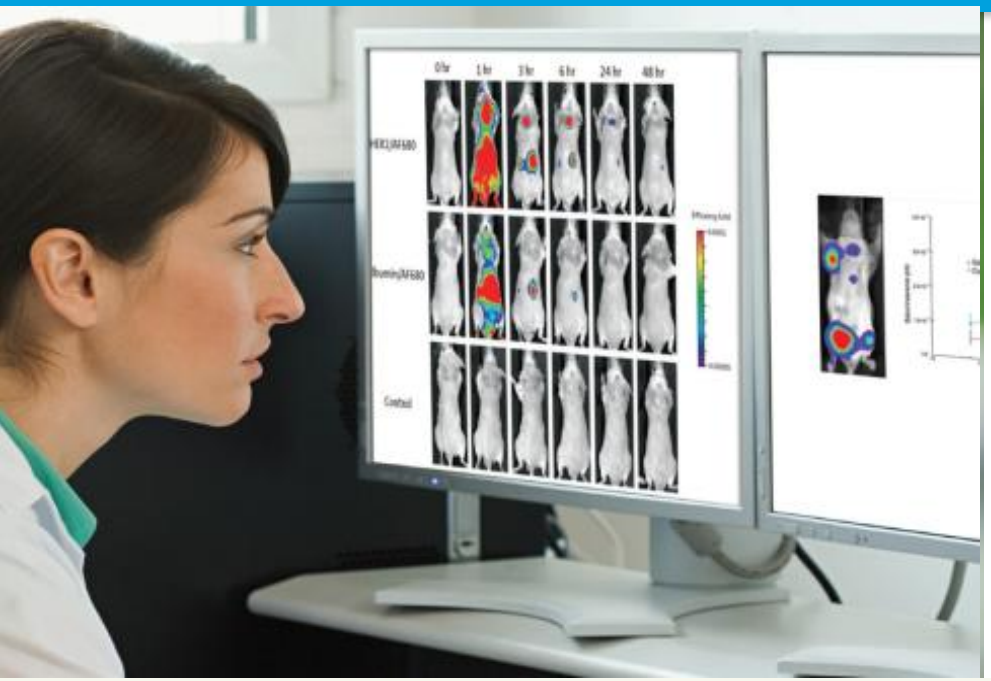
PerkinElmer
For the Better

HUMAN HEALTH | ENVIRONMENTAL HEALTH

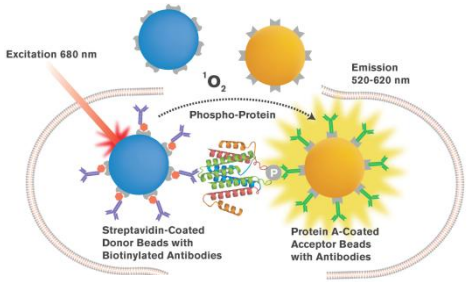


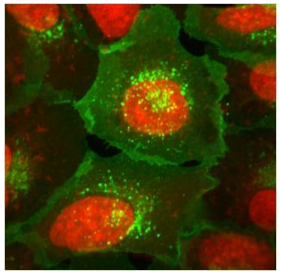
小動物光學影像技術在生物醫學上之應用

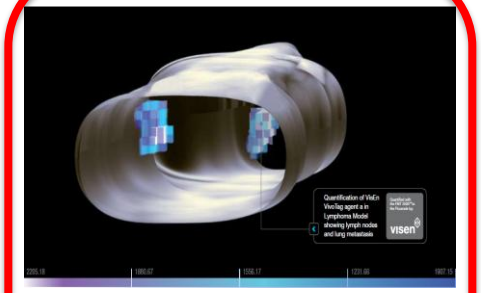
曾筱筑 產品應用專員
博克科技有限公司 J&H Technology Co., Ltd.
http://www.jnhtech.com.tw

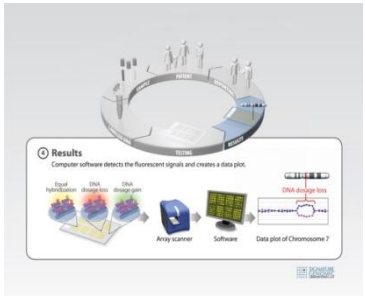
Rational

WELL → CELL → ANIMAL → HUMAN









Now , Bio-discovery with the FMT platforms we provide the world leading portfolio for translational disease research, drug discovery and clinical development

.. .integrating all stages of research workflow

Why animal imaging - natural bridge to the clinic -

- More and better information

 - real time read out of biology in context

 -earlier decision making process in drug discovery

- Non-invasive monitoring of

- biological processes

- disease progression

- therapy response

 -in various animal models e.g. for Cancer, CVD, Neurologicaly, Inflammation,…

- Longitudinal studies

 -Better data

 -Reducing # animals

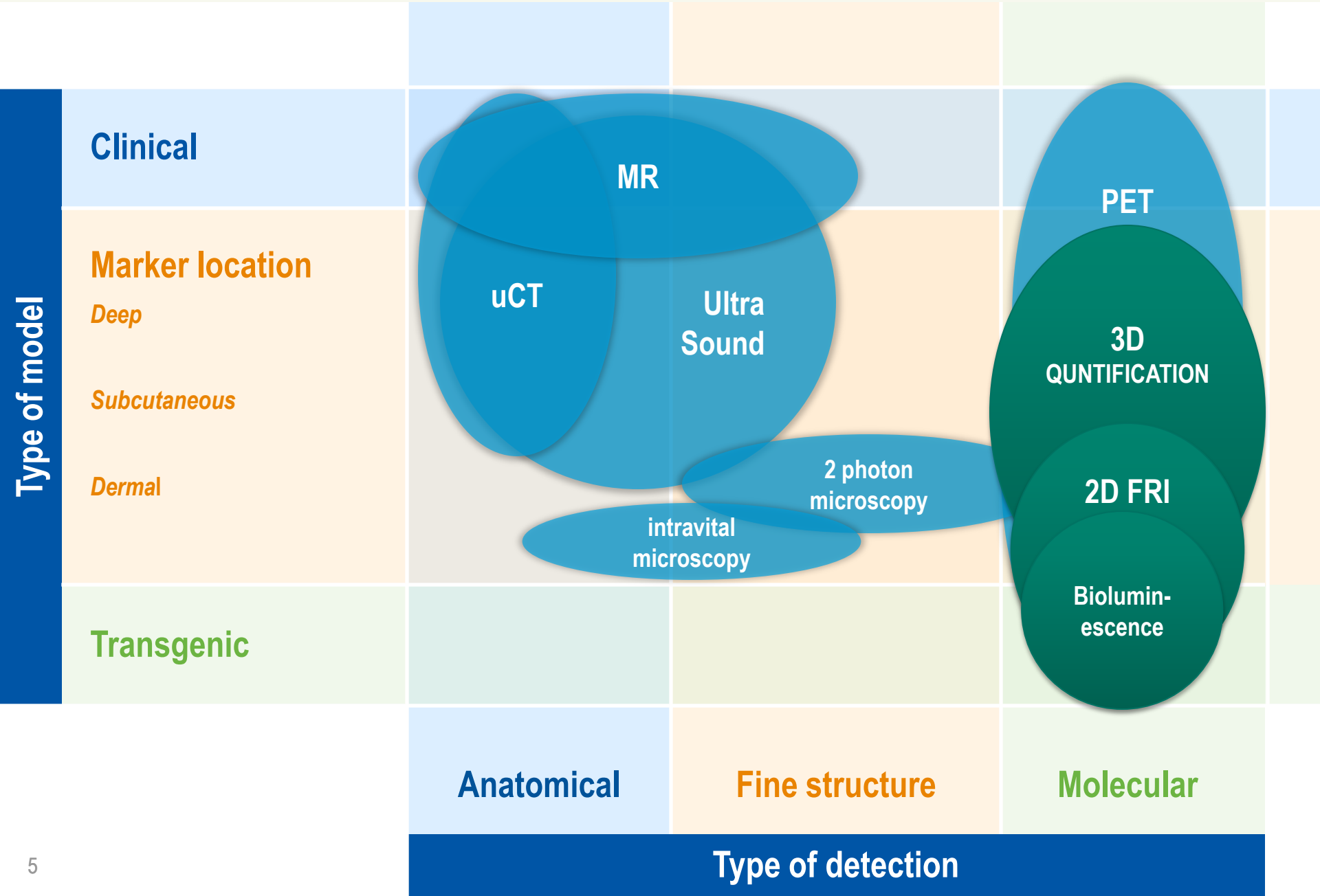
 -Cost savings for Institutes

- Translatability

-Predictive tools for clinical practice

4

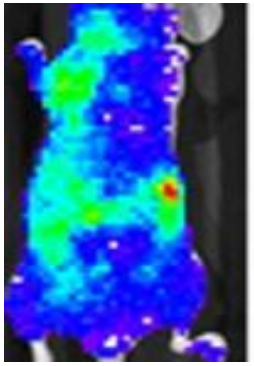
In Vivo Imaging Landscape

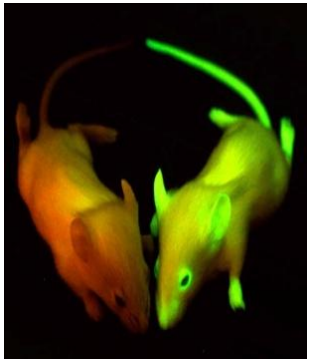


Optical Imaging Approaches

Bioluminescence & Fluorescent Proteins

- Powerful approach using animals/cells with modified genetics
- Uses promoter systems for deep understanding of underlying mechanisms





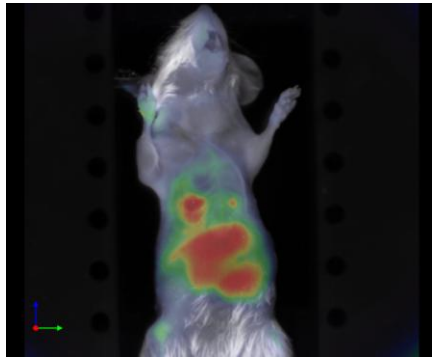
Bioluminescence & FPs

- Epifluorescence mostly, but brightness of luciferase imaging allows deep detection
- Research use only
- Not translatable

Fluorescent Agents (Red/NIR)

- Standard disease biology/models
- Injectable drug-like imaging agents to view biology

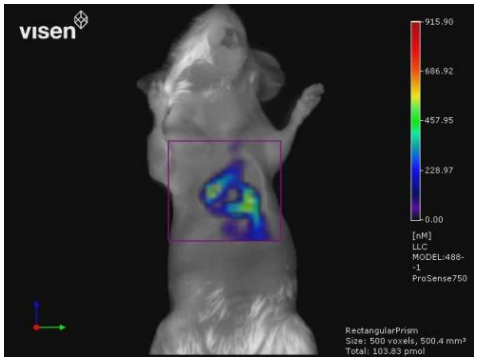
Epifluorescence



2D Fluorescence

- Qualitative images (2 dimensional surface reflectance imaging)
- Depth challenges with 2D in NIR
- Research and clinical applications

Tomography



3D Tomography

- Detection and quantification *in vivo* at all depths
- Tomographic datasets
- Technology and data for clinical translation

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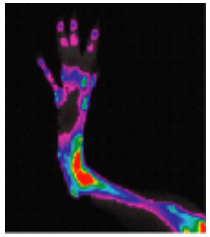
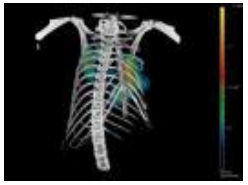
Tailored To Therapeutic Applications

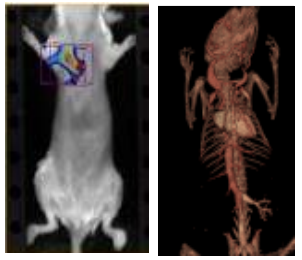


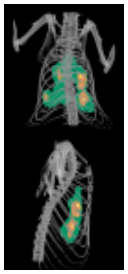
Inflammation



Oncology

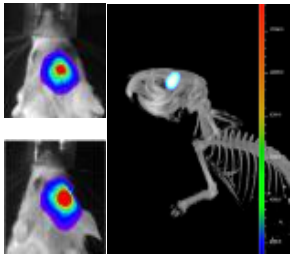
Cardiovascular Disease



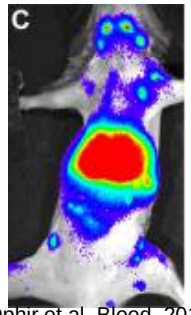


Infectious Diseases

Neuroscience

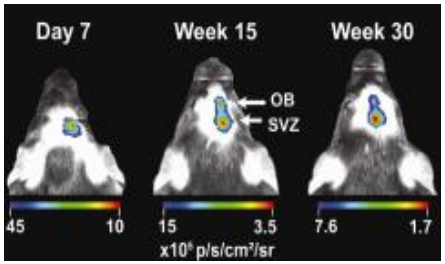


Immunology



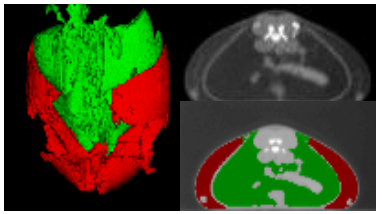
Ophir et al, Blood, 2010

Stem Cells



Reumers et al, Stem Cells, 2008

Metabolic Diseases



Full Range of Optical Imaging Platform (1700+ Installations worldwide)

PerkinElmer
For the Better

Lumina II

Entry level bioluminescent/ fluorescent imaging

Lumina XR

Lumina with X-ray overlay

Kinetic

Fast, Real-time molecular imaging

Spectrum

Quantitative 2D & 3D bioluminescence and fluorescence imaging

Spectrum CT

Seamlessly integrates optical and micro CT imaging (multi-modal)

FMT Series

Quantitative Fluorescence 3D Tomography System

Quantum FX

Fast, low dose µCT

Platform Positioning—BLI VS FLI

BLI & FLI

Lumina II

Low cost optical

BLI, FLI, CLI &

Cerenkov

Lumina XR

Lumina II with integrated X-ray

Kinetic

Real-time, video speed imaging

Spectrum

2D + 3D BLI + FLI

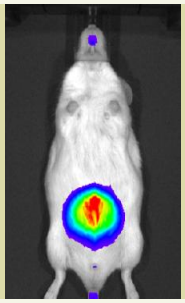
DyCE

Transillumination

DICOM import

Spectrum CT

Spectrum with integrated CT



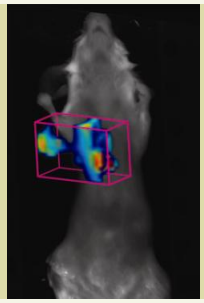
ONLY FLI

FMT

3D FLI

Transillumination

DICOM import



Platform Positioning—2D VS 3D

2D

Lumina II

Low cost optical

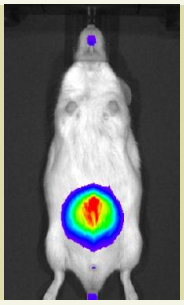
BLI, FLI, CLI & Cerenkov

Lumina XR

Lumina II with integrated X-ray

Kinetic

Real-time, video speed imaging



2D + 3D

FMT

3D FLI

Transillumination

DICOM import

Spectrum

2D + 3D BLI + FLI

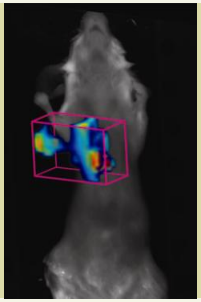
DyCE

Transillumination

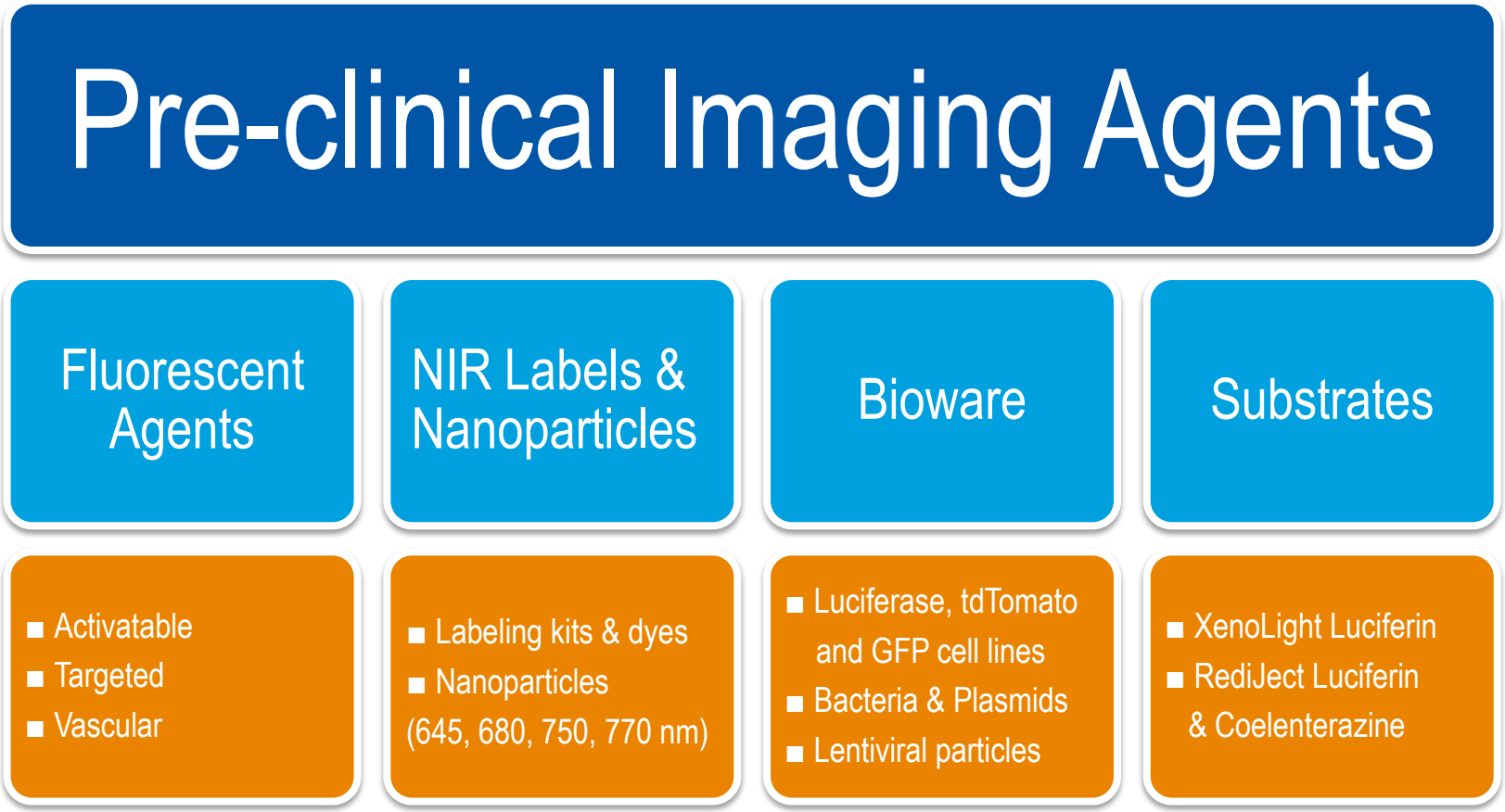
DICOM import

Spectrum CT

Spectrum with integrated CT

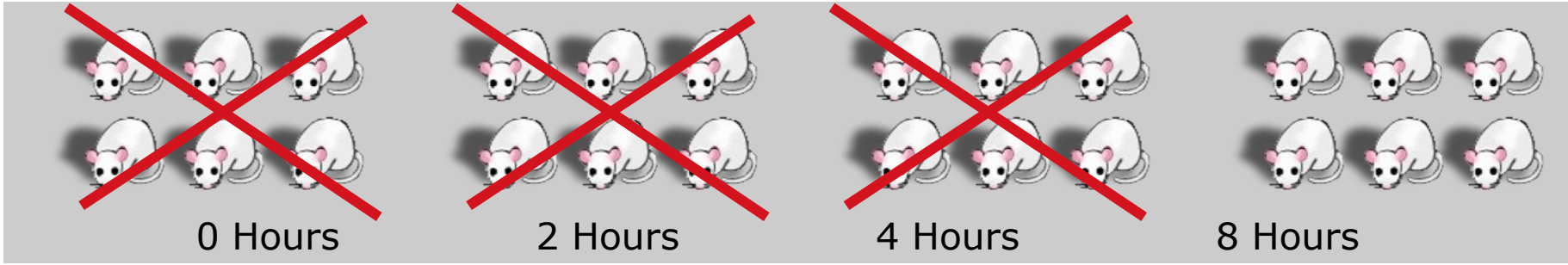


Pre-clinical *in vivo* Imaging Agents

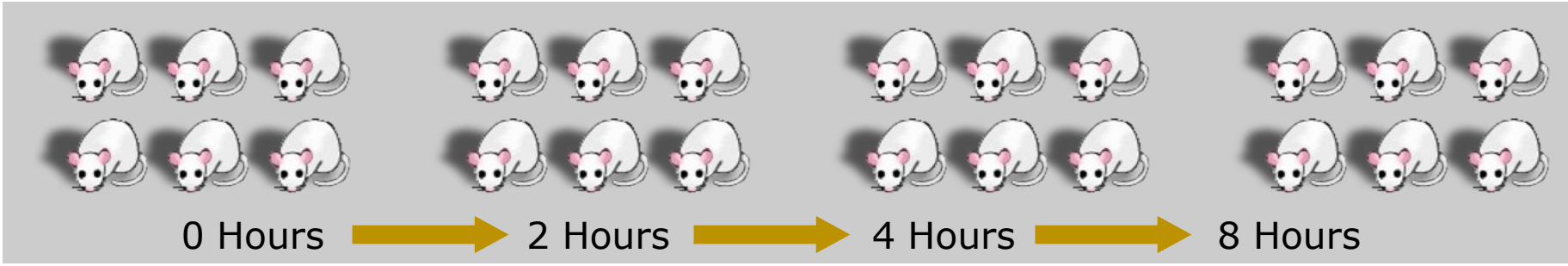


Current vs. BPI methodology

Current Methodology = 24 animals over four treatment points



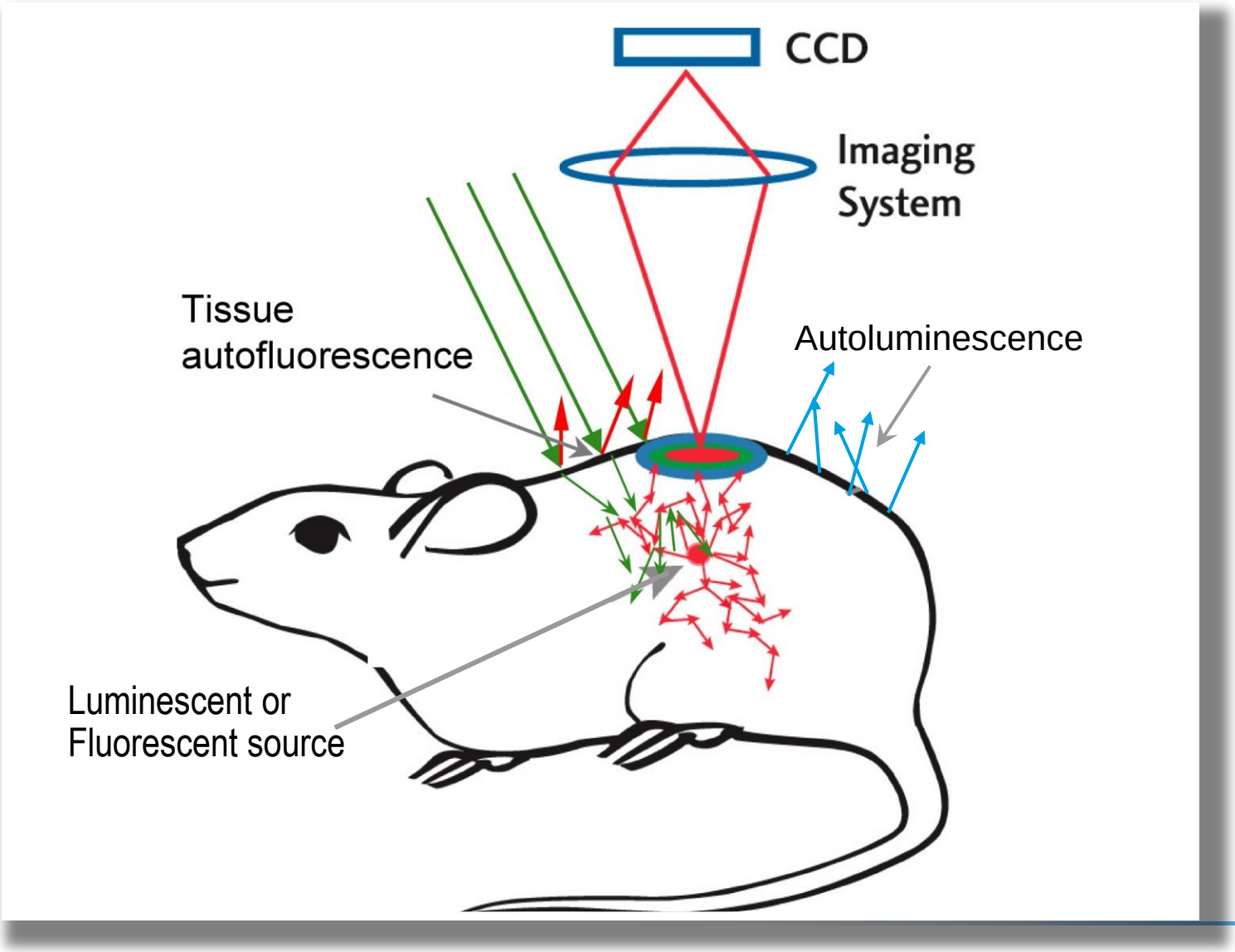
BPI Methodology = the same 6 animals over four treatment points



Same group of anesthetized test animals at each time point of an experiment uses far fewer animals than current methodology.

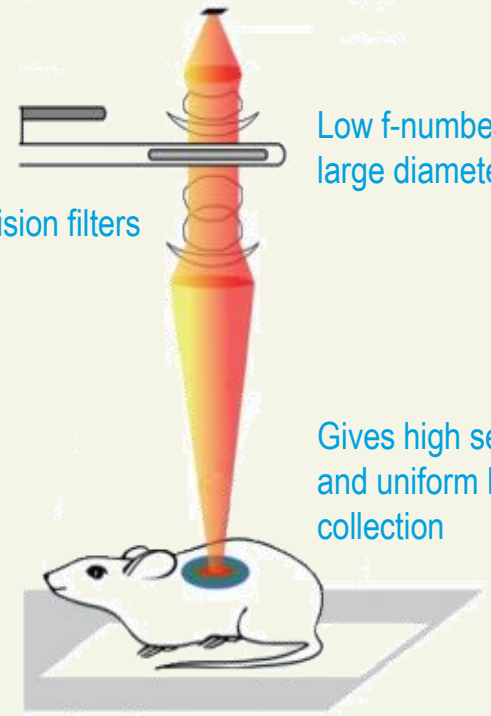
Bioluminescent Imaging

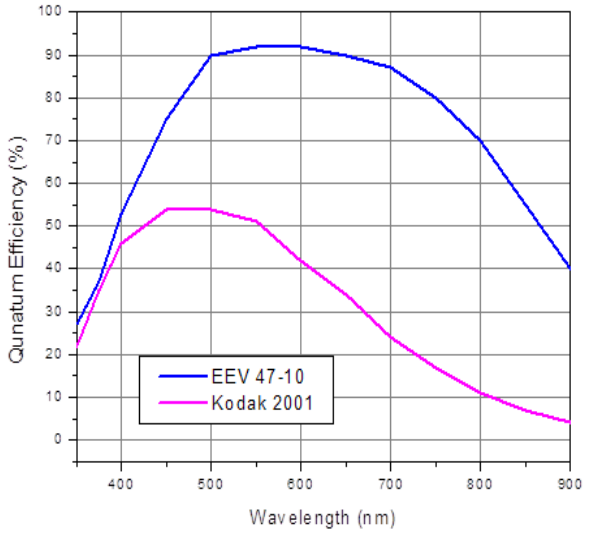
Challenges of in vivo optical imaging

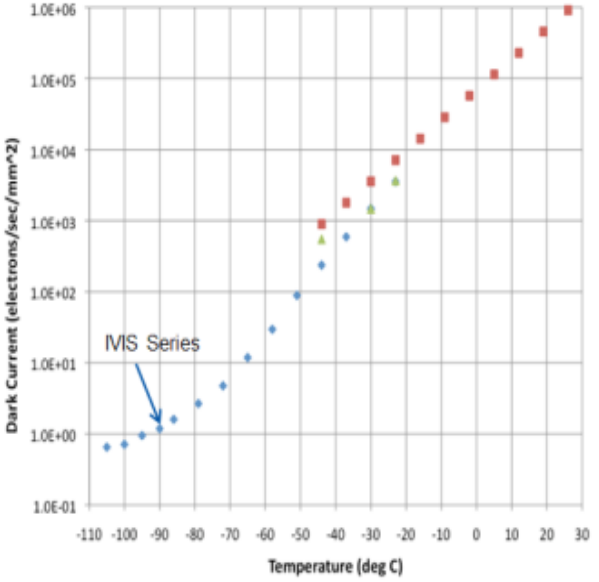


Bioluminescence Imaging Sensitivity

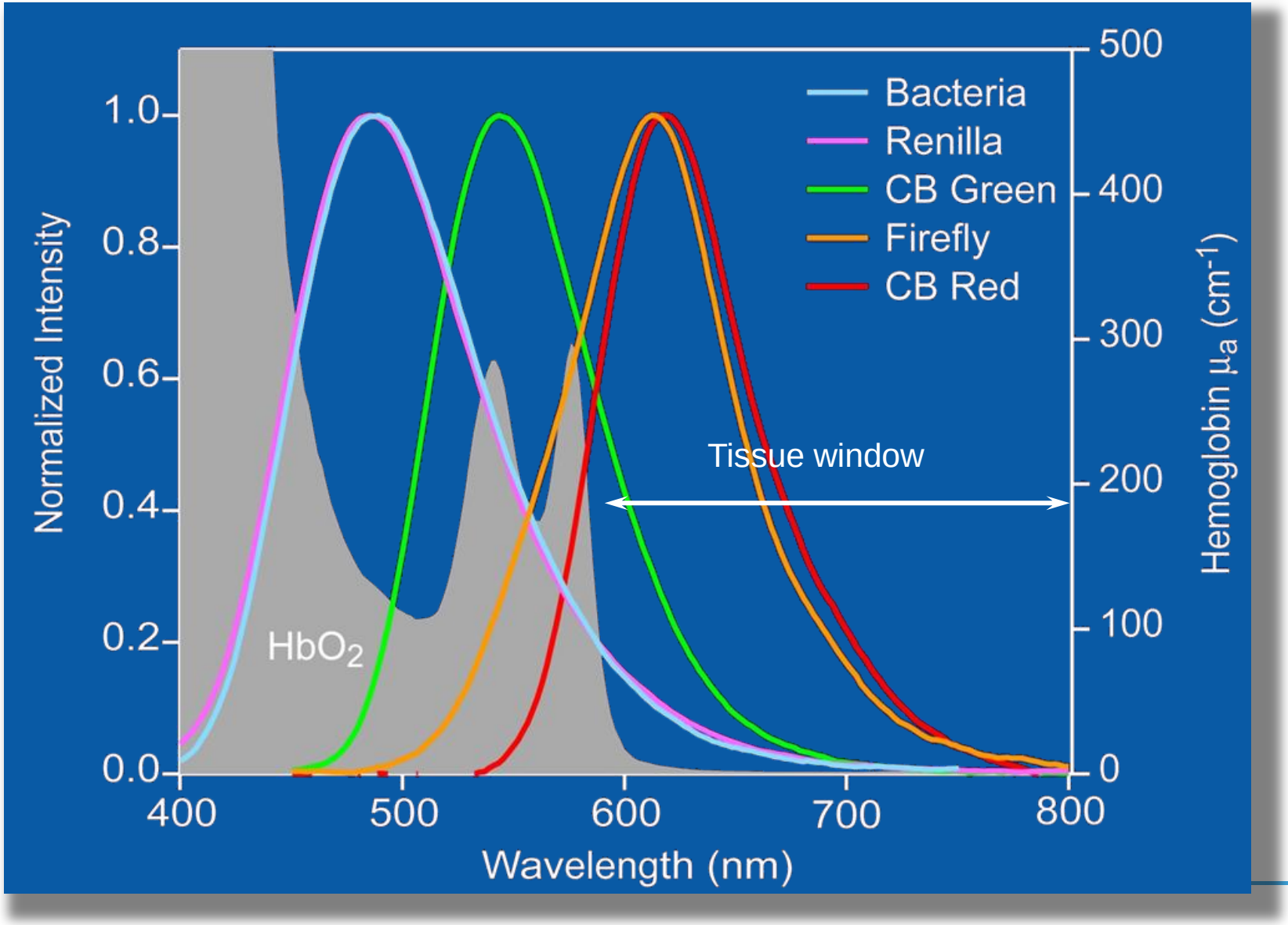
Back-thinned, back-illuminated, Grade 1 Cooled (-90C) camera with large CCD chip area for high sensitivity light detection





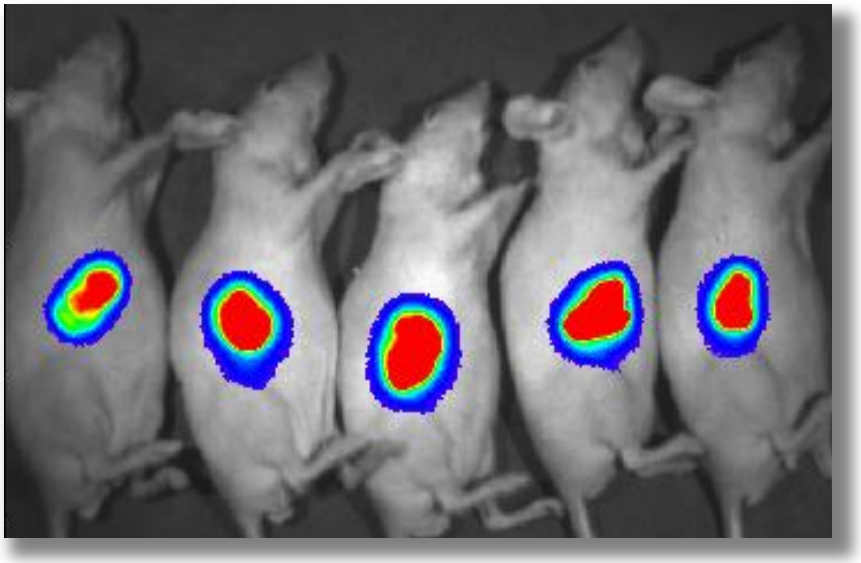


Emission spectra of common luciferases

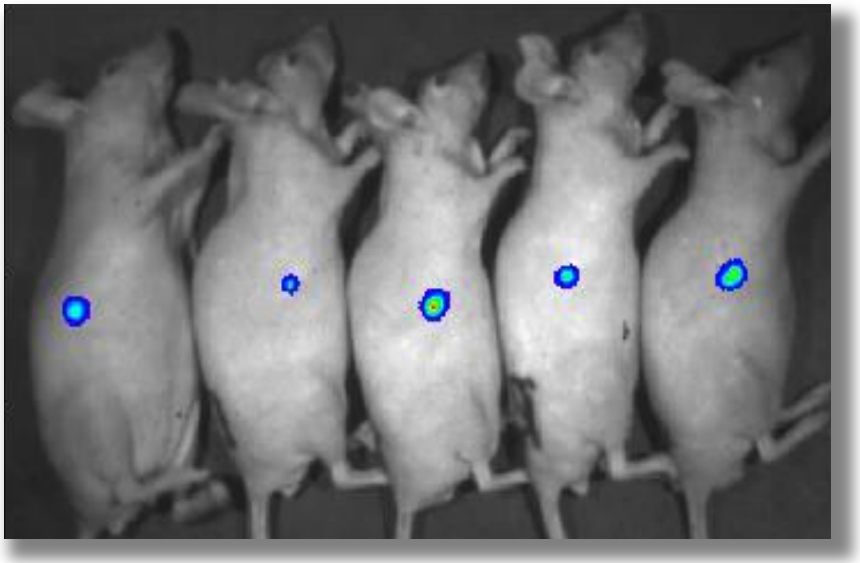


Detection of residual tumors using optical imaging

Subcutaneously implanted PC-3M2AC6 human prostate tumors labeled with luciferase



3 weeks of vehicle treatment

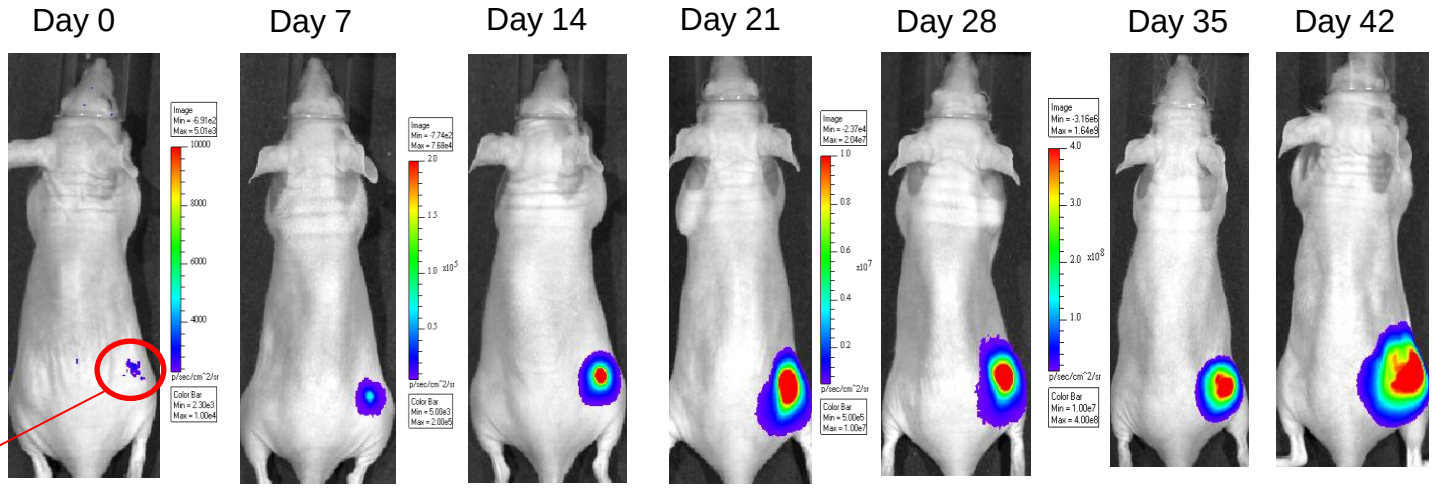


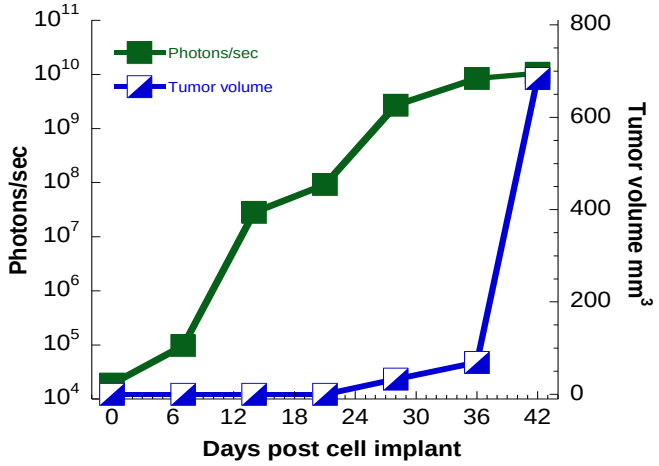
3 weeks of paclitaxel treatment
a false cure by palpation

Source: Novartis Institute for Biomedical Research / Xenogen Corporation

Longitudinal monitoring of tumor development

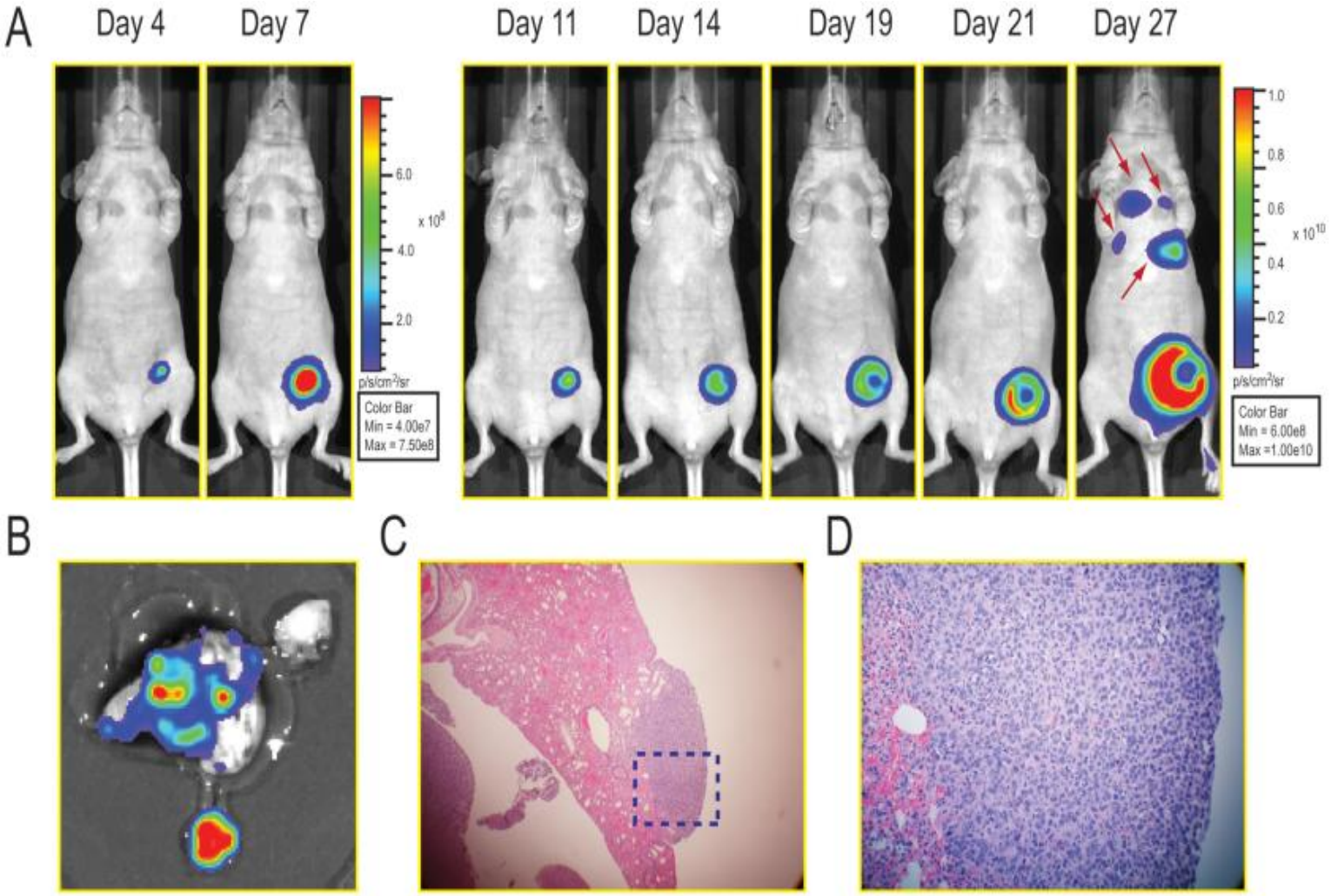
Bioware Ultra: 4T1-luc2





With Bioware Ultra one can start collecting data from Day 0, while with caliper measurements one has to wait at least 28 days to see any tumor growth

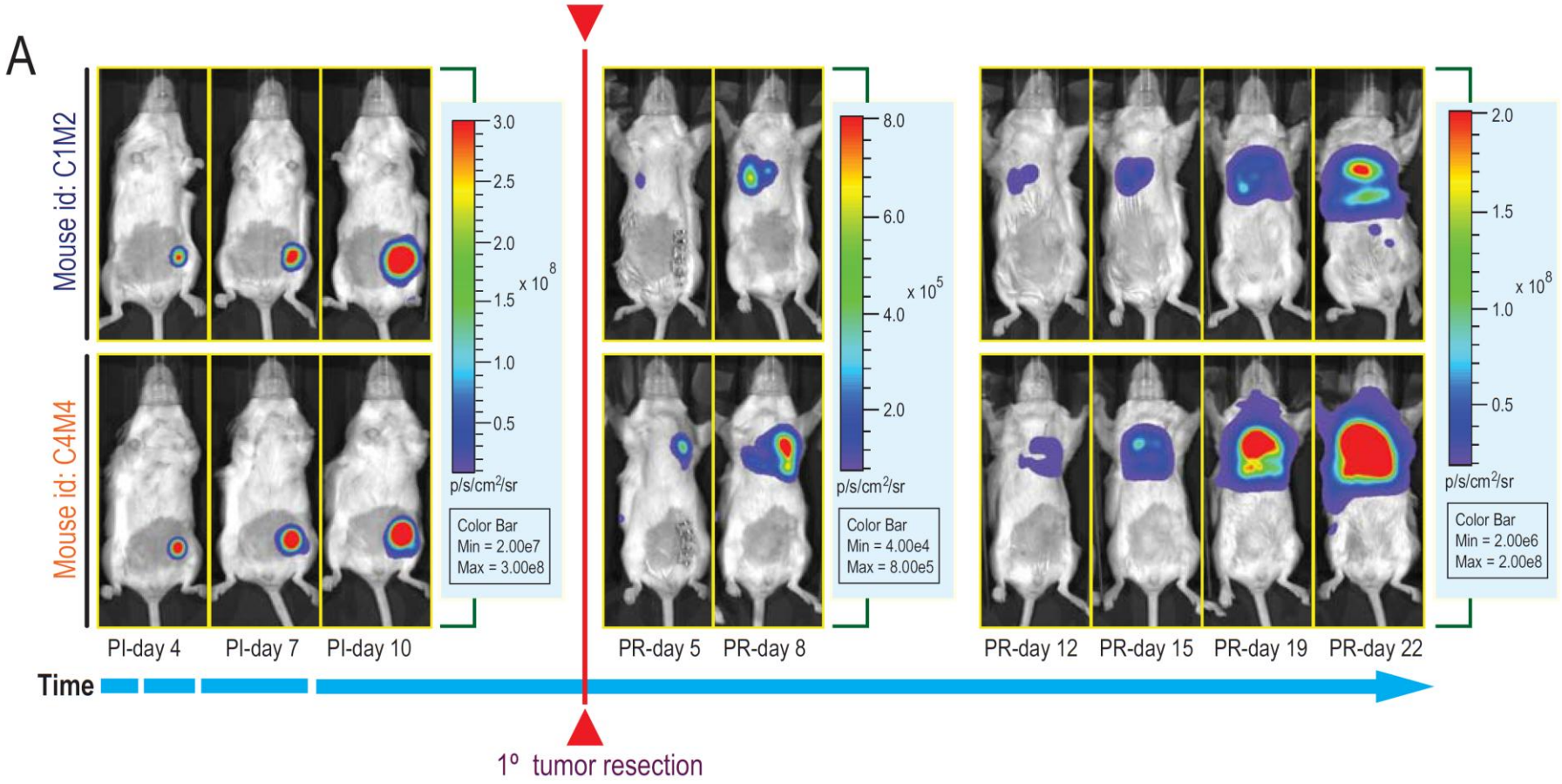
Non-Invasive Detection of Micrometastasis



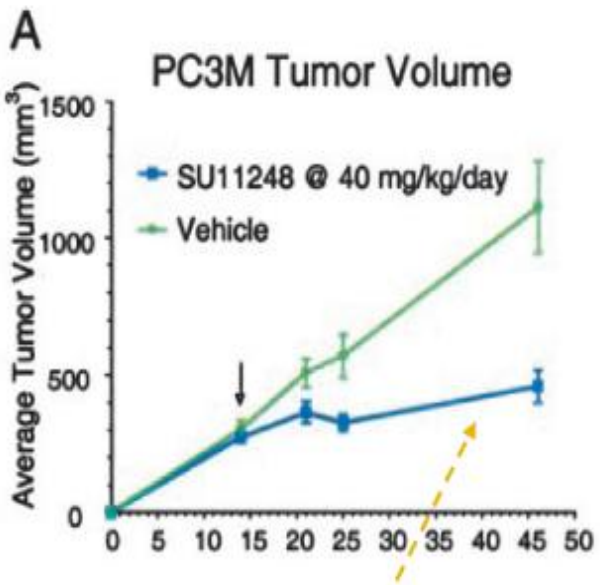
5×10^5 4T1-luc2-1A4 cells orthotopically into the abdominal mammary fat pads

Kim et al, PLoS ONE (2010)

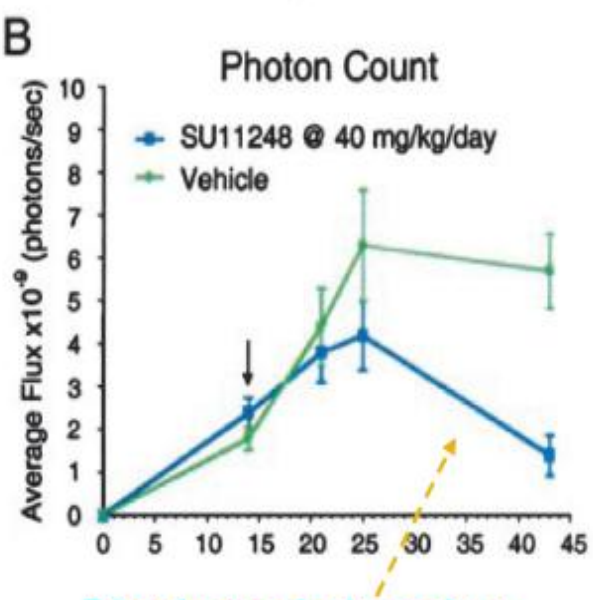
Detection of micrometastases



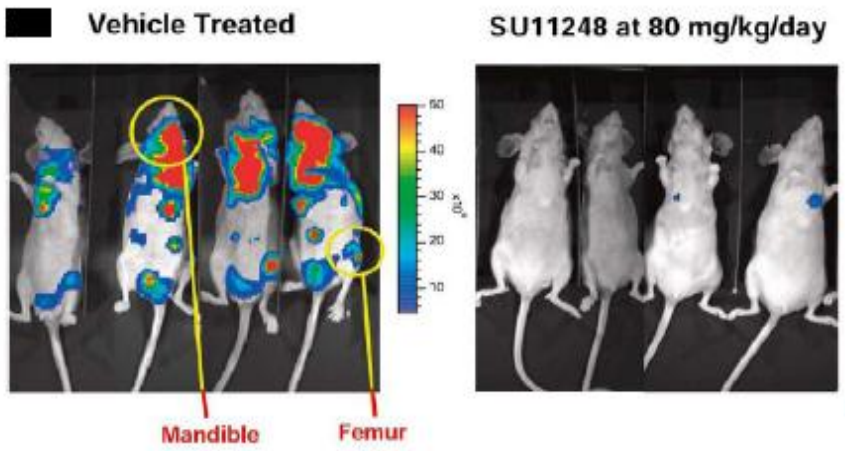
Sutent – Fast Tracked FDA Approval



Physical measurement
(tumor still getting bigger)

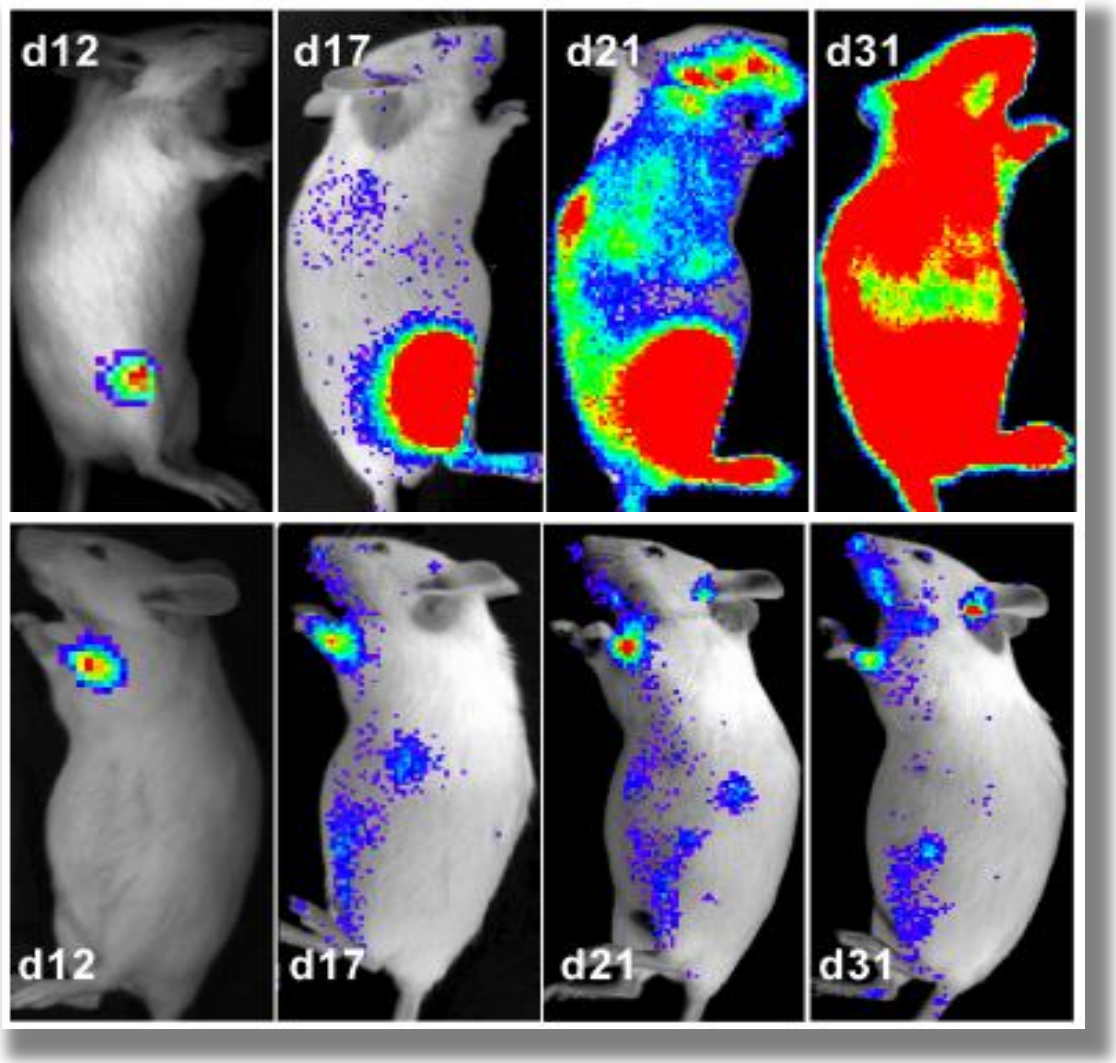


Biophotonic imaging
(tumor cells being killed)



Murray et al 2003

Hematopoiesis from a single HSC (KTLS cells)



Cao *et al*, 2004

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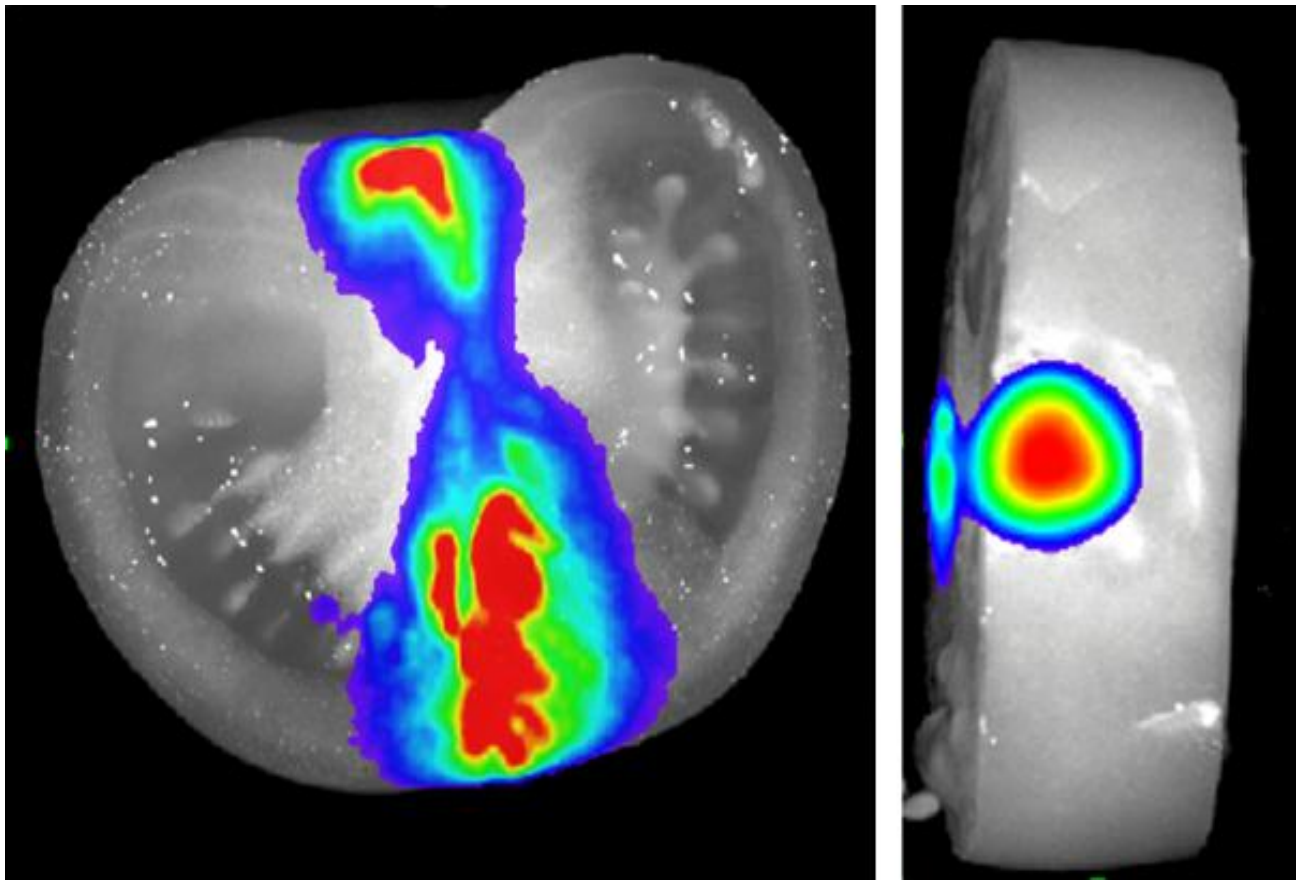
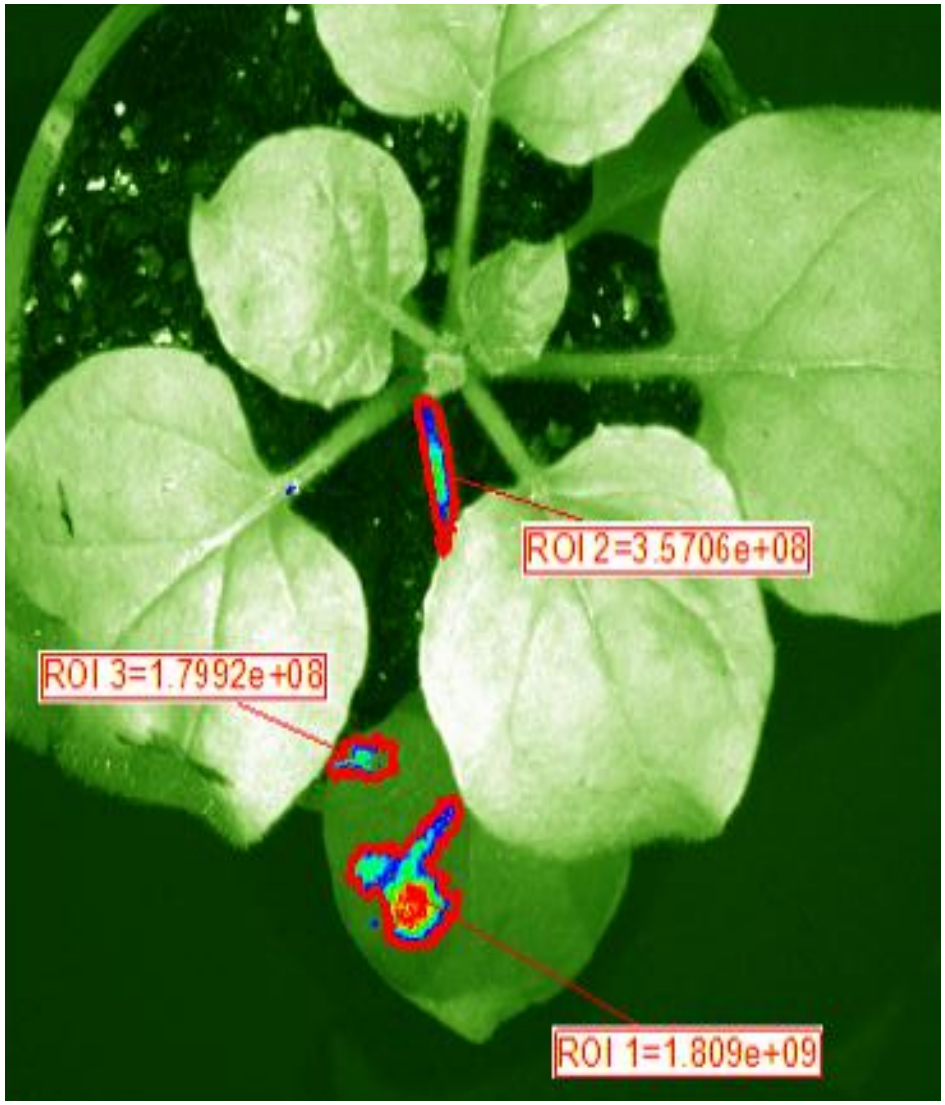
Enterotoxigenic E. coli (ETEC)

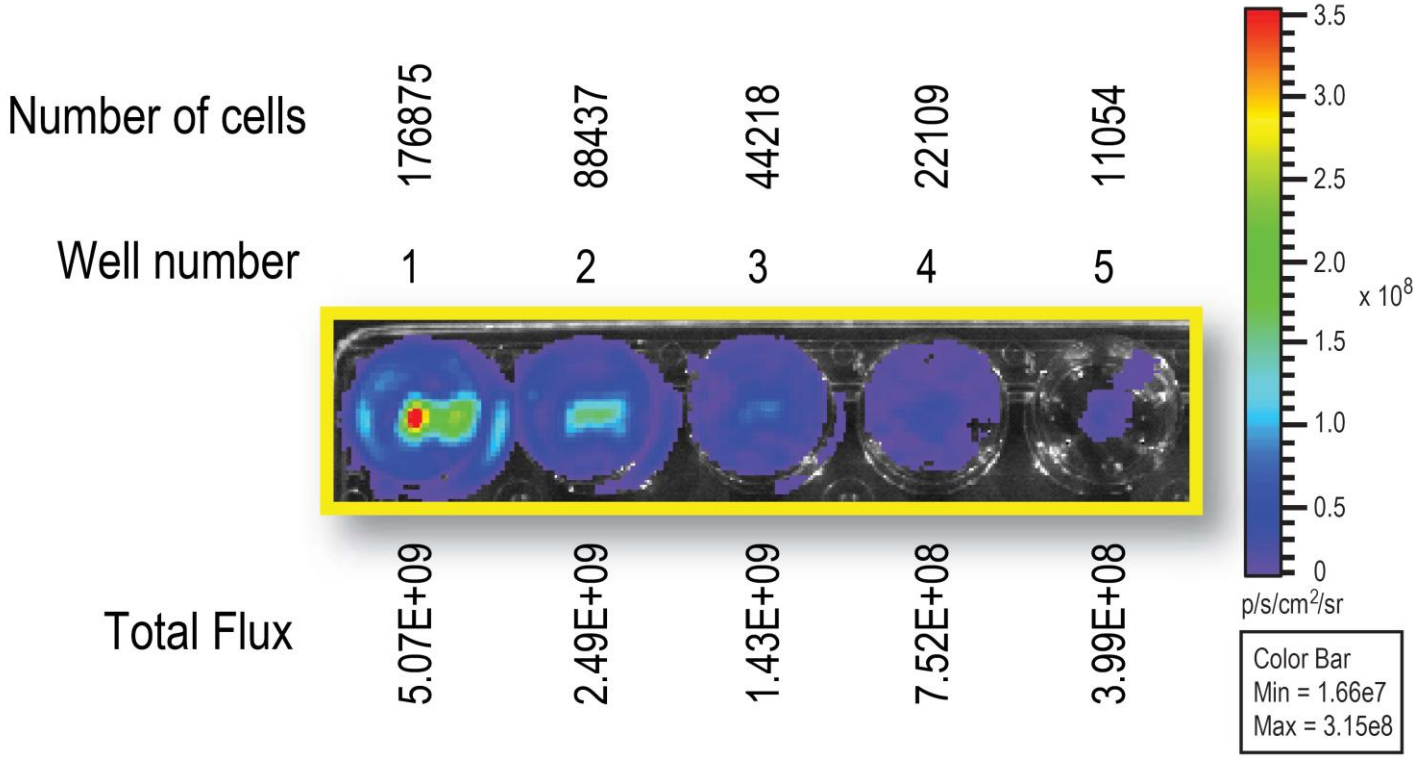


GFP fungal infection on tobacco plant



Direct proportional of cell number and bioluminescence

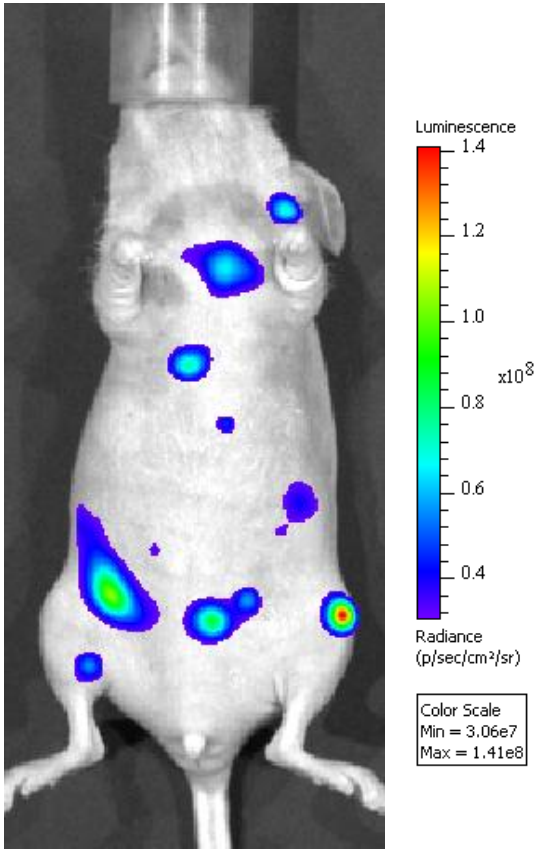
4T1-luc2 cell line



Bone metastasis detection by IVIS Spectrum and Lumina XR

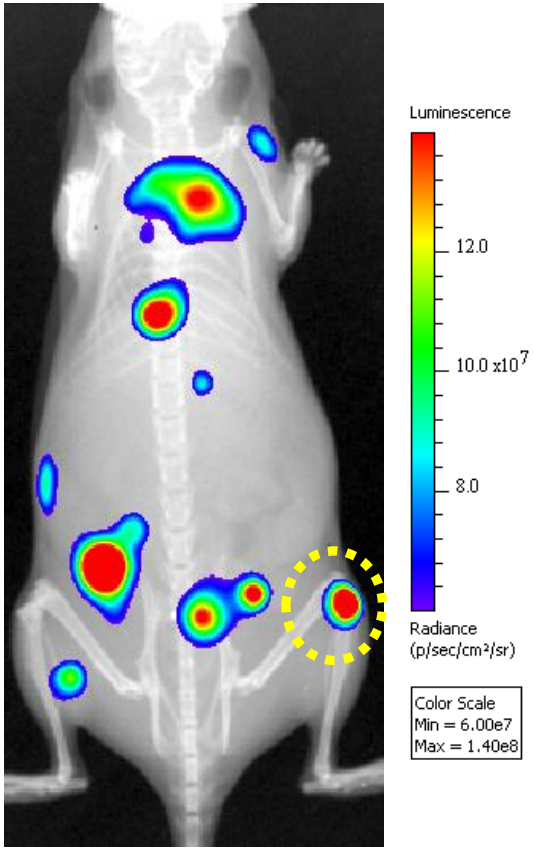
4T1-luc2 cells

Spectrum



Day 9

Lumina XR

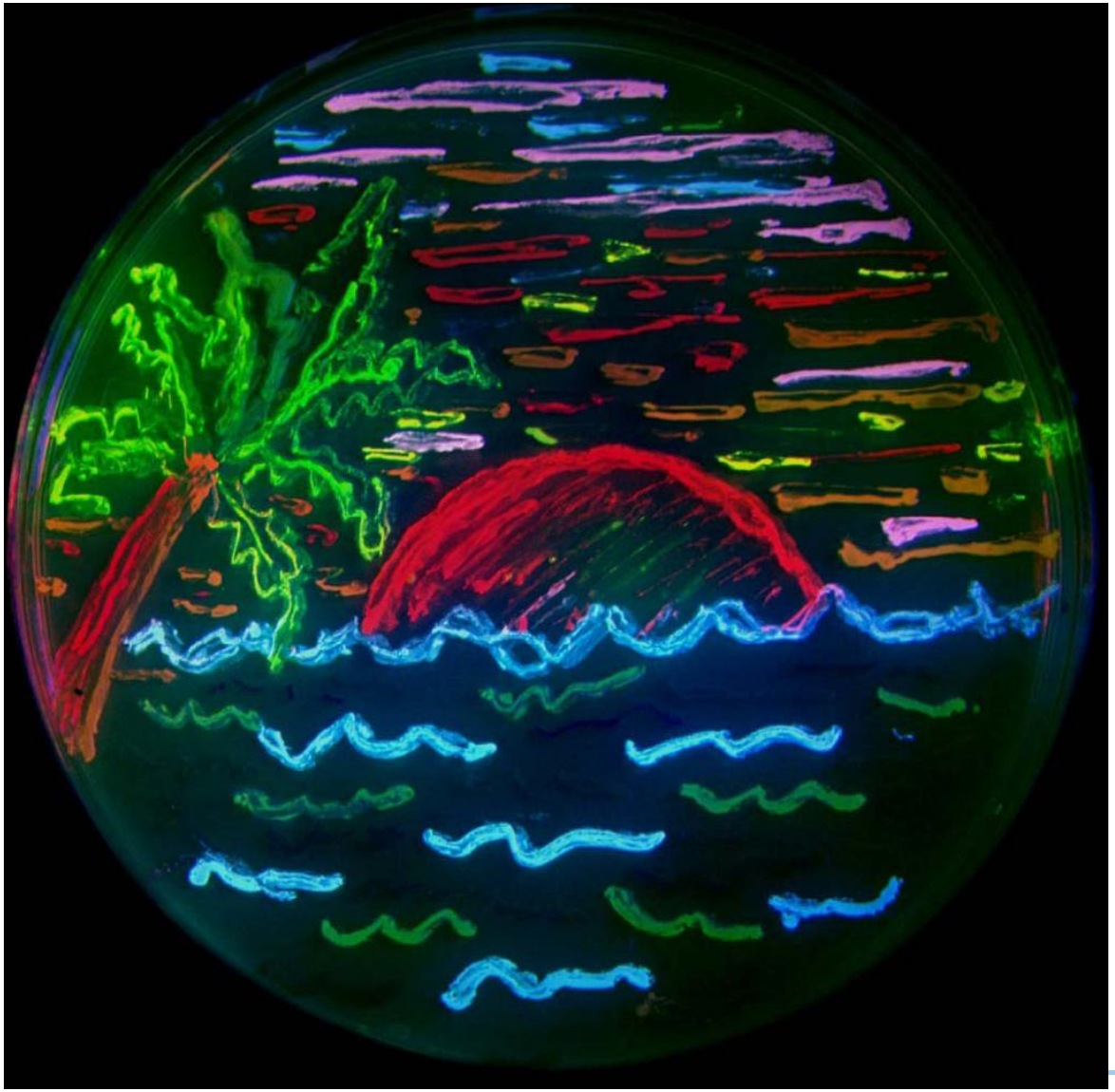


Day 9

Bioluminescent tumor cell lines

BIOWARE ULTRA	PART NUMBER	MODEL	*IN VITRO* LUCIFERASE EXPRESSION* (PHOTONS/SEC/CELL)
4T1-luc2	124087	Breast Cancer (Murine)	6500
HT1080-luc2	128092	Fibrosarcoma	2200
MDA-MB-231-luc2	124319	Breast Cancer	1300
PC-3M-luc2	124089	Prostate Cancer	1500
LnCaP-luc2	125055	Prostate Cancer	30
B16-F10-luc2	124734	Melanoma (Murine)	450
HCT 116-luc2	124318	Colorectal Cancer	1700
HT-29-luc2	124353	Colorectal Cancer	1590
Colo205-luc2	124317	Colorectal Cancer	200
U-87 MG-luc2	124577	Brain Cancer	1250
NCI-H460-luc2	124316	Lung Cancer	1170
EL4-luc2	124088	Lymphoma (Murine)	250
K562-luc2	124735	Leukemia	1285
MOLT-4-luc2	125057	Leukemia	330
ACHN-luc2	125056	Renal Cancer	860
BxPc3-luc2	125058	Pancreatic Cancer	370

Fluorescent imaging

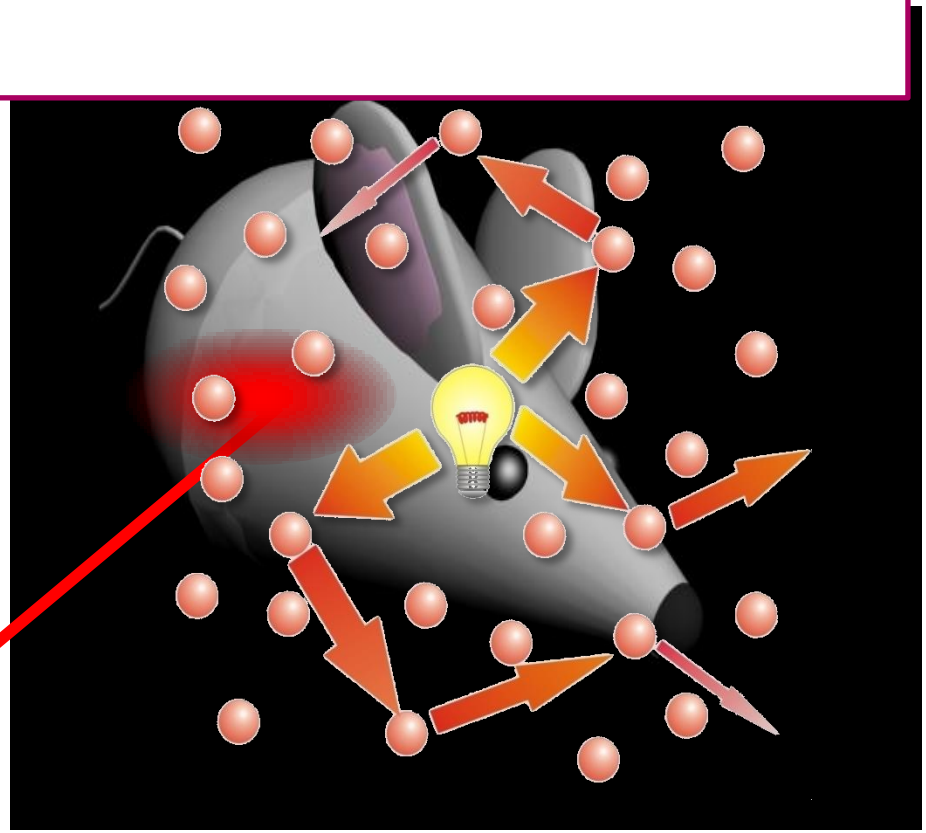


Challenges of Fluorescent Imaging

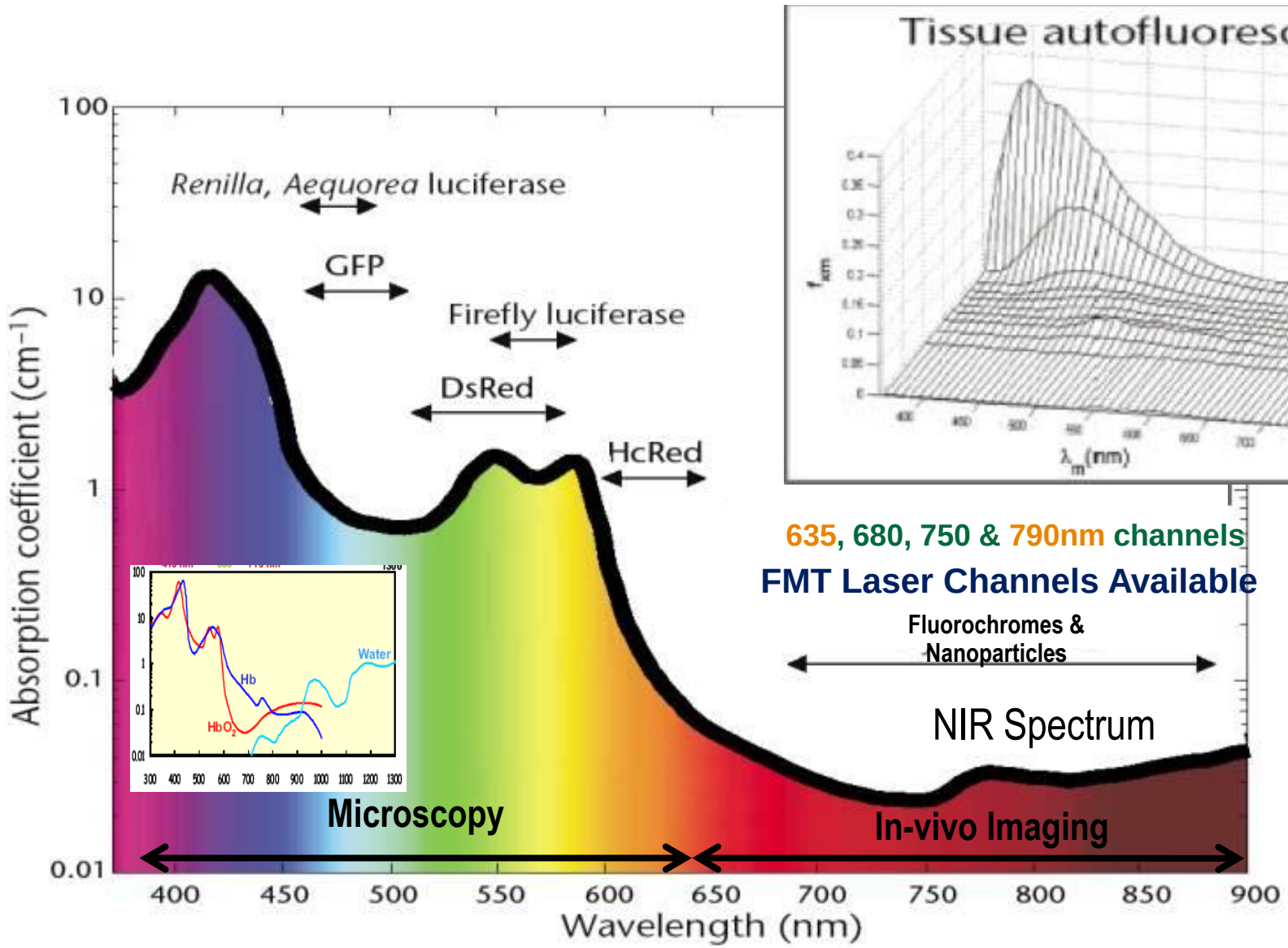
1. Tissue absorbance
2. Autofluorescence
3. Deep Tissue Signal

Light propagation in biological tissue

- Governed by Absorption & Scattering
  - Depth degeneracy
  - Compensating for tissue heterogeneity



Advantages of Imaging in the NIR Spectrum



The absorption spectrum for tissue in the visible and near infrared (NIR) regions

Why we use NIR?

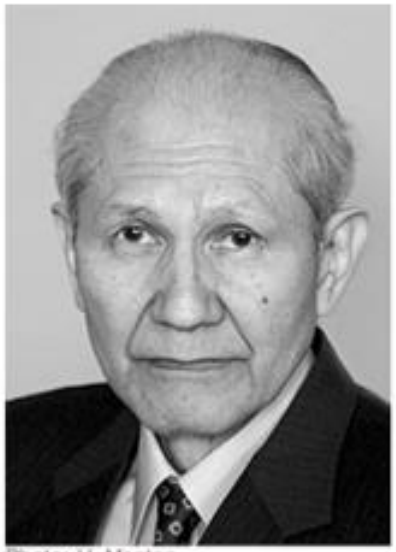


Photo: U. Montan

Osamu Shimomura

Photo: U. Montan

Martin Chalfie

Photo: U. Montan

Roger Y. Tsien

The Nobel Prize in Chemistry 2008 was awarded jointly to Osamu Shimomura, Martin Chalfie and Roger Y. Tsien *"for the discovery and development of the green fluorescent protein, GFP"*.

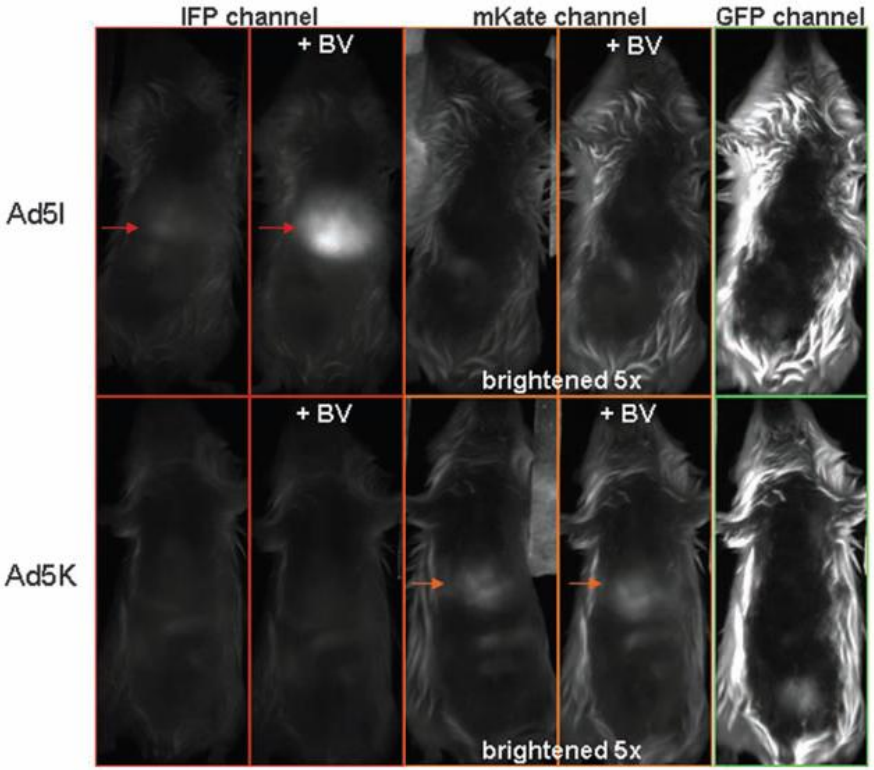
From:http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2008/#

Science
AAAS

Mammalian Expression of Infrared Fluorescent Proteins Engineered from a Bacterial Phytochrome

Xiaokun Shu, *et al.*

Science **324**, 804 (2009);
DOI: 10.1126/science.1168683



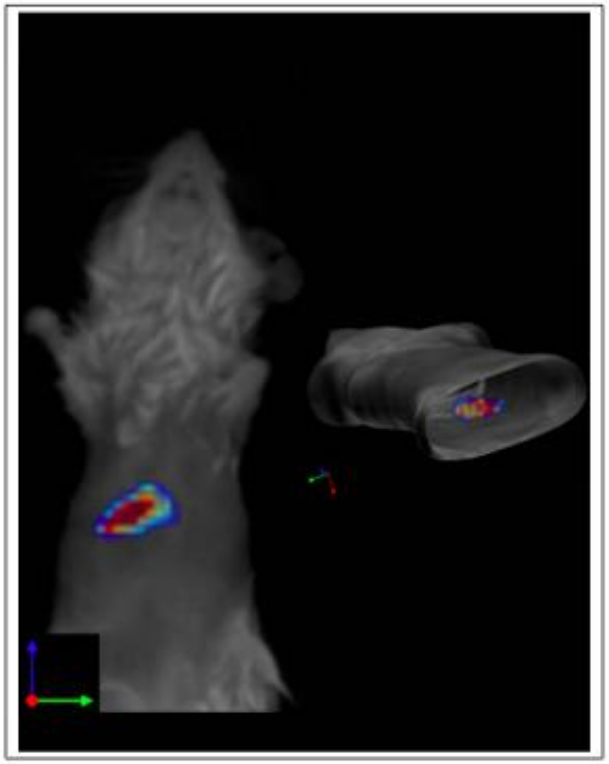


Fig. S9 Noninvasive fluorescence molecular tomographic (FMT) imaging of IFP-expressing mouse liver. Blue, green, and red arrows indicate rostral-caudal, left-right, and dorsoventral axes, respectively. Left: top view. Right: tilted view to show the 3D localization of fluorescence within the mouse.

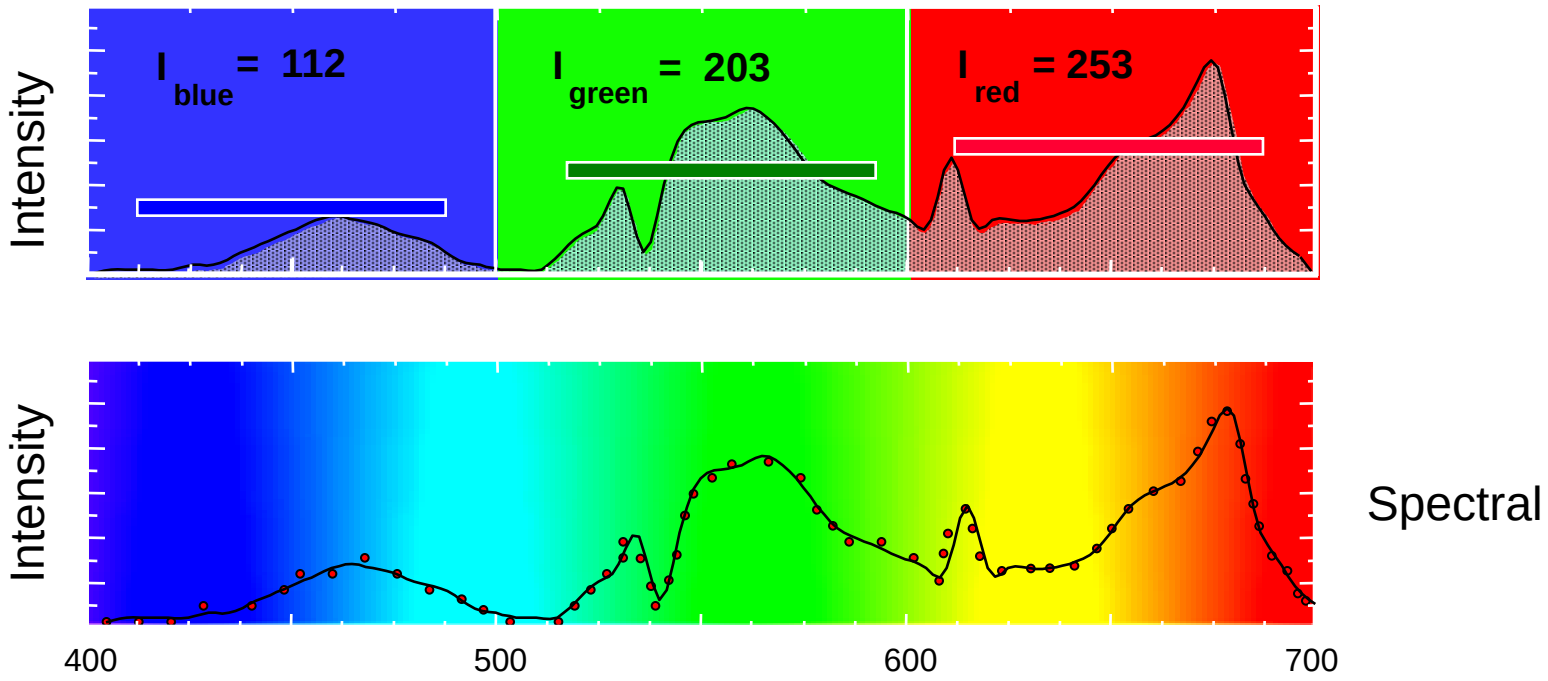
Spectral Unmixing Concept

Collecting images at many wavelengths

More than just RGB colors

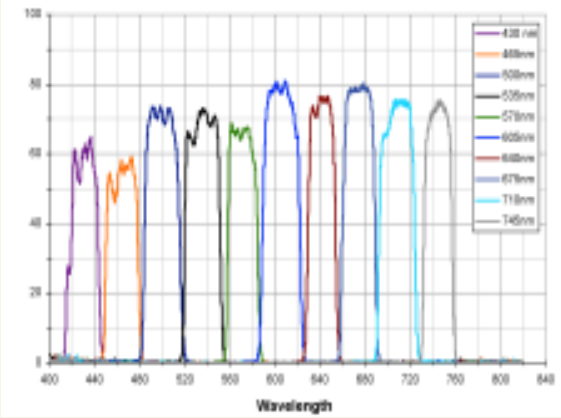
Full spectral information allows better “color” discrimination

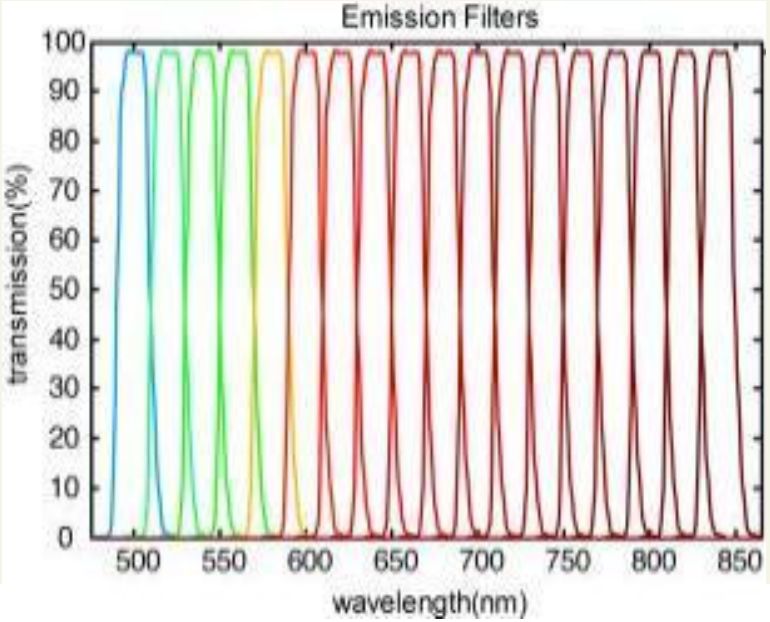
Distinguish colors that look the same to the eye



Spectral Unmxing

High Resolution Spectral Filters



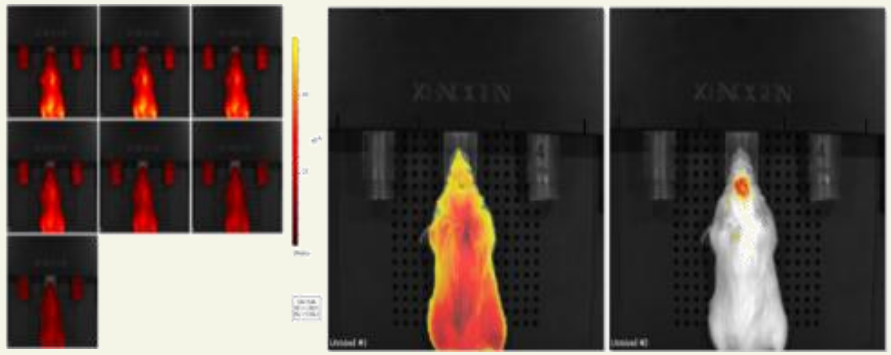


Spectral Unmxing Tools

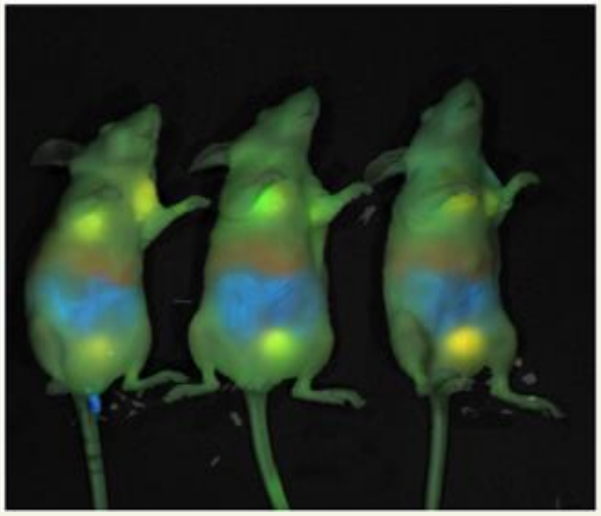
Spectral sequence

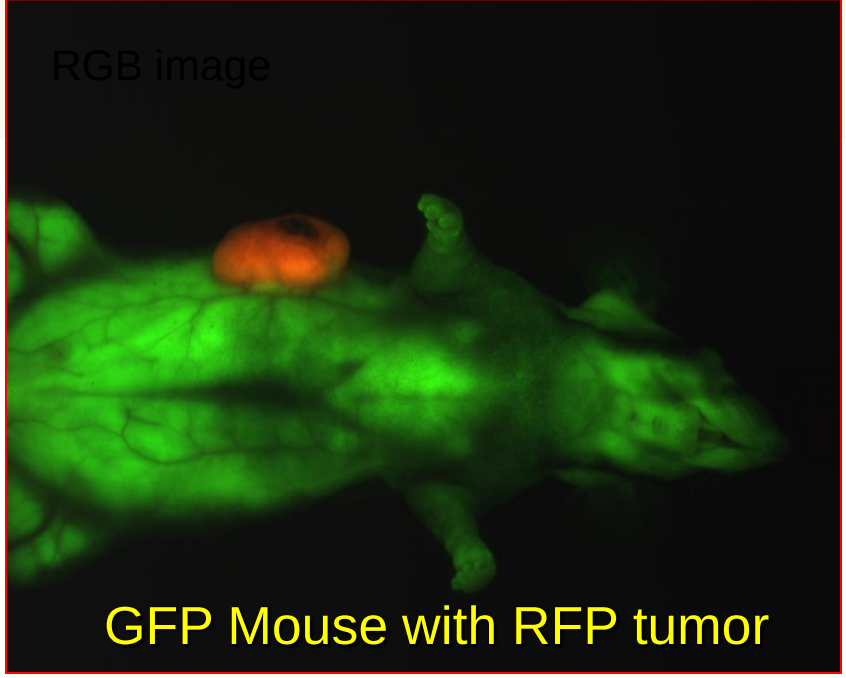
Unmixed Autofluorescence

Unmixed 600nm Dye Signal in Brain

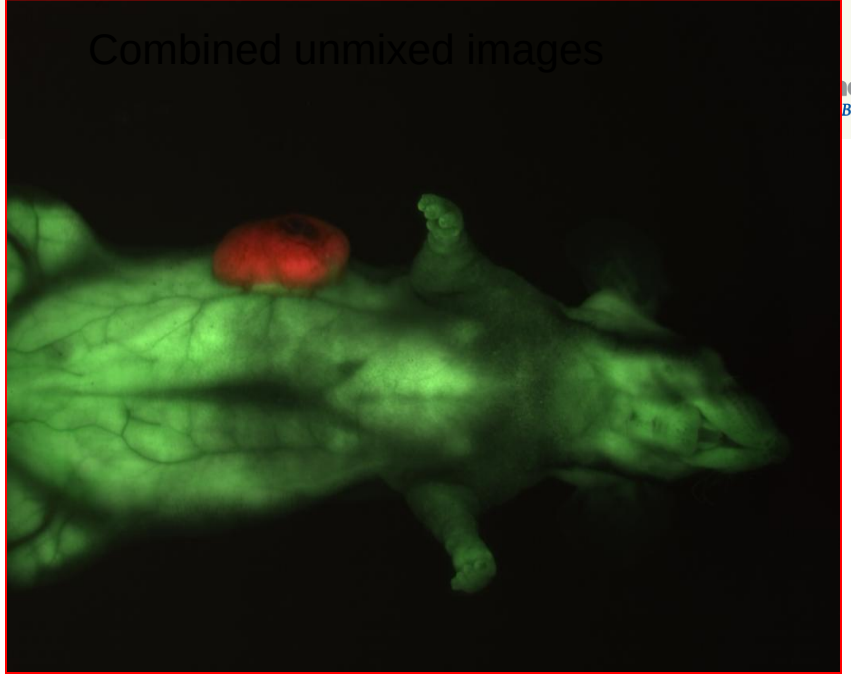


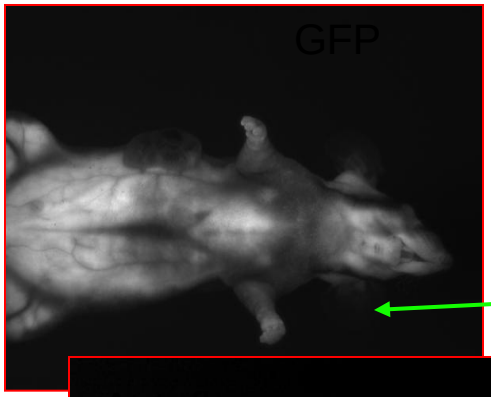
Data courtesy of Adrienne Scheck St. Joseph's Research Hospital, Phoenix, AZ

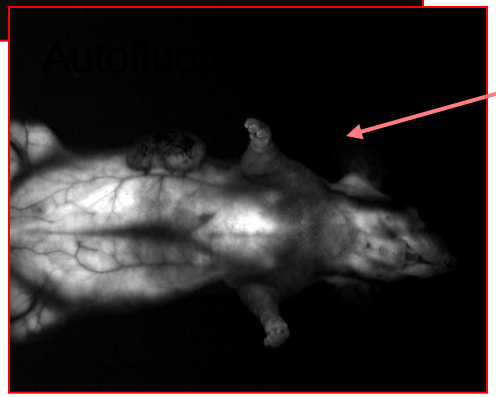


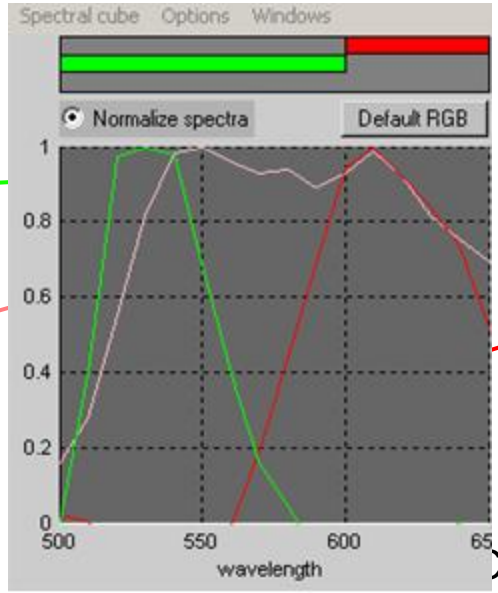


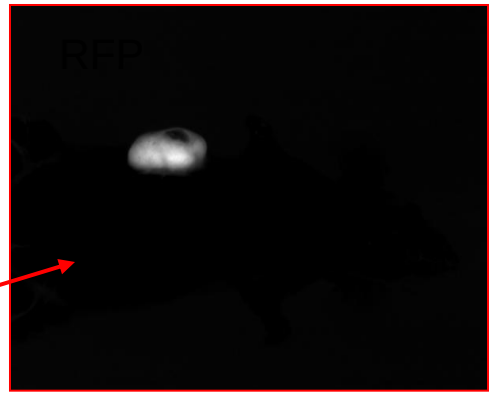
GFP Mouse with RFP tumor











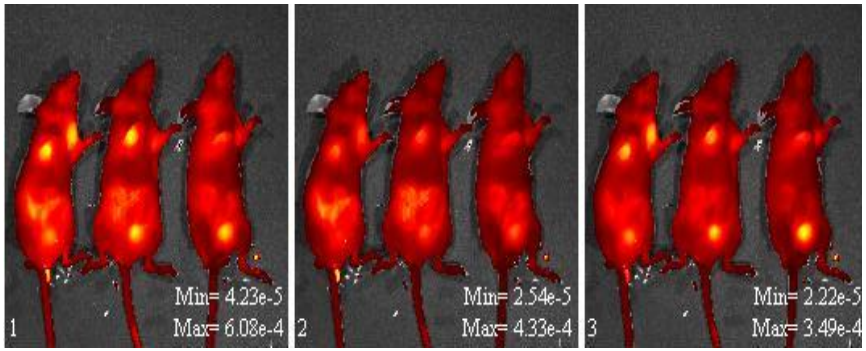
Calculated pure spectra

Sample courtesy of Anticancer, Inc.

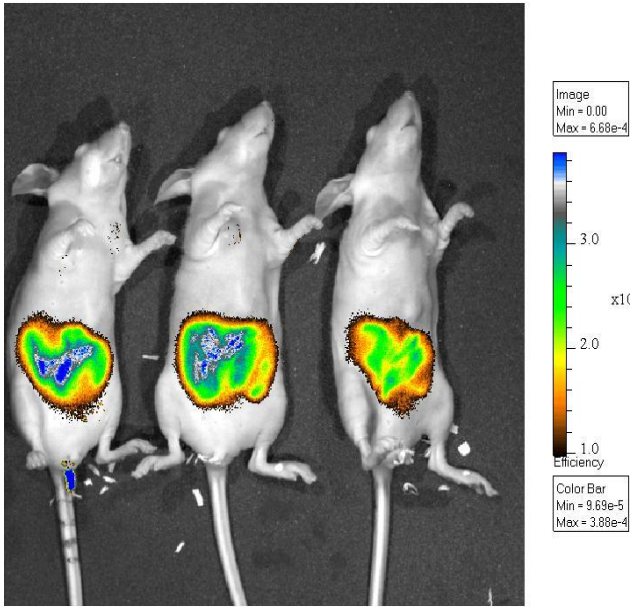
Spectral unmixing of activatable probes

4T1 cells

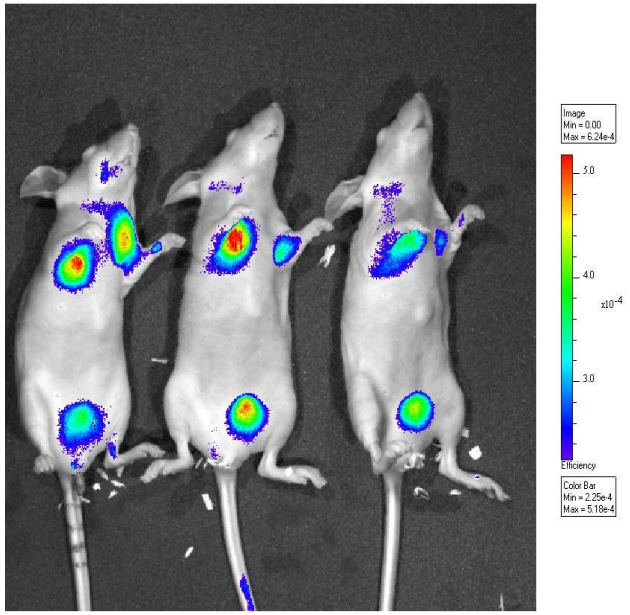
Raw Data



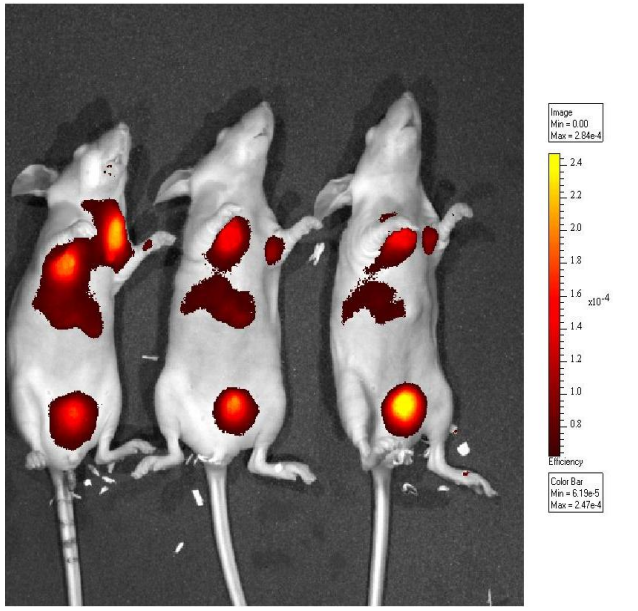
Food Background



Unmixed ProSense 680

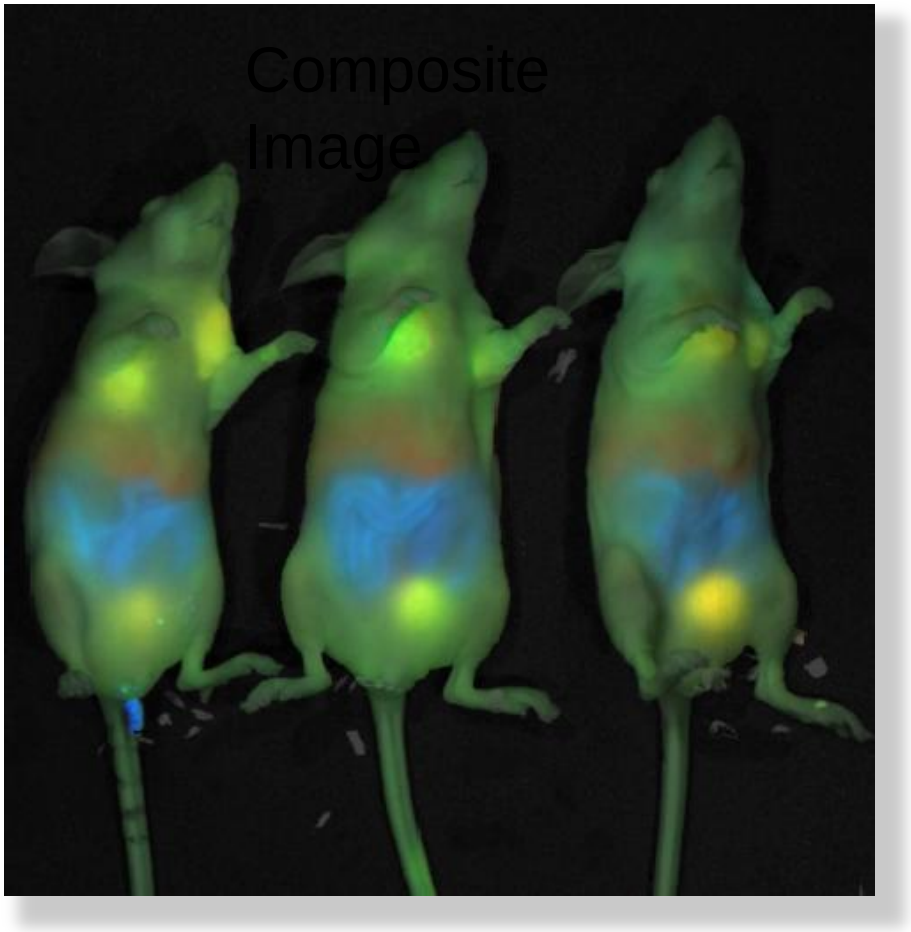


Unmixed MMPSense 750



Overlaid images

4T1 cells



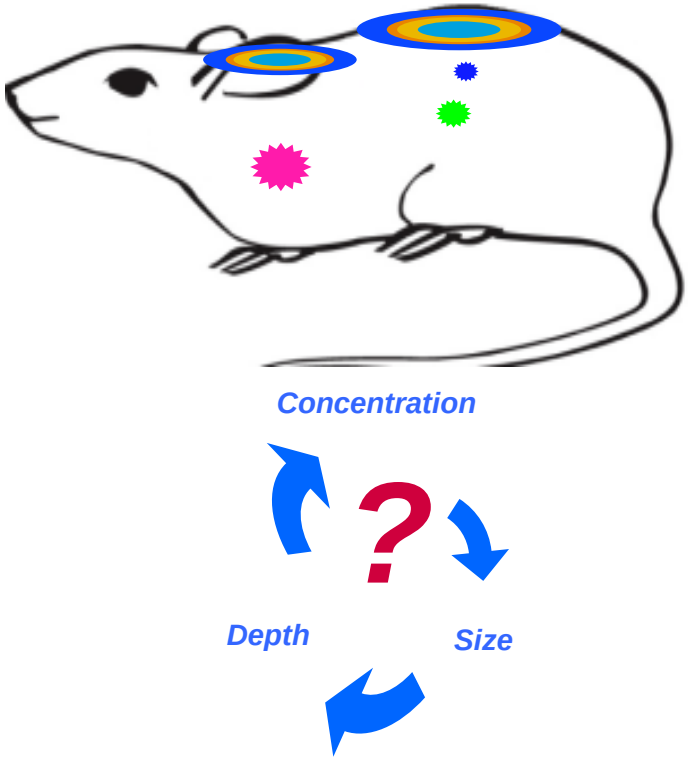
ProSense680 (Green), MMPSense750 (Red)
Chlorophyll signal in Food (Blue)

Challenges of Fluorescent Imaging

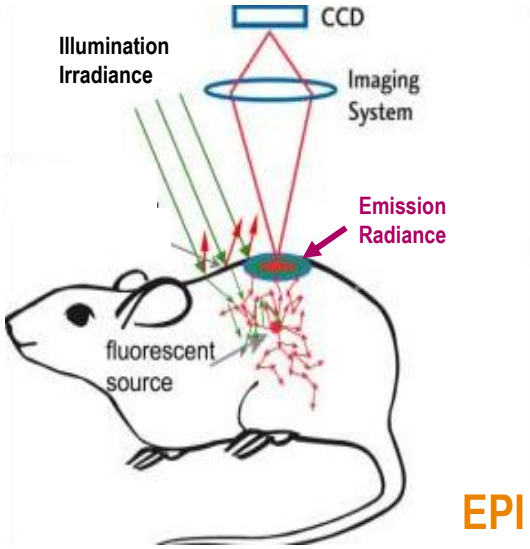
1. Tissue absorbance
2. Autofluorescence
3. **Deep Tissue Signal**

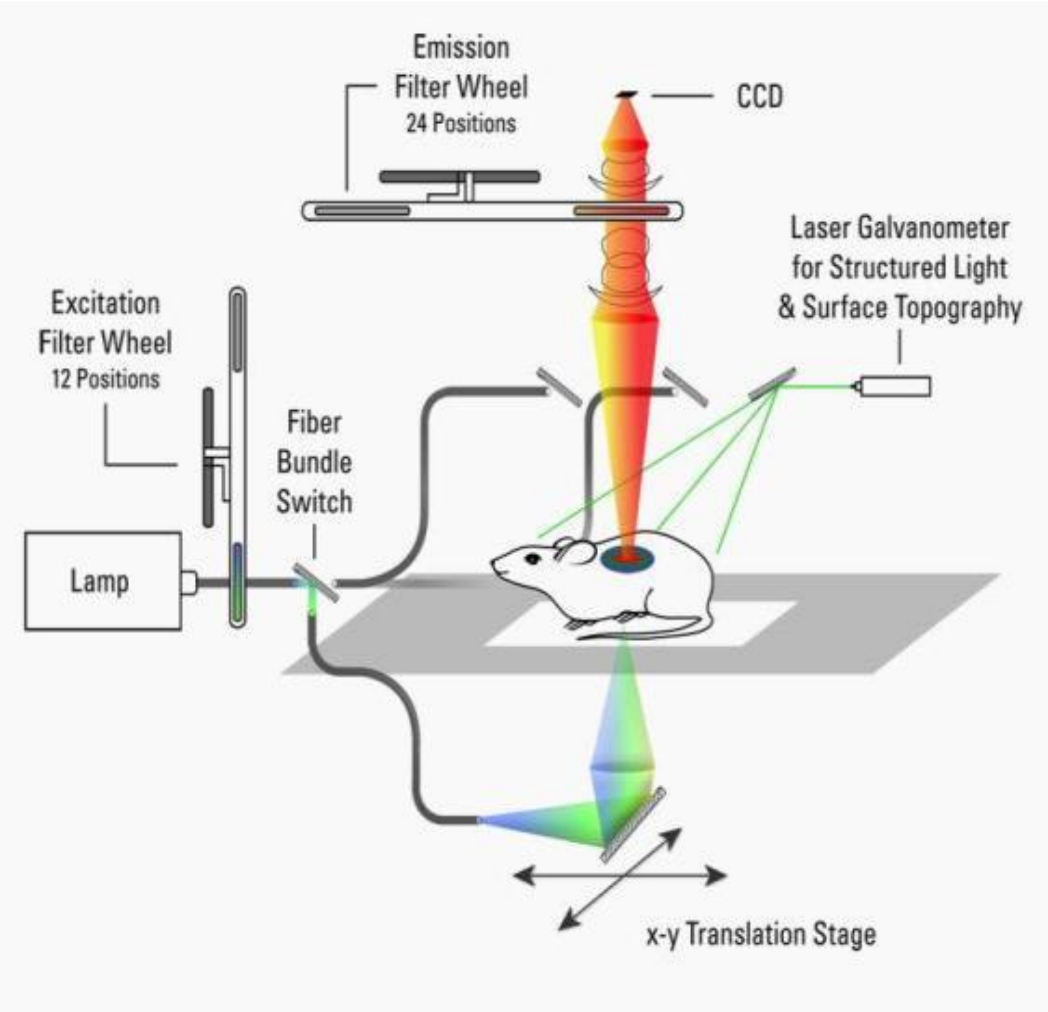
Why 3D Optical Tomography?--2D versus 3D imaging

- **2D成像僅能獲得信號到達體表的相對强度**
- 是否需要比較不同深度信號的强度？**2D成像無法比較不同深度的信號强弱**
- 是否要對信號進行定位和绝對定量？**2D成像無法定位，無法還原信號的體積訊息，無法絕對定量。**



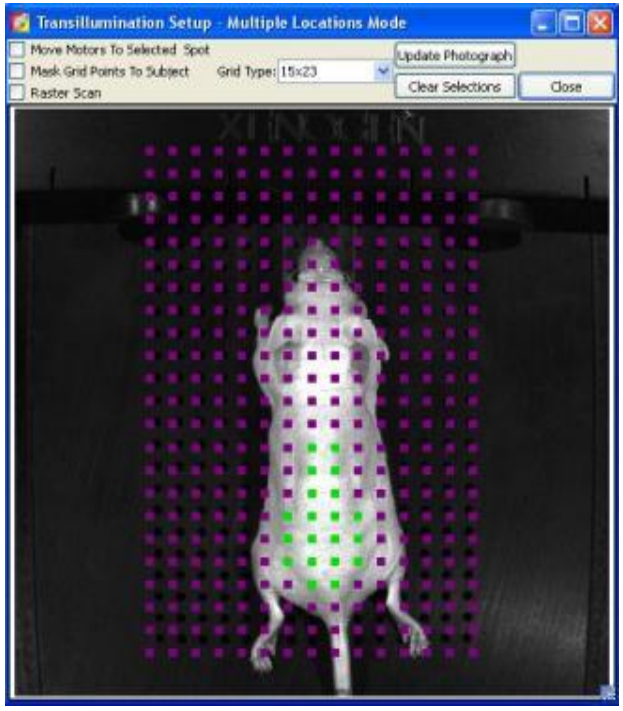
Transillumination Imaging—FMT & IVIS Spectrum

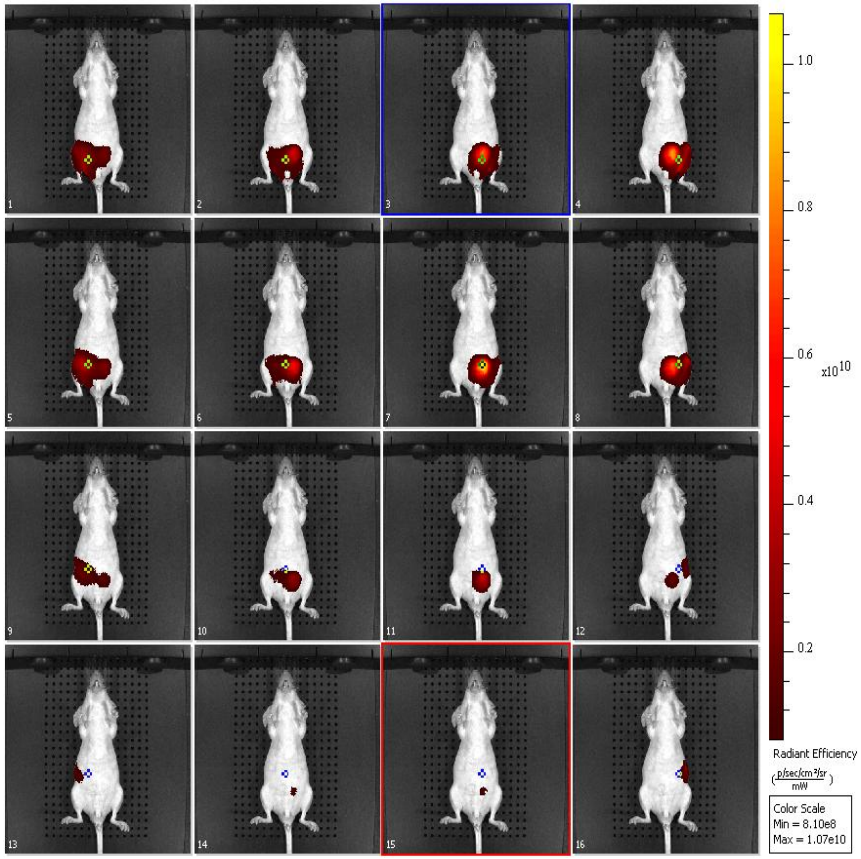




FLIT--Fluorescence Multipoint Transillumination

Spectrum



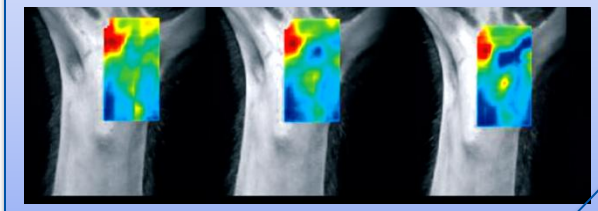


Solve Diffusion Equation for Source Location/Quantification

- Setup photon diffusion equations from each excitation source point to each image surface element
  - Assumes homogeneous tissue properties

Excitation Meas.

Fluorescence Meas.

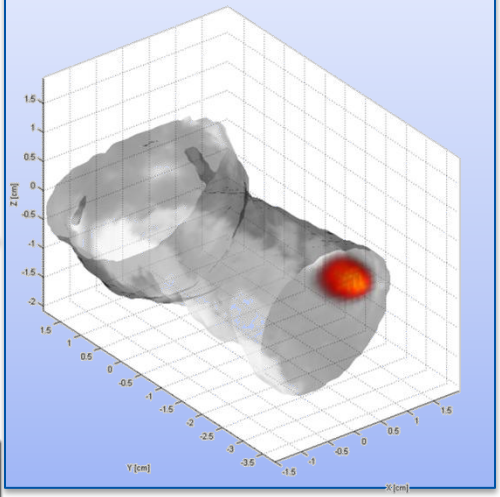


data

theory

Model

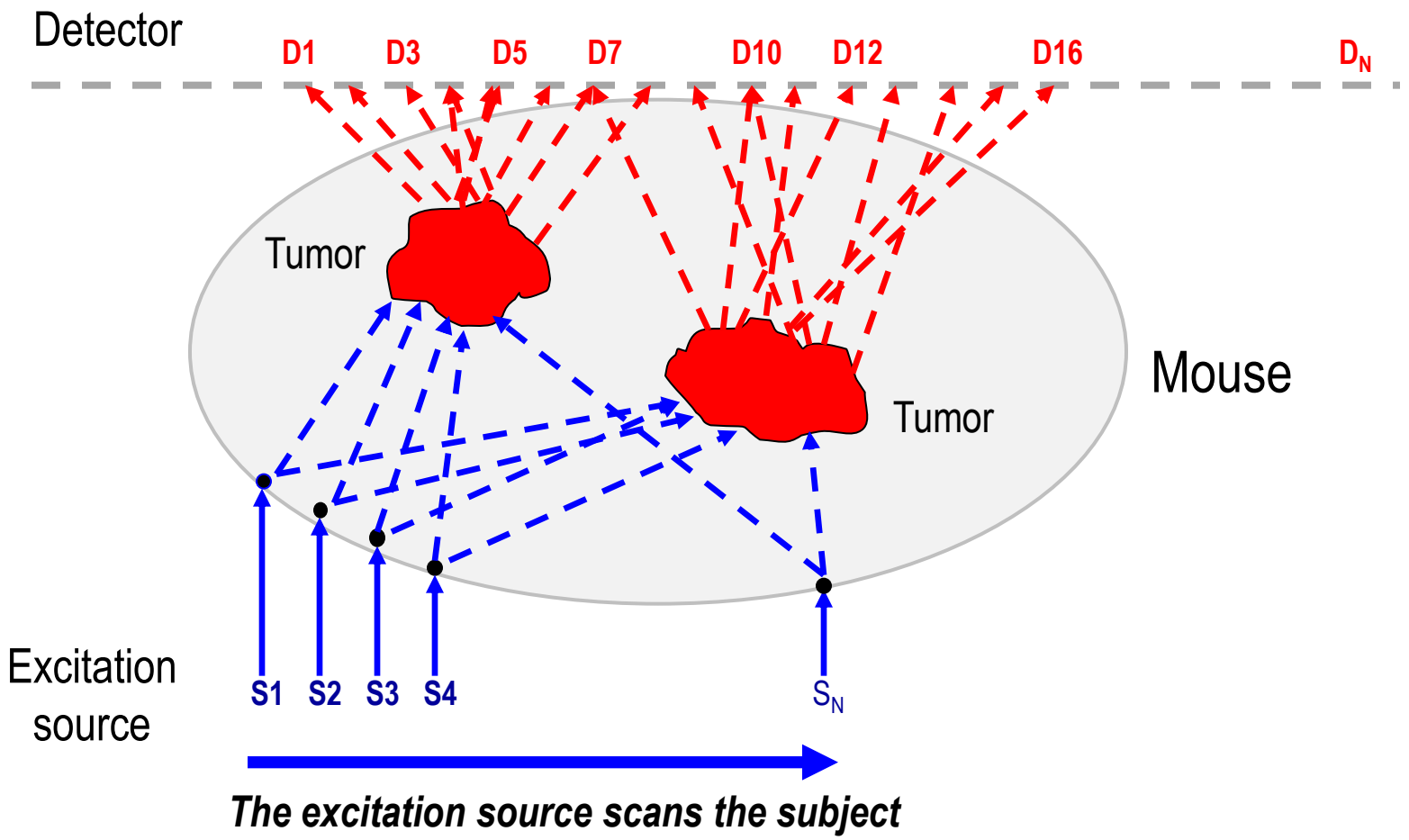
3D Reconstruction



- Solve system of equations for source location, shape, brightness
  - Non-negative least squares or algebraic reconstruction methods

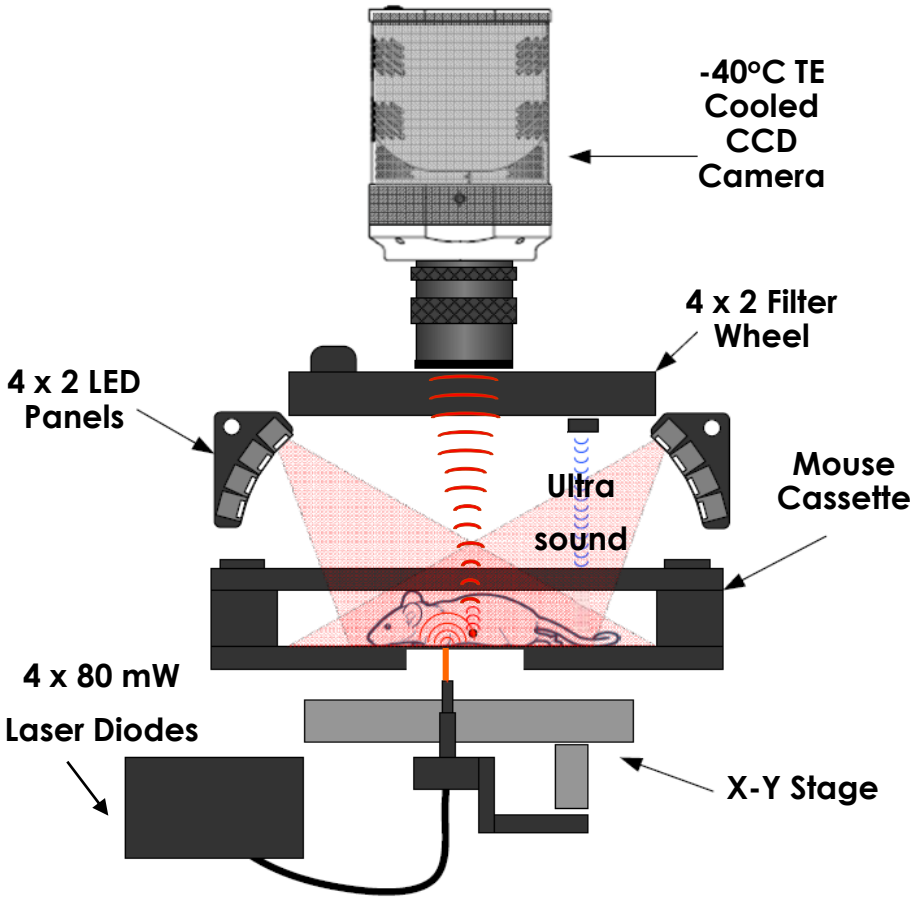
How is FMT Accomplished?

The detector collects multiple projections



Step 1: FMT Data Generation

- Reflectance Fluorescence Reference Image Acquired using LEDs
- Transillumination FMT Raster Scan using 80 mW lasers
- Tomographic Data Collected using a 512 x 512 pixel Thermoelectrically Cooled CCD Camera



Three Quick Steps to True Quantification:

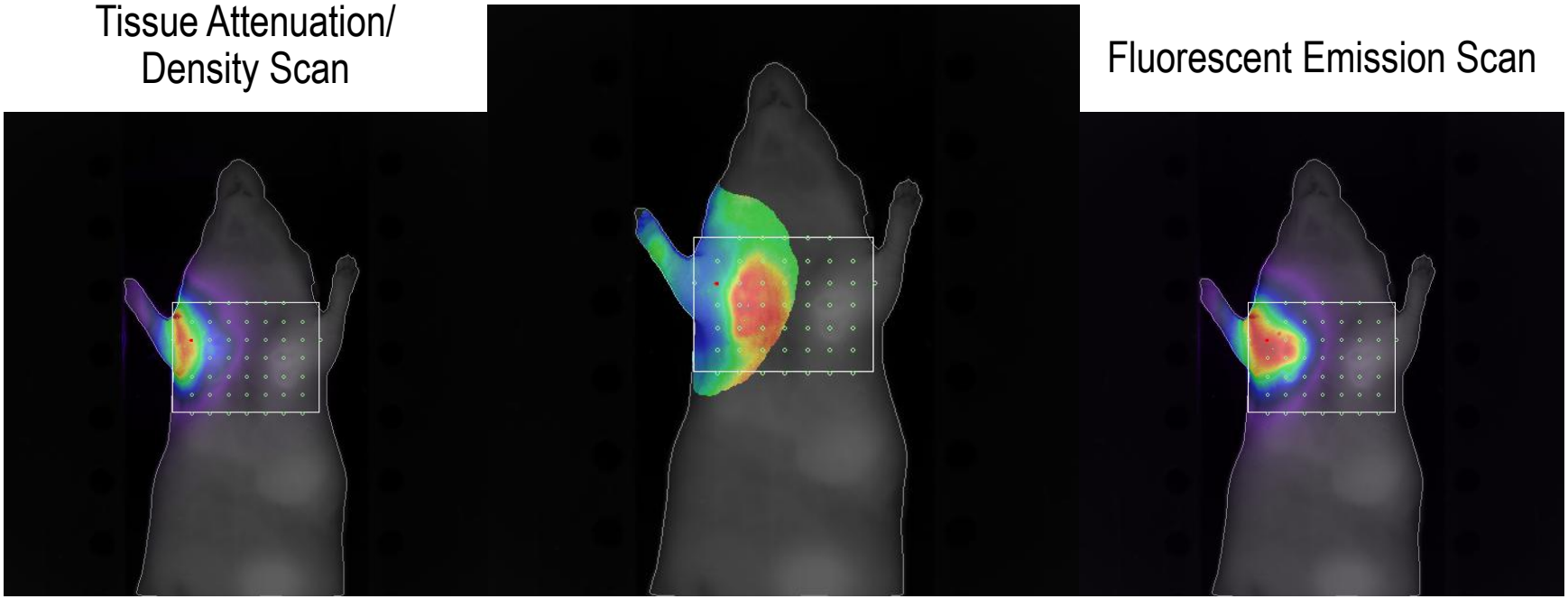
Step 2: FMT Normalization

Process all paired Absorption and Fluorescence acquisition data to generate normalized fluorescence measurements

Normalized Scan

Tissue Attenuation/ Density Scan

Fluorescent Emission Scan



Step 3: FMT Reconstruction

Fluorescence quantified to the picomole at each point in the subject, including deep tissue targets

Multi-Modality Imaging

Easily Enabling 3D Fluorescence images Fusion with CT, MR, SPECT & PET

Animal Cassette

Animal Cassette
inside **Multi-Modality Adaptor**

Quantitative FMT molecular data co-registered with anatomical CT data.

Cathepsin B activity is quantifies with PerkinElmer's **ProSense** fluorescent agent

Image courtesy of Dr. Ralph Weissleder, Massachusetts General Hospital, 2008

Multi-Modality Imaging
Easily Fusion with CT, MR, SPECT & PET

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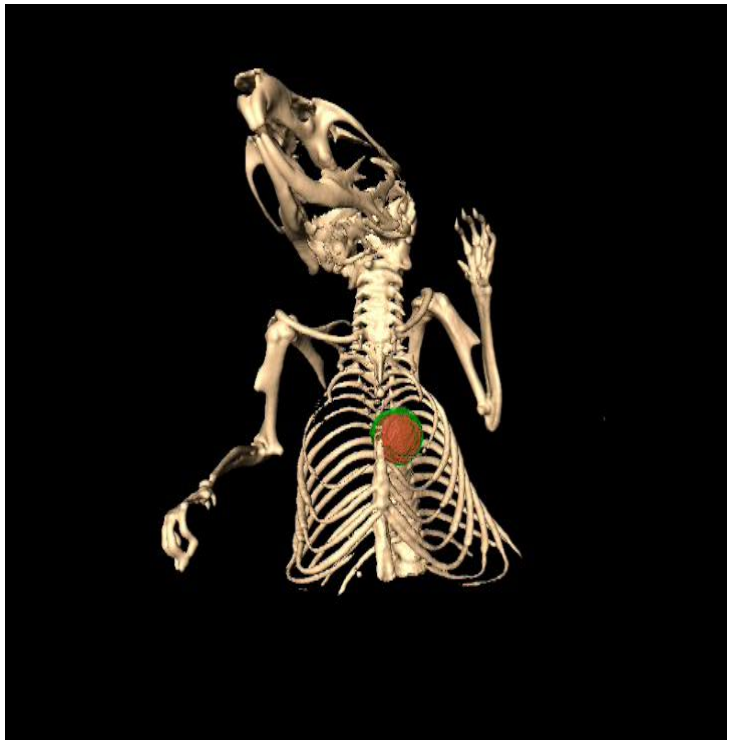
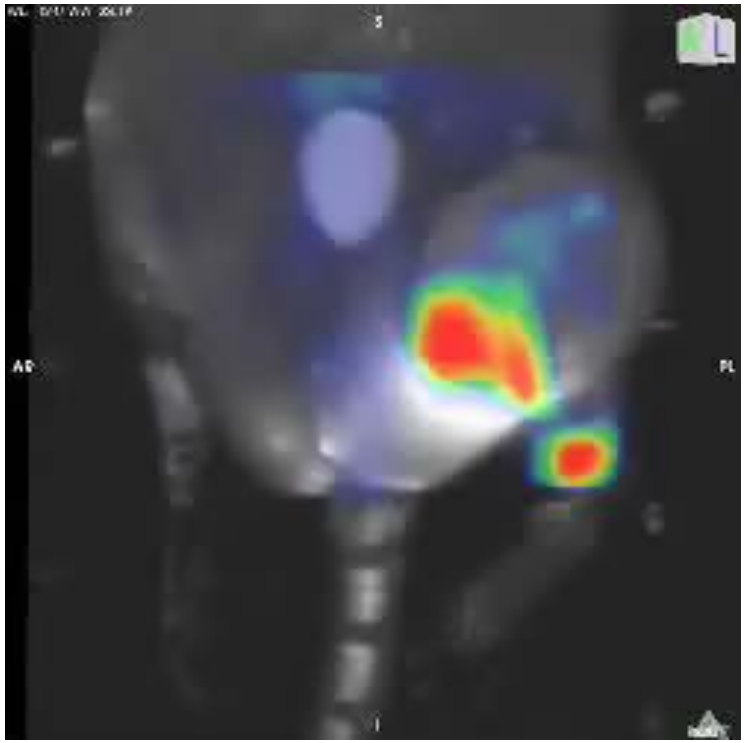
PerkinElmer Imaging Agents:
AngioSense® (Tumor vascularity)
ProSense® (Cathepsin activity)



Imaging of Tumor-Associated Macrophages (TAMs) using FMT-MRI fusion.



The color-coded optical images are used to quantitate three-dimensional maps of AMTA680 (VT680)

Images courtesy of Ralph Weissleder, Center for Molecular Imaging Research, Massachusetts General Hospital (Boston, MA)
Leimgruber et al., "Imaging of Tumor-Associated Macrophages" , Neoplasia (2009) 11, 459–468

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PerkinElmer In Vivo Imaging Agents

July 8, 2013

In Vivo Imaging Agent Platforms:

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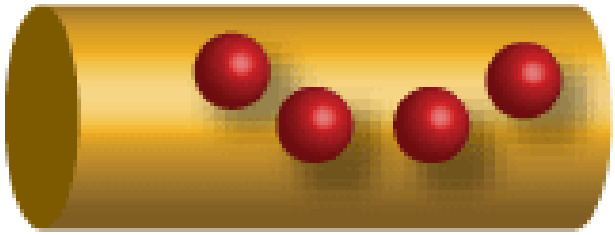
Agent Categories

	Vascular	Targeted	Activatable
Mechanism			
Detection	***Physiology***	***Biological Structure/Expression***	***Biological Function***
Value	**Increasing value of molecular information**		

Vascular Agents

- A range of highly fluorescent Physiologic Agents
- Remain stable and localized in the anatomy for various periods of time
- Always fluorescent, circulate with blood or move through GI tract
  - Designed for in vivo use
  - Limited in vitro applications



Monitor the integrity of the vascular system

Vascular Agents – Target Biology

AngioSense	680 750	Agent that remains localized in vasculature for 0-4 h; accumulates in tumours and arthritic joints at 24 h.	● Angiogenesis ● Arthritis ● Cardiovascular ● Infectious ● Inflammation ● Oncology ● Pulmonary ● Neurological ● Vascular
AngioSense IVM	680 750	Agent that remains in vasculature for 0-4 h; optimized for intraVital microscopy.	● Angiogenesis ● Arthritis ● Cardiovascular ● Vascular ● IntraVital Microscopy formulation (2 Photon Microscopy)
AngioSPARK	680 750	Pegylated fluorescent nanoparticles (5 doses); remains localized in vasculature.	● Arthritis ● Atherosclerosis ● Hypertension ● Inflammation ● Oncology ● Neurological ● Vascular
Genhance	680 750	Small molecule fluorescence agent. Use as a control or in vascular permeability imaging.	● Vascular
Superhance	680	Small molecule agent. Binds to albumin in blood for extended (30 m-1 h) vascular imaging.	● Angiogenesis ● Arthritis ● Inflammation ● Neurological
GastroSense	750	Agent to monitor gastric emptying and the impact of various drugs on gastric motility.	● Gastric Emptying ● Anatomical reference marker for the gastrointestinal tract

Monitor the integrity of the vascular system

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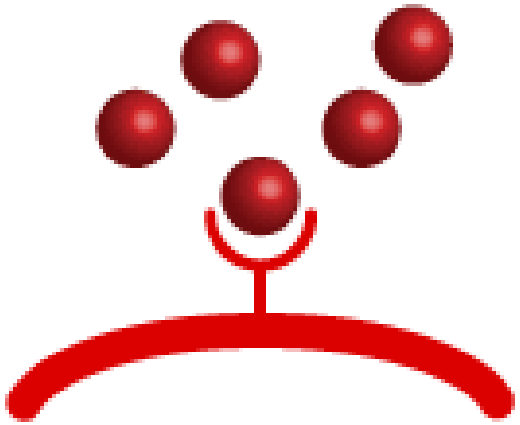
Targeted Agents

- Optimized agents that actively target and bind to specific biomarkers
  - Designed for *in vivo* use
  - *Emerging In vitro applications*



Target specific biomarkers

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Targeted Agents – Target Biology

IntegriSense	680 750	Targets integrin αvβ3 expressed in oncology, atherosclerosis and angiogenesis disease models	● Angiogenesis ● Atherosclerosis ● Oncology ● Neurological
Annexin-Vivo	750	Selectively membrane-bound phosphatidylserine exposed during the early stages of apoptosis	● Apoptosis ● Atherosclerosis ● Inflammation ● Oncology ● Neurological
OsteoSense	680 750 800	Bisphosphonate fluorescent bone agent for optimizing bone turnover through binding of hydroxyapatite Detect microcalcification and measure osteogenic (bone remodeling) activity	● Arthritis ● Atherosclerosis ● Bone Turnover ● Skeletal ● Oncology
HypoxiSense	680	Image Carbonic Anhydrase IX overexpression in tumours in response to regional tumour hypoxia	● Oncology
FolateR-Sense	680	Targeting Folate Receptor (**Folate receptor** Upregulated in highly metabolic cells (cancers and inflammatory cells)	•cancer and inflammation
BacteriSense	645	Combine to the membrane of Gram Positive and Negative bacteria	

Target specific biomarkers

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Targeted Agents – Target Biology

TLectinSense™	680	Tomato lectin employs a gold standard for vascular labelling, Highly sensitive to endothelial cell glycoproteins expression and ideal for labelling of tumour vascularization.. Enables the quantitation of vascular burden across different tumour cell lines. Broad imaging window from 6-24 hours. High correlation between signal when used ***in vivo*** **and** ***in vitro.***	
HER2Sense™	645	HER2Sense is based on the therapeutic antibody, Trastuzumab and PerkinElmer's proprietary VivoTag® fluorescent dye, optimized for use in living systems. Trastuzumab is a commercialized bio-therapeutic drug from Roche. Highly specific for the HER2/neu receptor and avoids systemic immune responses found in other antibody-based imaging agents	

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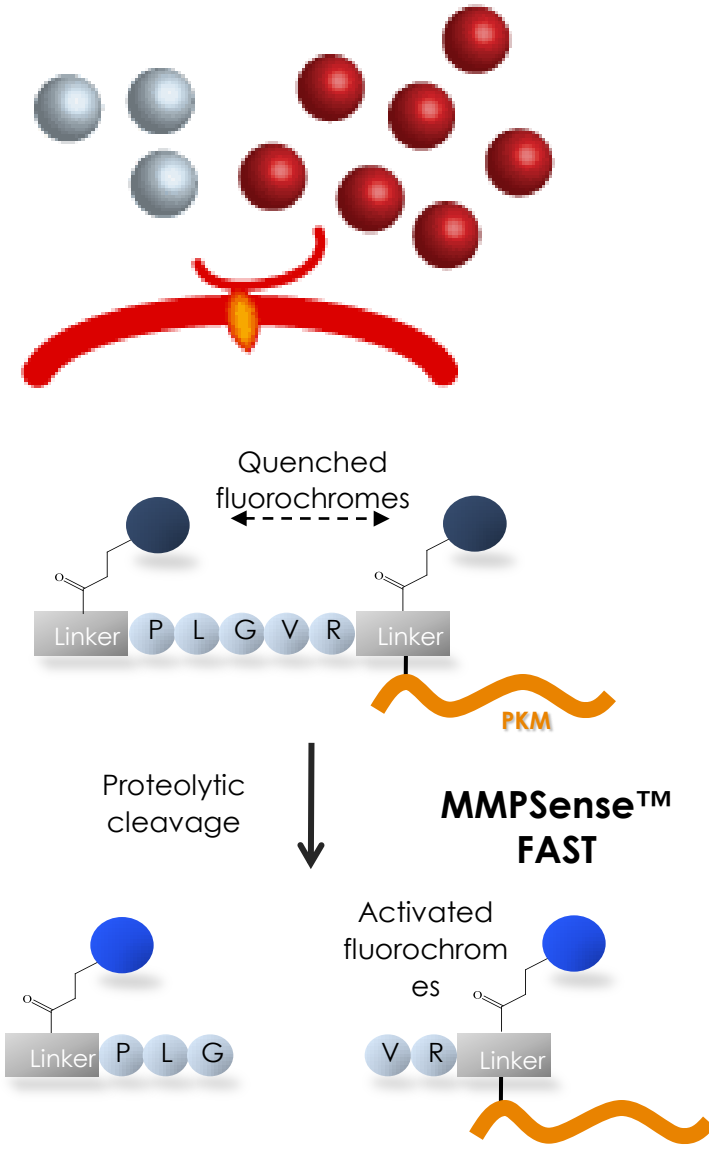
Activatable Agents

- Activatable Agents
  - Protein type
  - “Quenched” in their native state
  - Activated by a select panel of disease-associated proteases
    - Designed for *in vivo* use
    - *Emerging In vitro applications*



Monitor protease activity associated with disease state

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Activatable Agents – Target Biology

ProSense	680 750	Activated by **cathepsin B, L, S** and **plasmin**
ProSense Control	680 750	**Non-activatable analog** of ProSense for use as a negative control
ProSense FAST	750	**FAST version of ProSense**, with faster kinetics and a broader imaging window.
Cat B FAST	680 750	**Cathepsin B** selective **FAST** activatable agent
Cat K FAST	680	**Cathepsin K** selective **FAST** activatable agent
MMPSense	680	Activated by **MMP** (matrix metalloproteinases, including MMP-2, -3, -9 and -13)
MMPSense FAST	750	**MMP FAST** activatable agent
Neutrophil Elastase FAST	680	Activated by **elastase** produced by neutrophil cells using FAST
ReninSense FAST	680	A **renin-angiotensin FAST** activatable agent

Monitor protease activity associated with disease state

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Activatable Agents – Applications

ProSense	680 750	● Arthritis ● Oncology
ProSense Control	680 750	Negative control in ● Arthritis ● Oncology
ProSense FAST	750	● Oncology ● Inflammation
Cat B FAST	680 750	● Cardiovascular disease ● Oncology ● Inflammation ● Certain neurological diseases
Cat K FAST	680	● Oncology applications involving metastasis to the bone ● Broad range of bone applications including osteoporosis and bone changes following arthritis
MMPSense	680	● Oncology
MMPSense FAST	750	● Oncology ● Inflammation ● Pulmonary ● Cardiovascular disease
Neutrophil Elastase FAST	680	● Acute lung Injury Models ● Acute respiratory distress syndrome ● Emphysema ● Cystic Fibrosis ● COPD ● Wound Healing ● Rheumatoid Arthritis ● Ischemia-reperfusion
ReninSense FAST	680	● Cardiovascular disease ● Certain models of impaired renal function ● Chronic hyperthyroidism ● Hypertension ● Some neurological diseases

Monitor protease activity associated with disease state

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PerkinElmer's Fluorescent Imaging Agent Portfolio

PerkinElmer offers four categories of fluorescent *in vivo* imaging agents:

LABELS and NANOPARTICLES

VivoTag™ 680XL Protein Labeling Kit : designed for preparing fluorescently labeled antibodies, proteins or peptides for small animal in vivo imaging applications.

VivoTrack 680 : cell labeling agent that intercalates into the plasma membrane of primary cells and cell lines.

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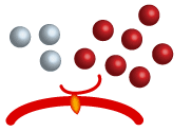
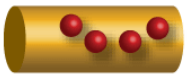
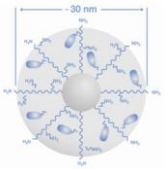
Agent Platforms: Robust Readouts *In Vivo*







Activatable	MMPSense™ 680
	MMPSense™ 645/750 FAST
	ProSense® 680
	ProSense® 750EX
	ProSense® 750 FAST™
	ProSense® Control 680/750
	Cat K 680 FAST™
	Cat B 680/750 FAST™
	Neutrophil Elastase 680 FAST™
	ReninSense 680 FAST™
Targeted	OsteoSense® 680EX/750EX/800
	IntegriSense™ 645/680/750
	Annexin-Vivo 750
	BacteriSense™ 645
	FolateRSense™ 680
	HypoxiSense™ 680
Physiologic	GastroSense™ 750
	Genhance™ 680/750
	Superhance™ 680
	AngioSense®-IVM 680/750
	AngioSense® 680/750EX
	AngioSPARK® 680/750
Labeling	VivoTag® 645/680/800
	VivoTag® 645/680/800
	VivoTag®-S 680/750
	VivoTag®-S 680/750
	VivoTag® 680/800 XL
	VivoTag® 680/800 XL
	AminoSPARK® 680/750

Preclinical Imaging

Enabling translational biomarker readouts of disease progression and therapeutic response

- Arthritis
- Bone Remodeling
- Cardiovascular Disease
- CNS Disorders
- Fibrosis
- Infectious Disease
- Inflammation
- Metabolic Disease
- NIR Labeled Dyes & Agents
- Oncology
- Pulmonary Disease
- Vascularity
- Vascular Biology
- Edema (Oedema)
- Wound Healing

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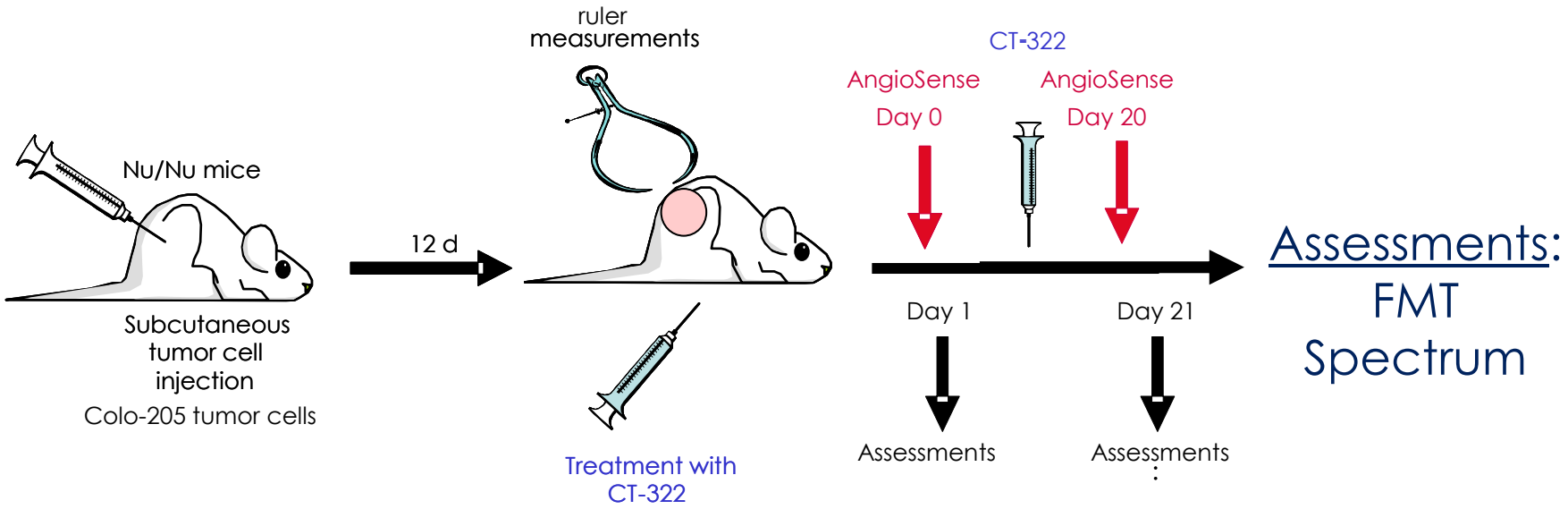
PerkinElmer's In Vivo fluorescence Imaging Applications

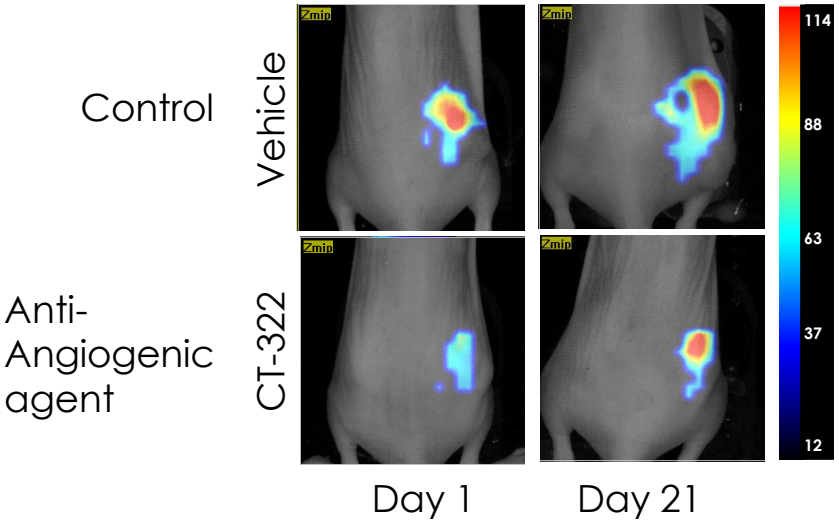
July 8, 2013

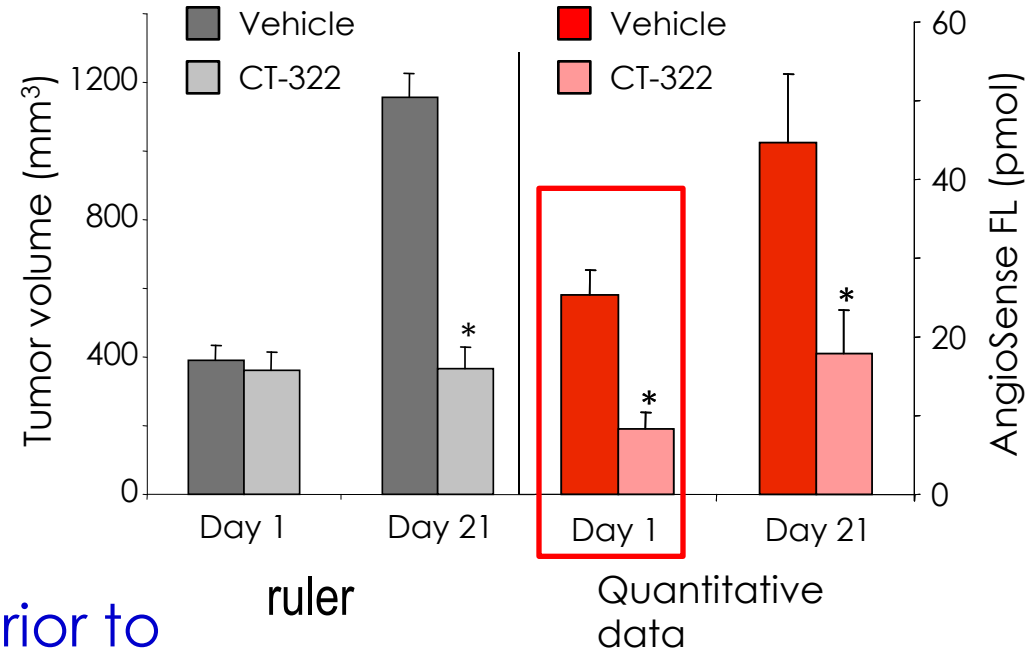
In Vivo Quantification of Therapeutic Response

- Therapeutic effect of anti-Angiogenic Adnectin, CT-322, on tumor vascularity in a xenograft model



Evaluating Anti-Angiogenic Agent in Tumor Model





FMT and AngioSense are superior to standard ruler in evaluating therapeutic response

4T1 Breast Cancer Lung Colonization Model

- 4T1 Mouse Breast Adenocarcinoma Cells
- IV Tail Injection of 0.5 - 5 x 10^5 Cells
- BALB/c Mice

Experimental Details

2 weeks

IV Tail Injection of
2 nmol/150 µL each of
ProSense™ 750 & AngioSense™ 680 **or** IntegriSense™ 750 & AngioSense™ 680

24 h

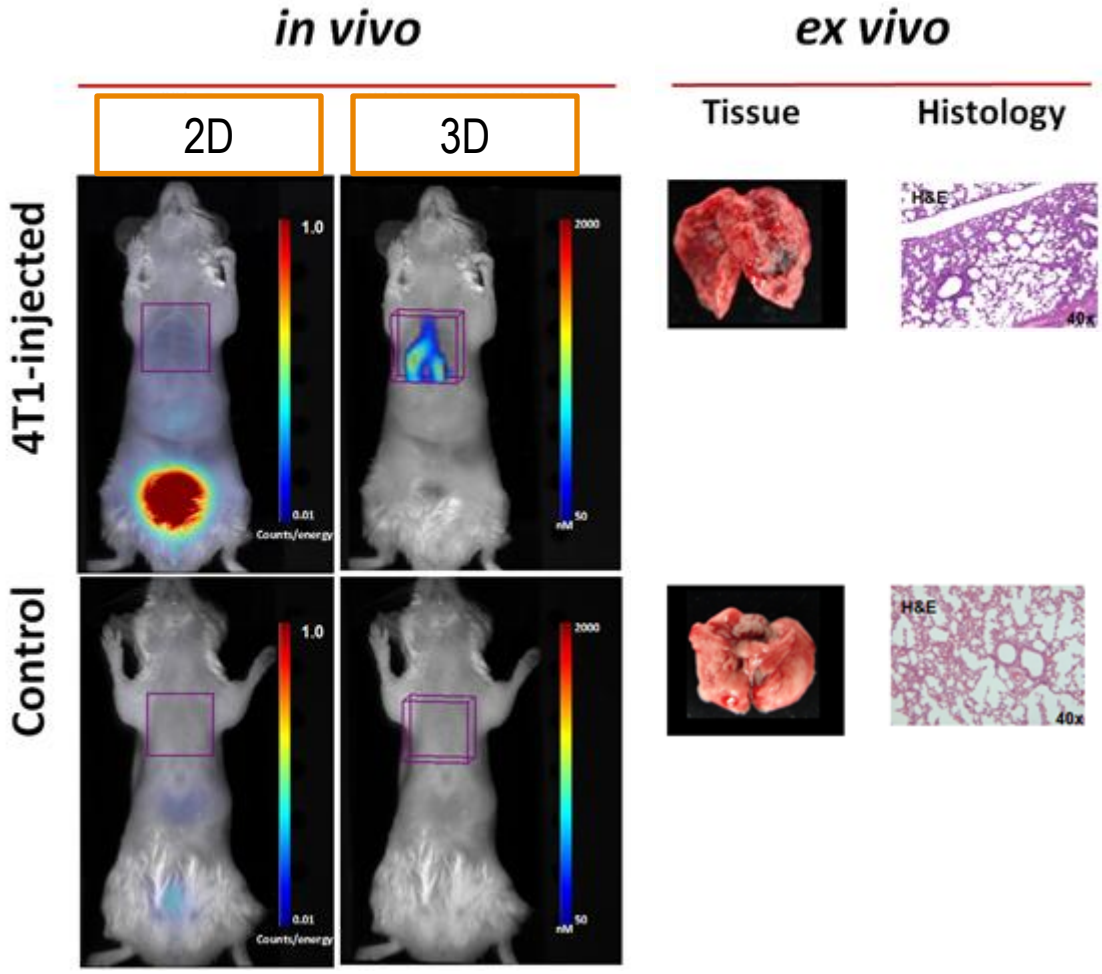
Assessments:

- FMT/spectrum Imaging *in vivo*
- Quantitative Analysis
- Lung Weight Measurements
- Histological Analysis (H&E Staining)

81

4T1 Breast Cancer Lung Colonization Model

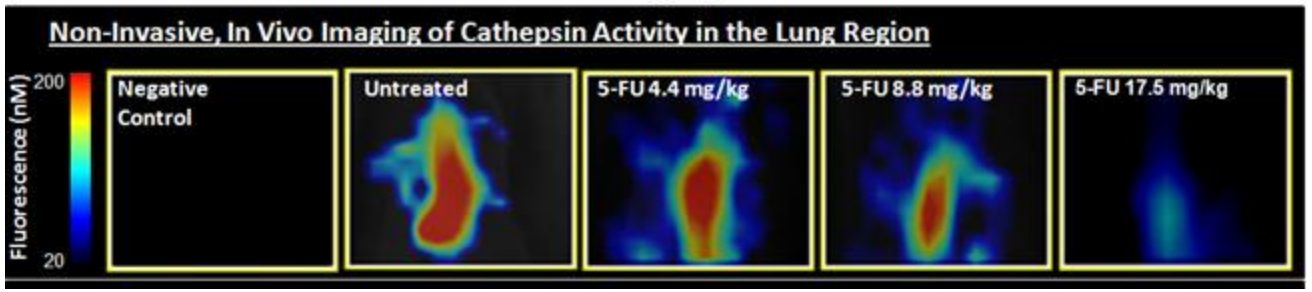
FMT 2500™ Imaging of Tumor Cathepsin Activity



- Using ProSense detect tumor-associated protease activity non-invasively in living animals
- Imaging results correlated well with Lung Weight measurements

82

Quantification of 5-Fluorouracil/2'-deoxyinosine (5-FU/2DI) with ProSense® 750



- Our 3D optical imaging system and ProSense successfully monitors prophylactic treatment in deep tissue compartments non-invasively
- Total fluorescence showed the greatest sensitivity in drug efficacy

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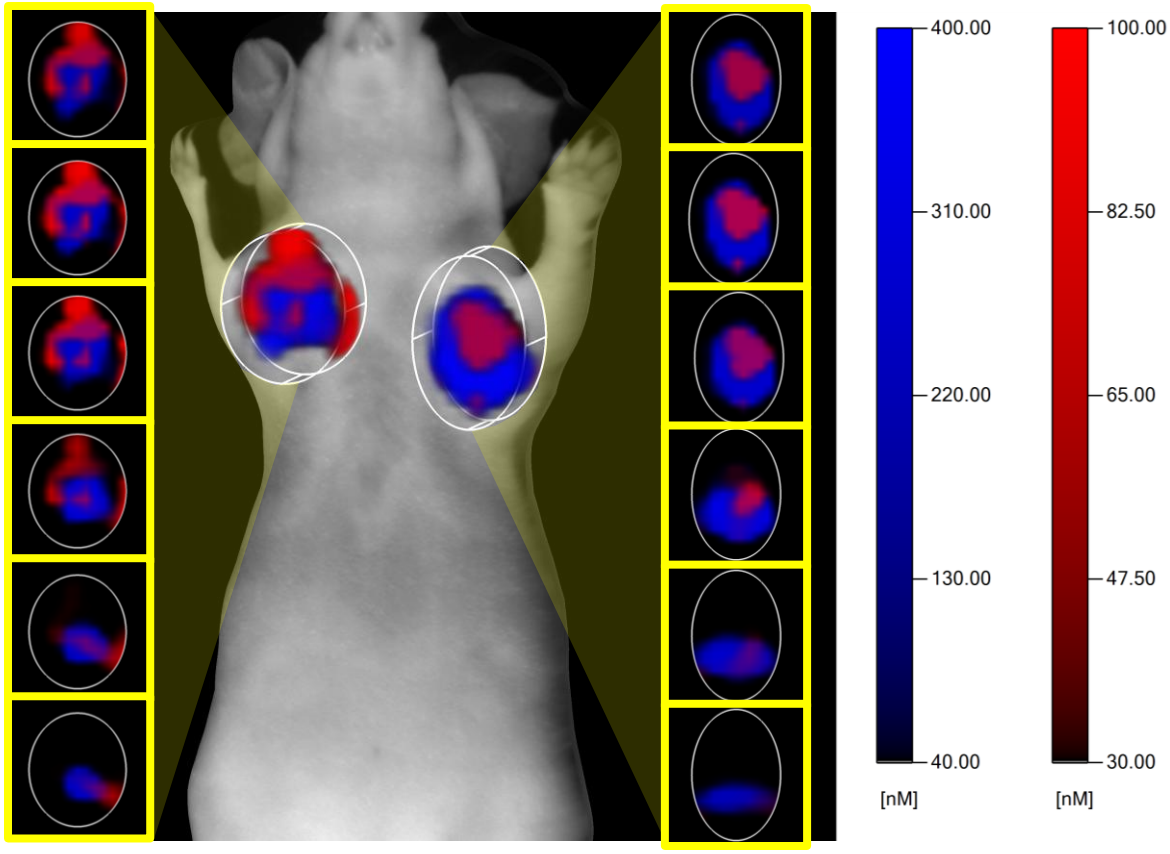
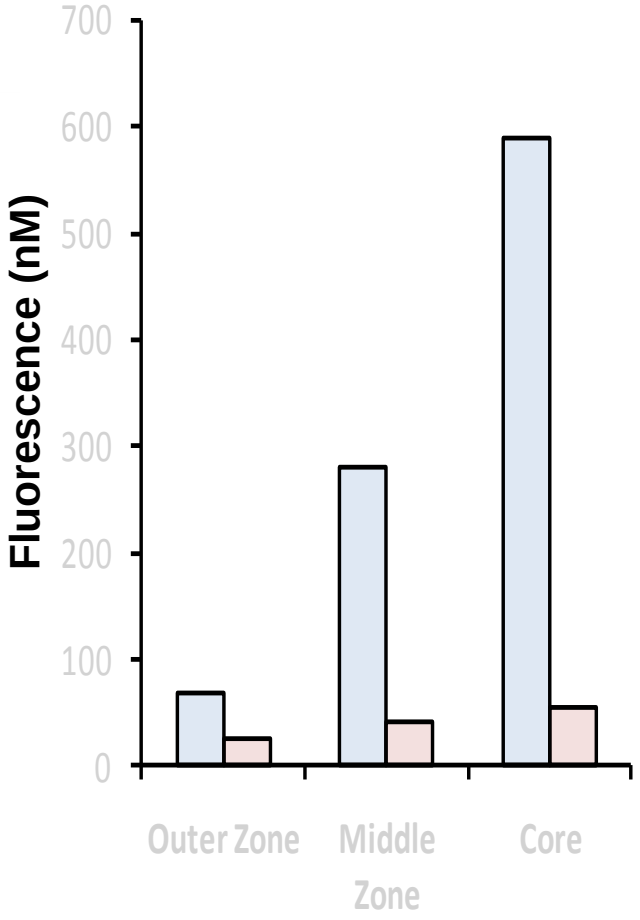
CA IX Agent: Assessing the Tumor Microenvironment

HeLa Tumor Xenografts on mammary fat pad:

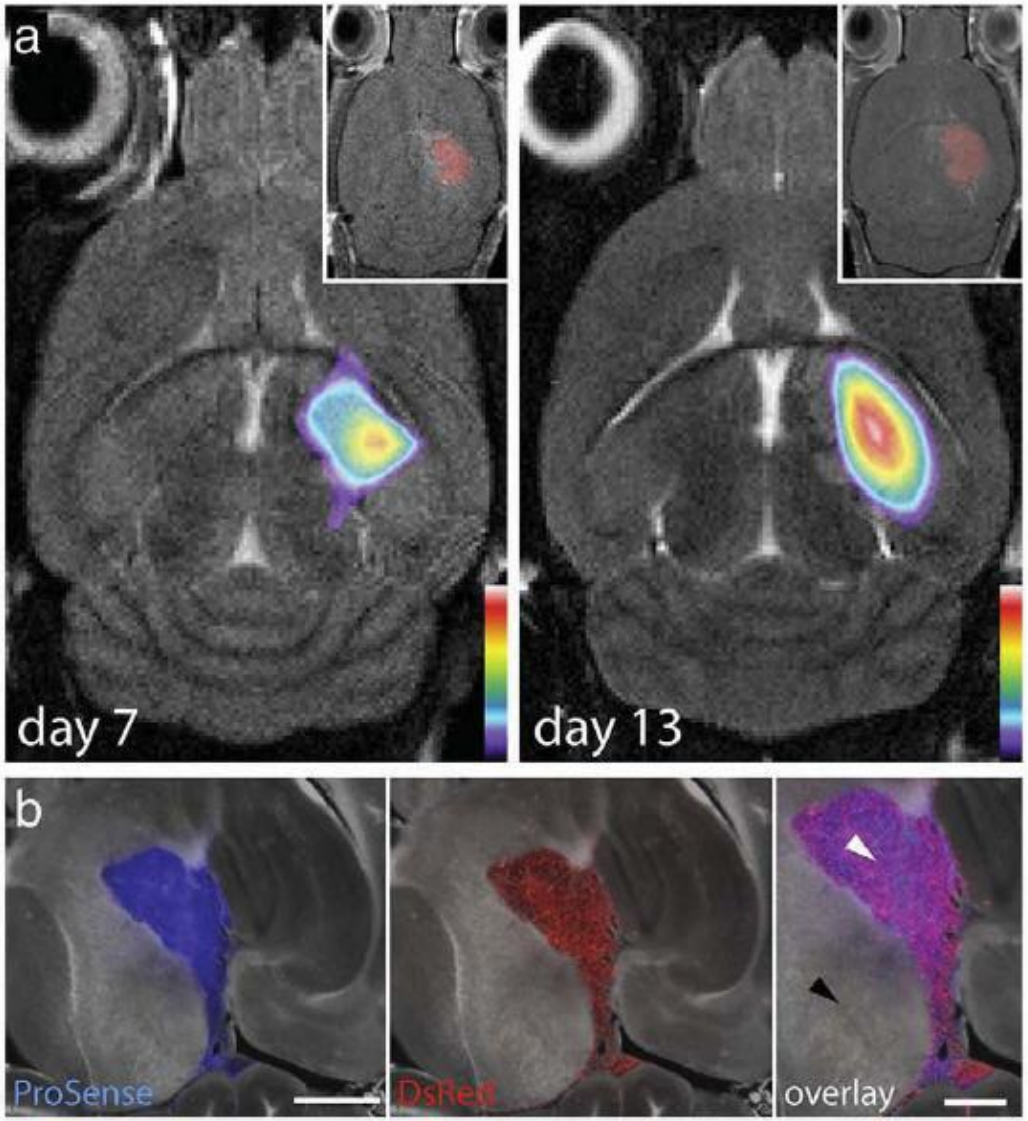
- Co-injection of CAIX Agent and AngioSense 750
- Tomographic region assessment – "virtual biopsy"

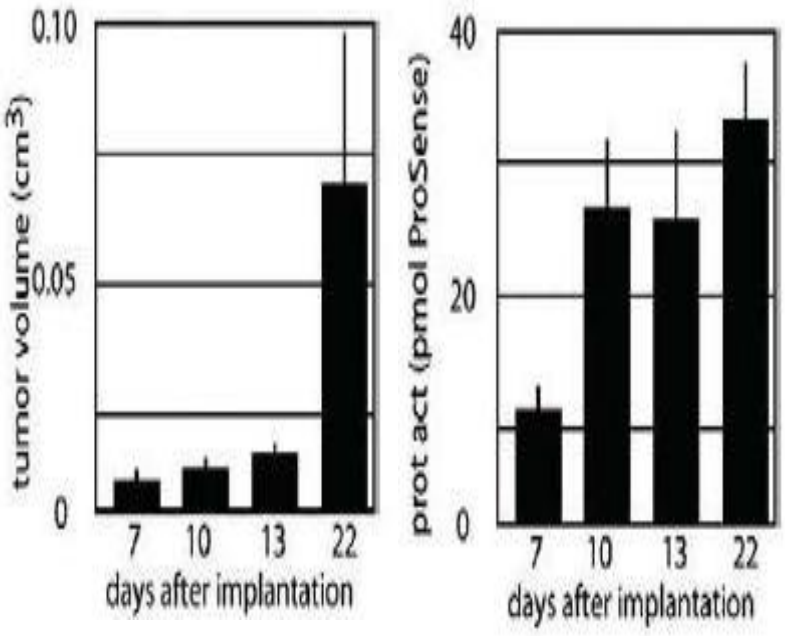




- CA IX agent co-localizes with ex vivo anti-CAIX and Pimo staining, further supporting specificity of in vivo localization to hypoxic regions

Brain Tumors





Combined fluorescence and MR imaging of brain tumors. IV ProSense, an activatable fluorescent probe for protease activity, was injected intravenously into glioma-bearing nude mice. **ProSense**, DSRed expression, and MR anatomical images aligned well and each effectively tracked tumor progression from 7 to 22 days.

McCann et al., NeuroImage, 2009

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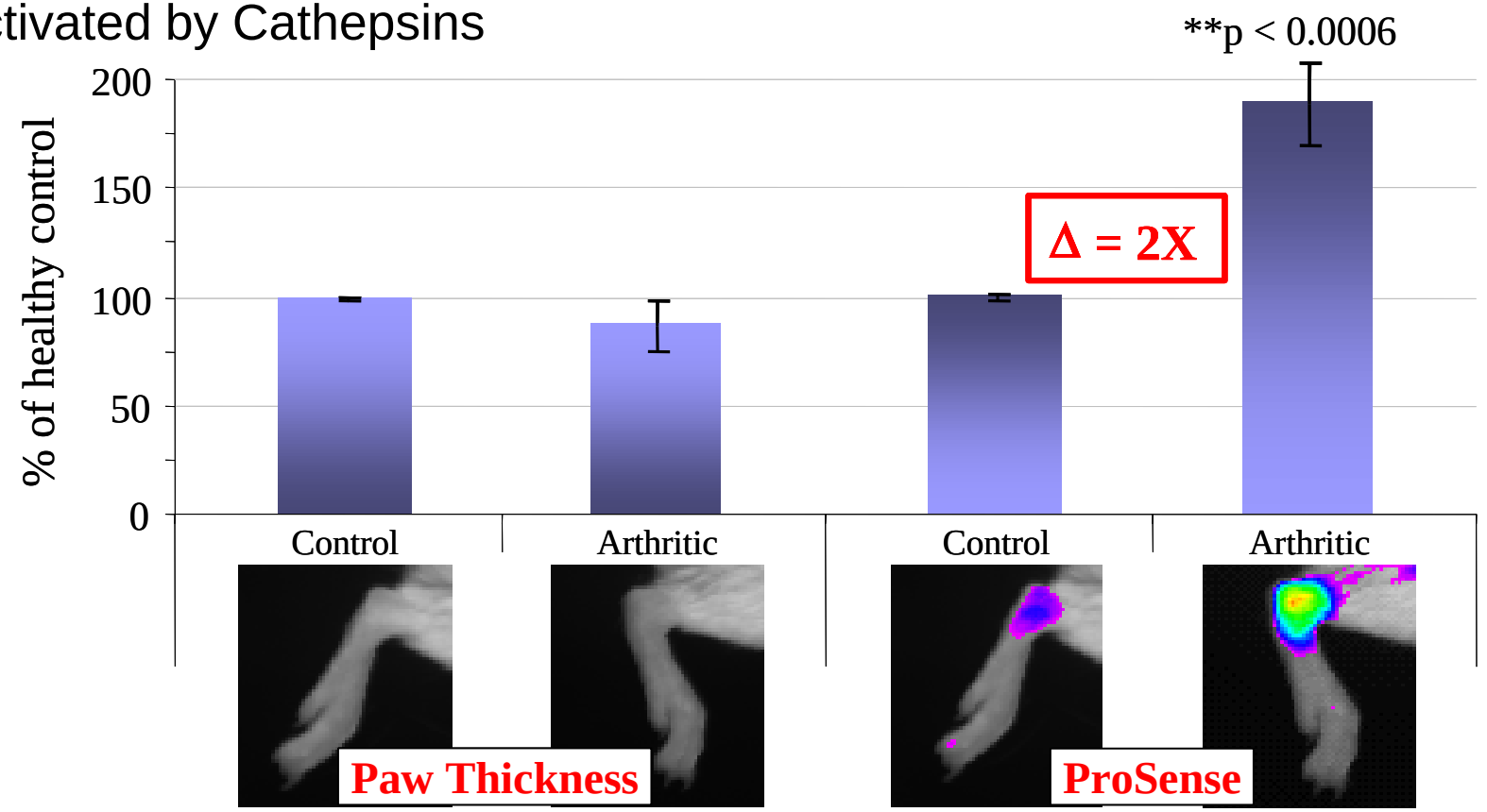
Arthritis applications

86

CAIA Model : ProSense & Early Disease (Day 4)

- Arthritis is not clinically detectable
- 24 hrs after ProSense probe injection
- Activated by Cathepsins

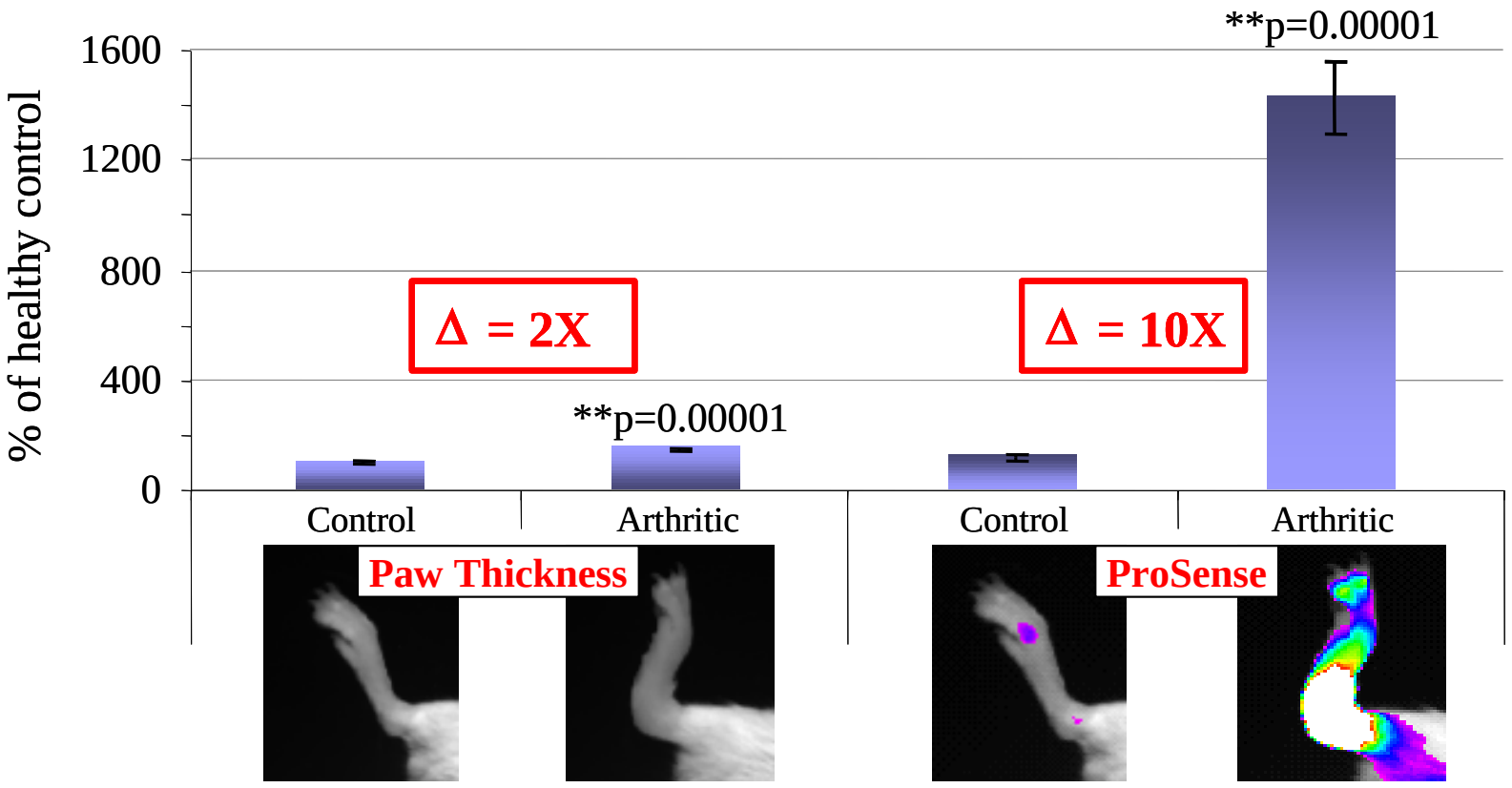


imaging with ProSense can detect disease at earlier time points, prior to detection by paw thickness

87

CAIA Model : ProSense & Late Disease (Day 8)

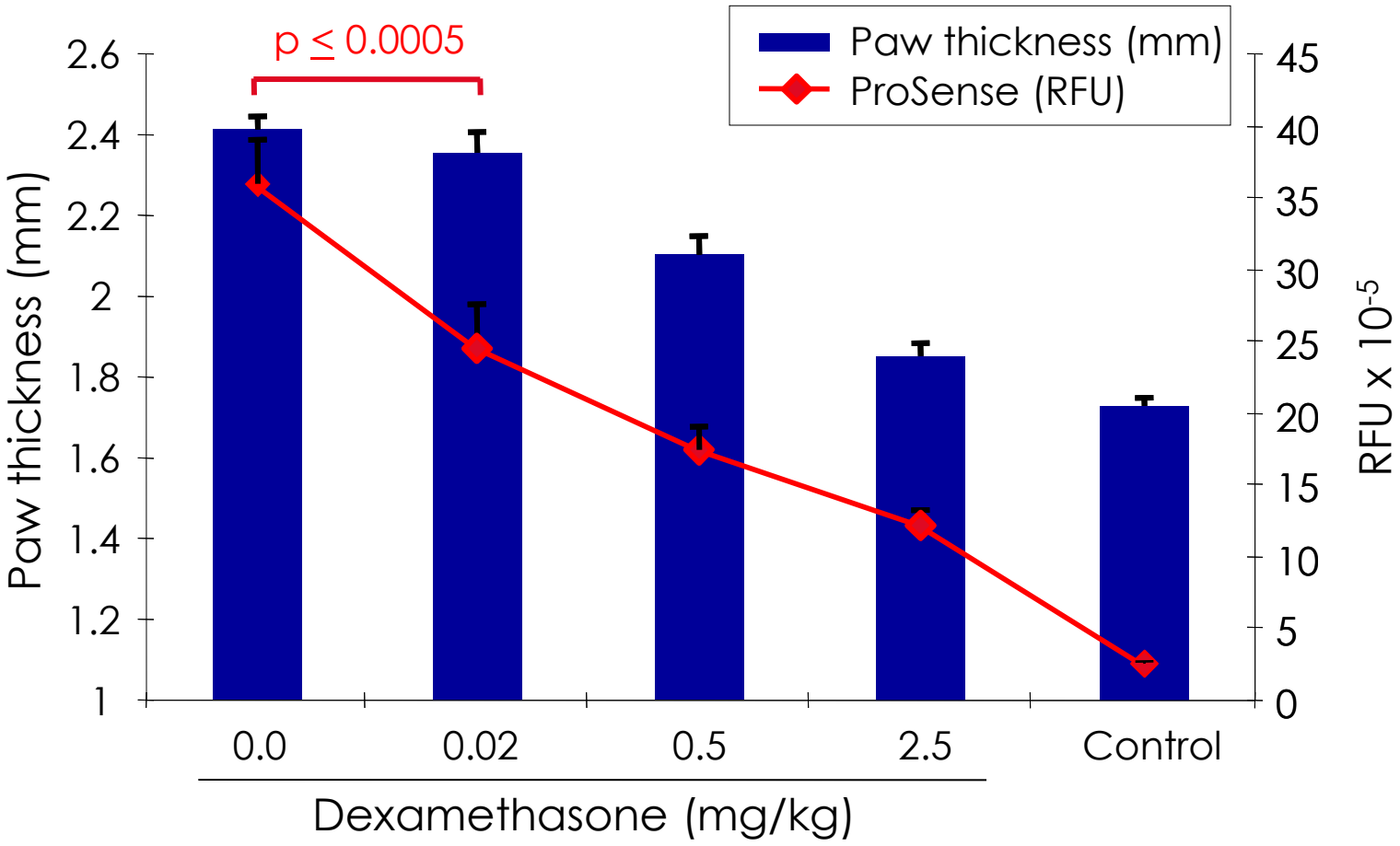
- Arthritis is clinically detectable and at its peak
- 24 hrs after ProSense probe injection



imaging with ProSense provides a 10-fold signal over control animals at the peak of the disease

88

- Dexamethasone: Days 5 & 6 following Collagen Ab Injection



ProSense correlates well with classical measures but is significant at lower doses

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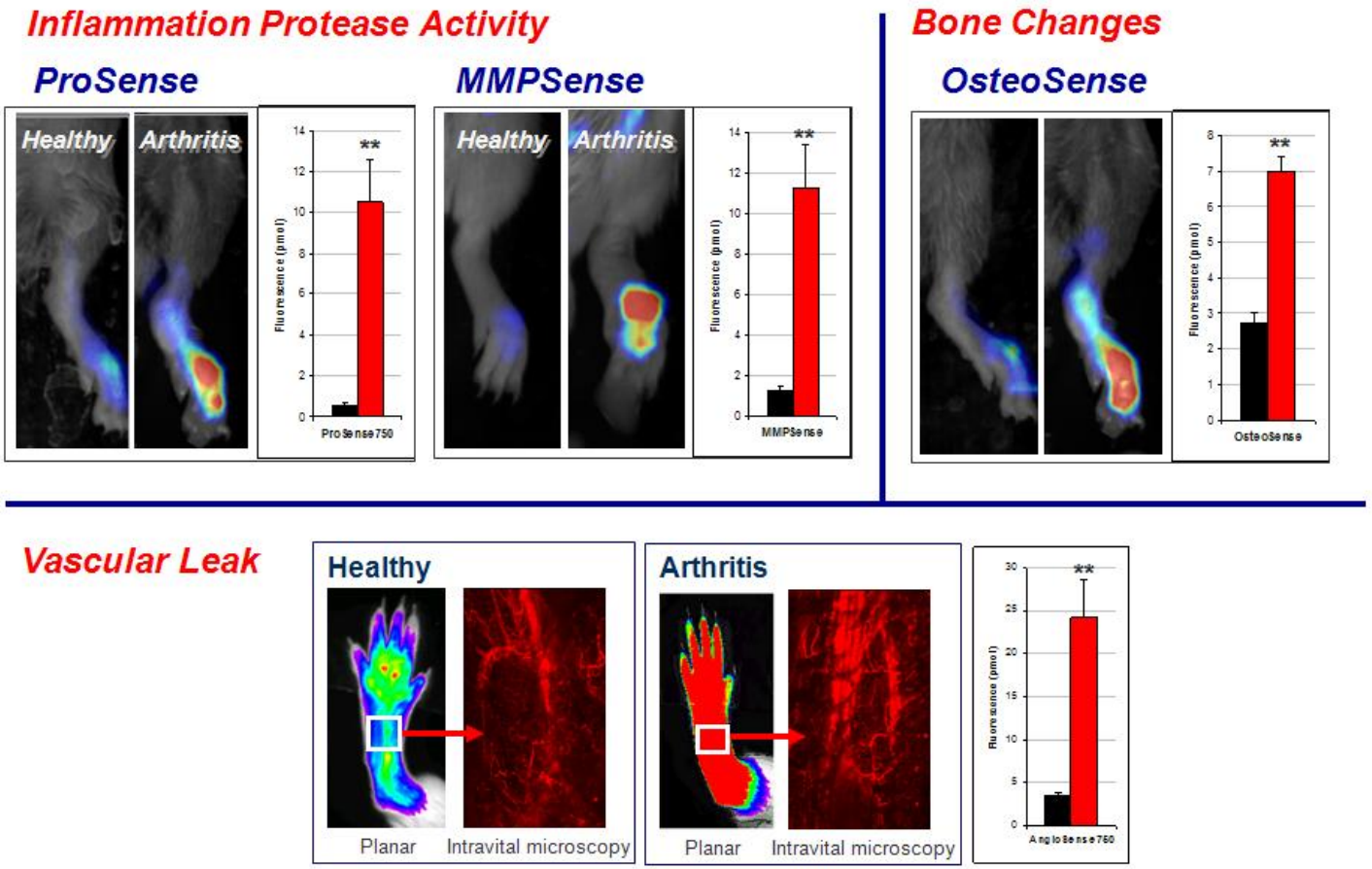
Targeted Agents – Inflammation: Multiplex Arthritis

Multiplex fluorescence Imaging



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Pulmonary Disease applications

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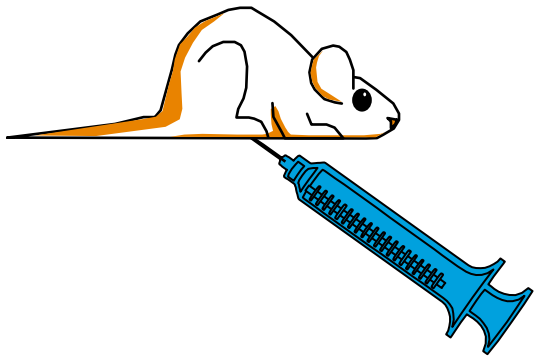
Ovalbumin (OVA)-induced Asthma

BALB/c mice



Assessments:

3D fluorescence Imaging
BAL cells
FRI lung *ex vivo*

Time 0 14d 21 23 25d

IntraPeritoneal sensitizations
OVA (50μg)/Alum (2mg)

IntraNasal challenges
OVA (100μg)

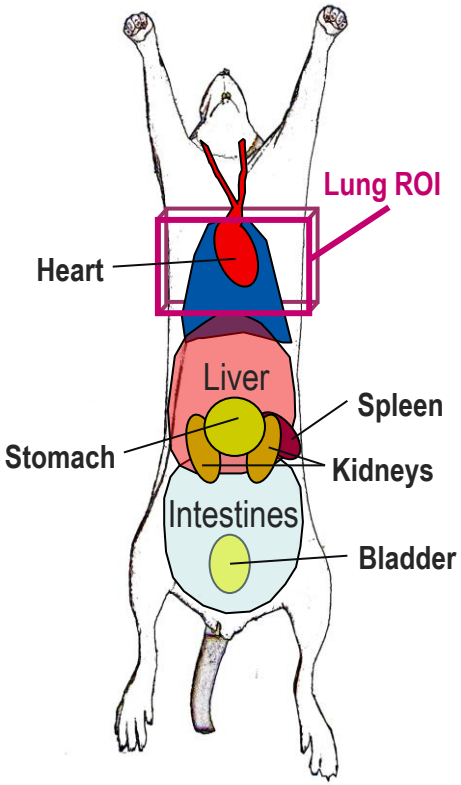
5nmol ProSense or
MMPSense

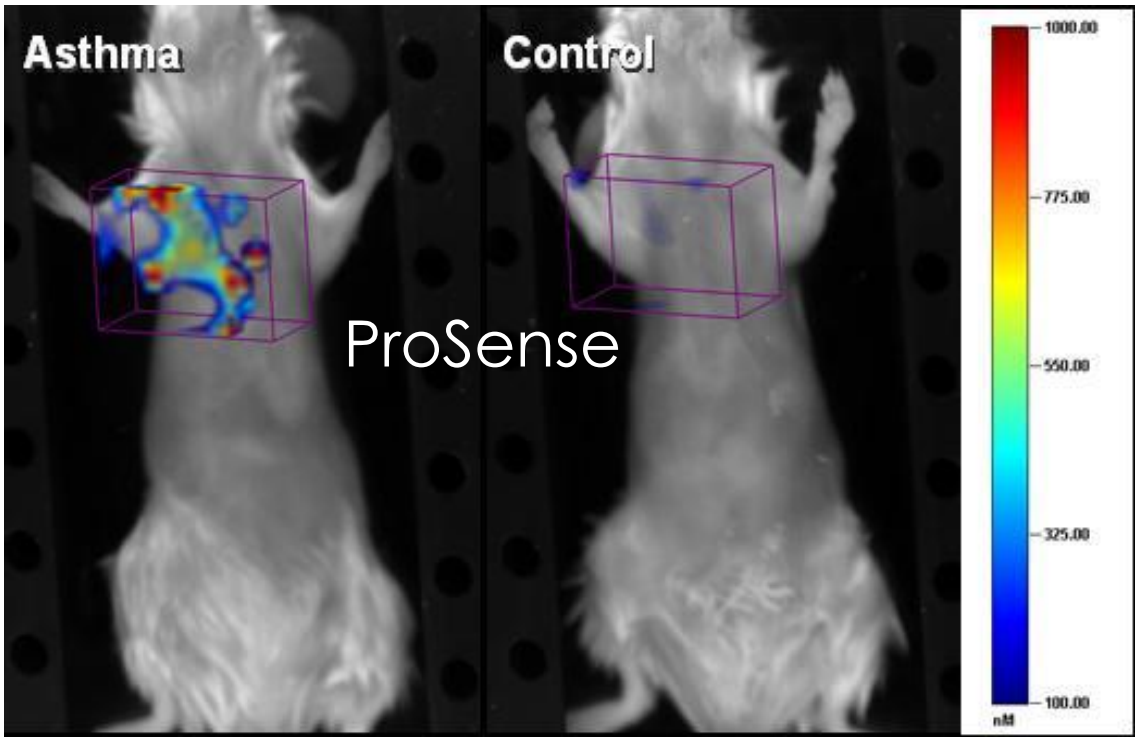
We adopted a standard model of murine asthma used in multiple research labs

BAL = Bronchoalveolar Lavage

Imaging Ovalbumin (OVA)-induced Asthma

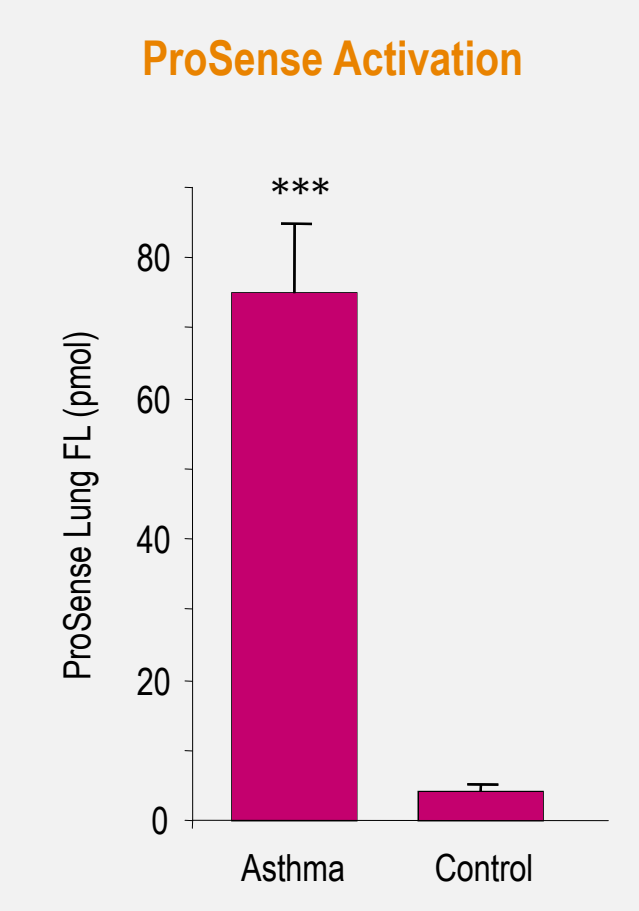
In vivo 3D Fluorescence Imaging

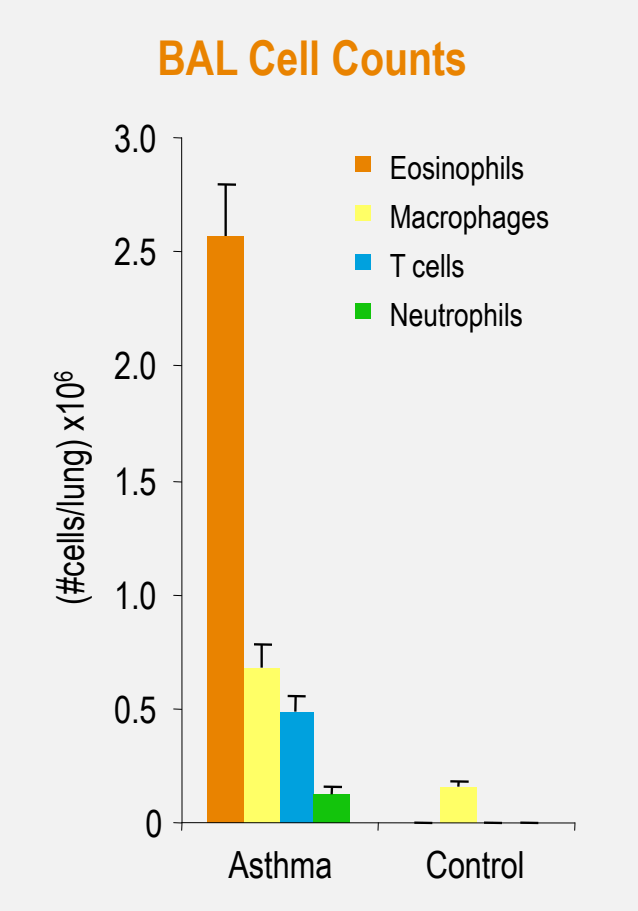




Asthma lung signal using ProSense is considerably higher and involves a larger volume than in control mice

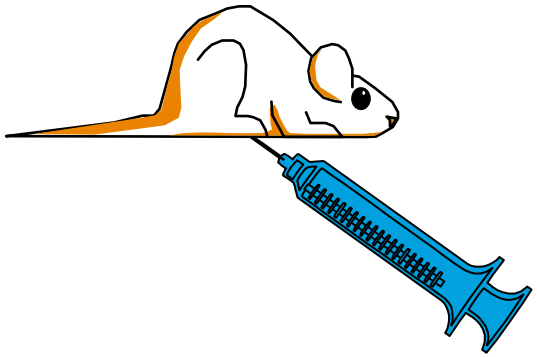
OVA-induced Asthma Comparison to BAL





FMT quantification of ProSense signal provides robust differences between asthma and control mice, in close agreement with the BAL cell assessment

Steroid inhibition of OVA-induced Asthma



BALB/c mice

Assessments:

3D fluorescence Imaging
BAL cells
FRI lung *ex vivo*

Time

0 — 14d — 21 — 23 — 25d

Intra**P**eritoneal sensitizations
OVA (50μg)/Alum (2mg)

Intra**N**asal challenges
OVA (100μg)

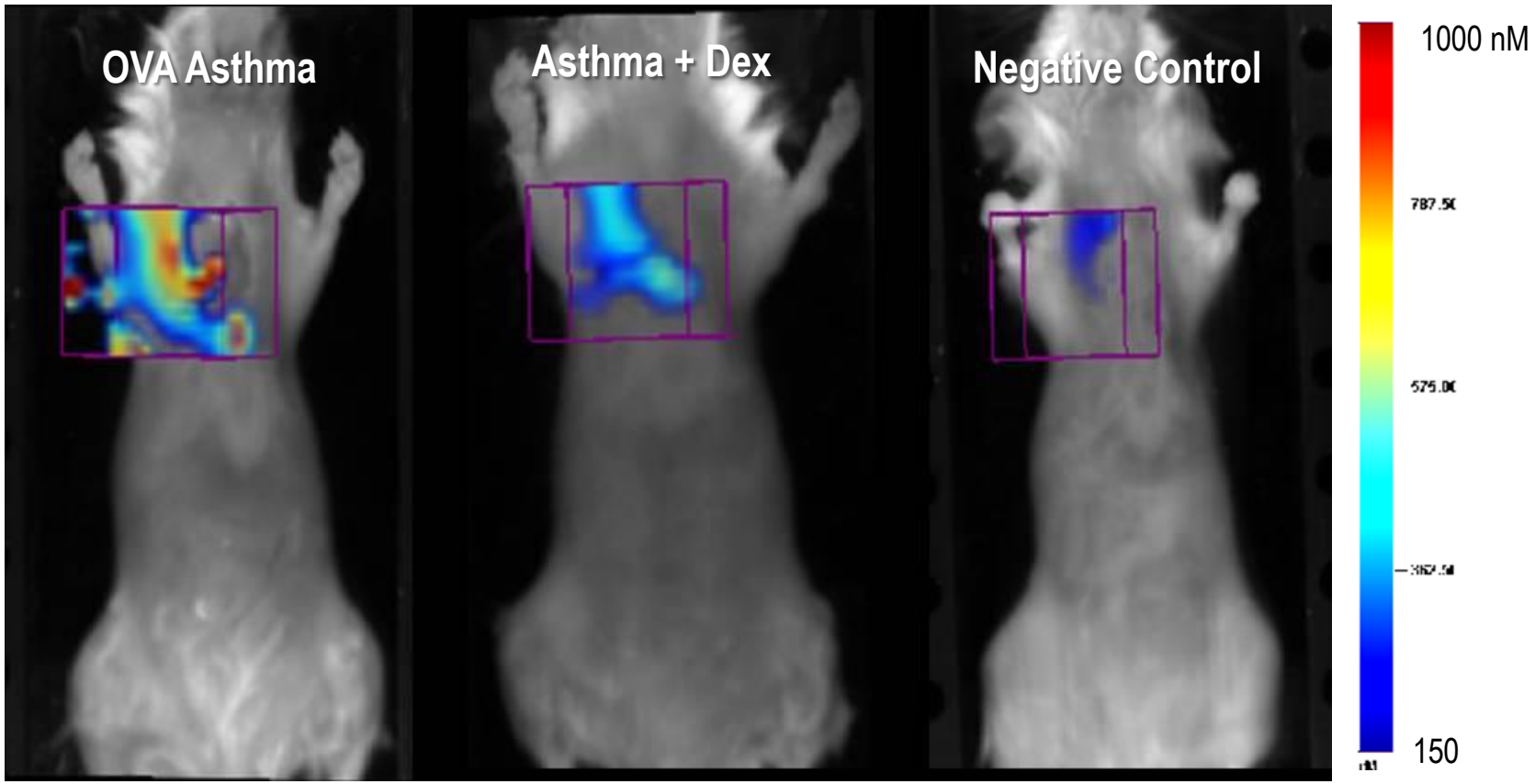
IP Dexamethasone
3mg/kg, 4h prior to IN

5nmol ProSense or
MMPSense

Steroids are a standard of care treatment for asthma

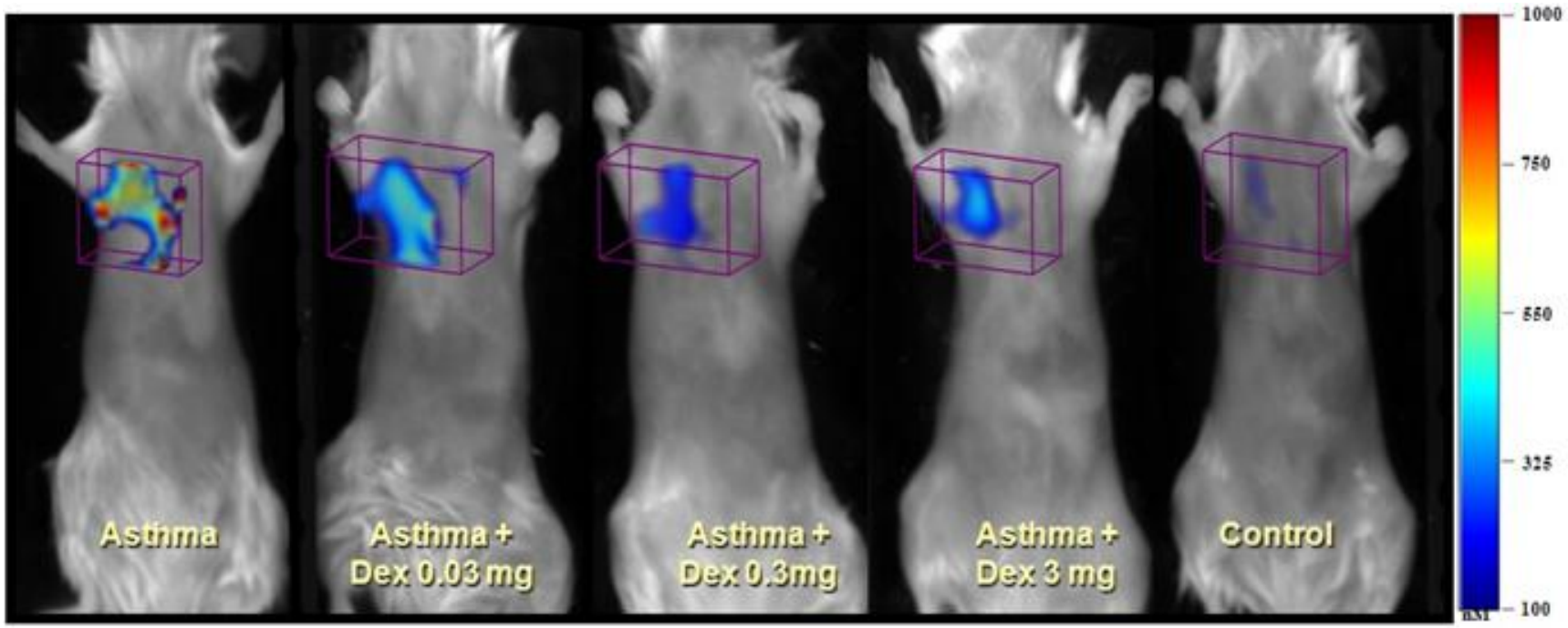
BAL = Bronchoalveolar Lavage

Dexamethasone Therapeutic Activity in Asthma



Tomographic images readily show clear differences in asthmatic, treated, and control mice

Dexamethasone Dose Response in Asthma

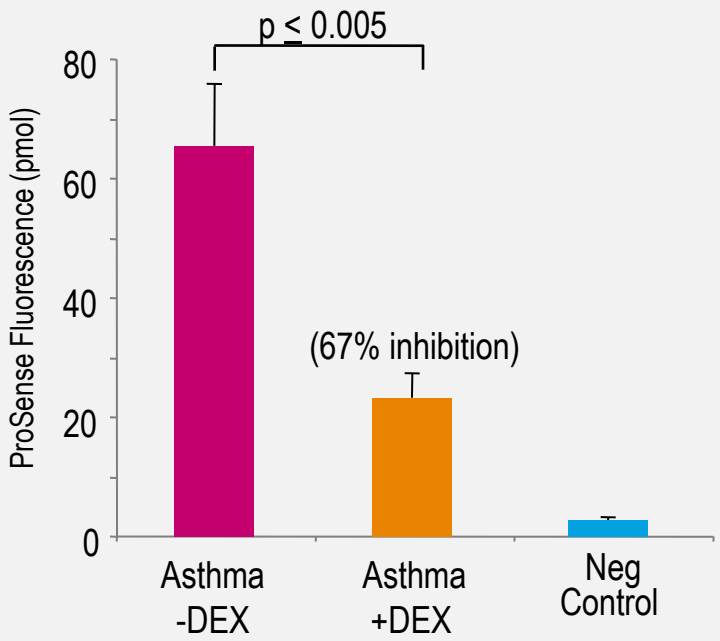


1

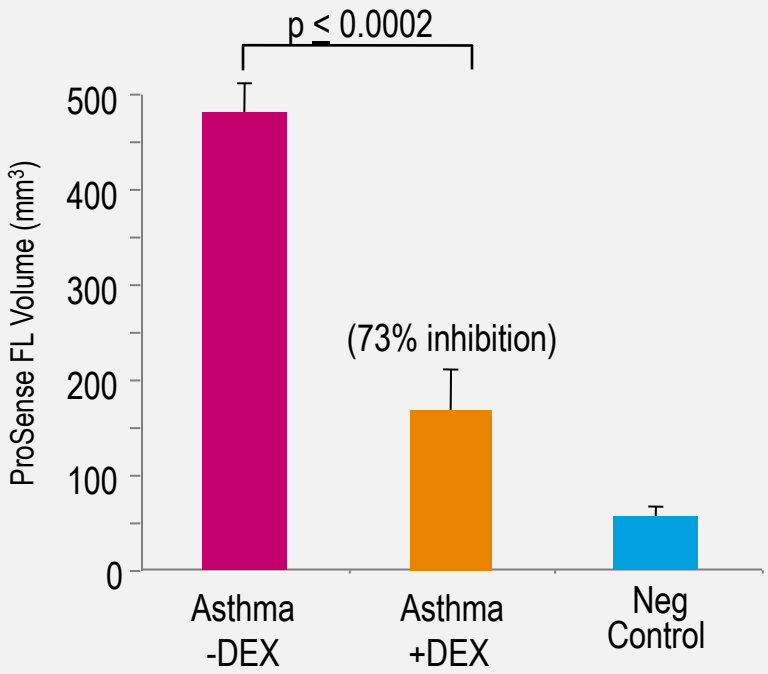
Quantifying Therapeutic efficacy in Asthma

Dexamethasone (DEX) treatment: 3mg/kg, days 18-21

ProSense 680 in Asthma: pmol



ProSense 680 in Asthma: Volume

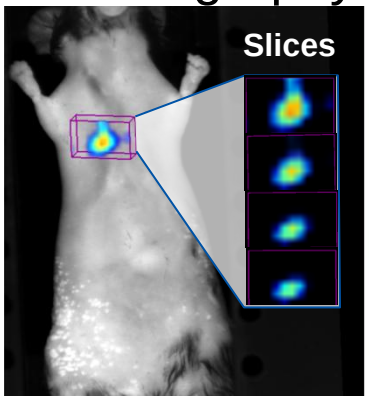


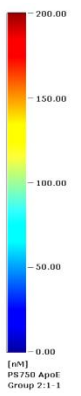
Asthma induces a 25-&9-fold increase in ProSense pmol and mm^3; Dexamethasone treatment decreases lung signal by ~70%

Atherosclerosis Applications

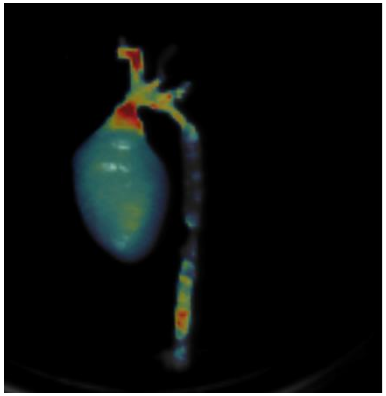
ApoE-/- mice fed HCD for 30 weeks
Pan-Cathepsin Agent

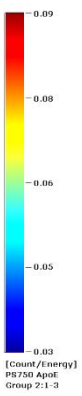
Tomography

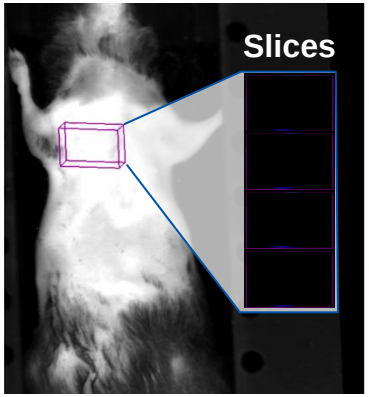


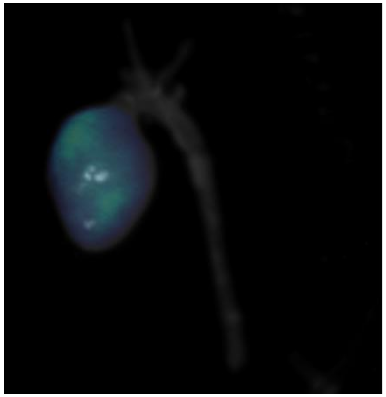


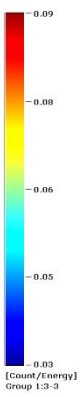
Tissue FRI



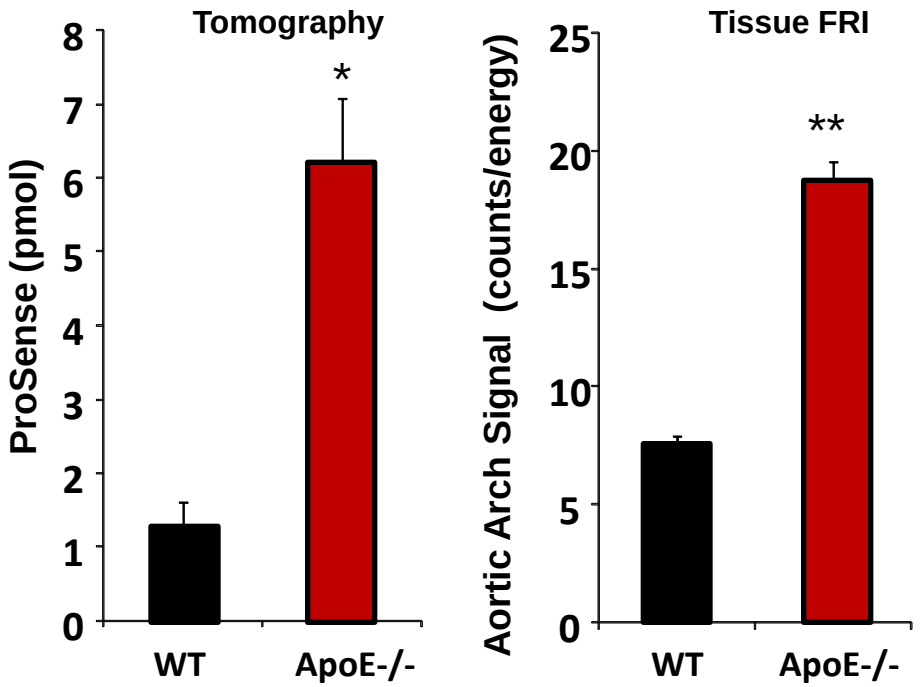








Quantification



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Disease progression in ApoE-deficient mice fed High Cholesterol Diet

Time on HCD	Biological Process *	Imaging Agent							
		ProSense	MMPSense	Cat B Fast	MMPSense FAST	IntegriSense	Annexin-Vivo	Cat K Fast	Osteosense
4-6 weeks	- monocyte adhesion - sporadic foam cells								
8-10 weeks	- early foam cell lesions - subendothelial progression								
10-15 weeks	- intermediate lesions - smooth muscle cell proliferation - fibrous caps								
15 weeks	- larger fibrous plaques - small necrotic cores								
20-30 weeks	- advanced plaques - increased necrosis								
30-40 weeks	- large, advanced plaques - progression to coronary arteries - large necrotic cores - partial medial destruction - calcification								

* Based on Nakashima et al., 1994

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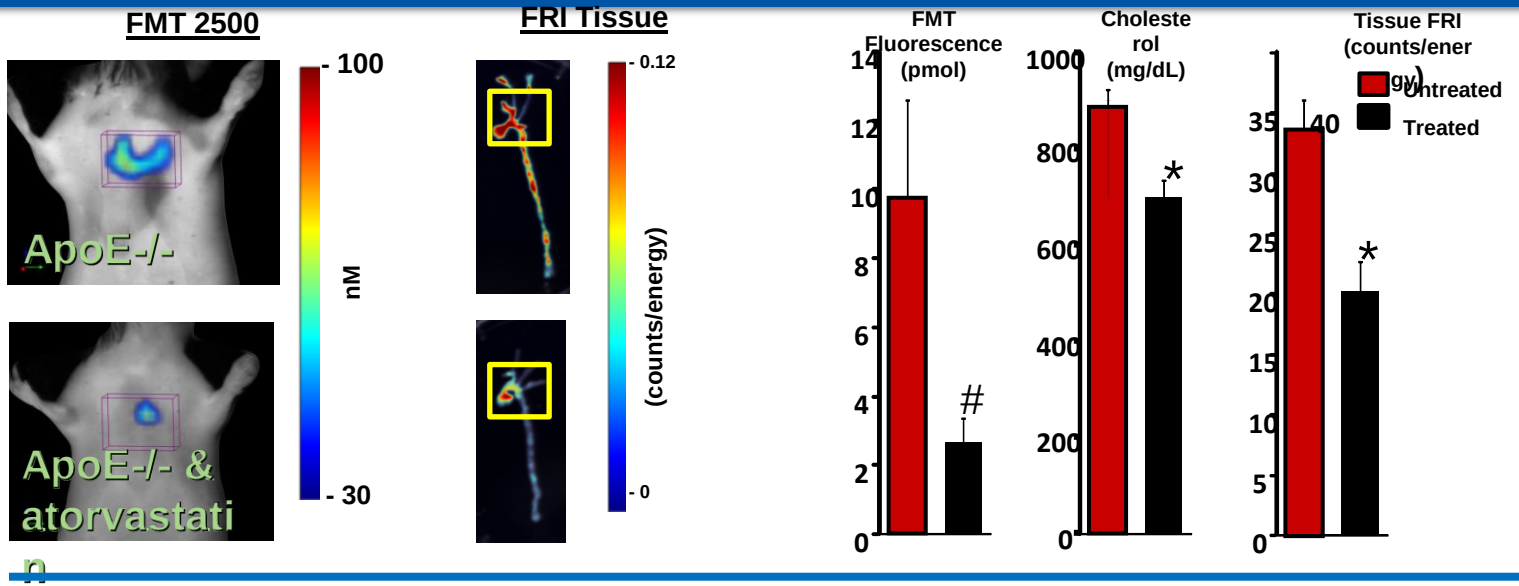
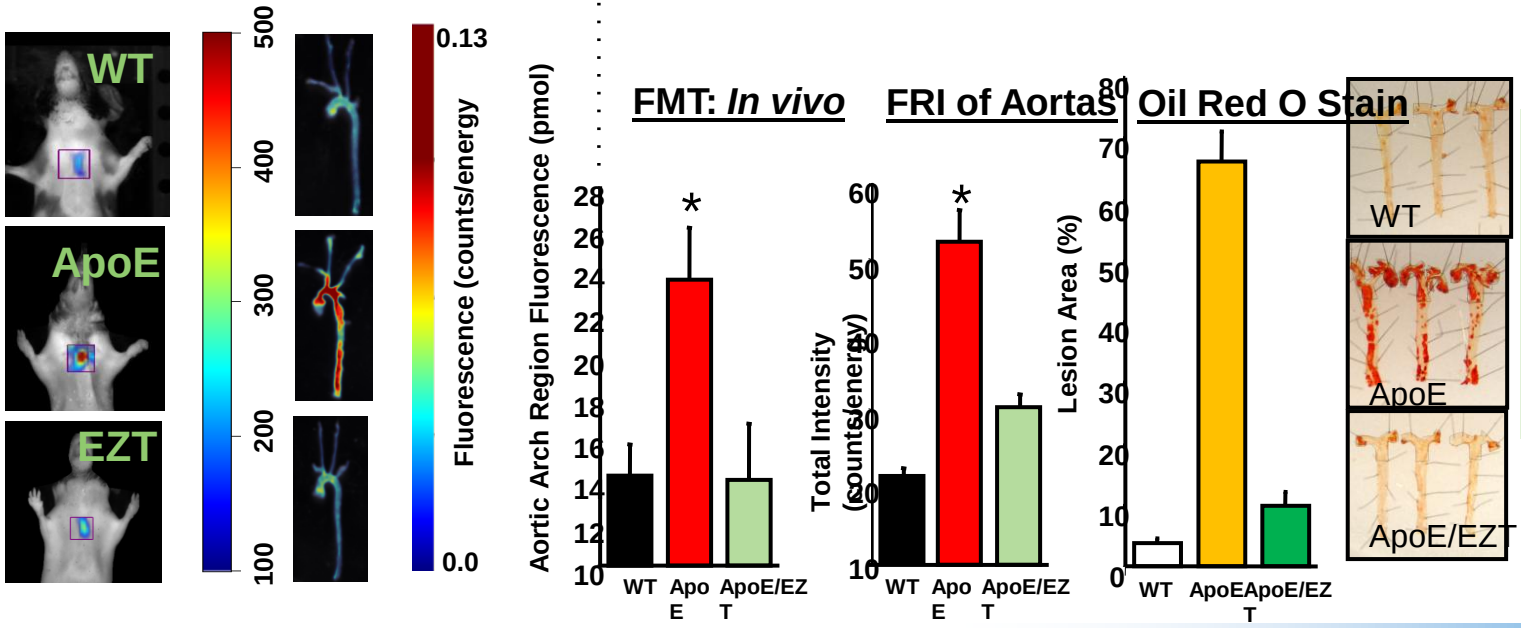
CVD Imaging: Quantifying Treatment Effects



ApoE-/- Mice on HCD: 30 weeks on Atorvastatin (0.01% wt/wt in chow), ProSense750 agent



ApoE-/- Mice on HCD: 25weeks on Ezetimibe (0.005% wt/wt in chow), CatK agent

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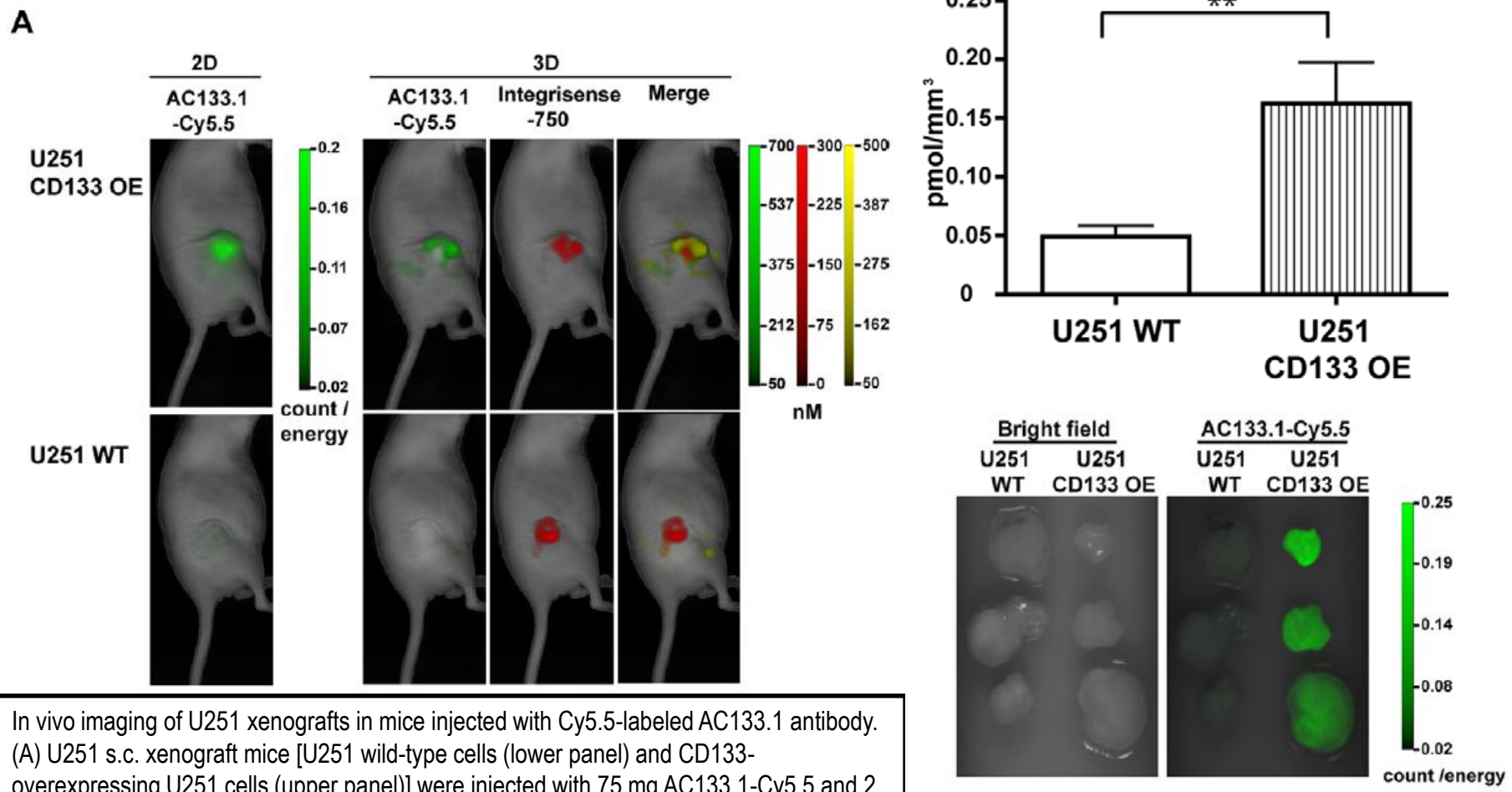
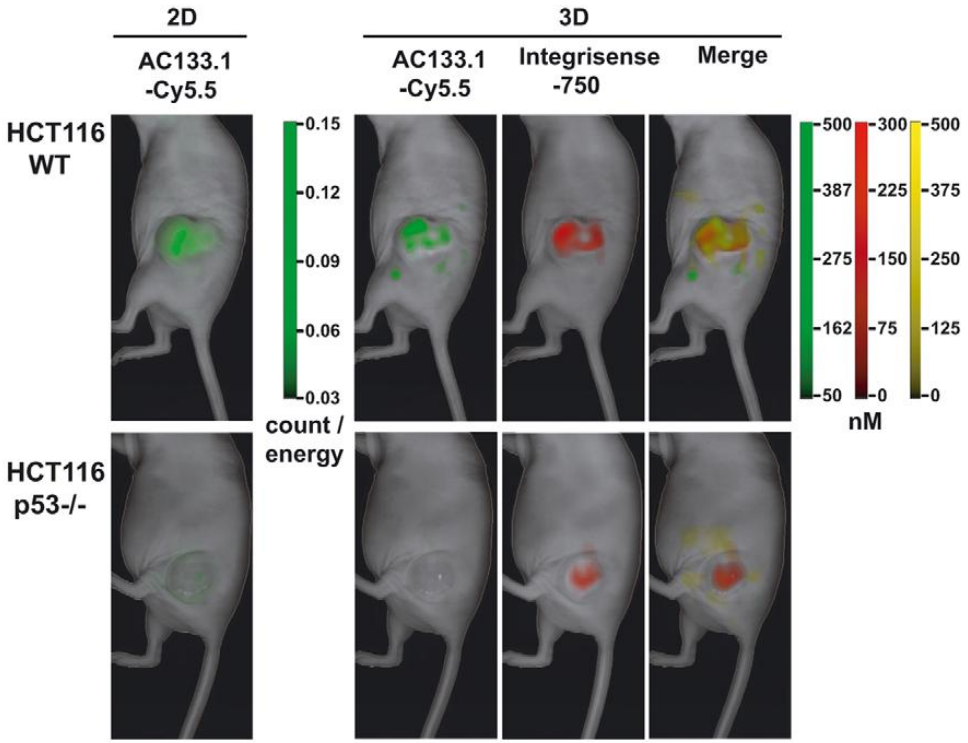
cancer stem cell application

1

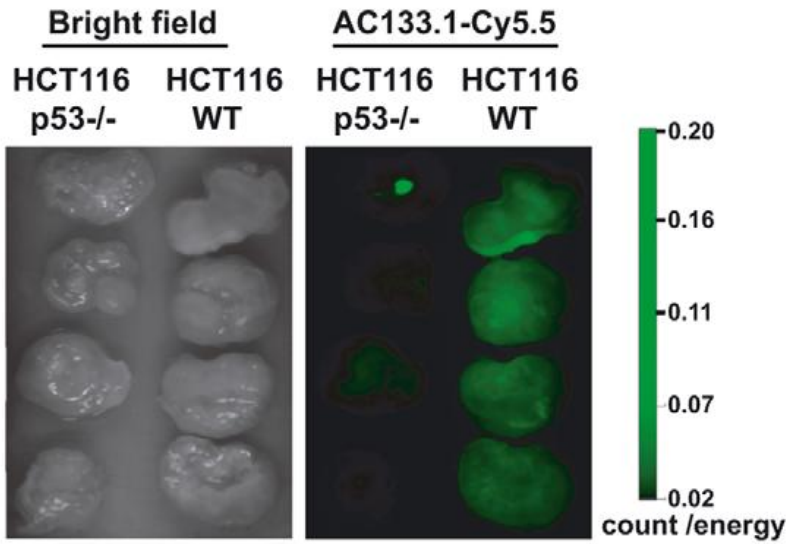


In vivo imaging of U251 xenografts in mice injected with Cy5.5-labeled AC133.1 antibody. (A) U251 s.c. xenograft mice [U251 wild-type cells (lower panel) and CD133-overexpressing U251 cells (upper panel)] were injected with 75 mg AC133.1-Cy5.5 and 2 nmol of IntegriSense 750. 7 days later, the mice were imaged using the VisEn FMT-1500 Fluorescence Molecular Tomography system.

Citation: Tsurumi C, Esser N, Firat E, Gaedicke S, Follo M, et al. (2010) Non-Invasive In Vivo Imaging of Tumor-Associated CD133/Prominin. PLoS ONE 5(12):e15605. doi:10.1371/journal.pone.0015605



In vivo imaging of HCT116 xenografts in mice injected with Cy5.5-labeled AC133.1. (A) HCT116 s.c. xenograft mice [HCT116 wild-type cells (upper panel) and HCT116 p532/2 cells (lower panel)] were injected with 75 mg AC133-Cy5.5 and 2 nmol of IntegriSense 750. One



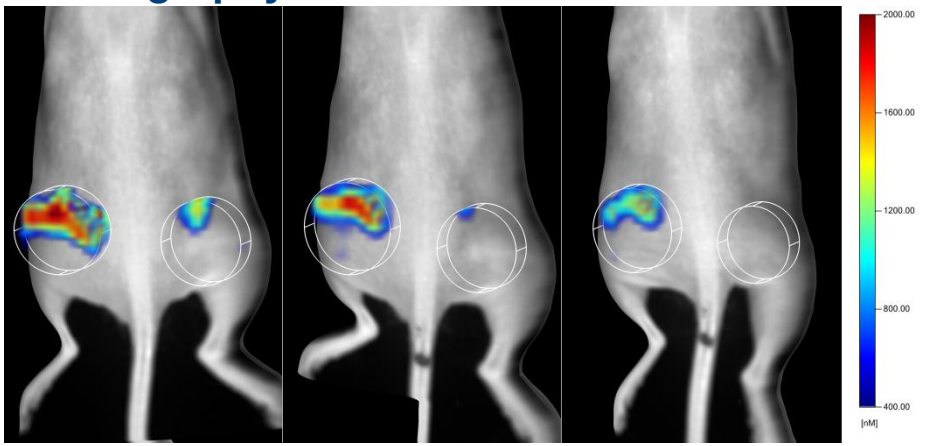
(C) Signal intensity of isolated tumors 9 days after AC133.1-Cy5.5 injection. Tumors were resected from mice and imaged with an FMT-1500 system. WT, wild-type

bacteria infection applications

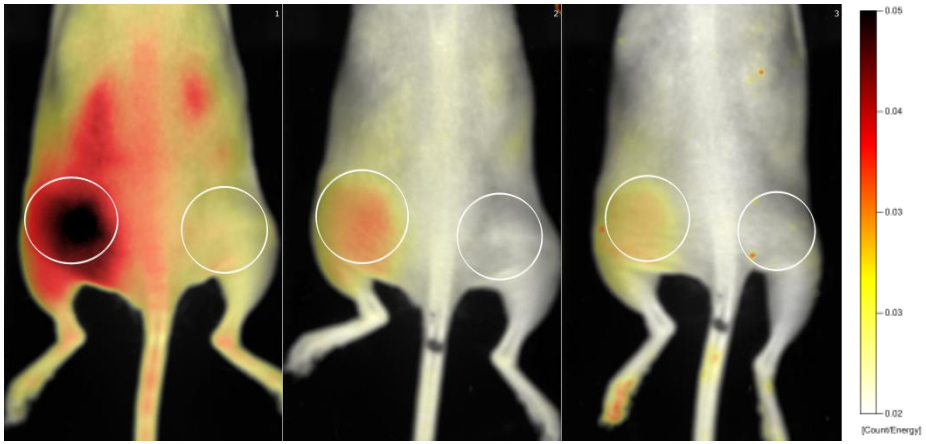
In vivo imaging of S. epidermidis infections

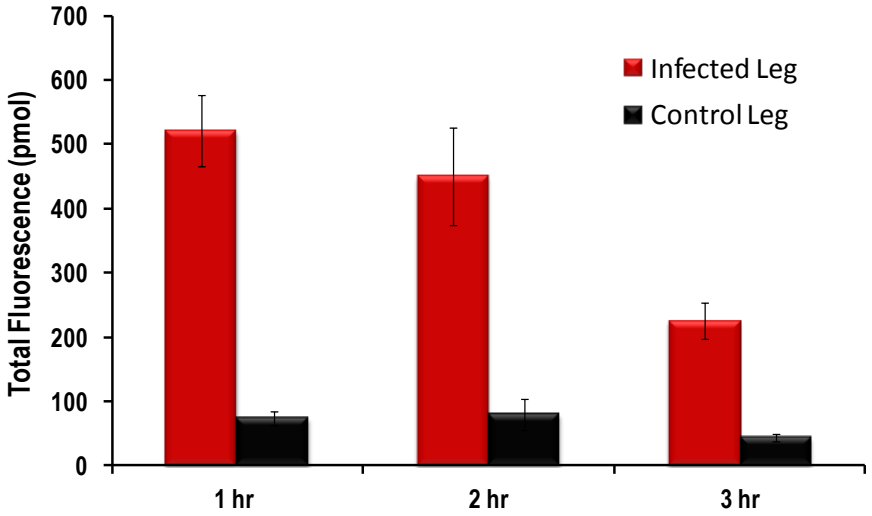
- SKH-1 E female mice, aged 6-8 weeks, were injected IM with 10^8 CFUs of S. Epidermidis in the flank region.
- 24 hours after bacteria injection, mice were injected with 5 nmoles of VM3235
- 1, 2, & 3 hours following agent injection, mice were imaged on the 3D fluorescence Imaging with emphasis on the flank area

Tomography



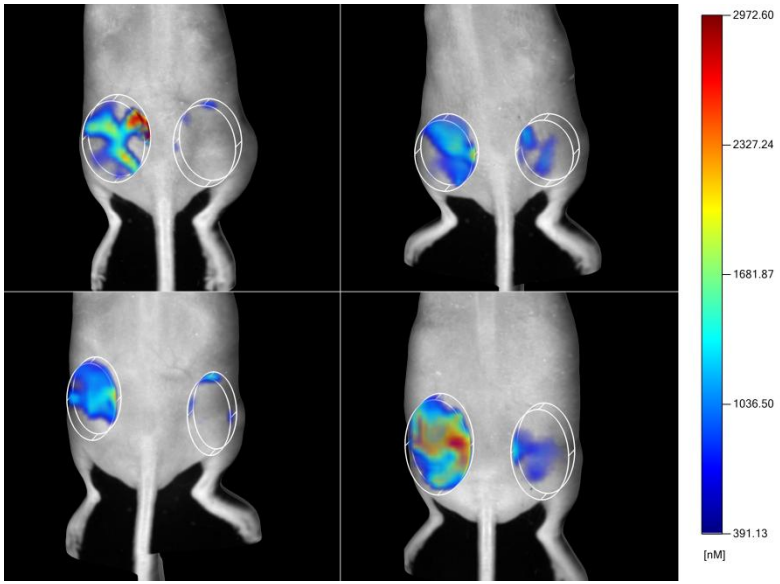
Planar

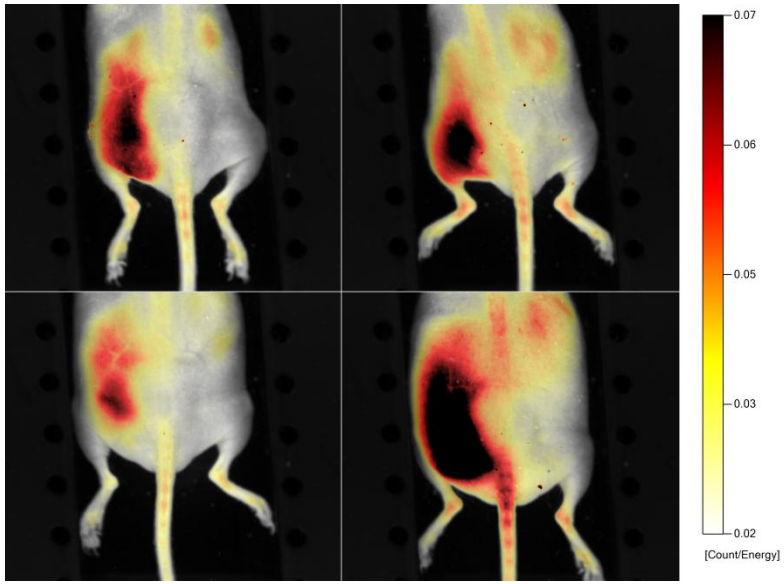


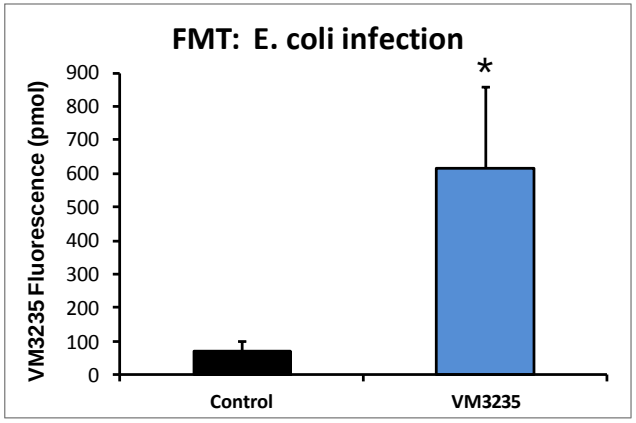


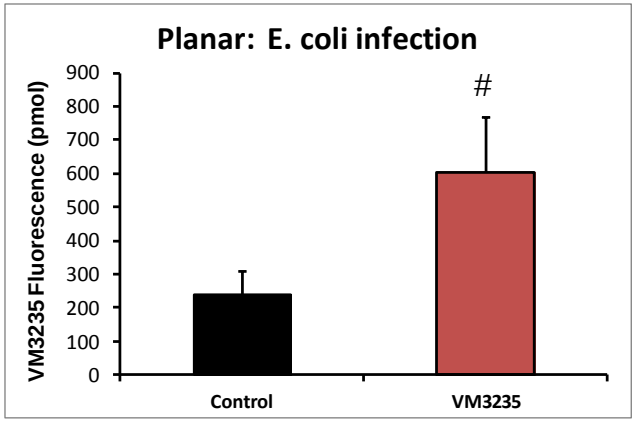
In Vivo Imaging of *E. Coli* Infection

- 18 SKH-1 E female mice, aged 6-8 weeks, were injected IM with 1 x 10^8 CFUs of E. coli in the flank region.
- 24 hours after bacteria injection, mice were injected with 5 nmoles of VM3235
- 1 hour following agent injection, mice were imaged on the 3D fluorescence Imaging with emphasis on the flank area





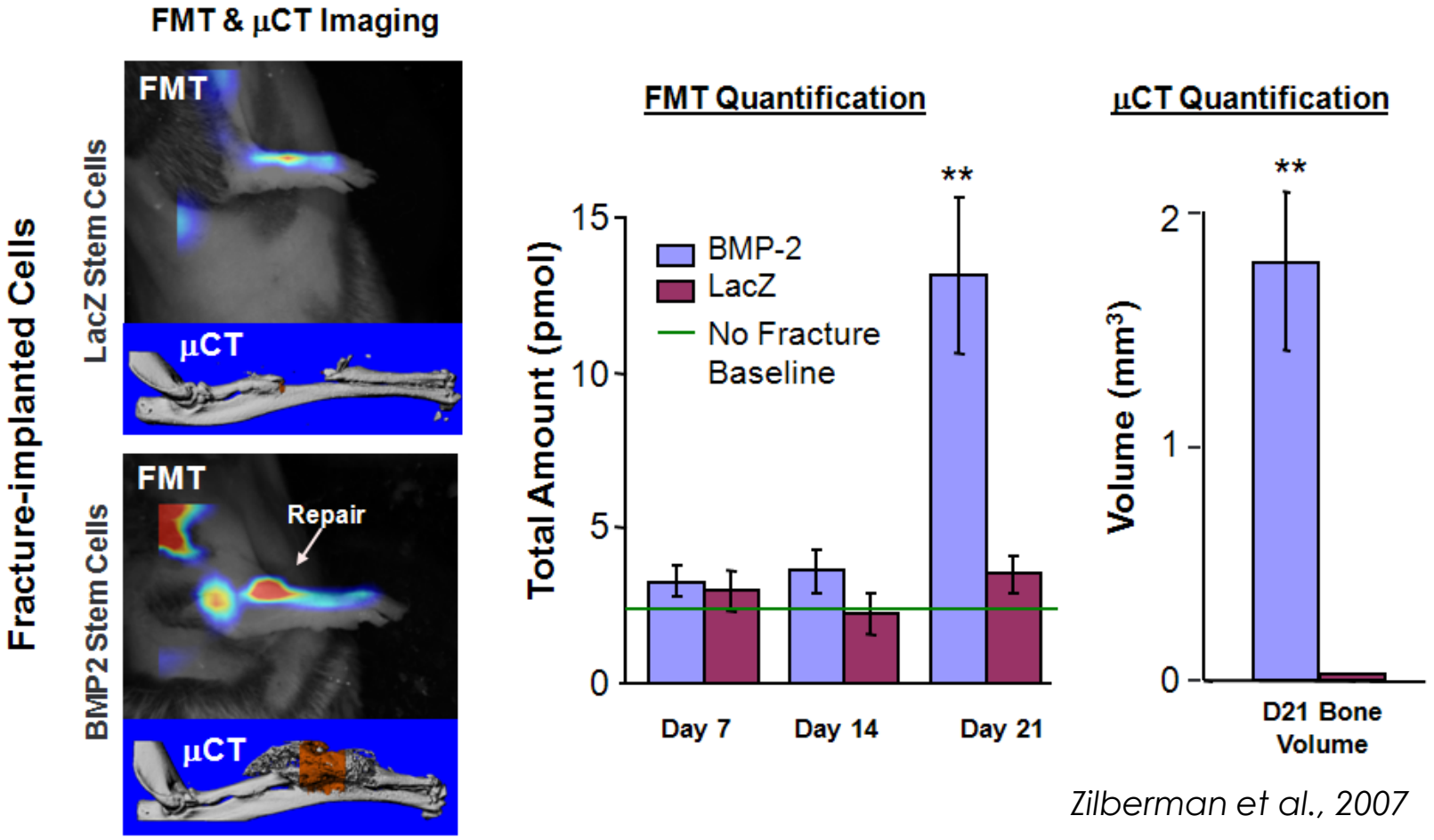




bone healing application

Measurement of Radial Non-union Fracture

- Healing induced by BMP-expressing stem cells



Zilberman et al., 2007

Our 3D fluorescence Imaging system and OsteoSense can be used to quantify BMP-induced bone healing

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