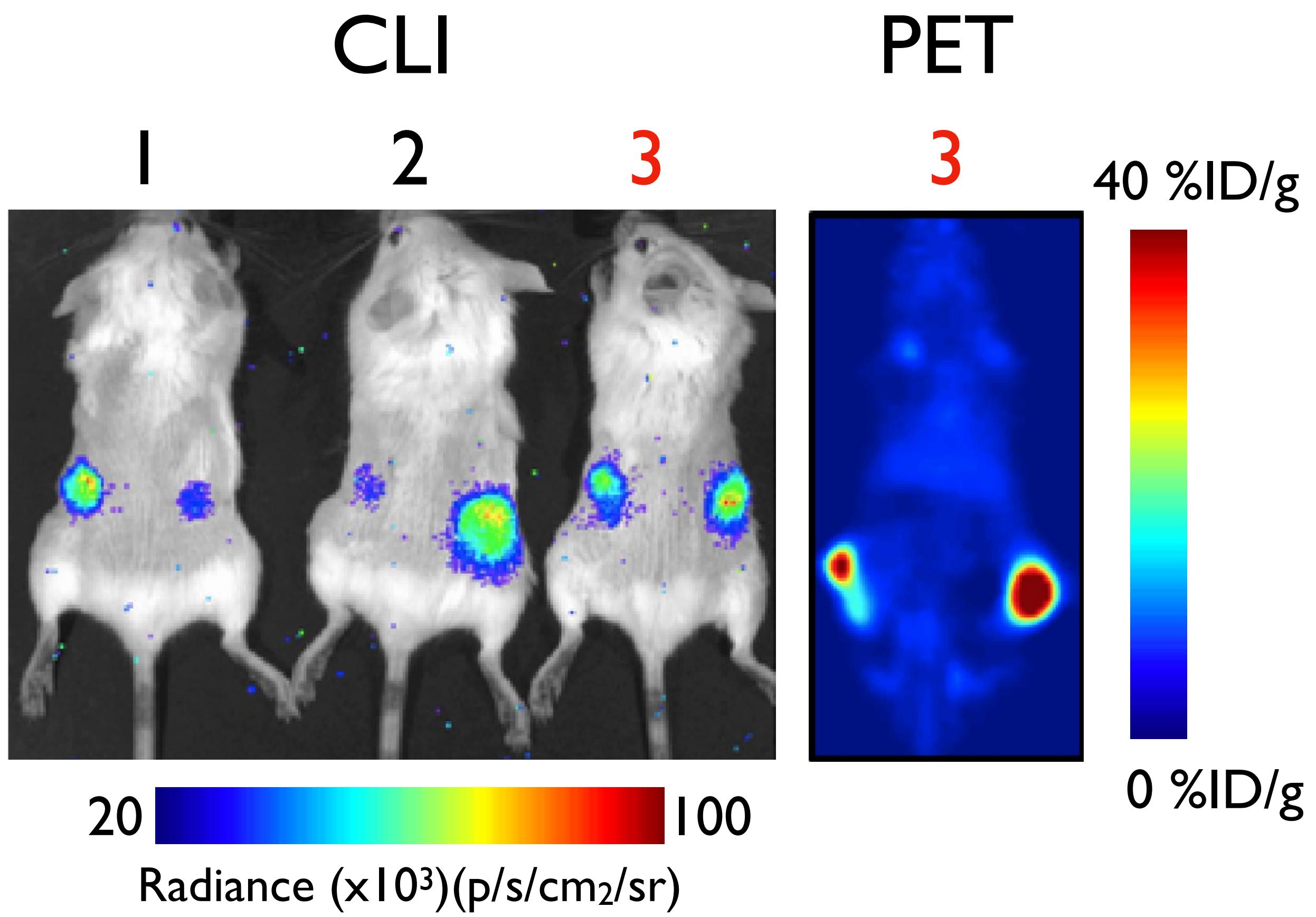
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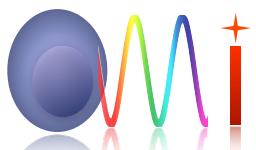
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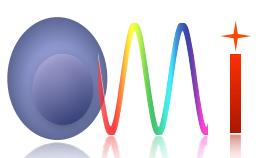
Cerenkov luminescence imaging - huh?

Preclinical concepts

Clinical translation

Theranostics

Outlook - and then some



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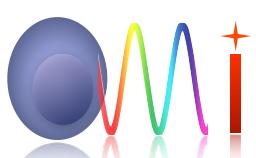
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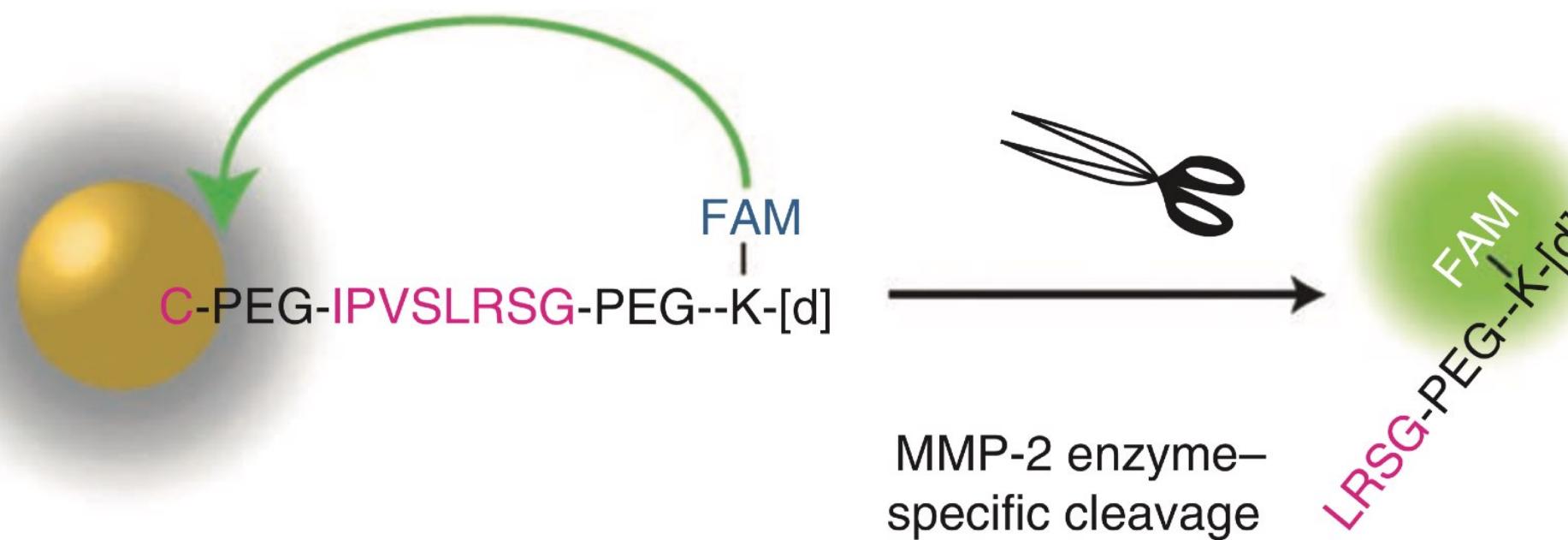
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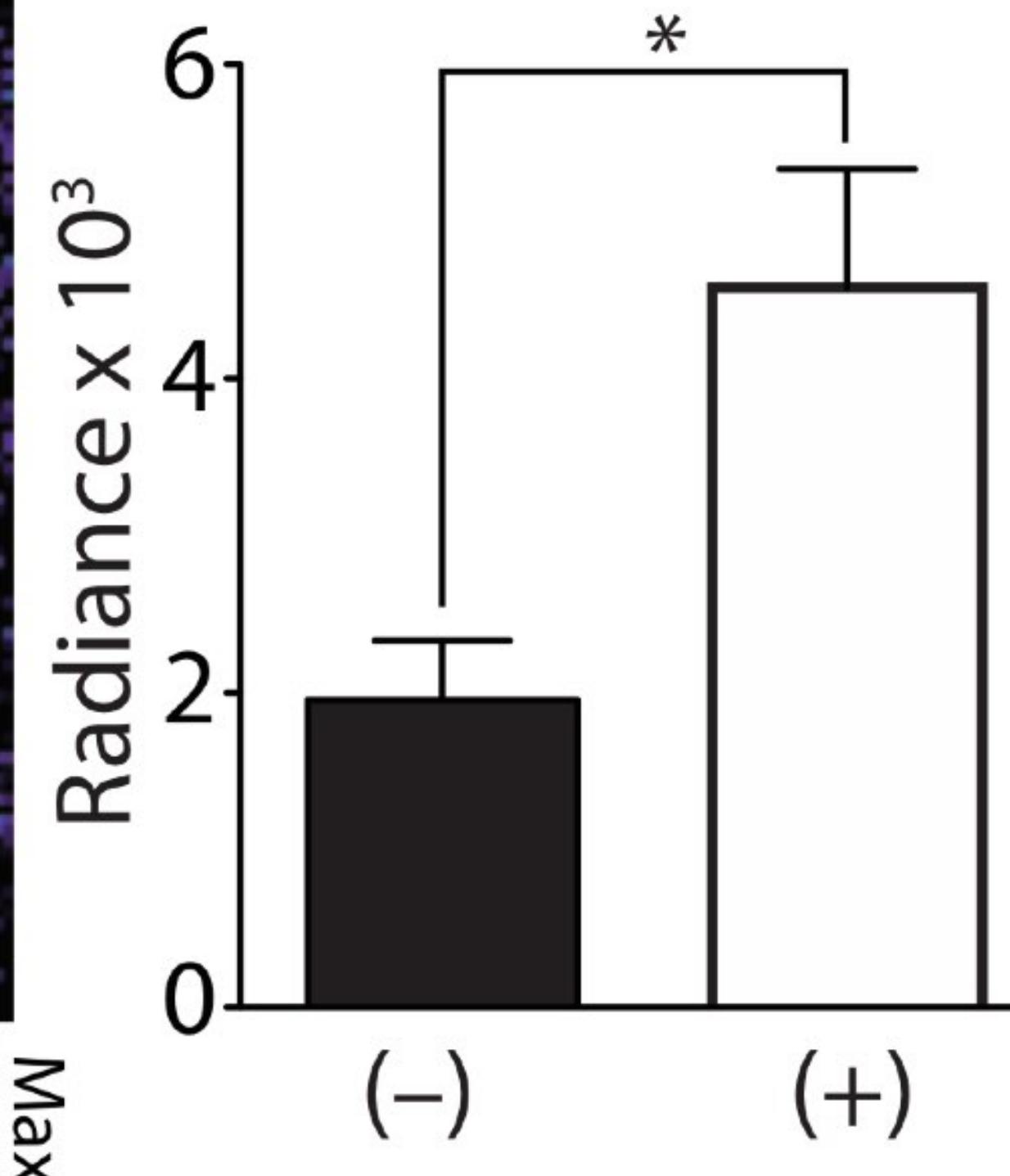
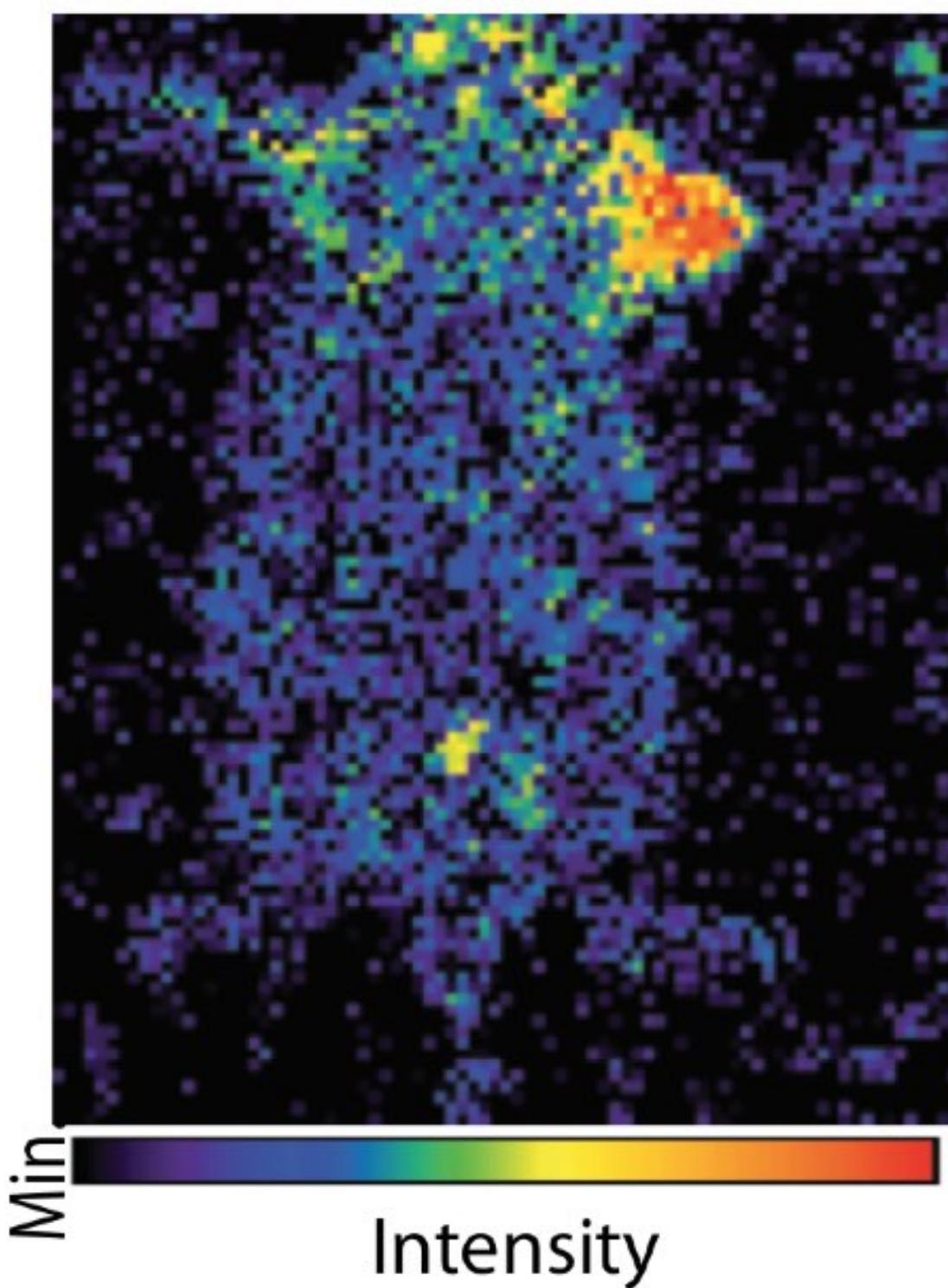
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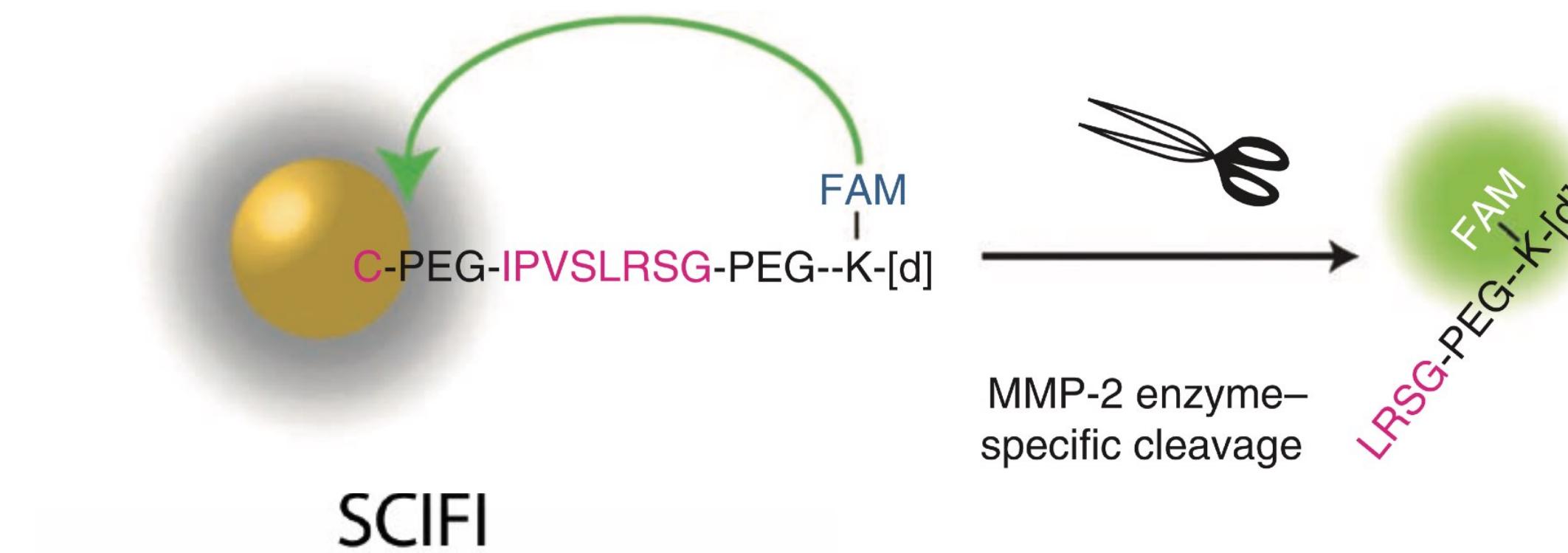
Imaging MMP-2 activity



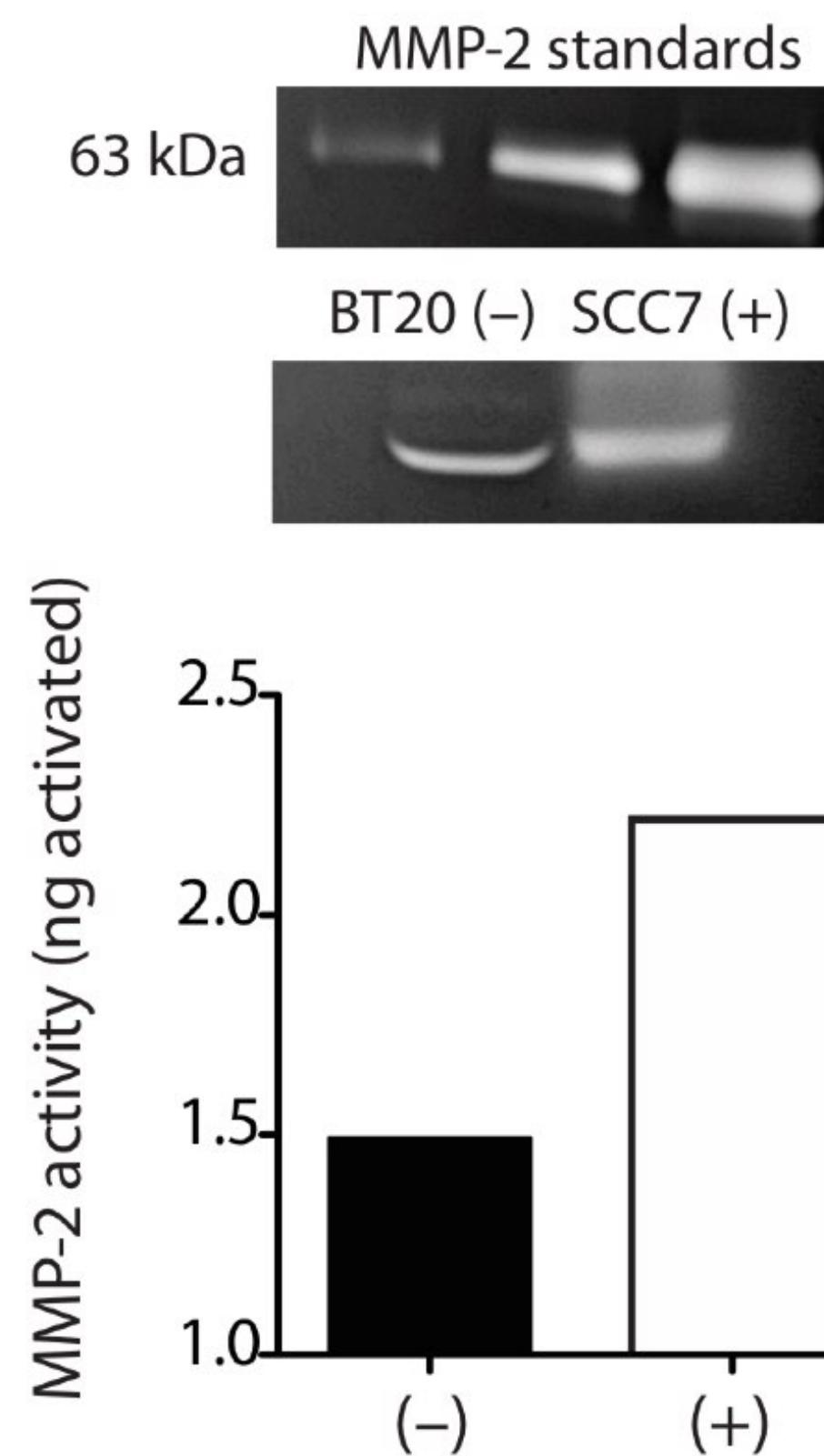
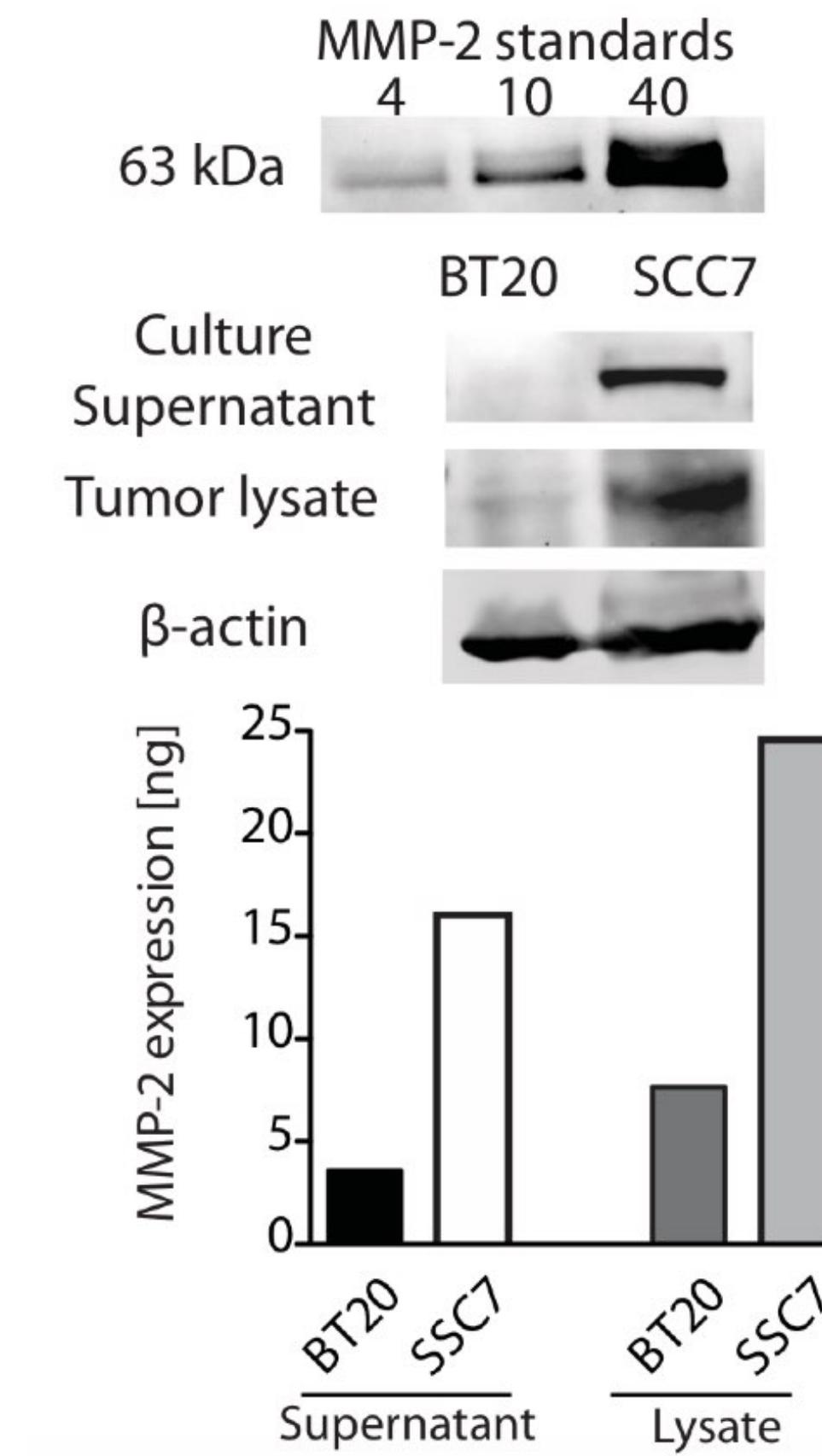
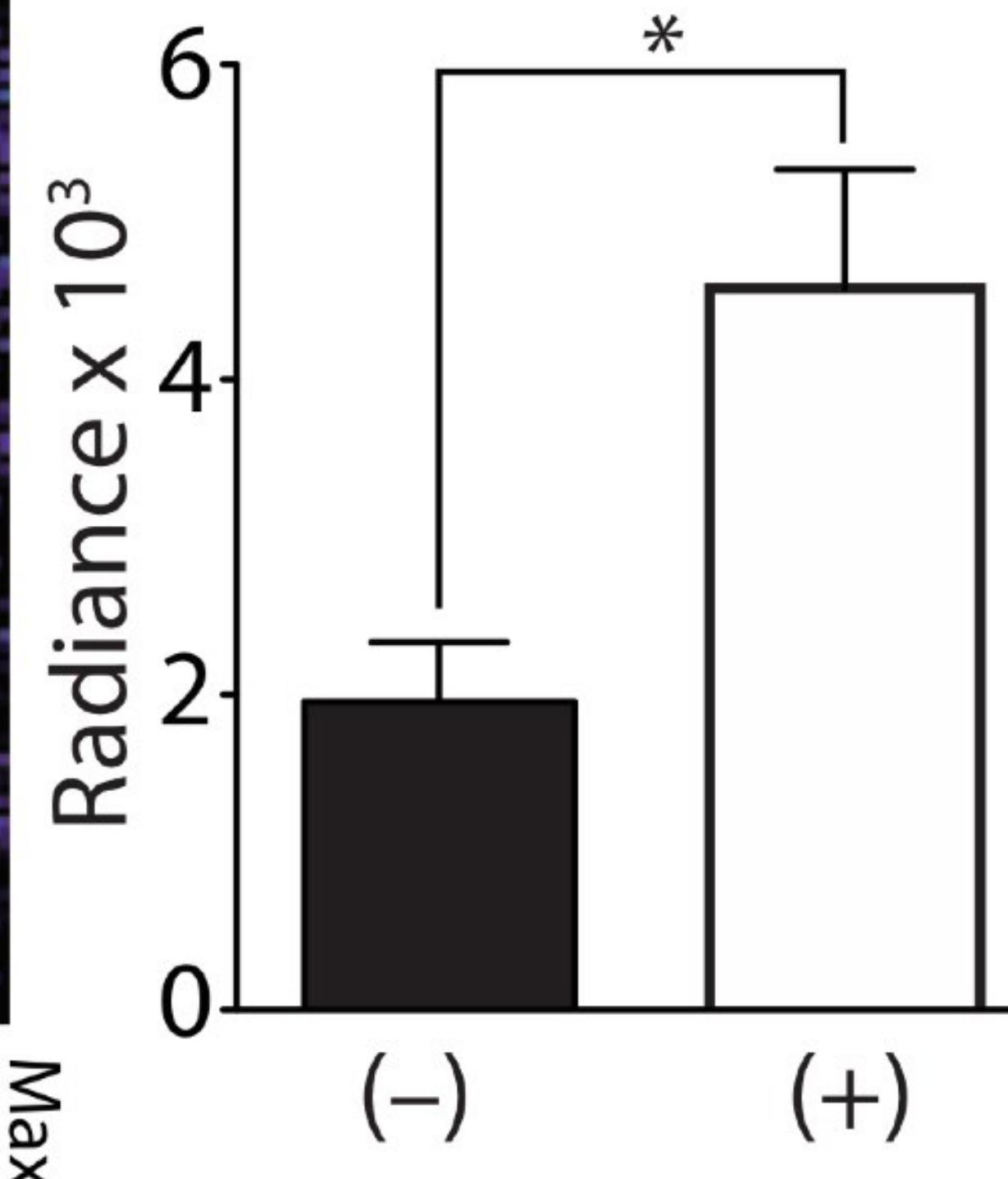
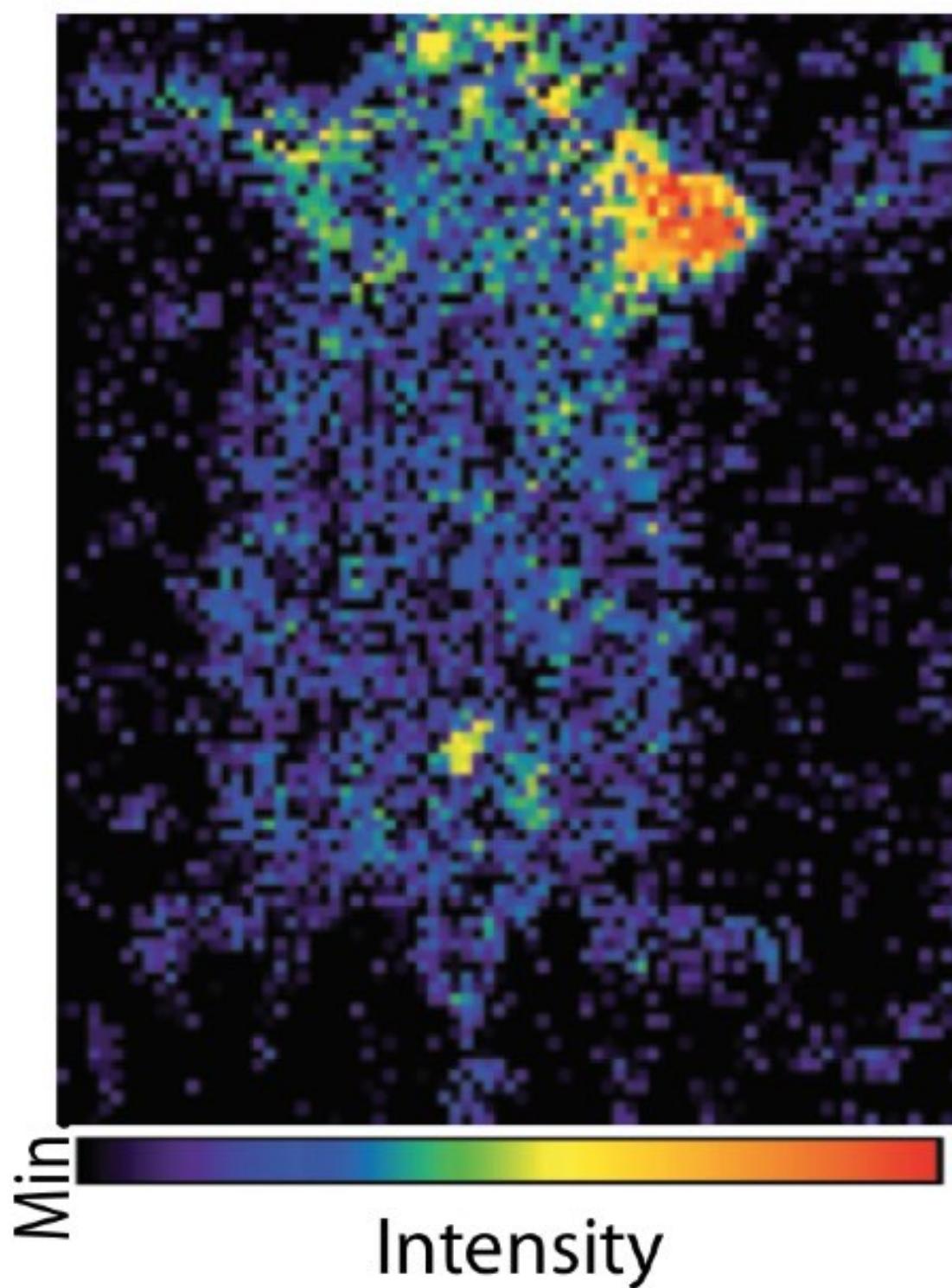
SCIFI



Imaging MMP-2 activity



SCIFI

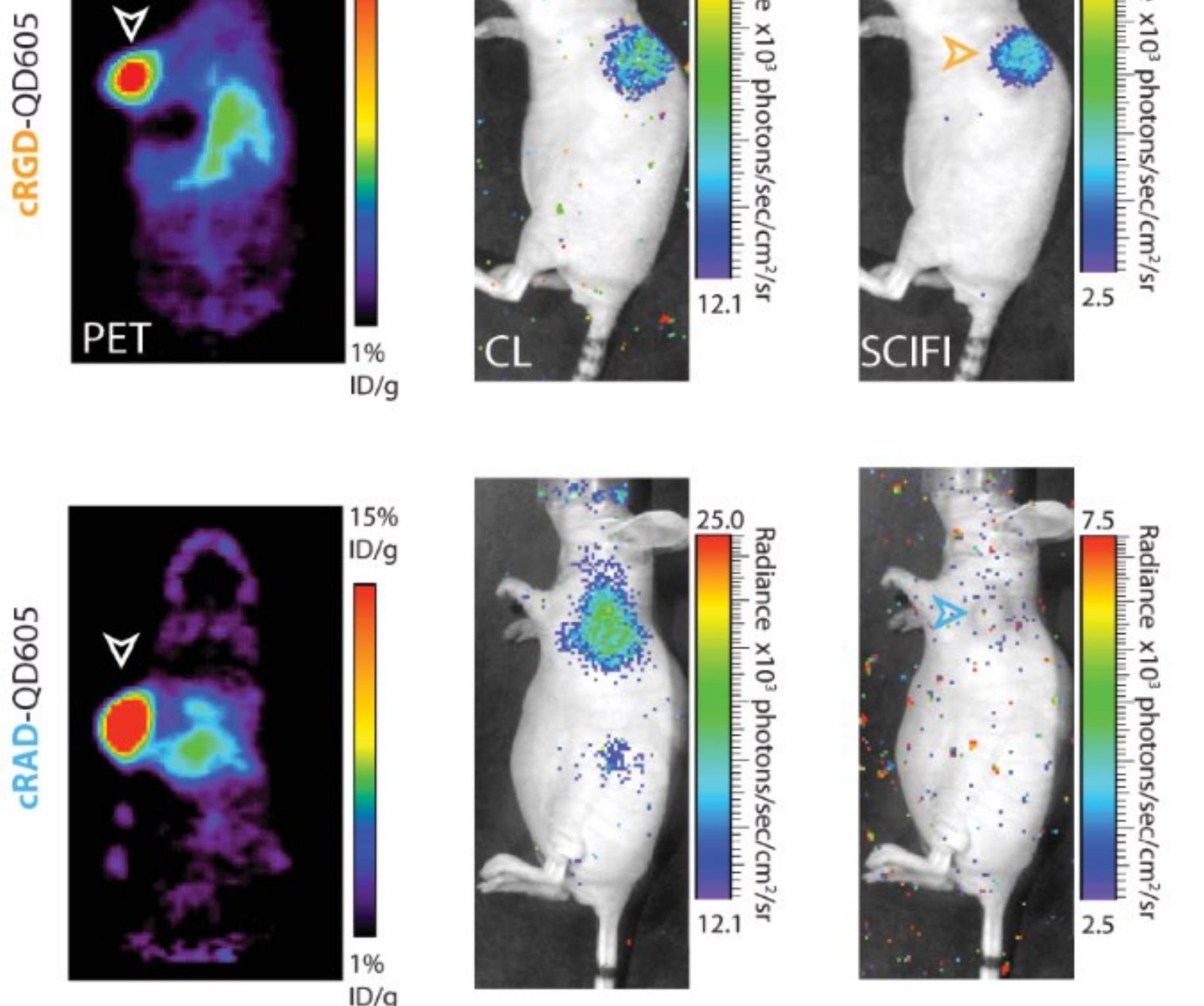
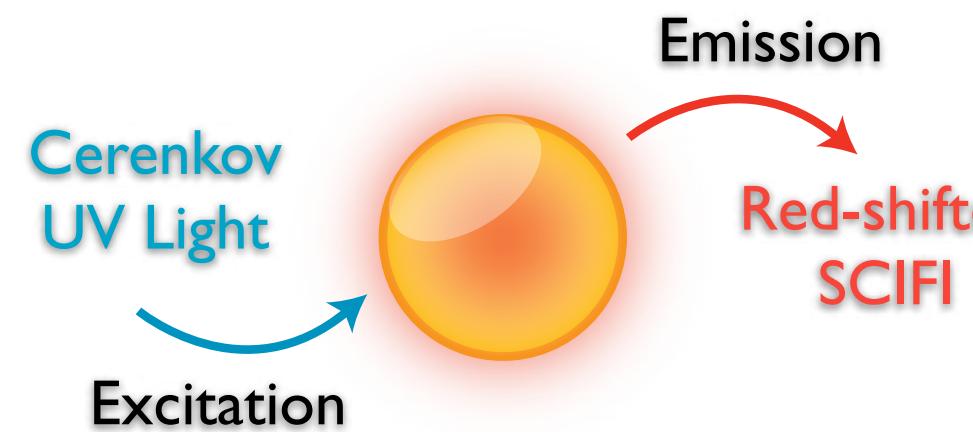


Spectral Shift = SCIFI



D Thorek

Secondary Cerenkov-Induced Fluorescence Imaging

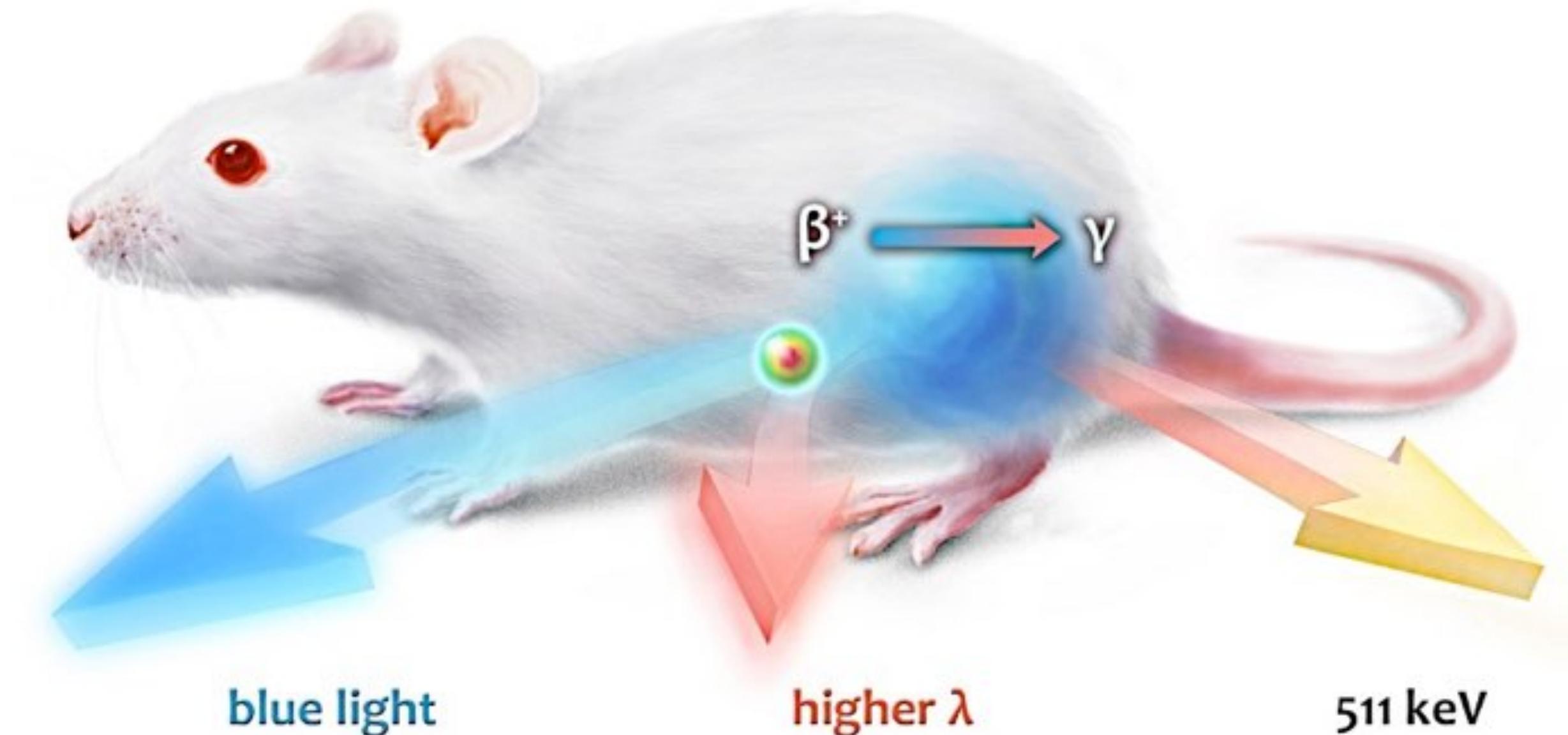
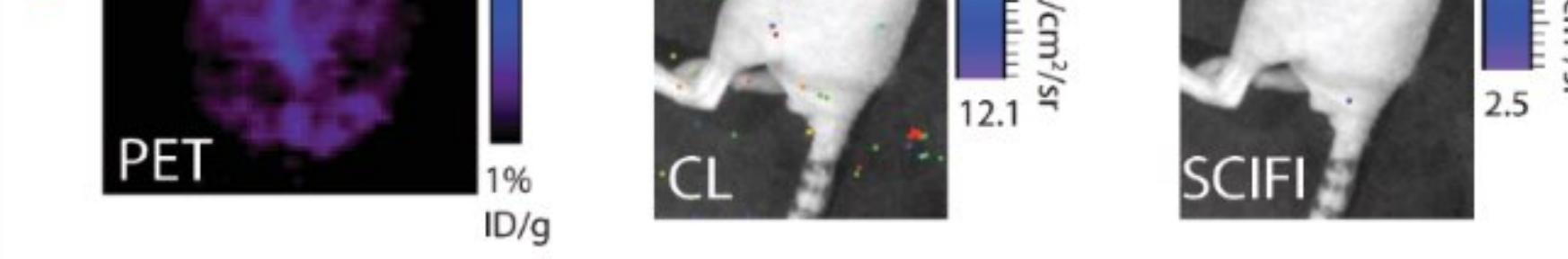
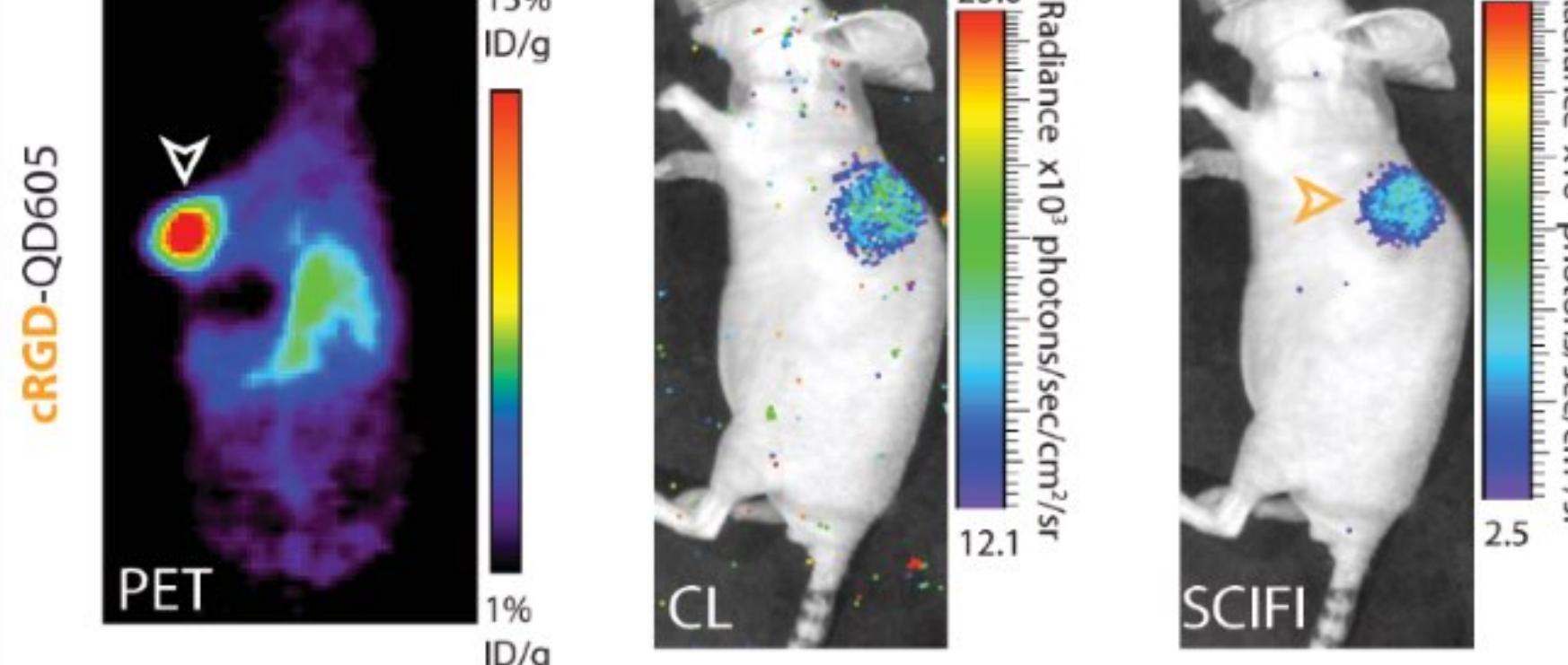
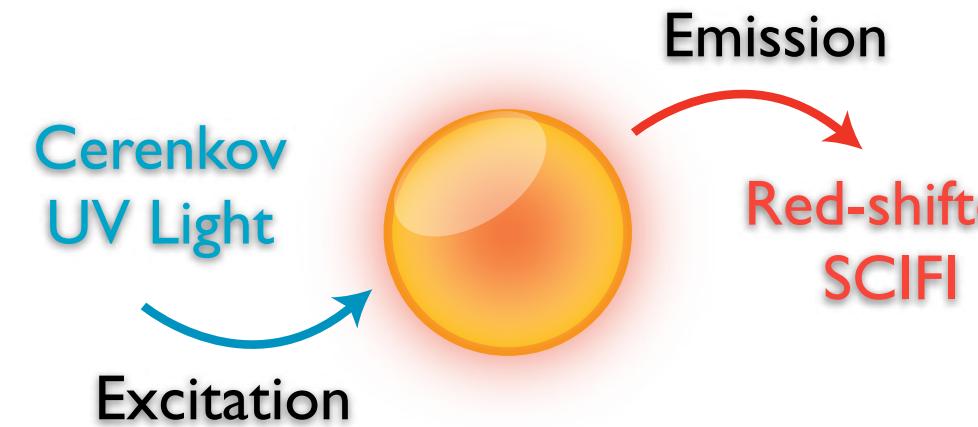


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Cerenkov light
from radionuclide

Emission from dye
excited by Cerenkov

PET image

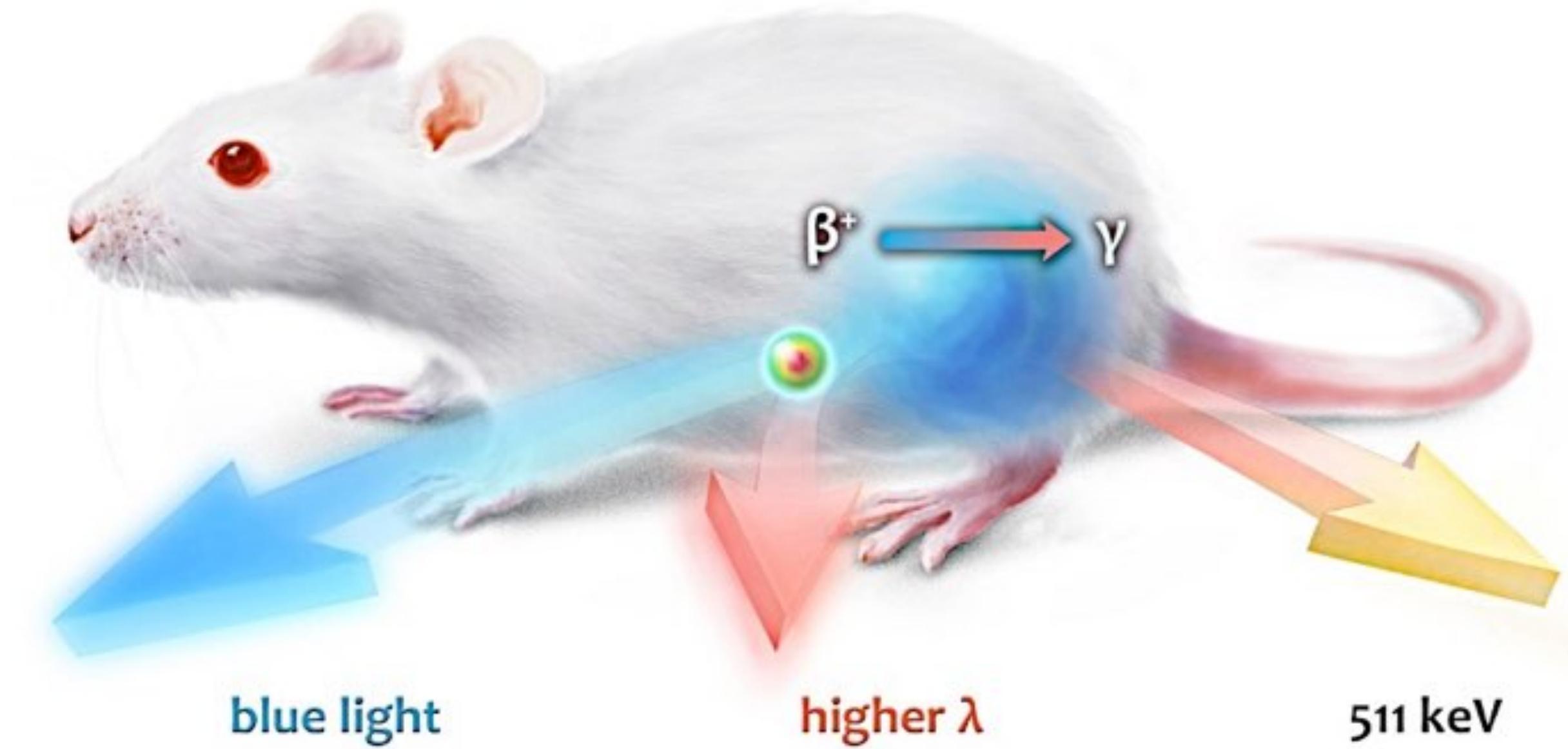
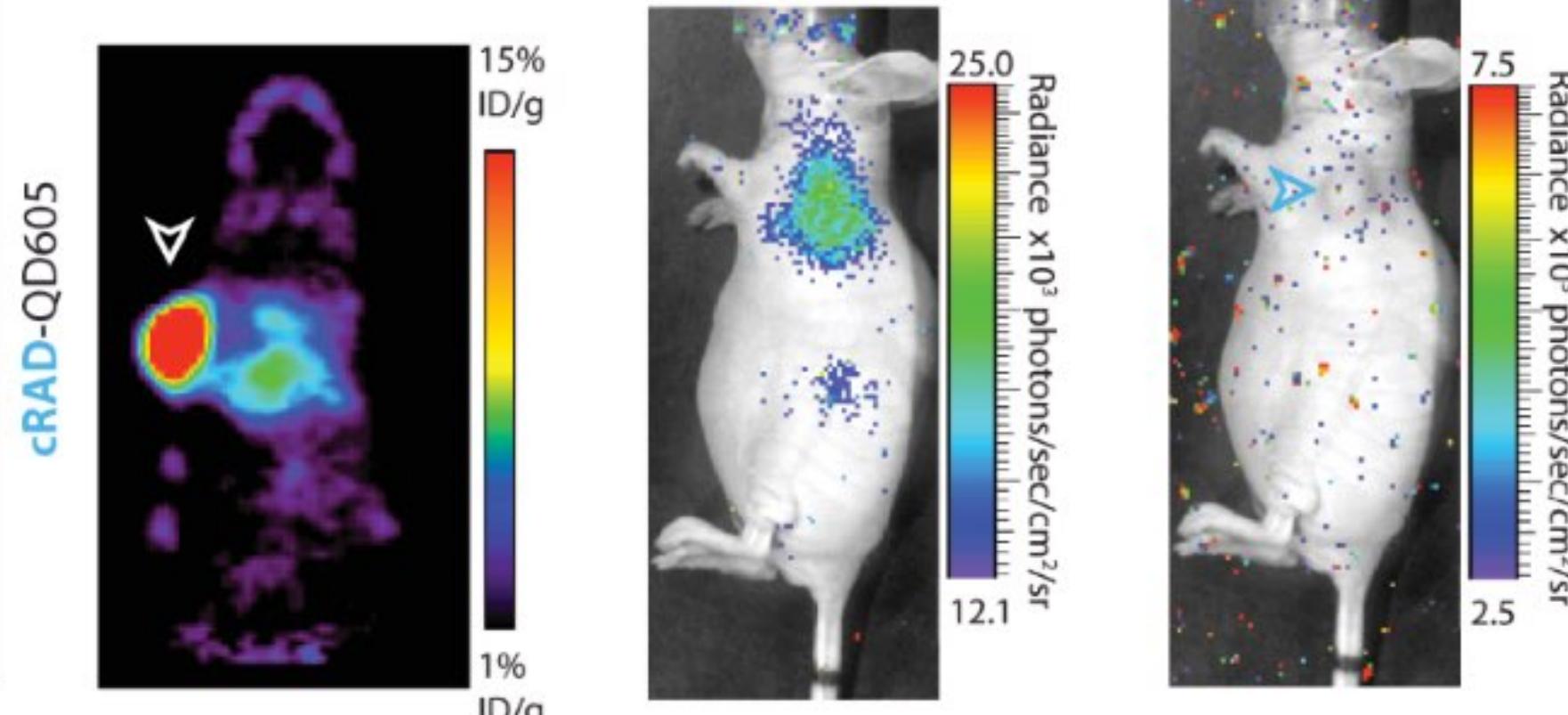
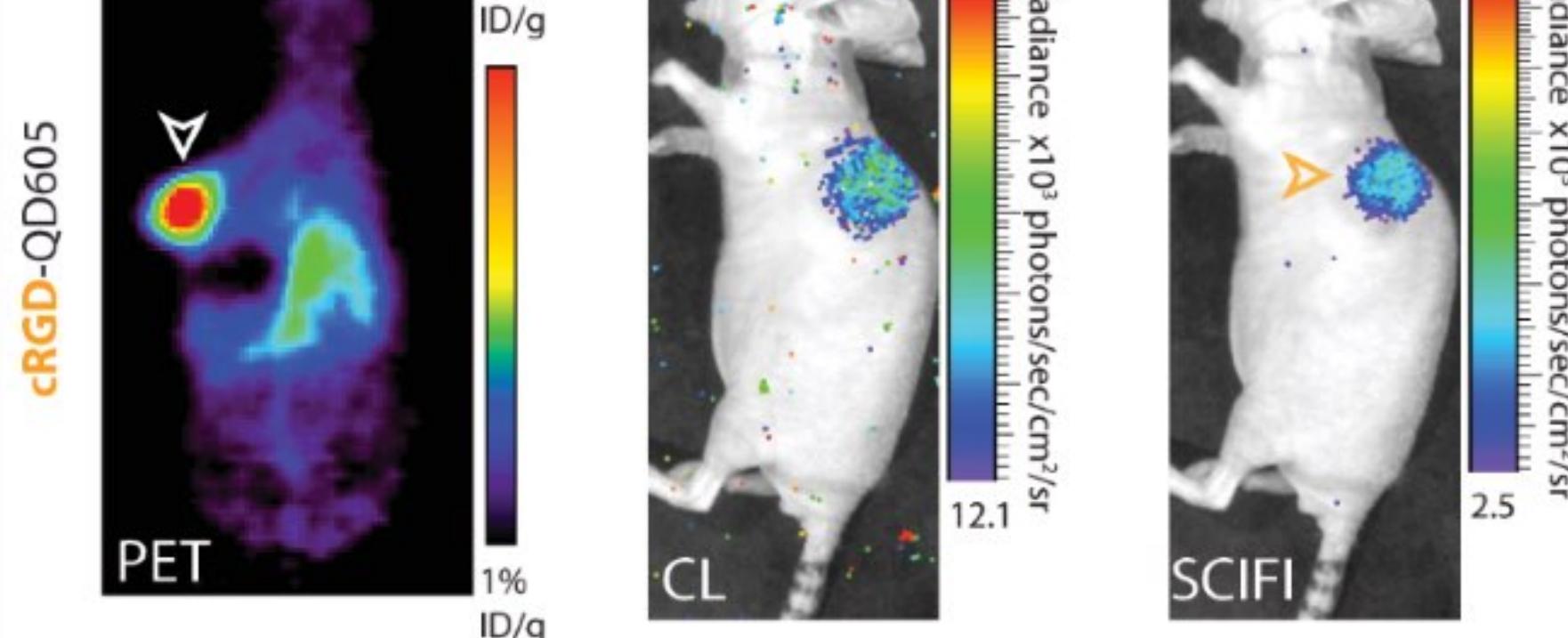
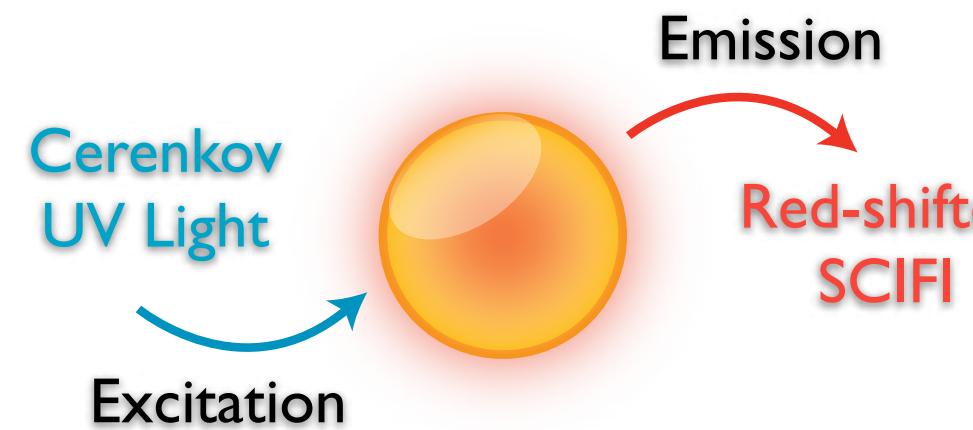


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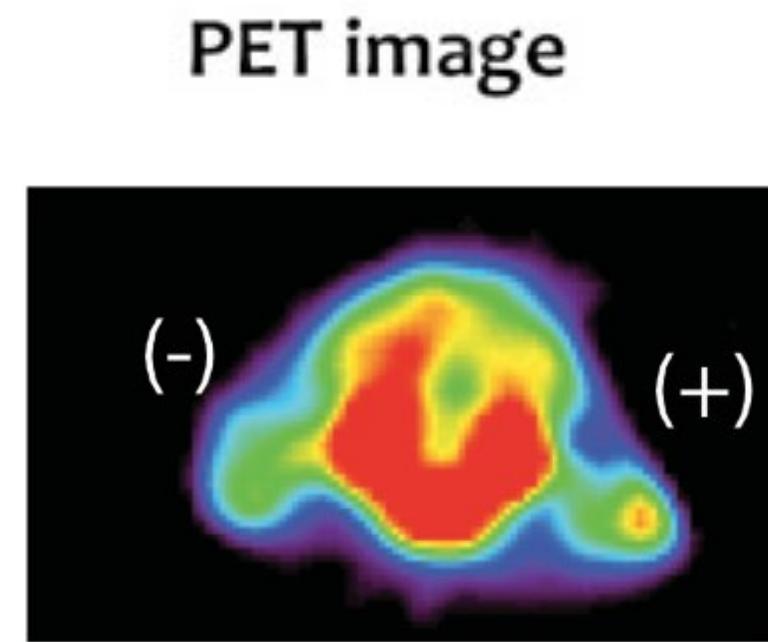
D Thorek

Secondary Cerenkov-Induced Fluorescence Imaging



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Emission from dye
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PET: Metabolism

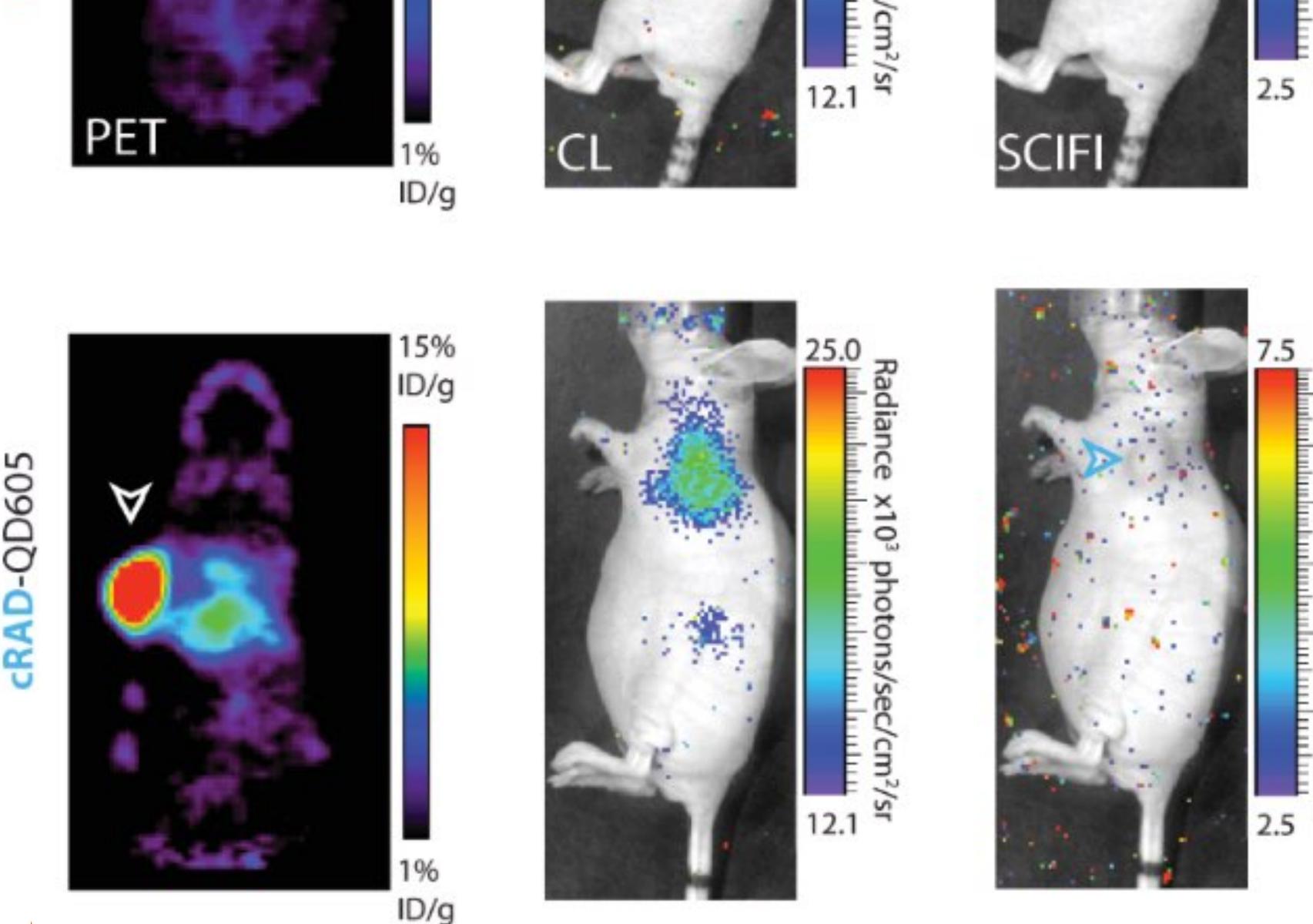
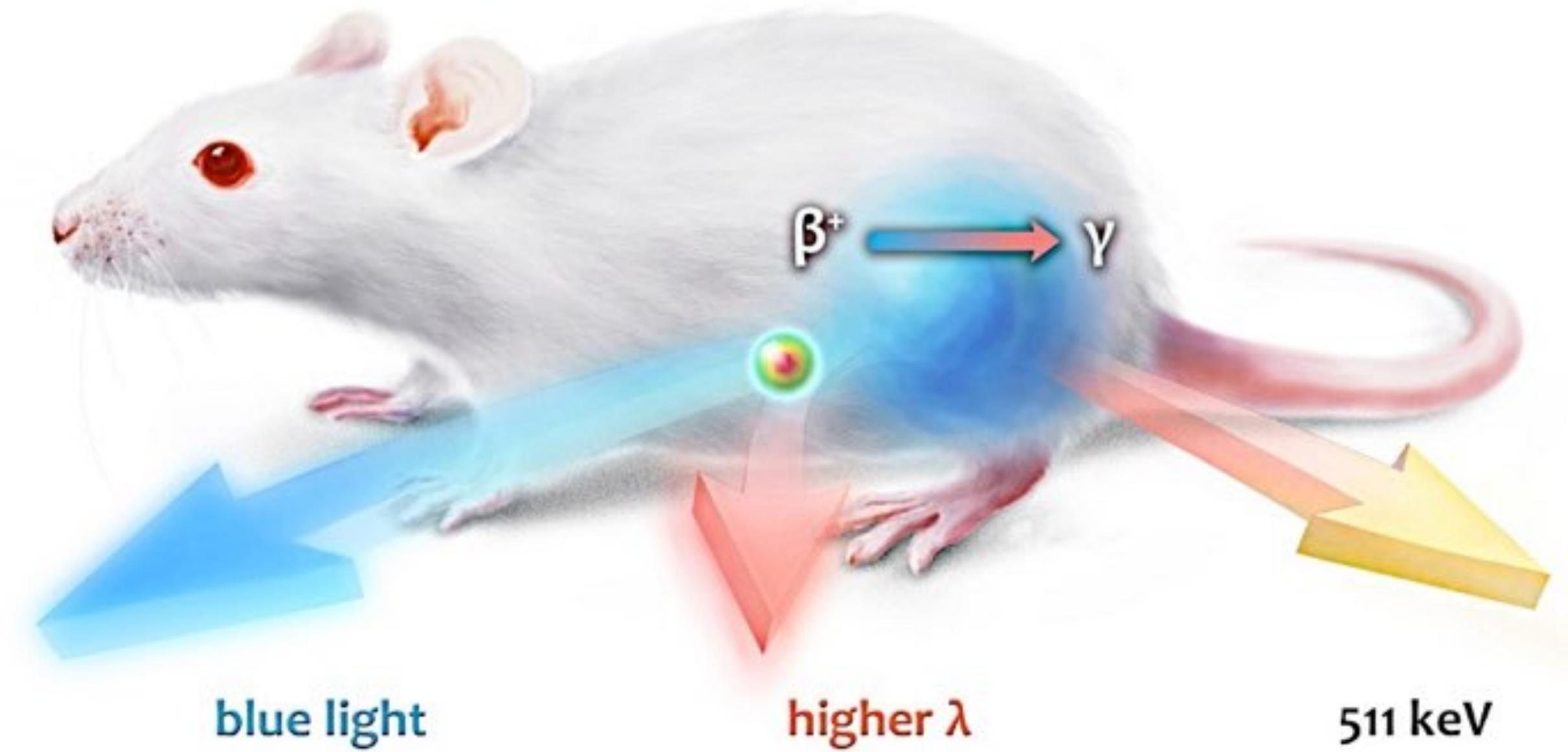
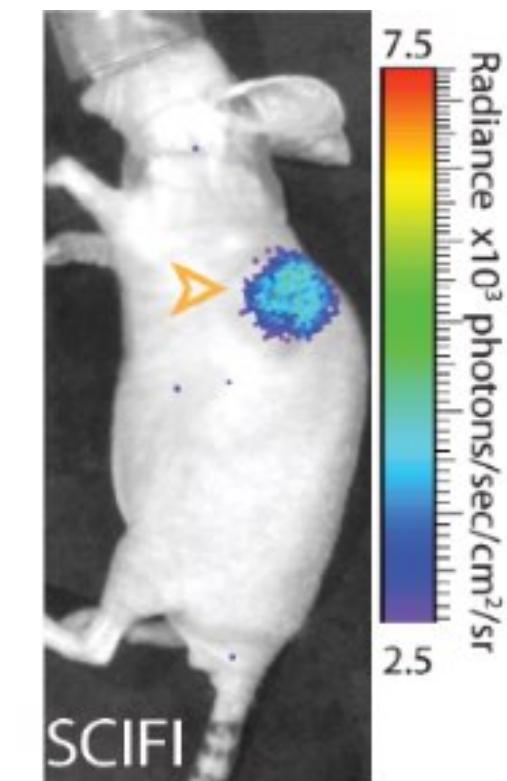
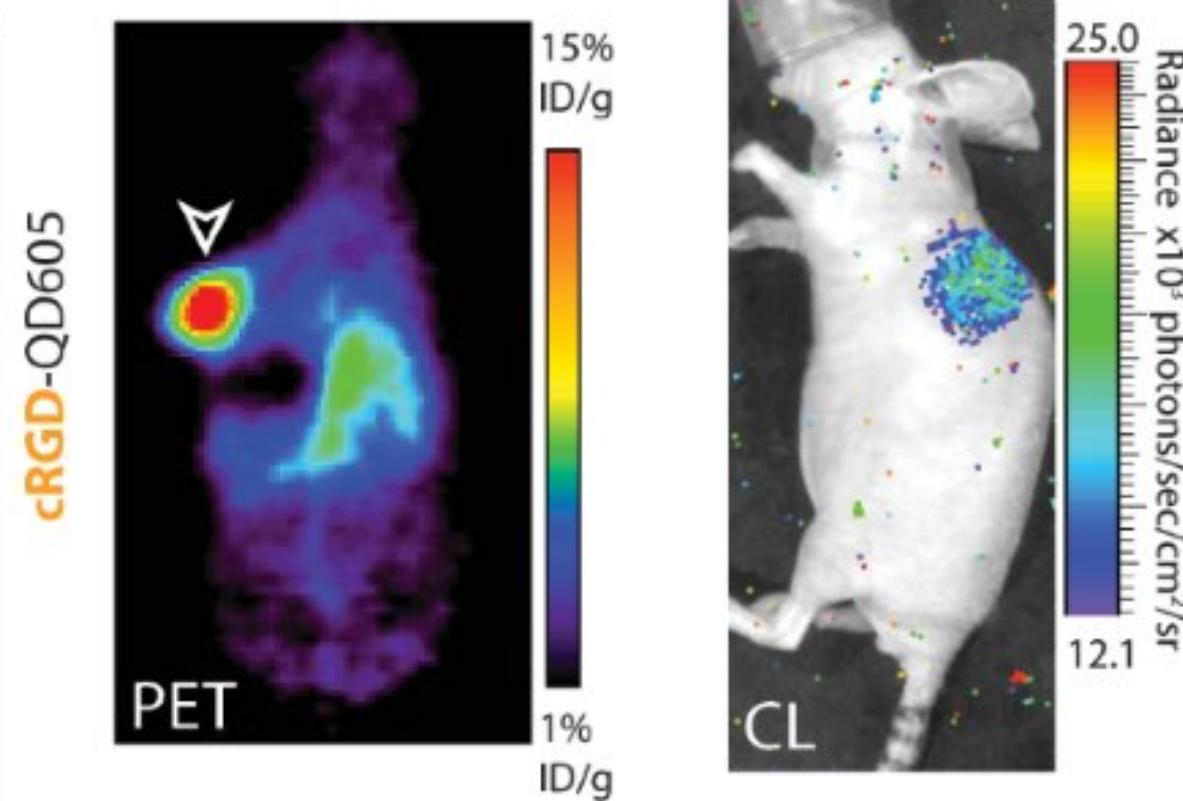
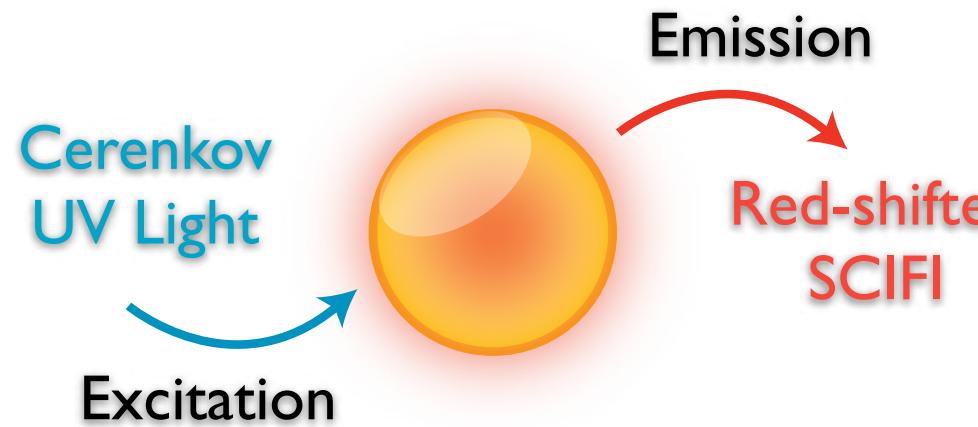


Spectral Shift = SCIFI



D Thorek

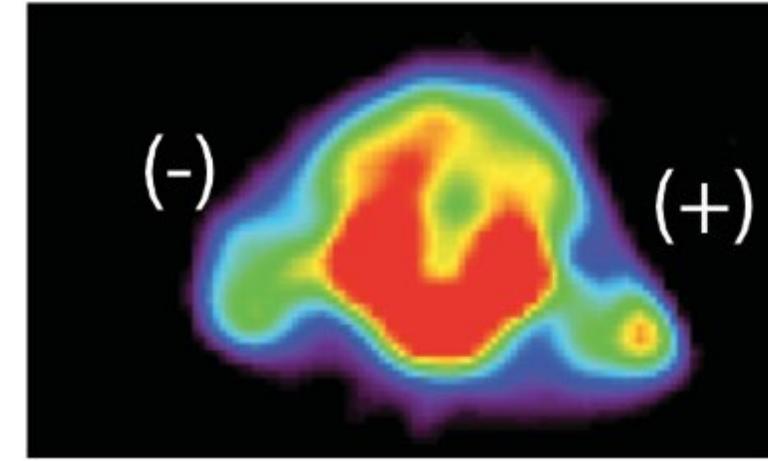
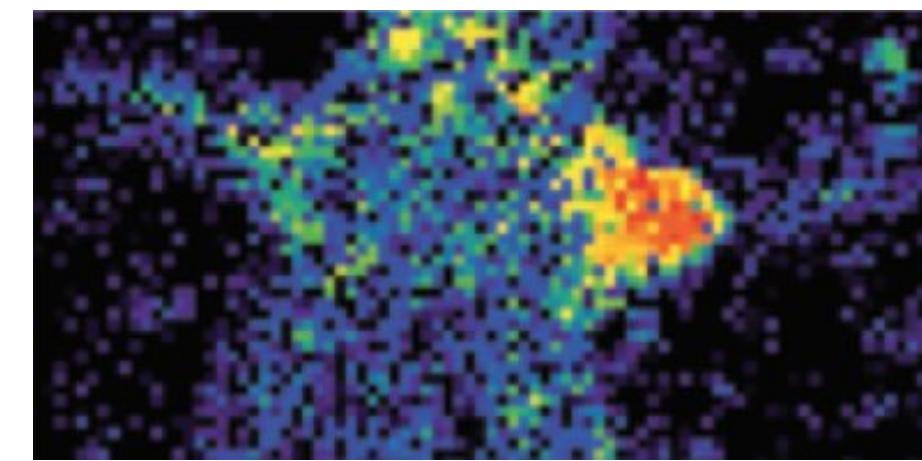
Secondary Cerenkov-Induced Fluorescence Imaging



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PET image



SCIFI: MMP-2 activity PET: Metabolism

Shaffer, Pratt and Grimm (2016) Nature Nanotech 12(2):106



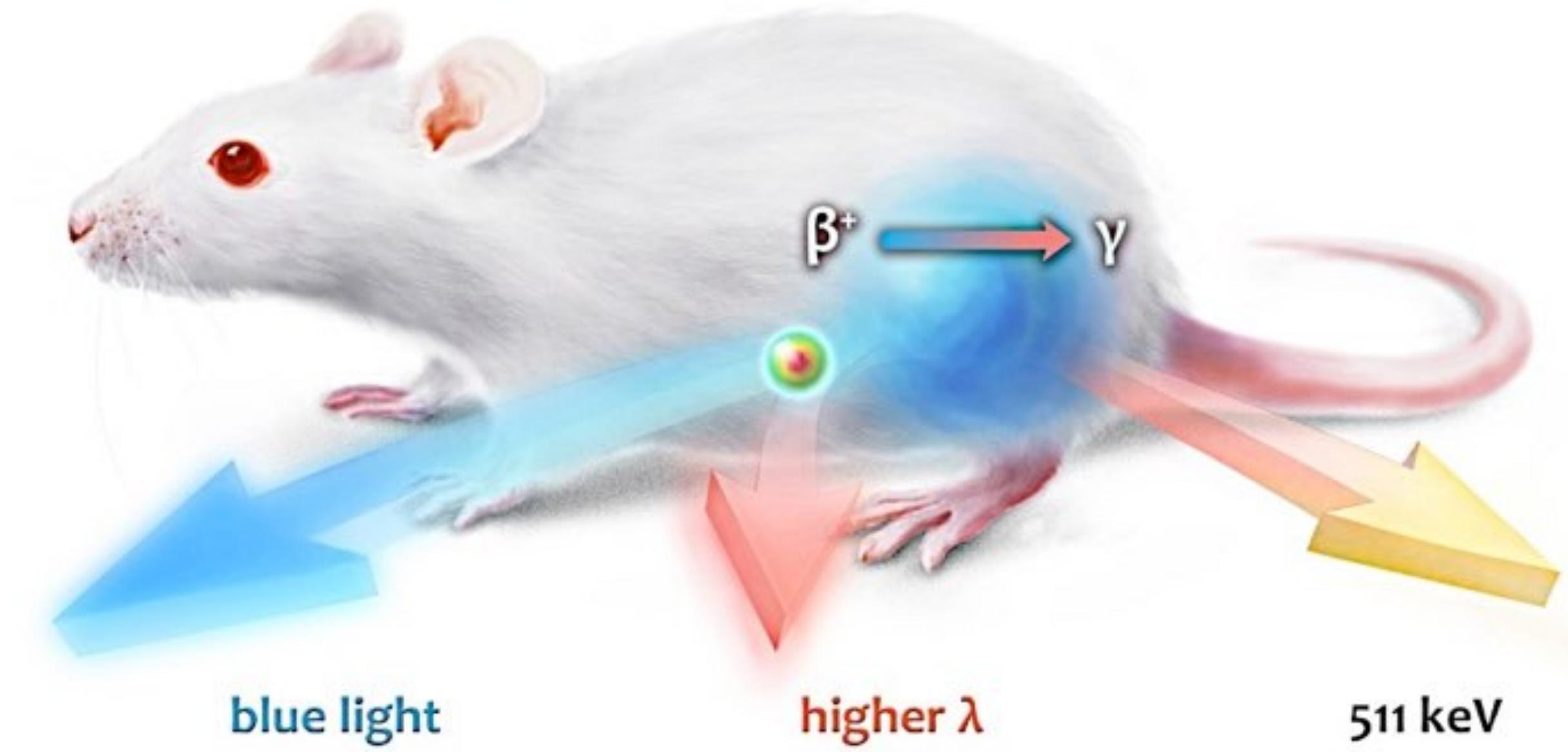
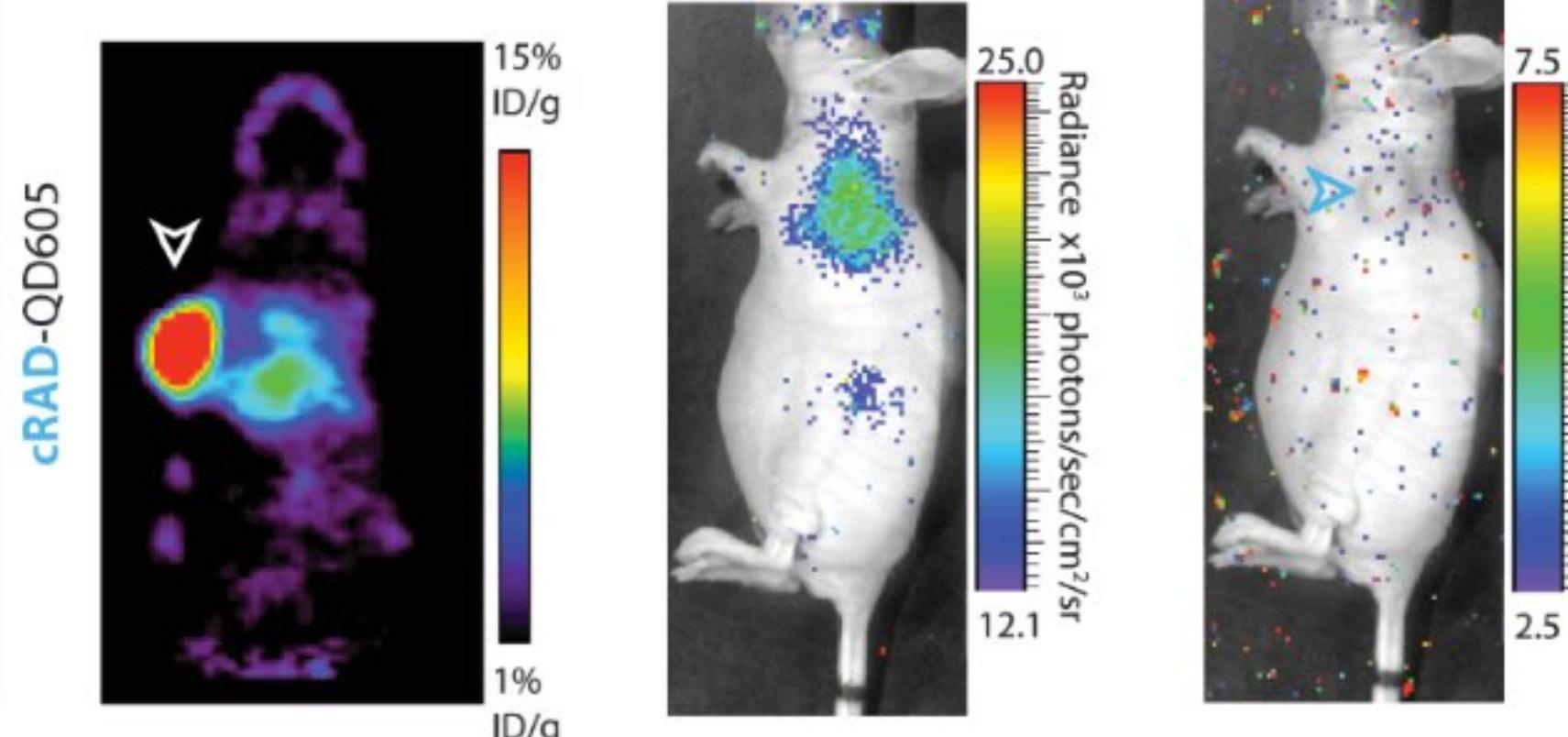
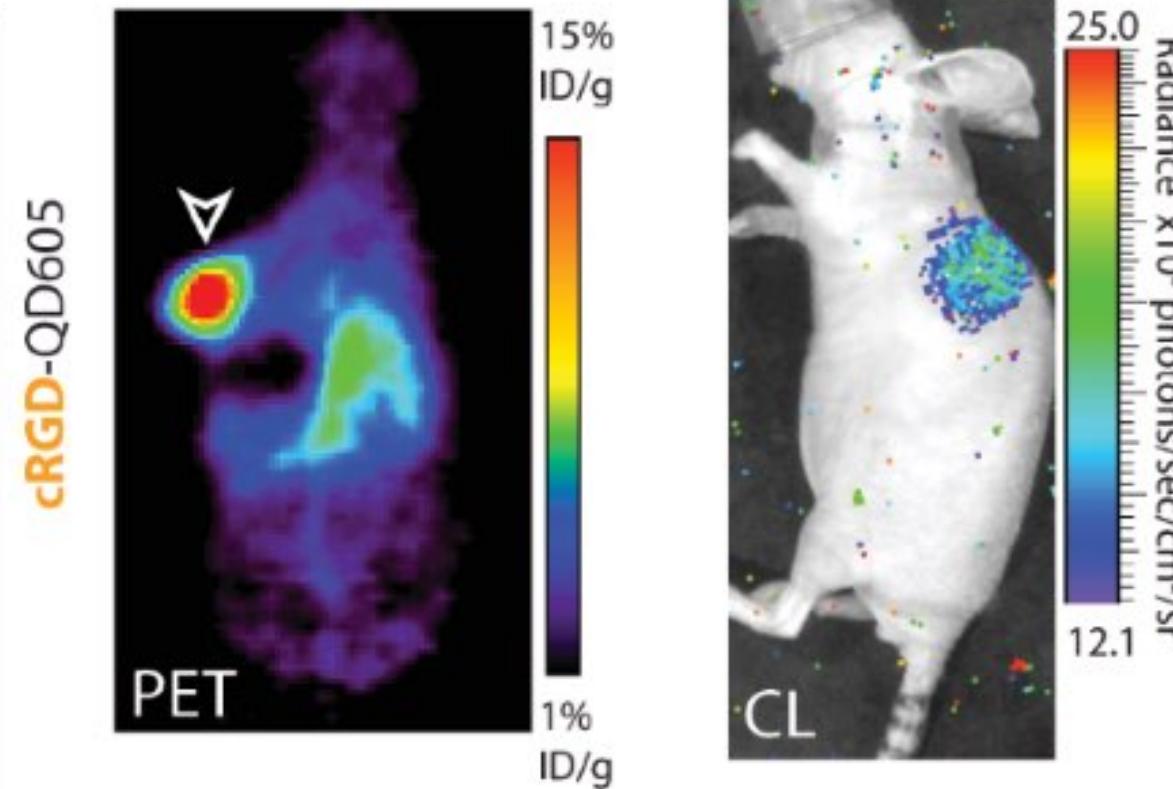
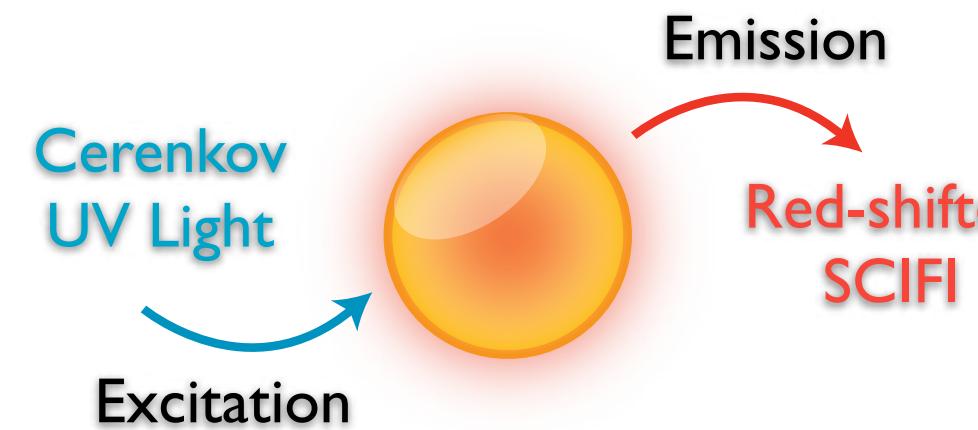
1884

Spectral Shift = SCIFI

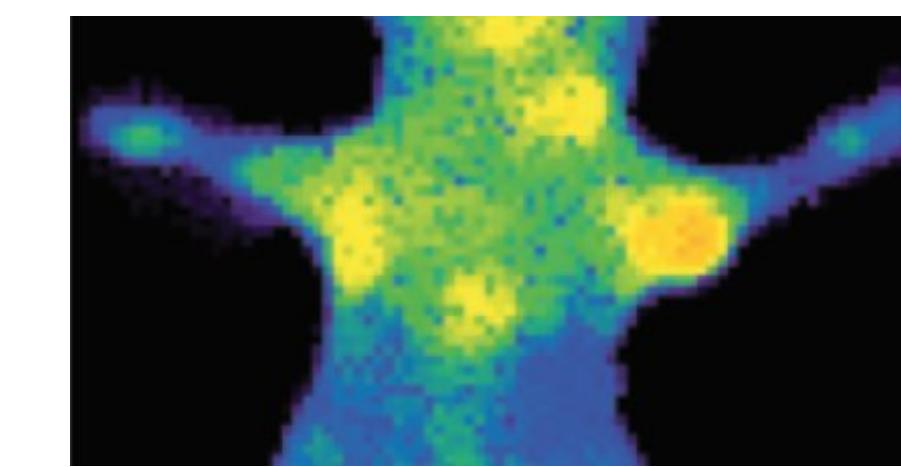


D Thorek

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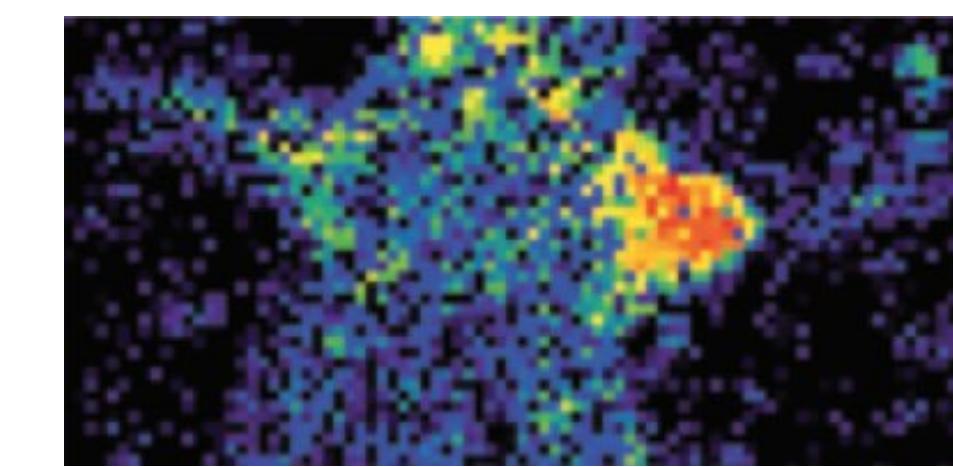


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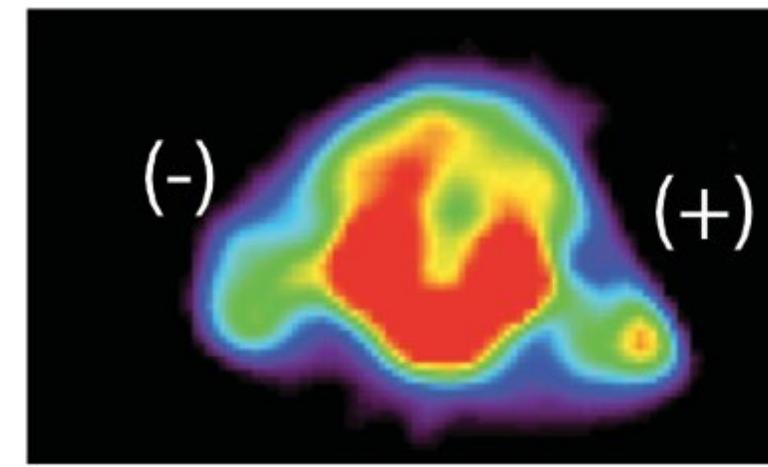
CLI: Metabolism

Emission from dye
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SCIFI: MMP-2 activity

PET image

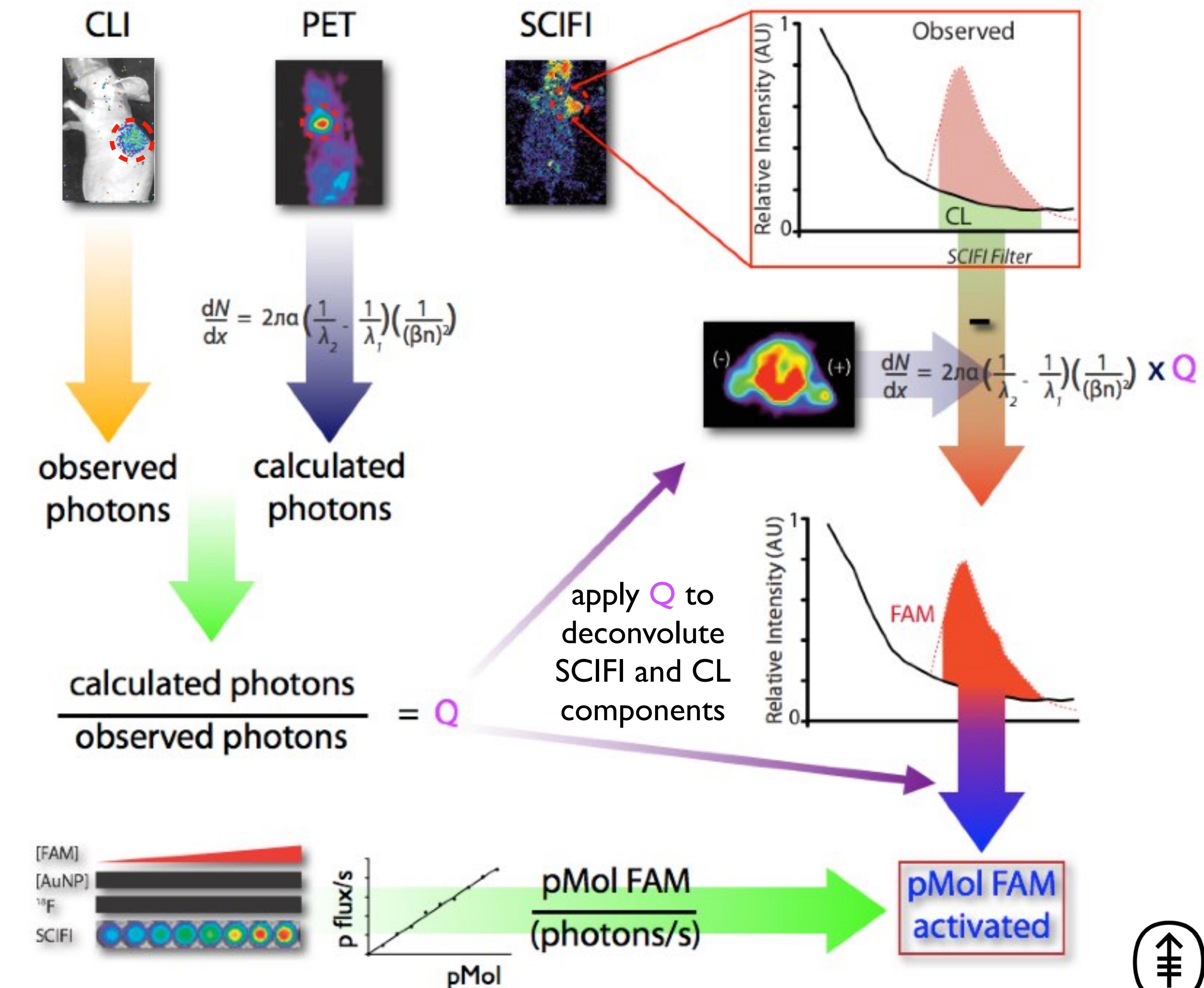


PET: Metabolism



Quantitative imaging

- CLI/SCIFI is truly multimodal
- Same agent for CL and PET
- F&T equation to quantify
- Only absolute quantitative optical method
- PET provides internal standard

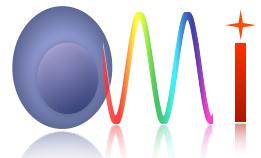


Radioactivated agents

Fluorescent footprint of FDG



S Das



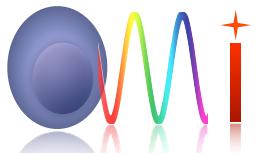
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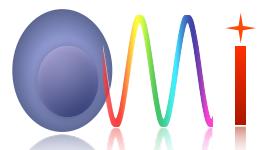
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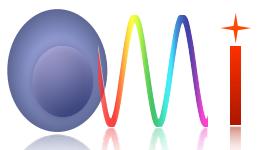
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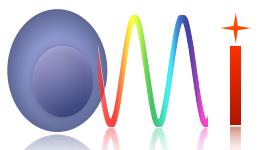
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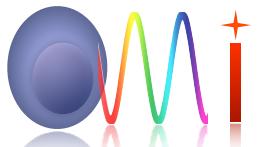
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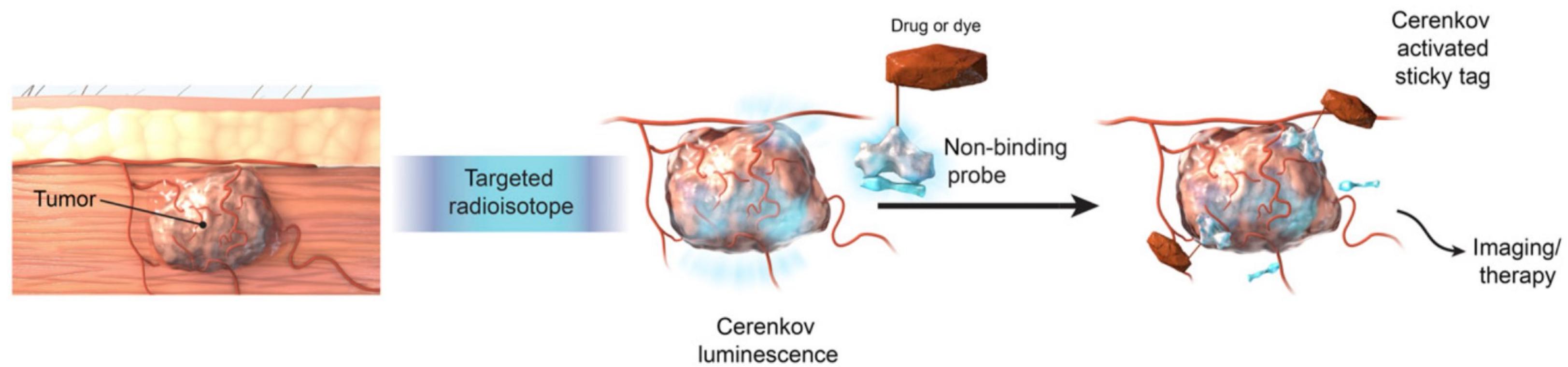
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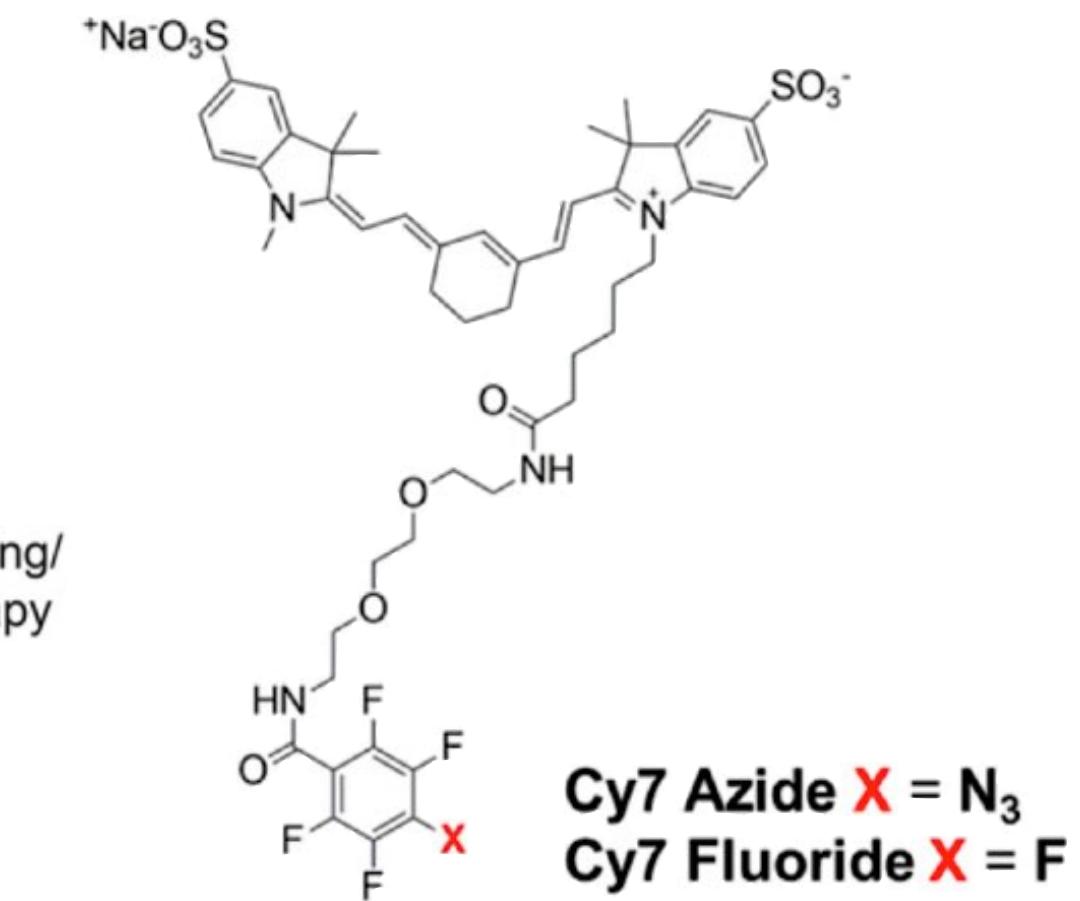
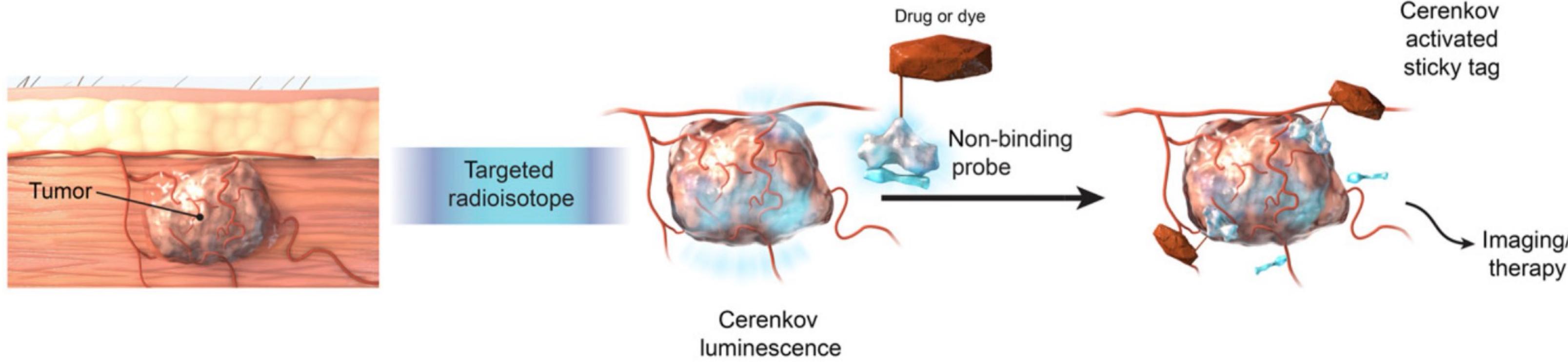
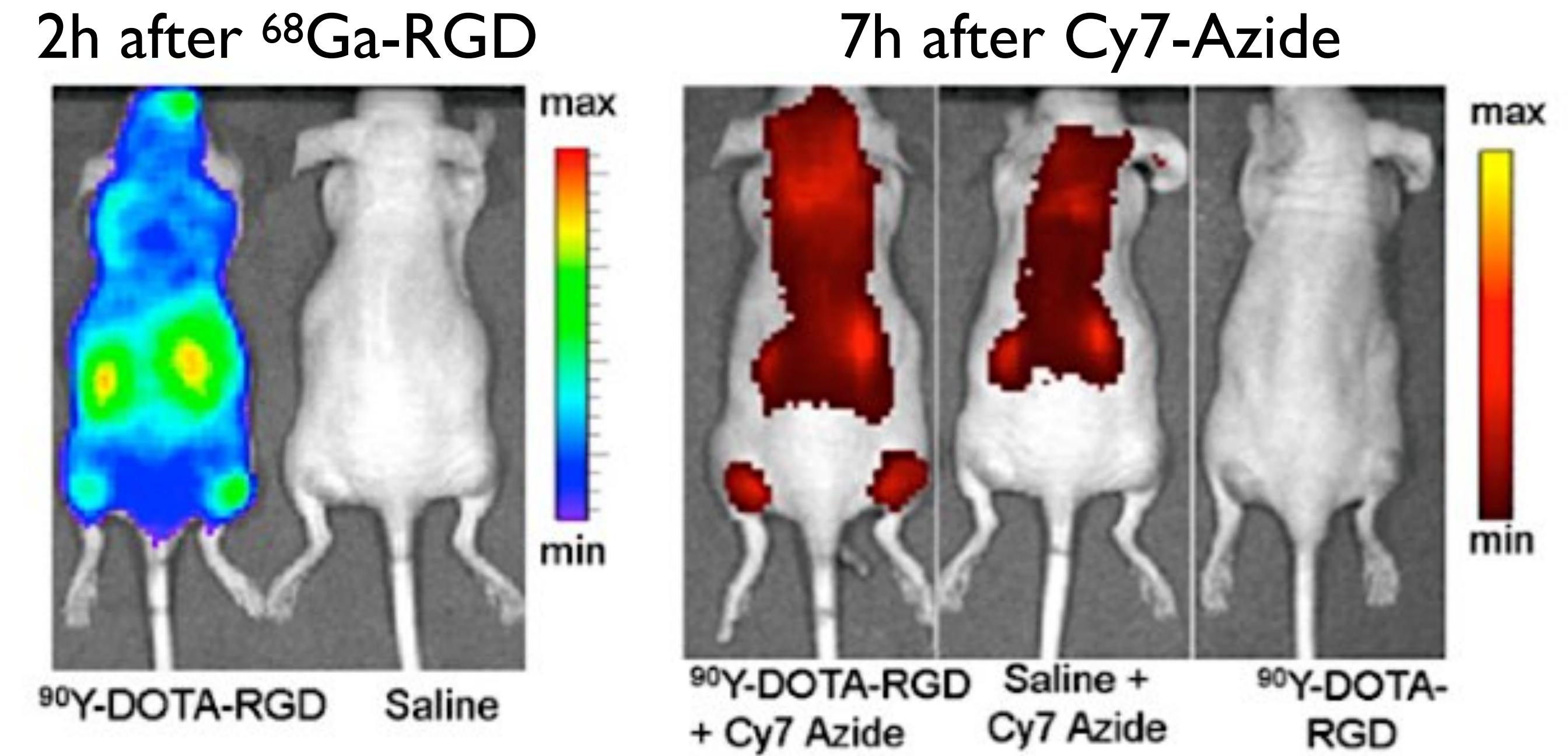
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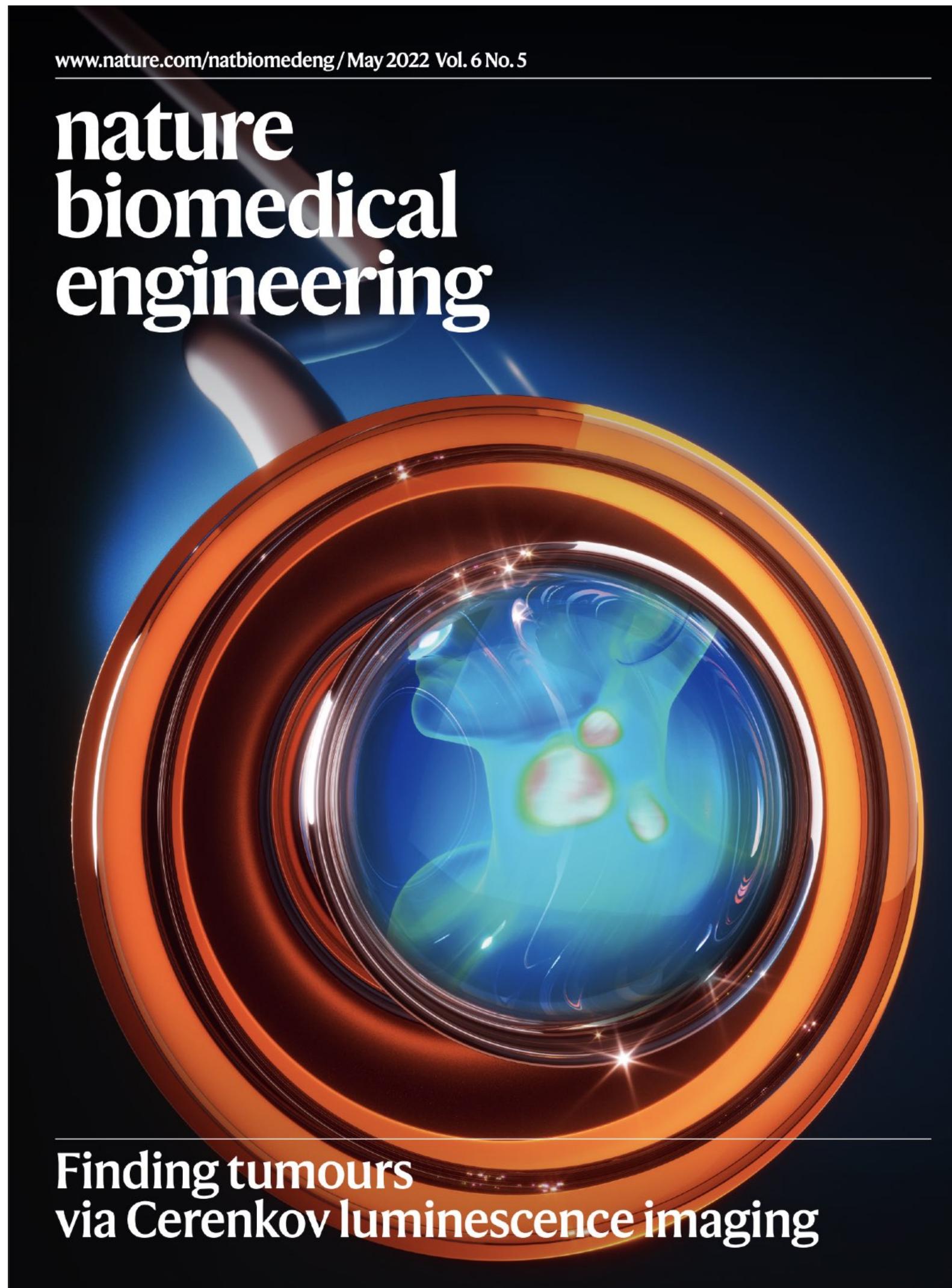
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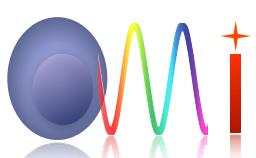
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Preclinical concepts

Clinical translation

Theranostics

Outlook - and then some



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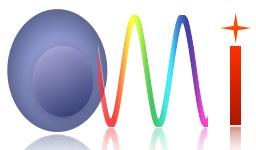
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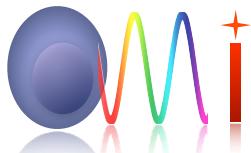
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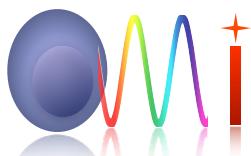
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- US has 7 PET scanners / 10^6 people, Latin America 0.3 and India 0.07!



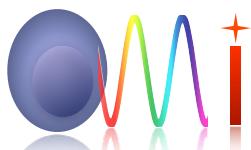
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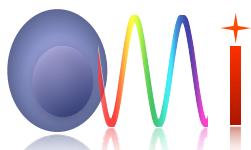
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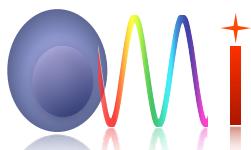
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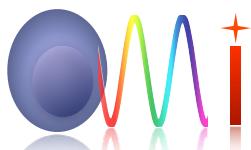
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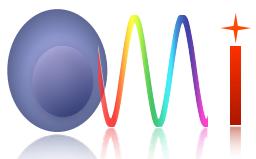
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 - Monitoring of a-based therapies, cheaper alternative to SPECT



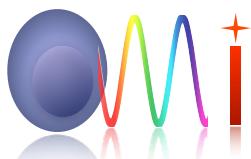
Challenges

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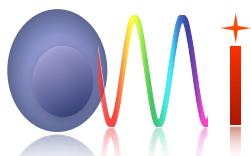
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- Especially challenging in any clinical setting



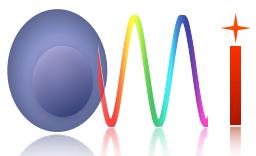
Challenges

- Biggest challenge is low SI, need to exclude ambient light
- Especially challenging in any clinical setting
 - Radioactive exposure of surgeons and patients



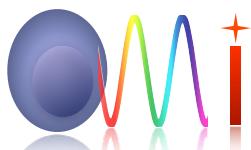
Challenges

- Biggest challenge is low SI, need to exclude ambient light
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 - Radioactive exposure of surgeons and patients
- "Clinical CLI considered impossible" (thanks, reviewer 3)



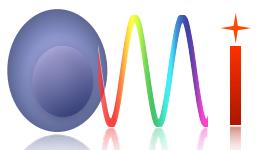
Challenges

- Biggest challenge is low SI, need to exclude ambient light
- Especially challenging in any clinical setting
 - Radioactive exposure of surgeons and patients
- "Clinical CLI considered impossible" (thanks, reviewer 3)
- Solutions:



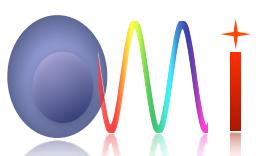
Challenges

- Biggest challenge is low SI, need to exclude ambient light
- Especially challenging in any clinical setting
 - Radioactive exposure of surgeons and patients
- "Clinical CLI considered impossible" (thanks, reviewer 3)
- Solutions:
 - *Back table* approach (*ex vivo*)



Challenges

- Biggest challenge is low SI, need to exclude ambient light
- Especially challenging in any clinical setting
 - Radioactive exposure of surgeons and patients
- "Clinical CLI considered impossible" (thanks, reviewer 3)
- Solutions:
 - *Back table* approach (*ex vivo*)
 - Specialized clinical Cerenkov imaging system (*in vivo*)



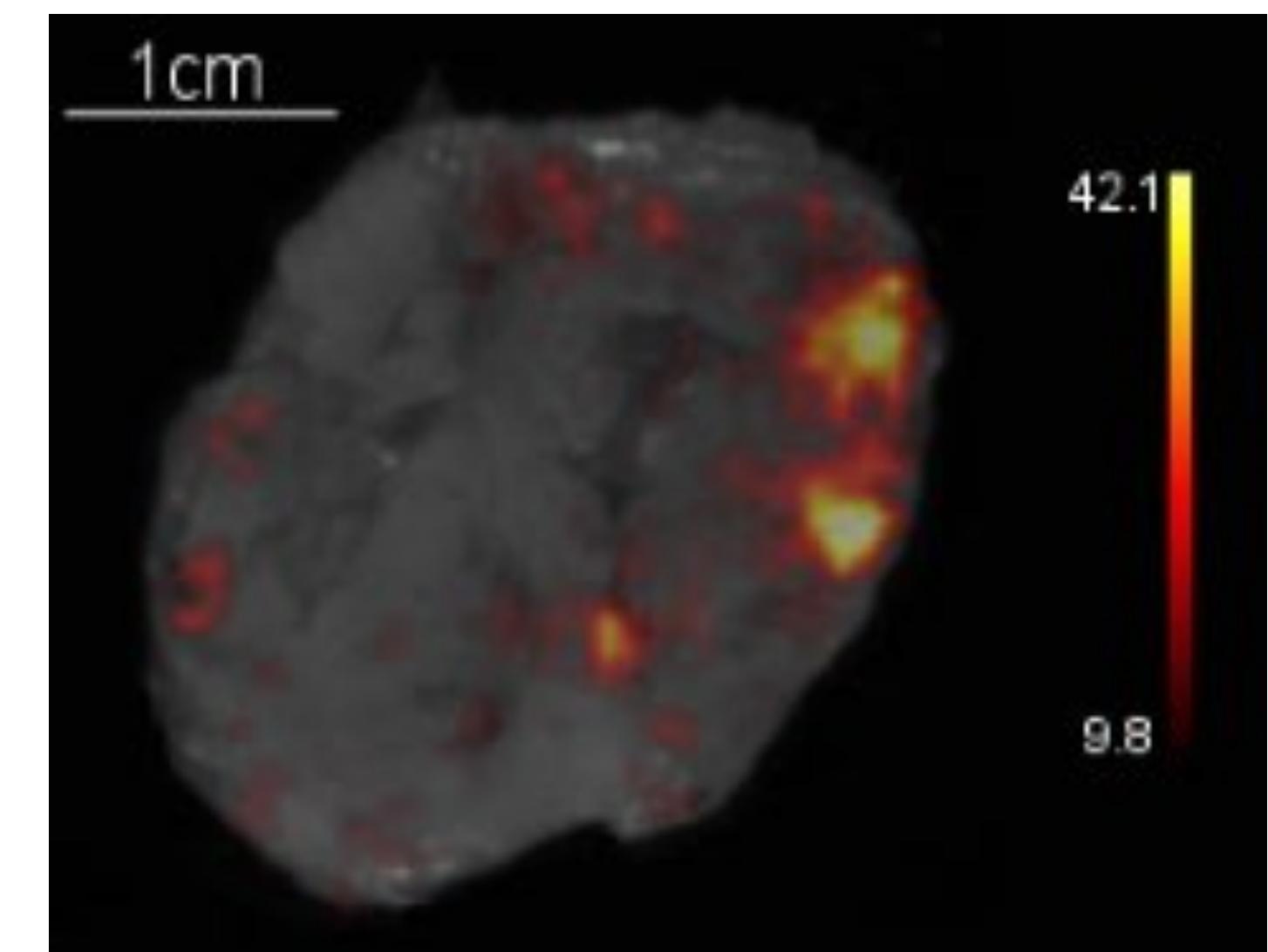
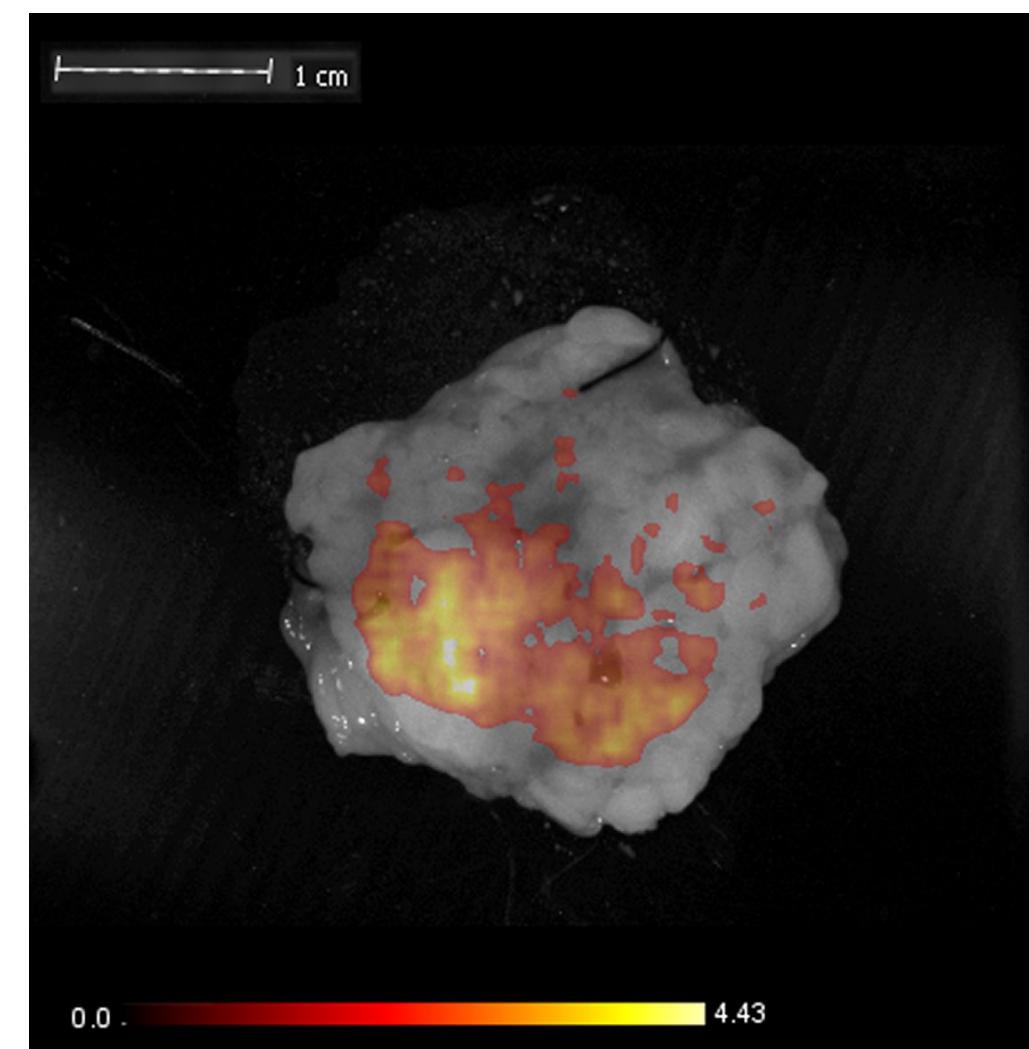
Challenges

- Biggest challenge is low SI, need to exclude ambient light
- Especially challenging in any clinical setting
 - Radioactive exposure of surgeons and patients
- "Clinical CLI considered impossible" (thanks, reviewer 3)
- Solutions:
 - *Back table* approach (ex vivo)
 - Specialized clinical Cerenkov imaging system (in vivo)
 - Expanding the spectral range



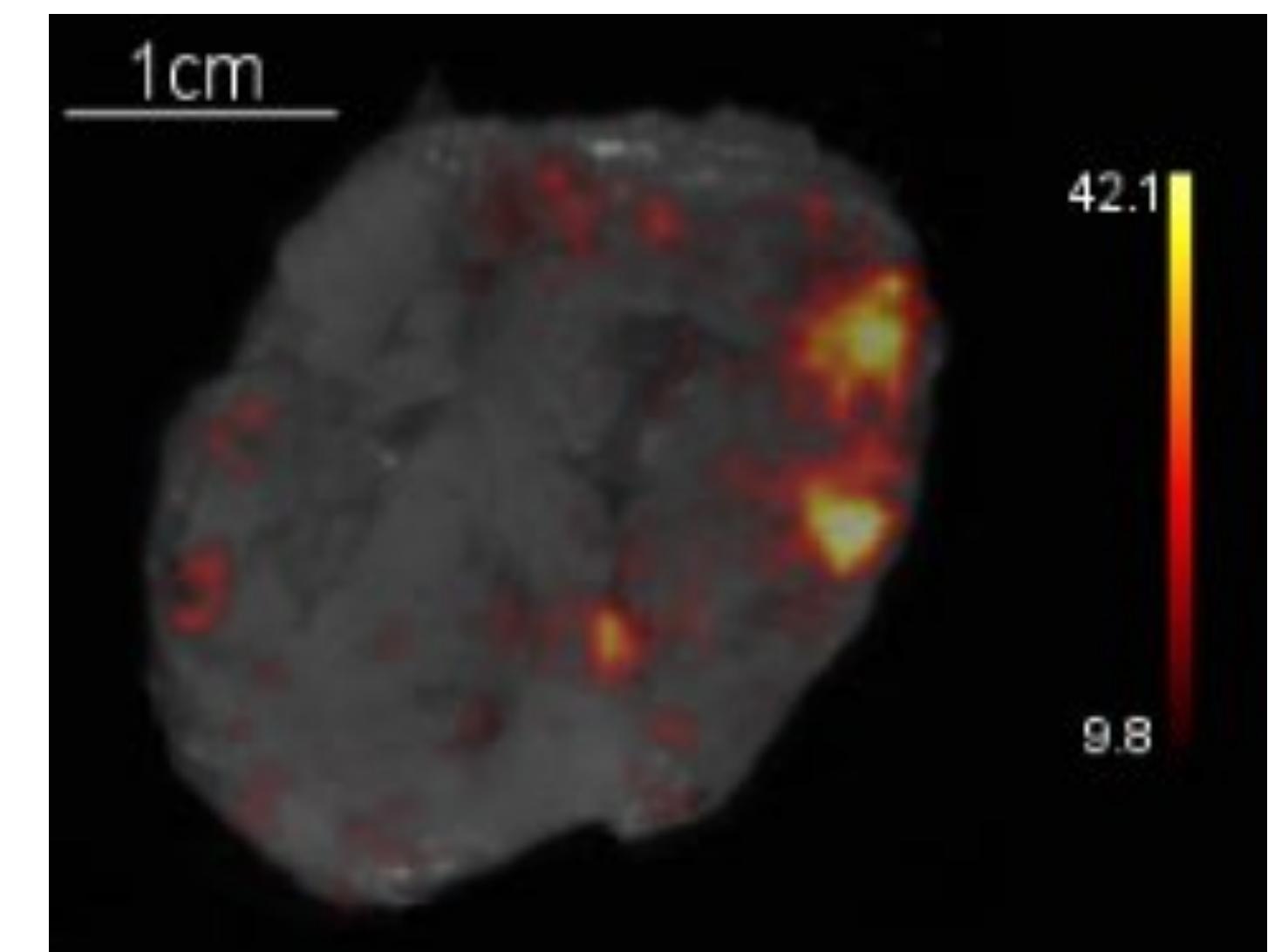
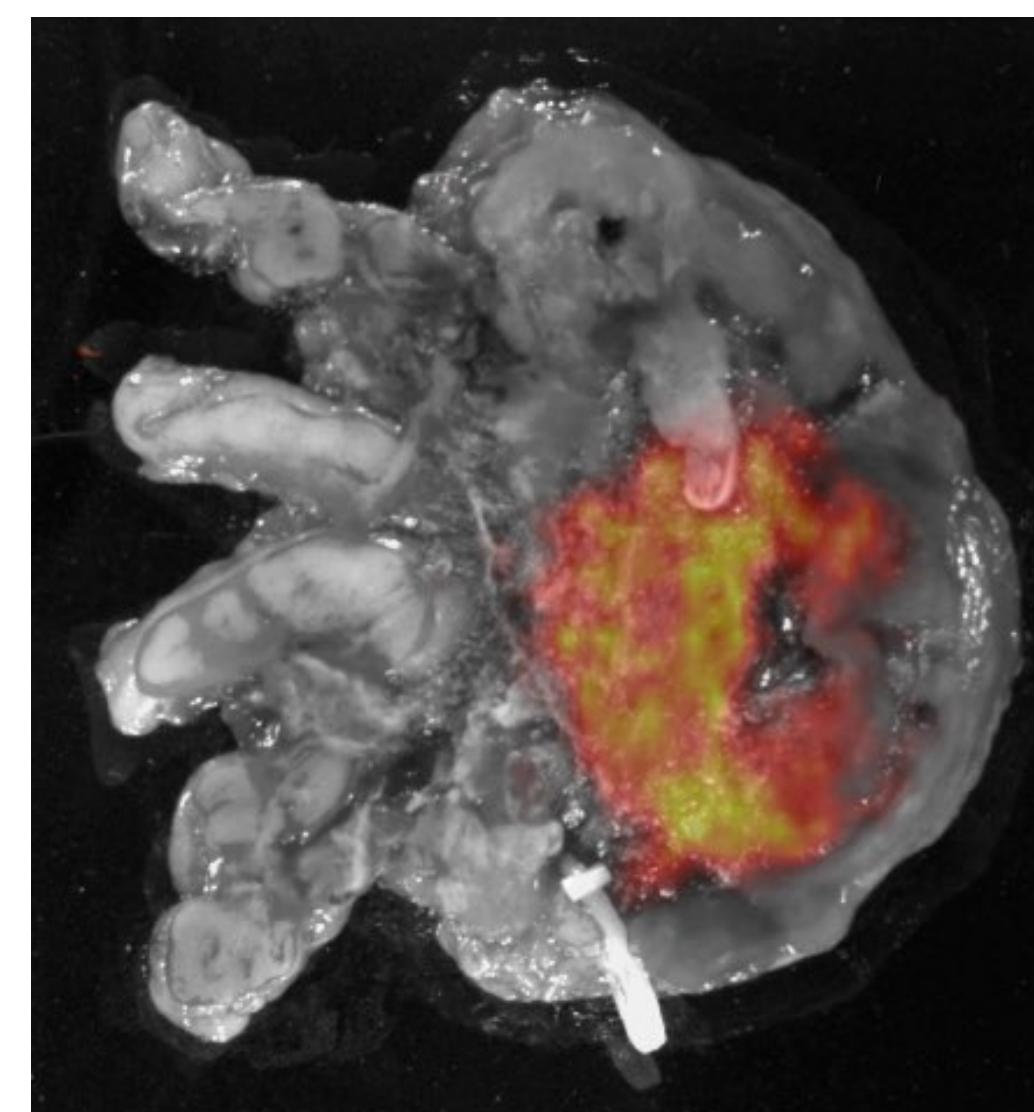
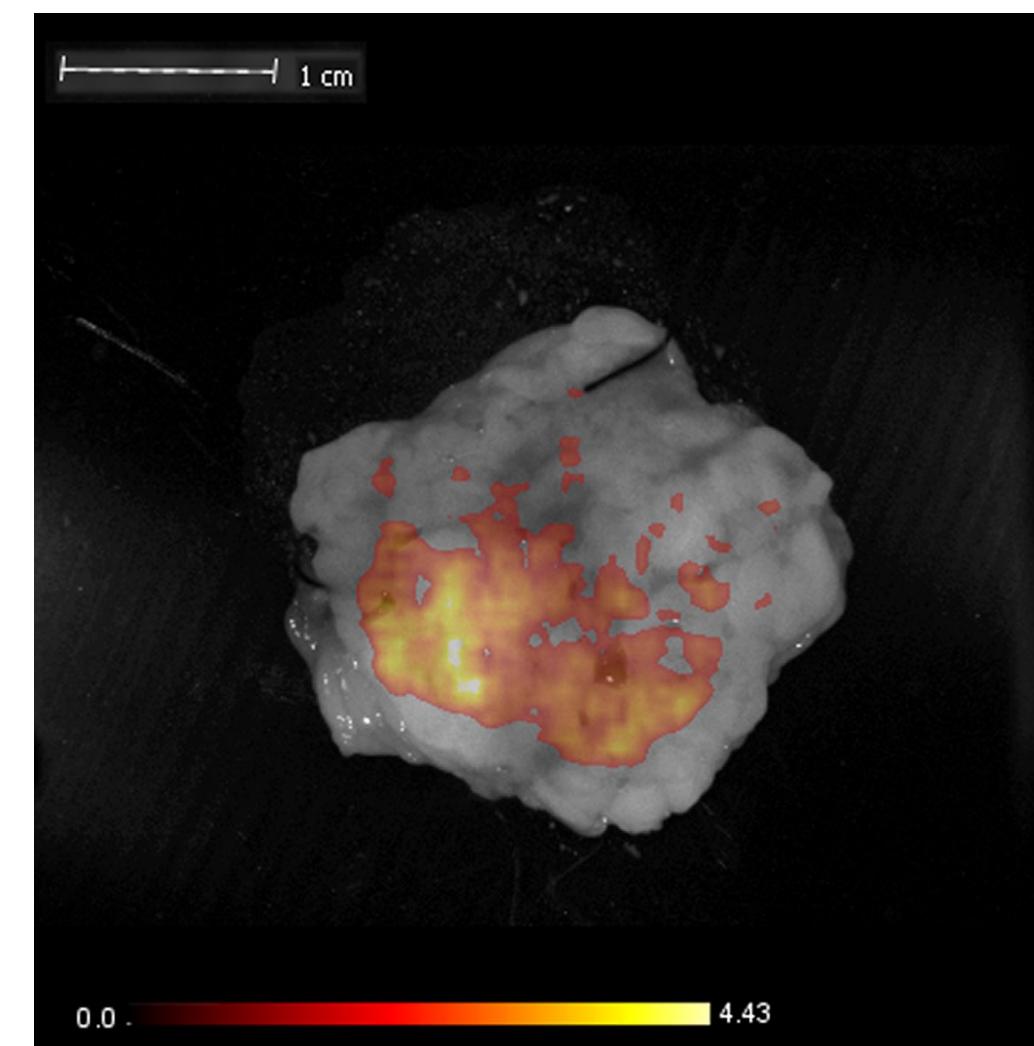
Back Table imaging

LightPath™



Back Table imaging

LightPath™



Cerenkov imaging system

Optical Fibre bundle
Flexible support arm

Optical Fibre bundle

Monitor support arm

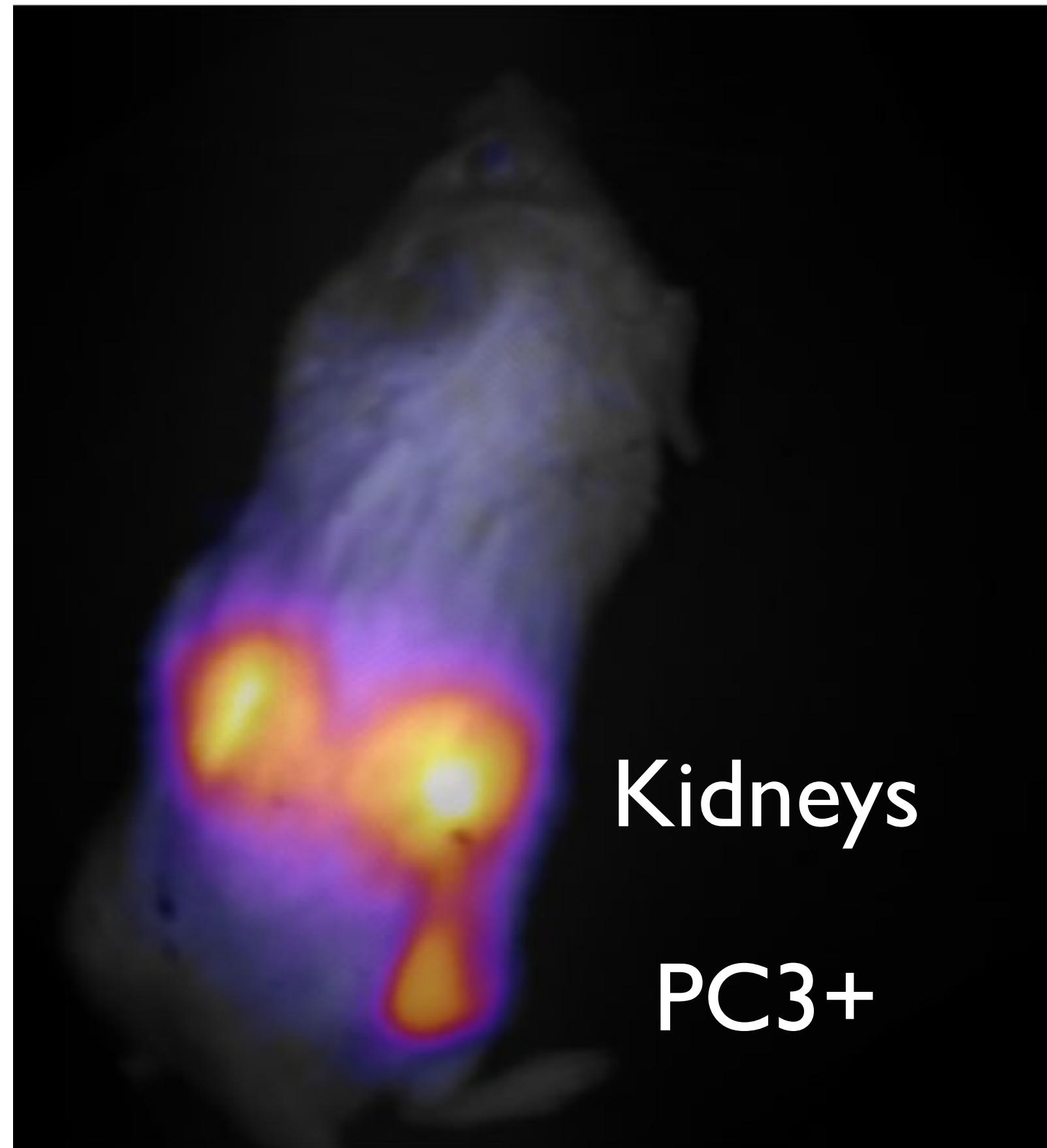
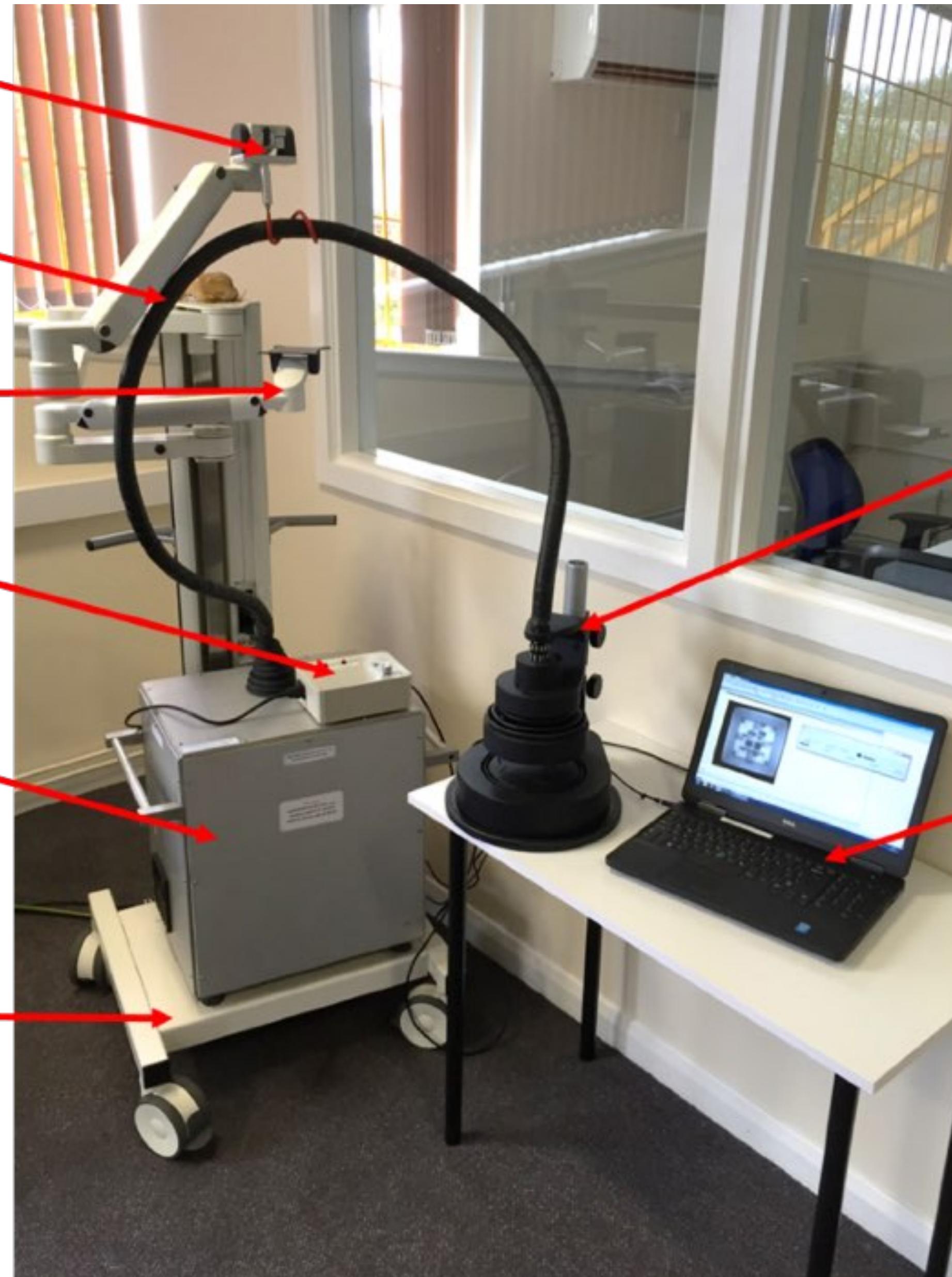
Interlock and LED
control box

Lead shielded
Instrument containing
EMCCD camera and
optical filter

Instrument trolley

Pre-clinical enclosure
including reference
capture LEDs

Notebook computer
for control and
image storage



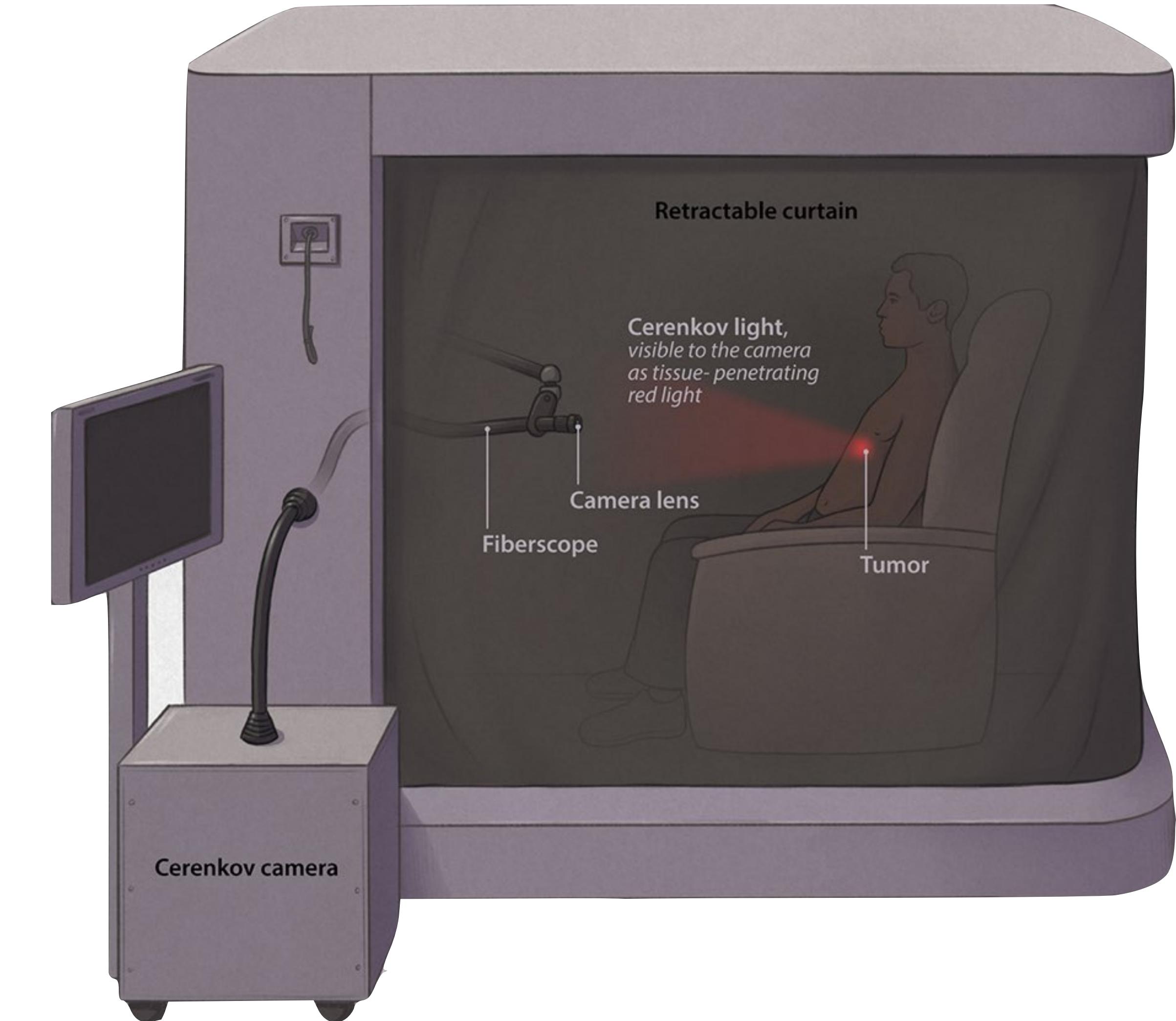
Cerenkov imaging system



E Pratt

M Skubal

B McLarney



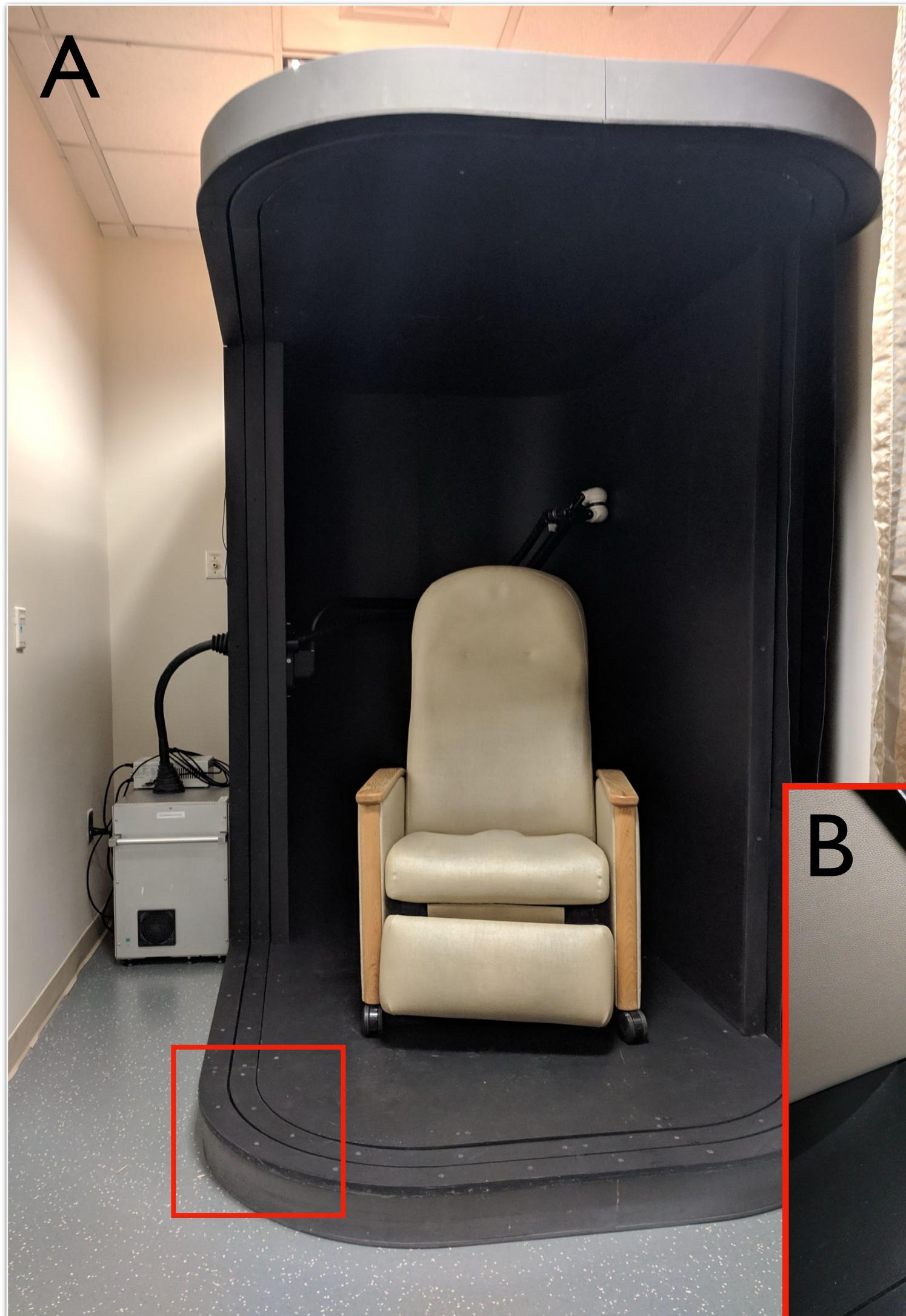
Pratt E et al. (2022) Nature Biomedical Engineering 6:5 559



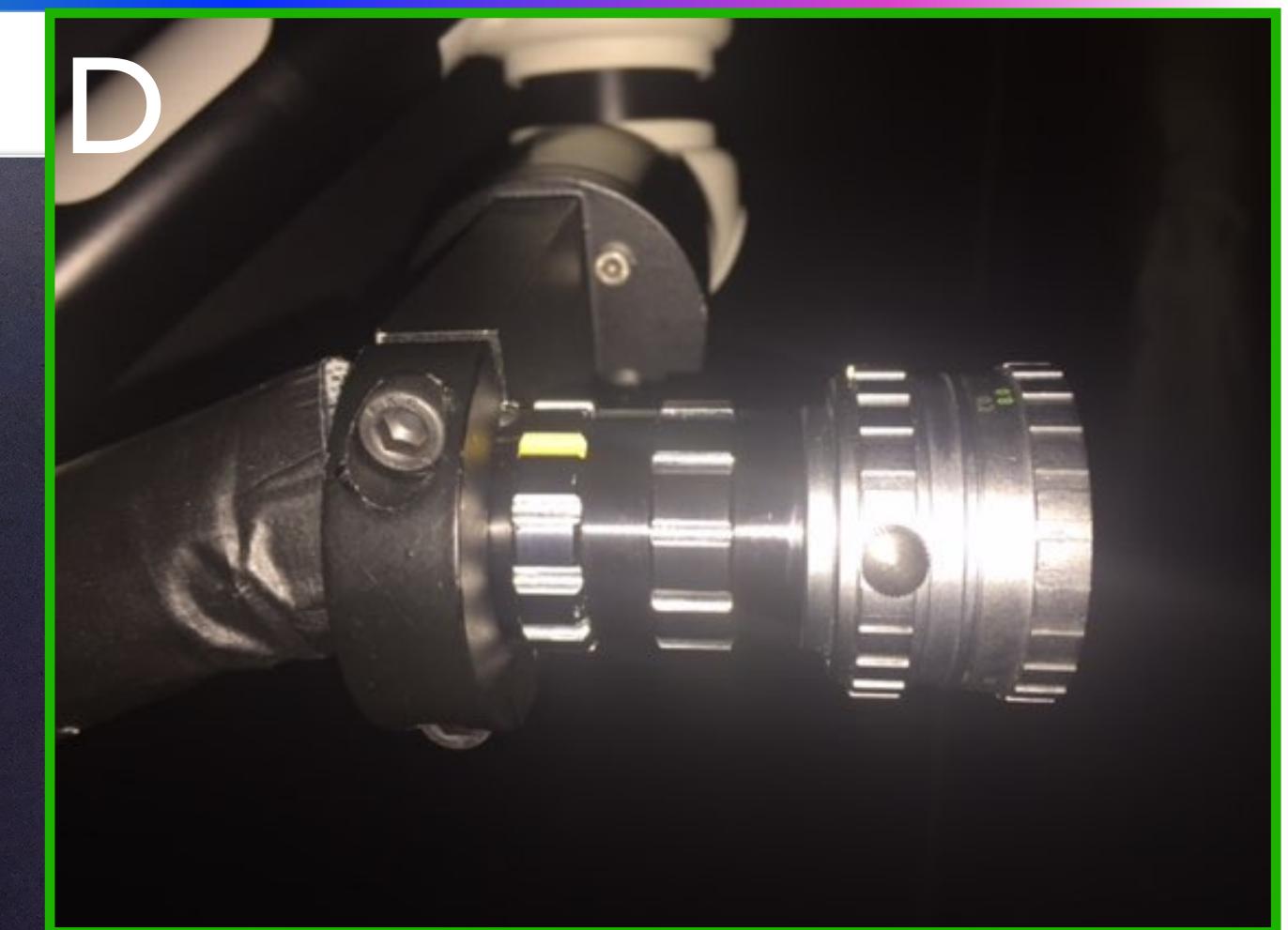
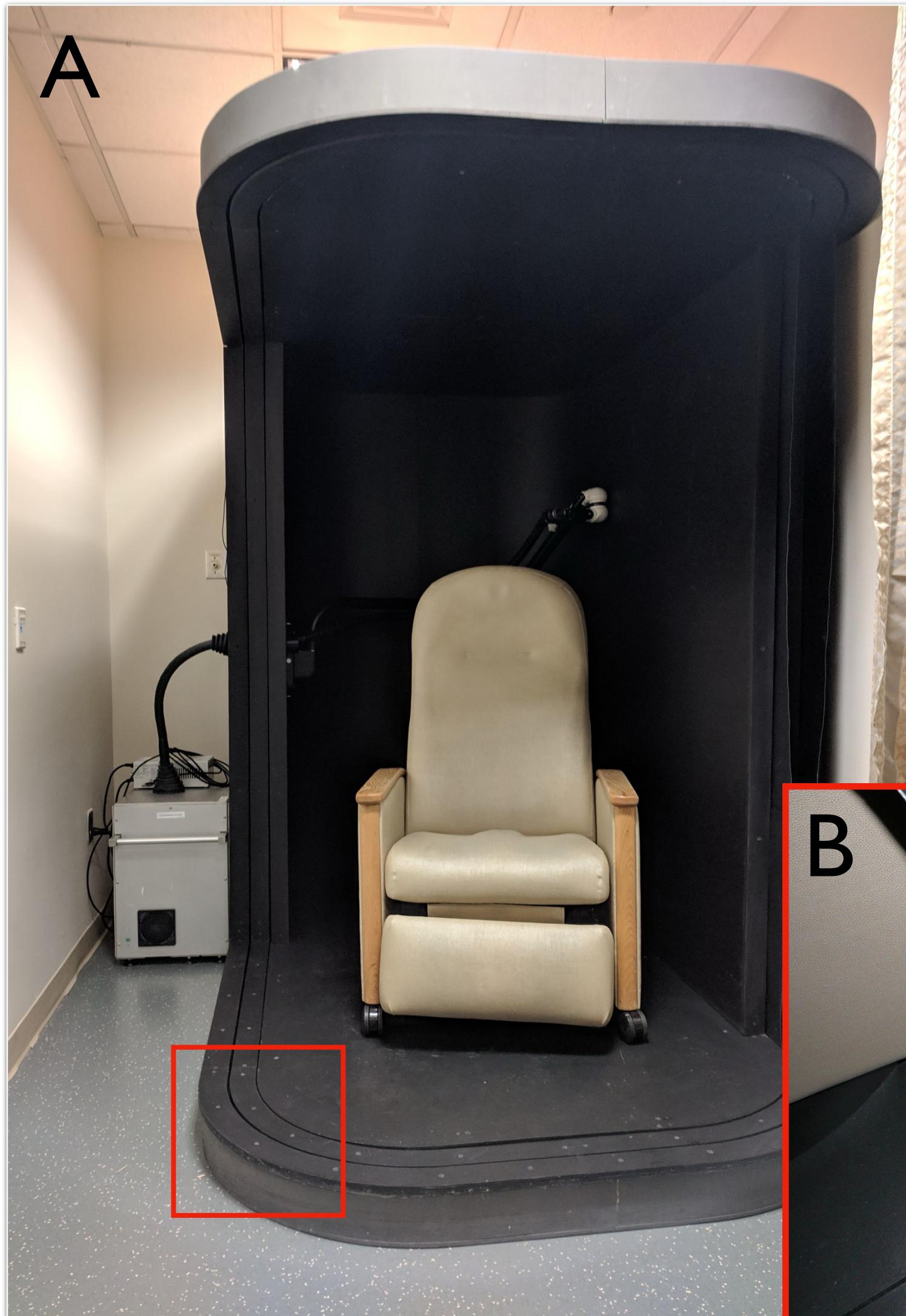
Clinical Fiberscope



Clinical Fiberscope



Clinical Fiberscope



Clinical Fiberscope

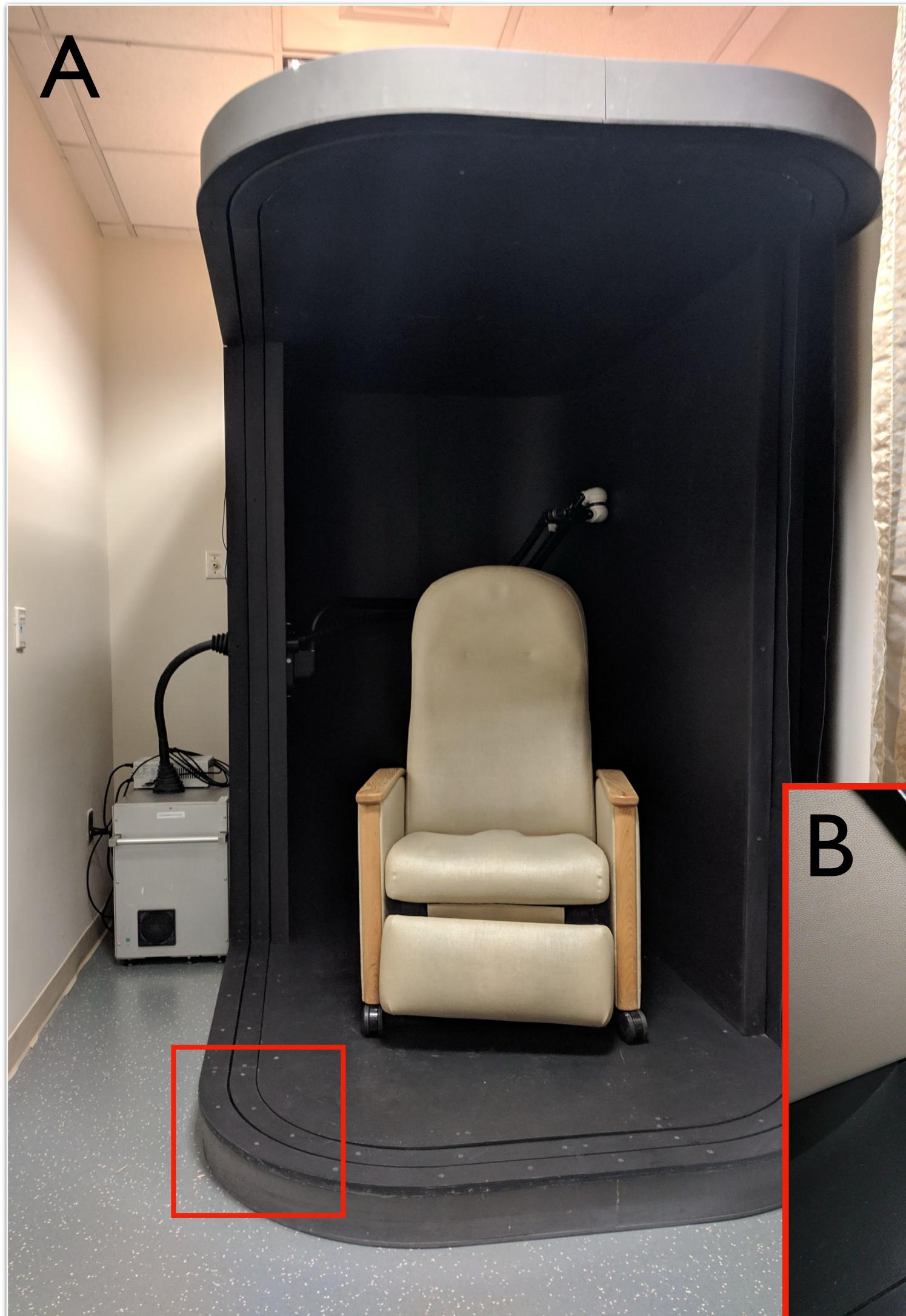
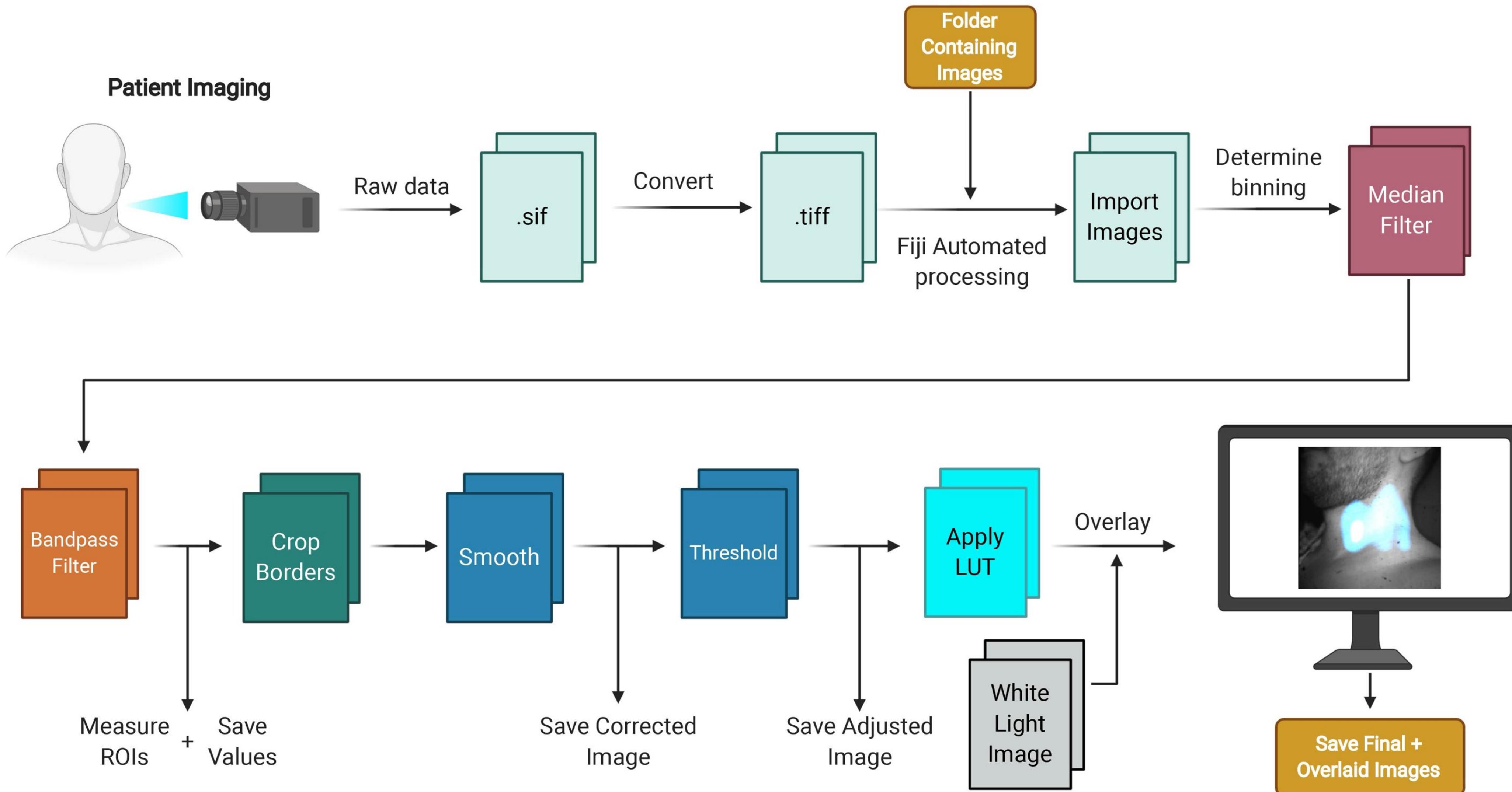


Image Processing



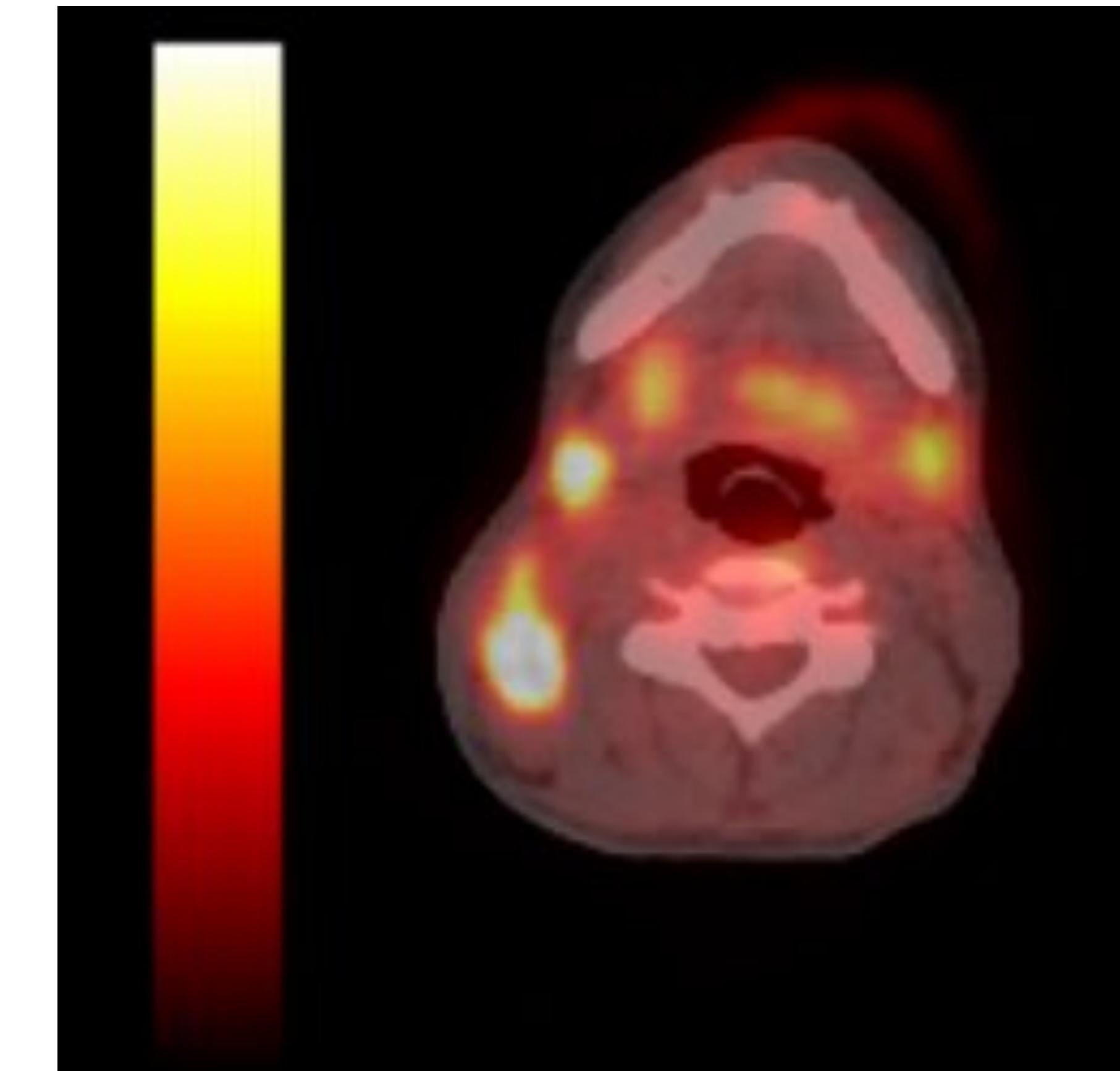
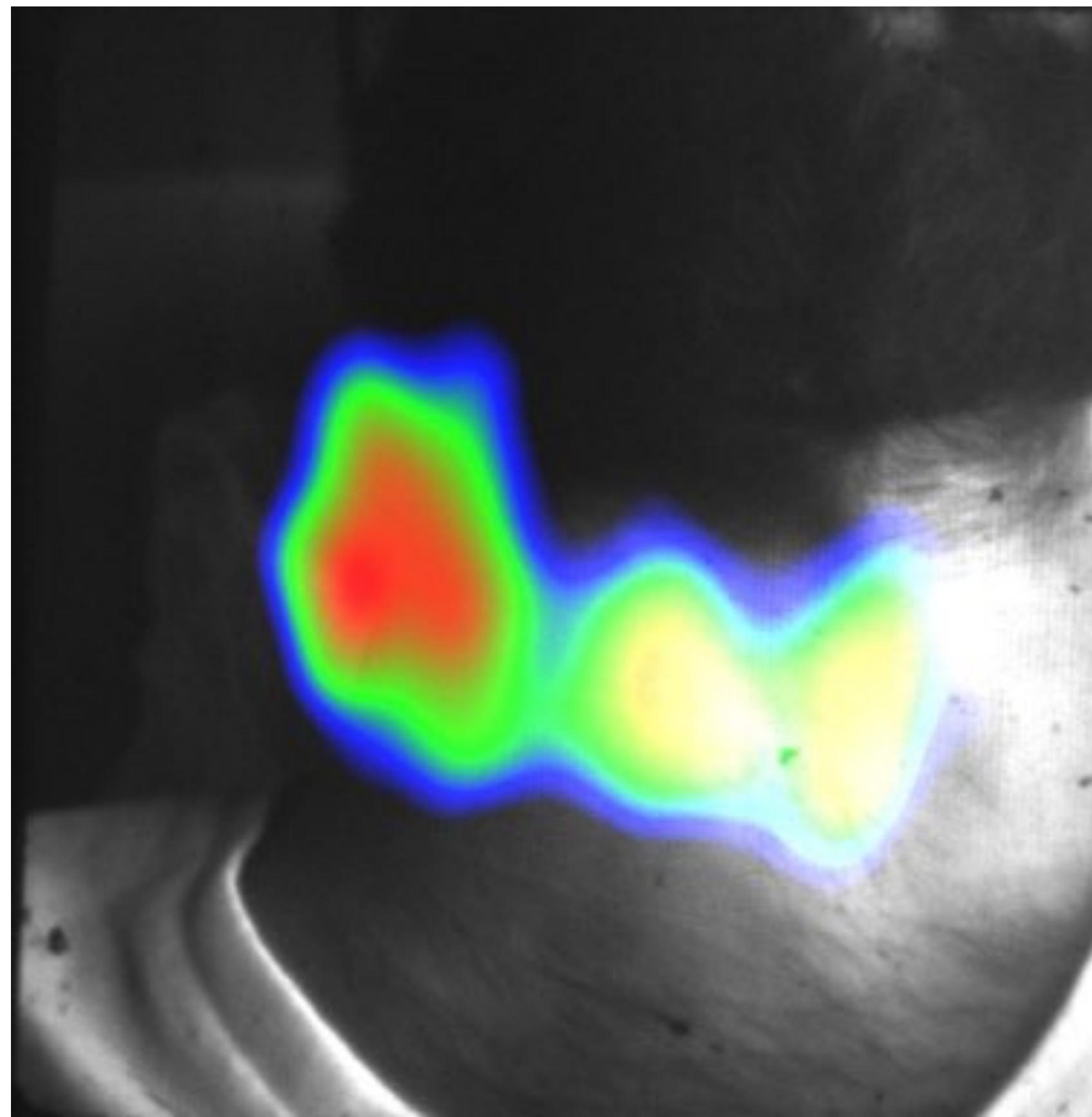
Imaged tracers

Radiopharmaceutical	Indication	Clinical imaging mode	Typical dose mCi (GBq)	Cerenkov light generated by isotope (photons/decay) ^{35,36}	Total possible Cerenkov light at injection (photons/second) x 10 ⁹	Number of patients imaged
Na ¹³¹ I	Thyroid cancer adjuvant therapy	SPECT	100-200 (3.7-7.4)	0.669	5.0	25
¹⁸ F-FDG	General disease staging	PET	10-14.9 (0.37-0.55)	1.32	0.7	20
⁶⁸ Ga-DOTATATE	Neuroendocrine PET imaging	PET	4.4-5.5 (119-149)	33.9	6.3	28
¹⁷⁷ Lu-DOTATATE	Neuroendocrine radiotherapy	SPECT	188-200 (6.9-7.4)	0.141	1.0	26
²²³ RaCl ₂	Metastatic castration-resistant prostate cancer therapy	None (separate PET or SPECT scan)	0.091-0.177 (0.0033-0.0065)	28.0104 (with daughters)	0.2	7

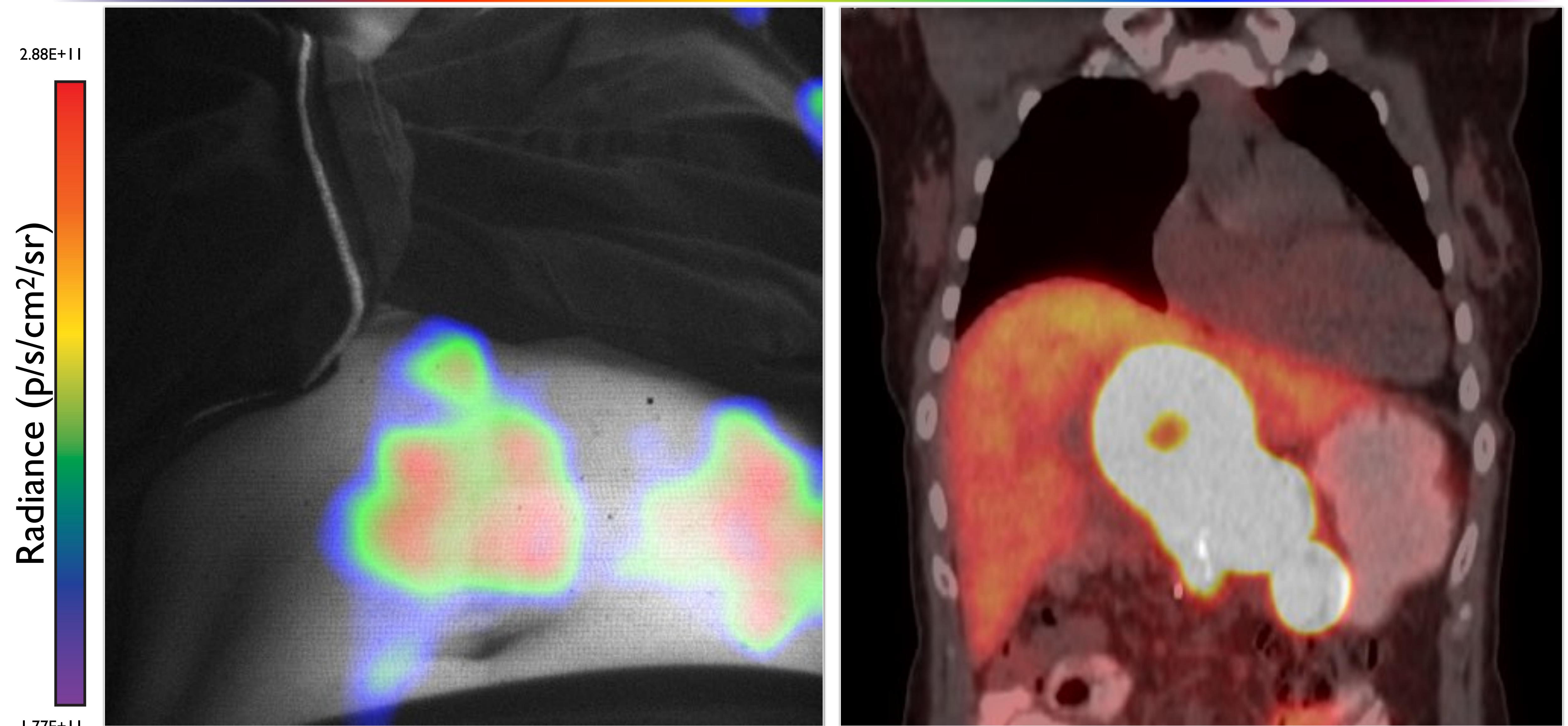
Table 1. Radiotracers and details of accrual for IRB 17-538 specifying range of radiotracer administered and number of patients accrued at time of writing. Details reflect range of administered activity to the patient and computed Cerenkov light based on (35,36).

^{18}F -FDG Imaging

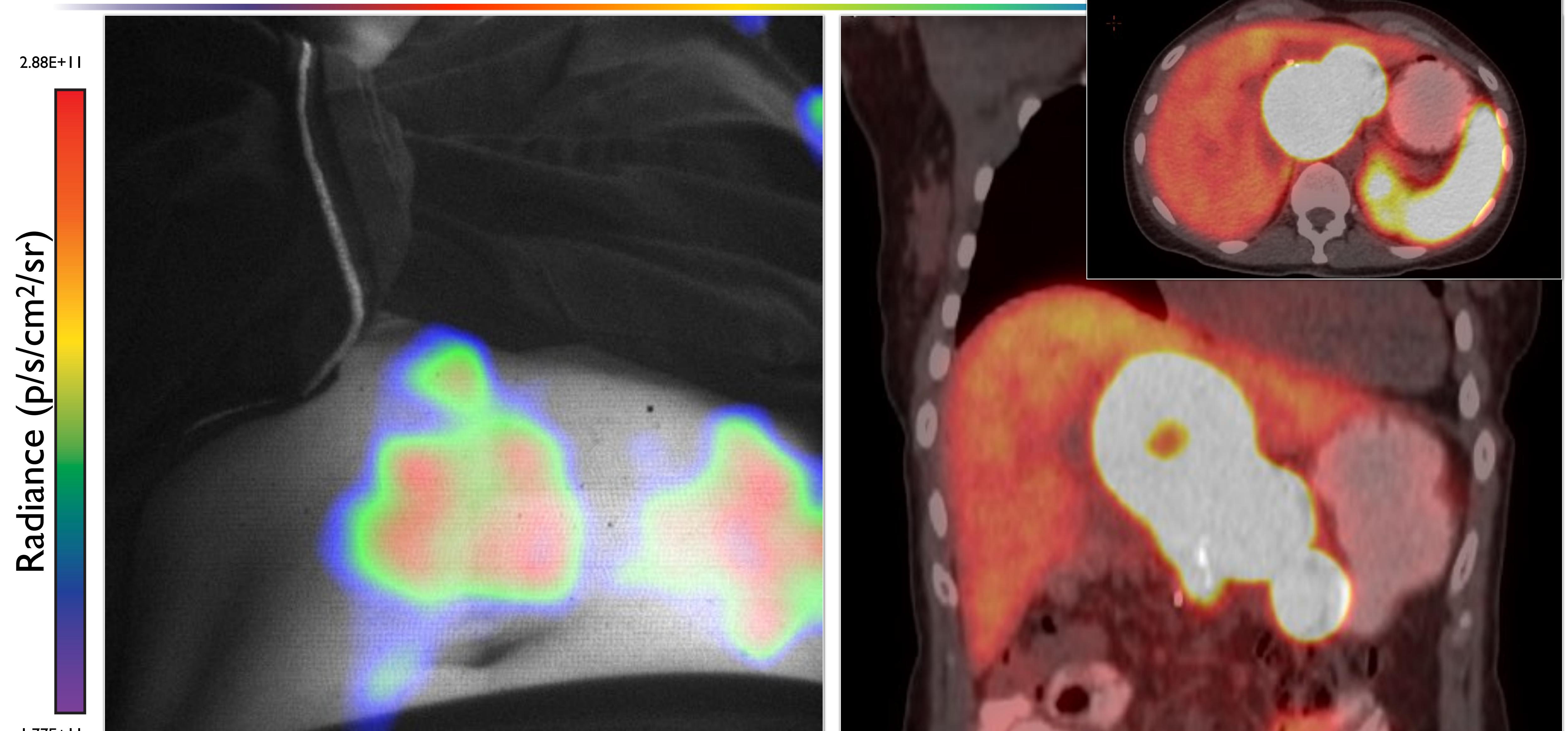
^{18}F -FDG 12.1 mCi iv (4.7 μCi locally)



^{68}Ga -DOTATATE



^{68}Ga -DOTATATE



Overview



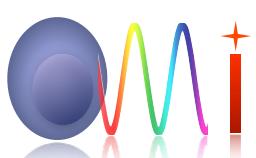
Cerenkov luminescence imaging - huh?

Preclinical concepts

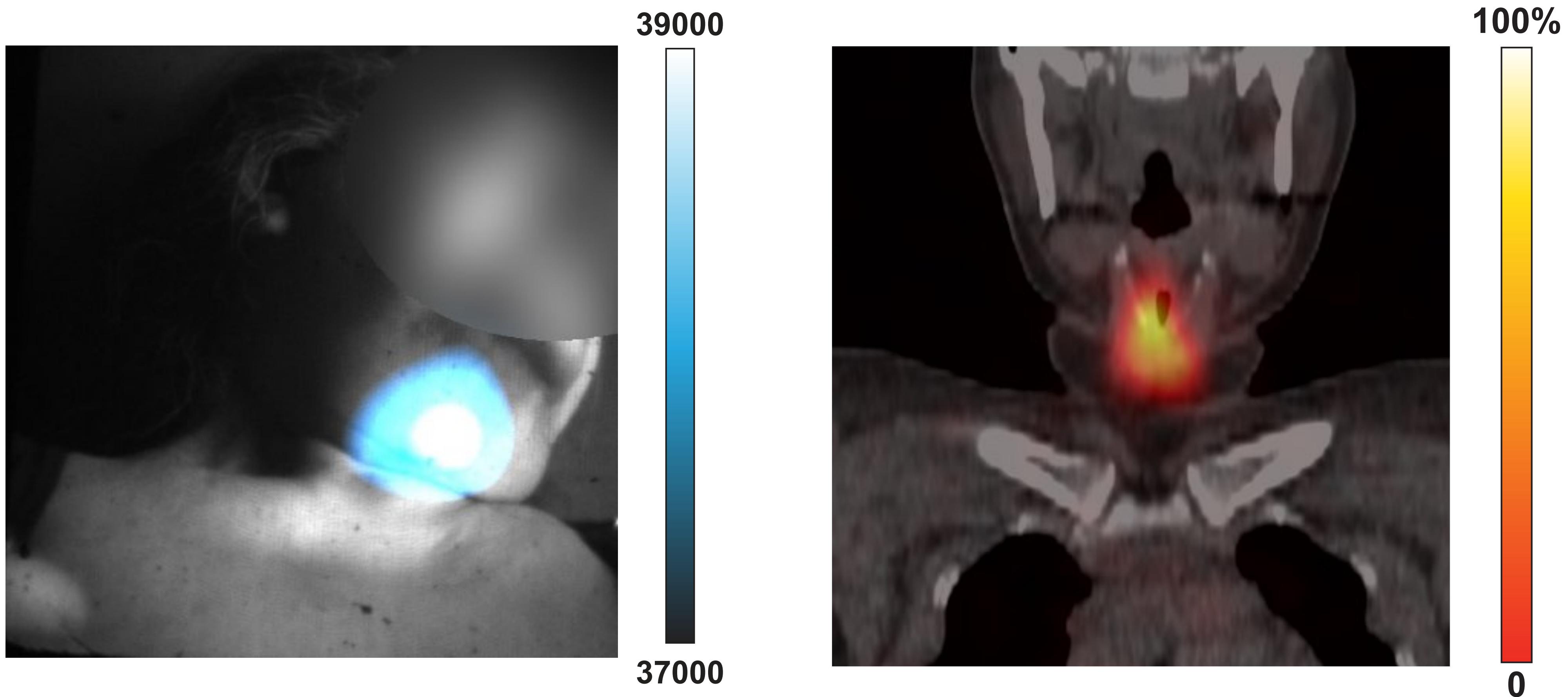
Clinical translation

Theranostics

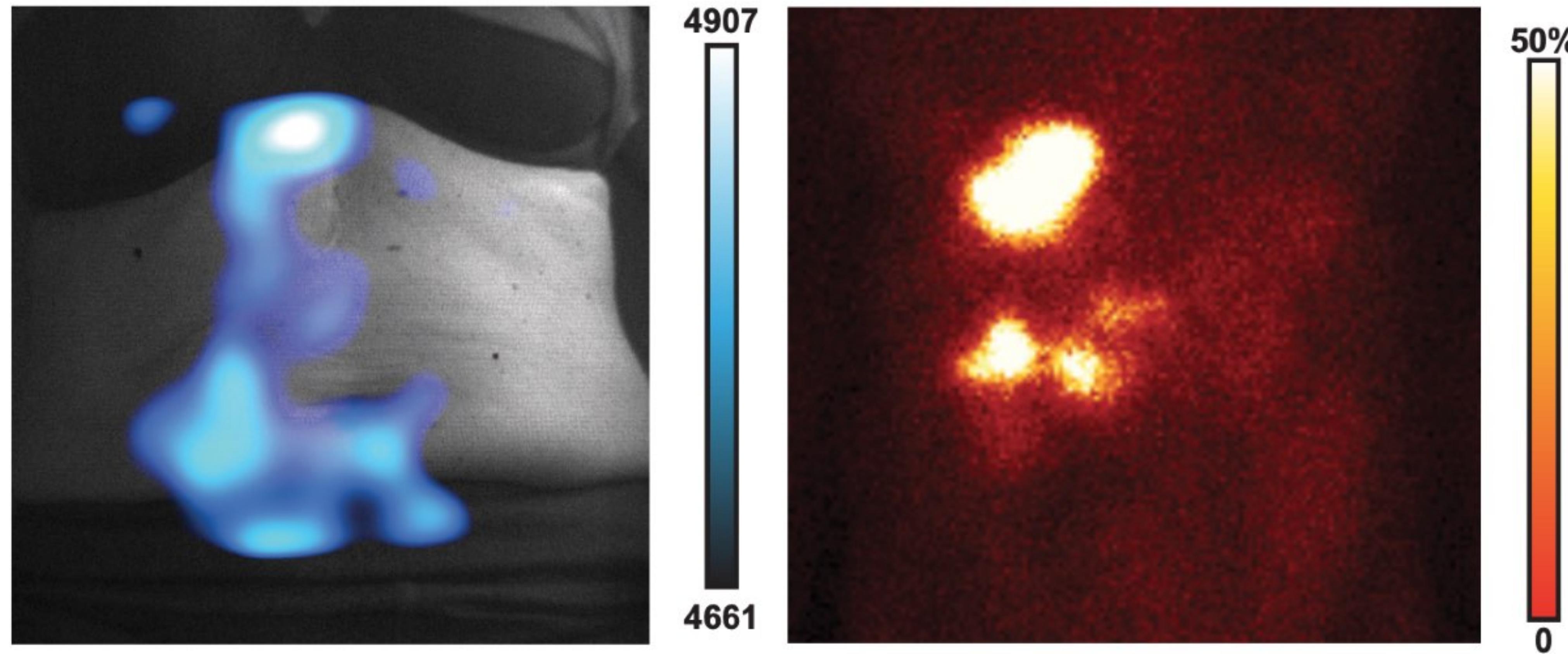
Outlook - and then some



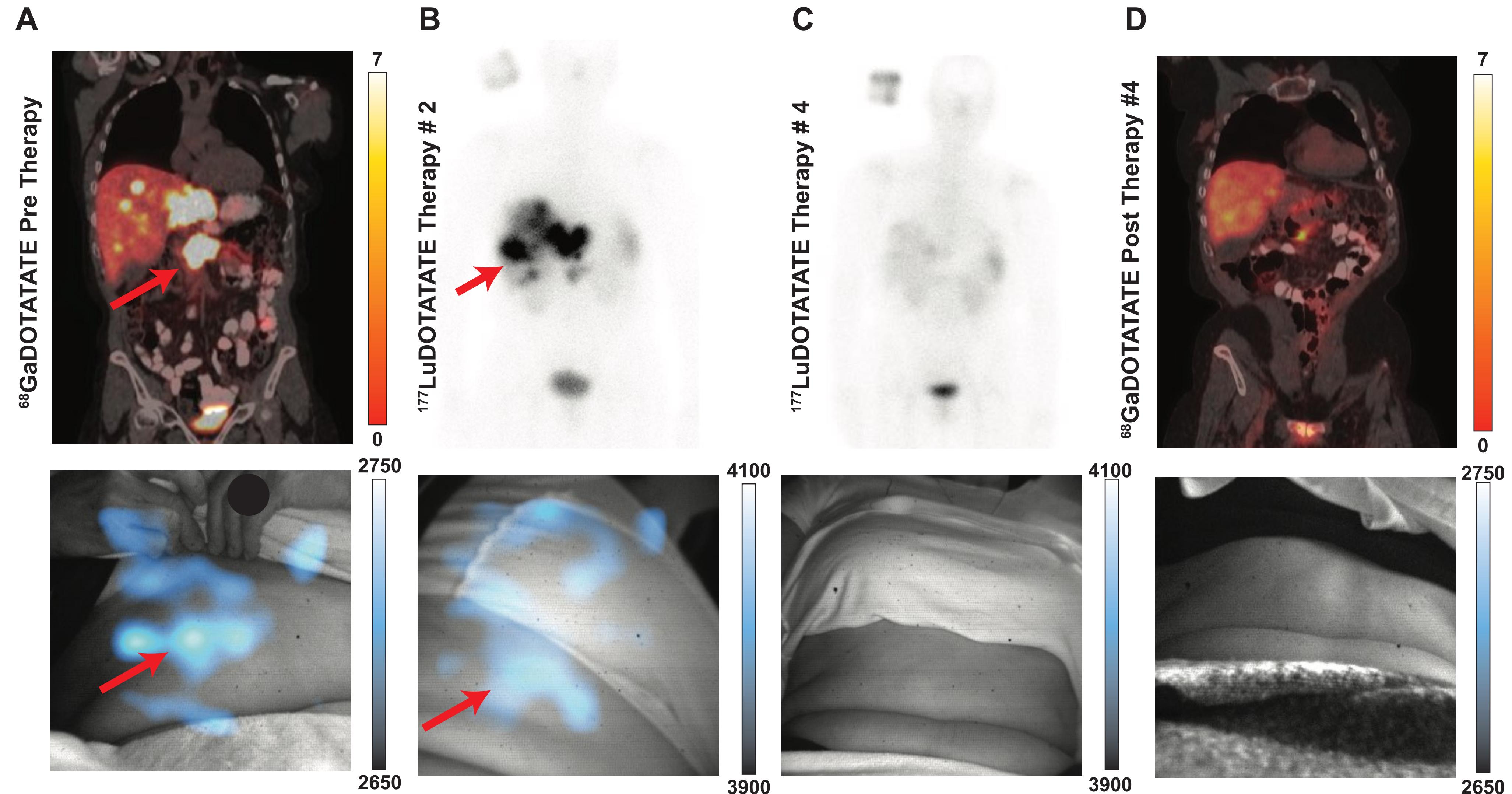
^{131}I Iodide



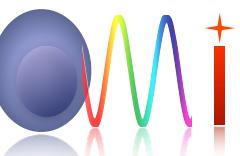
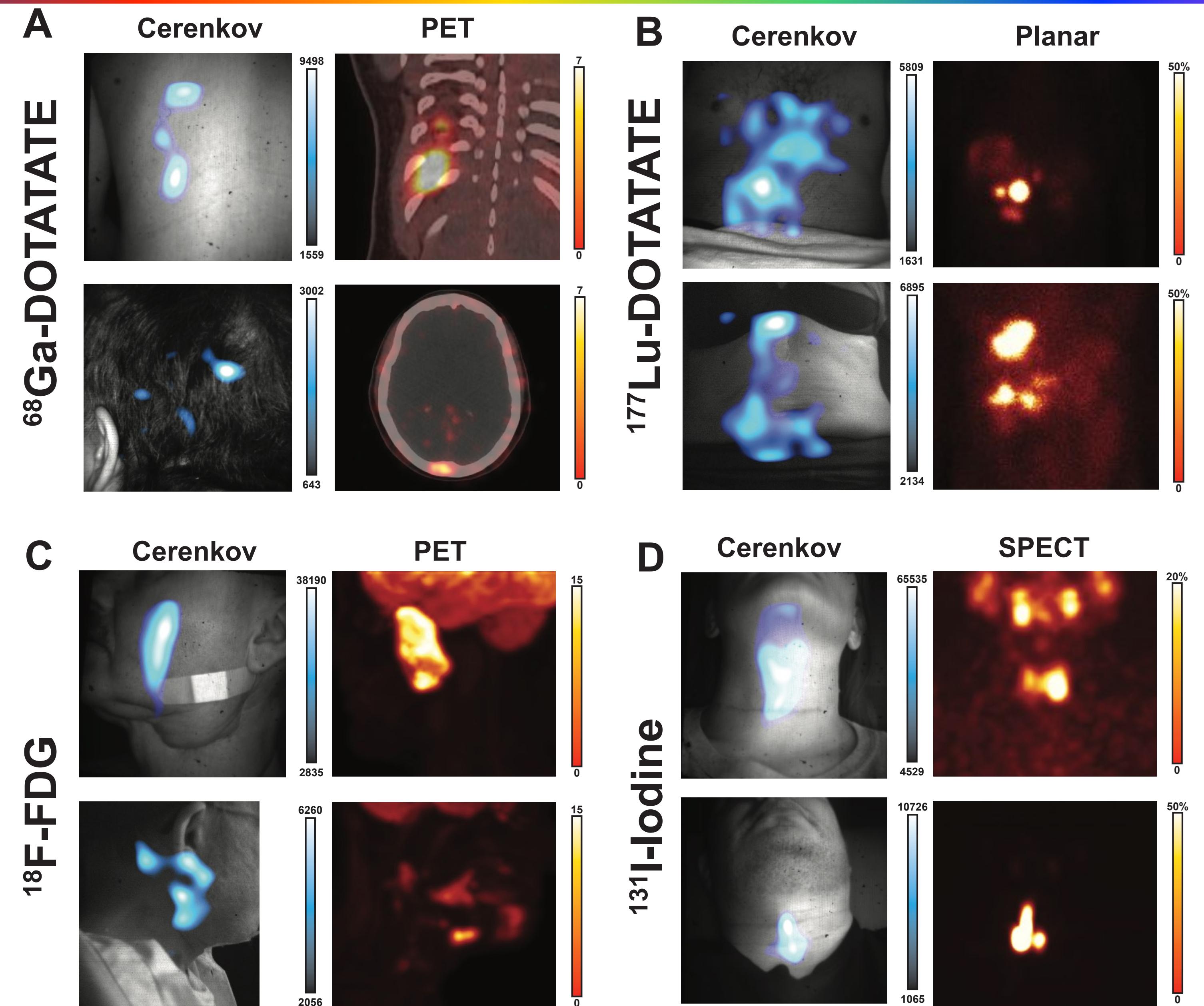
^{177}Lu -DOTATATE



Lutathera therapy monitoring



Additional patients

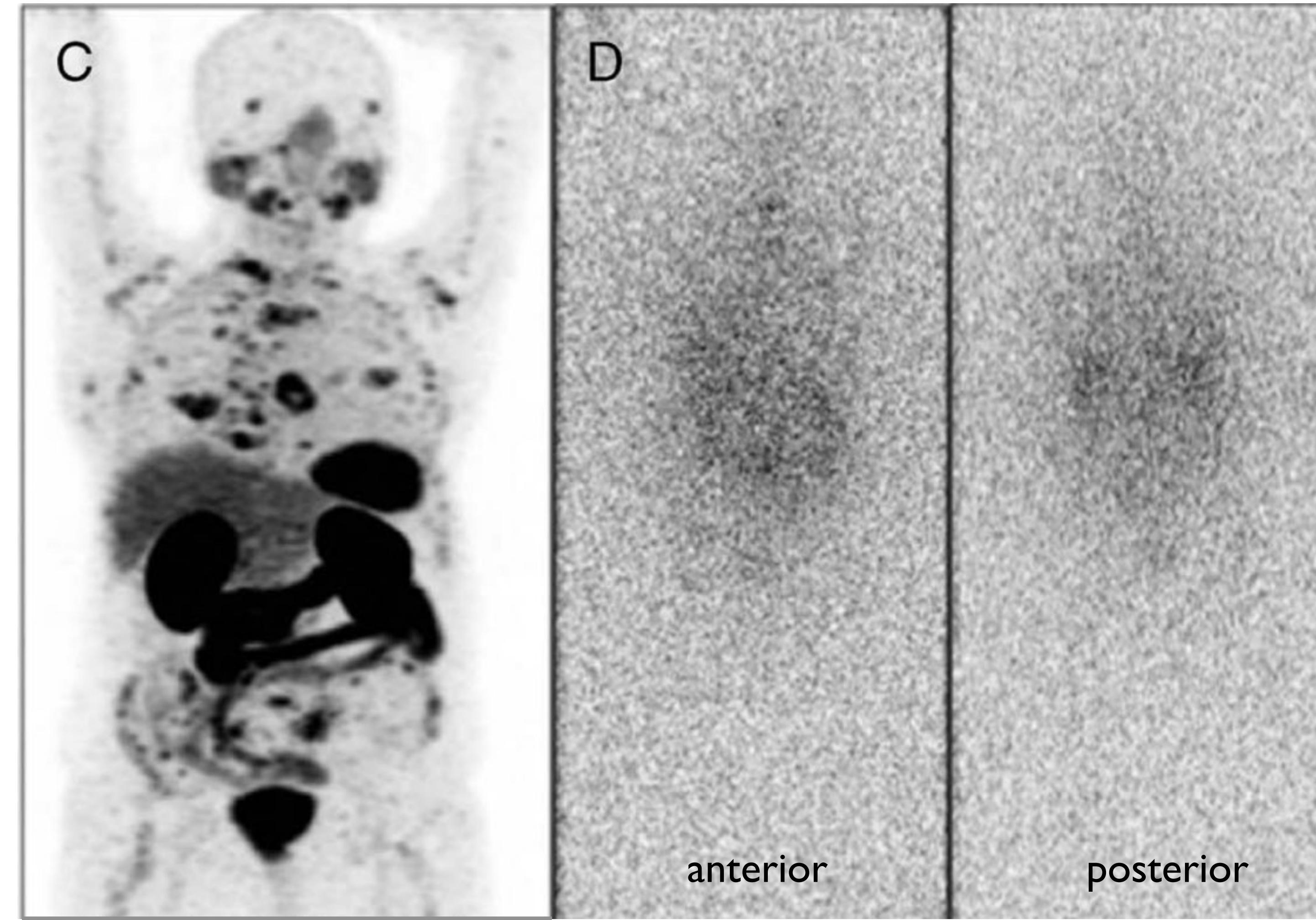


Imaging of α -emitters currently difficult



^{68}Ga -PSMA-11

Imaging of α -emitters currently difficult

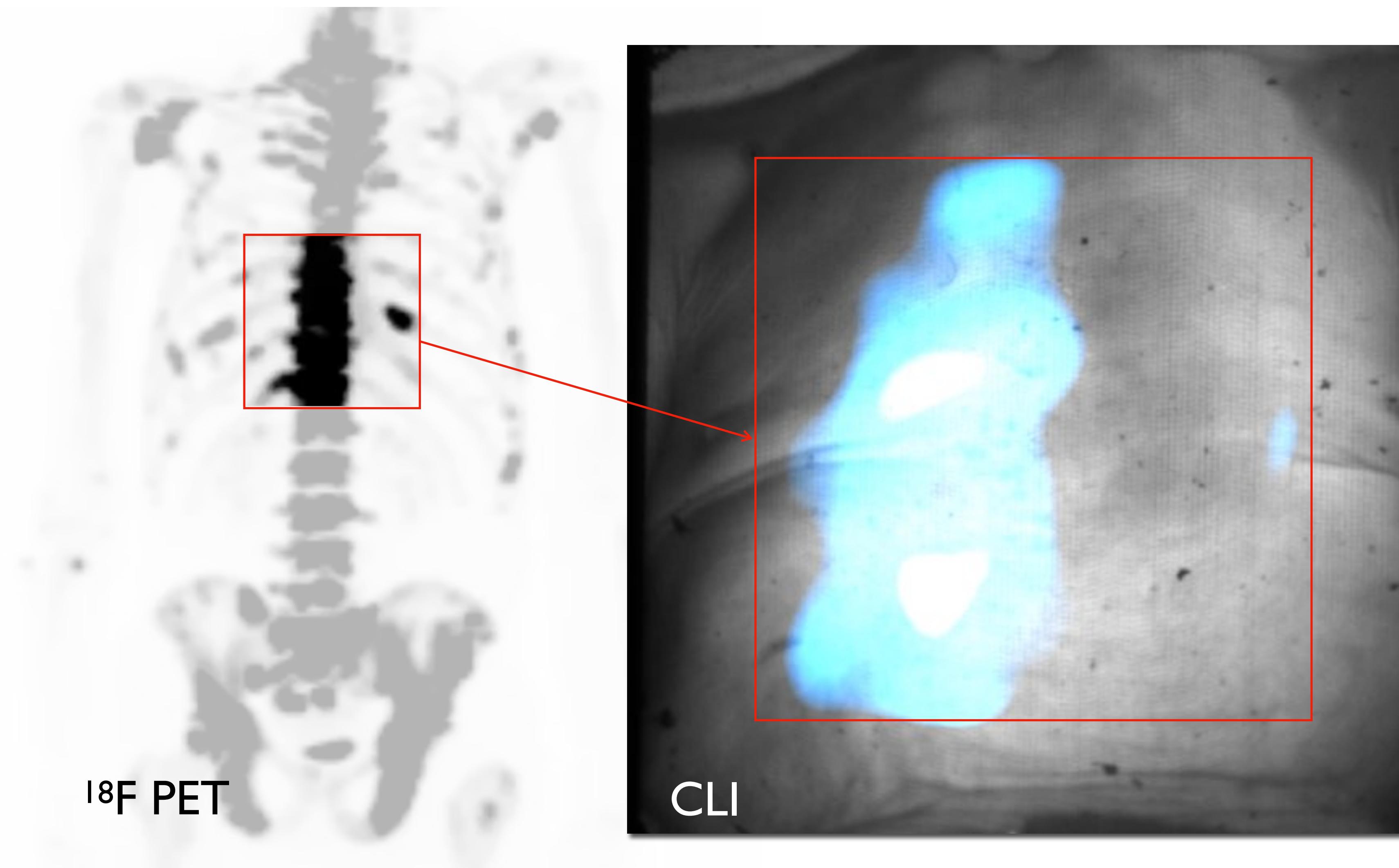


^{68}Ga -PSMA-11

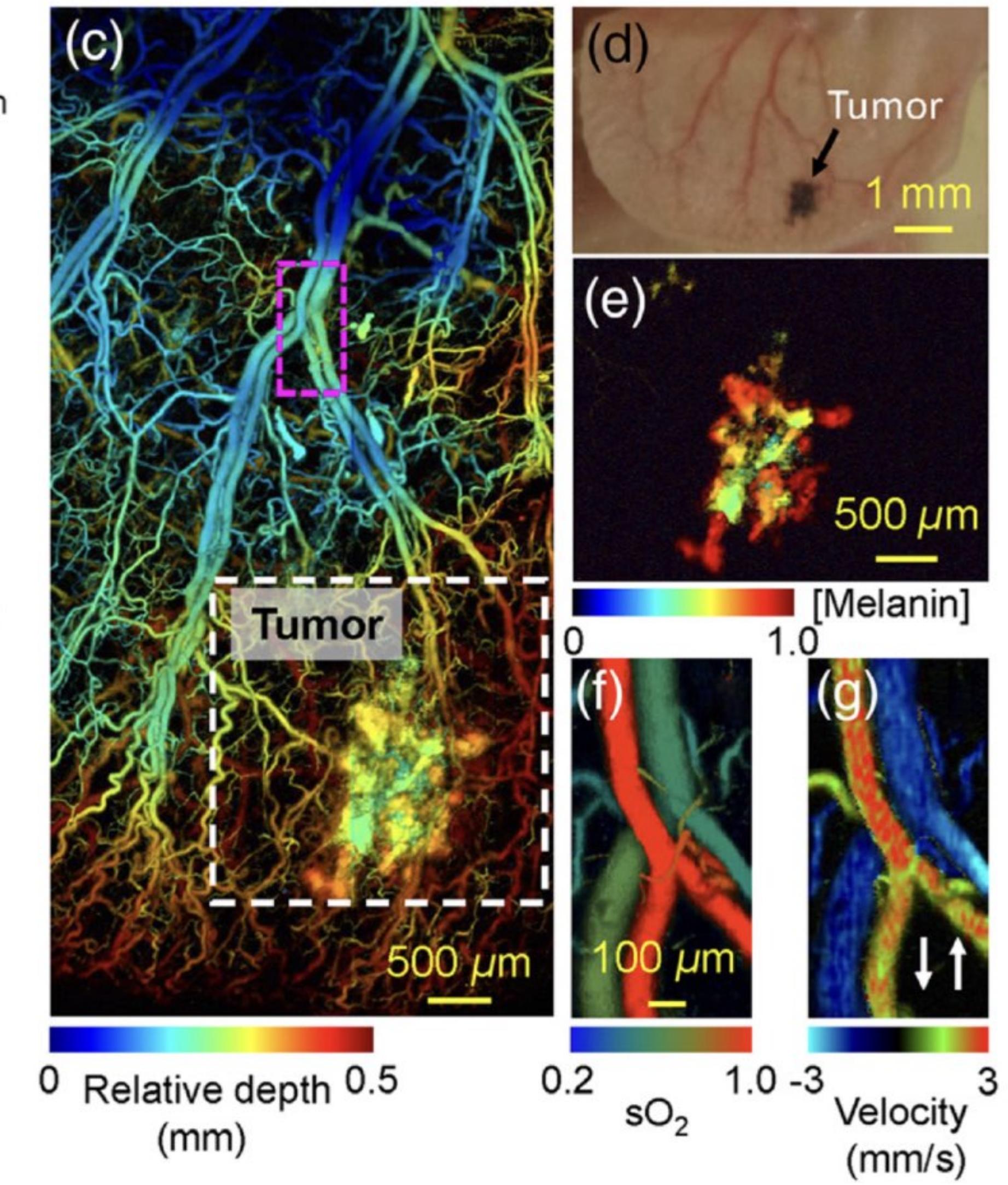
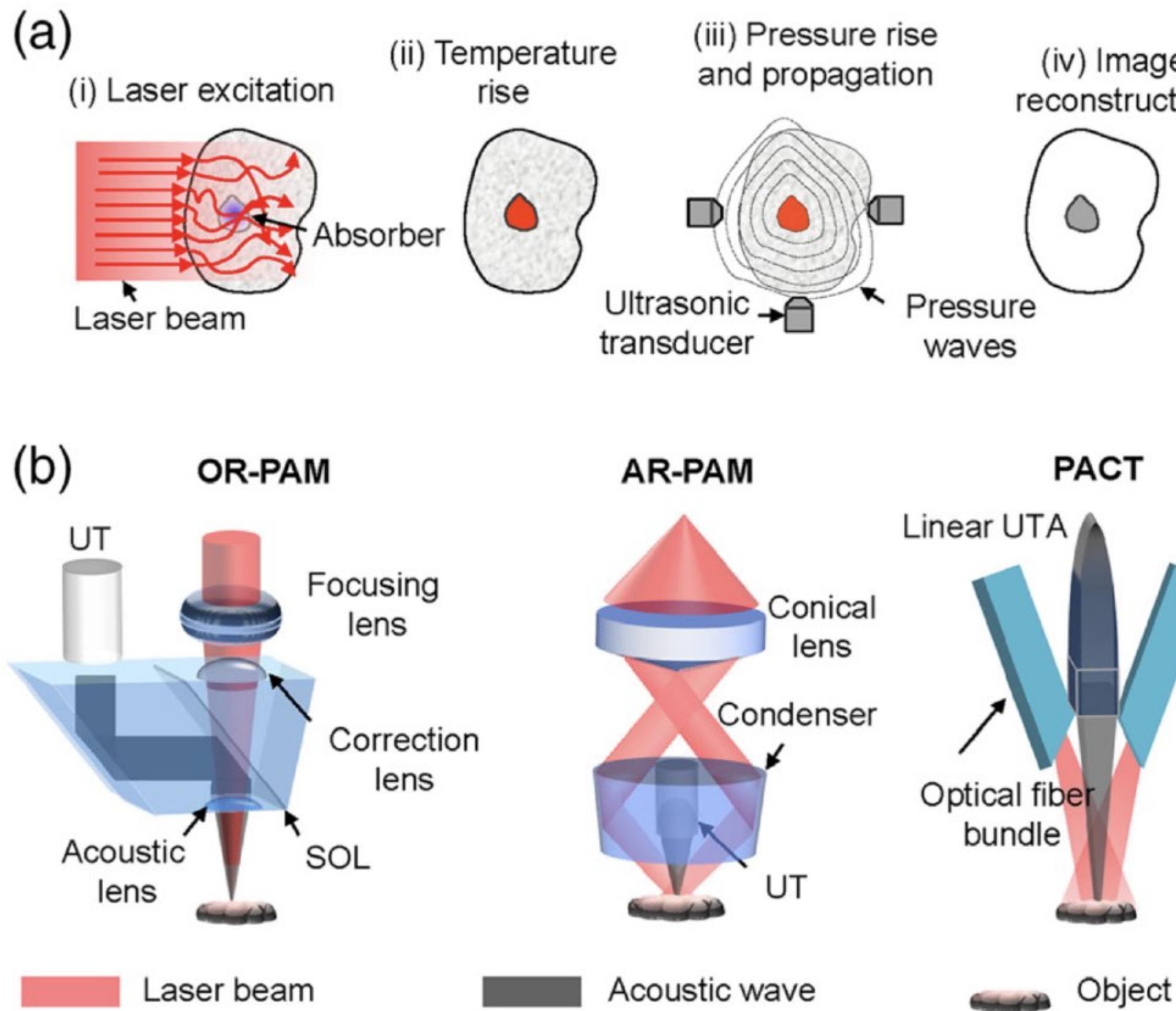
^{225}Ac -PSMA-617



CLI of α -emitters in the visible

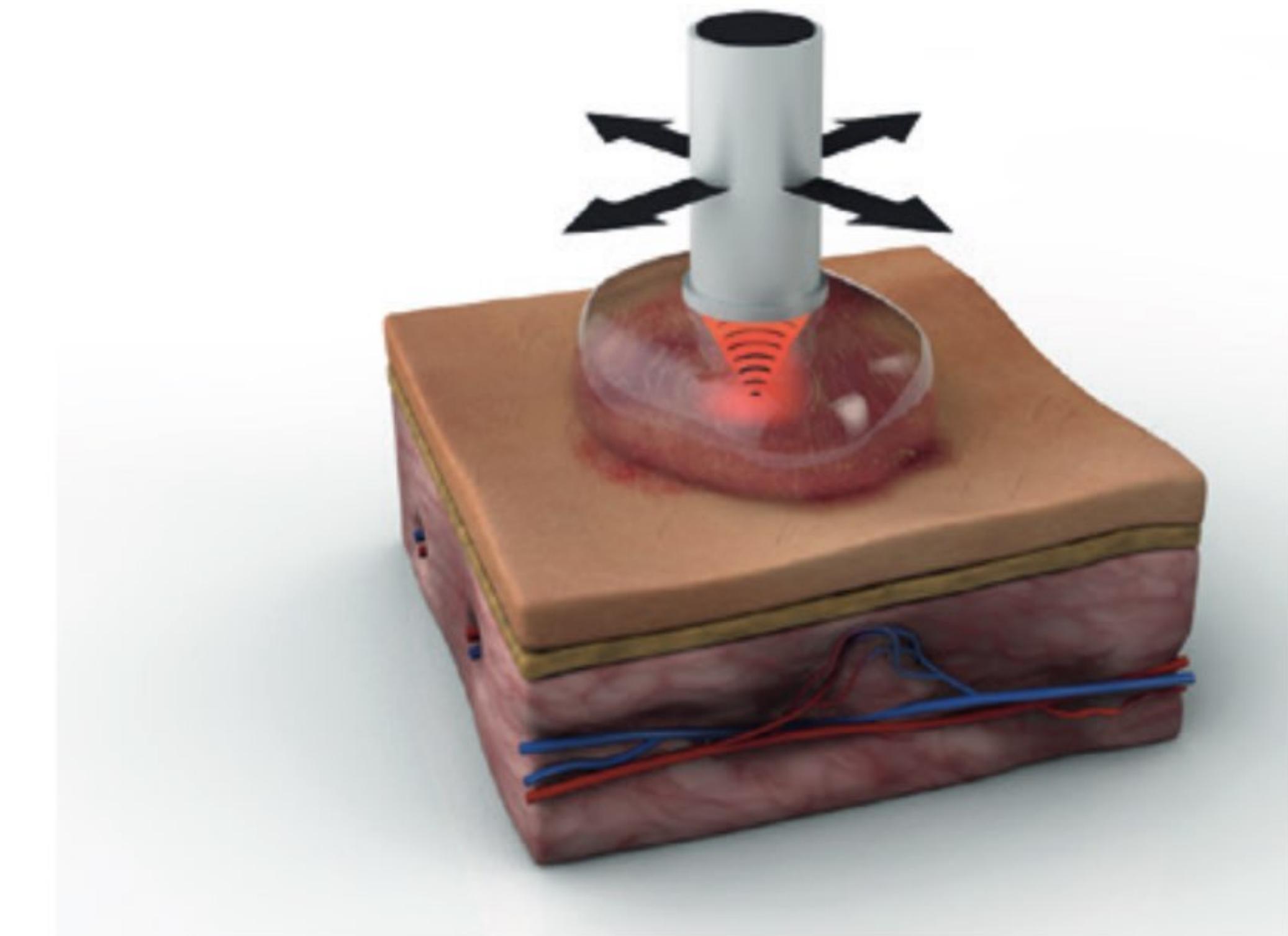
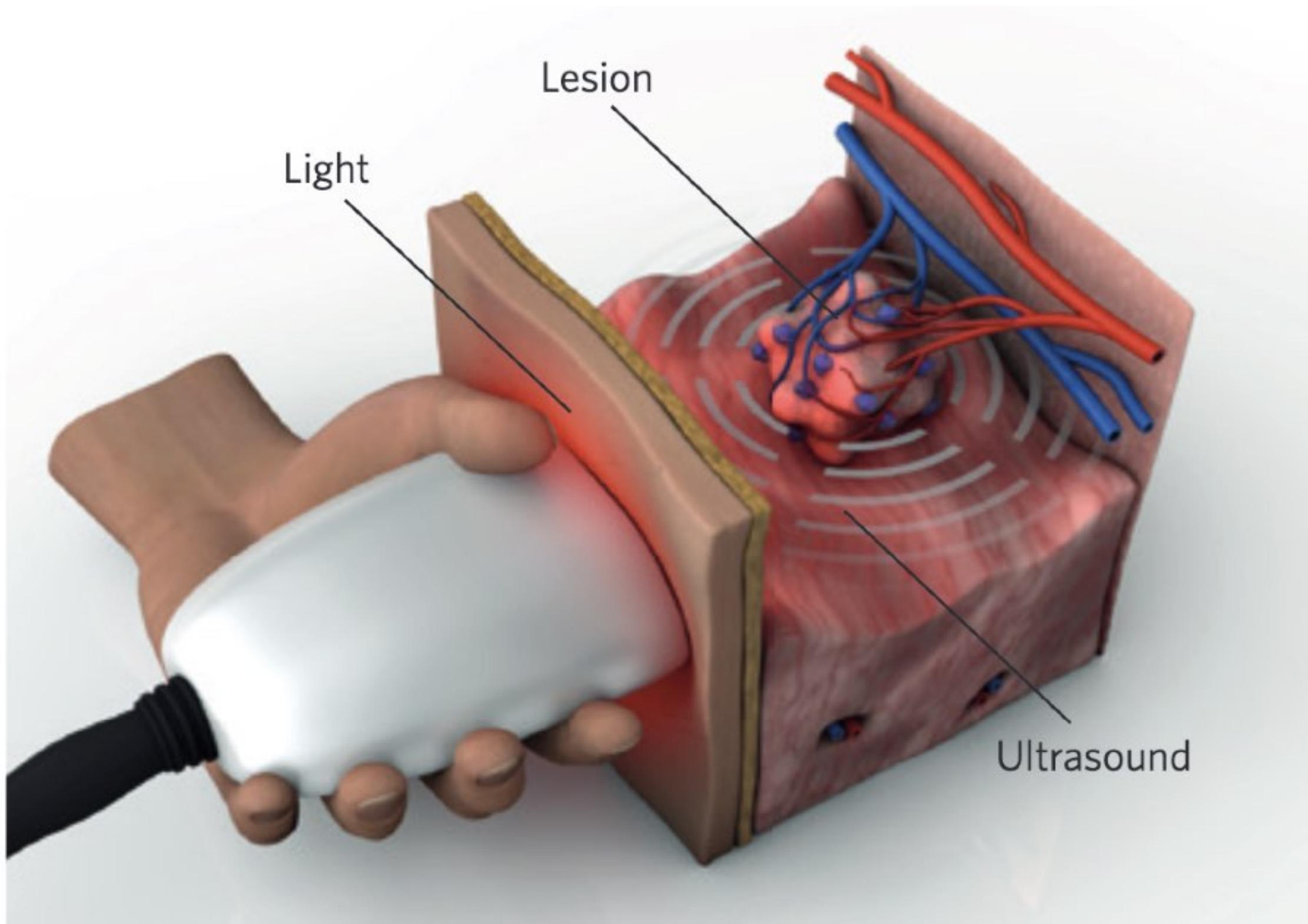


Listening to the light

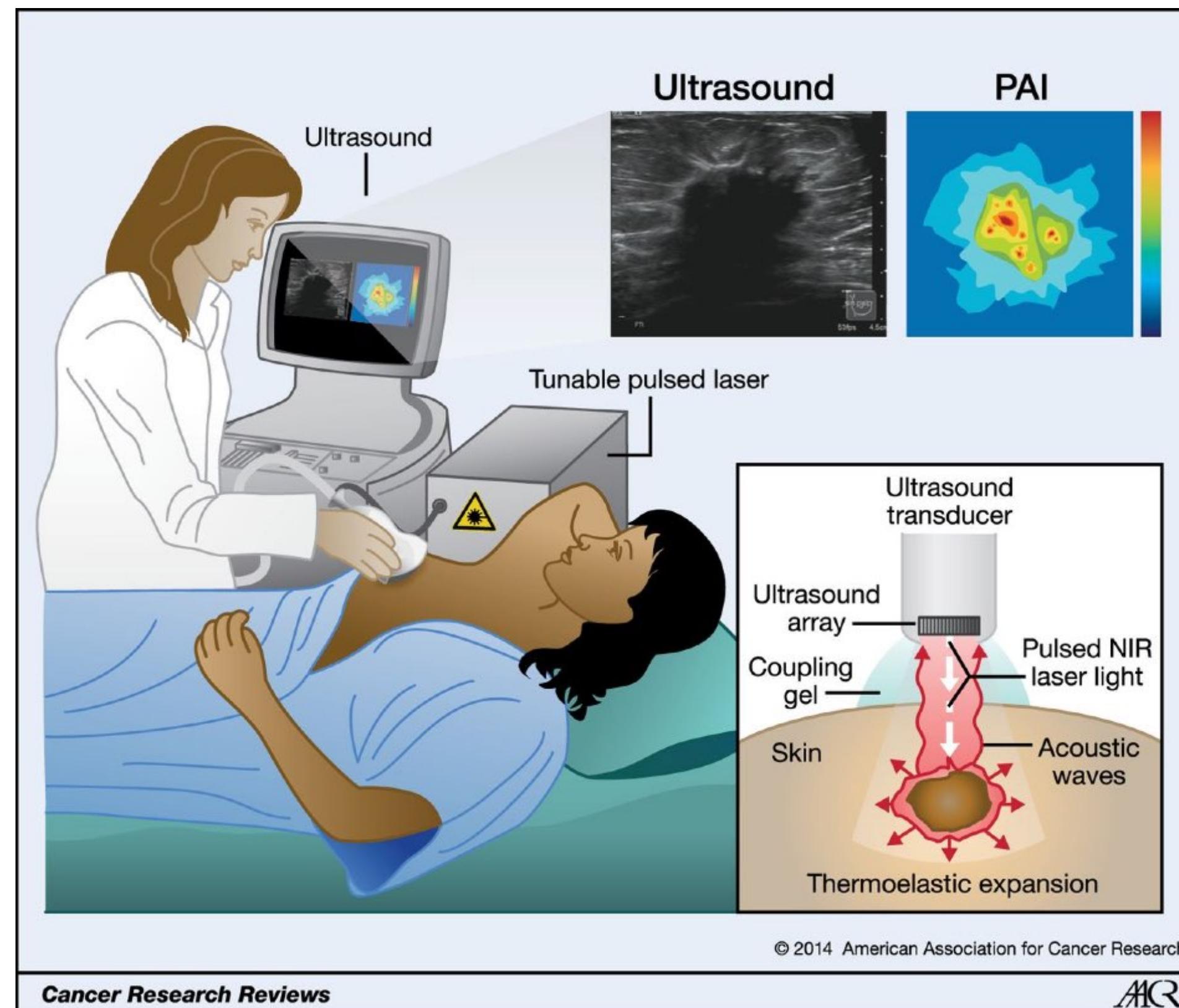


Optoacoustic Imaging

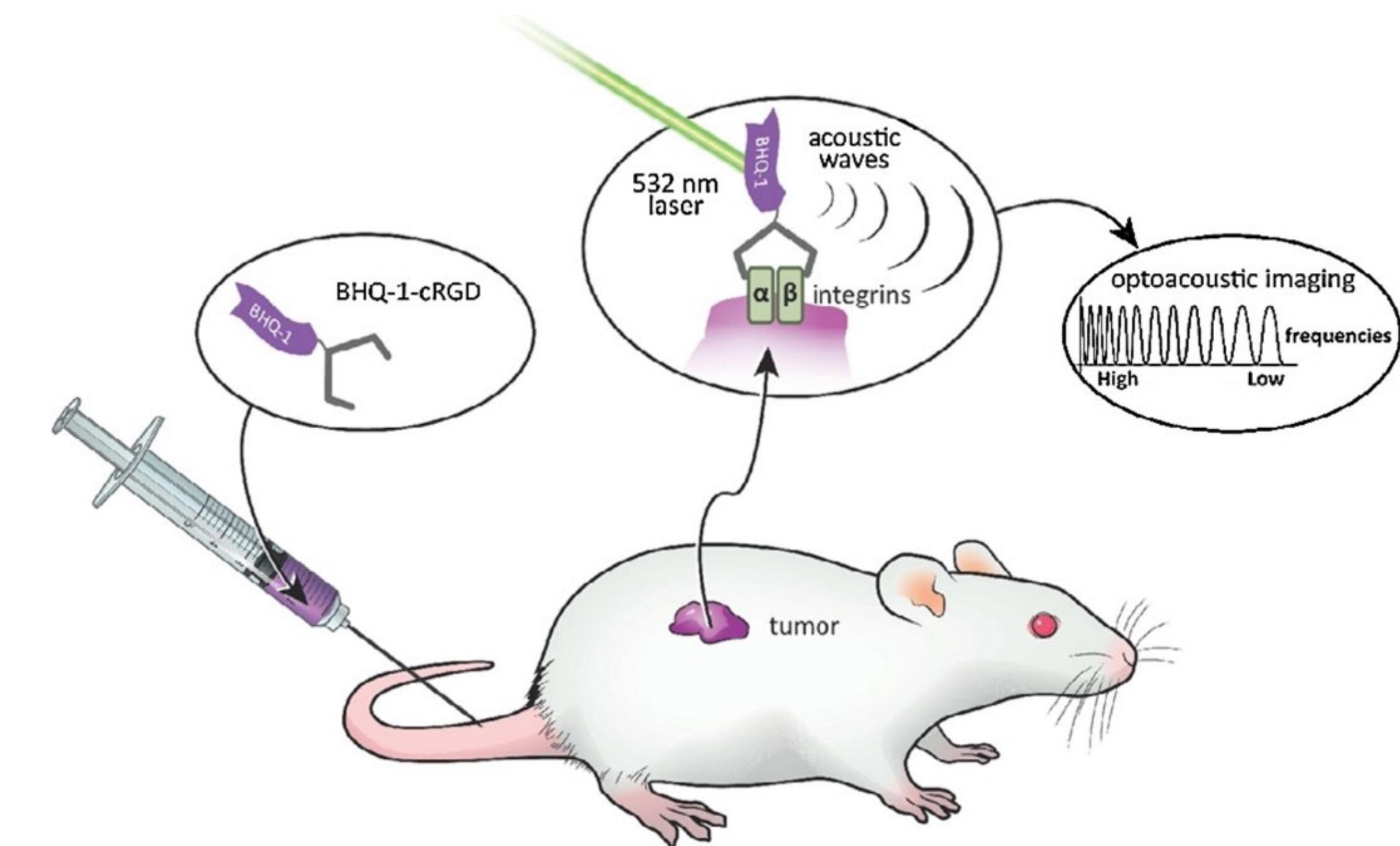
Light in and Sound out: Listening to the light



Optoacoustic Imaging



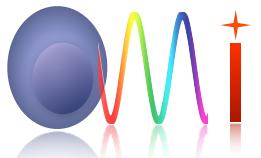
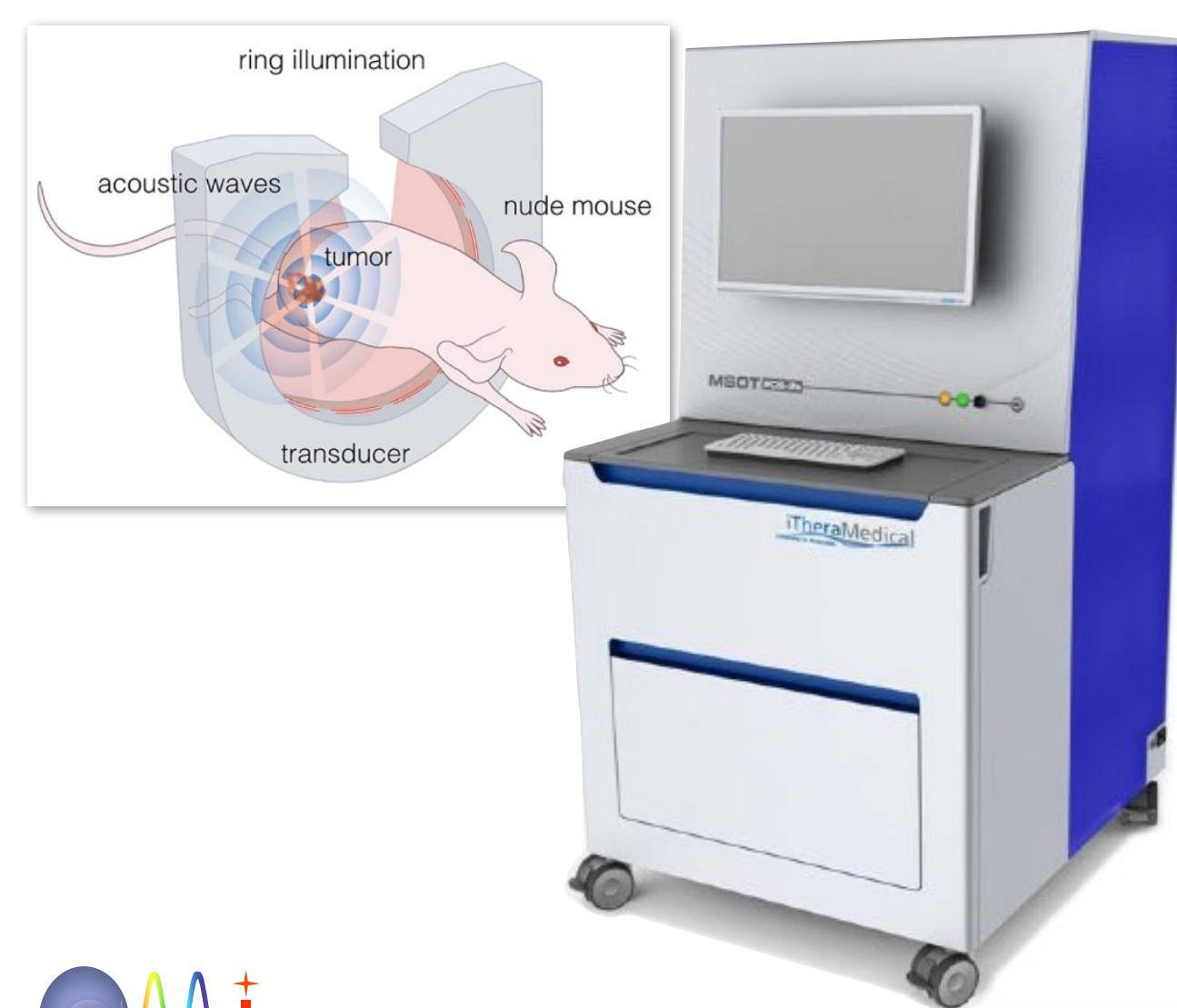
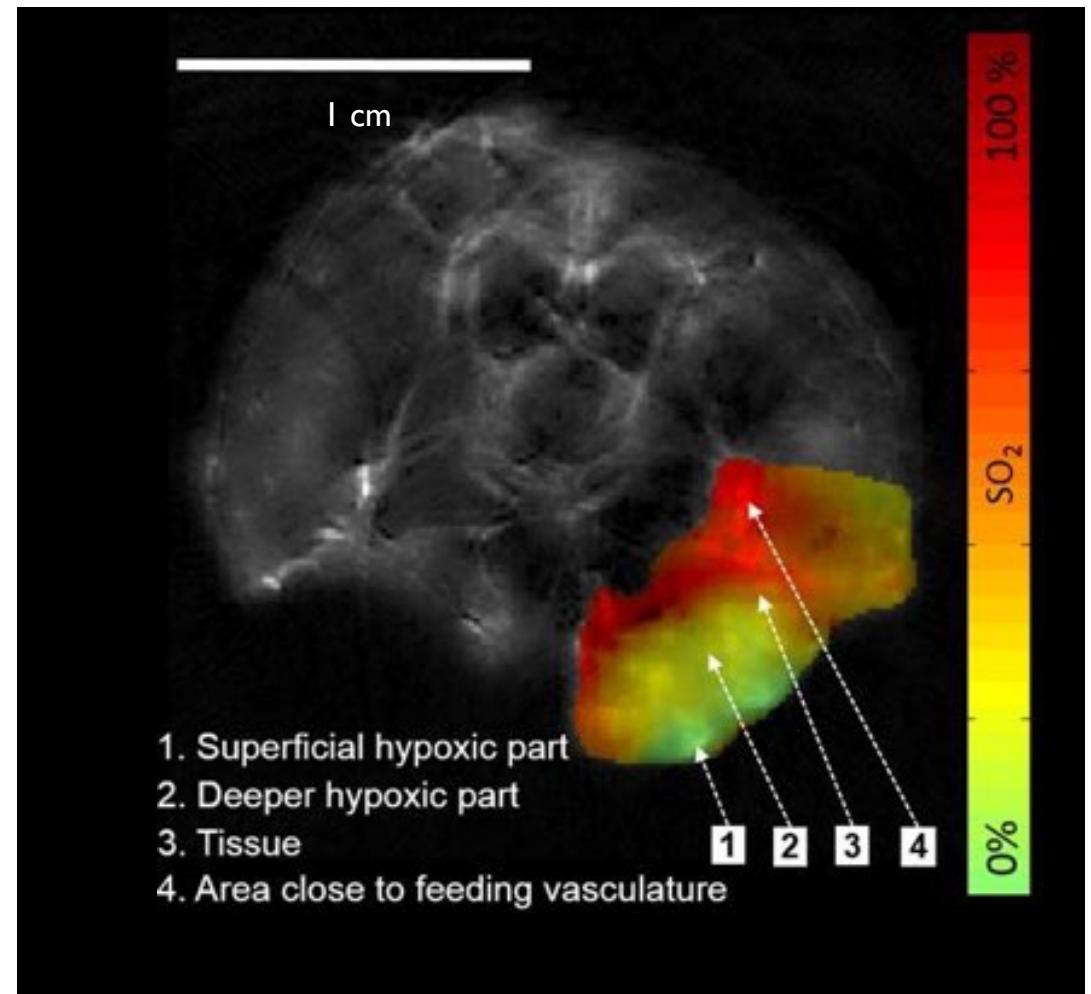
Zackrisson A et al. (2014) Cancer Research 74(4):979



Haedicke K et al. (2017) Photoacoustics 17(6):1

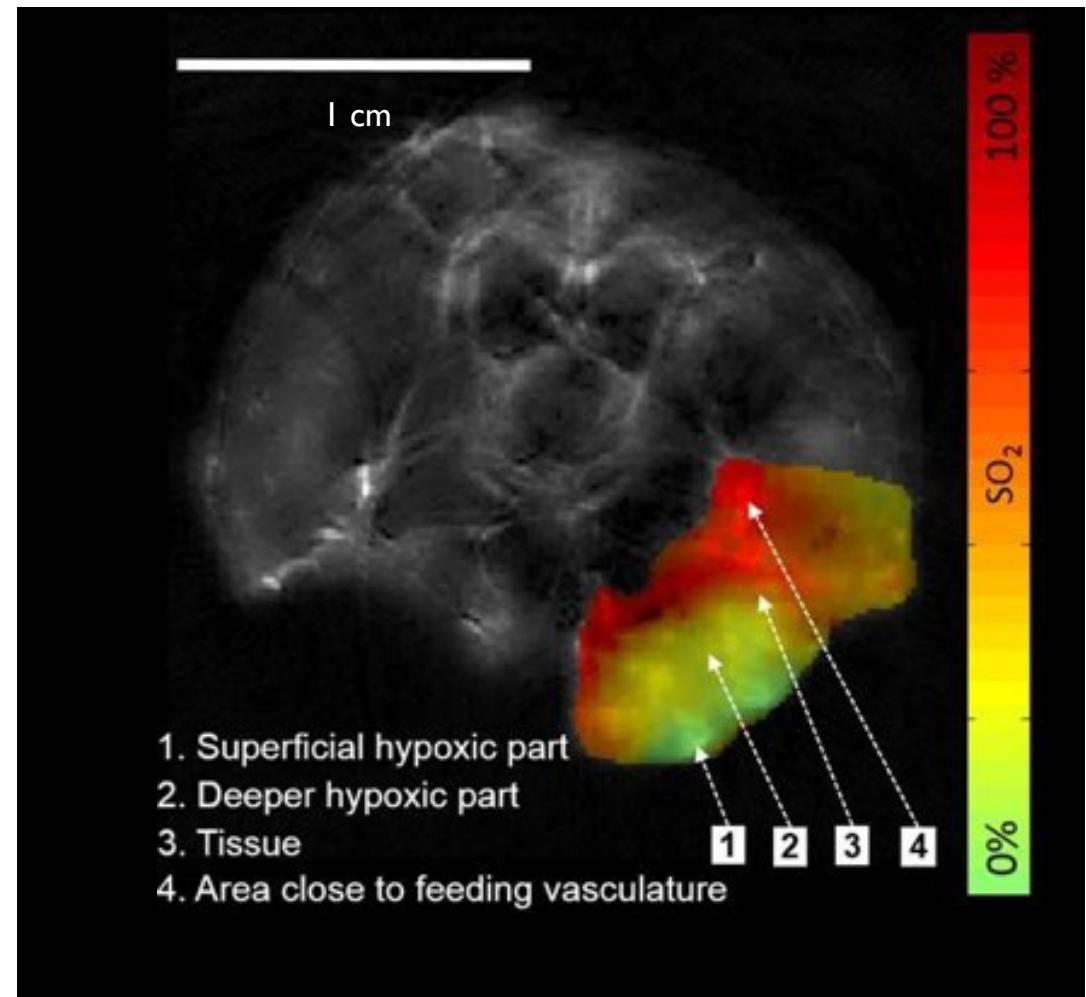
From macro to micro

MSOT: mm resolution

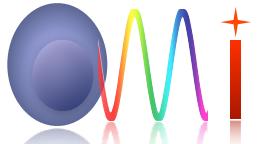
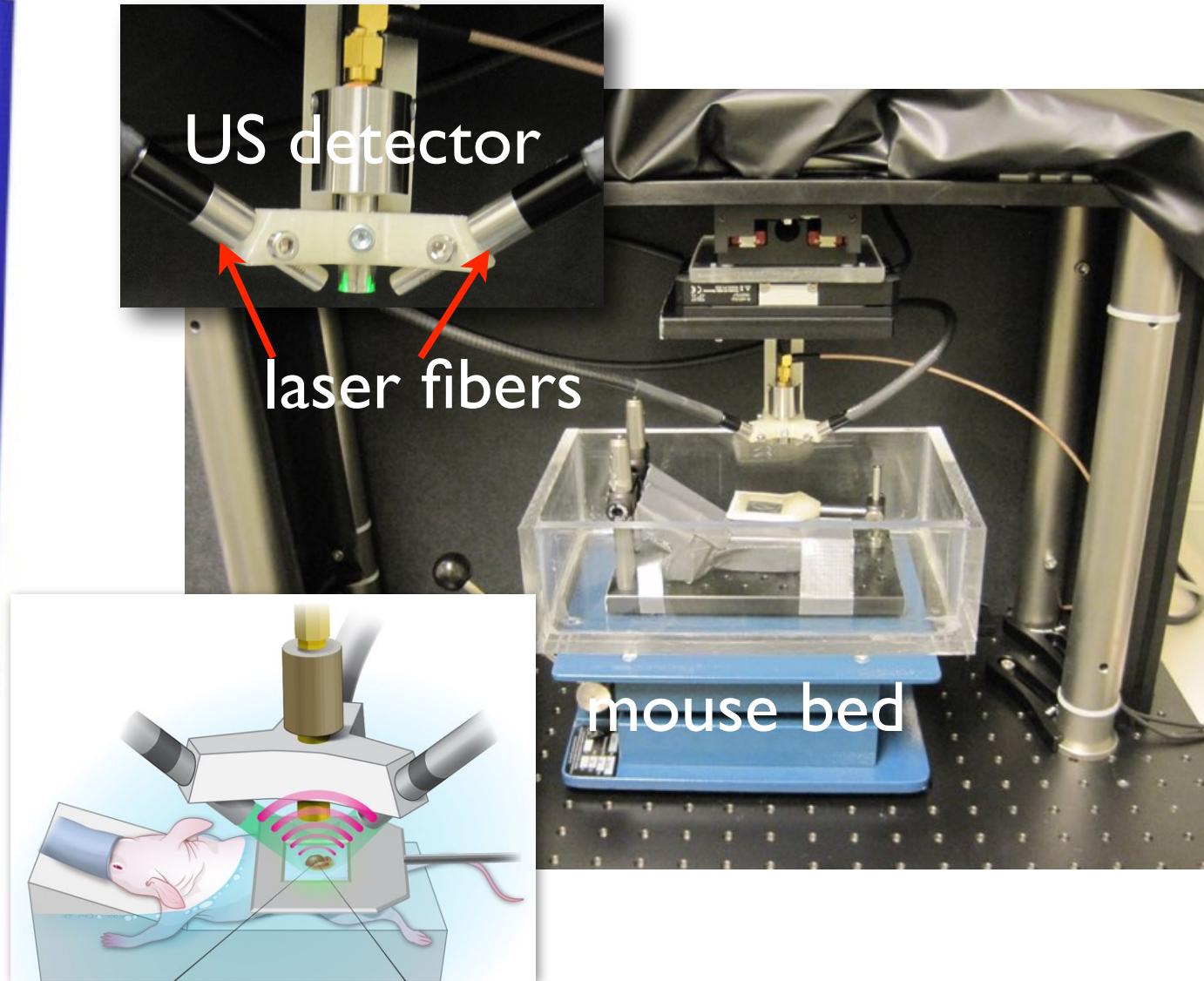
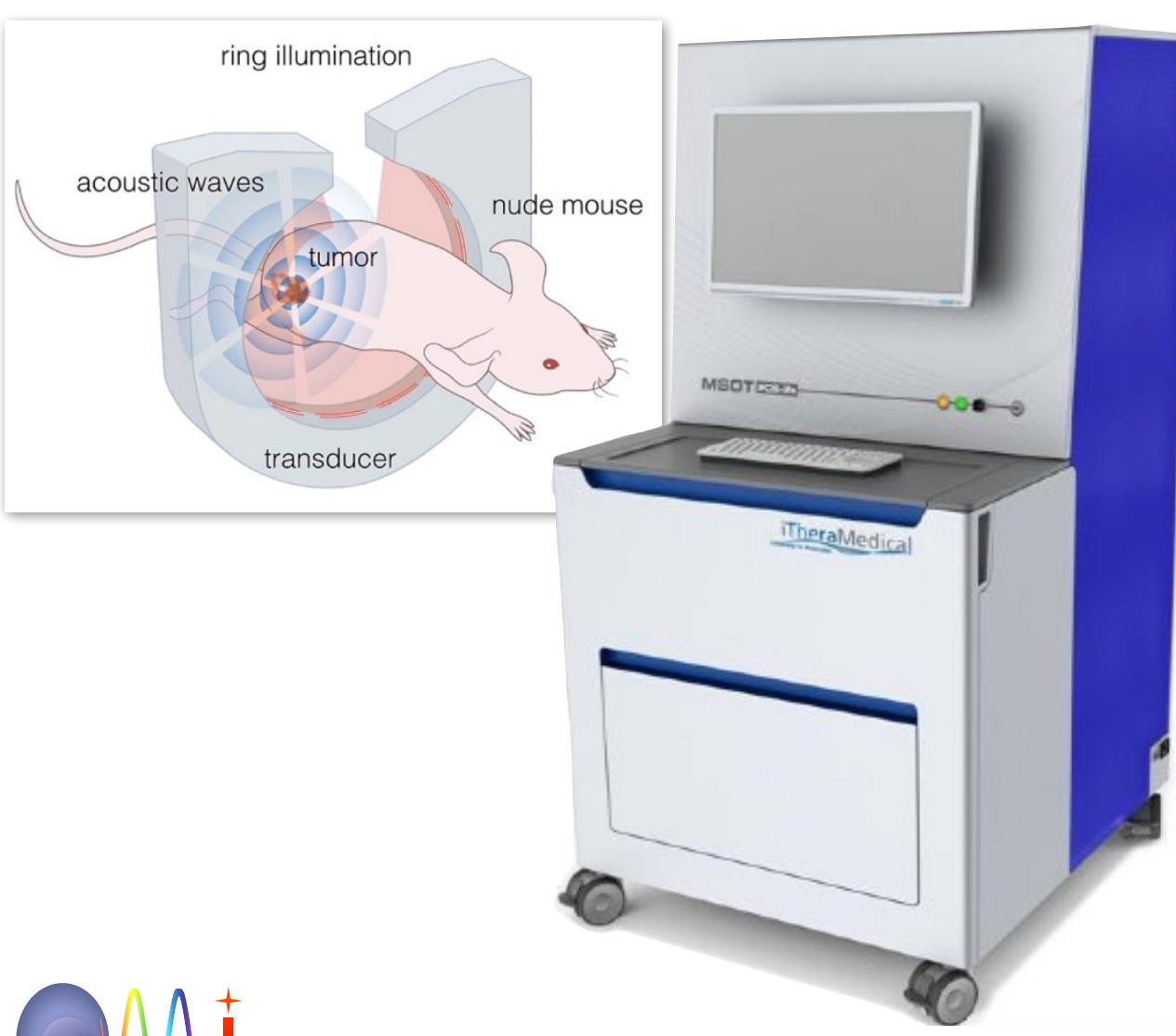
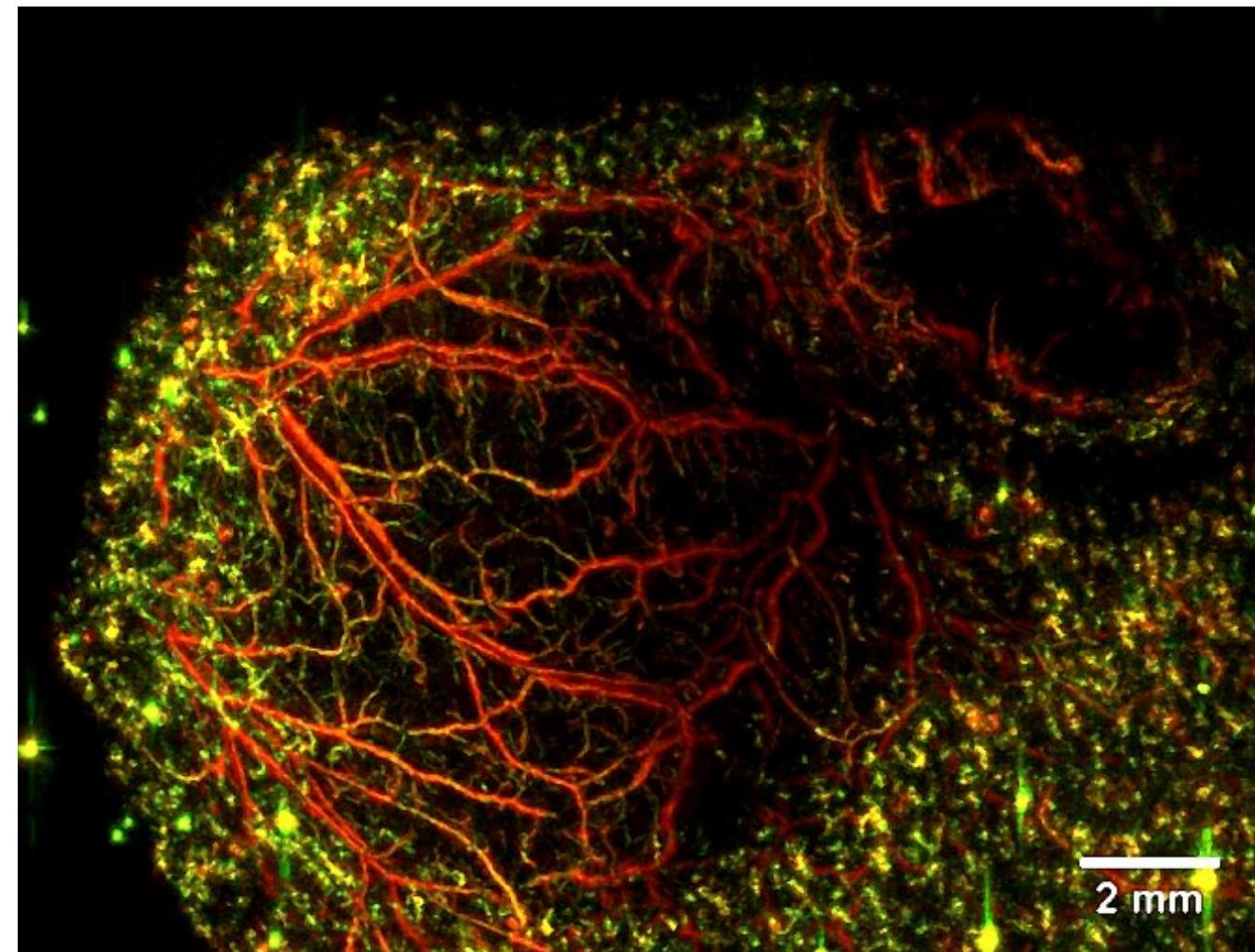


From macro to micro

MSOT: mm resolution

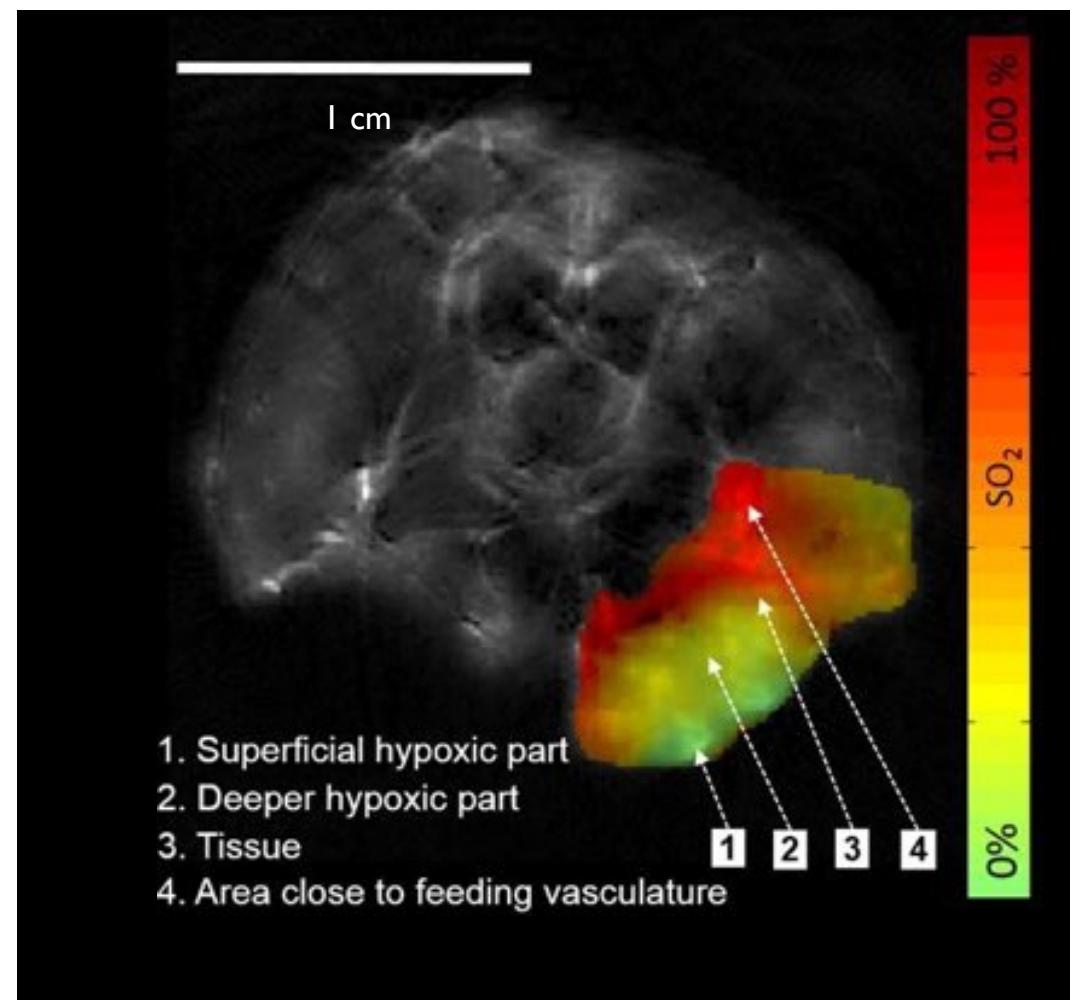


RSOM: μm resolution

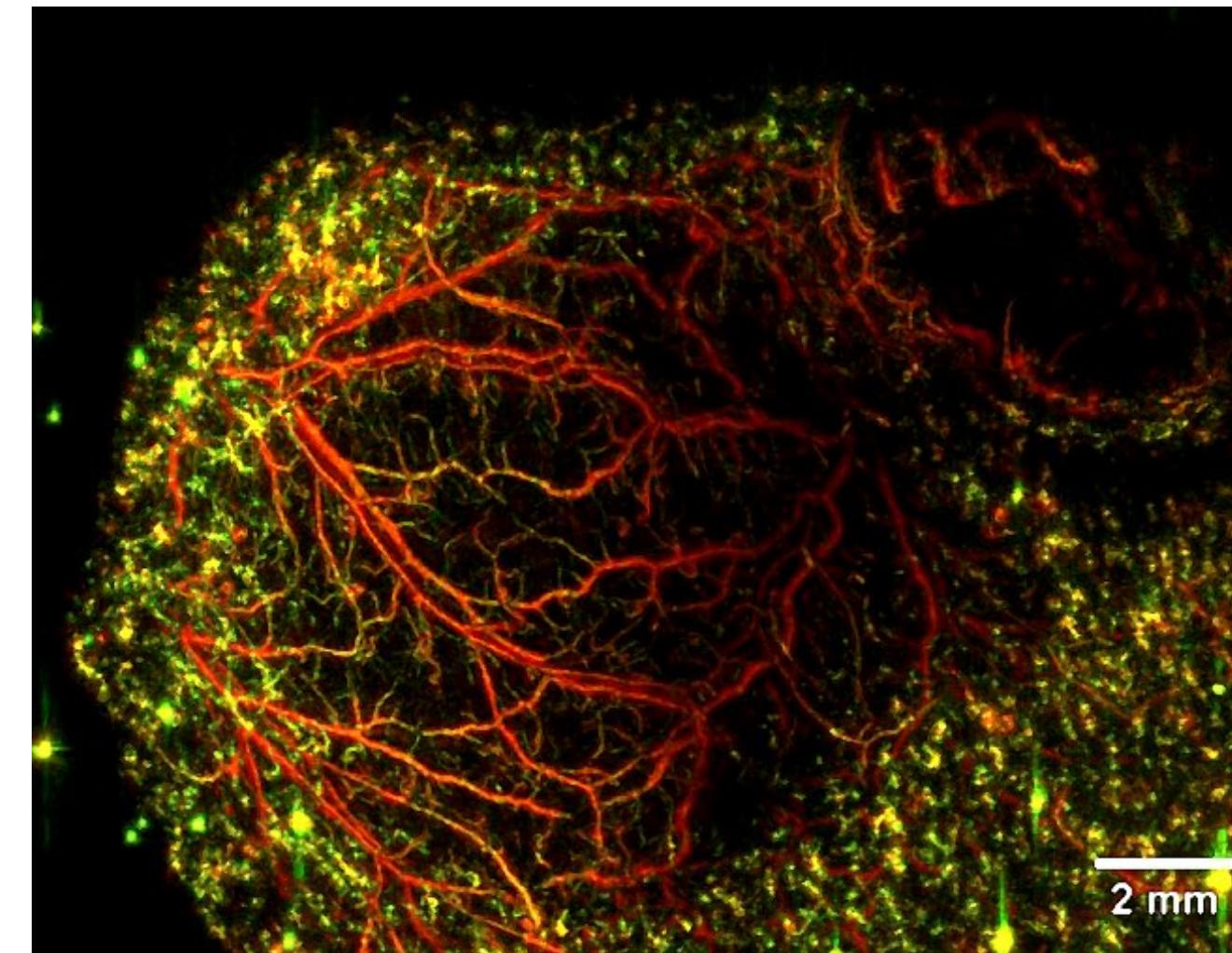


From macro to micro

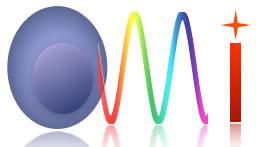
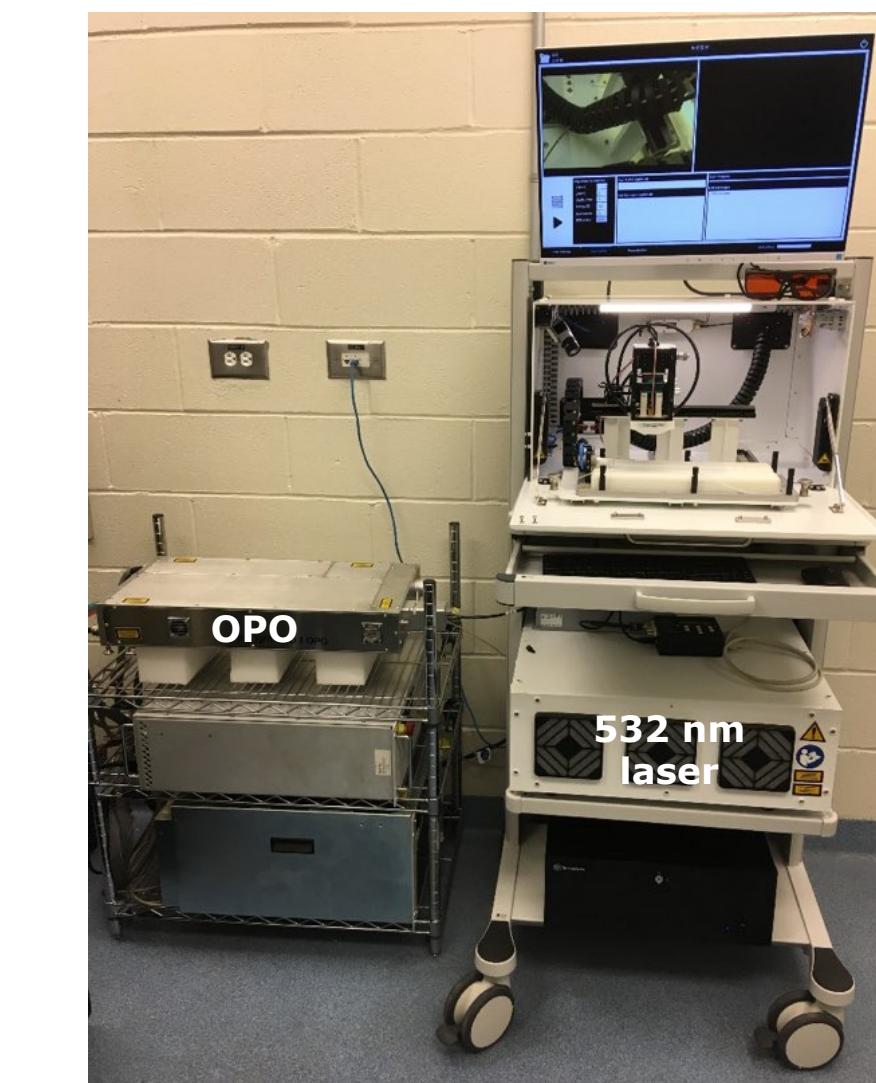
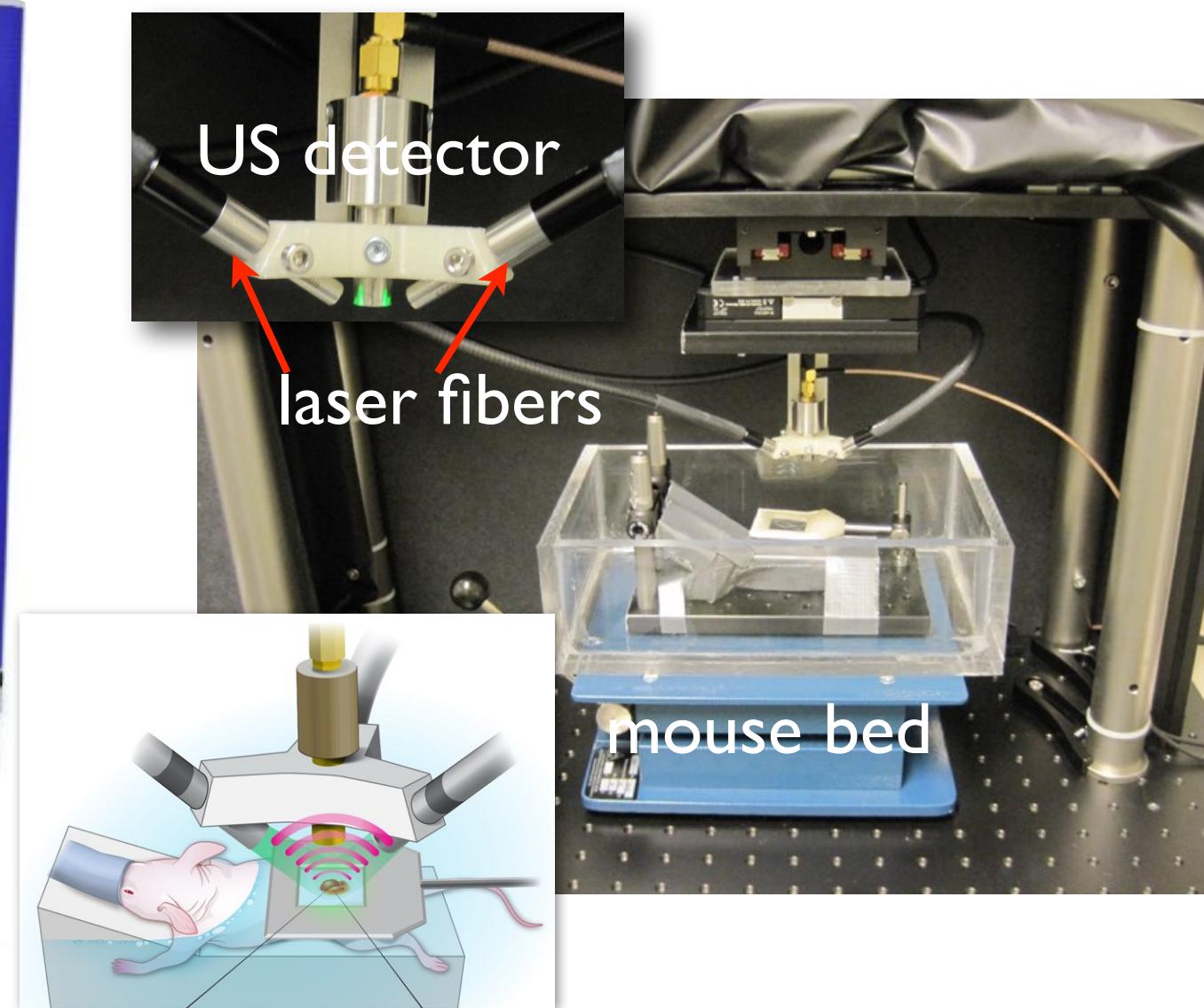
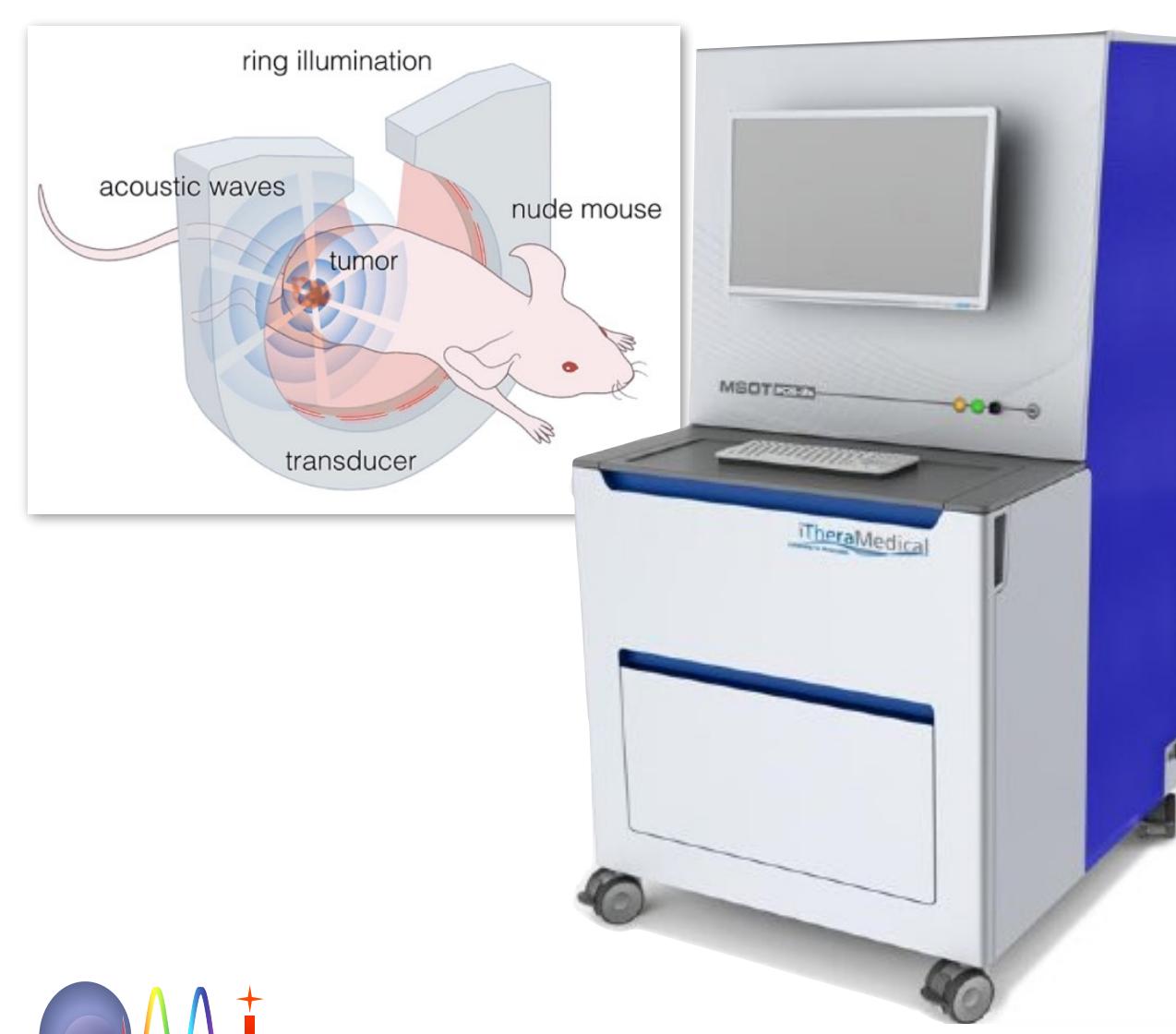
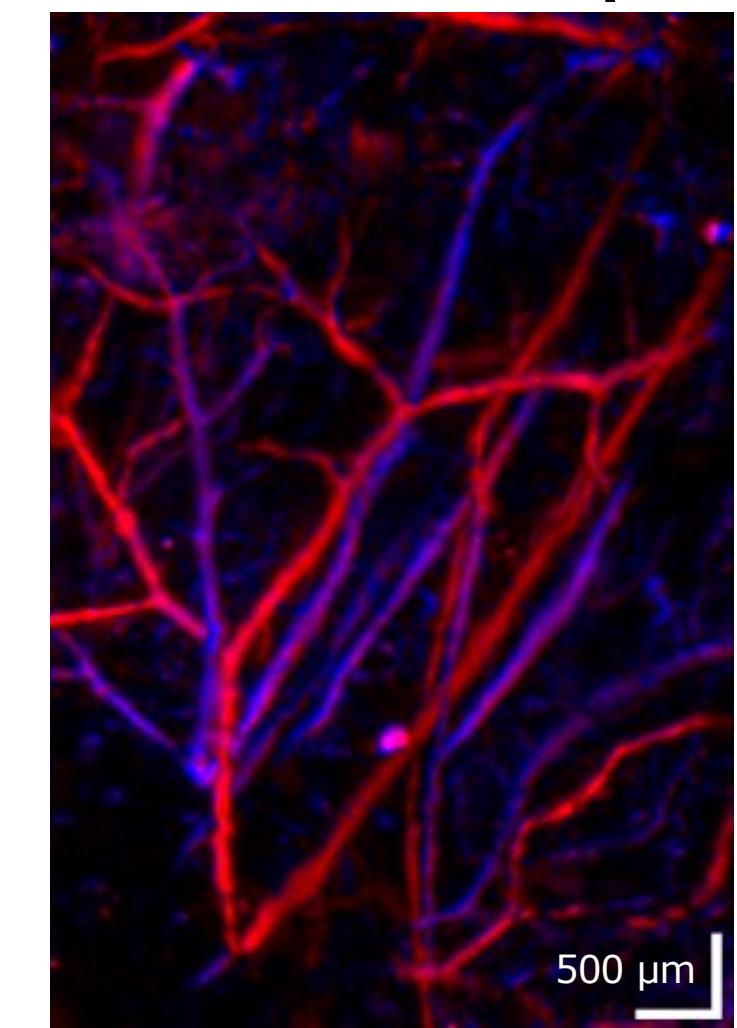
MSOT: mm resolution



RSOM: μm resolution

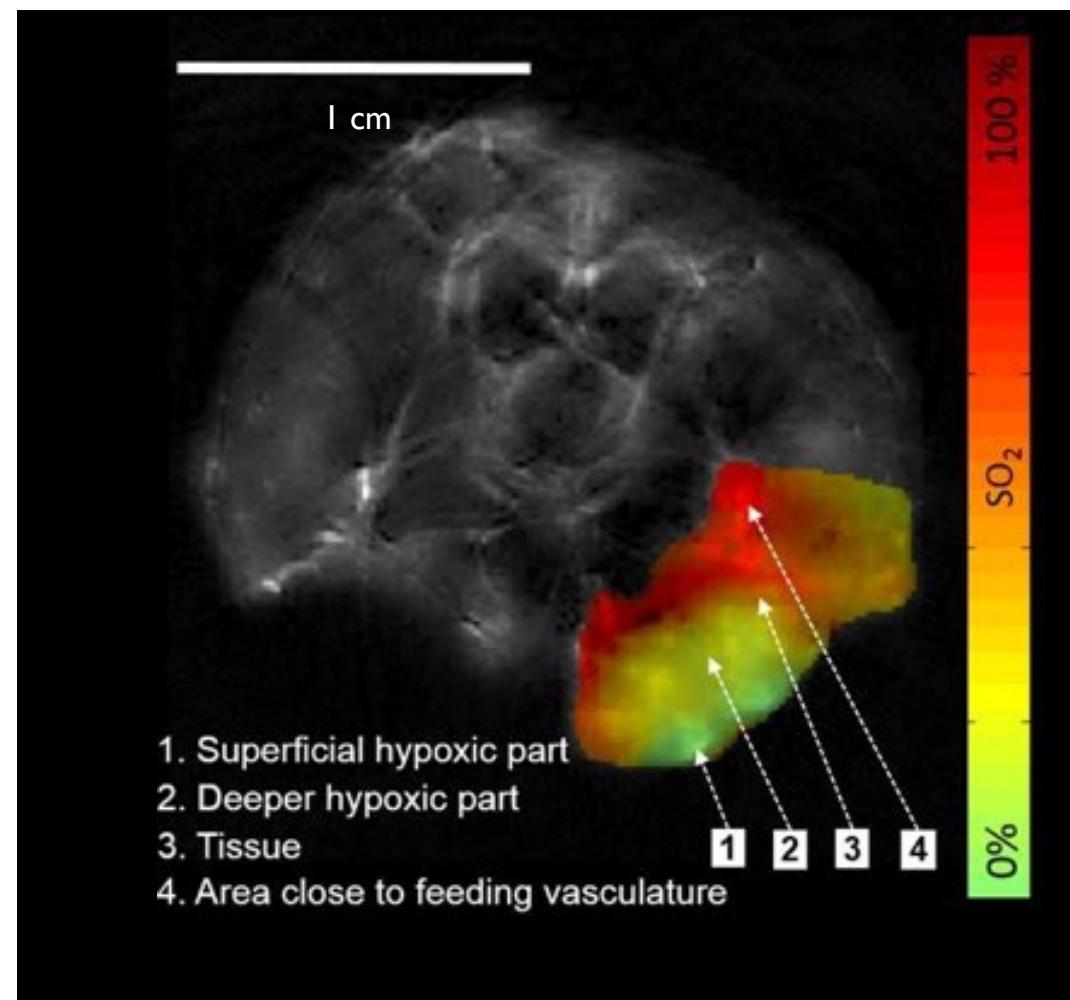


mRSOM: multispectral

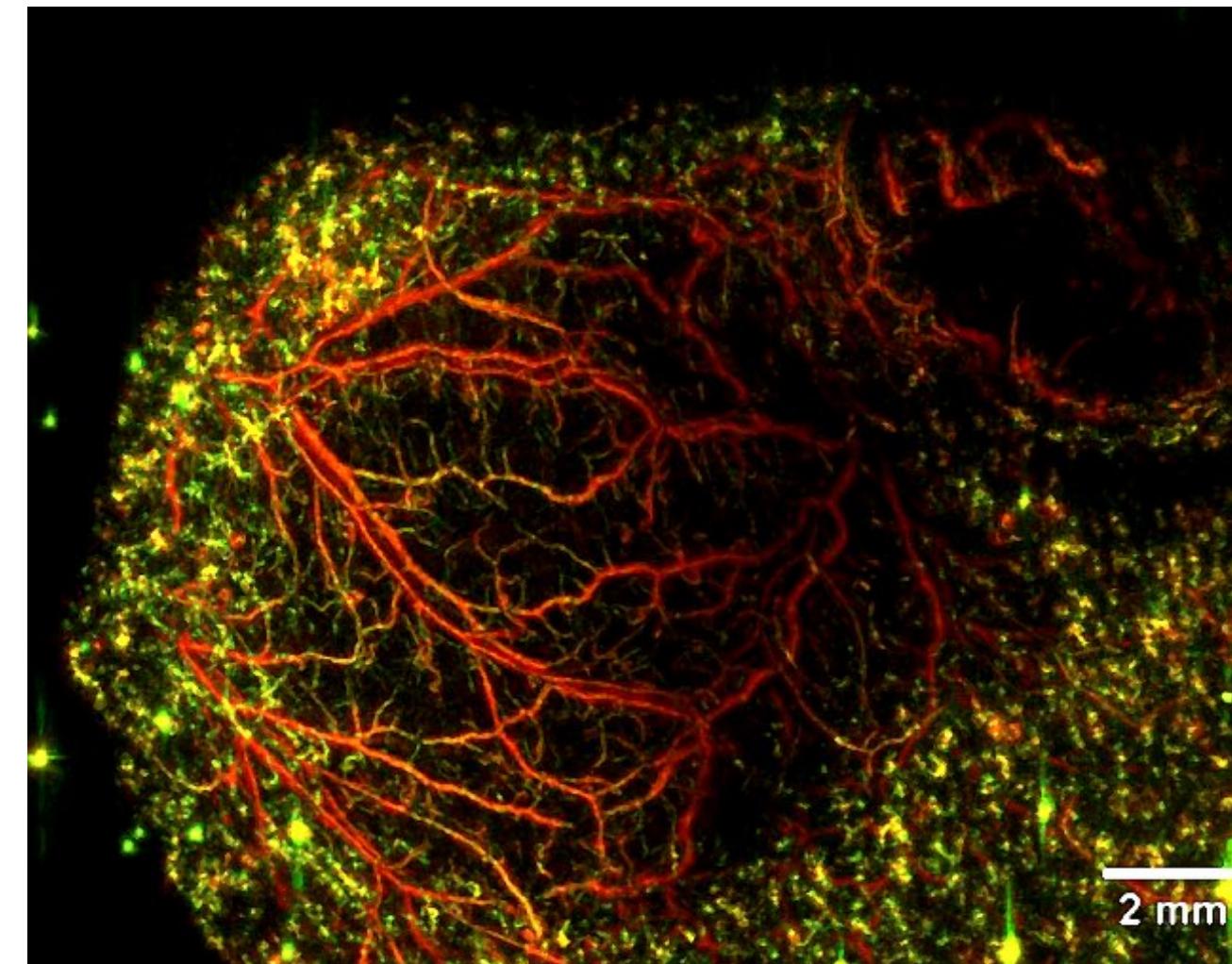


From macro to micro

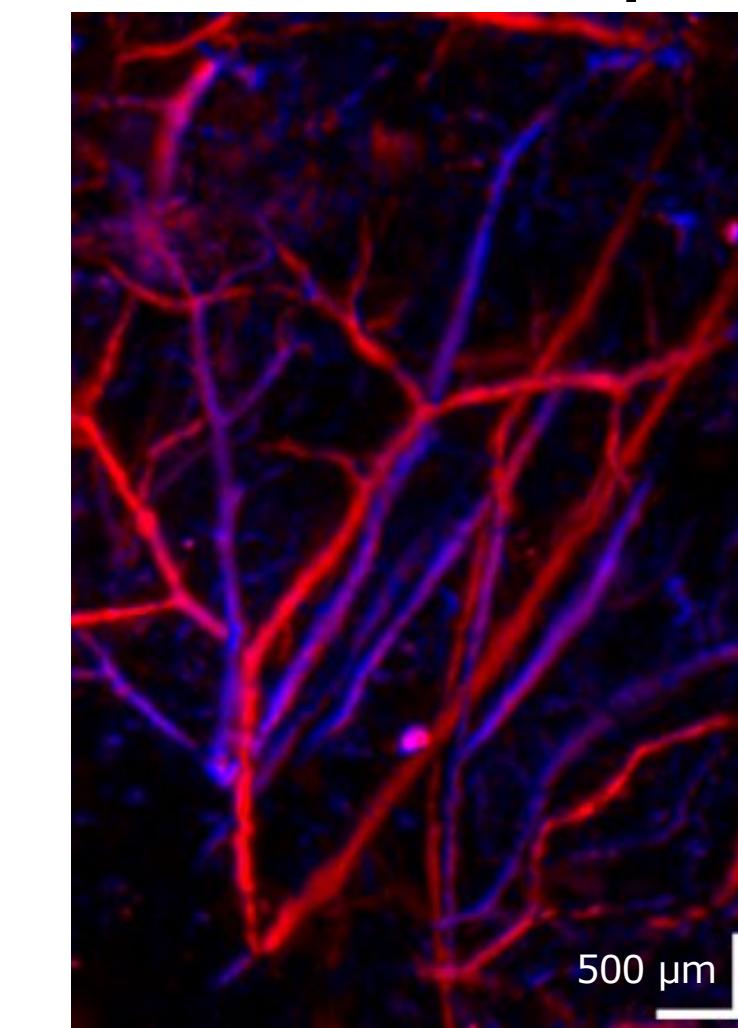
MSOT: mm resolution



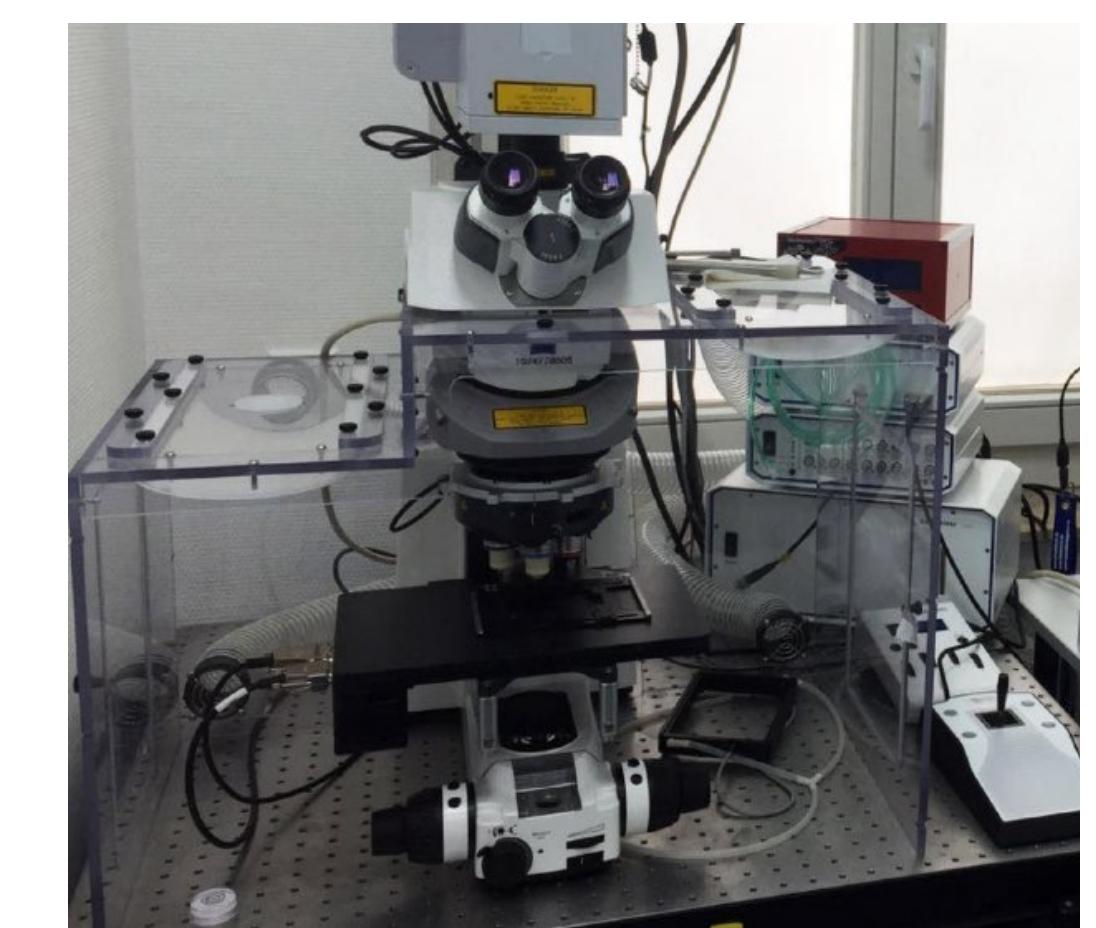
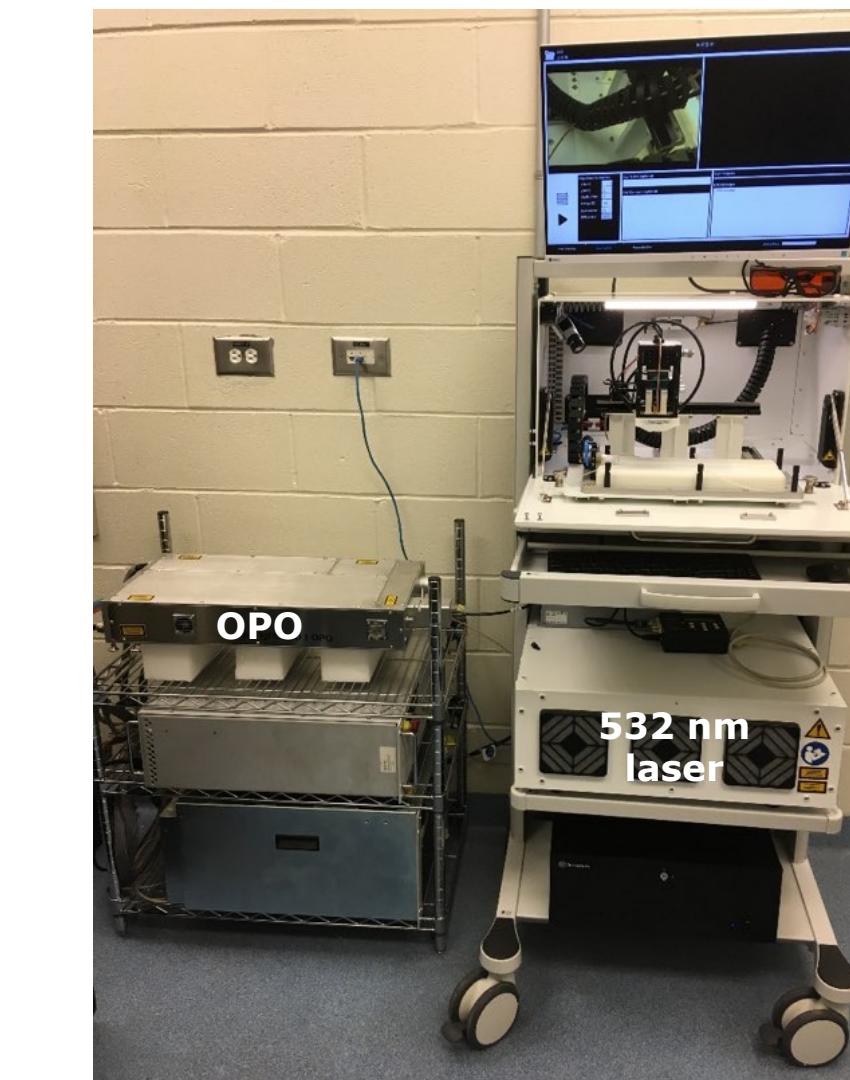
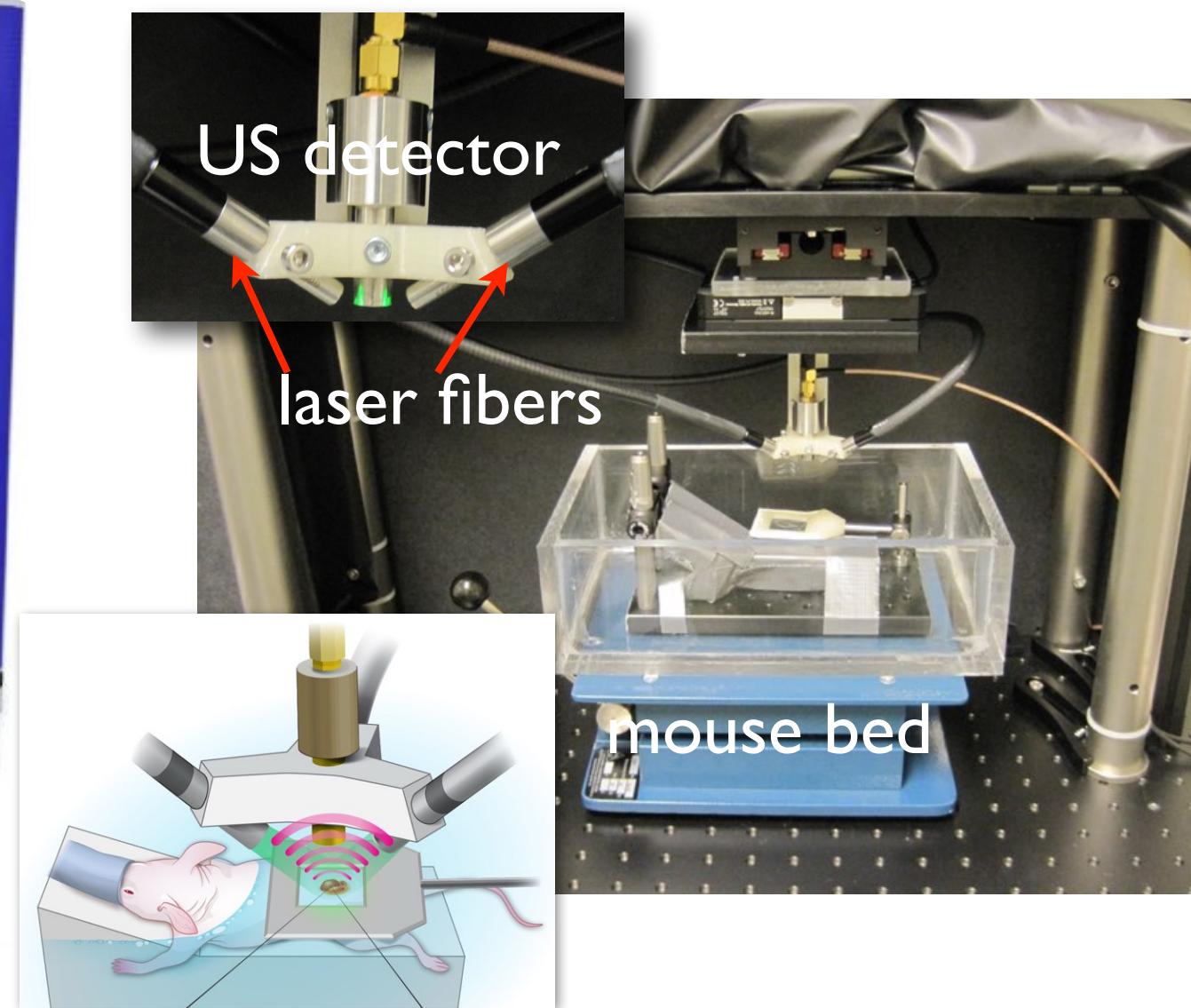
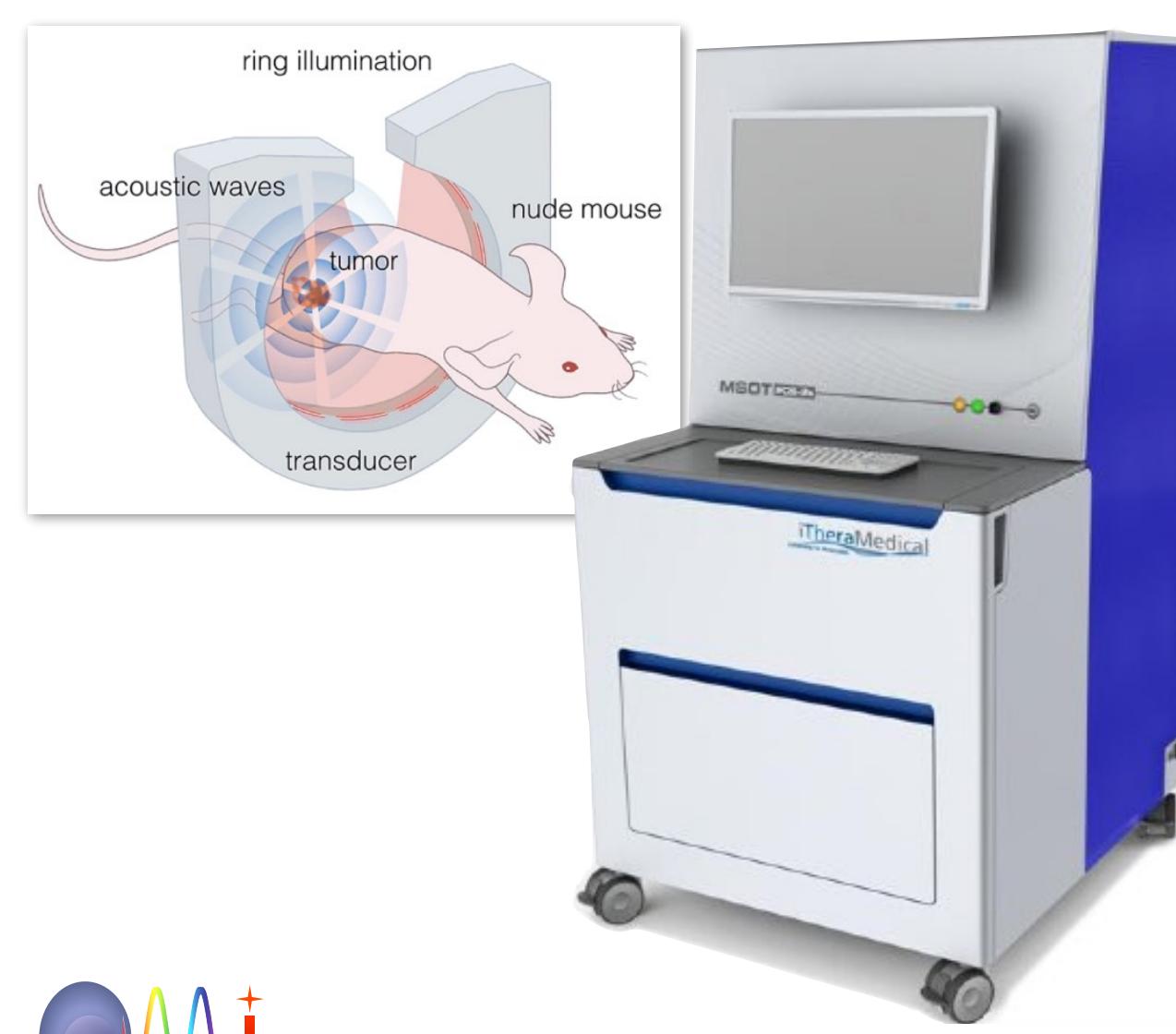
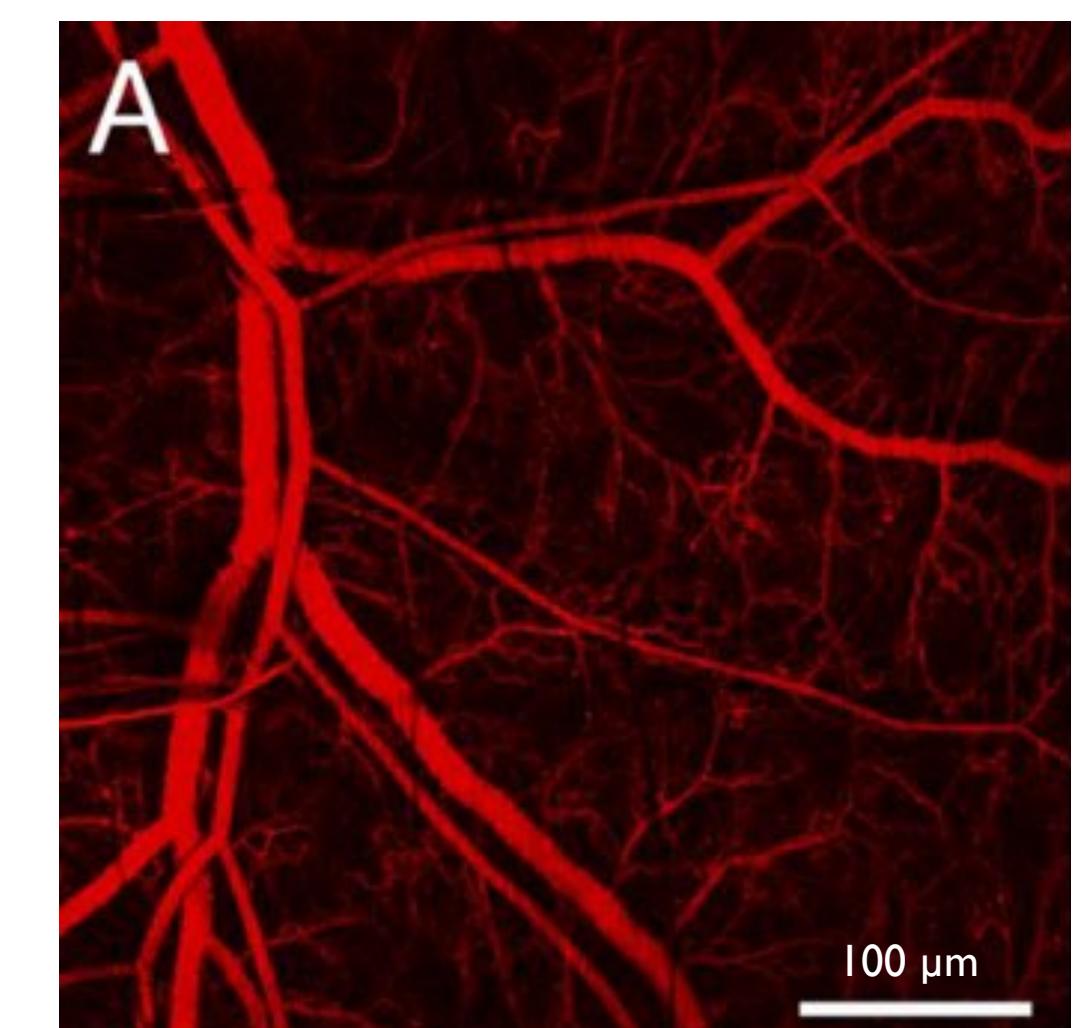
RSOM: μm resolution



mRSOM: multispectral



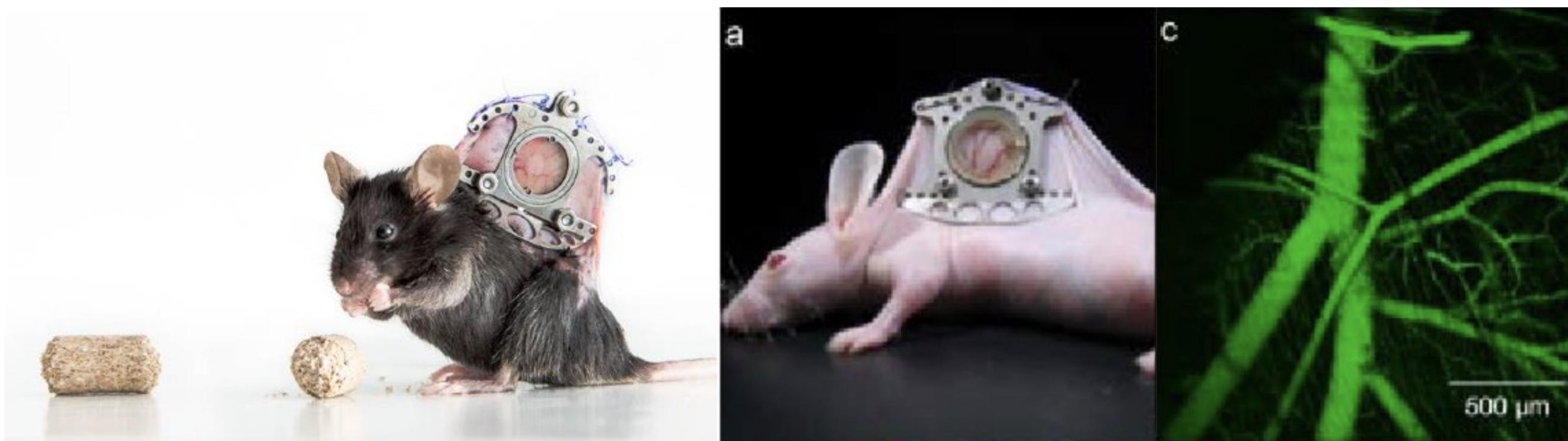
Intravital microscopy



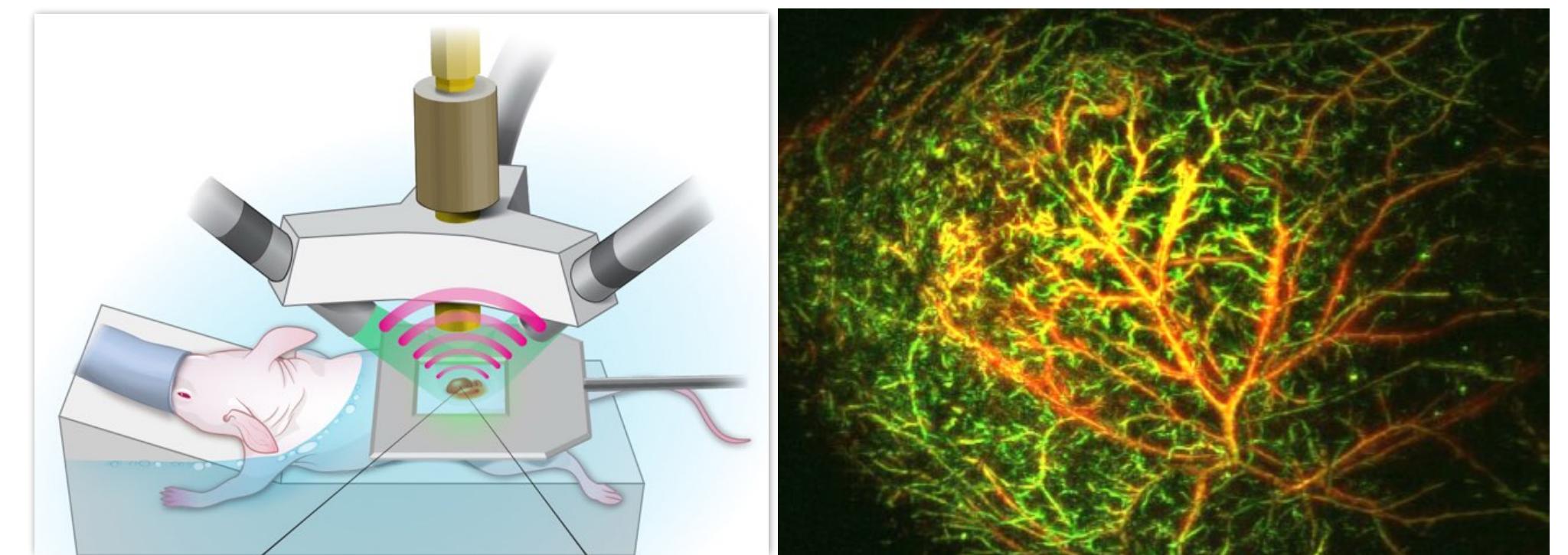
Weigert et al (2013) JCB 201(7):969 / Uni Münster

Skin chamber vs. RSOM

Intravital microscopy



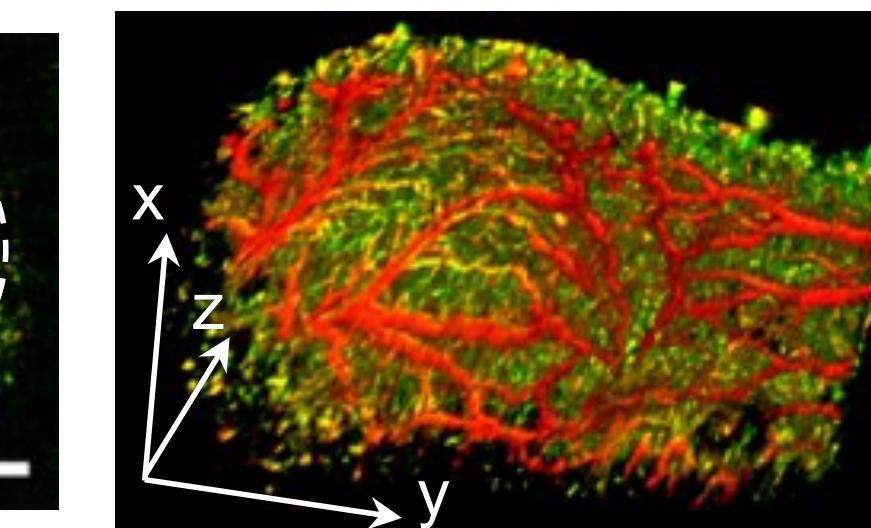
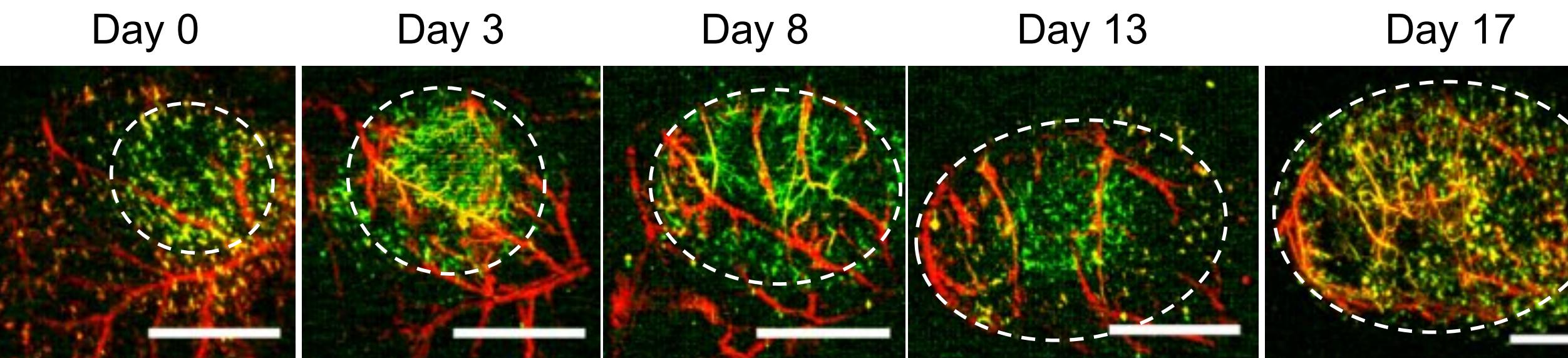
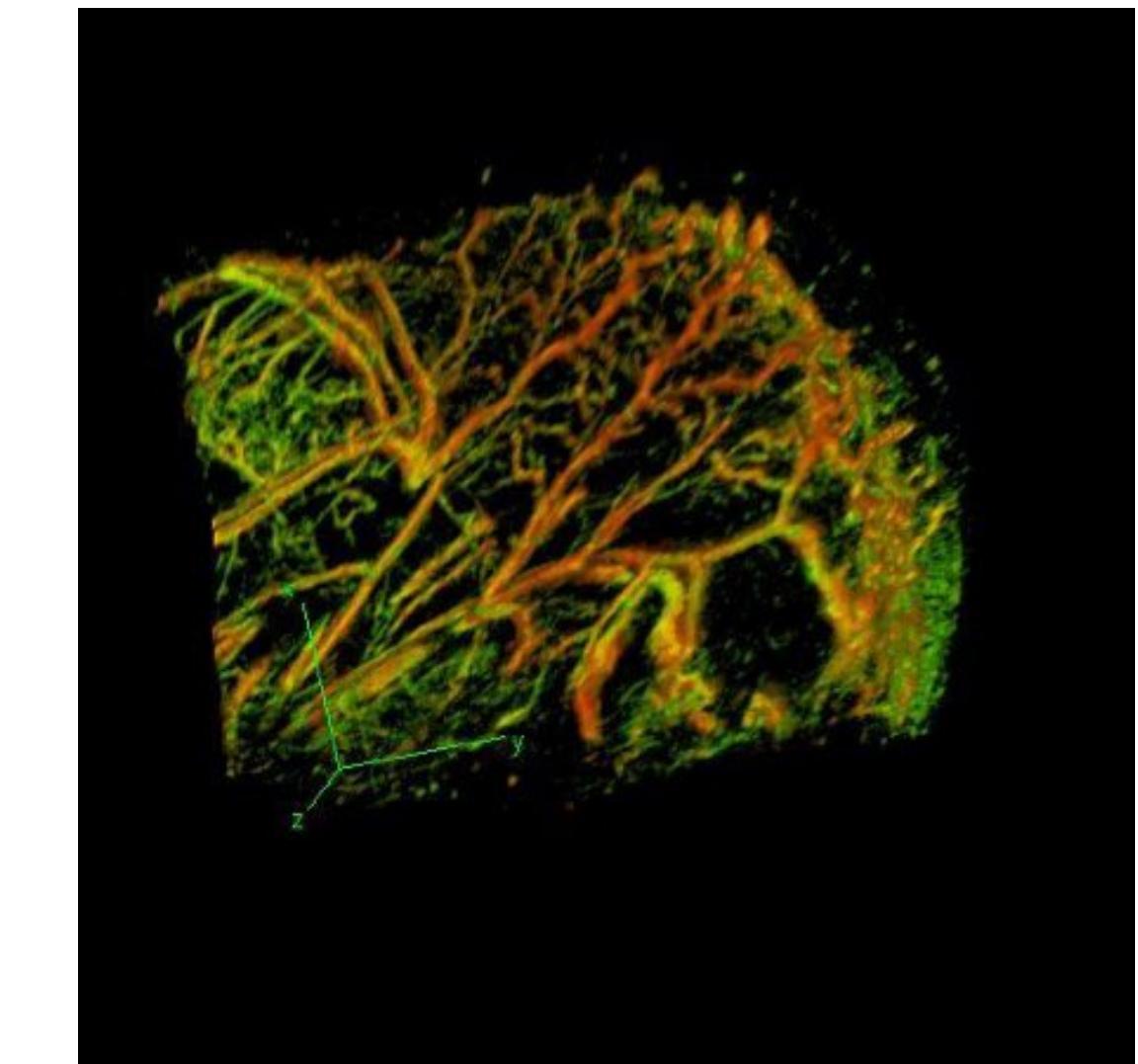
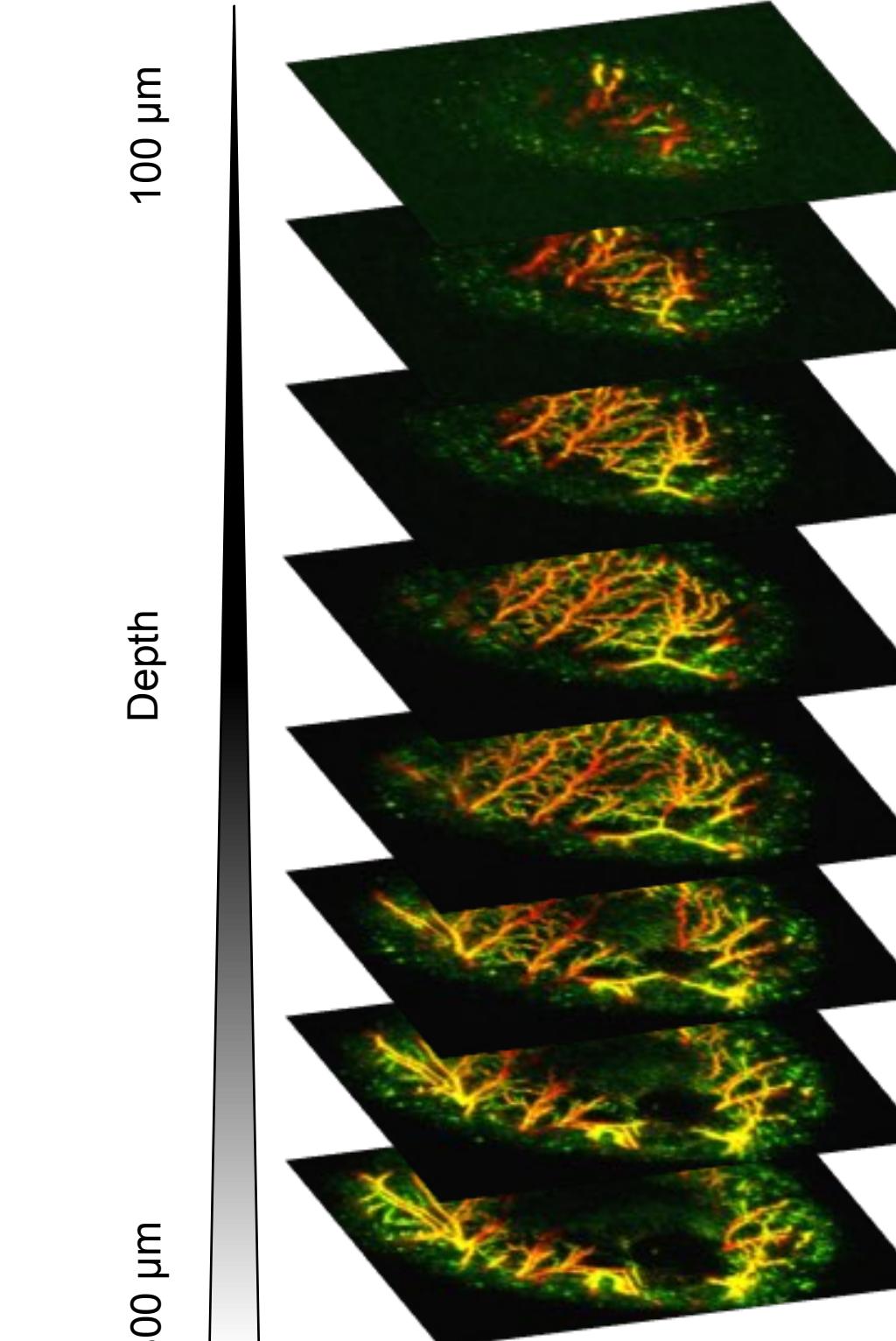
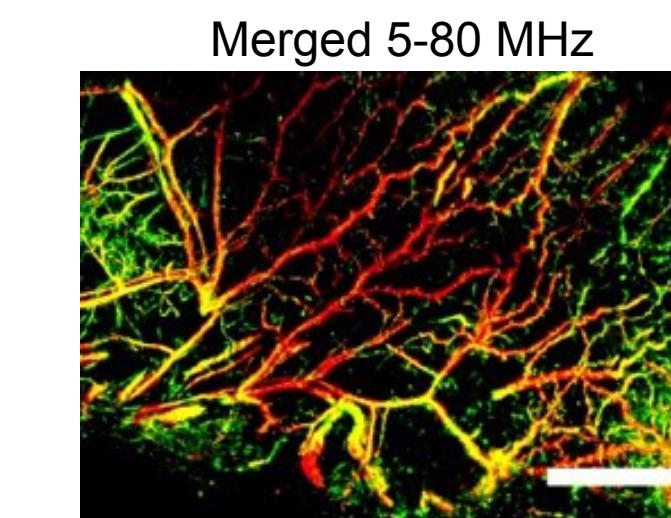
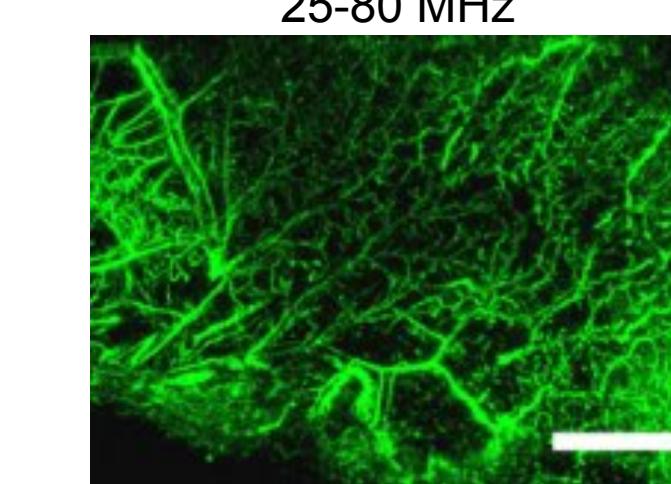
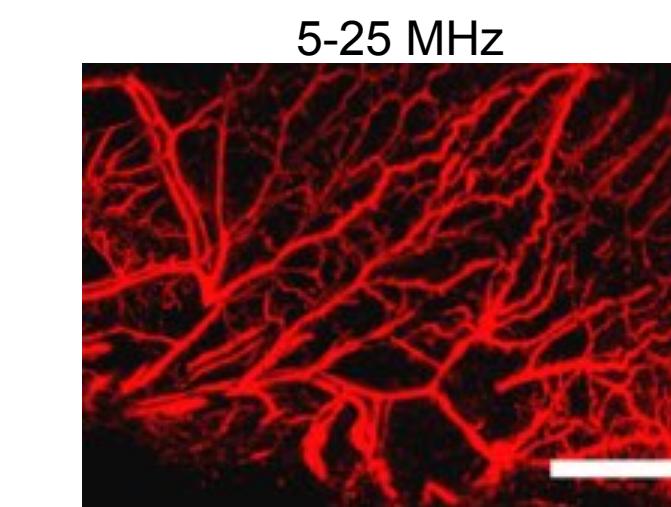
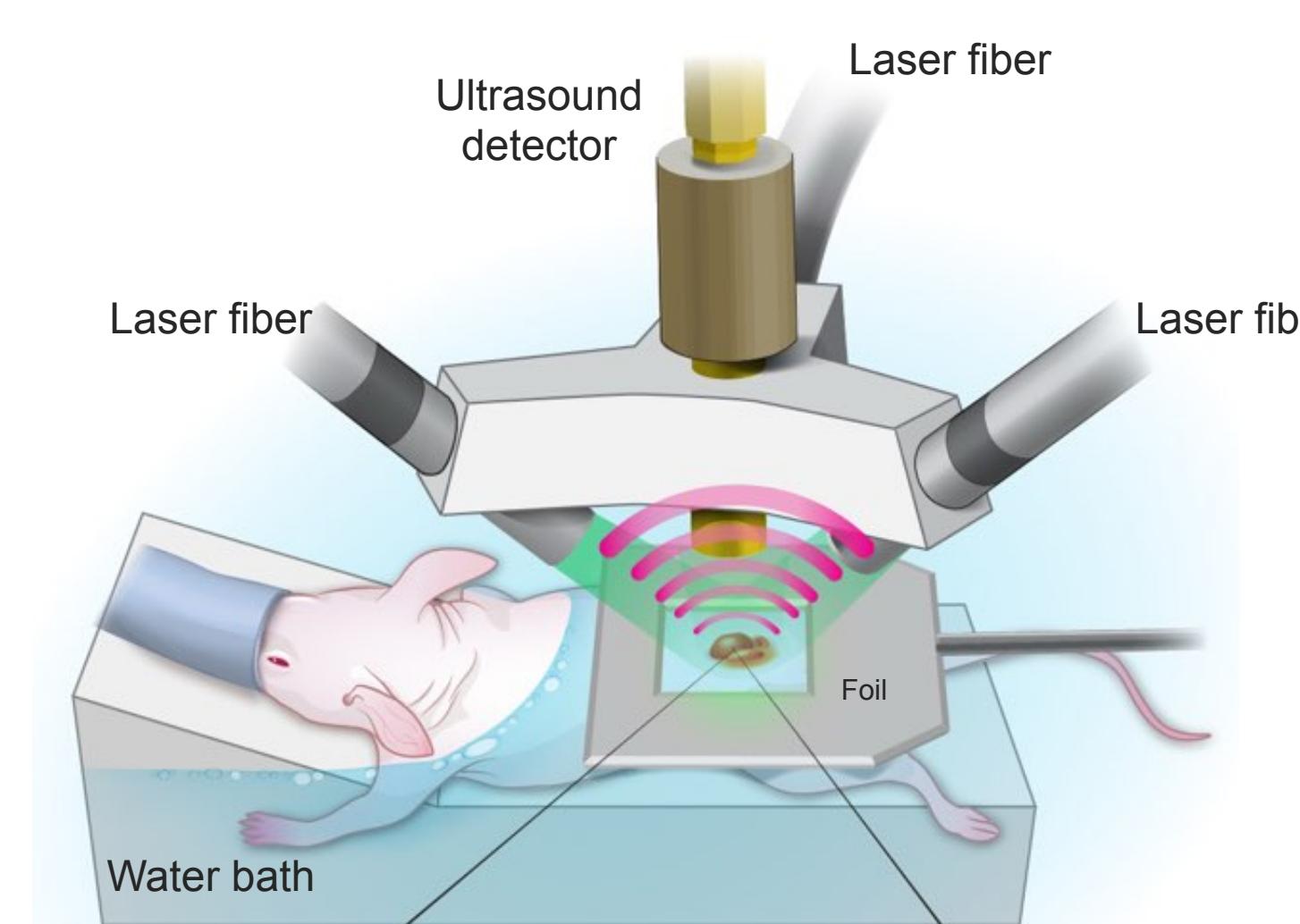
Optoacoustic imaging



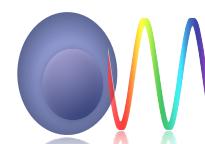
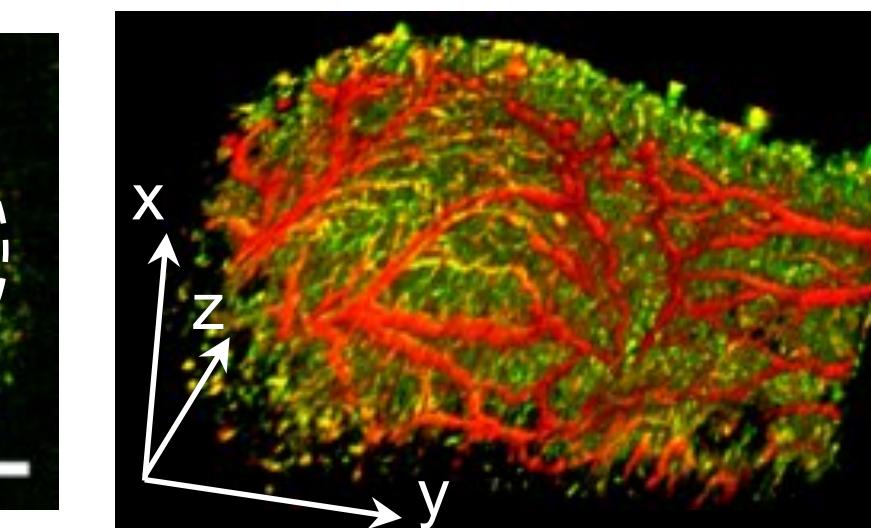
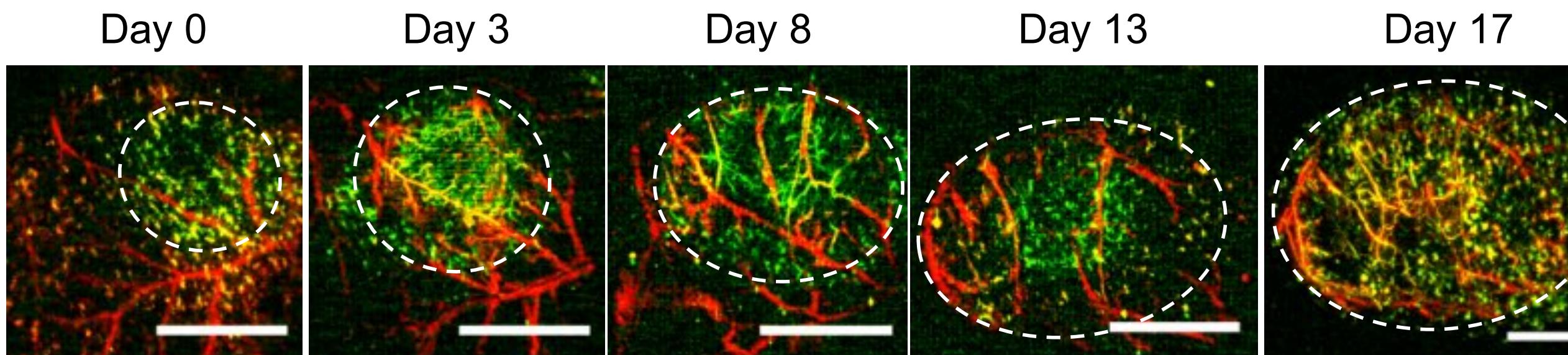
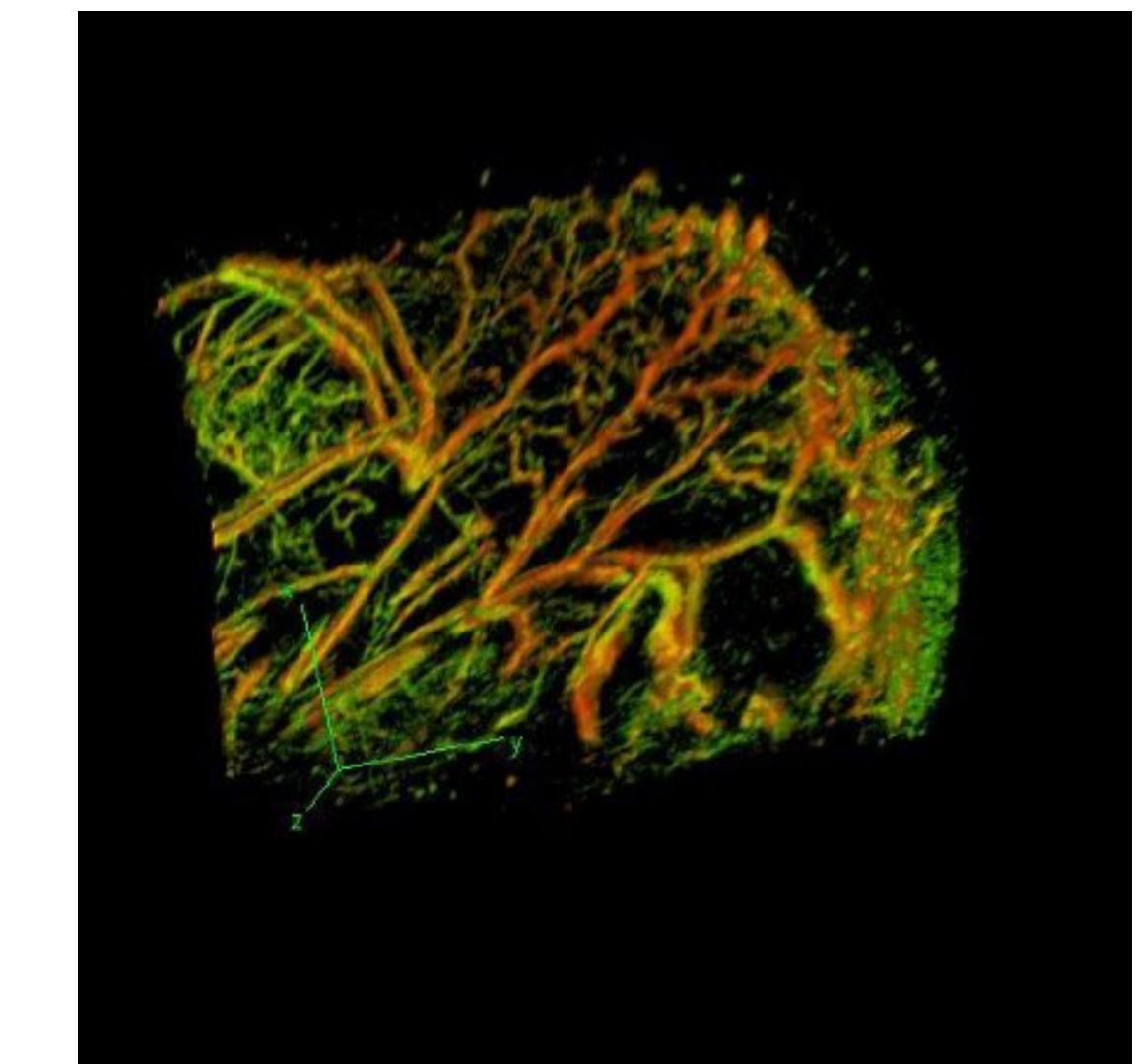
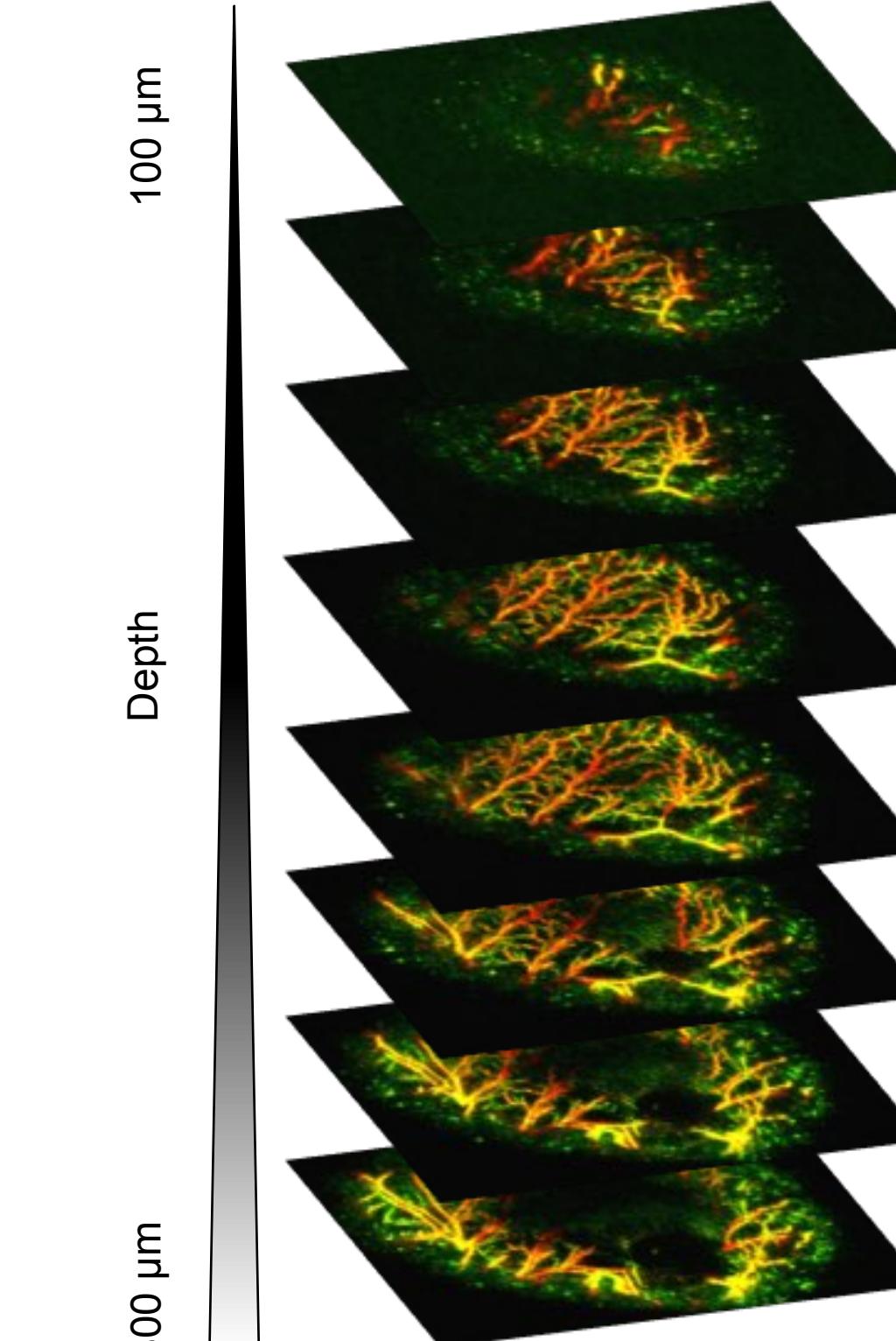
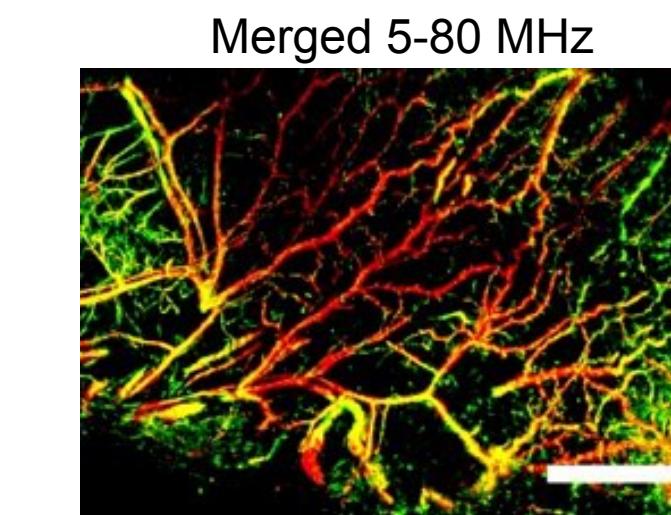
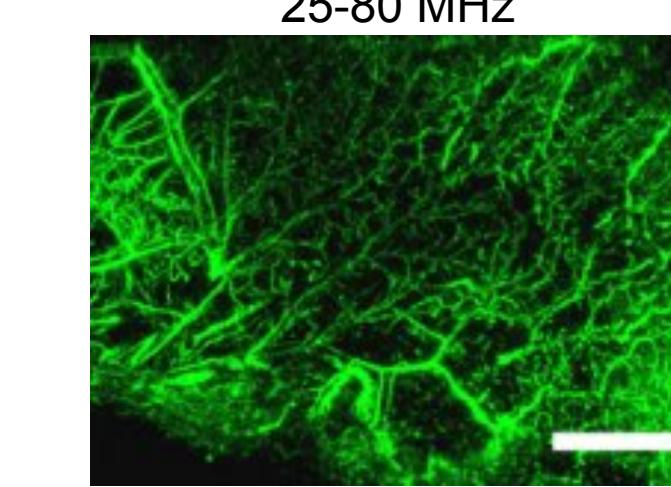
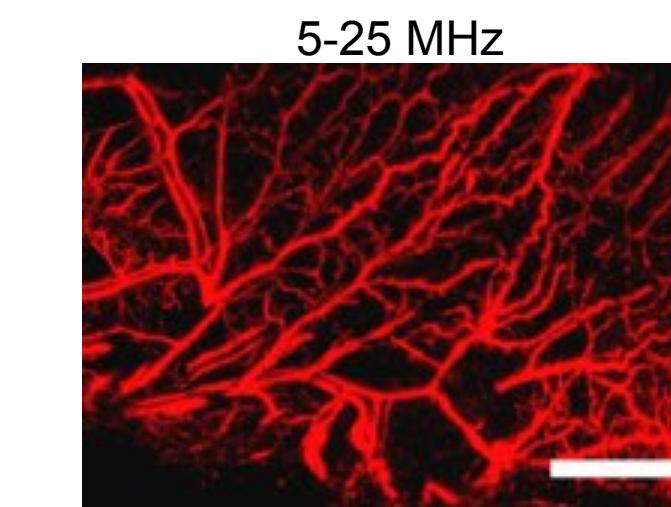
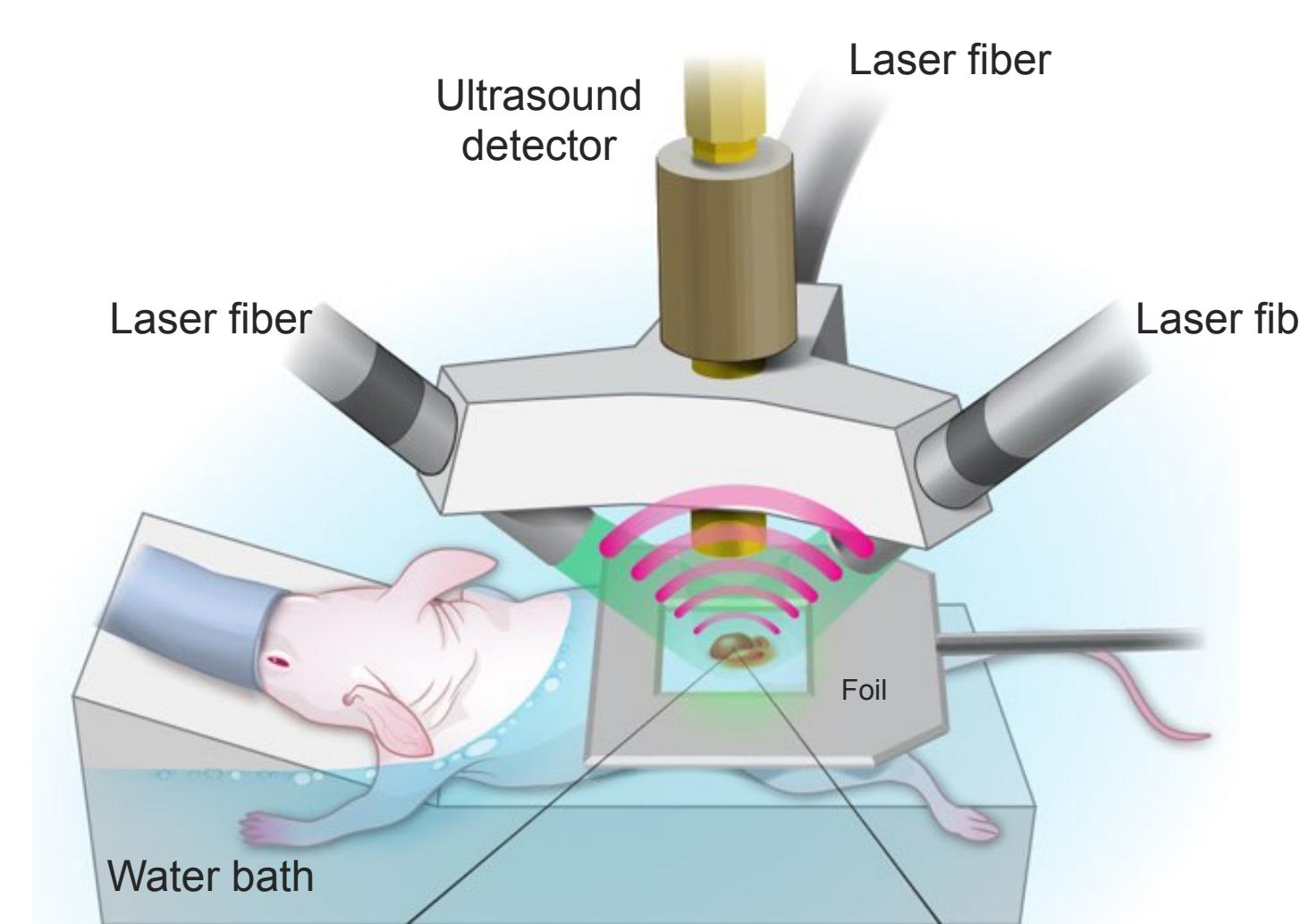
- Invasive windows or skin chambers
- Chamber can influence results (e.g. inflammation)
- Highest magnification but small FOV
- Laborious experiments limit number

- Non-invasive
- No effects onto tumor
- High magnification but global (mesoscopy)
- Longitudinal studies in many animals possible

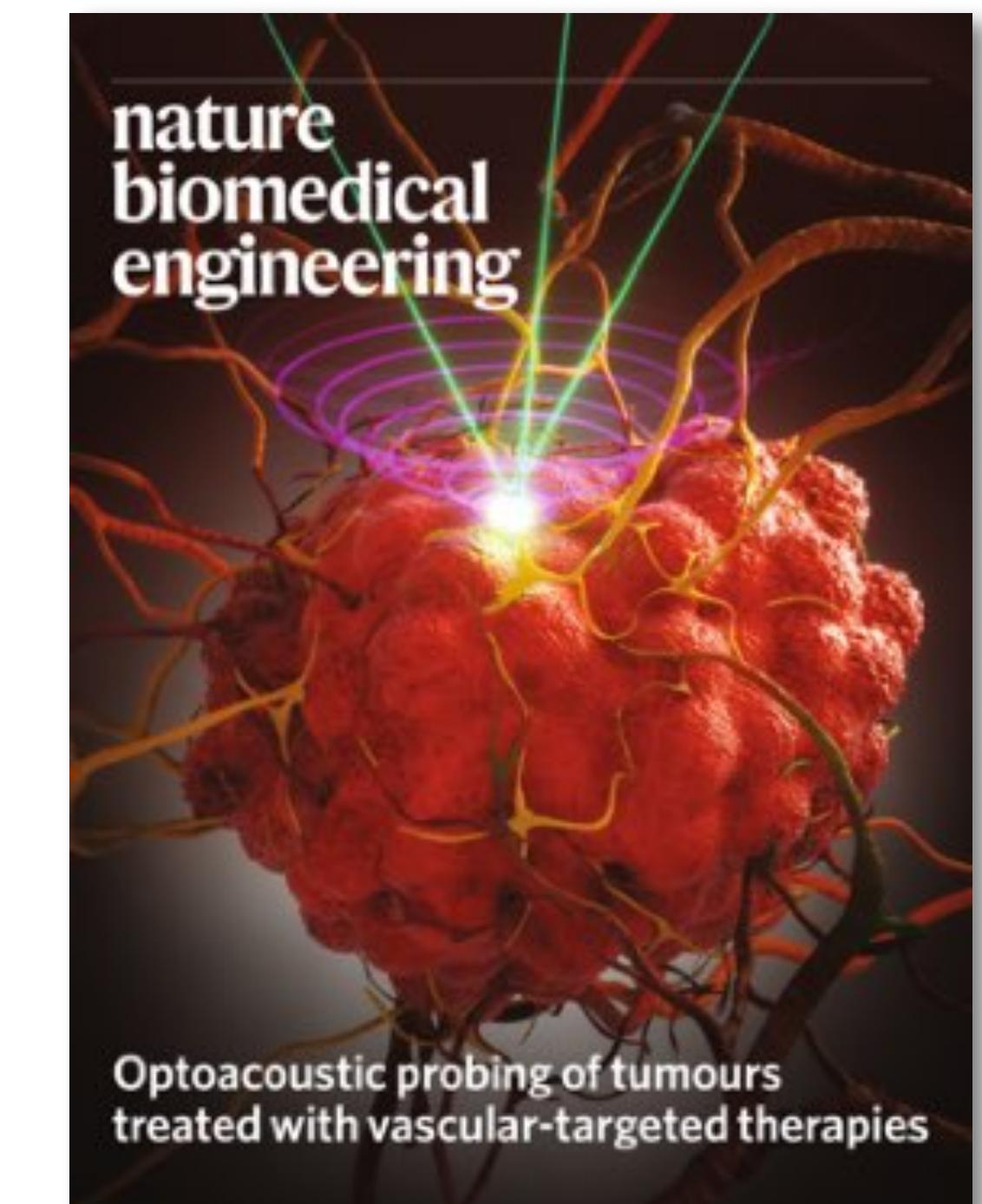
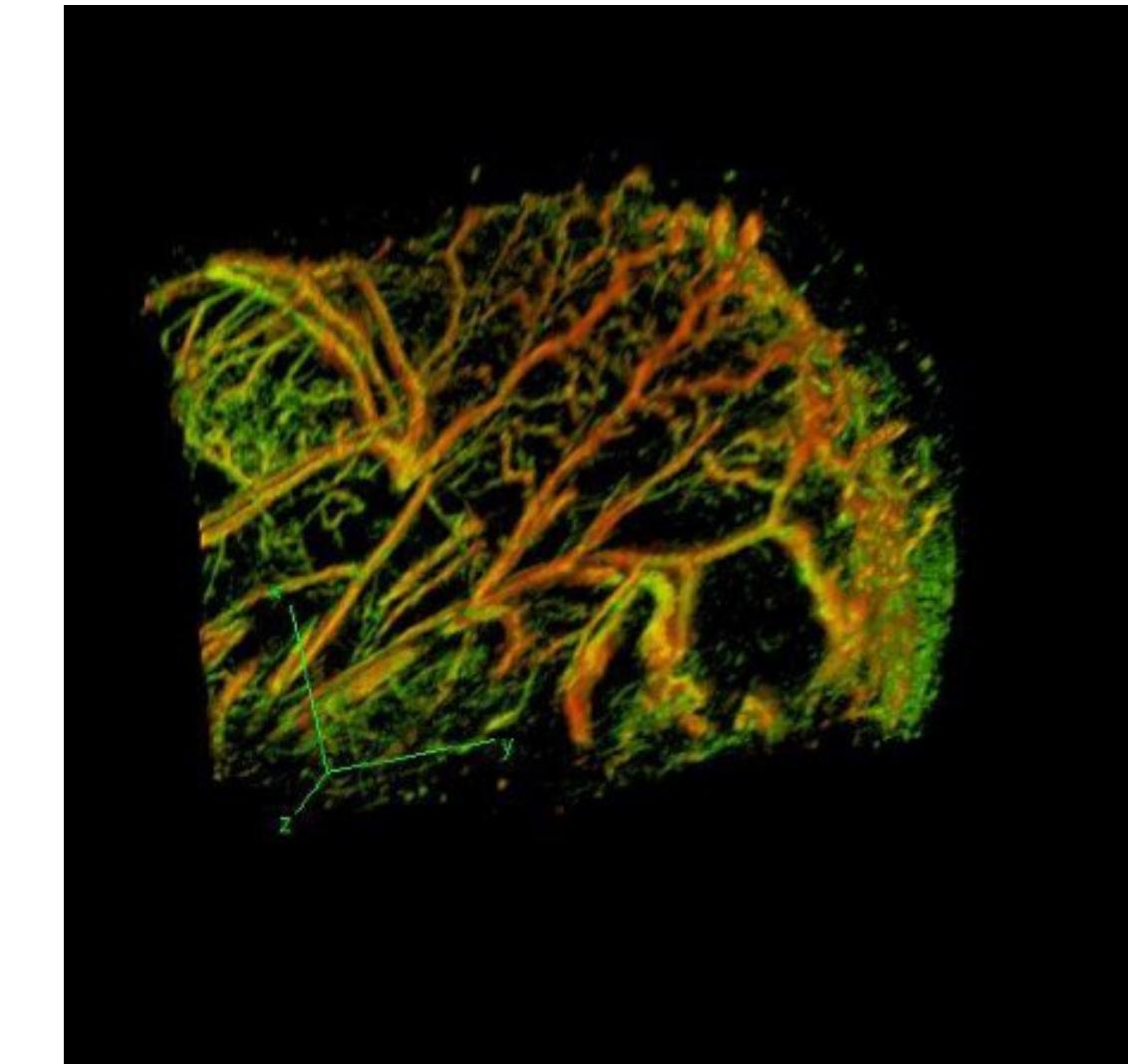
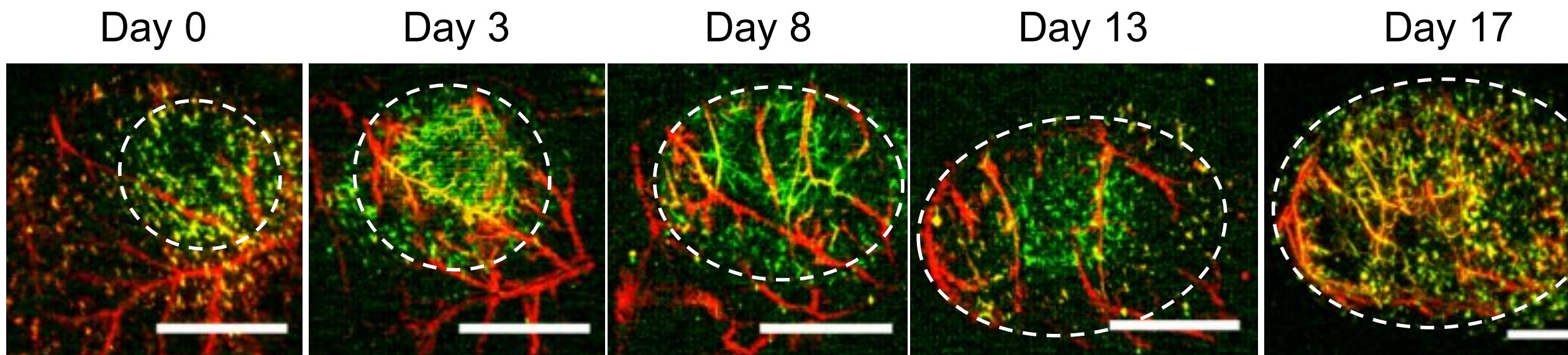
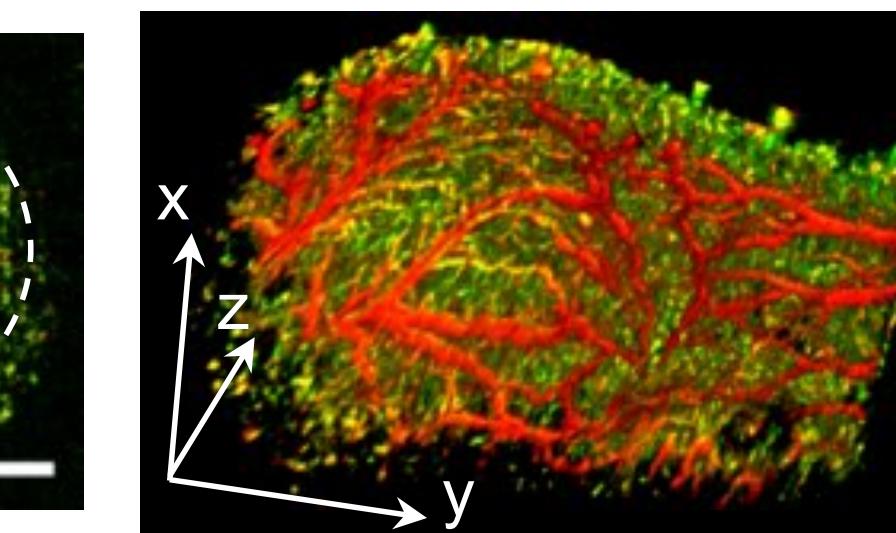
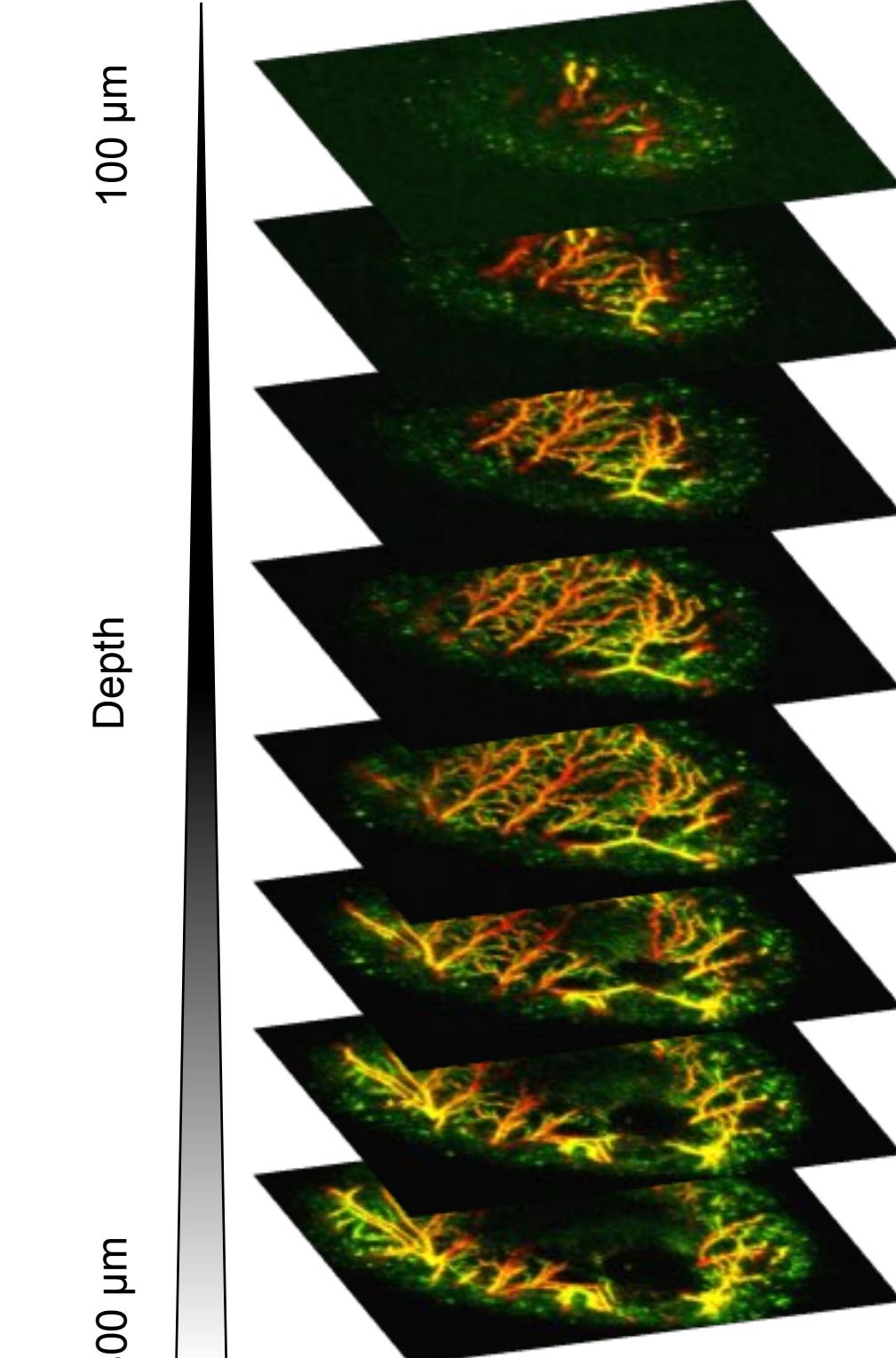
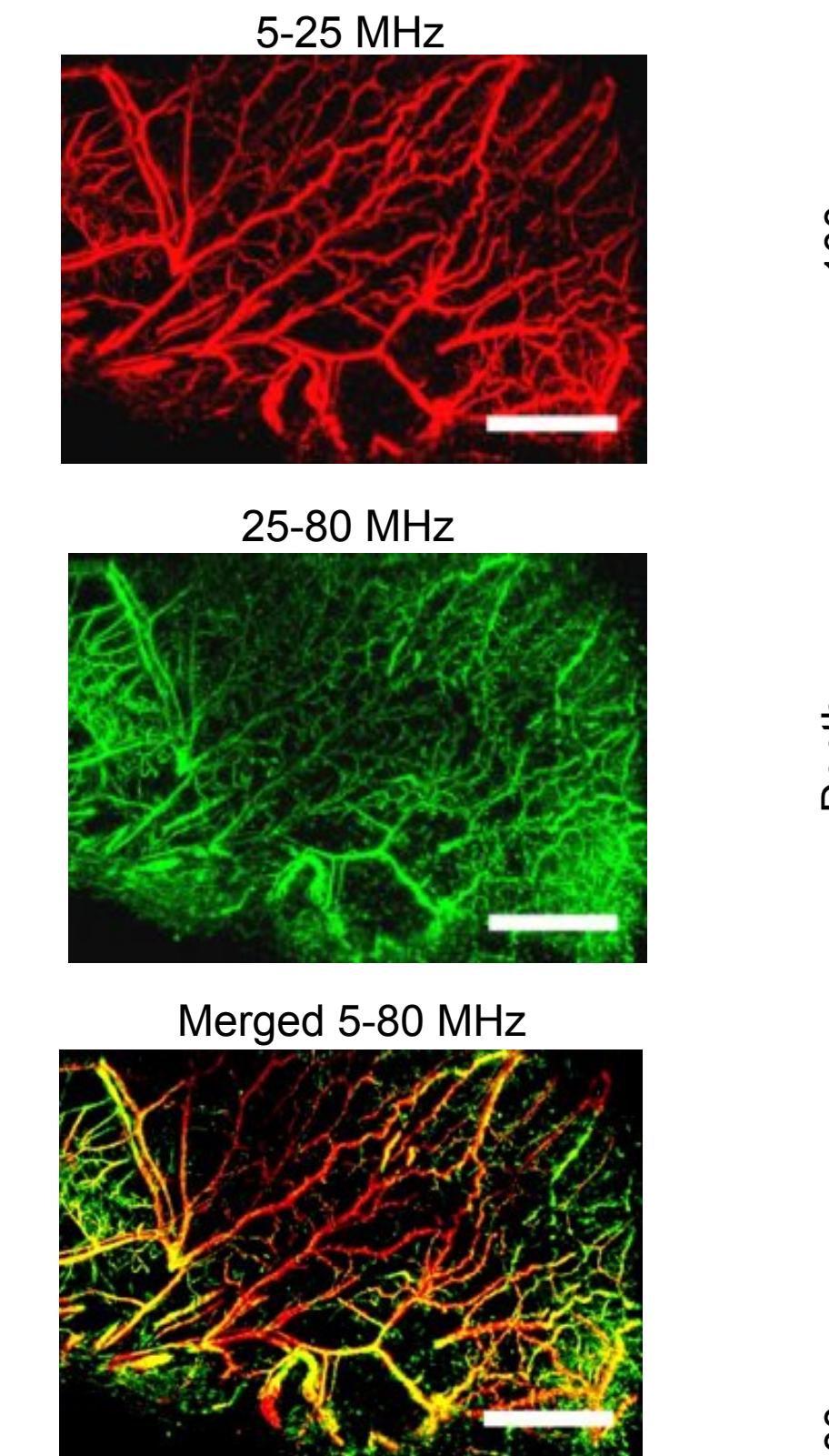
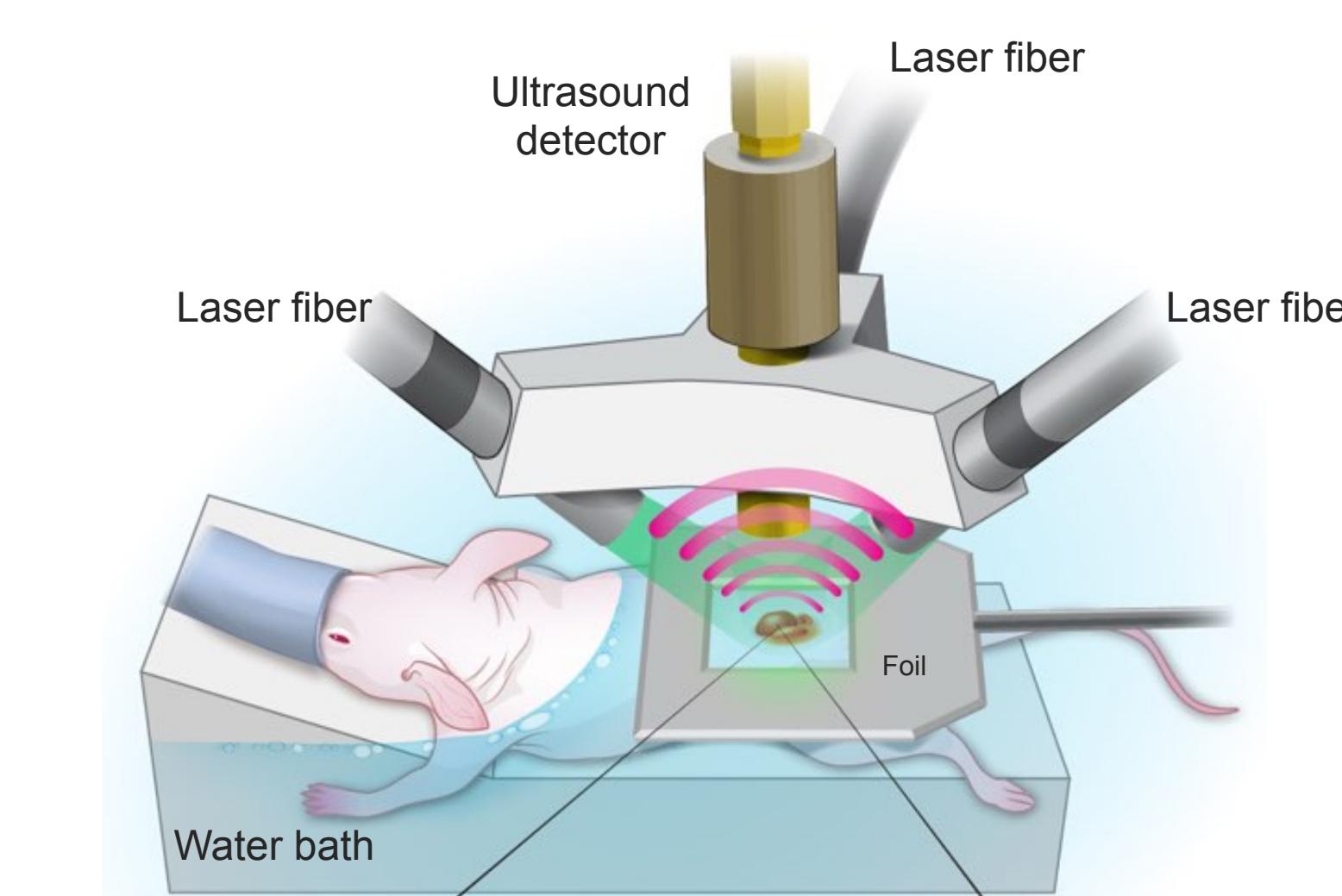
Raster Scanning Optoacoustic Mesoscopy



Raster Scanning Optoacoustic Mesoscopy



Raster Scanning Optoacoustic Mesoscopy

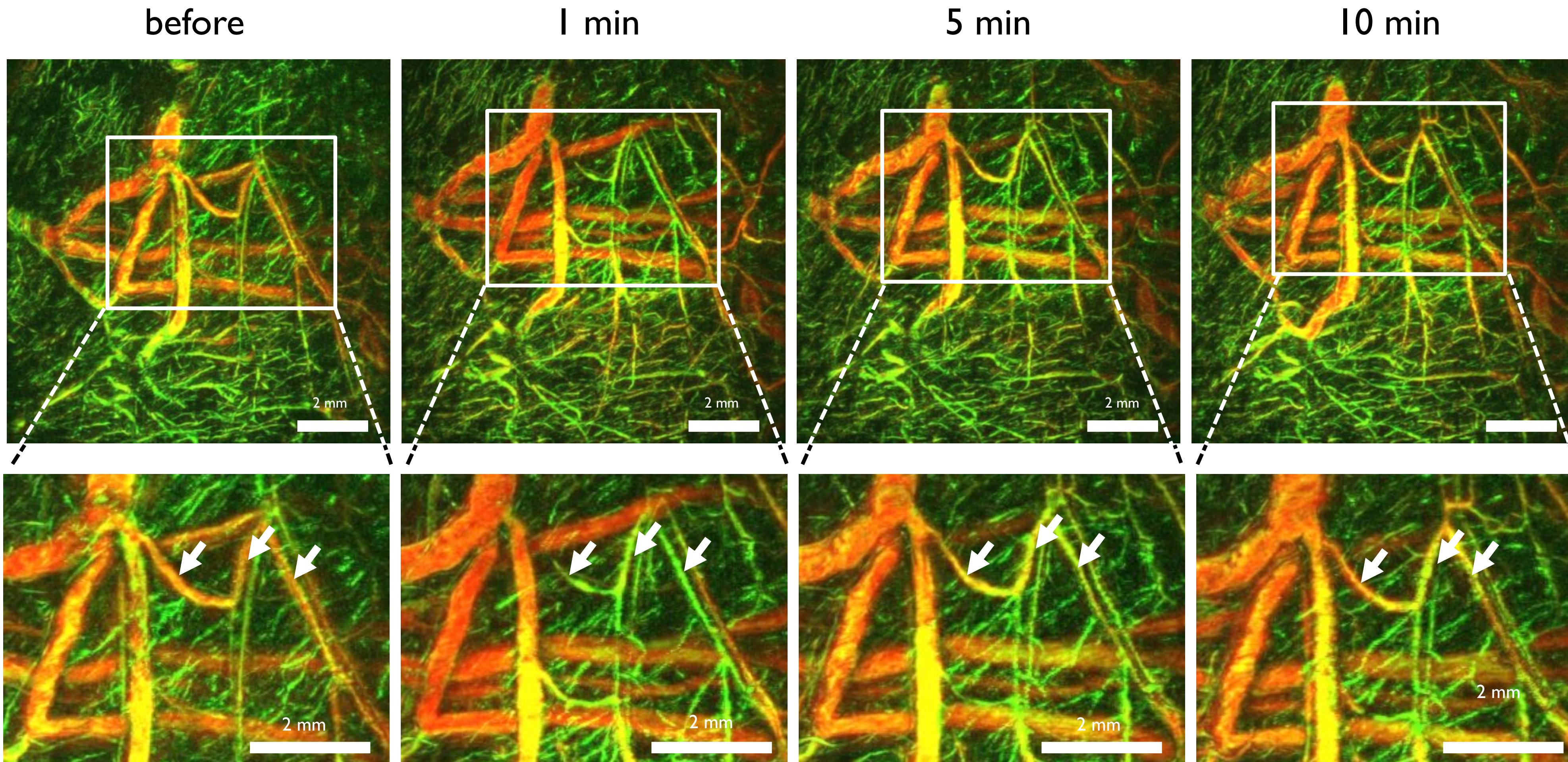


Pharmacologic reactions of vessels



K. Haedicke

Epinephrin intravenous



CT26 tumor

Haedicke K et al (2020) Nature Biomedical Engineering (4): 286-97



Imaging vascular-targeted therapy

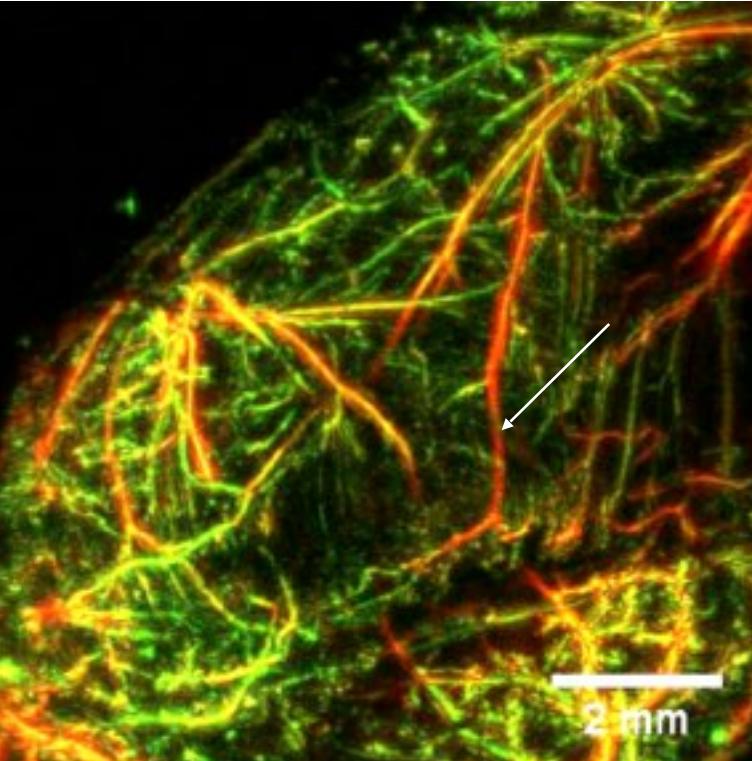


K Haedicke J Coleman

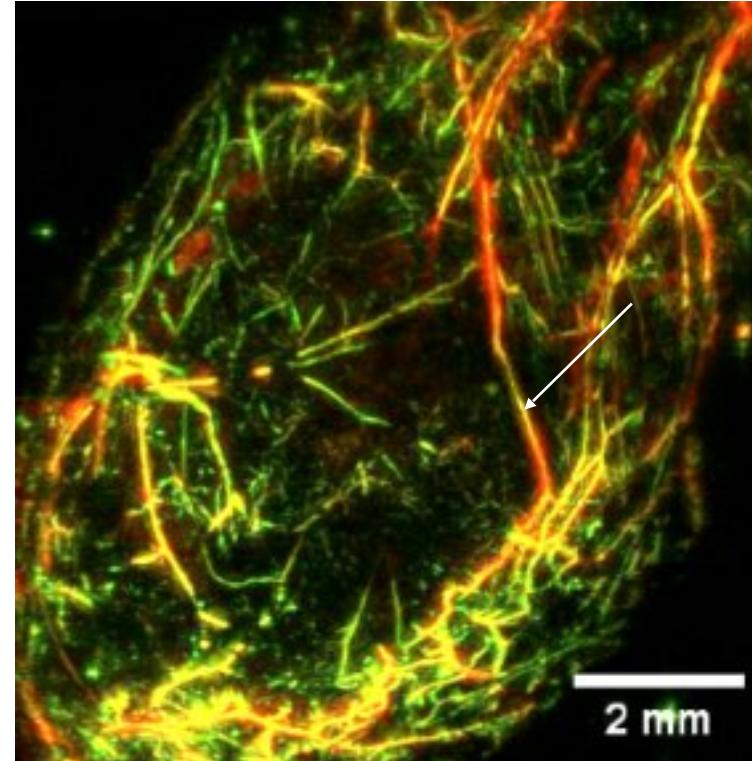
A Scherz

WST-11

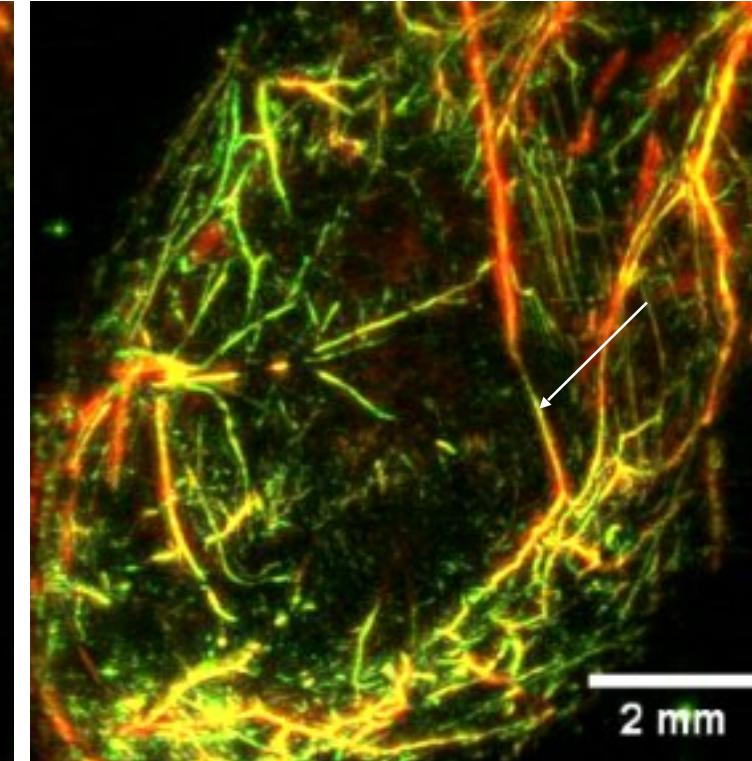
Pre



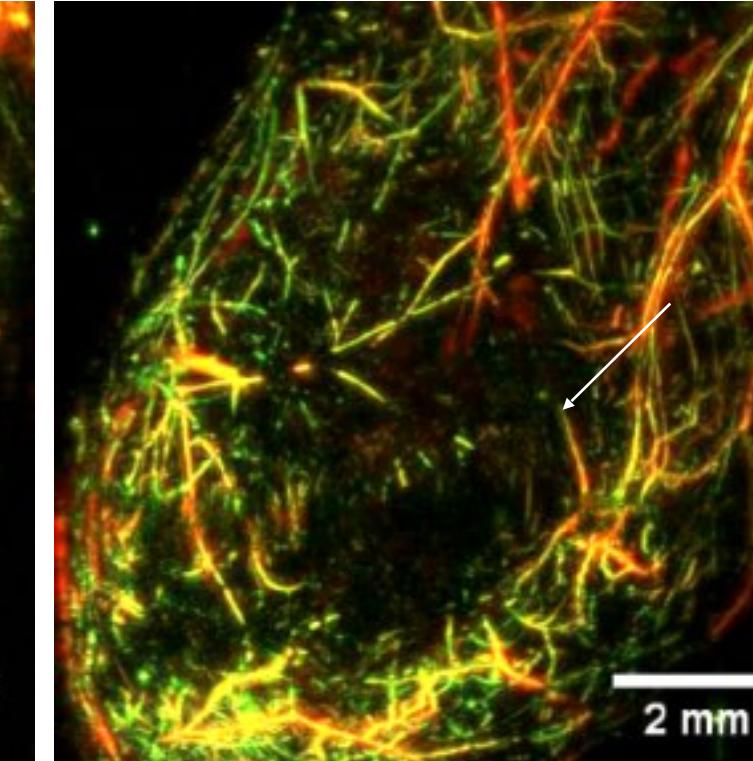
5 min



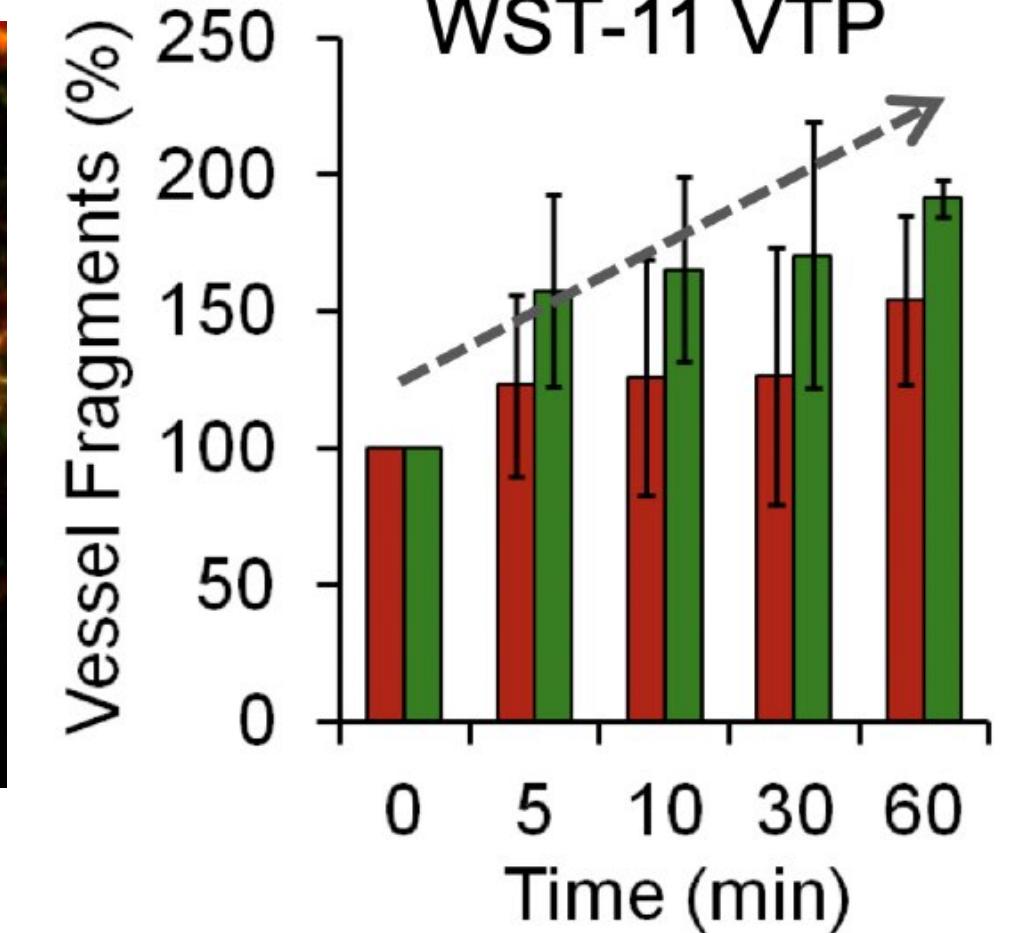
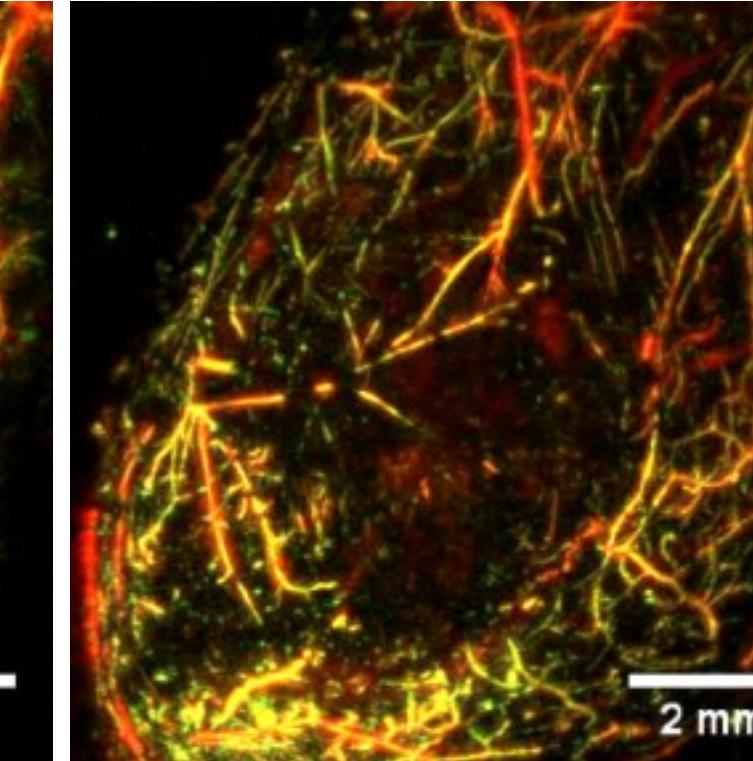
10 min



30 min

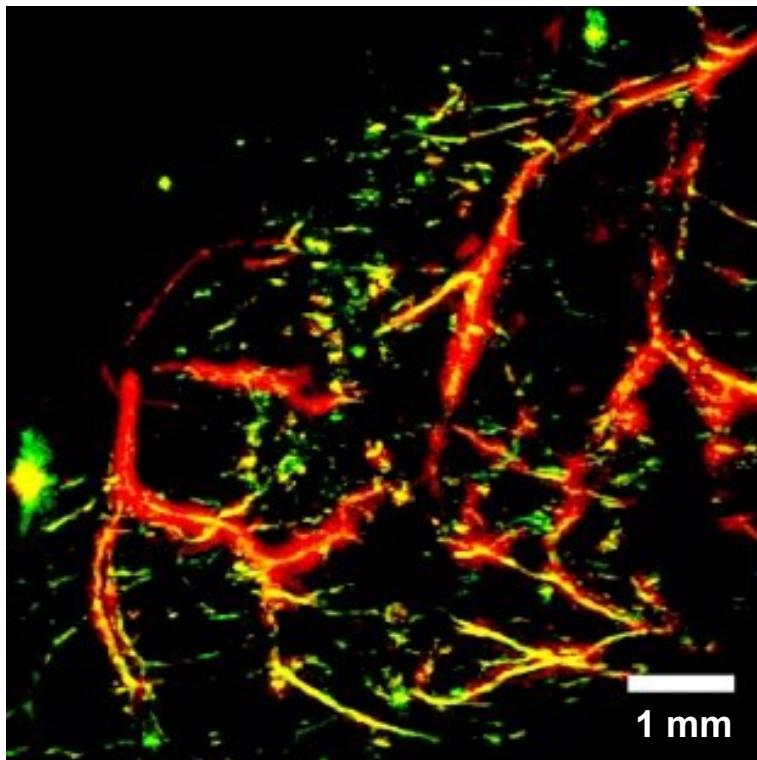


60 min

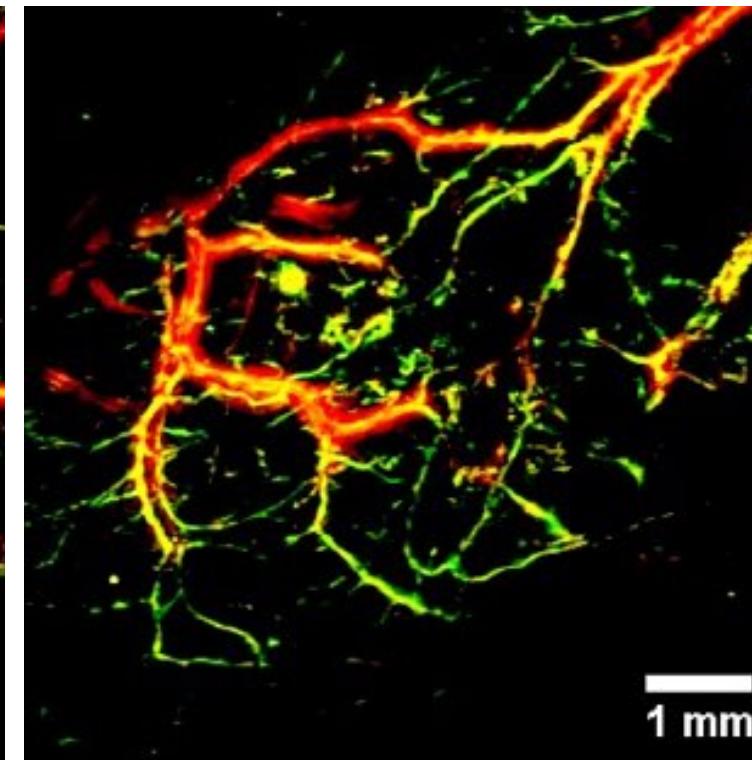


WST-11 + HCA

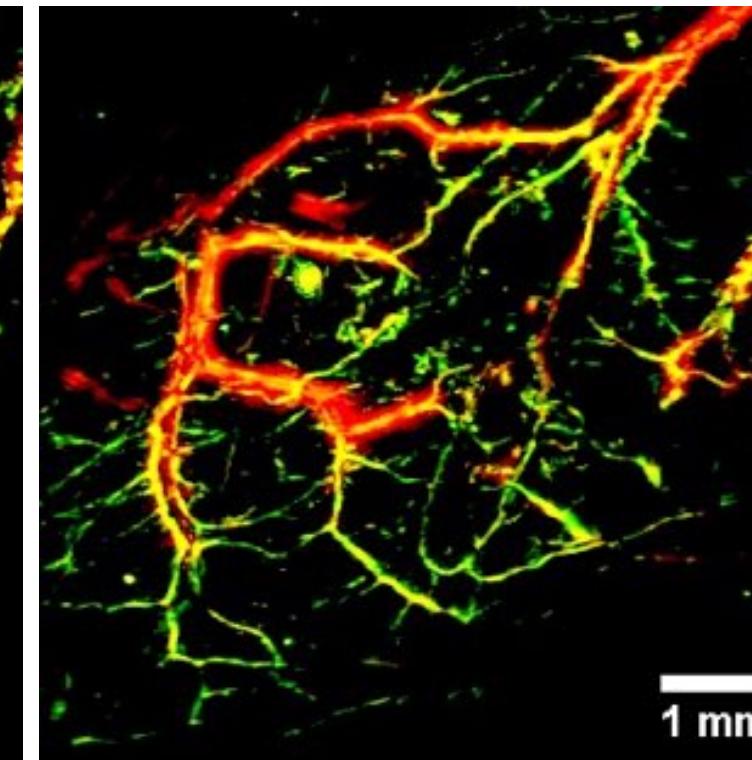
Pre



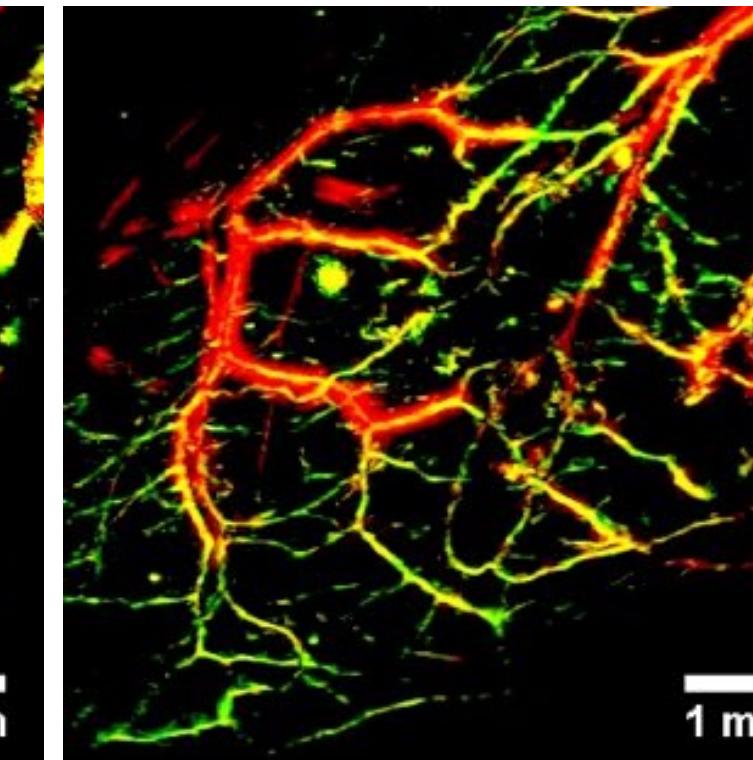
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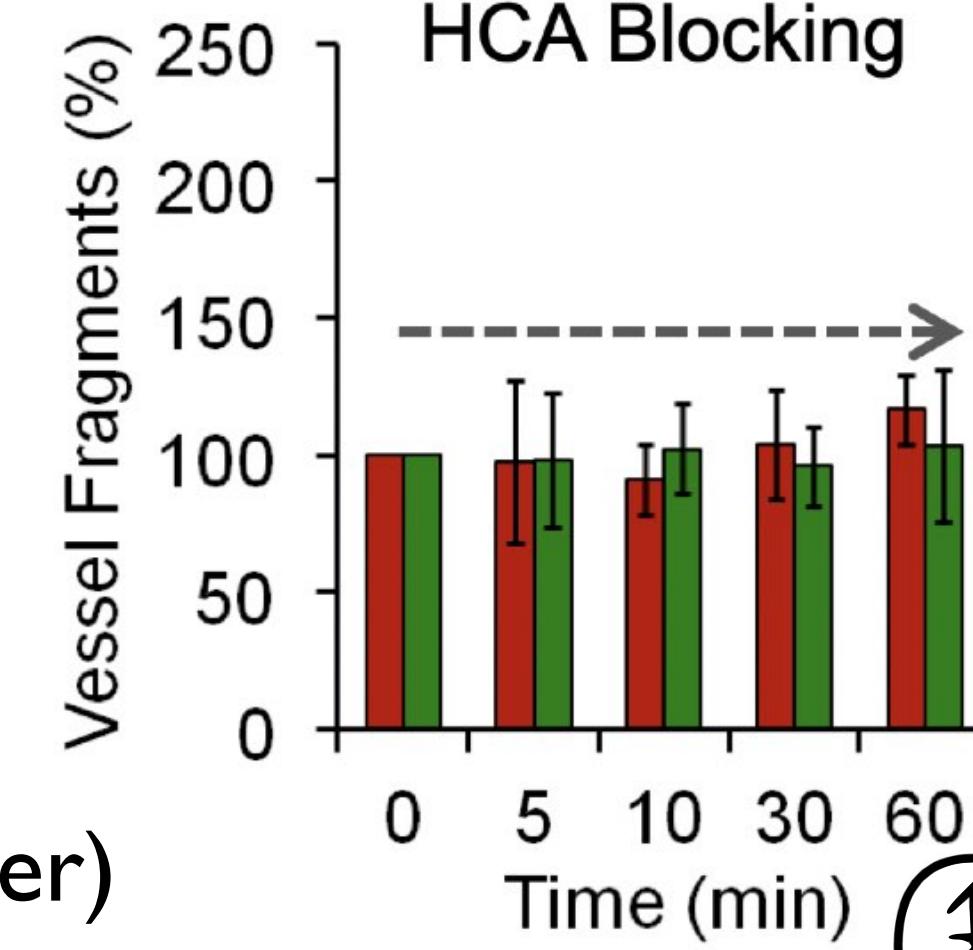
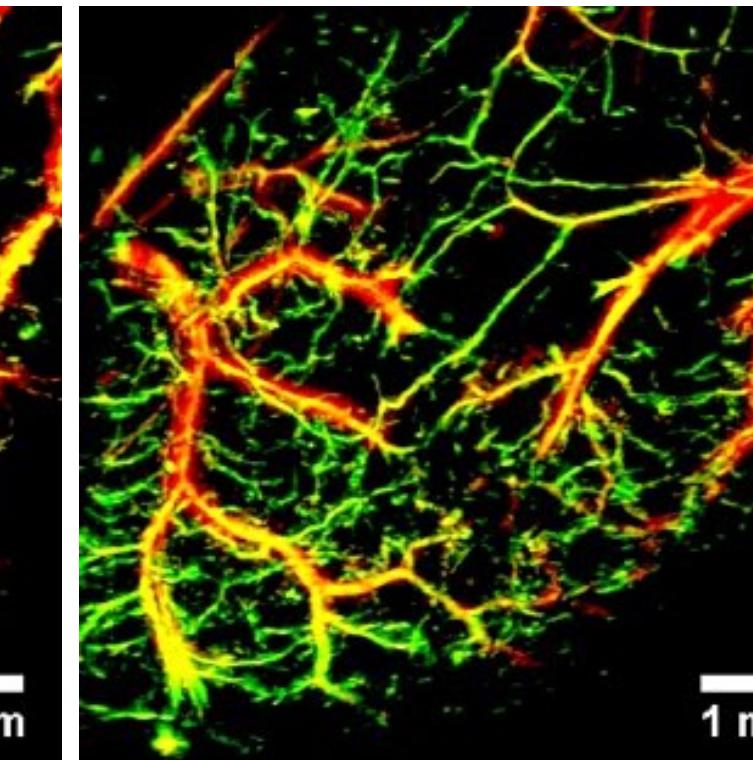
10 min



30 min



60 min

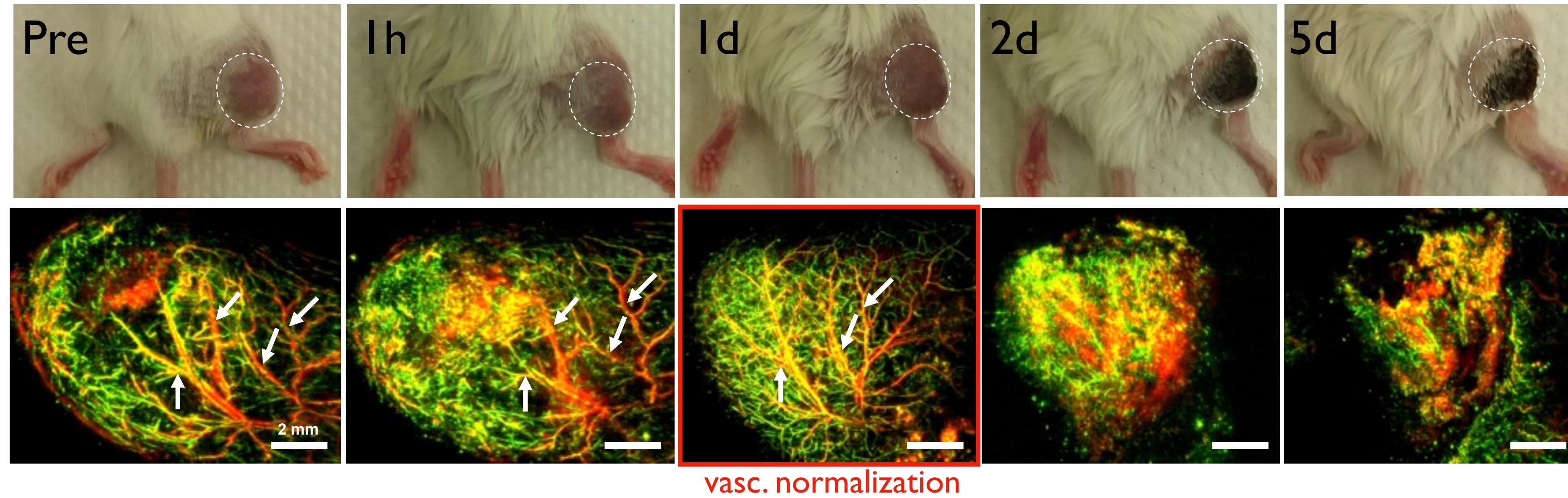


WST-11 = vascular-targeted PDT agent

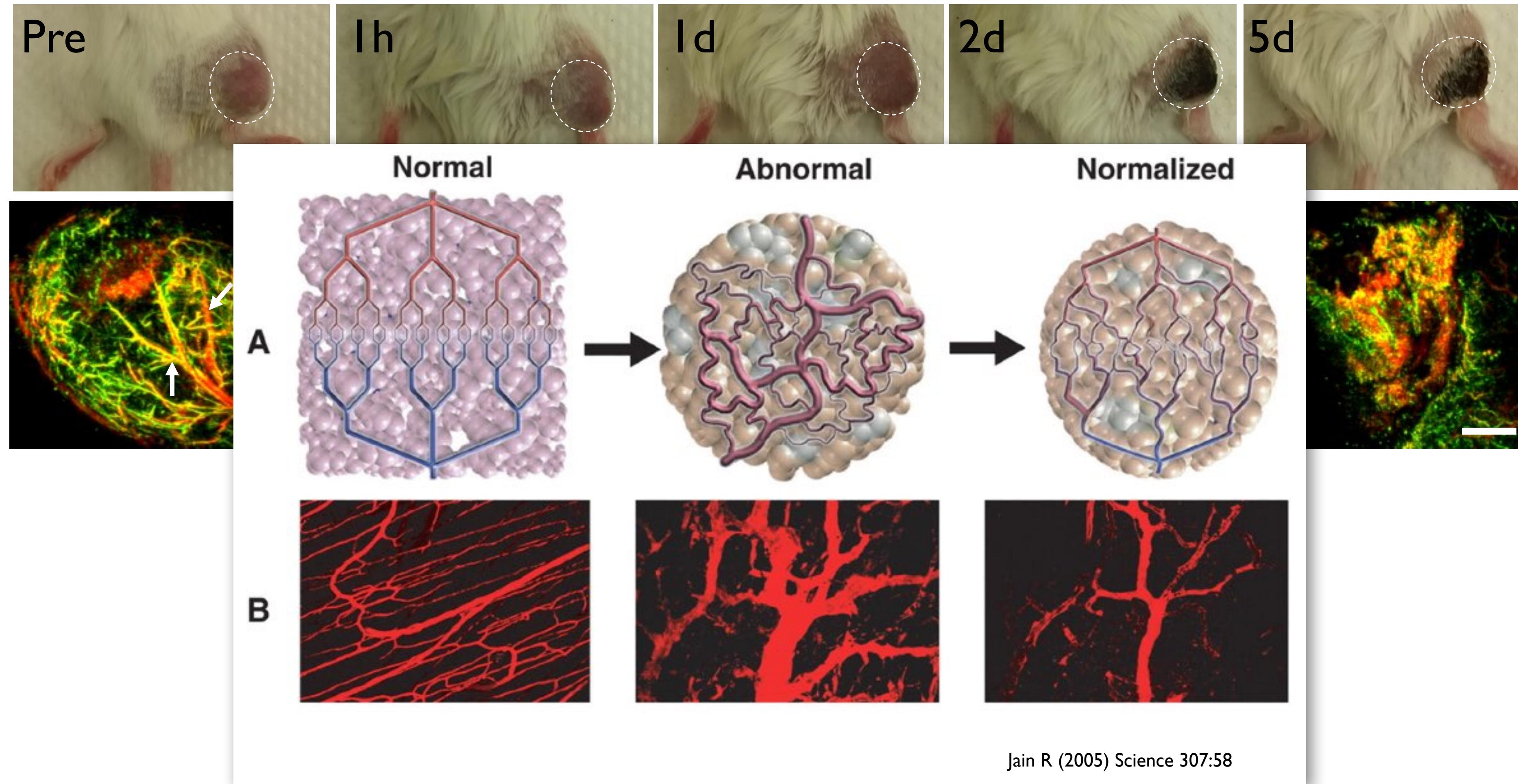
HCA = Hydroxycobalamin (NO scavenger)



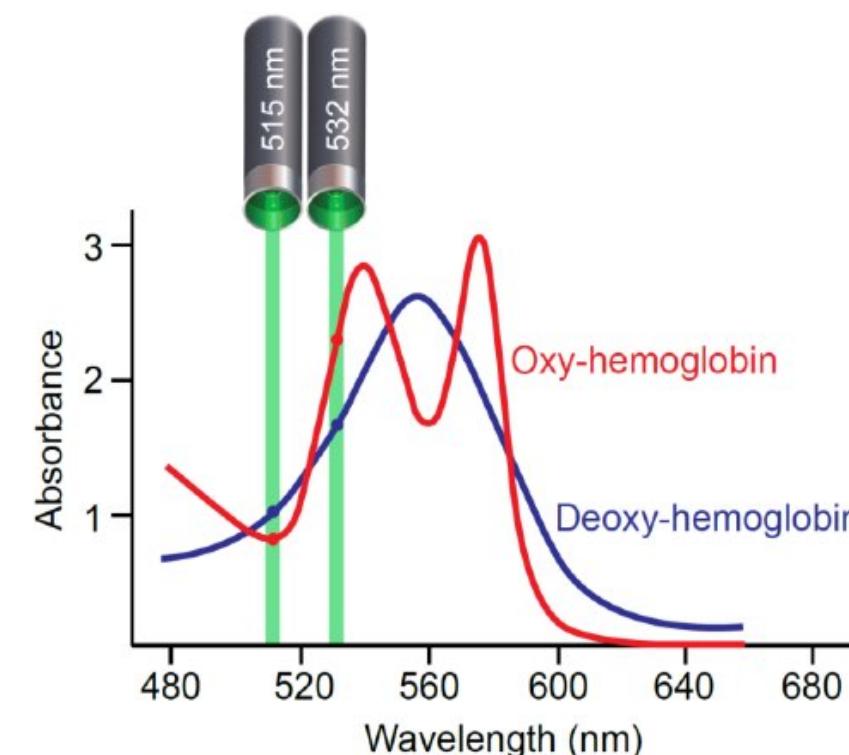
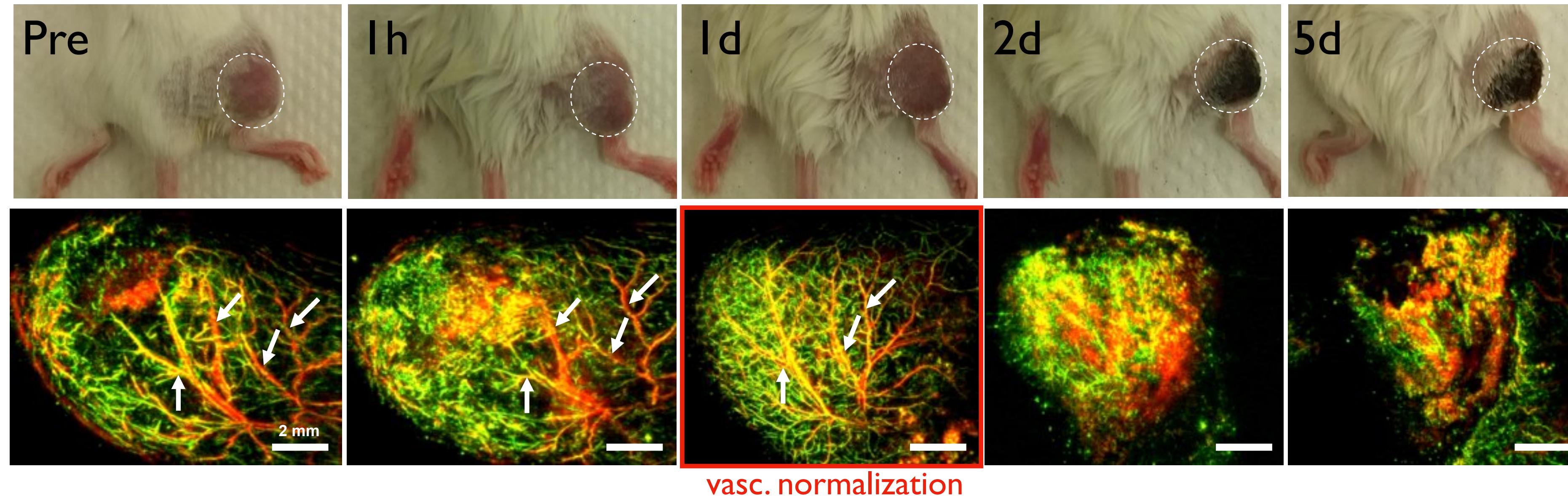
Imaging therapy at work - later time points



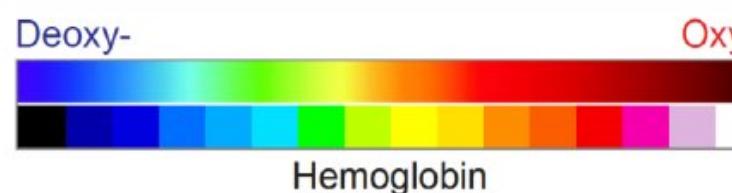
Imaging therapy at work - later time points



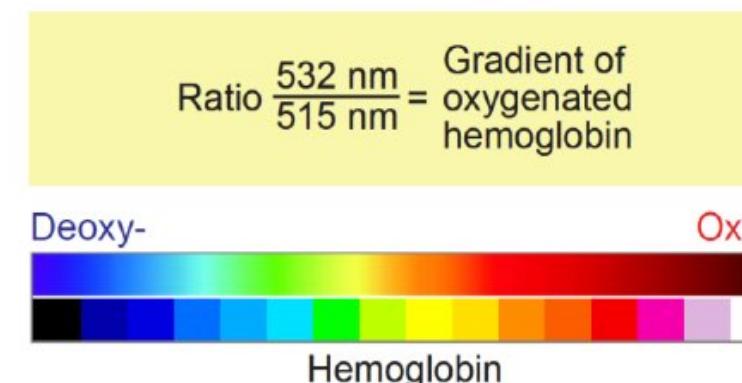
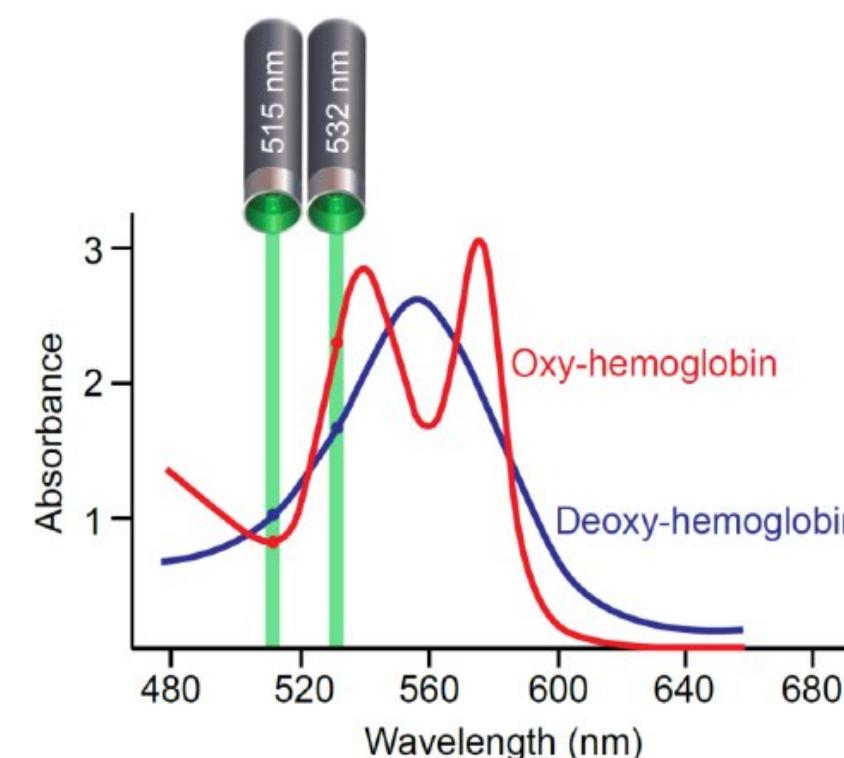
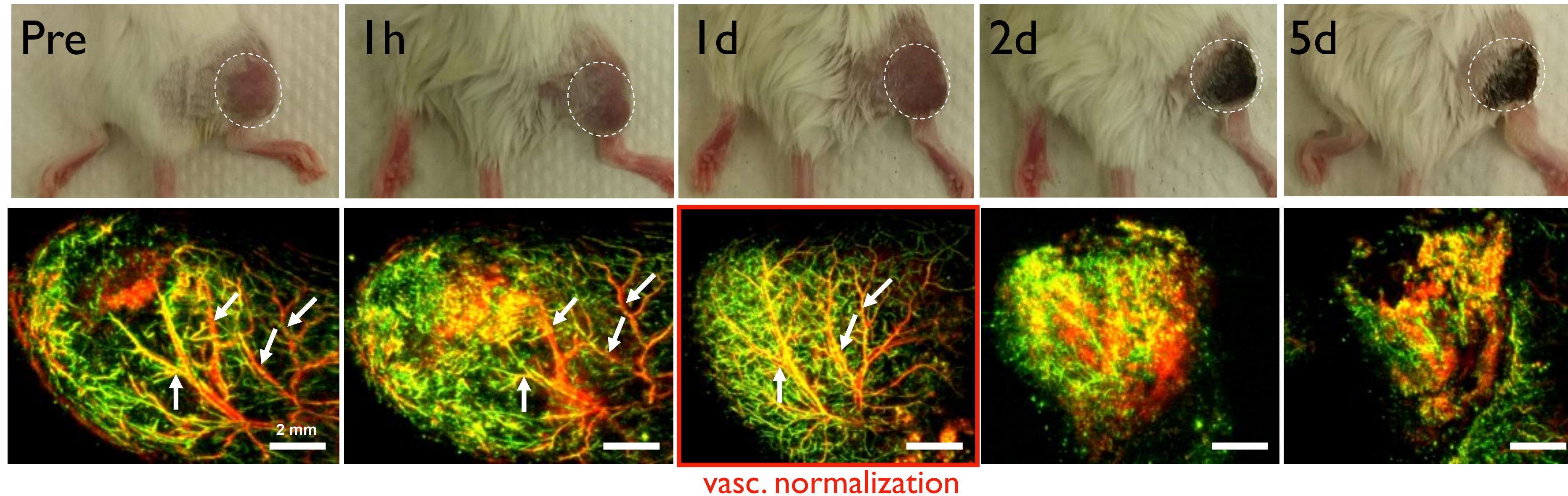
Imaging therapy at work - later time points



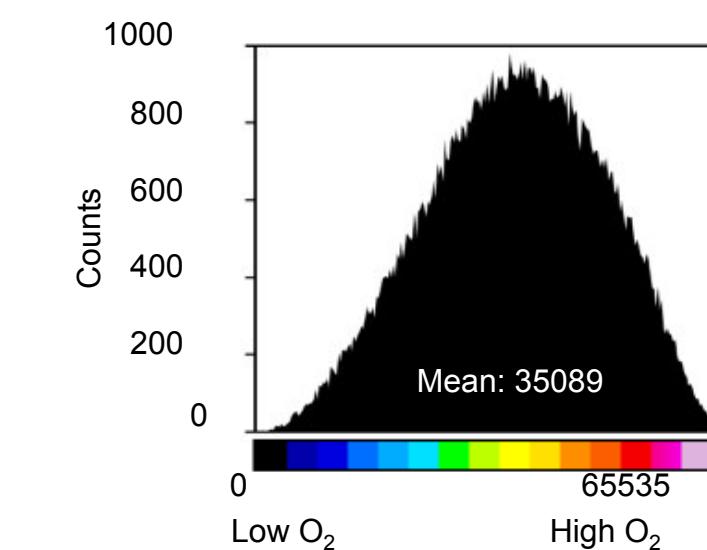
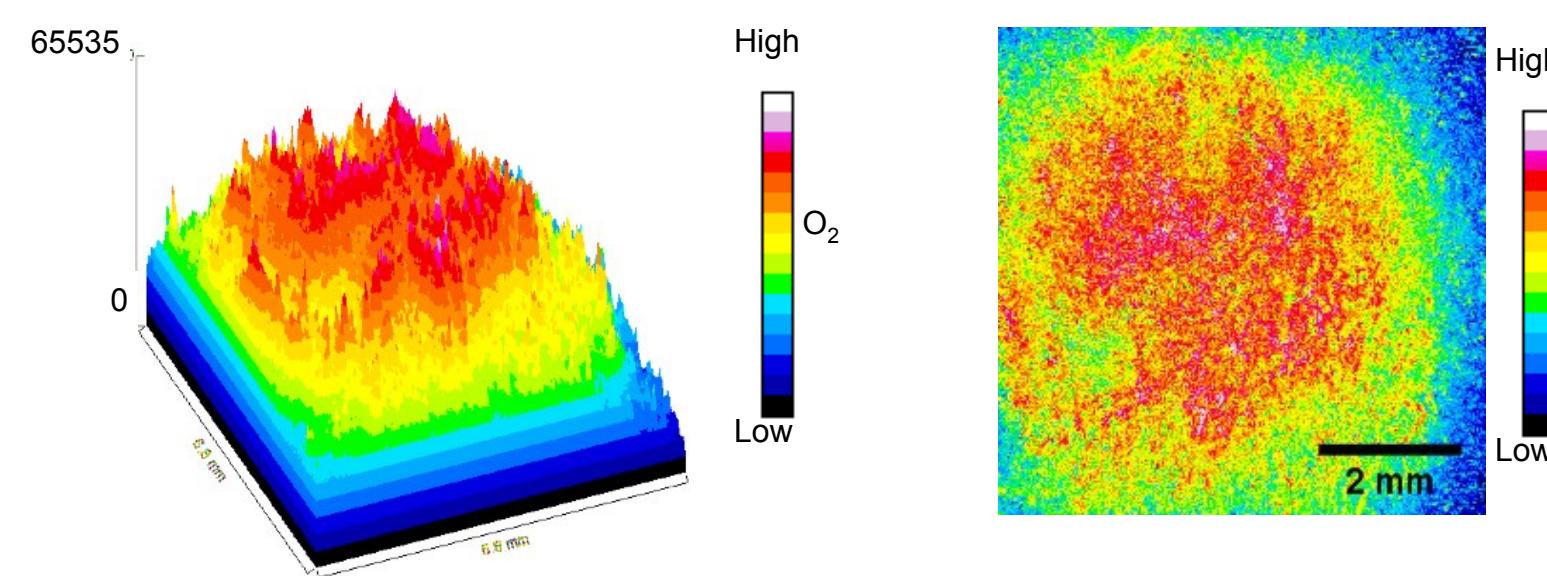
Ratio $\frac{532 \text{ nm}}{515 \text{ nm}}$ = Gradient of oxygenated hemoglobin



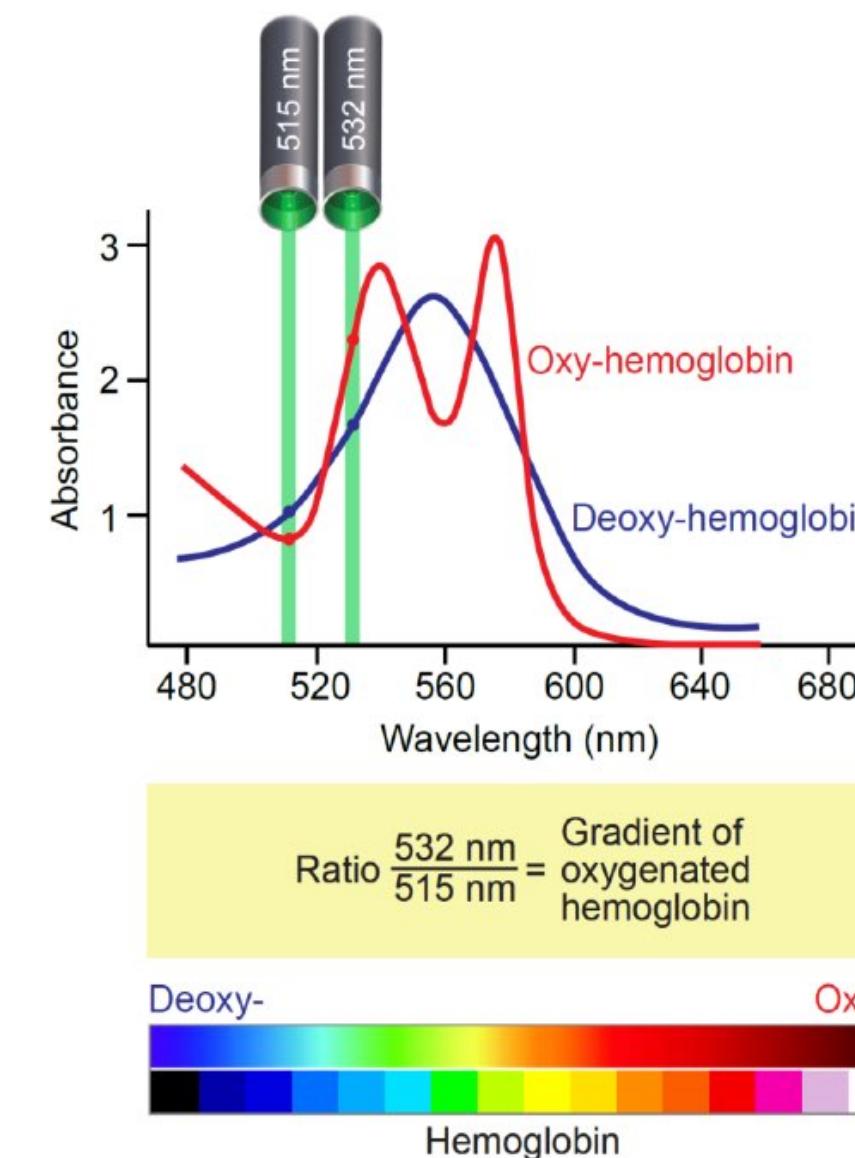
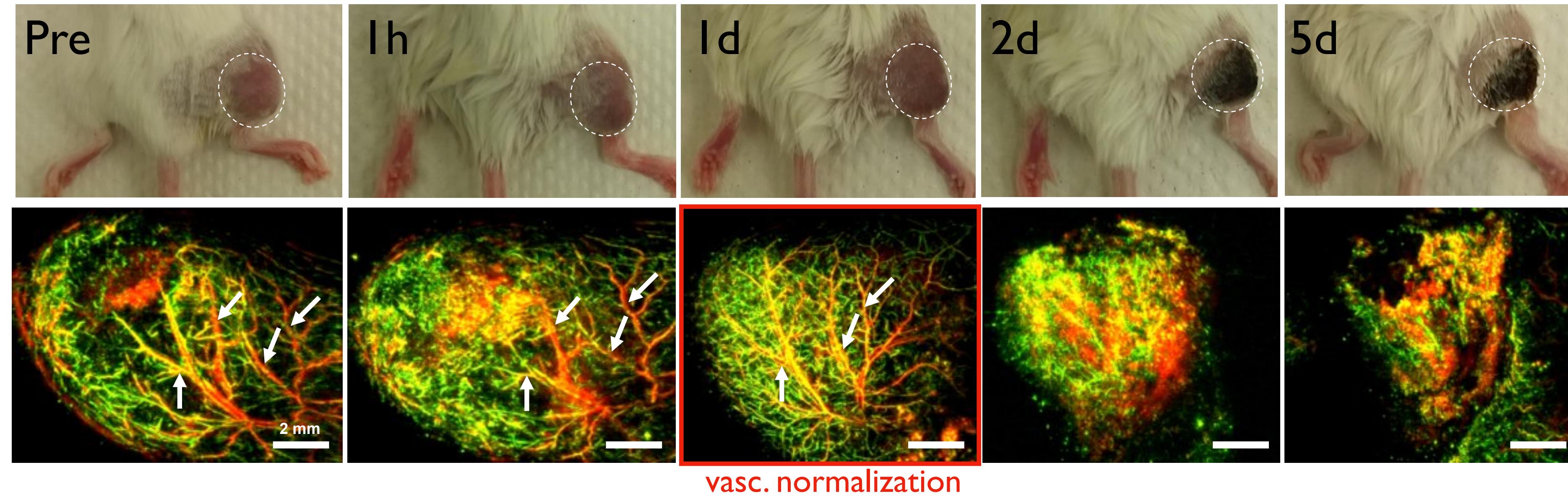
Imaging therapy at work - later time points



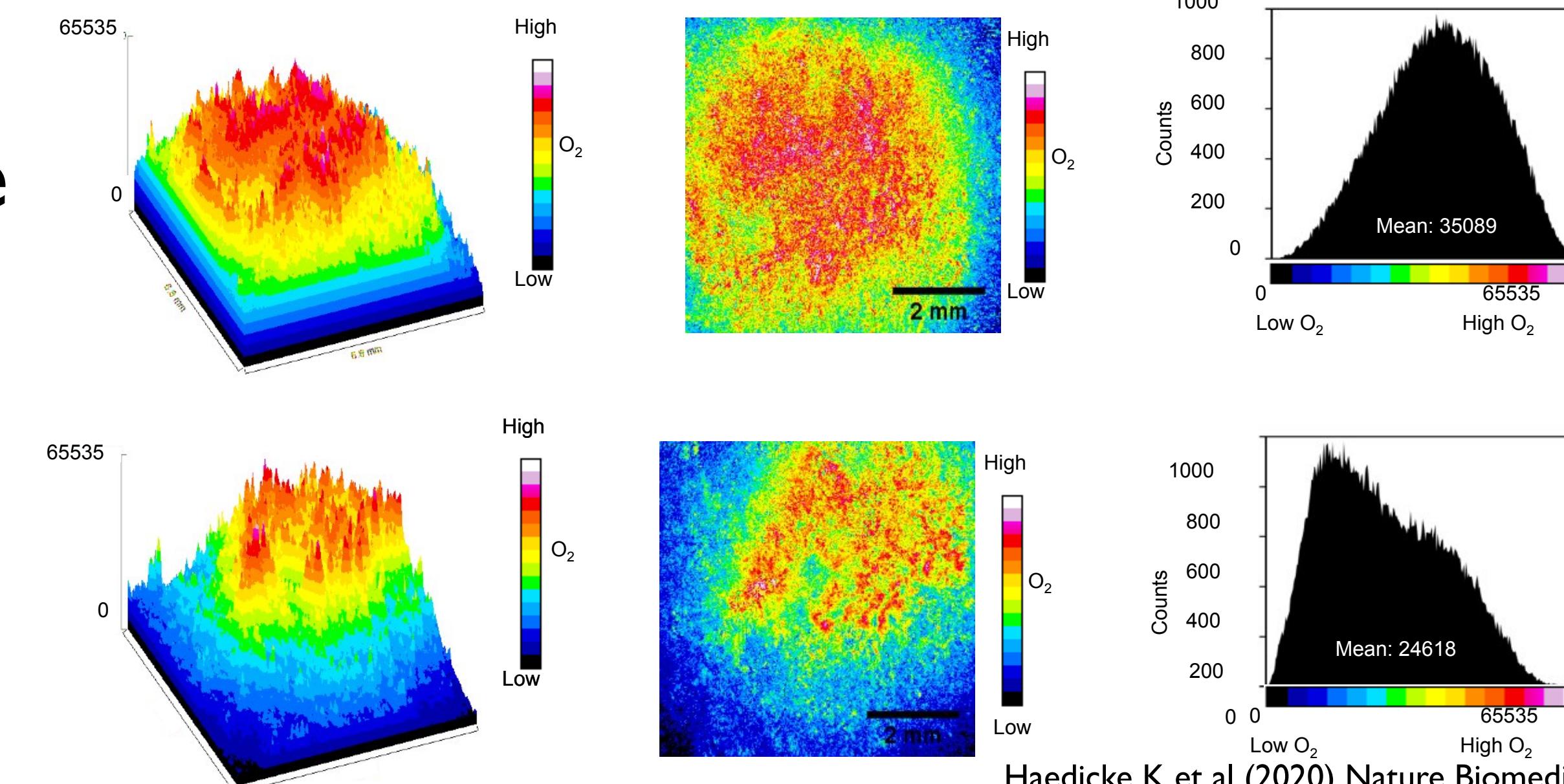
Pre



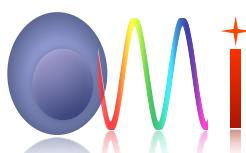
Imaging therapy at work - later time points



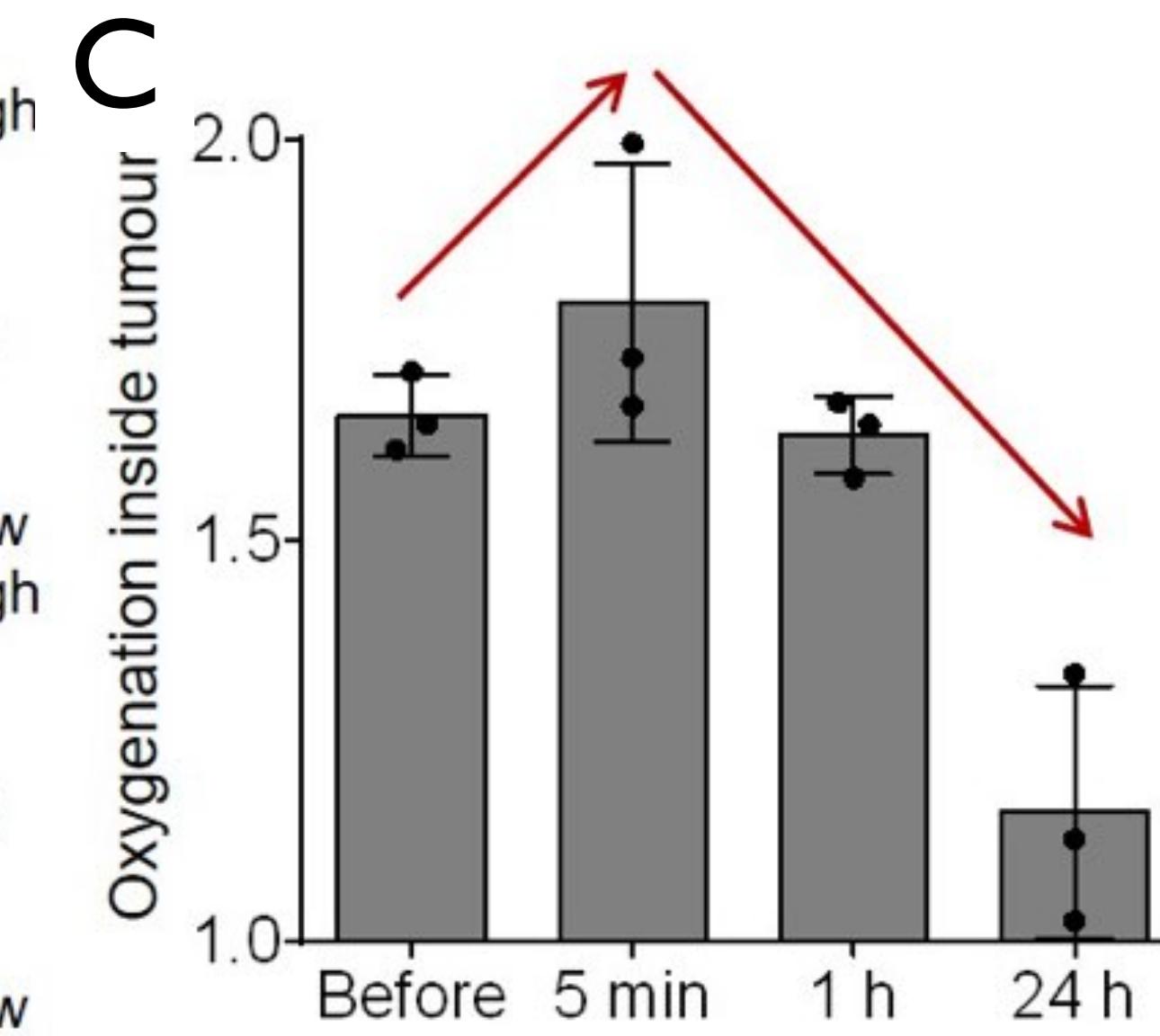
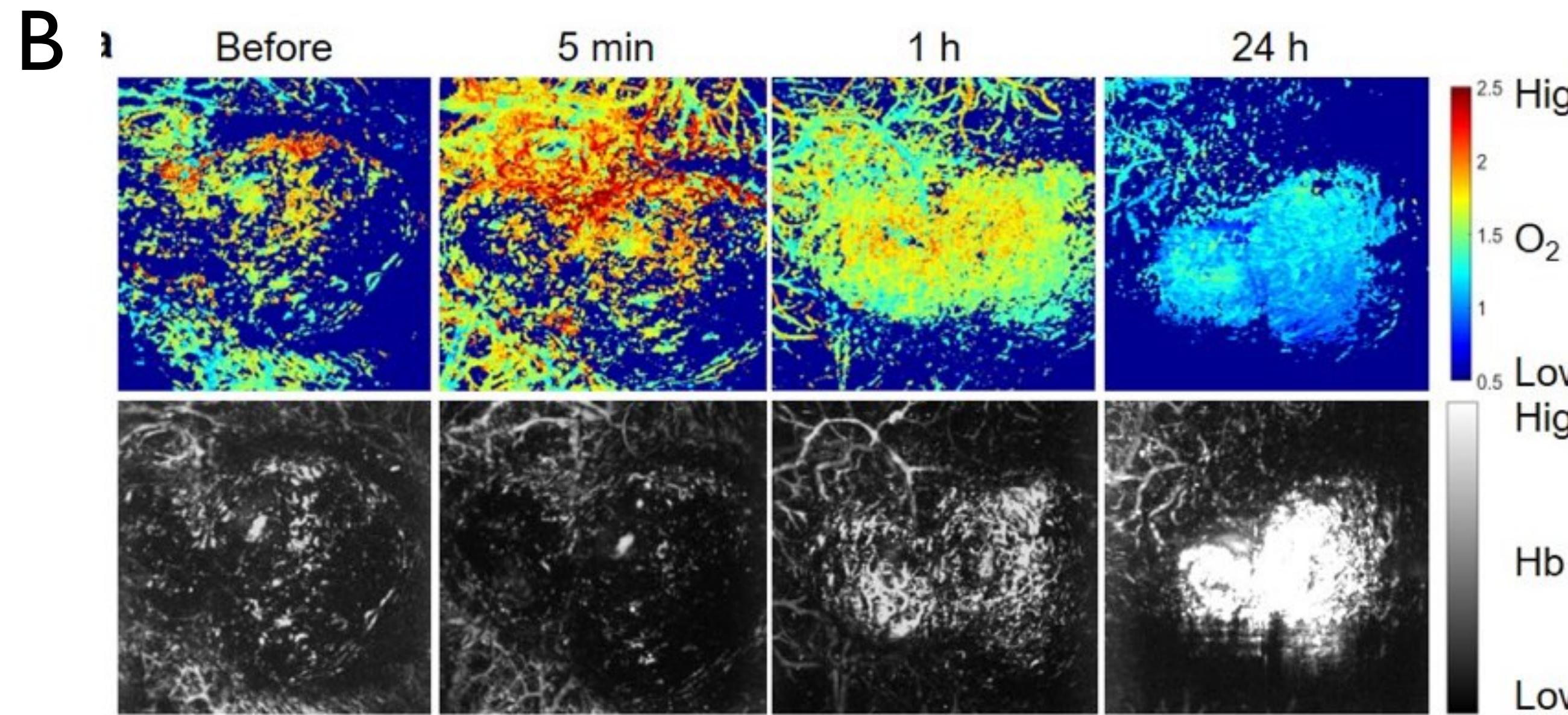
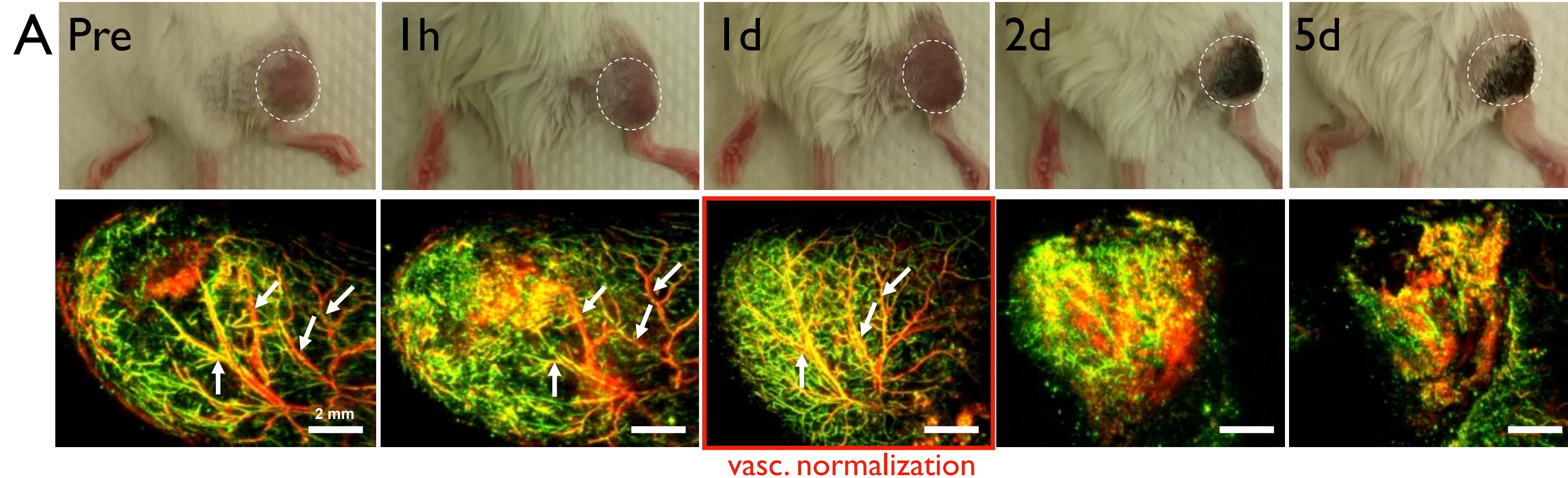
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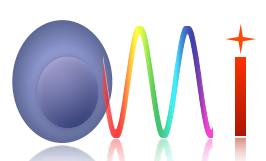
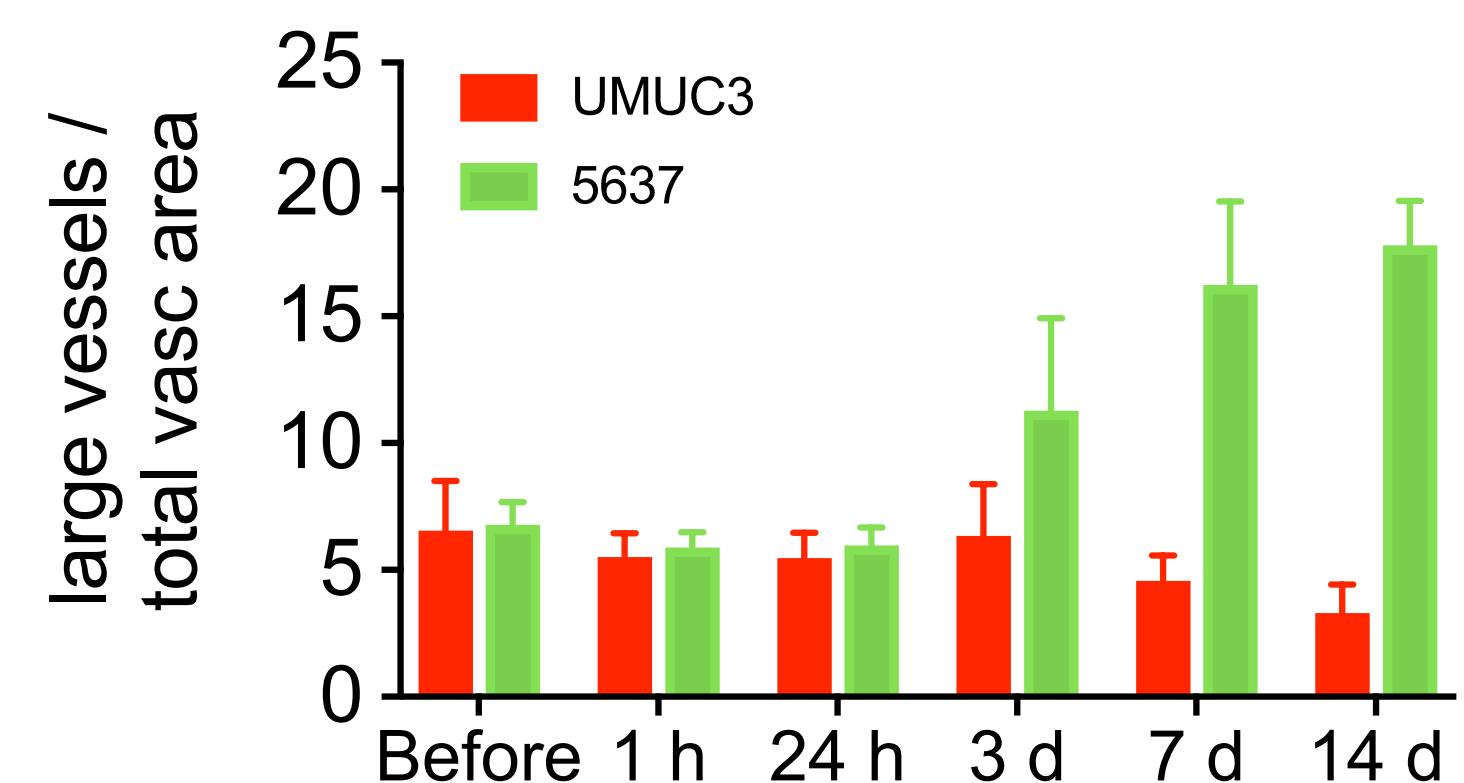
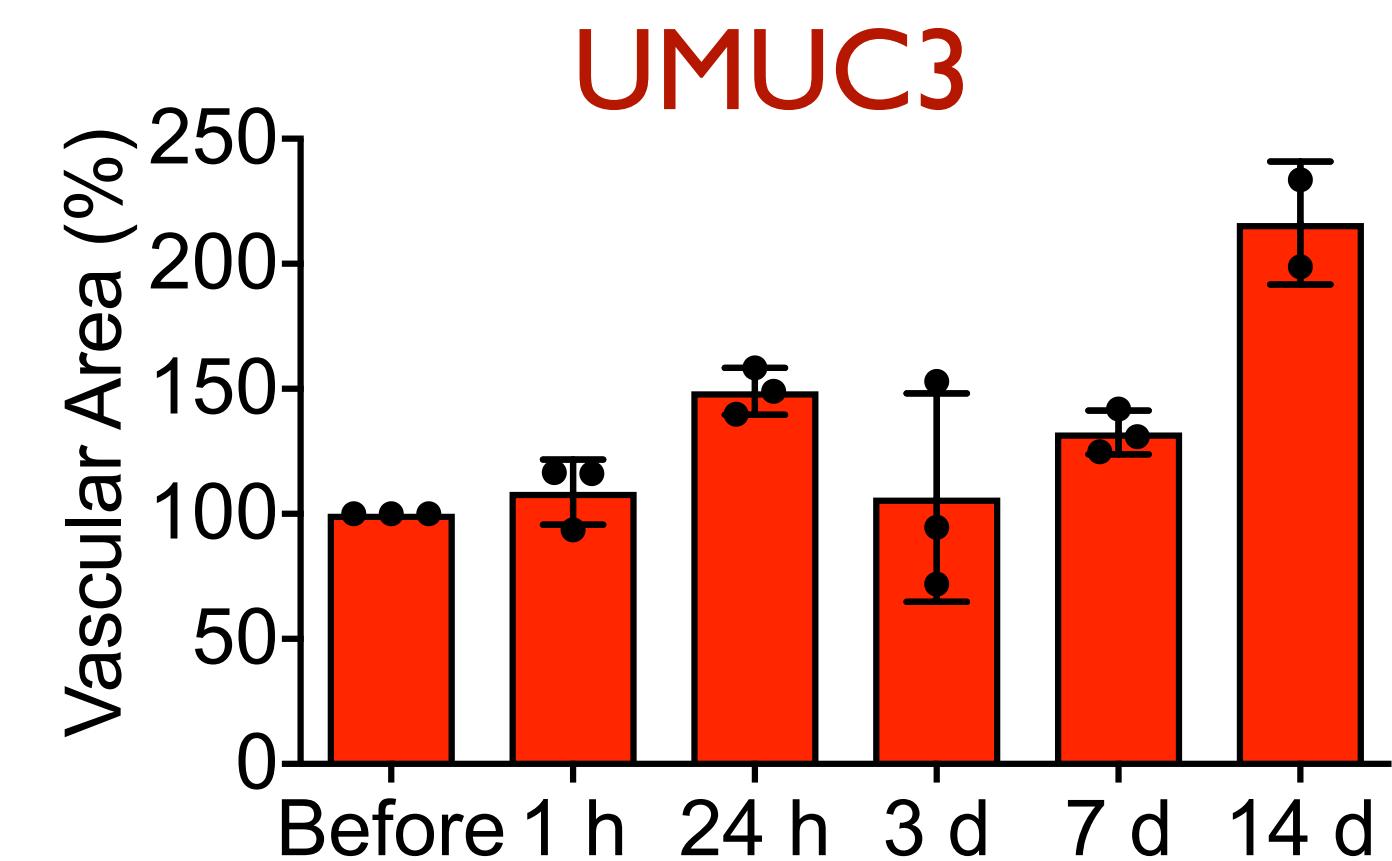
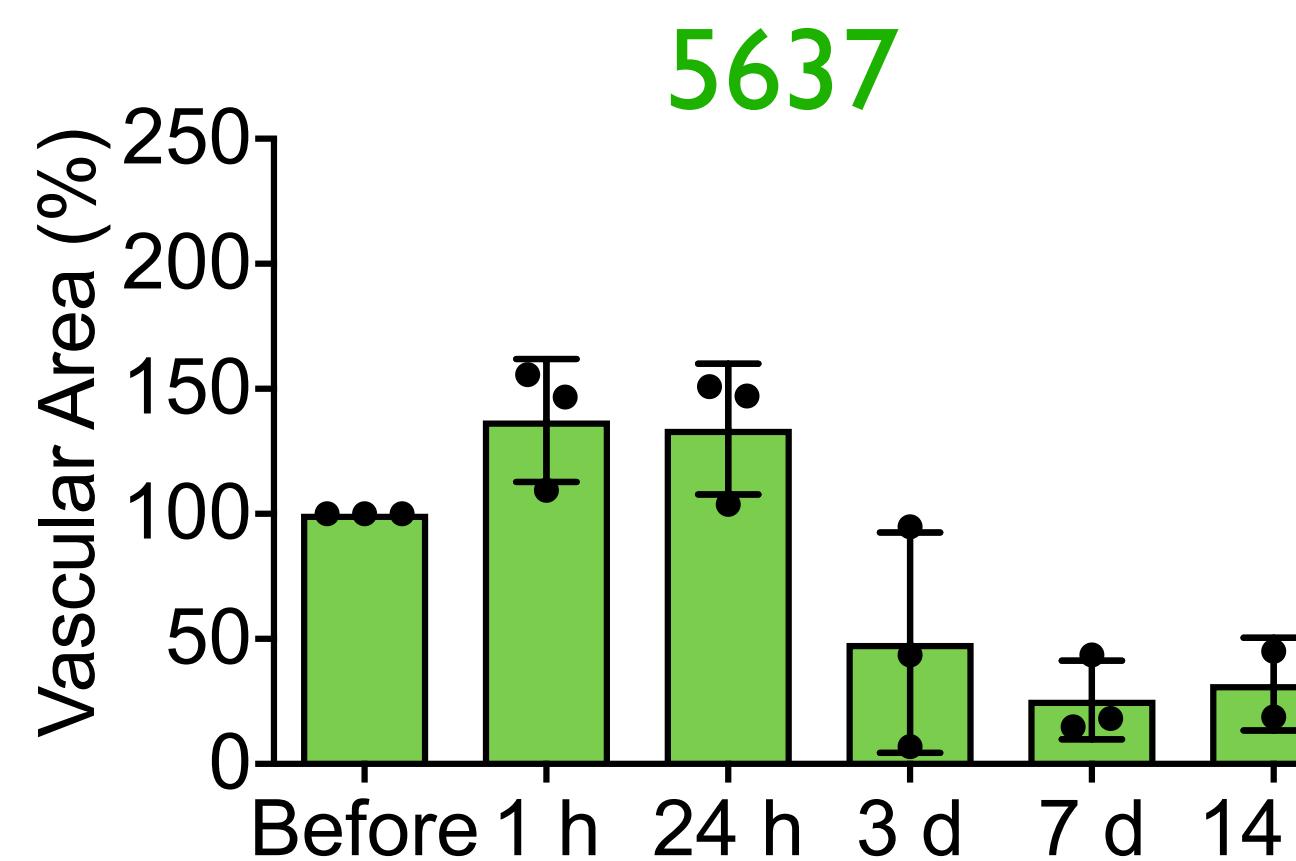
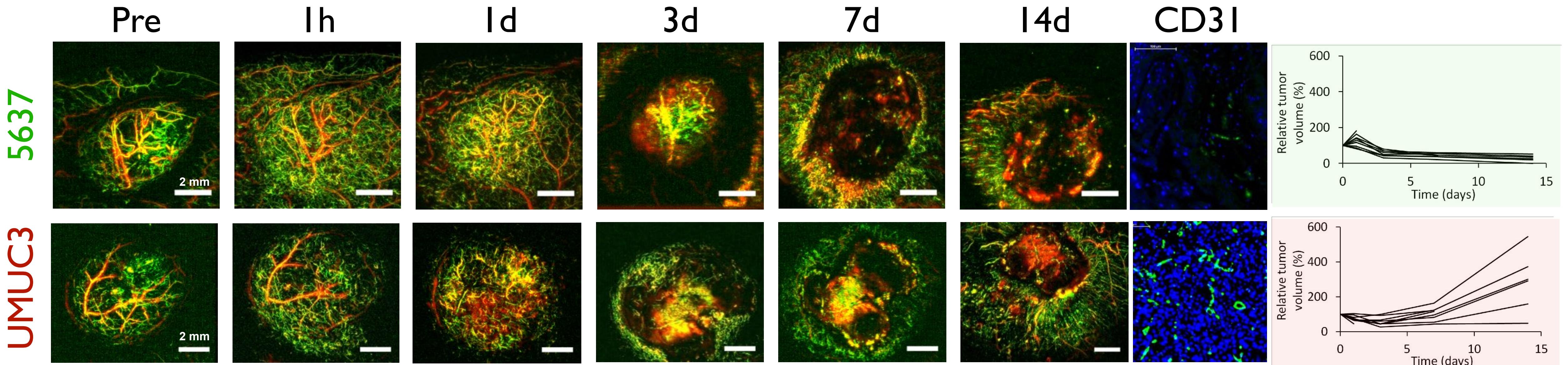
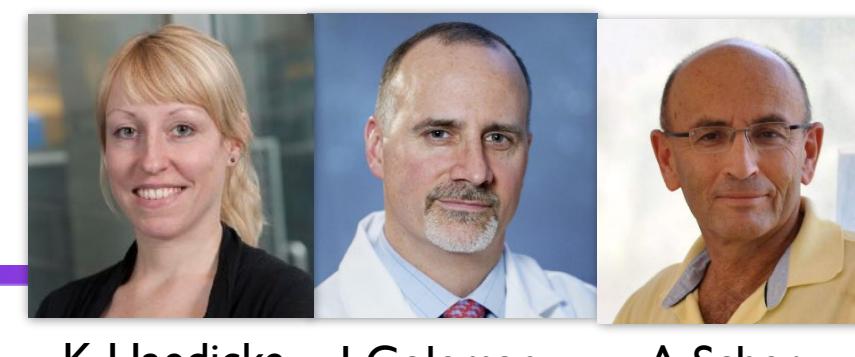
1h



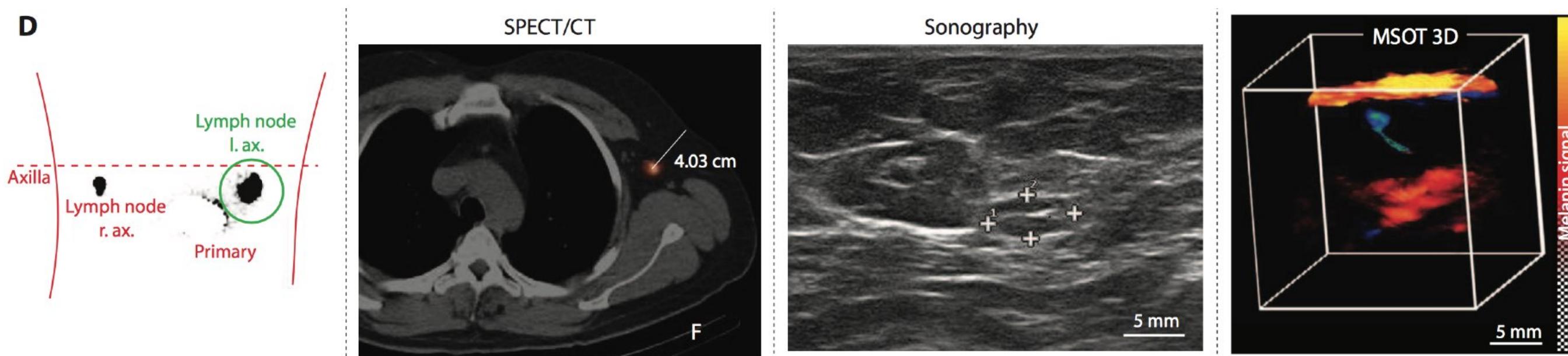
Imaging therapy at work - later time points



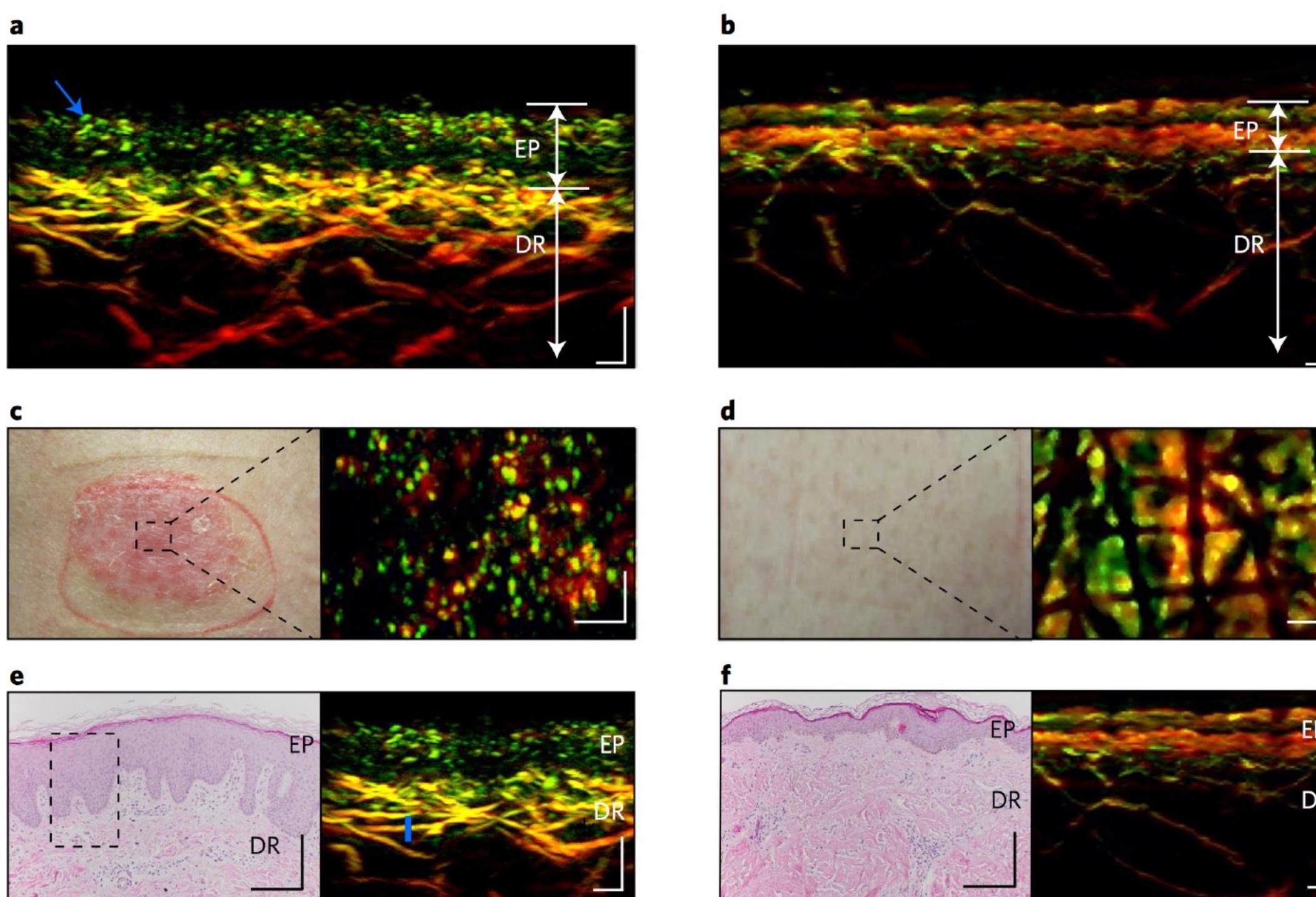
Predicting therapy response



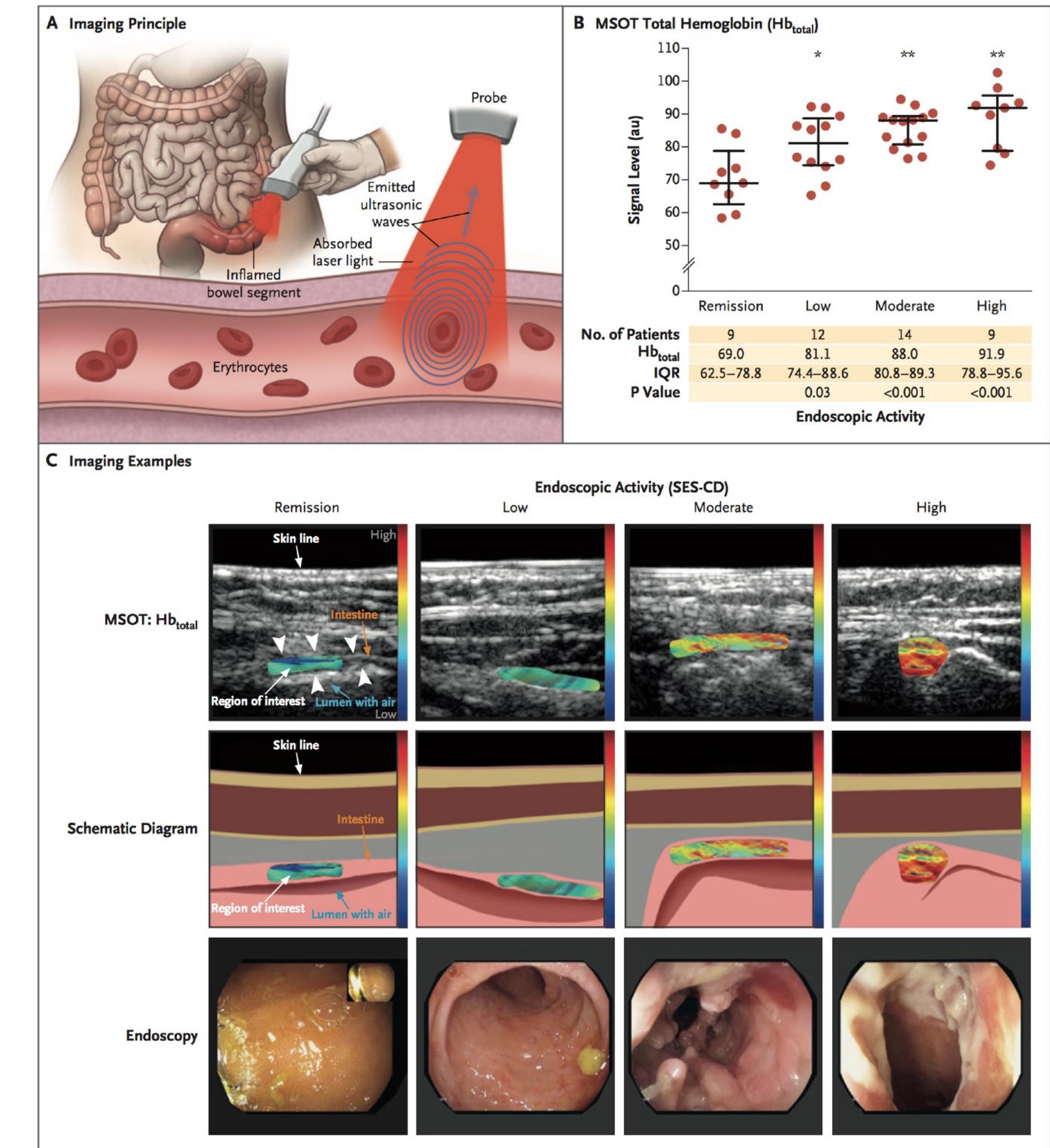
Clinical Optoacoustic Imaging



Stoffels I et al. (2015) Science Transl Med 7(317)



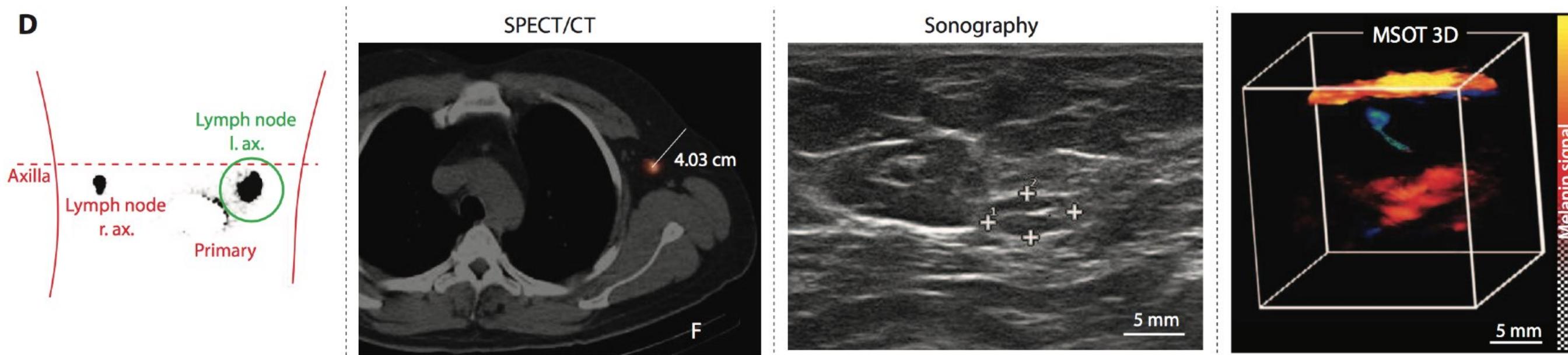
Aguirre J et al. (2017) Nature BME 1:0068



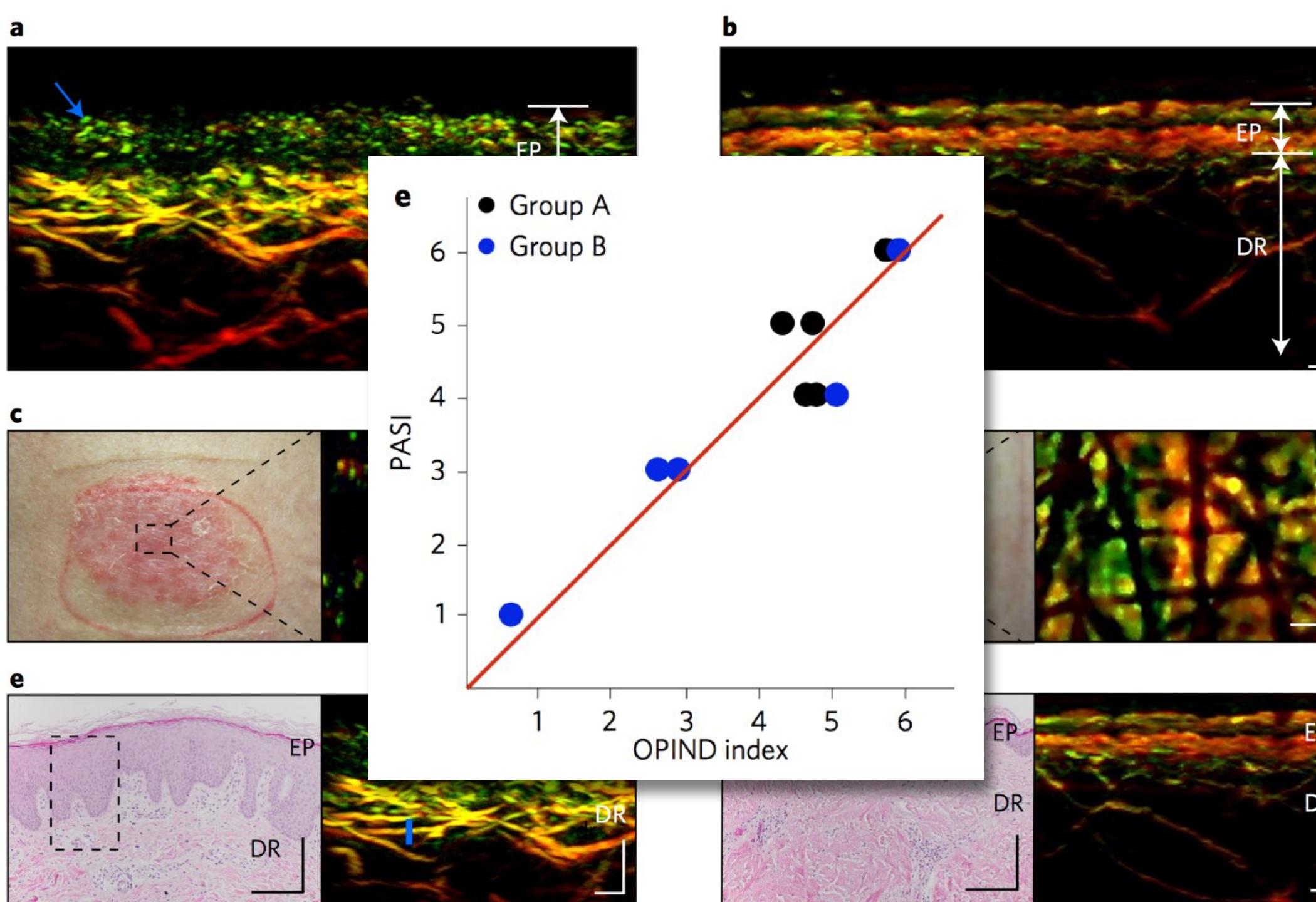
Knieling F et al. (2017) NEJM 376(13)



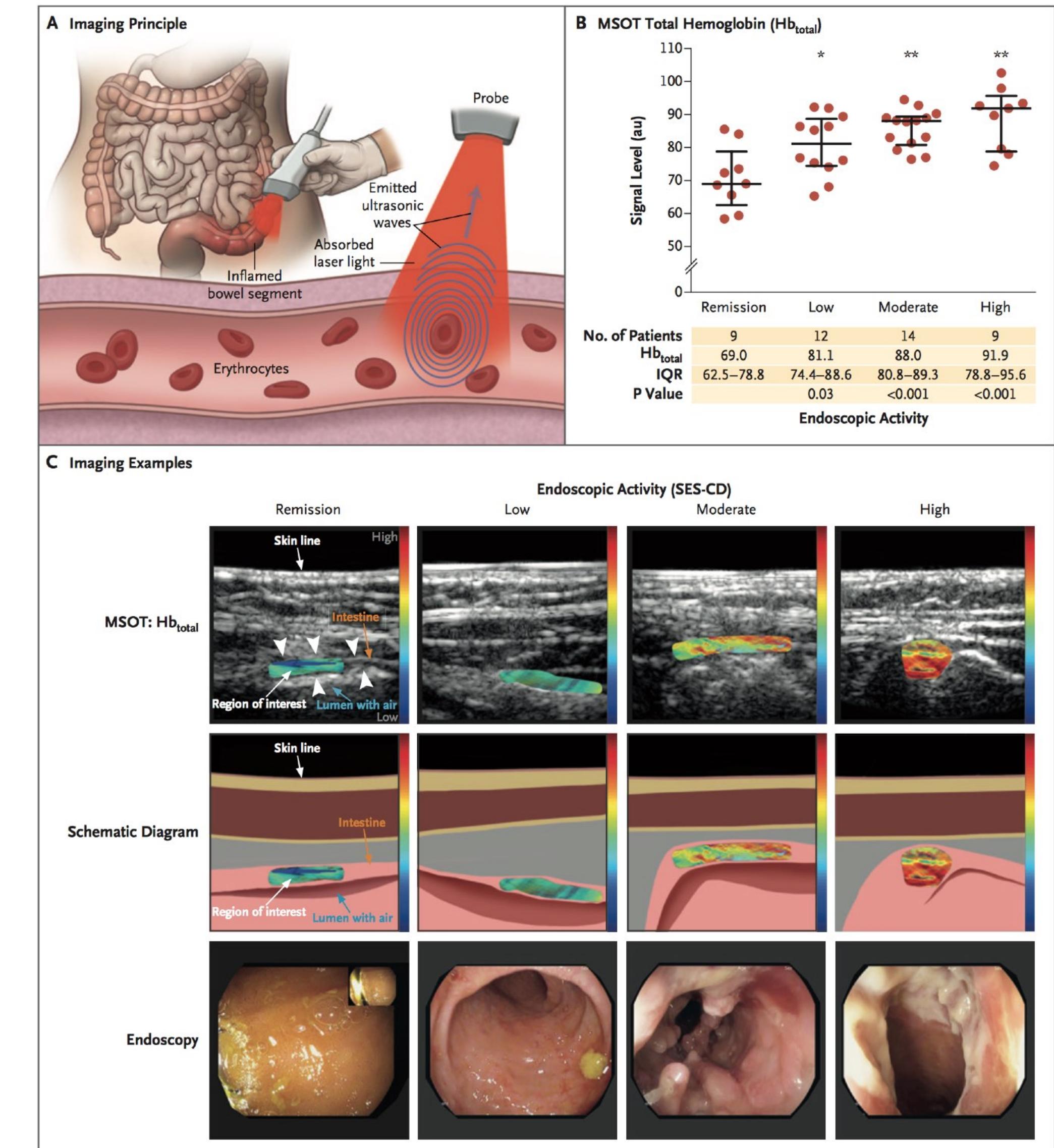
Clinical Optoacoustic Imaging



Stoffels I et al. (2015) Science Transl Med 7(317)

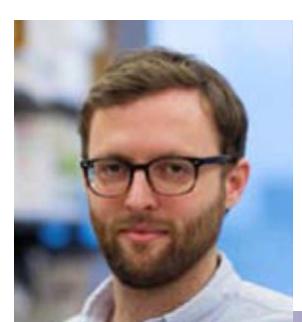


Aguirre J et al. (2017) Nature BME 1:0068



Knieling F et al. (2017) NEJM 376(13)



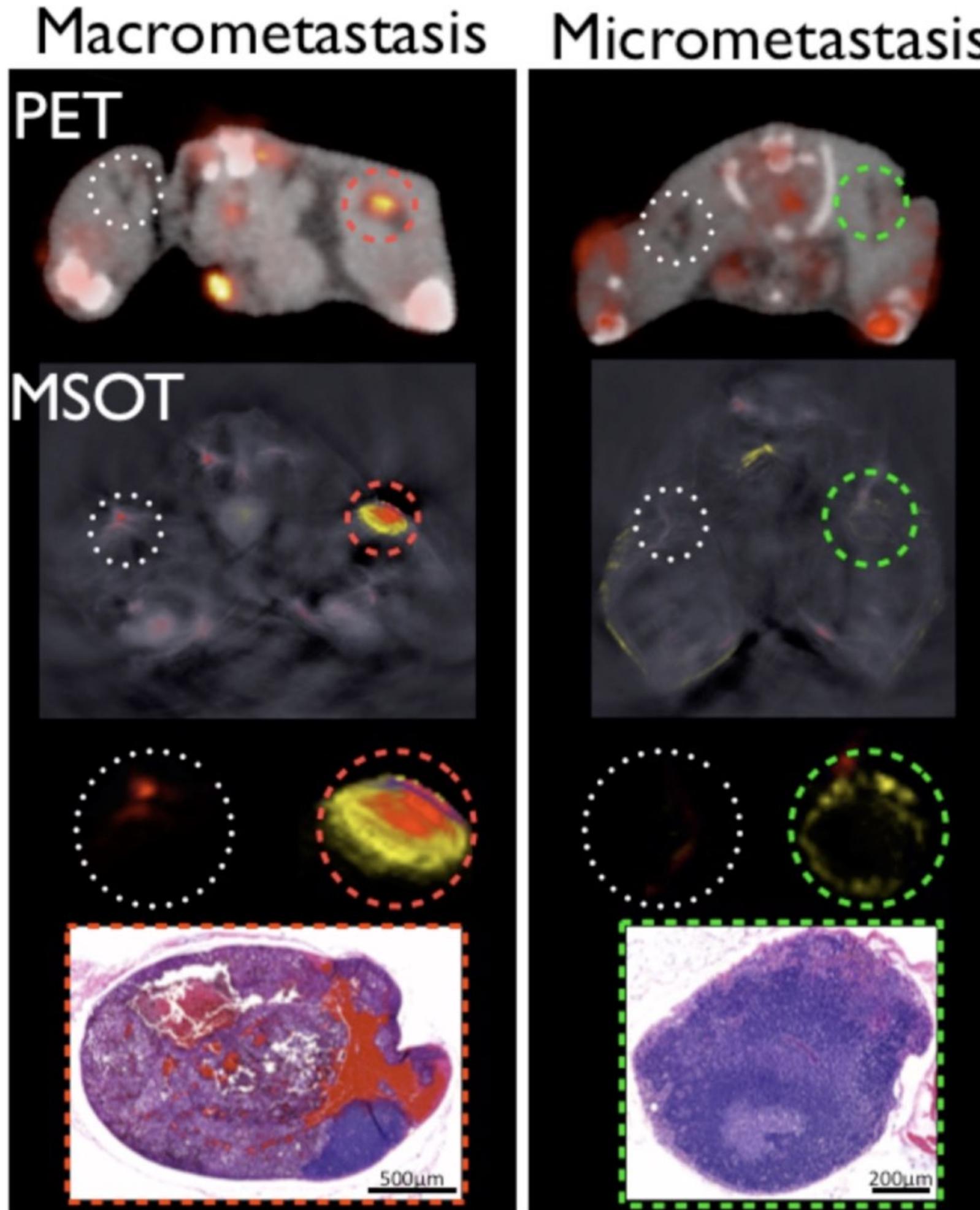


Melanin as contrast agent

V Neuschmelting

Melanoma model

Lymph node metastases





Melanin as contrast agent

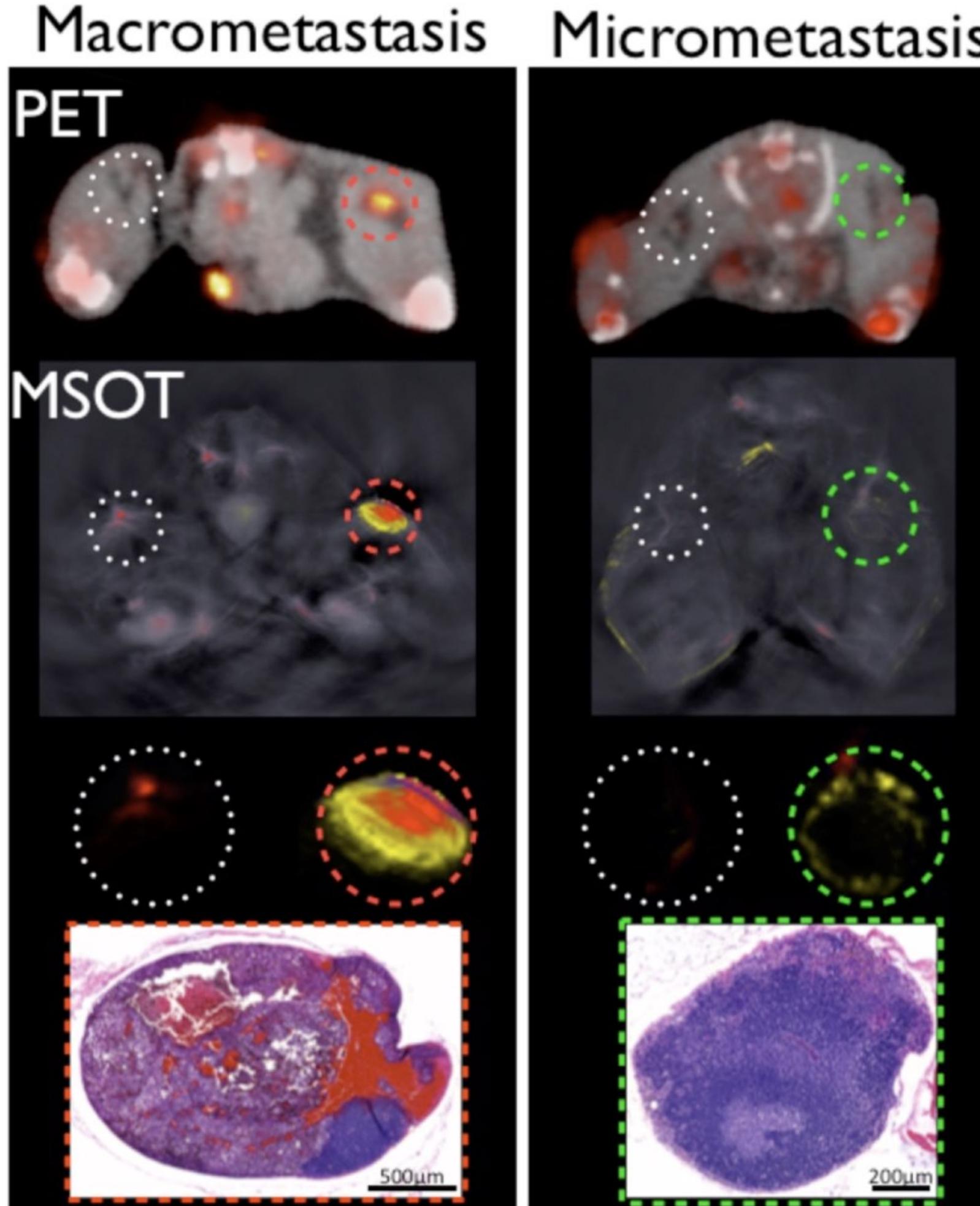


V Neuschmelting

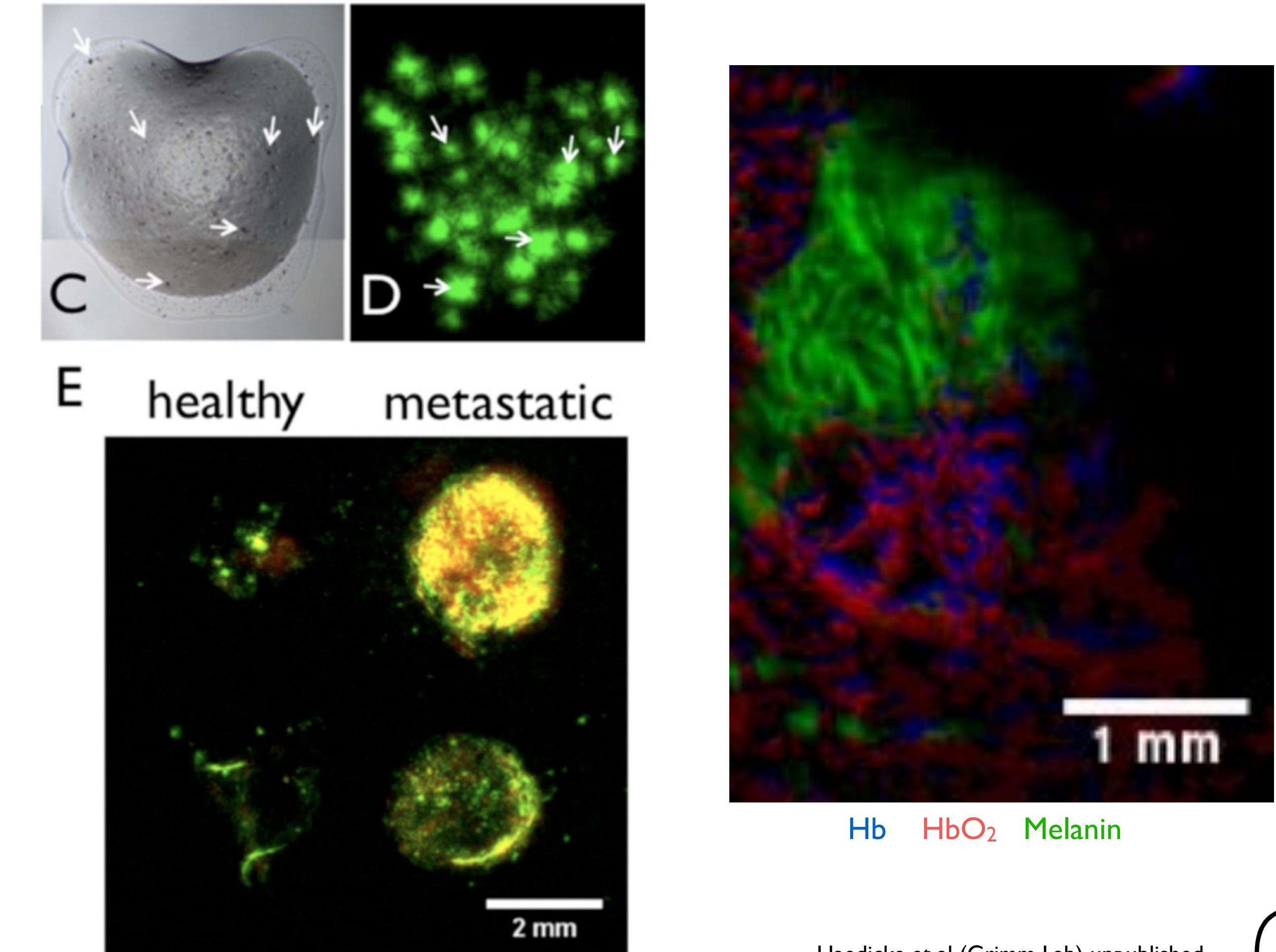
K Haedicke

Melanoma model

Lymph node metastases



mRSOM

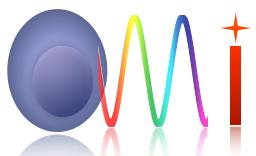
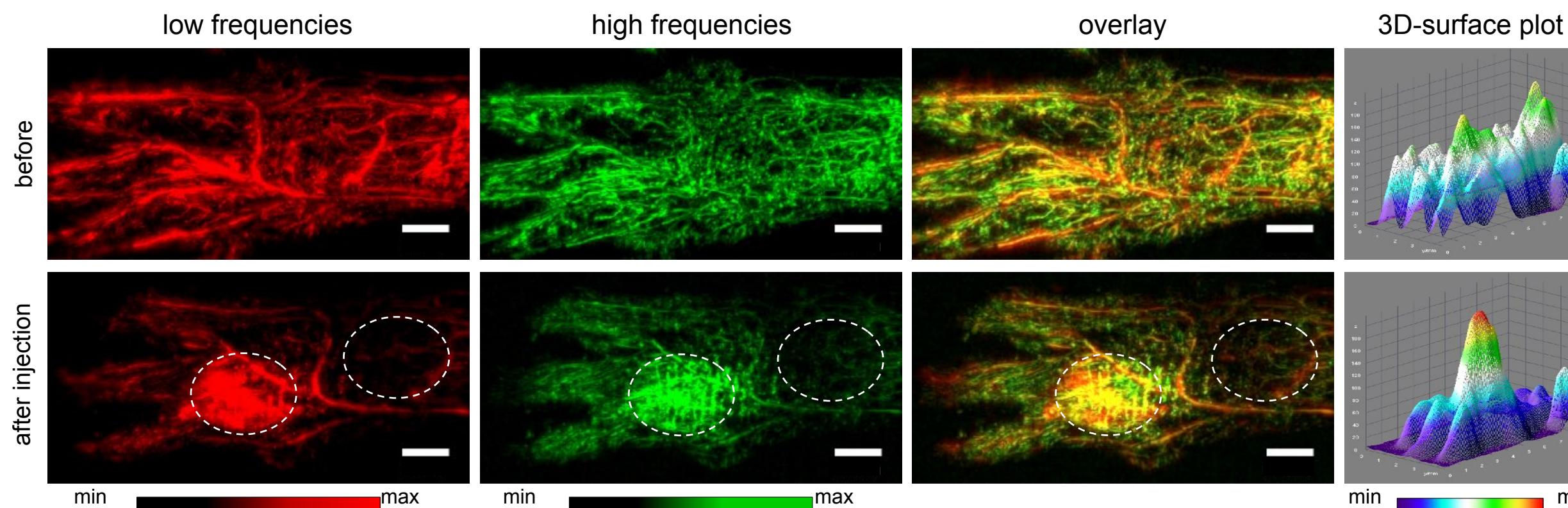
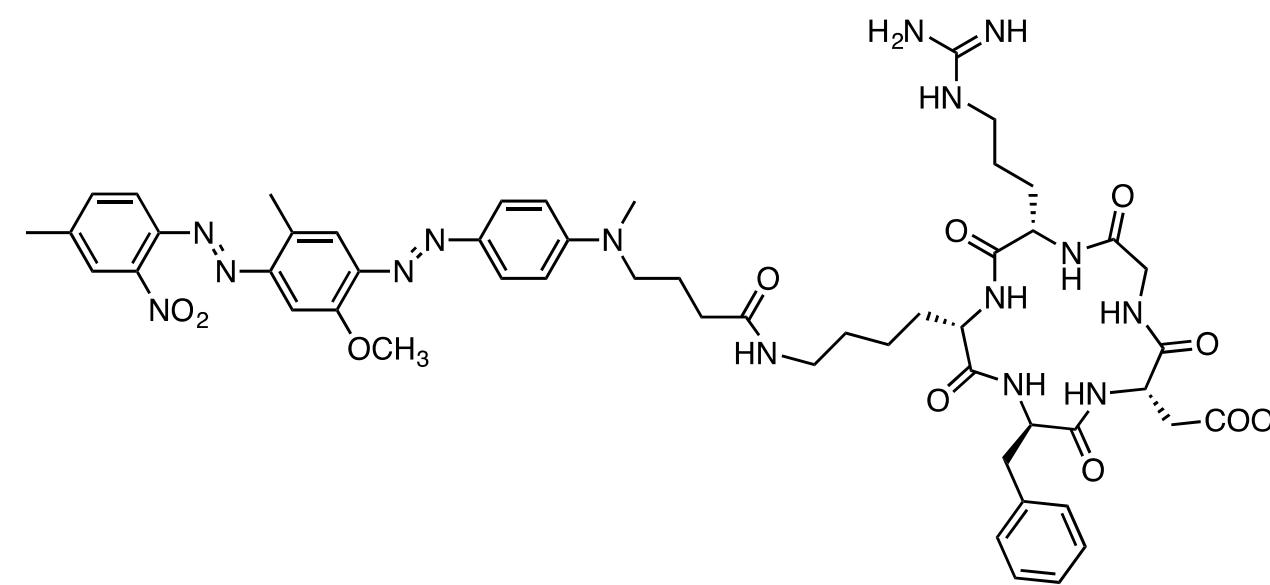




K Haedicke

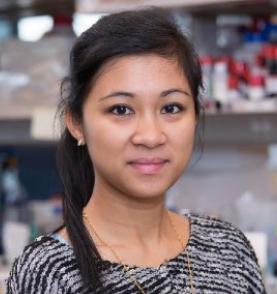
Quenchers as contrast agents

BHQ-1-RGD





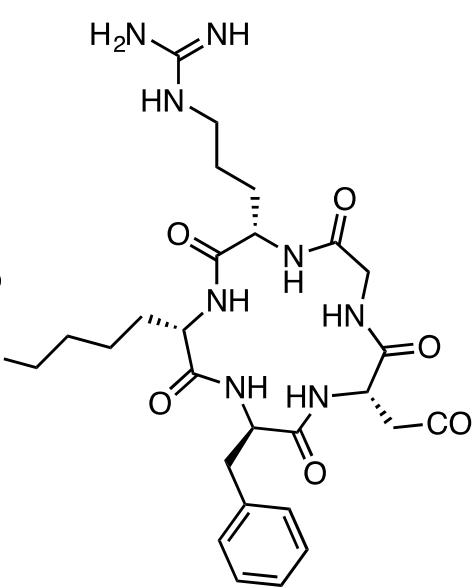
K Haedicke



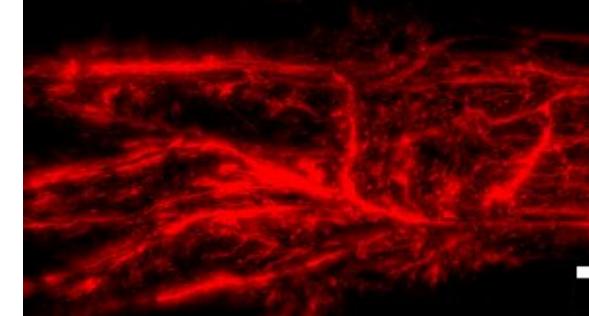
S Roberts

Quenchers as contrast agents

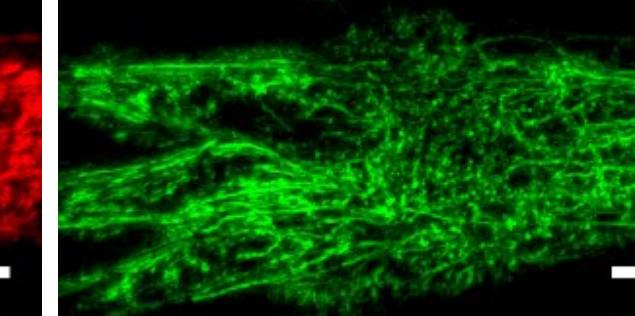
BHQ-1-RGD



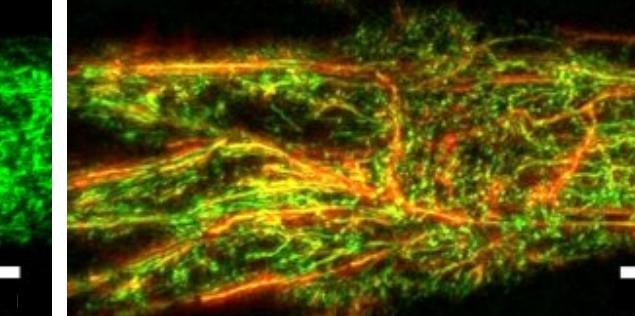
low frequencies



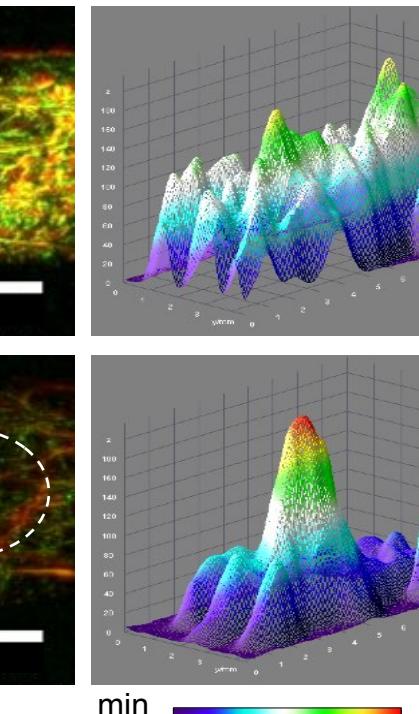
high frequencies



overlay



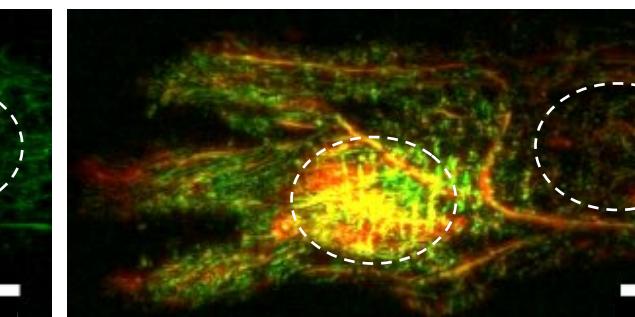
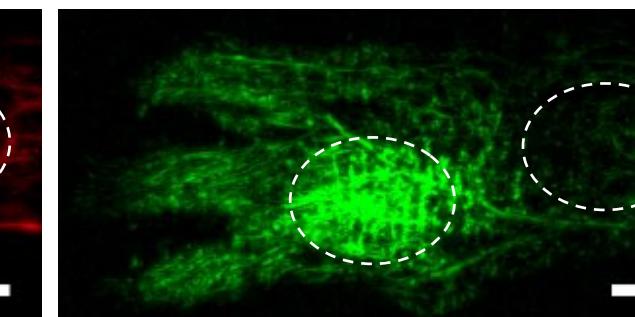
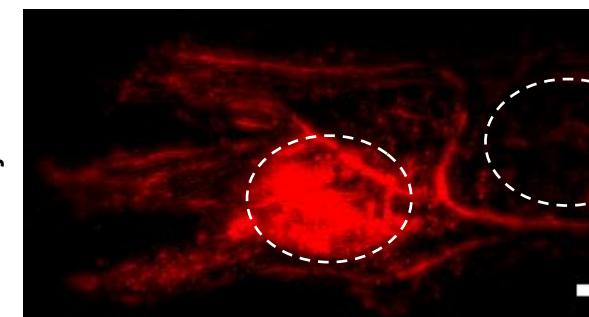
3D-surface plot



min max

min max

after injection



min max

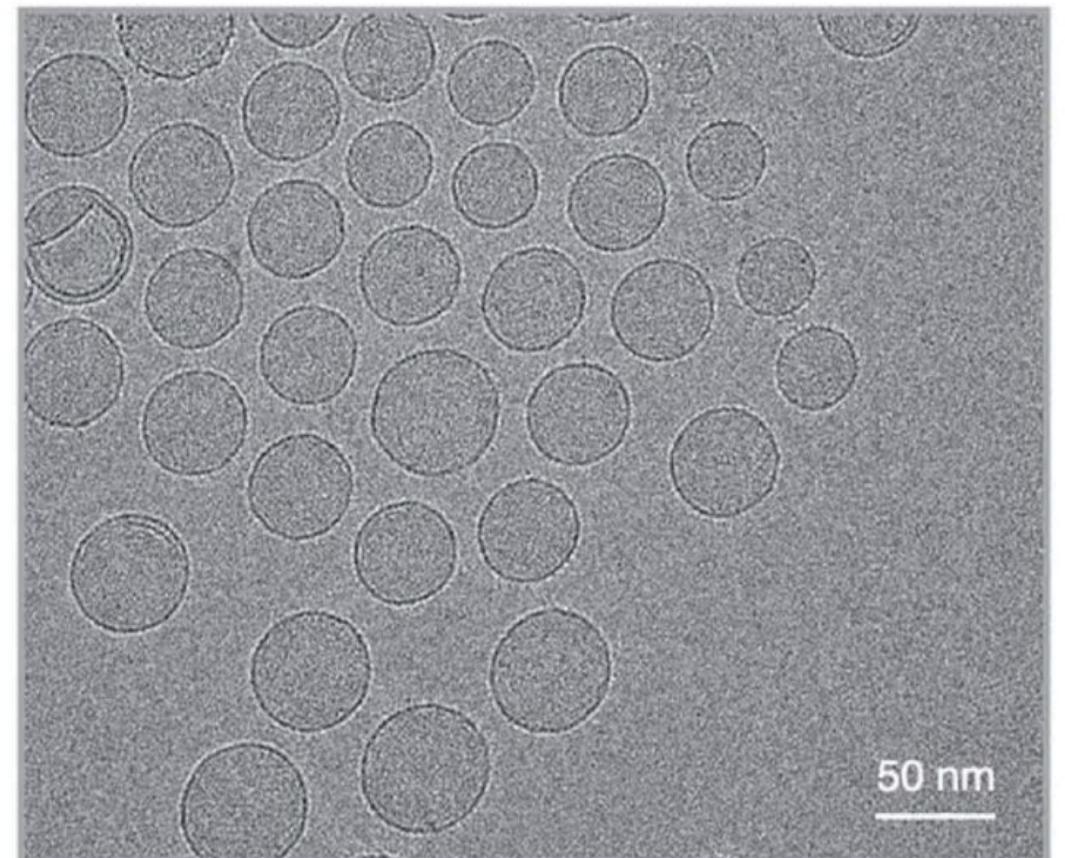
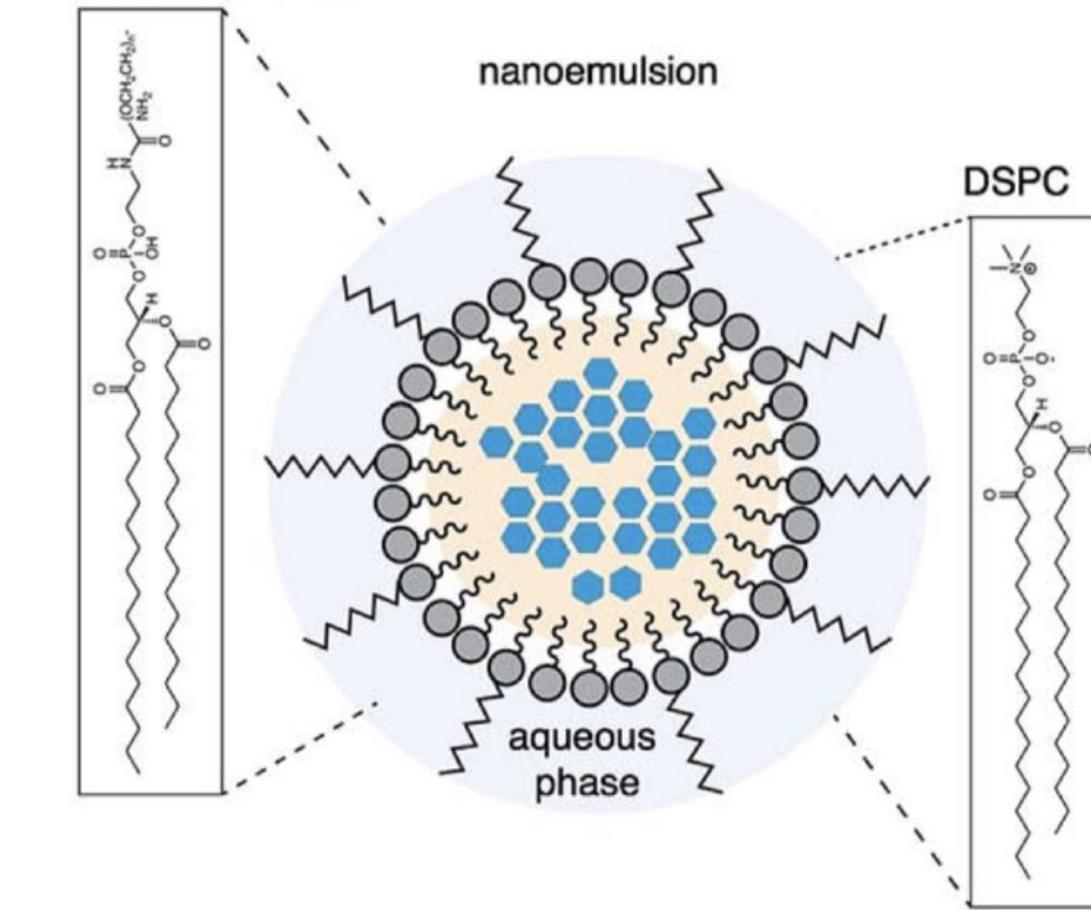
formulate
lipids: oil: NIR dye
1.0:0.5:0.01 weight ratio

sonicate
13 mins
60% duty cycle
30% output power

purify + concentrate

nanoemulsion

DSPE-PEG2000





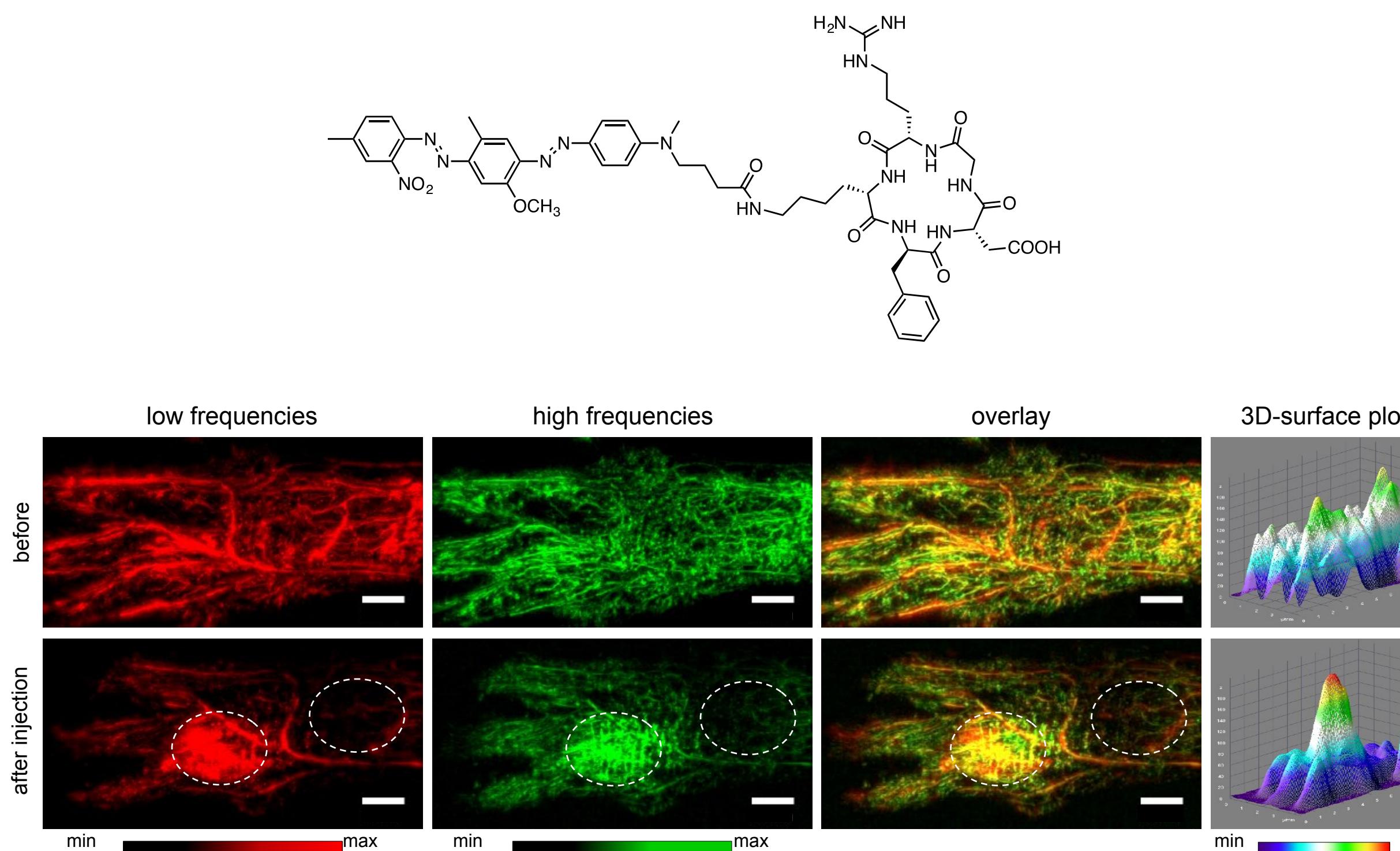
K Haedicke



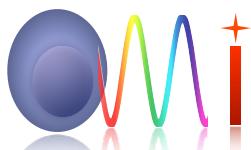
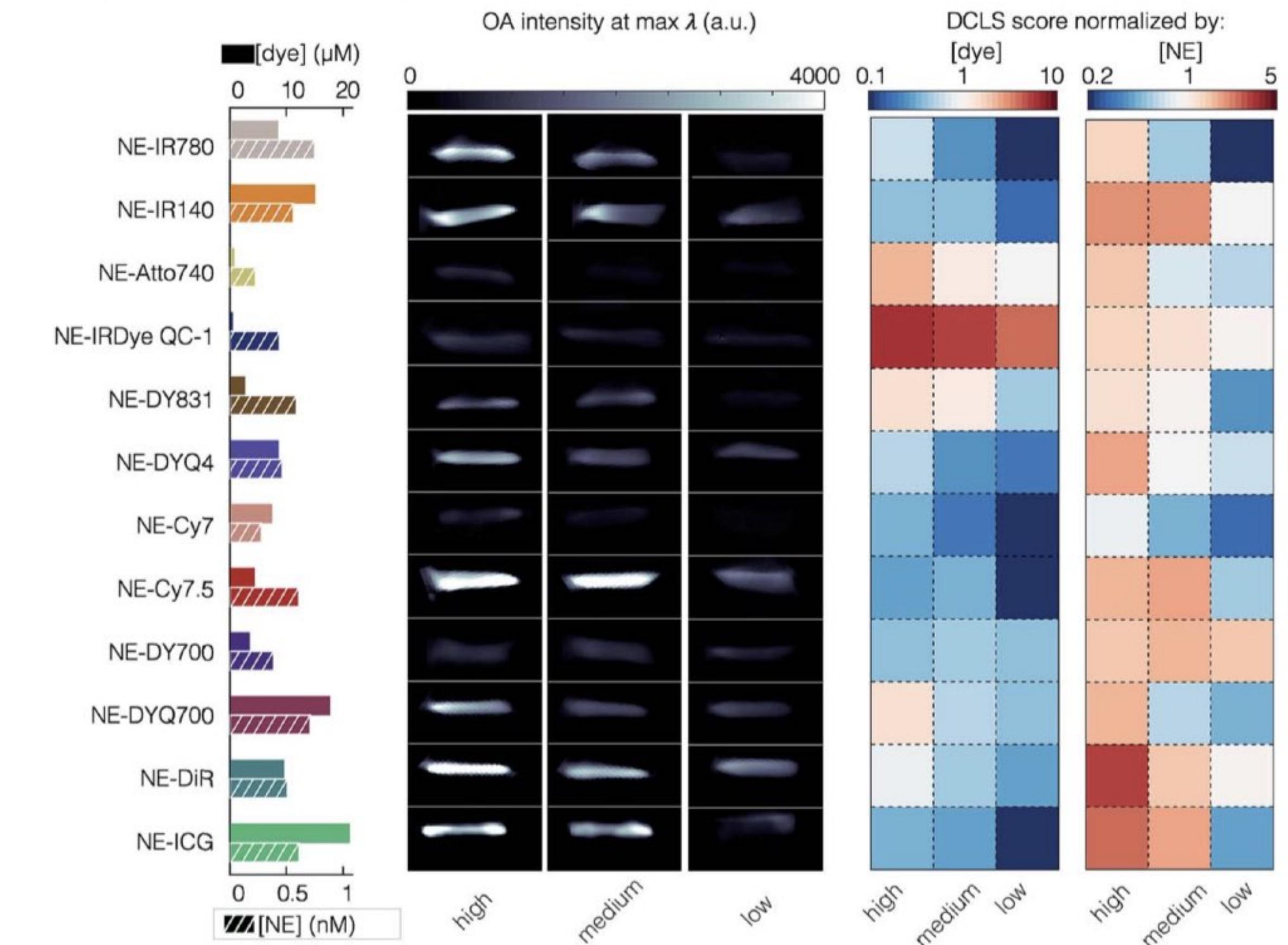
S Roberts

Quenchers as contrast agents

BHQ-1-RGD

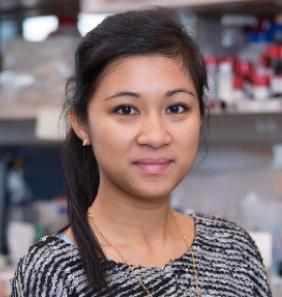


Library of quenchers





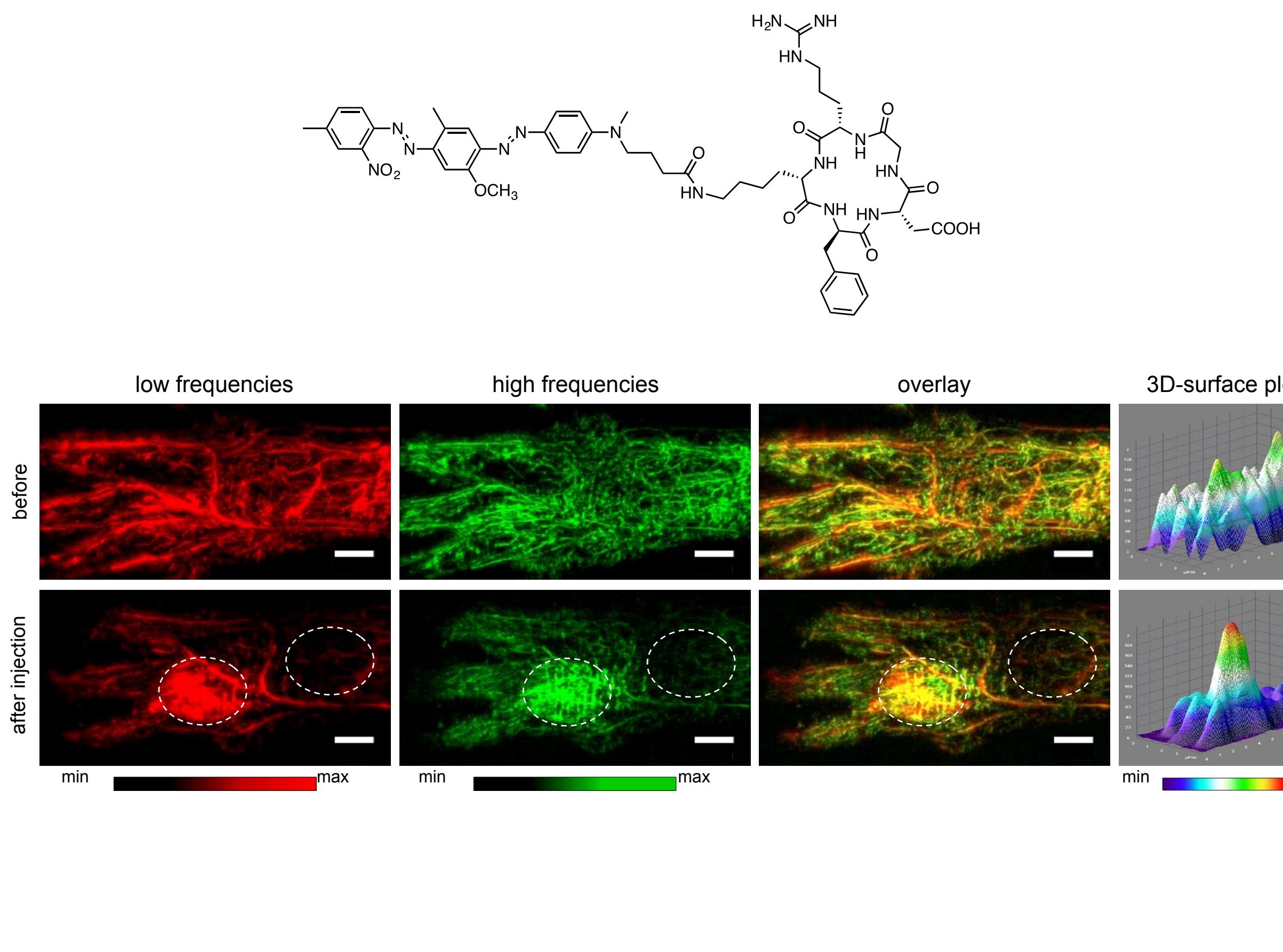
K Haedicke



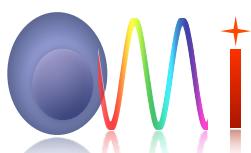
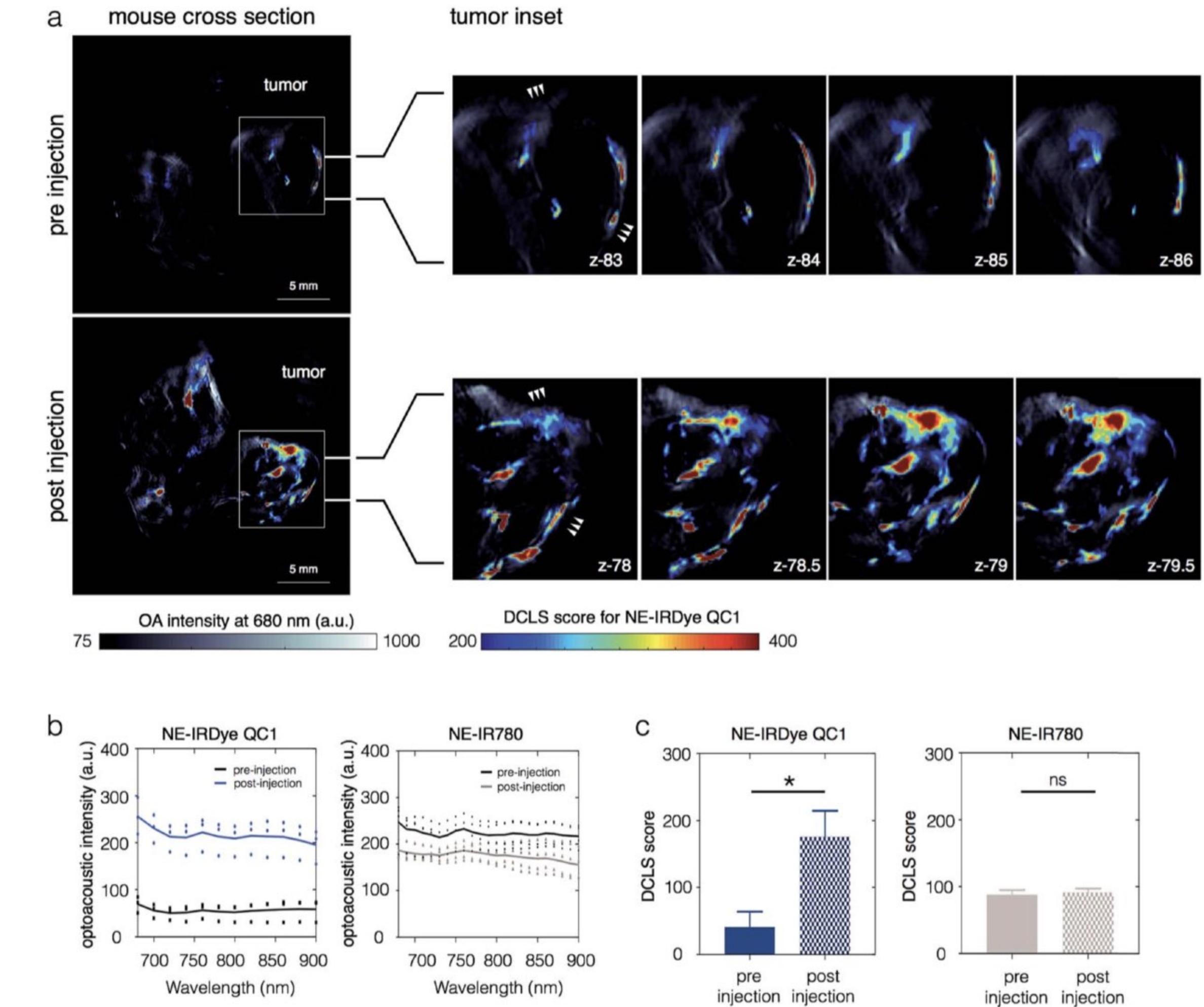
S Roberts

Quenchers as contrast agents

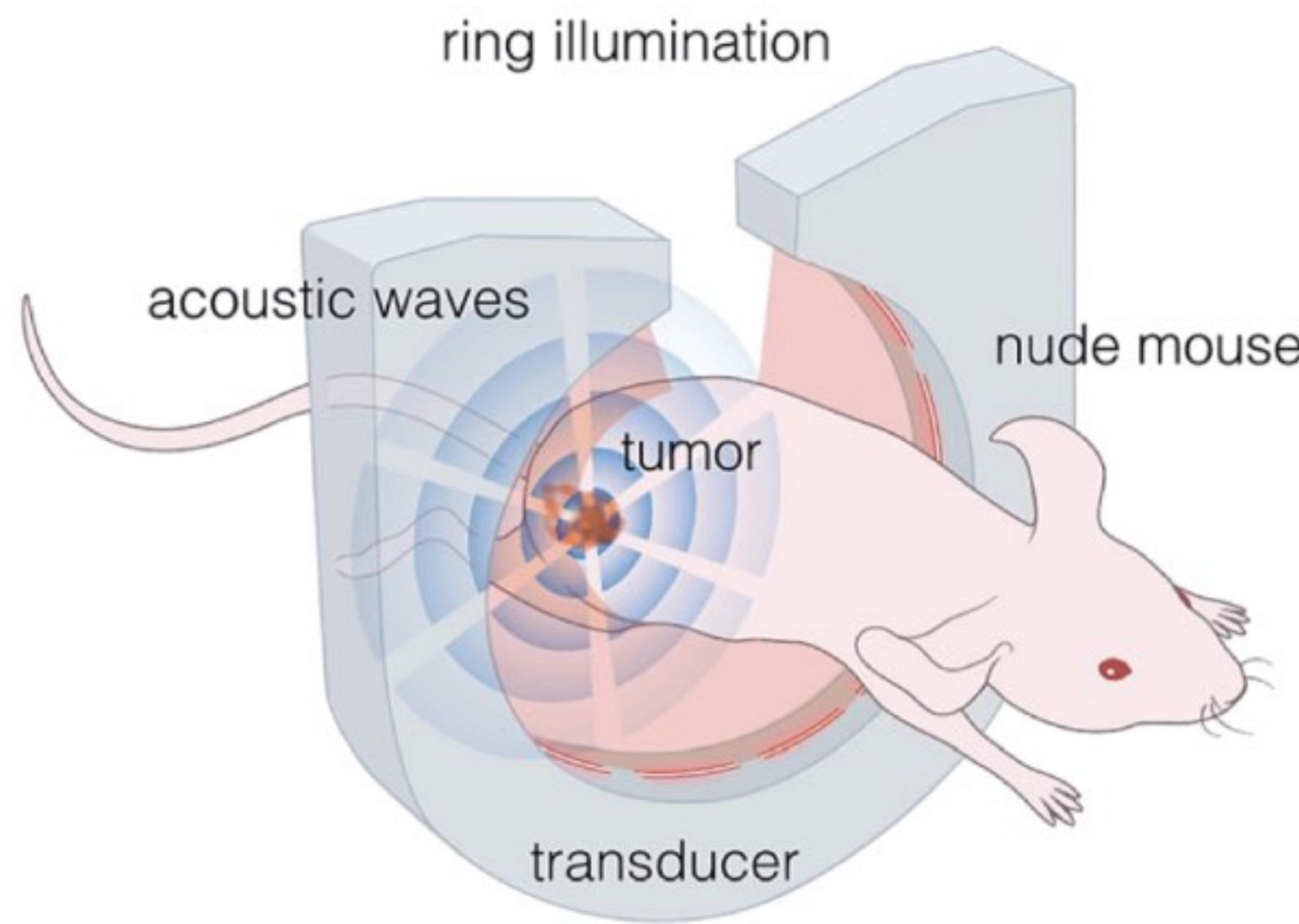
BHQ-1-RGD



Library of quenchers



MSOT



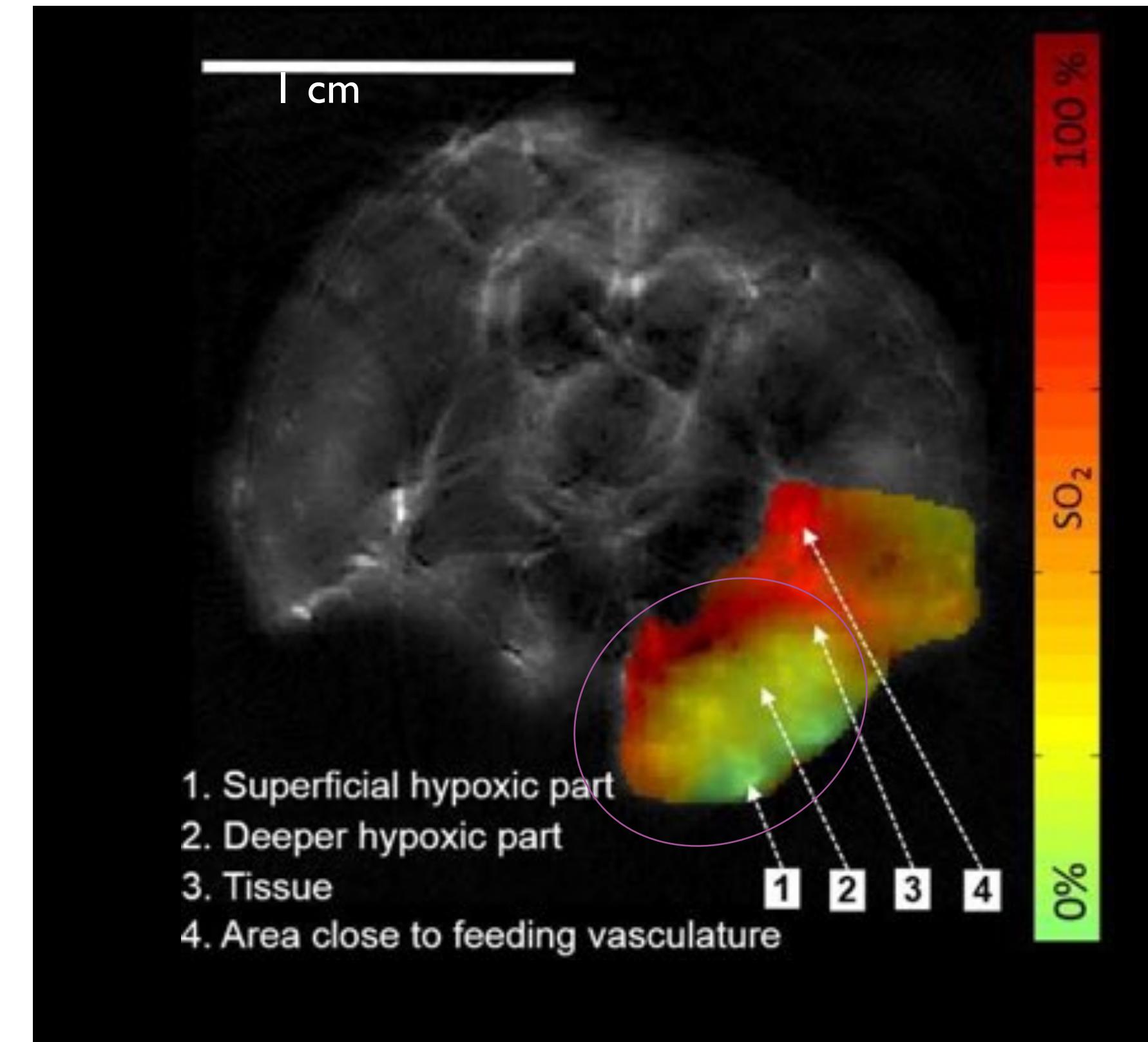
LASER:

680–900 nm
10 ns pulses
100 mJ

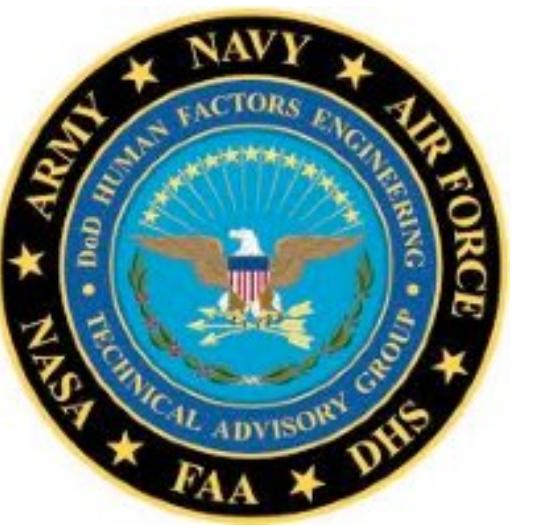
US:

256 elements
270° array

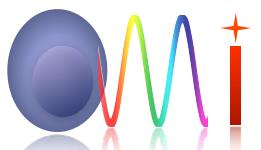
5 MHz
150 μm resolution



Acknowledgements



NIH R01-EB033000
NIH R01-CA257811
NIH R56-EB030512
NIH R01-CA257811
MSKCC Society, ETC
Past DOD and NIH grants



Wonder is around every corner

