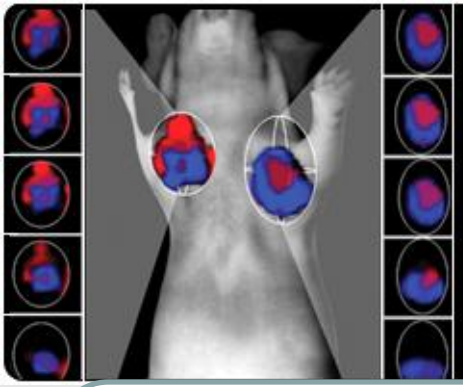

Science Webinar Series

PLEASE STAND BY… The webinar

DETERMINING THE IMPACT OF NEW THERAPEUTIC APPROACHES: ADVANCING IMAGING IN ANIMALS

will begin shortly…

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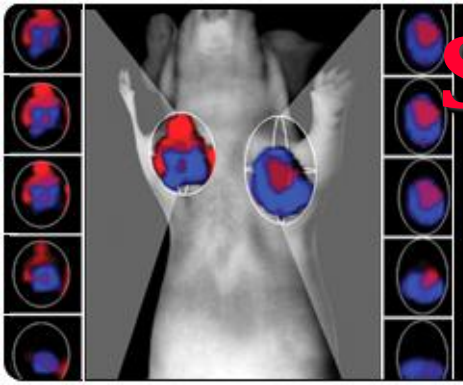
if you need help



Science Webinar Series

Determining the Impact of New Therapeutic Approaches: Advancing Imaging in Animals

7 December, 2011

Brought to you by the *Science*/AAAS Custom Publishing Office

Participating Experts:

Patrick McConville, Ph.D.
Molecular Imaging, Inc.
Ann Arbor, MI

Matthias Nahrendorf, M.D., Ph.D.
Harvard Medical School
Boston, MA

IN VIVO IMAGING OF DRUG RESPONSE AND FMT: A CRO PERSPECTIVE

Patrick McConville, Ph.D.
CSO/COO - Molecular Imaging, Inc.

Presentation Outline

- Background: imaging in drug research
  - Brief history/evolution
  - Rationale for use
- Image based disease end points
  - Anatomical, functional and molecular imaging end points
  - Image based biomarker: definition
  - Surrogate marker
  - Probe facilitated imaging of efficacy
    - RA model/optical probe example
- Imaging probe based biomarkers and FMT
  - Rationale for FMT in drug discovery and development
  - Example 1: protease and bone imaging in RA
  - Example 2: acute inflammation in sponge granuloma
  - Example 3: tumor burden
  - Future applications

Molecular Imaging™

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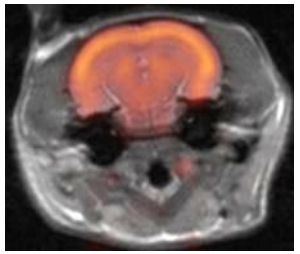
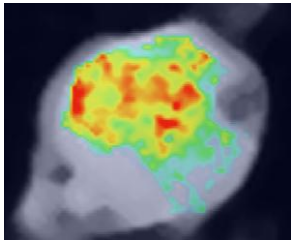
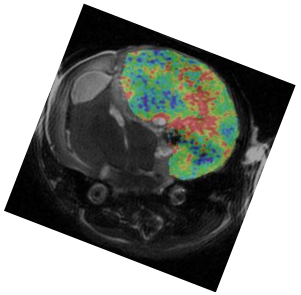
Preclinical imaging: a brief history







- 70s: Major clinical imaging developments
- 80s: Widespread use of clinical imaging for diagnosis
- 90s: Translation of imaging technology for rodent work
- Last decade:
  - introduction of dedicated rodent imaging systems
  - substantial development of new imaging probes
    - MR, CT, PET, optical, SPECT, ultrasound,
  - pharmaceutical industry invests and relies on imaging technology
- Last 5-10 years: *anatomical* → *functional/molecular*; *diagnostic* → *efficacy*; *academia* → *industry*
- Next 5-10 years: *efficacy* → *safety/toxicology*

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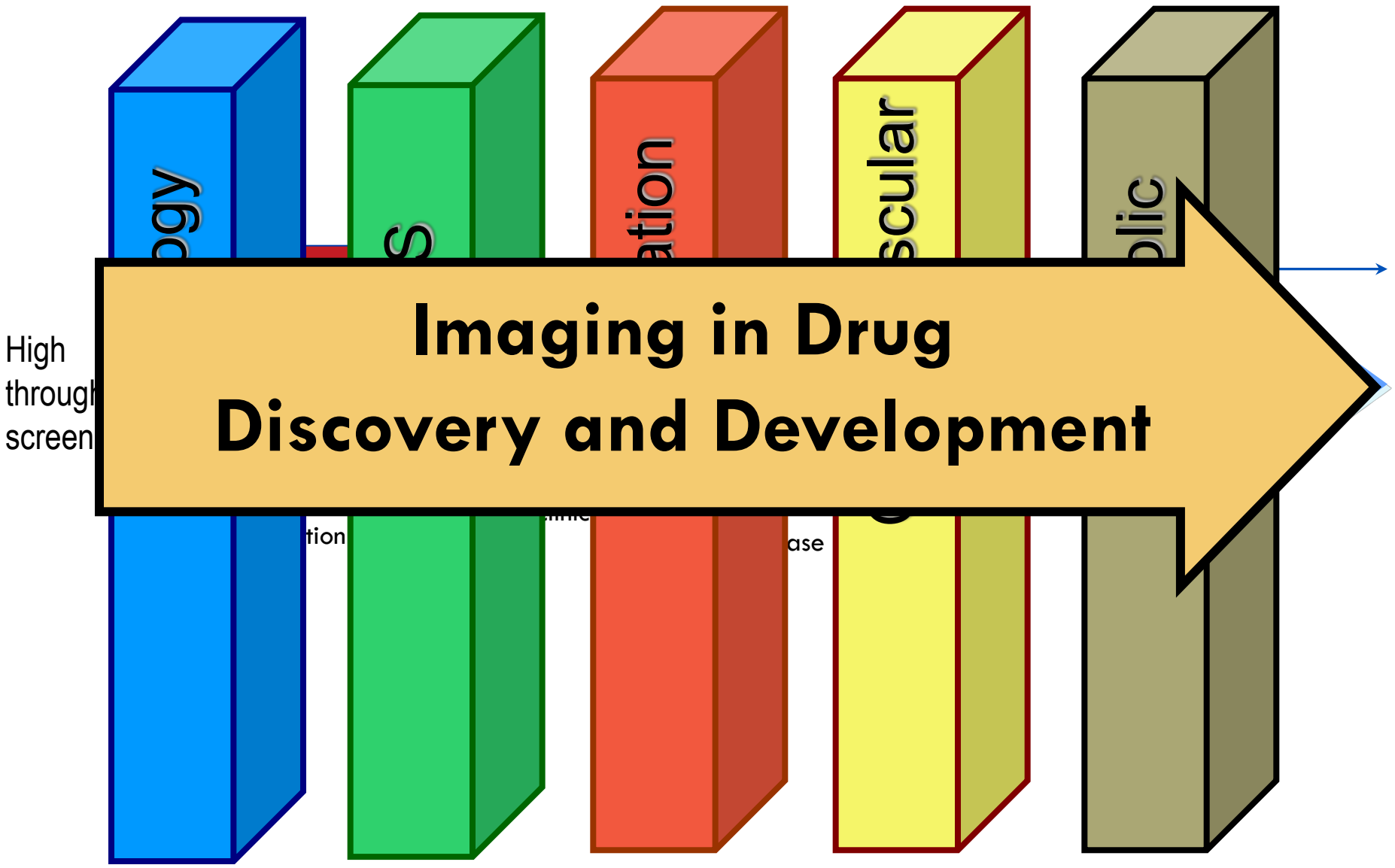
Preclinical imaging: *evolution*

WAS	IS
Modality centric	Modality agnostic
Decentralized	Centralized
A complex technology for physicists and engineers	A black box technology for multi-disciplinary scientists
A tool for disease diagnosis	A tool for disease progression and therapeutic response
Expensive	Expensive
Not a standard in drug development	A standard in drug development
In academic institutions	In industry

Molecular Imaging™

in vivo Imaging in Drug Research



in vivo Imaging in Drug Research

in vivo Imaging in Drug Research: Why ?

PET

- Faster ?
  - ⇒ Early prediction
    - Eg. imaging inflammatory cell recruitment
- Better resolved ?
  - ⇒ Tissue, sub-tissue, cellular
    - Eg. imaging of tissue heterogeneity

MRI

CT

- More relevant ?
  - ⇒ Access to unique, mechanistic endpoints
    - Eg. imaging of cathepsin activity
- Translational ?
  - ⇒ Discovery/development continuum
    - Eg. MRI and PET image based biomarkers

Optical/FMT

- Cost effective ?
  - ⇒ Yes, if one or more of the above is true

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In Vivo Imaging in Drug Research

ANATOMICAL

- Microscopy
- Morphology
- Structure
- Bone resorption/loss
- Implanted devices
- Imaging of plaques
- Vascular mapping
- Myocardial infarction
- Medical devices

FUNCTIONAL

- Hypoxia
- Proliferation
- Inflammation
- Blood flow
- Perfusion
- Metabolism
- Ejection fraction
- Hydration

MOLECULAR

- Necrosis
- Apoptosis
- Receptor occupancy
- Metabolite levels
- Biodistribution
- Protease activity
- Immune cell tracking
- Cell migration
- Target modulation

In vivo imaging in safety and toxicology

In Vivo Imaging in Drug Research

ANATOMICAL

- Microscopy
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- Vascular mapping
- Myocardial infarction
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FUNCTIONAL

- Hypoxia
- Proliferation
- Inflammation

Image-based Quantifiable Parameter

- Ejection fraction
- Hydration

MOLECULAR

- Necrosis
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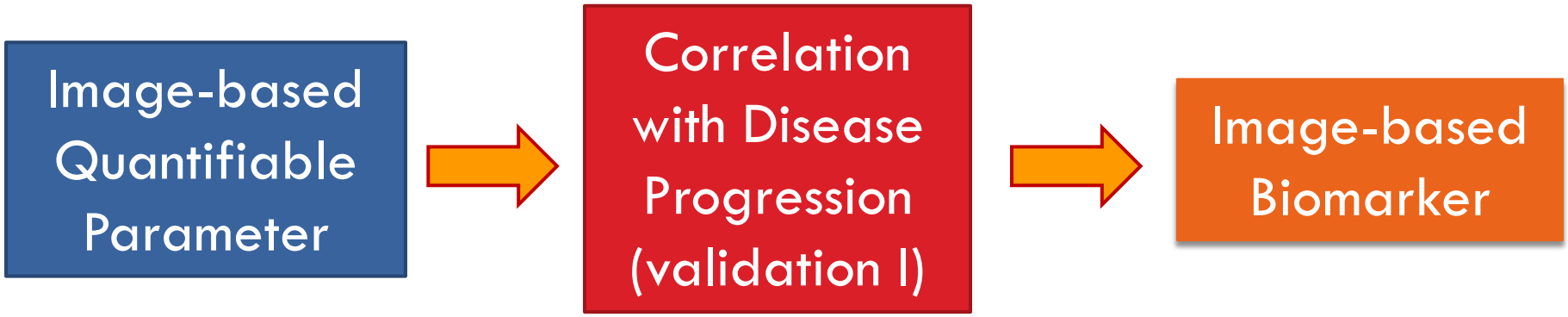
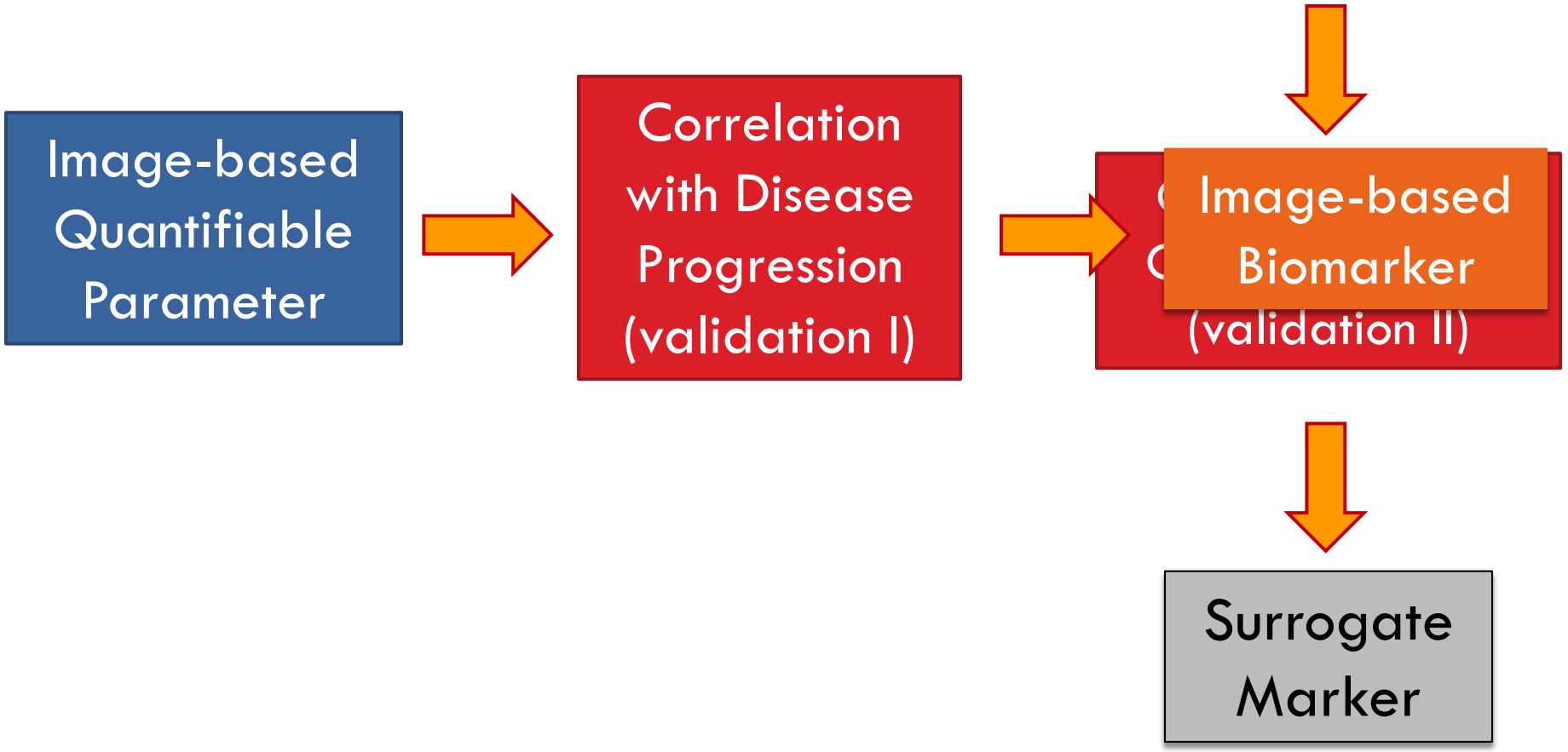
In vivo imaging in safety and toxicology

In Vivo Imaging in Drug Research



In Vivo Imaging in Drug Research



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Molecular Imaging™

Biomarker access through imaging probes

- Imaging probe
  - Molecule or nanoparticle designed to modulate imaging contrast
- Degree of signal or contrast modulation is generally dependent on:
  - probe concentration (voxel based)
  - Tissue access
  - PK/PD
  - Degree of uptake (for captured probes)
  - Degree of activation (for conditional probes)

Probe Type	Examples
Targeted	Receptors (eg. integrins, estrogen R, VEGF R) Bone (eg. hydroxyapetite) Proteins (eg. VEGF)
Conditionally 'captured'	Metabolic cycle (eg. FDG) Cell cycle (eg. FLT) Hypoxic cells (eg. MISO)
Conditionally activated probes	pH Proteases (eg. caspases, cathepsins, MMPs)

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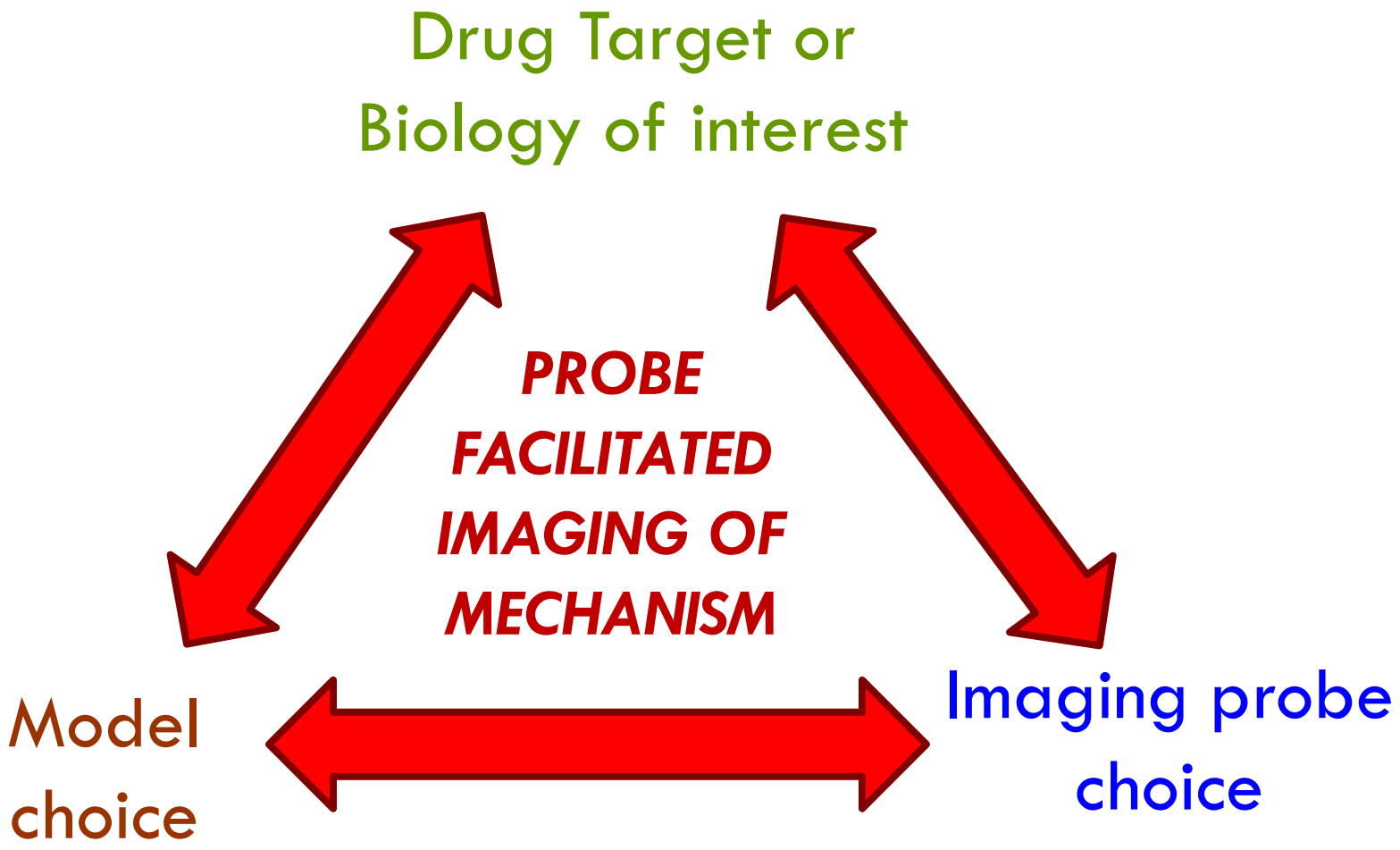
Imaging probes: drug research concept



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Why FMT ? - the CRO perspective

- Quantitative, three-dimensional imaging
- High throughput, efficient imaging
  - probe multiplexing
  - 10-20min per subject for image runs of up to 50+ animals possible
- Available biomarkers bounded only by probe developers
  - rapidly increasing commercial availability
  - access to prior large probe patent estates
  - technology is now emerging from major probe discovery labs
- True molecular imaging
  - disease mechanism
  - drug response mechanism
- Applications readily cross disease states and into safety
- Clinical translation potential

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Validation: the CRO perspective

- 'Pharma-ready' validation
  - Biomarker readout **correlates** with:
    - disease progression
    - response to therapy
  - **Correlation**
    - traditional clinical measurements
    - traditional biomarkers
    - histopath
  - Study design and limitations understood
    - image timing
    - probe clearance
    - uncoupling or interference
    - study powering
  - Advantage/value vs traditional
    - uniqueness; more predictive
    - time saving
    - clinically translatable

Understood for:

- *EACH probe or biomarker*

in

- *EACH model*

with

- *EACH treatment*

Molecular Imaging™

Example: Mouse RA

Validation: 'Pharma-ready'

Optical tomographic imaging discriminates between disease-modifying anti-rheumatic drug (DMARD) and non-DMARD efficacy in collagen antibody-induced arthritis

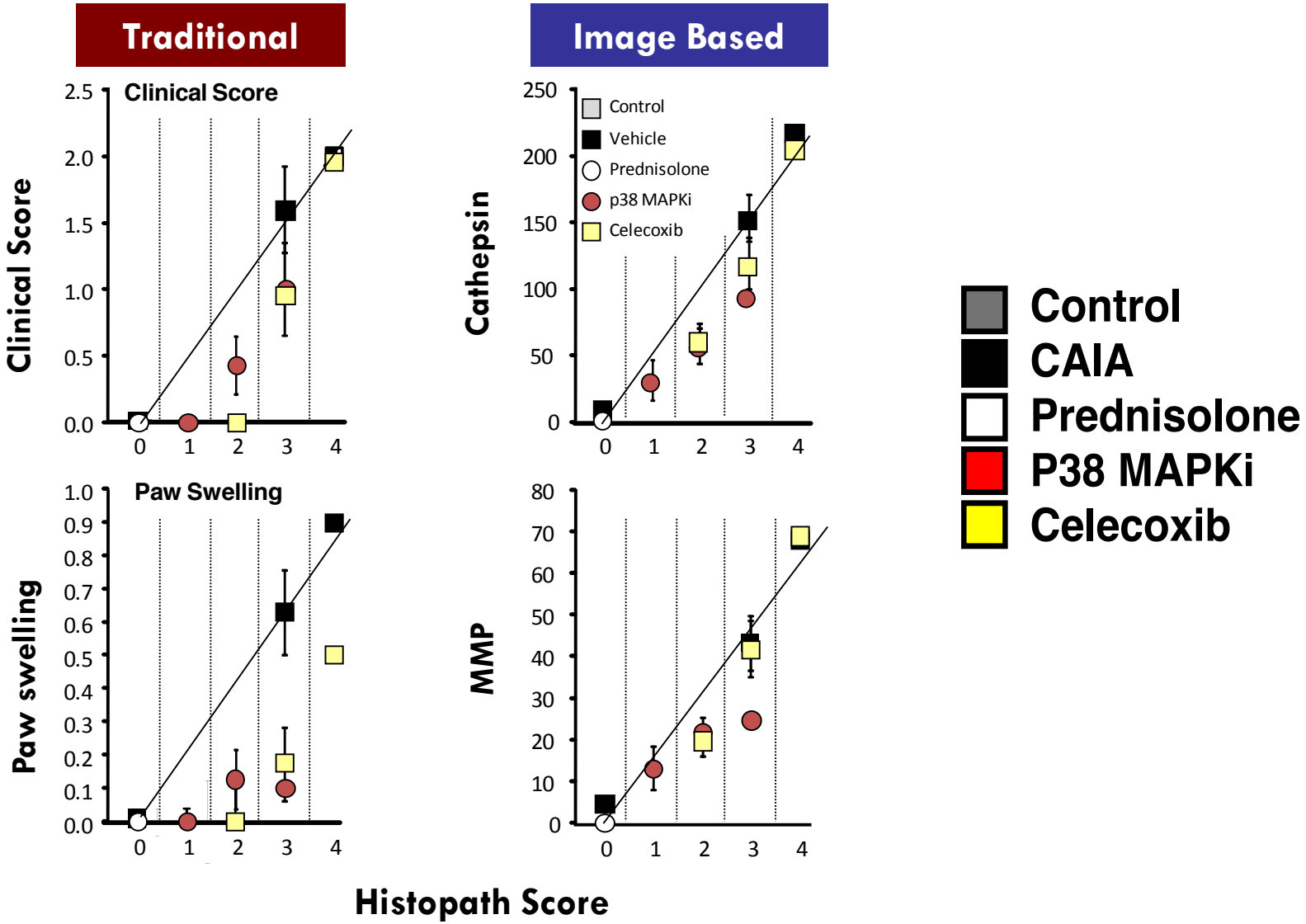
Arthritis Research & Therapy 2010, **12**:R105 doi:10.1186/ar3038

Jeffrey D Peterson[1], Timothy LaBranche[2], Kristine O Vasquez[1], Sylvie Kossodo[1], Michele Melton[2], Randall Rader[2], John T Listello[2], Mark A Abrams[2], and Thomas P Misko[2]

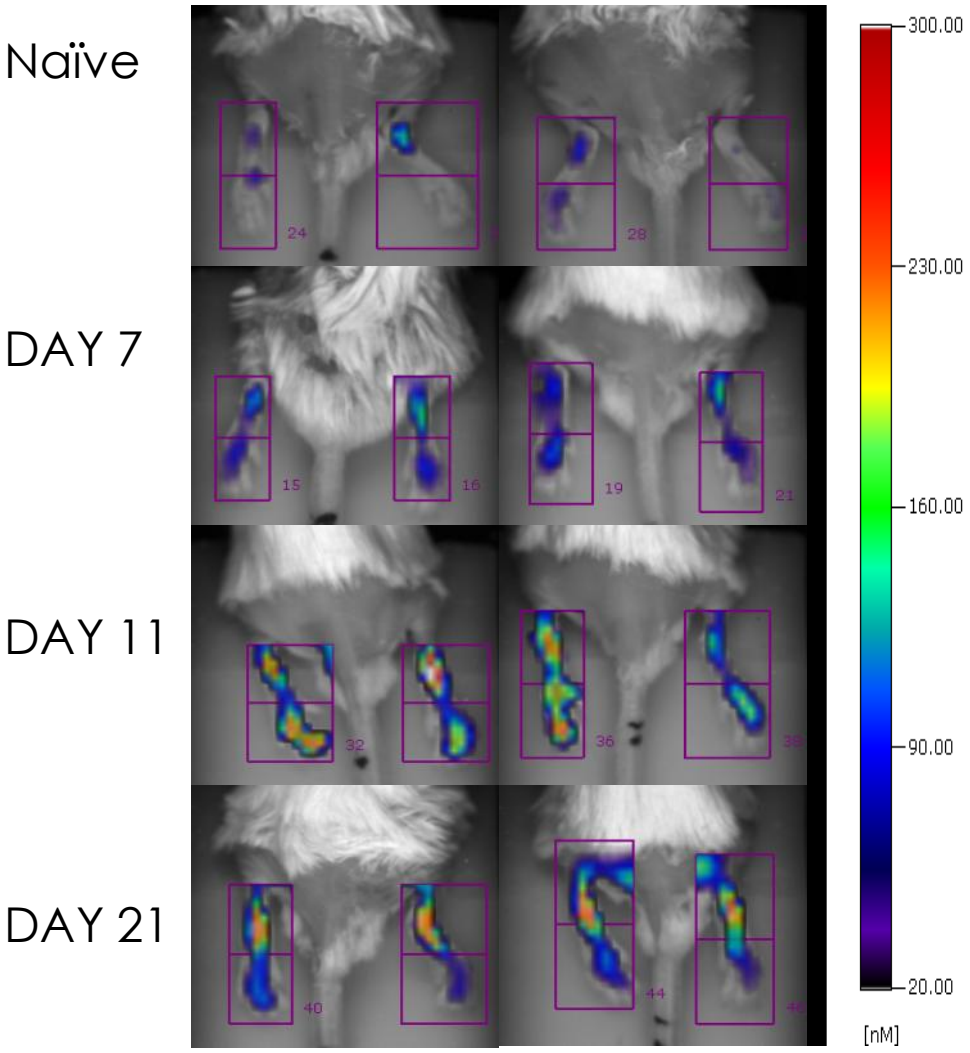
[1] VisEn Medical Inc, 45 Wiggins Ave, Bedford, Massachusetts 01730, USA; [2] Pfizer Global Research & Development, 700 Chesterfield Parkway West, Chesterfield, St. Louis, Missouri 63017, USA.

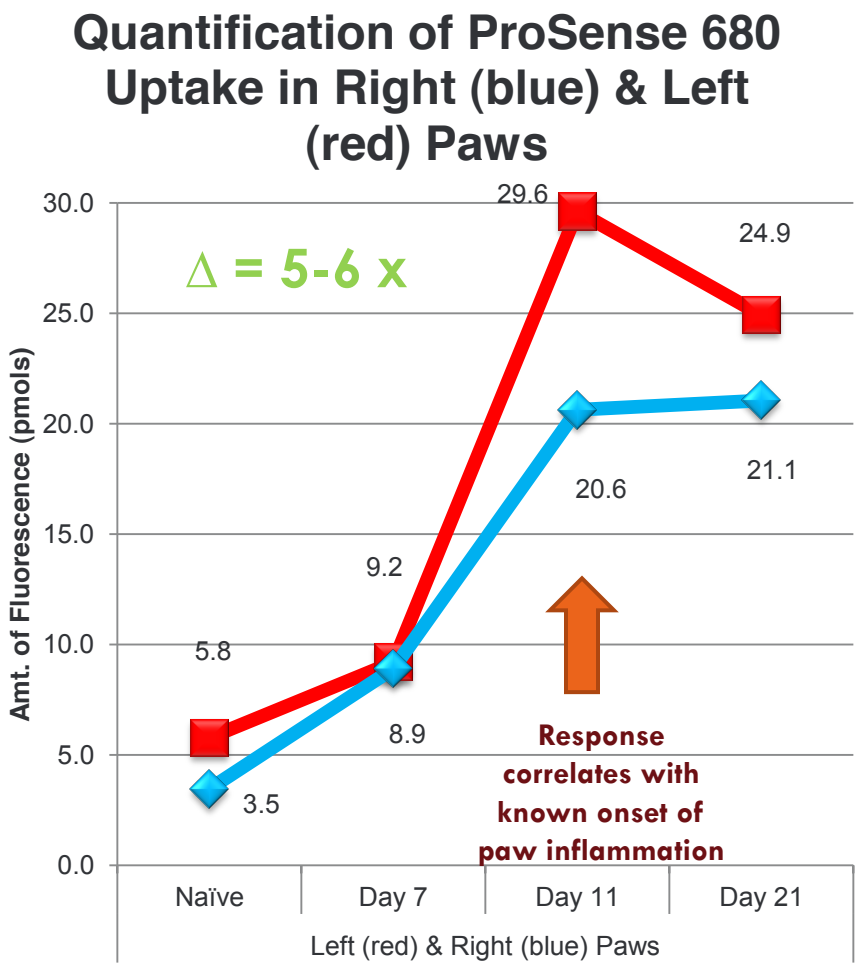
Histopath Correlation

Traditional *in vivo* vs image based end points



RA: Inflammation imaging with ProSense





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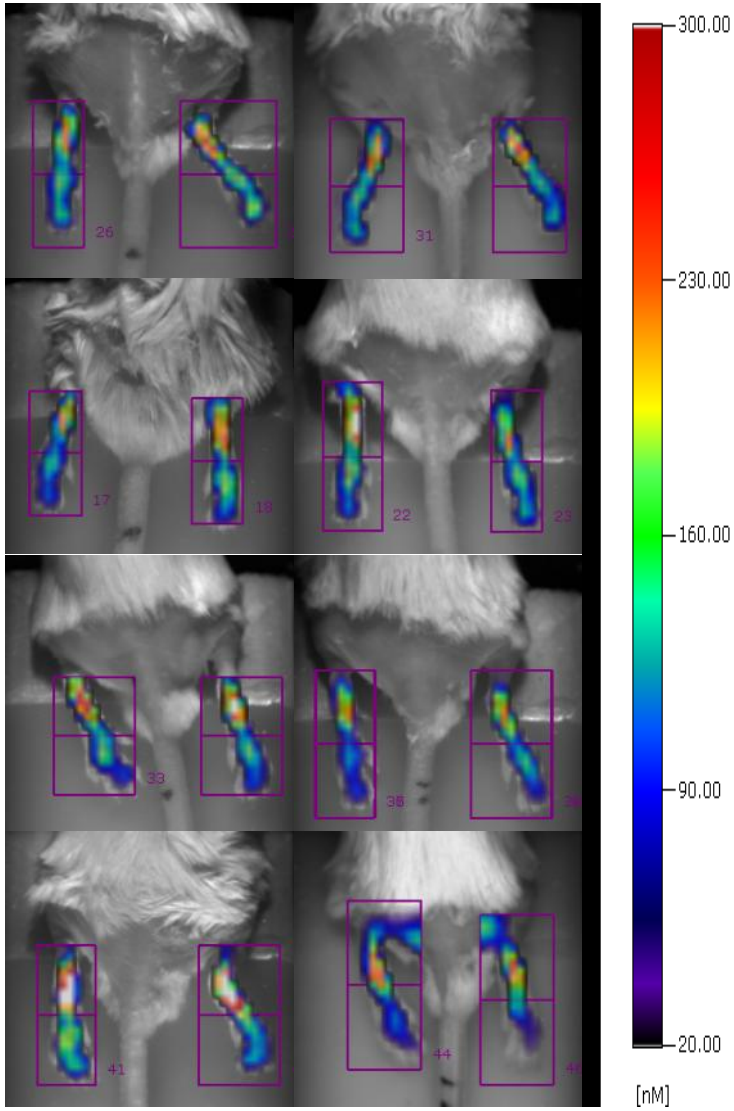
RA: Bone imaging with OsteoSense

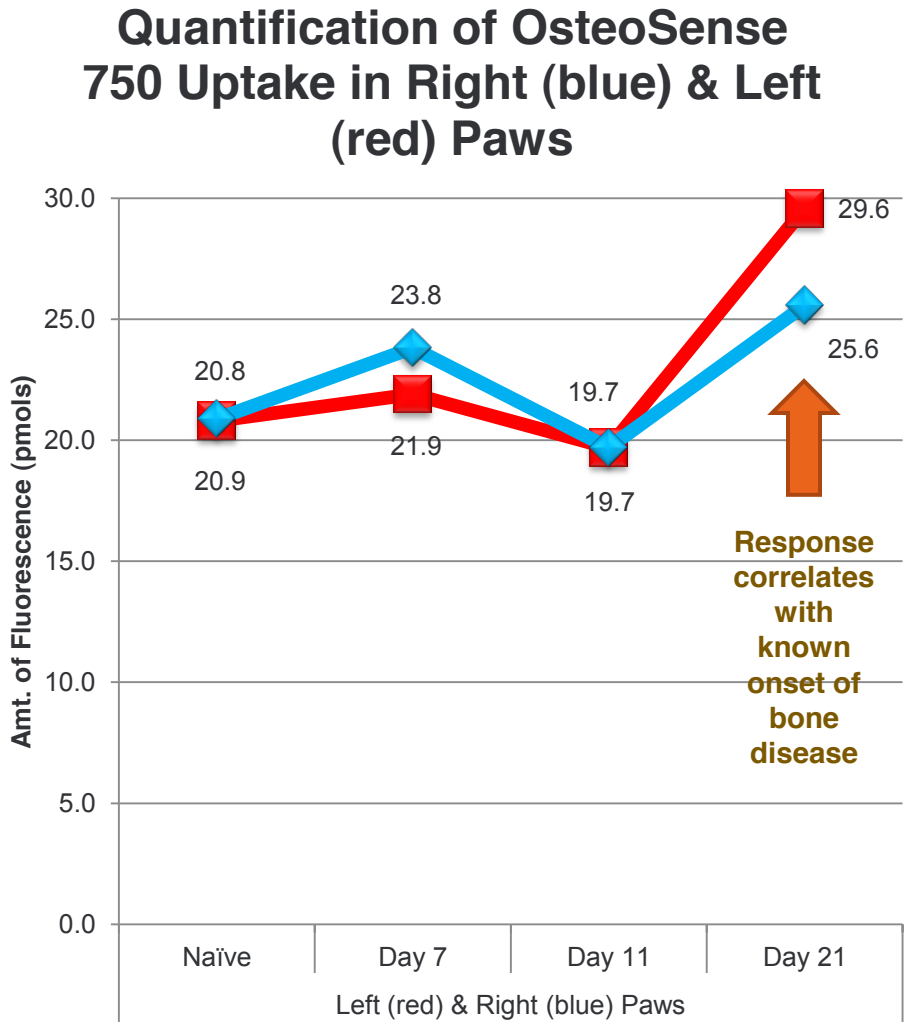
Naïve

DAY 7

DAY 11

DAY 21





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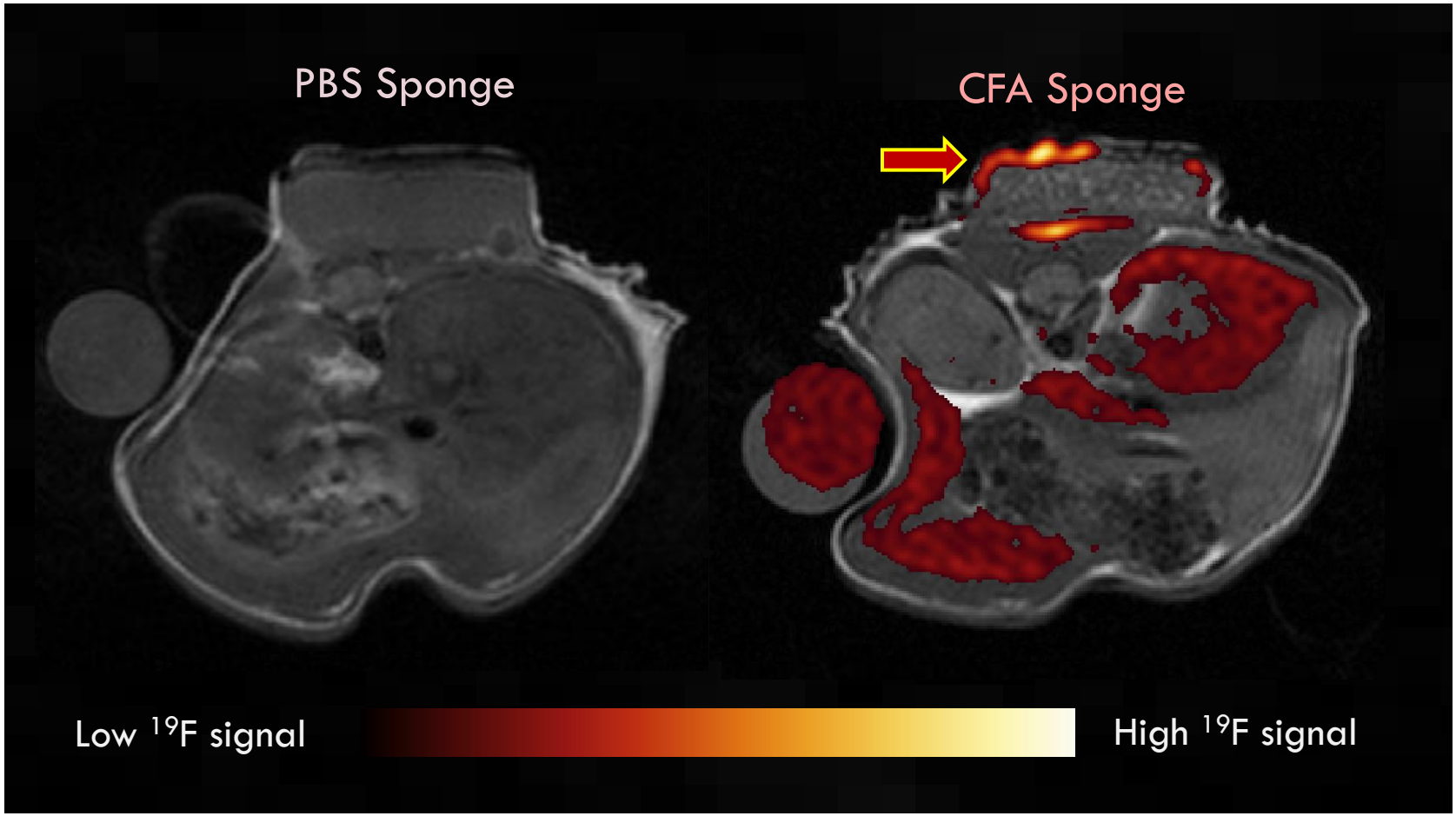
Example: Acute inflammation

Mouse sponge granuloma model

^{19}F MRI: Imaging of Macrophages



V-Sense in Sponge Granuloma Model of Acute Inflammation

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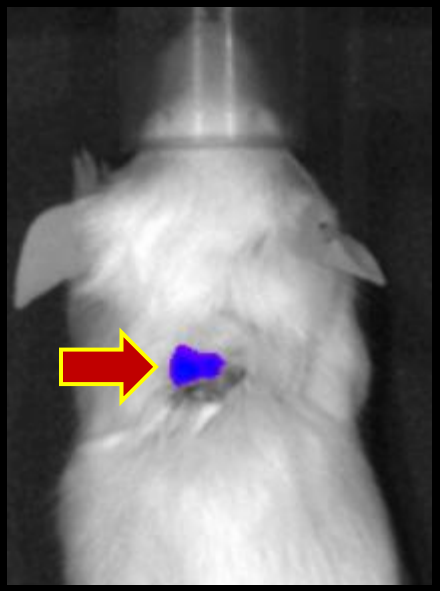
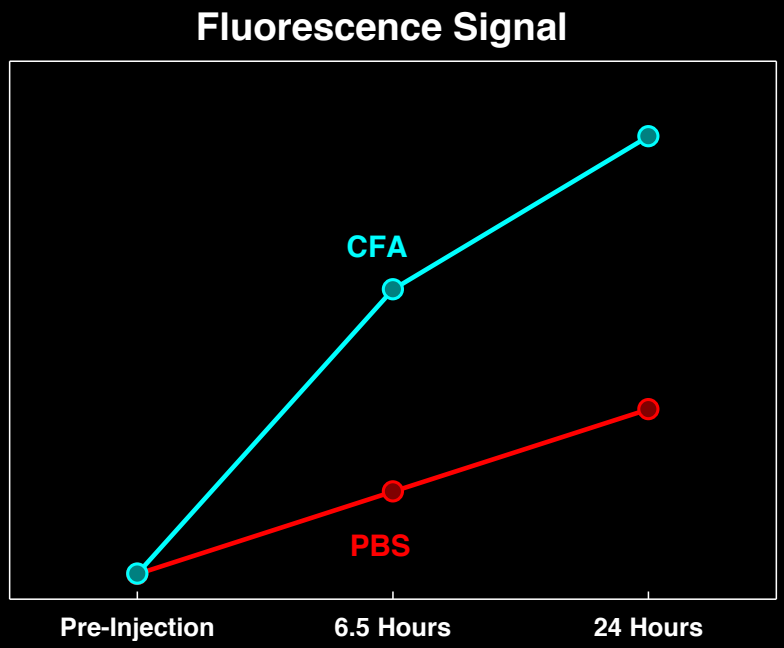
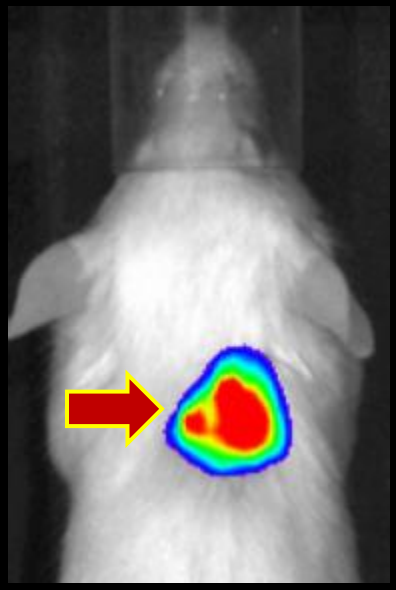
Cathepsin Imaging: Acute Inflammation

PBS Sponge Implant





CFA Sponge Implant



24 Hours Post-injection

Sponge Granuloma Model of Acute Inflammation

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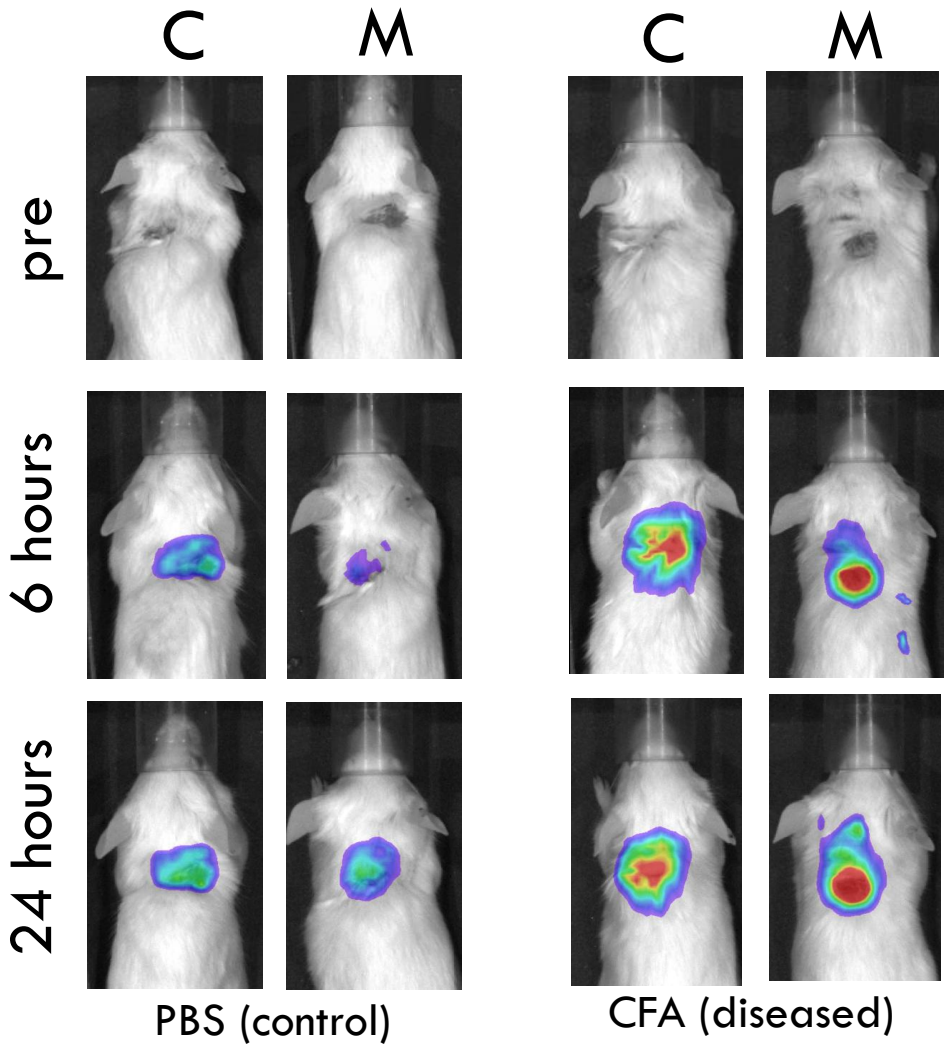
Activated probes in acute inflammation

Sponge Granuloma Model of Acute Inflammation



C: Cathepsin activation (Prosense)

M: MMP activation (MMP Sense)

Greater cathepsin and MMP activity was detected in CFA sponges (diseased animals), compared with PBS sponges (controls) 6h and 24h after probe injection.

Molecular Imaging™

Example: Tumor imaging

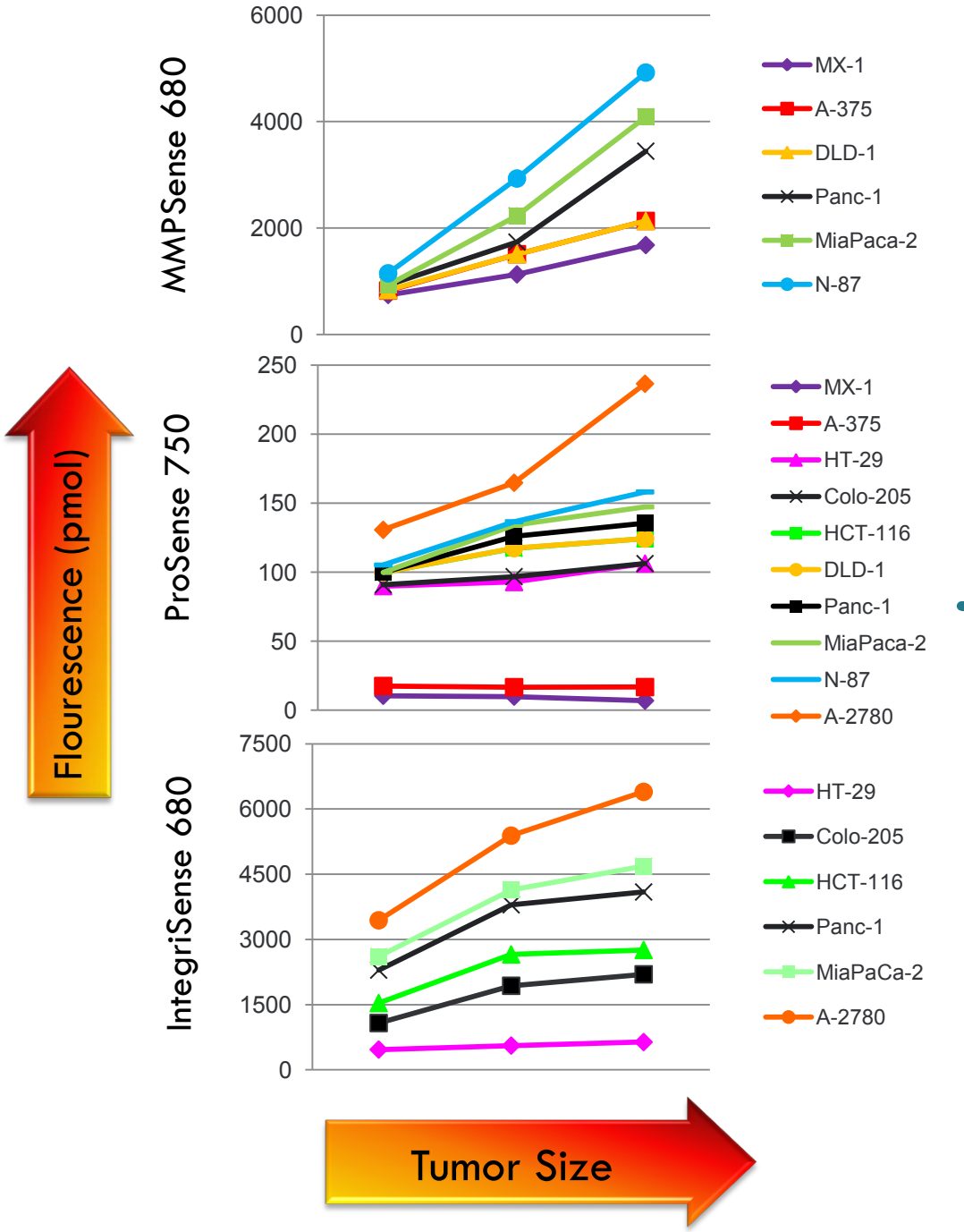
- Feasibility of tumor burden measurement across a broad panel of models
- Testing imaging throughput and workflow (104 scans in a 24h period)

FMT imaging in tumor models

Study #	Study Name	Description	Mouse Strain	# of Mice	# FMT In-vivo Scans	Agent 1 Required	Agent 1: Doses Required	Agent 2 Required	Agent 2: Doses Required
1	CAIA	In-vivo imaging & Quantification of Collagen Antibody-Induced Arthritis (CAIA) Model in mice							
		Control Mouse #1	Nu/Nu	2	2	ProSense 680	1	OsteoSense 800	1
		Experimental Mice #2-#8	Nu/Nu	6	14	ProSense 680	7	OsteoSense 800	7
2	Bone Metastasis	In-vivo imaging & Quantification of Bone metastasis from Prostate Adenocarcinoma (PC-3M-luc) in murine models							
		Exp. Mice #1-#3	Nu/Nu	1	2	ProSense 680	1	OsteoSense 800	1
4	Breast Adenocarcinoma	In-vivo Imaging & Quantification of Sub-Q tumours of Breast Adenocarcinoma (MX-1) in murine models							
		Exp. Mice #1-#3	Nu/Nu	1	2	MMPSense 680	1	ProSense 750	1
5	Breast Adenocarcinoma	In-vivo Imaging & Quantification of Sub-Q tumours of Breast Adenocarcinoma (A-375) in murine models							
		Exp. Mice #1-#3	Nu/Nu	1	2	MMPSense 680	1	ProSense 750	1
6	Large Cell Lung Carcinoma	In-vivo Imaging & Quantification of Sub-Q tumours of Lung Carcinoma (H-460) in murine models							
		Exp. Mice #1-#3	Nu/Nu	1	2	MMPSense 680	1	ProSense 750	1
7	Colorectal Carcinoma	In-vivo Imaging & Quantification of Sub-Q tumours of Colorectal Carcinoma (HT-29) in murine models							
		Exp. Mice #1-#3	Nu/Nu	1	2	IntegriSense 680	1	ProSense 750	1
8	Colorectal Carcinoma	In-vivo Imaging & Quantification of Sub-Q tumours of Colorectal Carcinoma (HCT-116) in murine models							
		Exp. Mice #1-#3	Nu/Nu	1	2	IntegriSense 680	1	ProSense 750	1
9	Colorectal Carcinoma	In-vivo Imaging & Quantification of Sub-Q tumours of Colorectal Carcinoma (Colo-205) in murine models							
		Exp. Mice #1-#3	Nu/Nu	1	2	IntegriSense 680	1	ProSense 750	1

FMT imaging in tumor models

Study #	Study Name	Description	Mouse Strain	# of Mice	# FMT In-vivo Scans	Agent 1 Required	Agent 1: Doses Required	Agent 2 Required	Agent 2: Doses Required
10	Gastric Carcinoma	In-vivo Imaging & Quantification of Sub-Q tumours of Gastric Carcinoma (N-87) in murine models							
		Exp. Mice #1-#3	Nu/Nu	1	2	MMPSense 680	1	ProSense 750	1
11	Colorectal Adenocarcinoma	In-vivo Imaging & Quantification of Sub-Q tumours of Colorrectal Adenocarcinoma (DLD-1) in murine models							
		Exp. Mice #1-#3	Nu/Nu	1	2	MMPSense 680	1	ProSense 750	1
12	Pancreatic Carcinoma	In-vivo Imaging & Quantification of Sub-Q tumours of Pancreatic Carcinoma (Panc-1) in murine models							
		Exp. Mice #1-#3	Nu/Nu	1	2	MMPSense 680	1	ProSense 750	1
13	Pancreatic Carcinoma	In-vivo Imaging & Quantification of Sub-Q tumours of Pancreatic Carcinoma (MiaPaca-2) in murine models							
		Exp. Mouse #1-#2	Nu/Nu	1	2	MMPSense 680	1	ProSense 750	1
14	Pancreatic Carcinoma	In-vivo Imaging & Quantification of Sub-Q tumours of Pancreatic Carcinoma (MiaPaCa-2) in murine models							
		Exp. Mice #1-#3	Nu/Nu	1	2	IntegriSense 680	1	AngioSense 750	1
15	Bone Metastasis	In-vivo Imaging & Quantification of Bone Metastasis from Prostate Adenocarcinoma (PC-3M-luc) in murine models							
		Exp. Mice #1-#3	Nu/Nu	1	2	IntegriSense 680	1	AngioSense 750	1
16	Pancreatic Carcinoma	In-vivo Imaging & Quantification of Sub-Q tumours of Pancreatic Epithelioid Carcinoma (Panc-1) in murine models							
		Exp. Mice #1-#3	Nu/Nu	1	2	IntegriSense 680	1	AngioSense 750	1
17	Ovarian Adenocarcinoma	In-vivo Imaging & Quantification of Sub-Q tumours of Ovarian Adenocarcinoma (A2780) in murine models							
		Exp. Mice #1-#3	Nu/Nu	1	2	IntegriSense 680	1	ProSense 750	1
			Totals	**52**	**104**	**N/A**	**52**	**N/A**	**52**



FMT technology in tumor models

CONCLUSIONS

- Can be used to locate tumors
- Can be used to track tumor growth
- Best probe for each model should be determined
- Imaging throughput not limiting in running large, powered industry drug response studies

ADVANTAGES

- Does not require transfected line (eg. luciferase)
- Facilitates rapid use of new patient derived models
- Deep tissue models not limiting

Future expanded applications ?

To come …

- Biodistribution
  - Huge current emphasis on targeted biologics
- Cell tracking
  - Increasing focus on cell based therapies
- Pulmonary disease
  - COPD, Pulmonary fibrosis
  - Lack of non-invasive biomarkers for preclinical study
- Inflammatory Bowel Disease
  - Lack of robust preclinical end points
- Atherosclerosis
  - Lack of non-invasive end points
  - Preclinical imaging remains deficient in athero models
  - Hybrid athero/metabolic models
- Obesity and metabolic disease
  - Lack of mechanistic end points
  - New biomarkers
- Neuro-degenerative diseases
  - MS: eg. EAE model
  - Alzheimer's
  - Parkinson's
- Systemic tumor models
  - Leukemia
  - Lymphoma
  - Metastasis
  - Imaging burden AND mechanism in tumors
    - primary, patient derived models
    - genetically well characterized models
    - target modulation

Imaging outlook including FMT

- Proof of principle has been established for most of these examples
- Further widespread adoption and application needed
- More comprehensive validation – qualified biomarkers

Expanded use and benefit in pharmaceutical research

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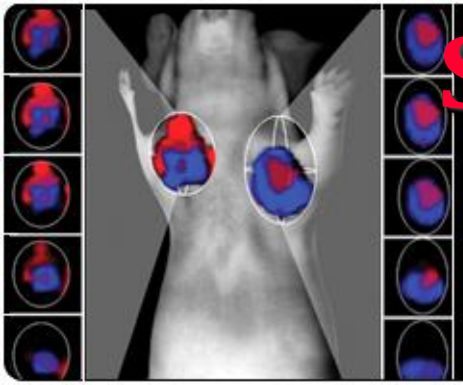

Science Webinar Series

Determining the Impact of New Therapeutic Approaches: Advancing Imaging in Animals

7 December, 2011

Brought to you by the *Science*/AAAS Custom Publishing Office

Participating Experts:

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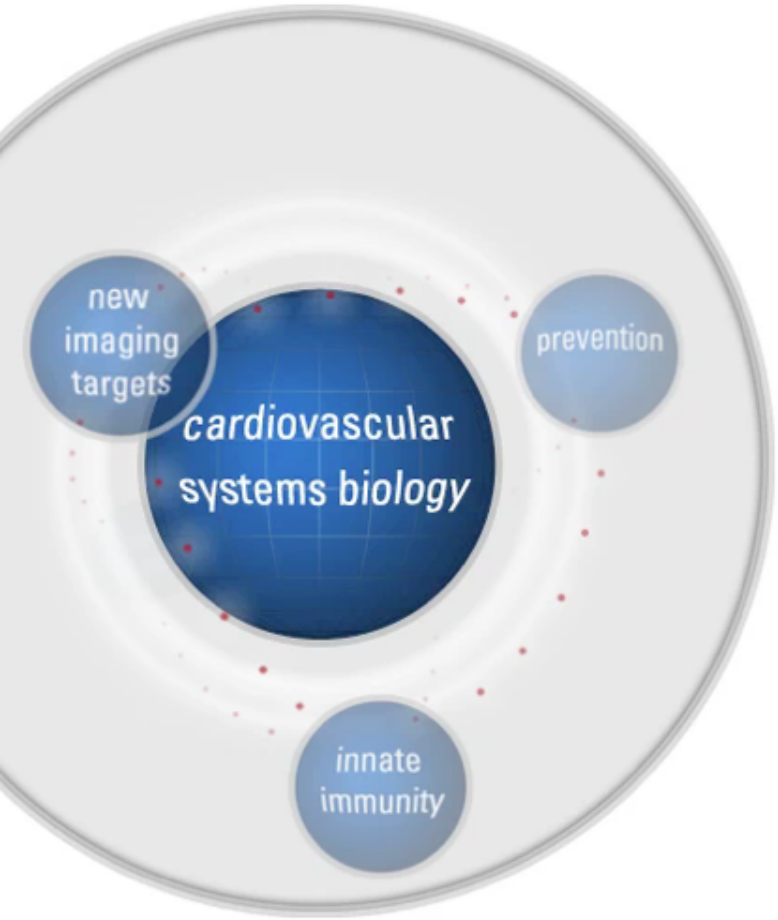
Molecular Imaging, Inc.
Ann Arbor, MI

Matthias Nahrendorf, M.D., Ph.D.
Harvard Medical School
Boston, MA



Why consider Fluorescence Tomography for basic research?

Matthias Nahrendorf

MGH Center for Systems Biology
http://csb.mgh.harvard.edu/investigator/matthias_nahrendorf

CSB

MGH 1811

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Fluorescence Molecular Tomography Advantages

- Non-invasive sensing of fluorescent molecular agents and fluorescent proteins
- Fully quantitative: tracer concentration in 3D
- Multiplex imaging to assess biomarker networks (up to 4 channels)
- High thoughput: 5 min scan time
- Versatility - combine with FACS and fluorescence histology

Fluorescence Molecular Tomography Limitations

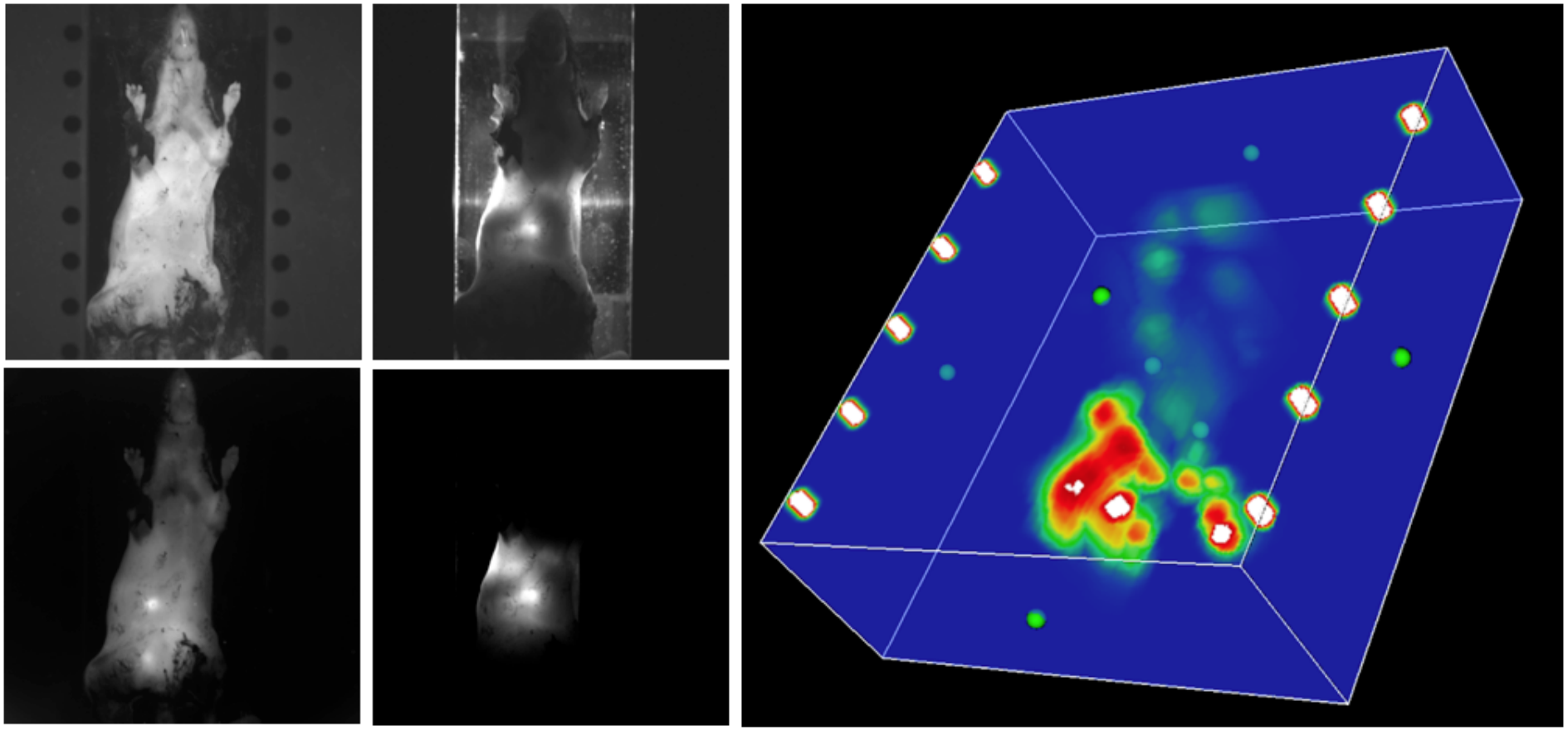
- Only mouse and rat (limited penetration depth of light)
- Spatial resolution ~1mm
- Spatial information can be supplemented with hybrid anatomic modality
- Autofluorescence (remove hair, non-fluorescent diet)

Fluorescence Molecular Tomography
How does it work?

visible light

transillumination
1 of 80 point sources

reconstructed 3-dimensional FMT data set

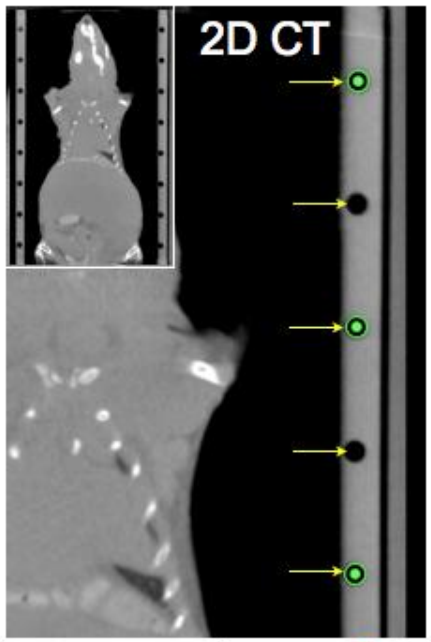


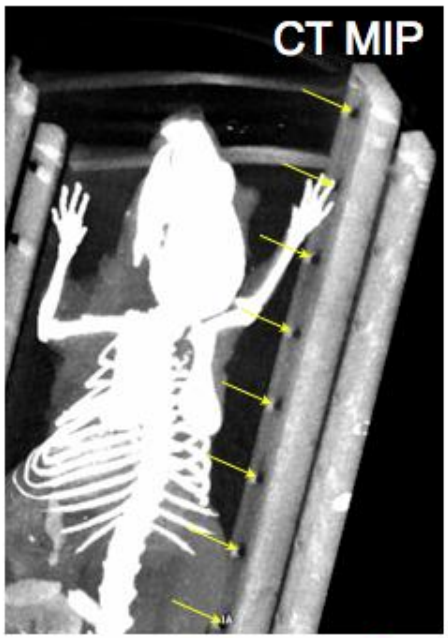
planar FRI

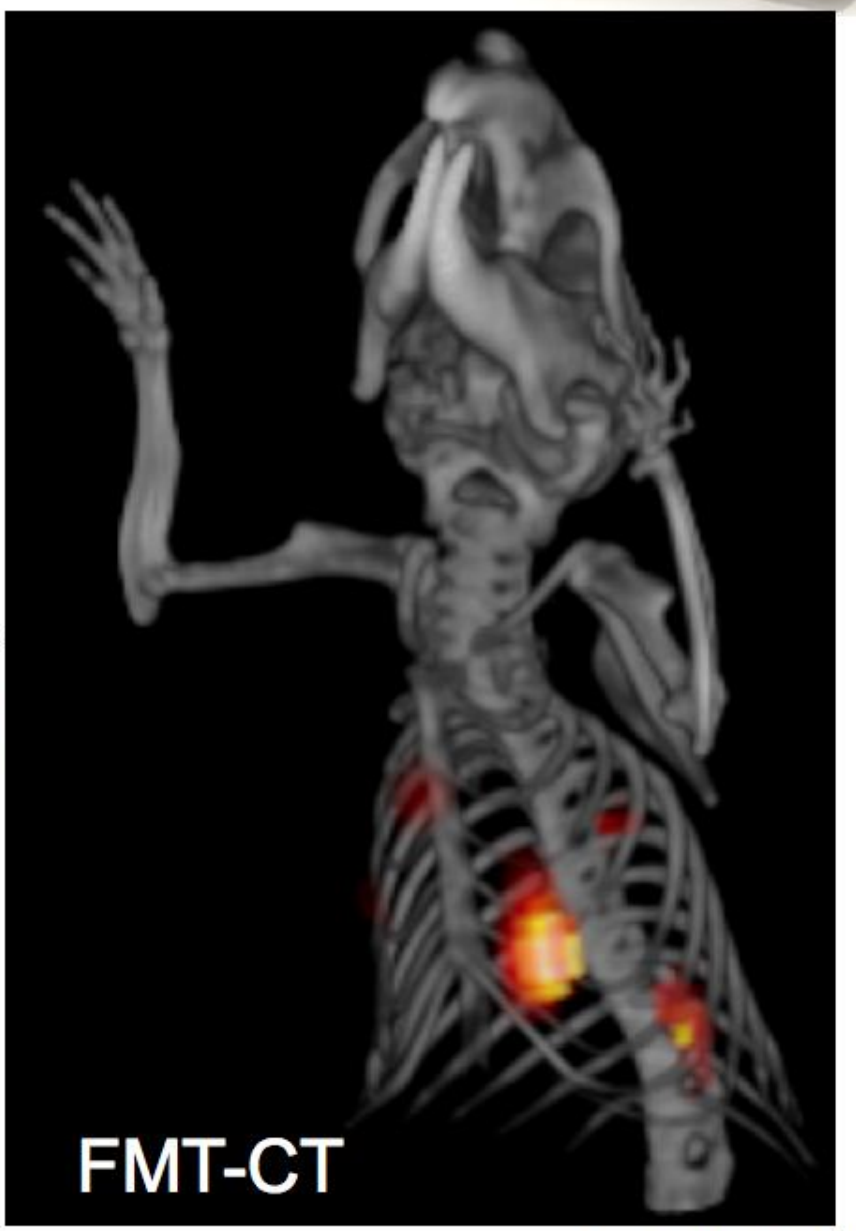
fluorescence
1 of 80 point sources

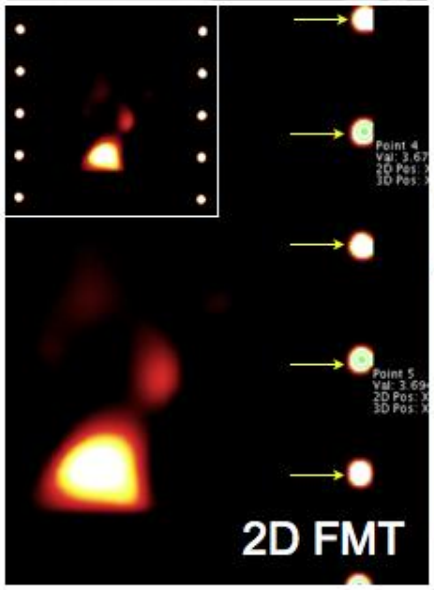
Circ Cardiovasc Imaging 2008,1:244

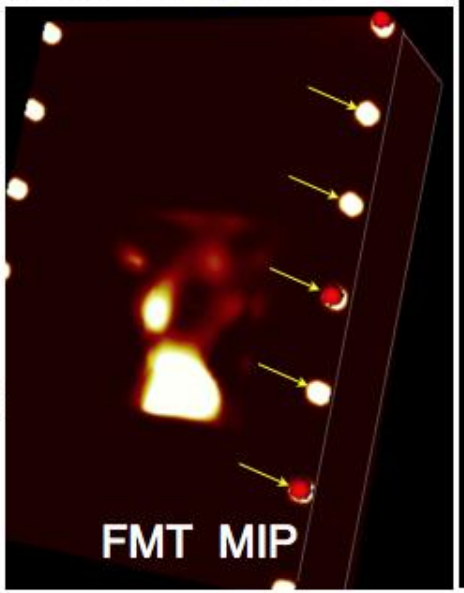
In vivo FMT-CT image fusion





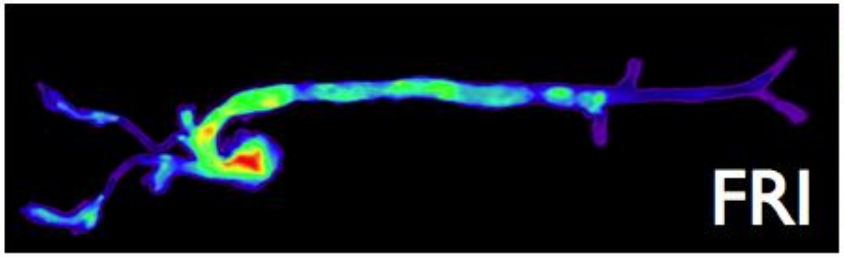


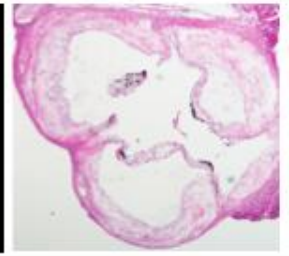




JACC 2010;55:1629

FMT-CT in Atherosclerosis





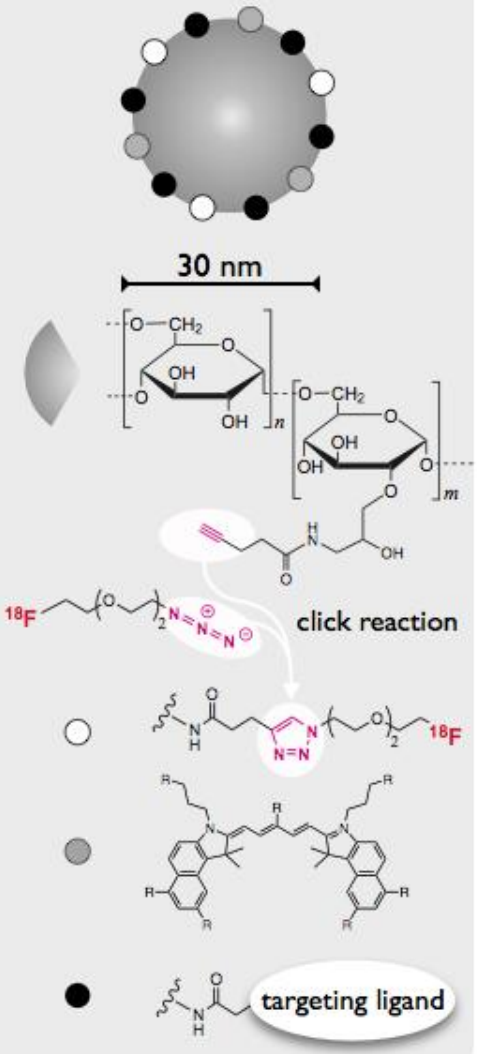
aortic root

apoE$^{-/-}$ mouse, 24hrs after 5nmol Prosense IV

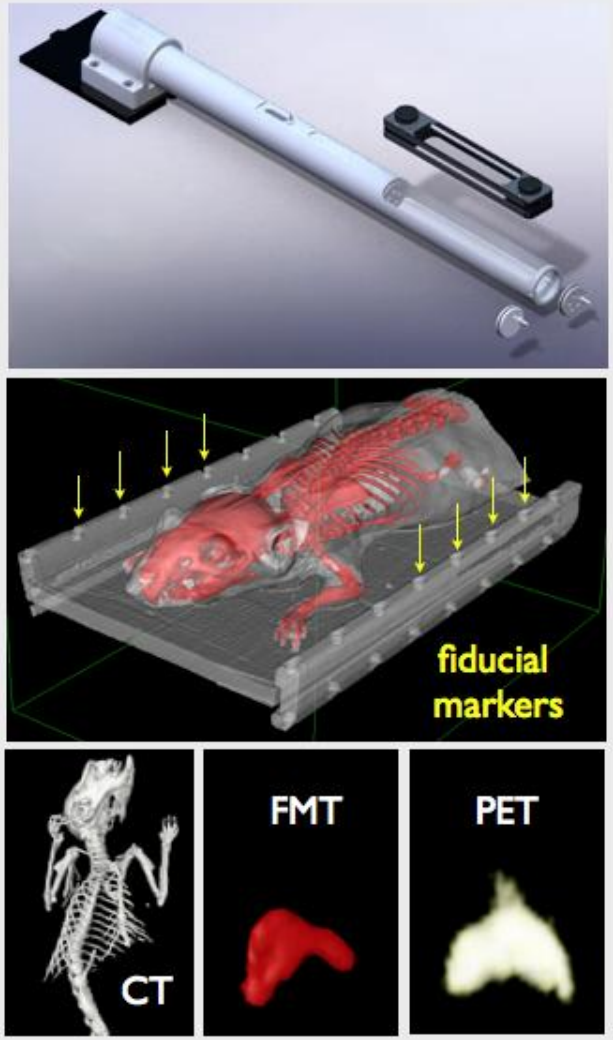
ATVB 2009;29:1444

FMT-CT: Typical Experiment

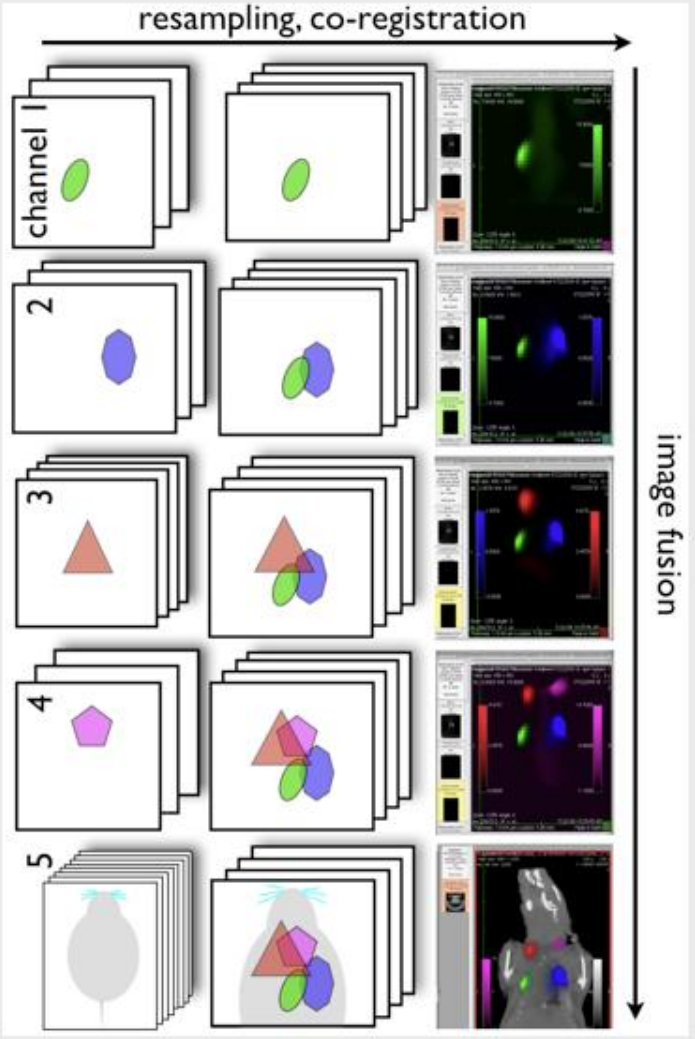
A. NP platform



B. Image acquisition

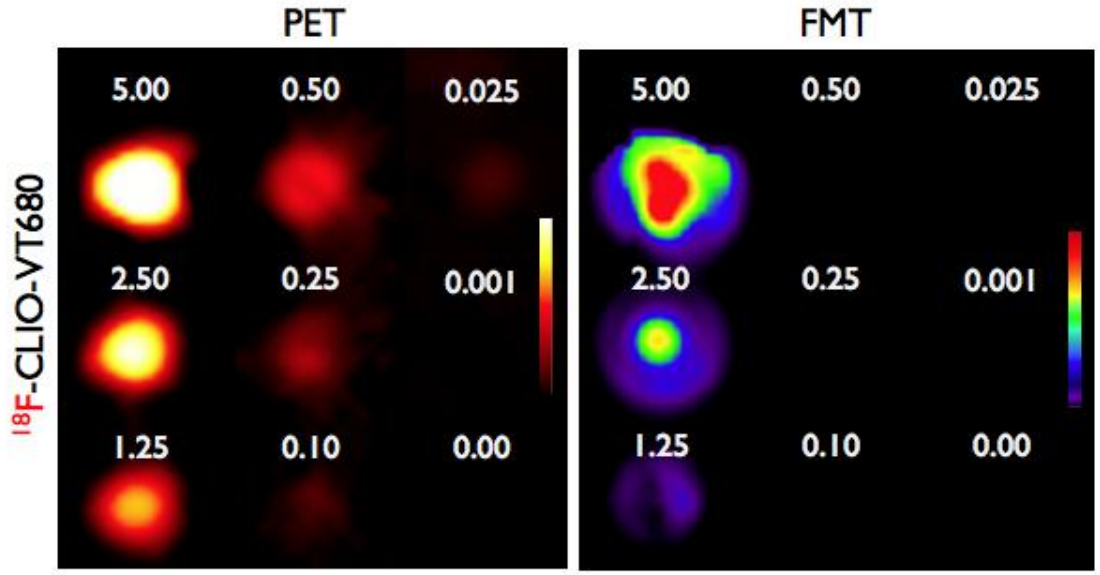


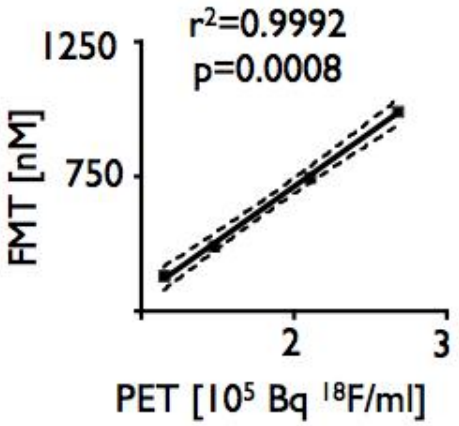
C. Fusion

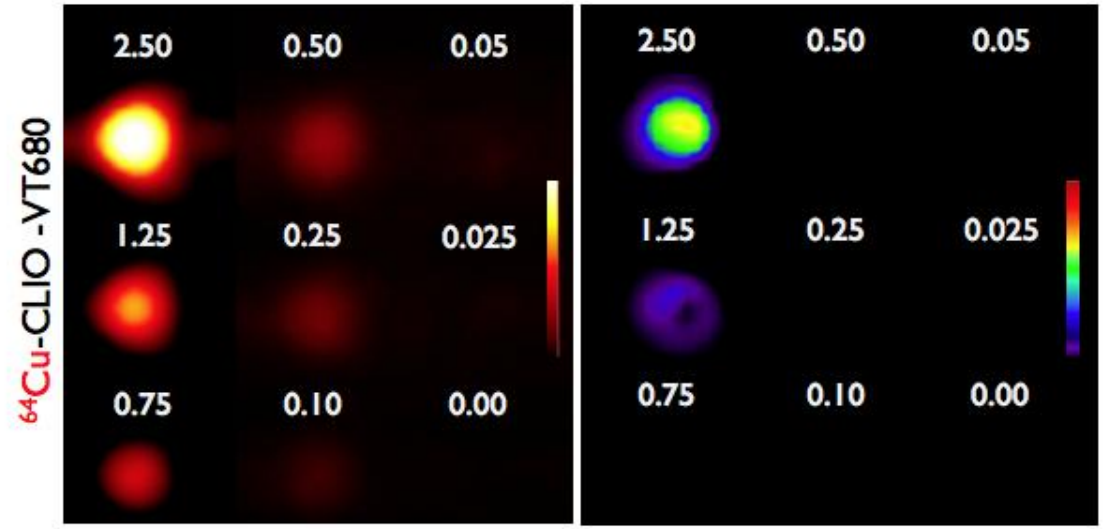


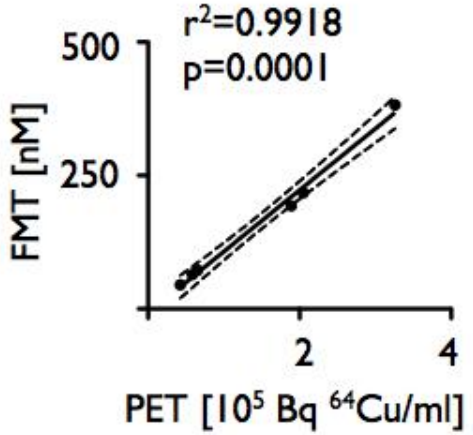
PNAS 2010;107:7910

FMT-CT: Validation against PET



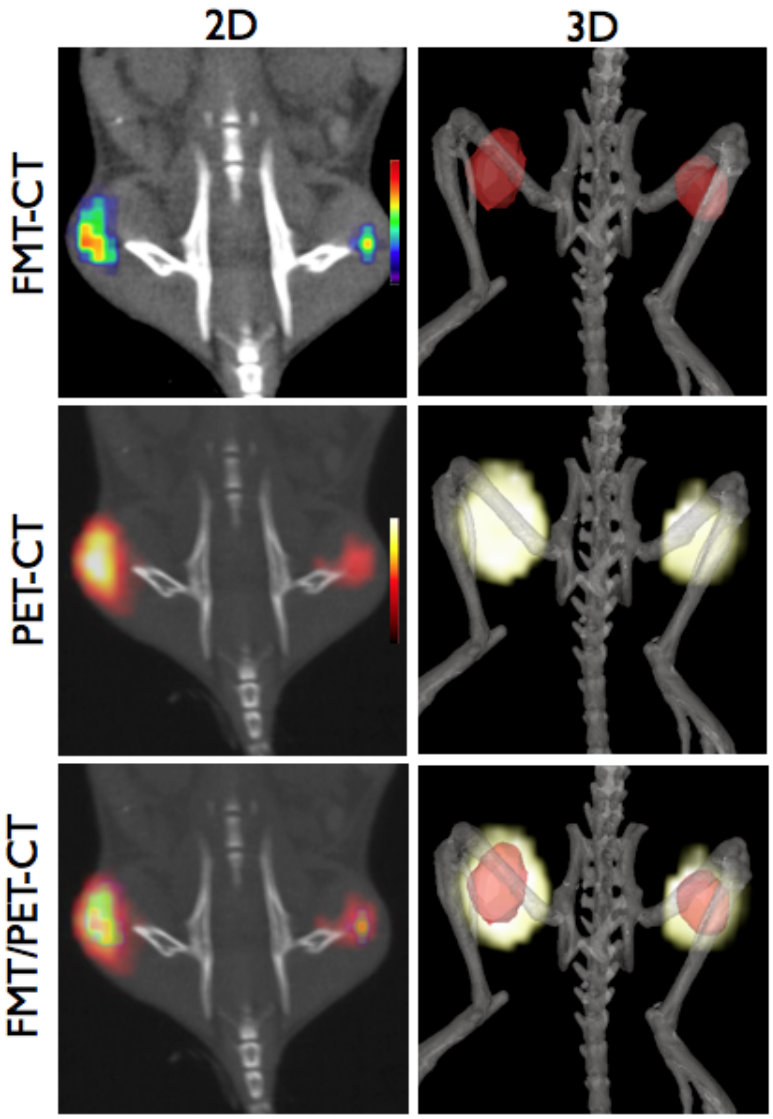


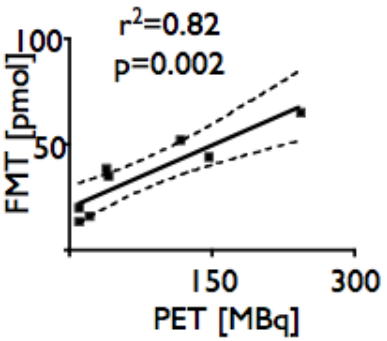


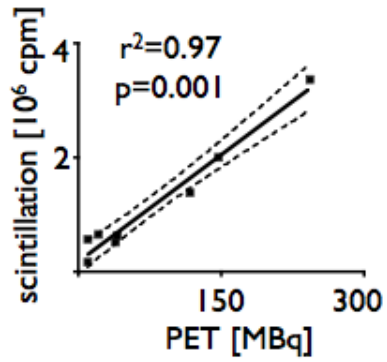


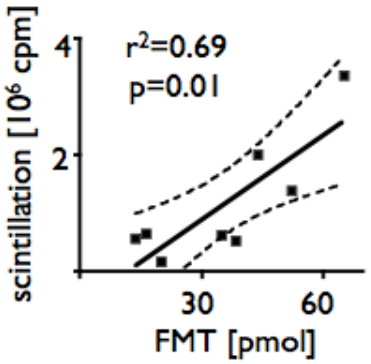
PNAS 2010;107:7910

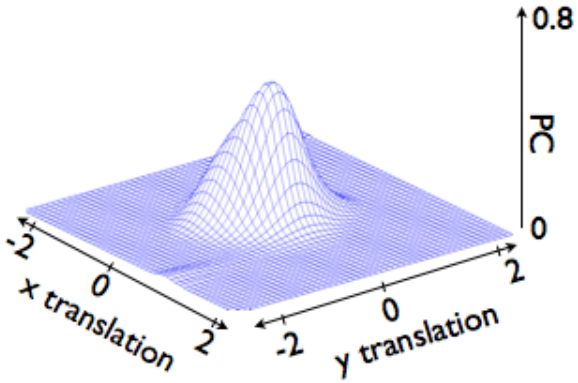
FMT-CT: Validation against PET

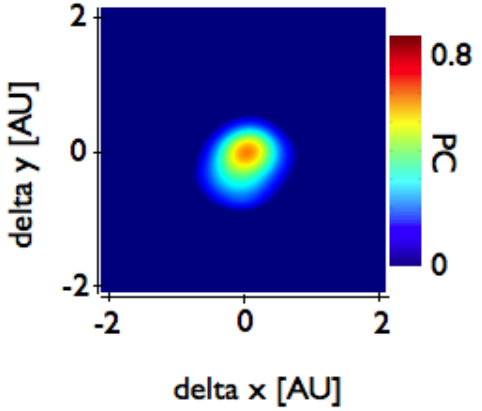






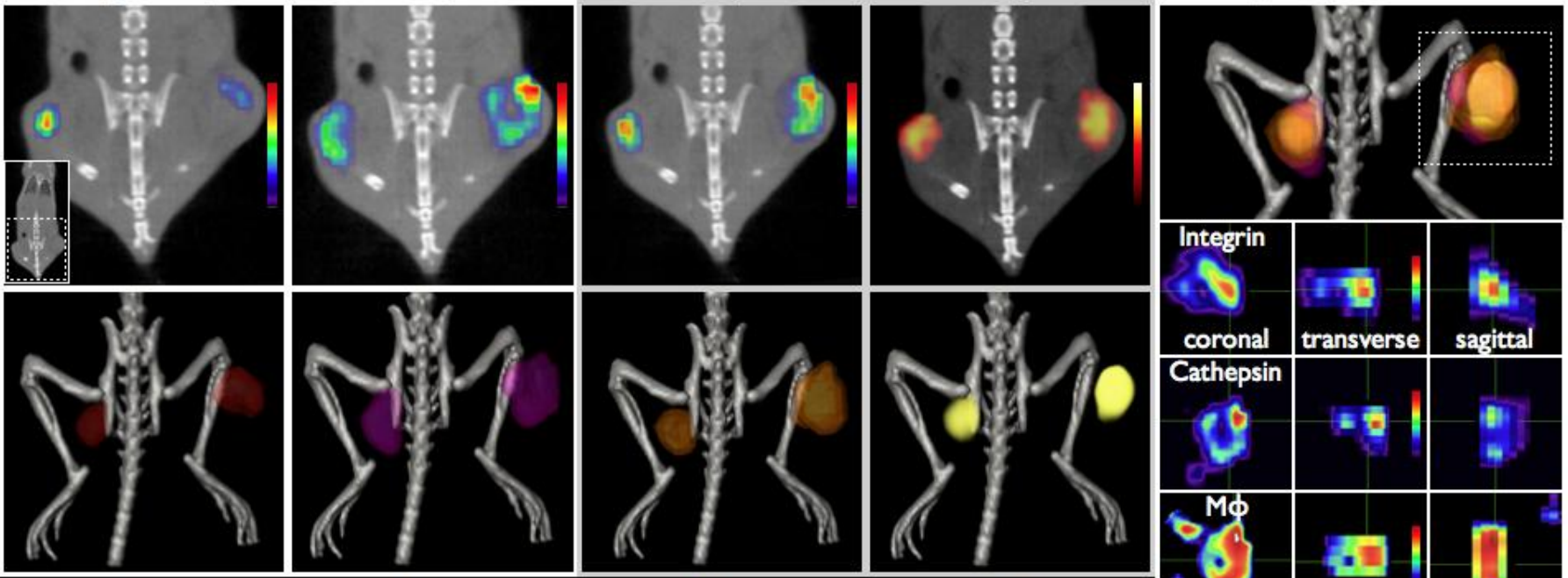






PNAS 2010;107:7910

Multichannel FMT/PET-CT in tumor bearing mice



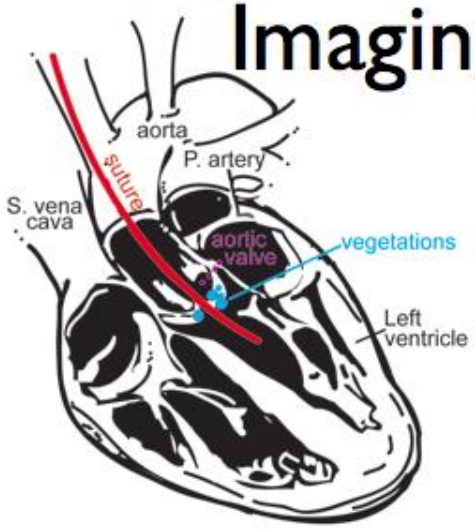
Ex	630 nm	750 nm	680 nm	NA
Em	650 nm	780 nm	700 nm	NA
PET	NA	NA	NA	511 kev
CT	80 Kvp	80 Kvp	80 Kvp	80 Kvp

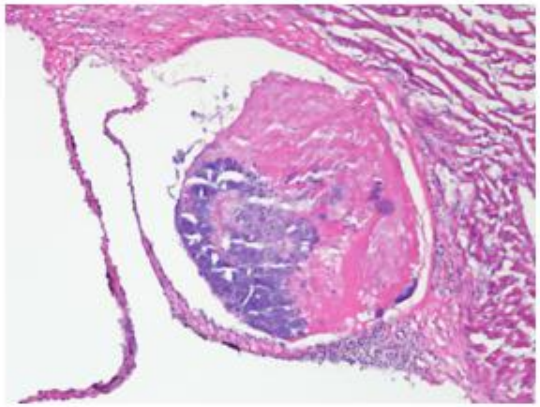
Same NP (^{64}Cu-CLIO-VT680)

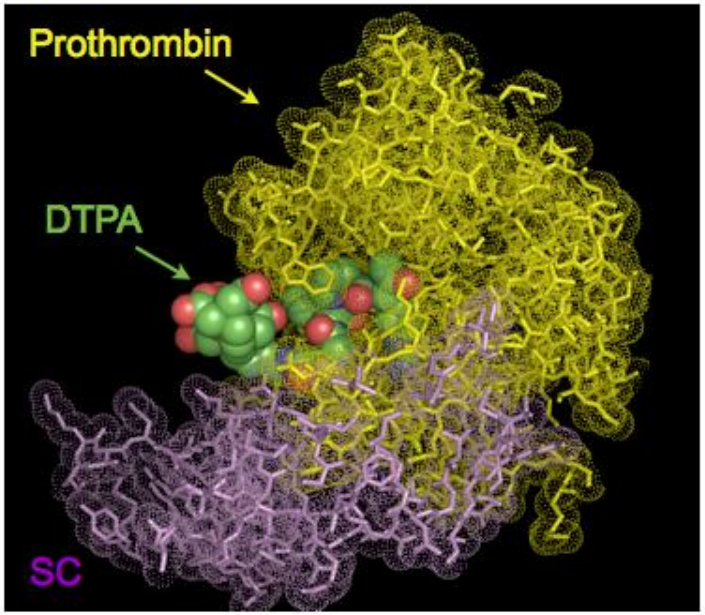
PNAS 2010;107:7910

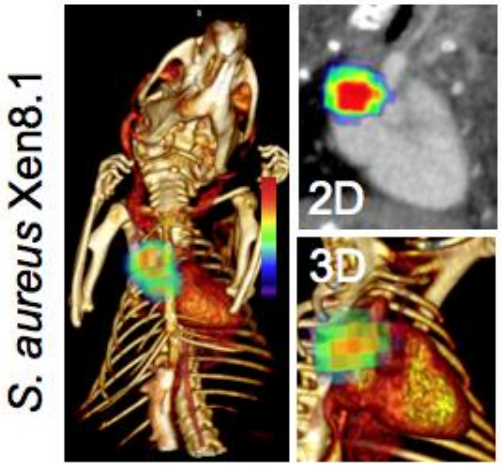
Application: Probe development

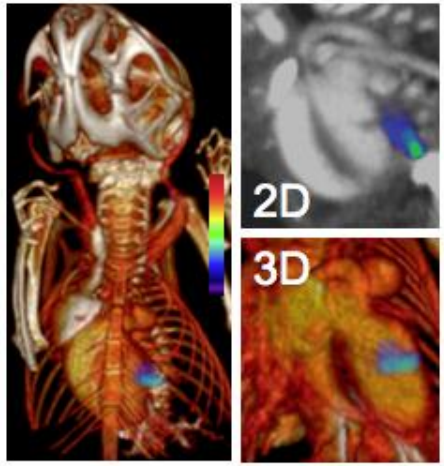
Imaging of Staph aureus endocarditis

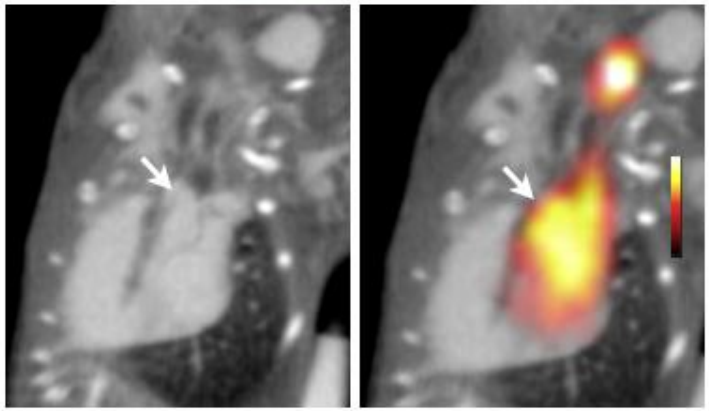








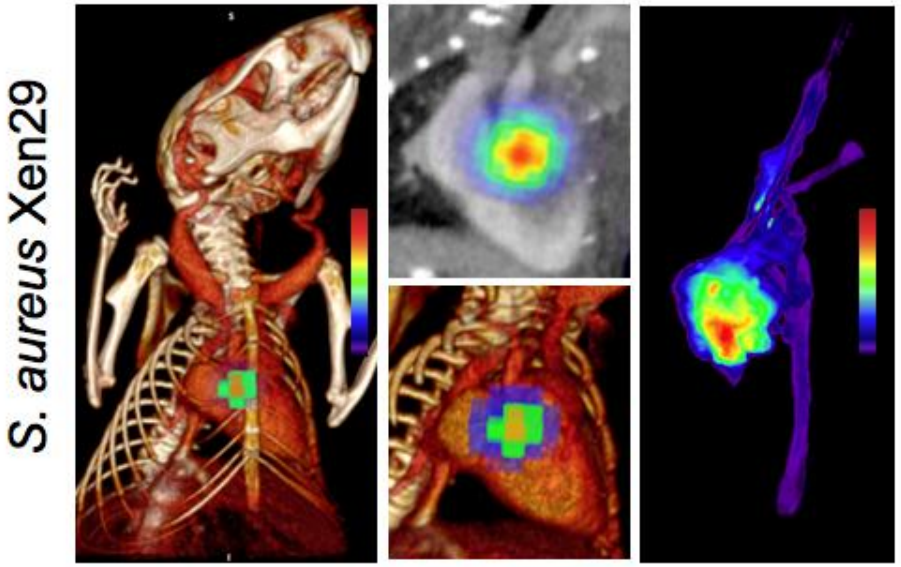


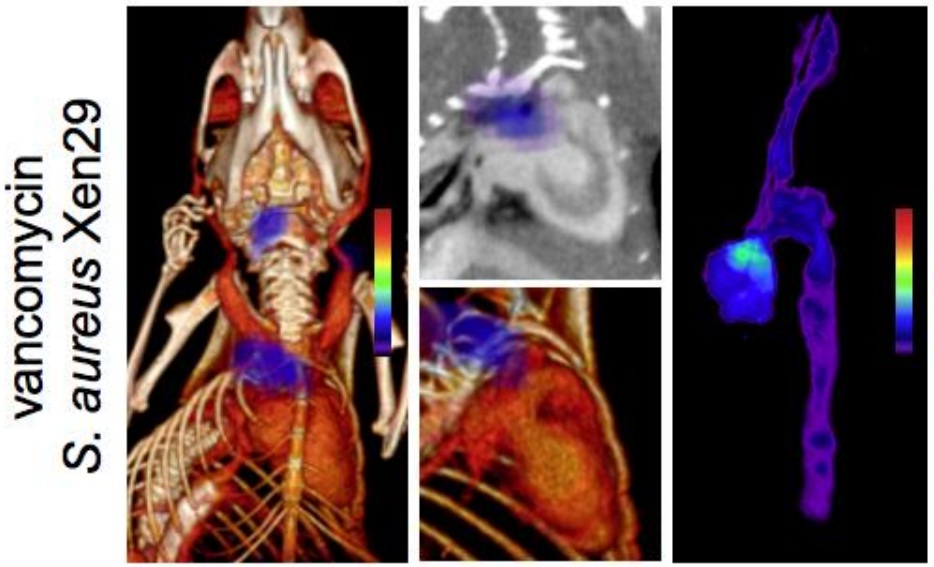


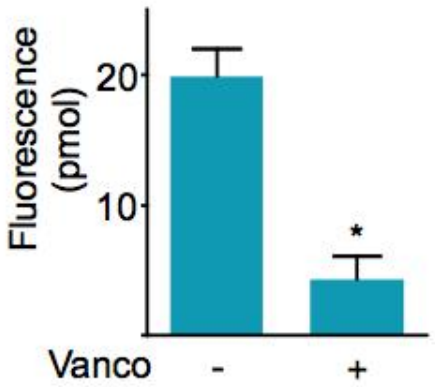
FMT provides proof of principle and motivates PET agent development

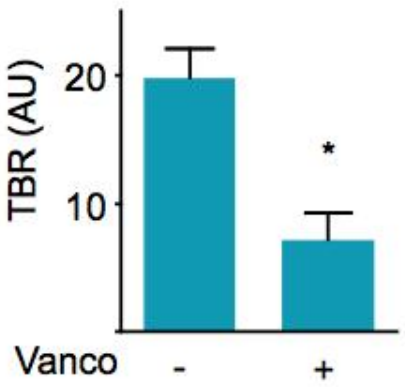
Nat Med 2011;17:1142

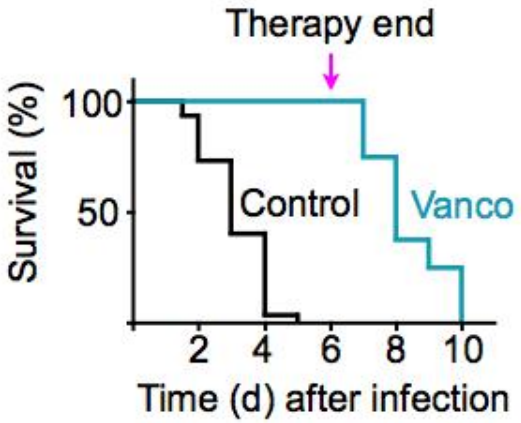
Application: Therapeutic monitoring Vancomycin in S. aureus infection







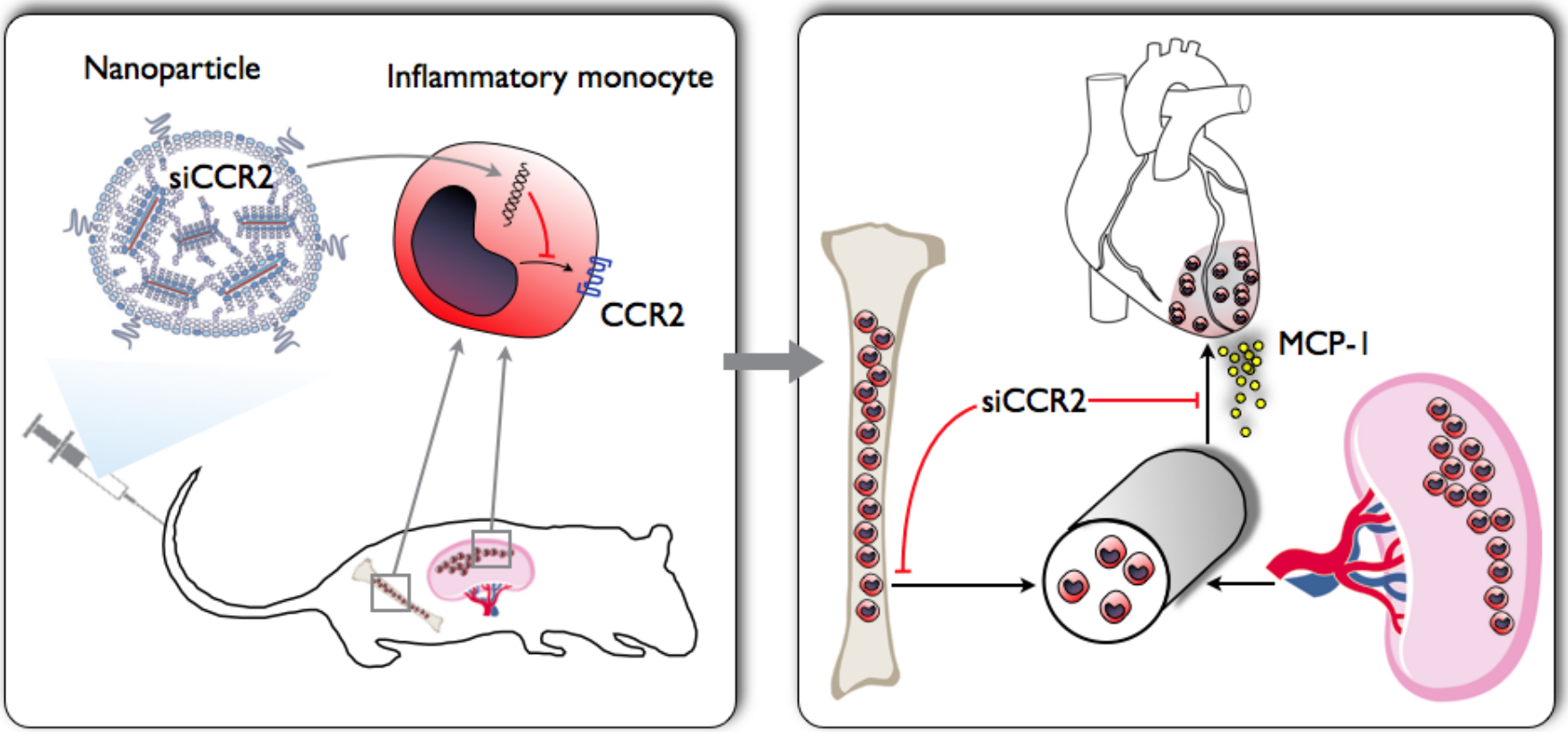




Nat Med 2011;17:1142

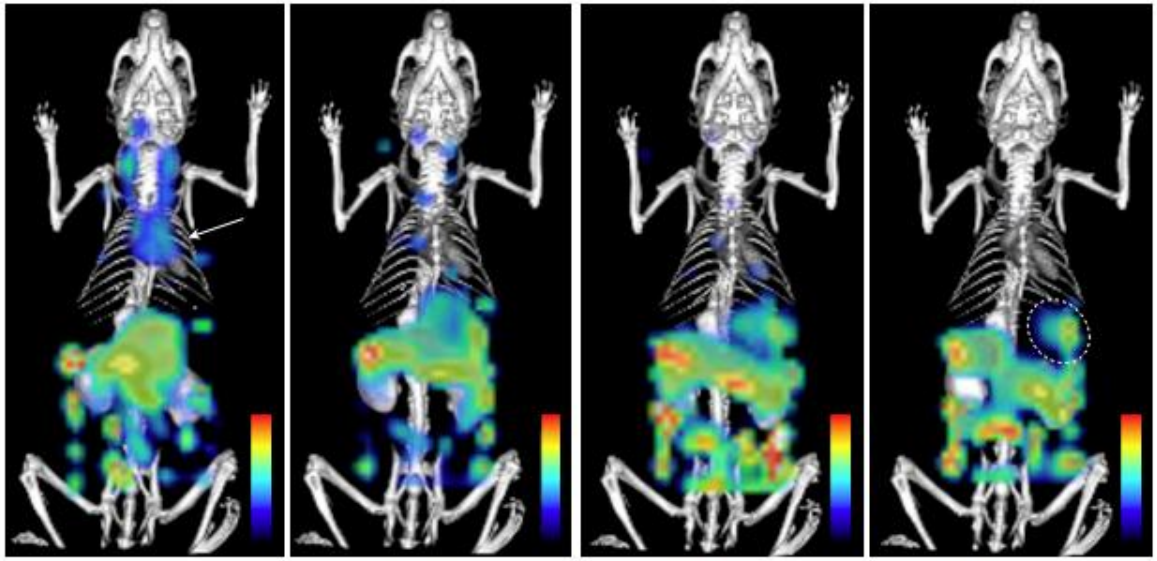
Application: Biodistribution Imaging

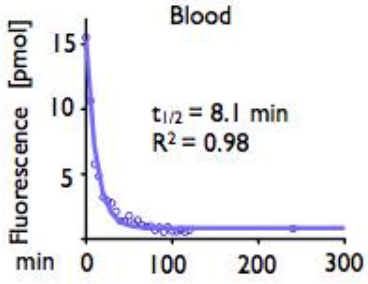
Fluorescently labeled siRNA encapsulated into leukocyte-targeting nanoparticles

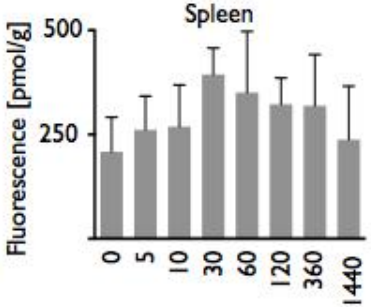


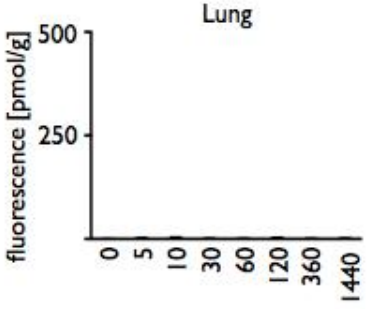
Nat Biotechnol 2011;29:1005

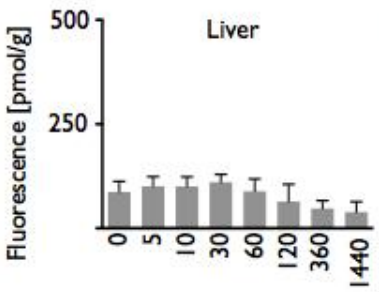
Application: Biodistribution Imaging

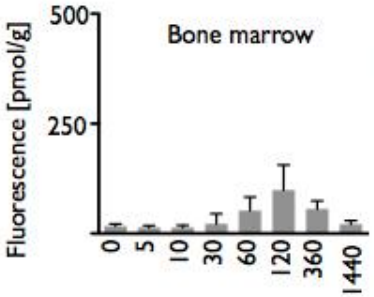


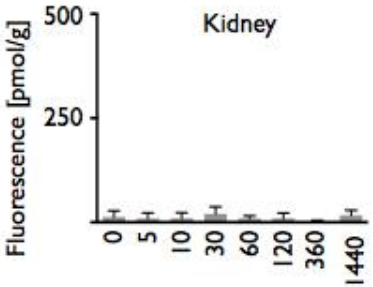


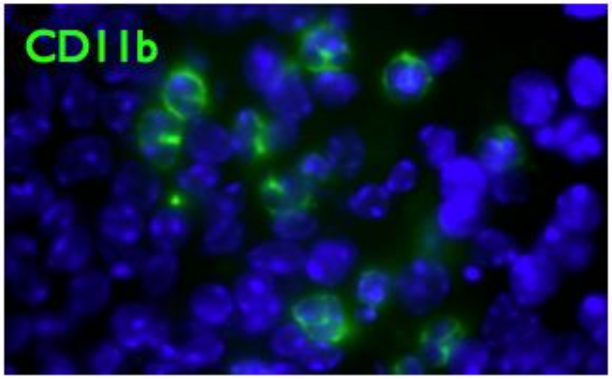


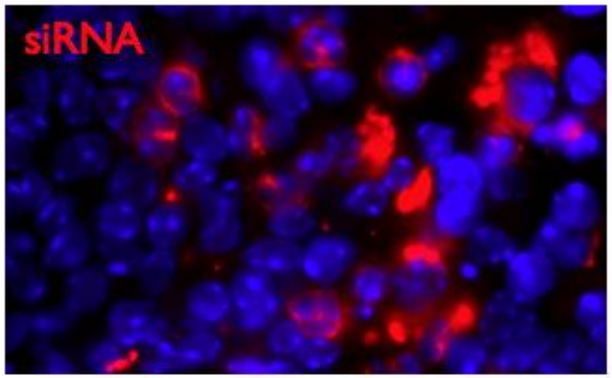


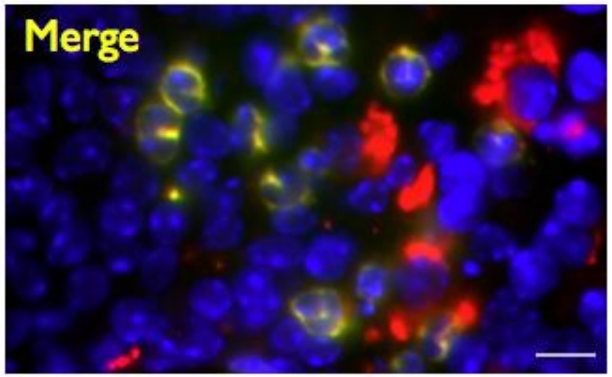






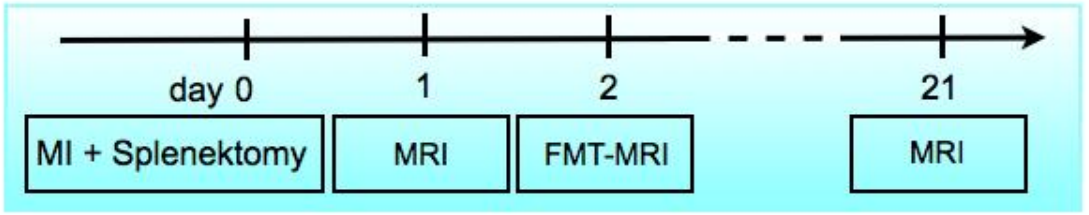


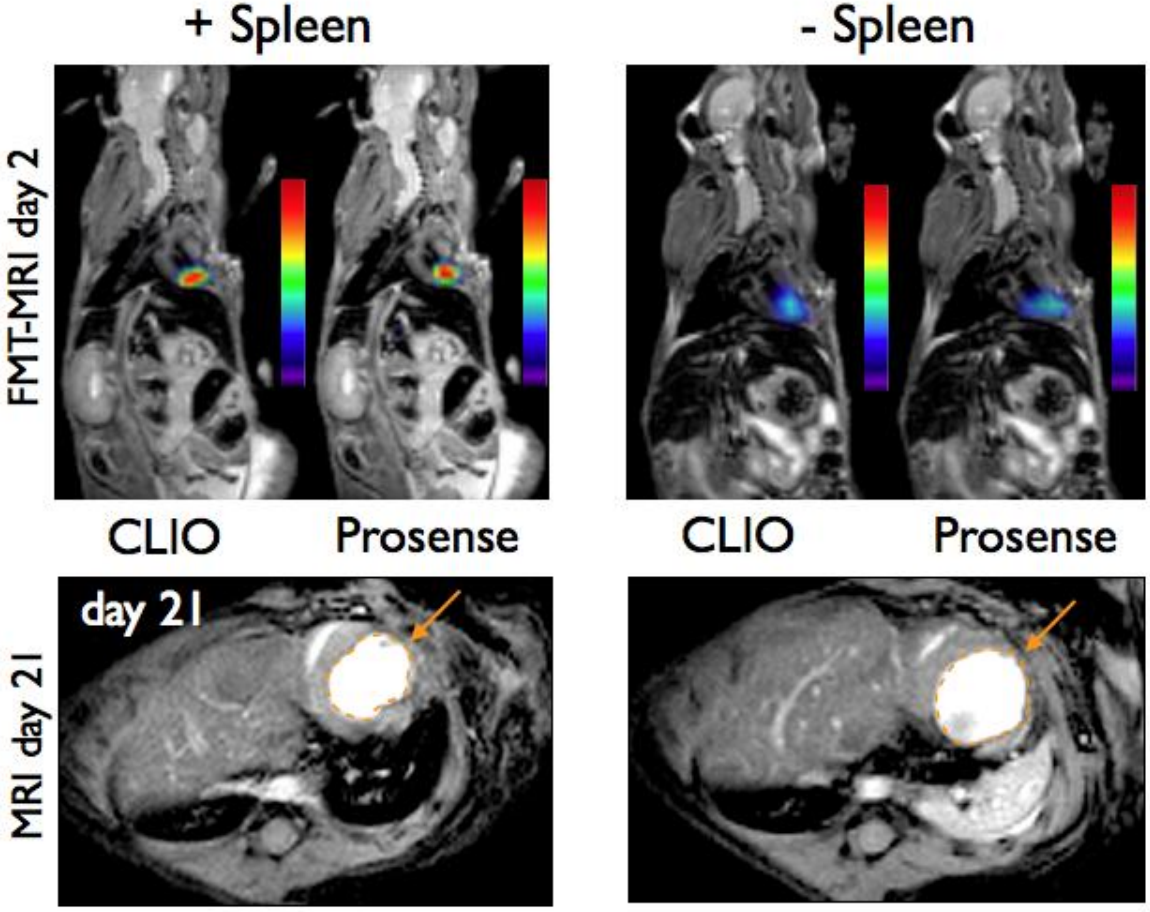


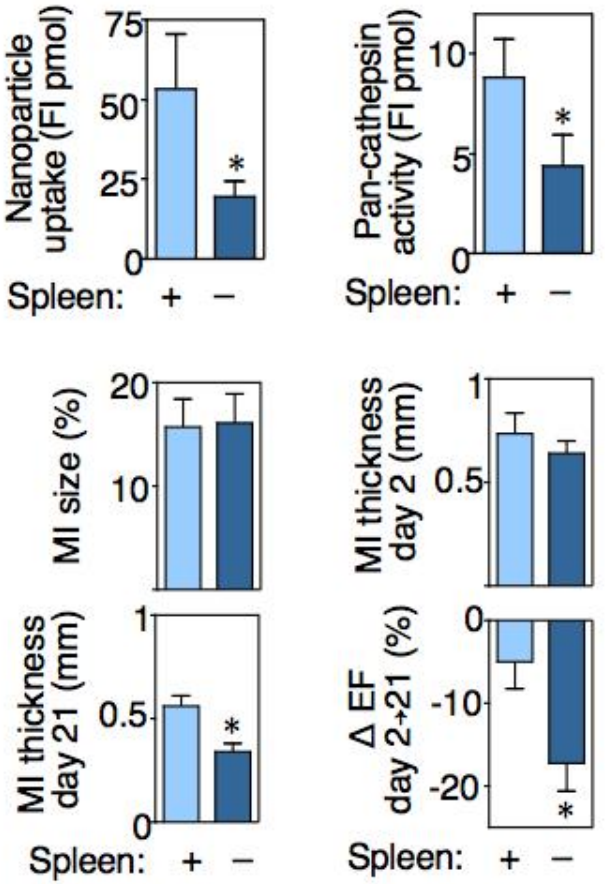


Nat Biotechnol 2011;29:1005

Application: Integrated non-invasive protocols probing basic biology







Science 2009;325:612

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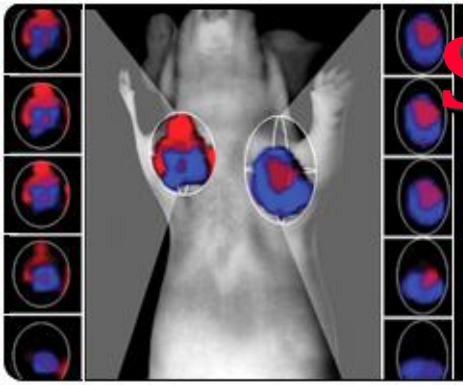
Alnylam Pharmaceuticals



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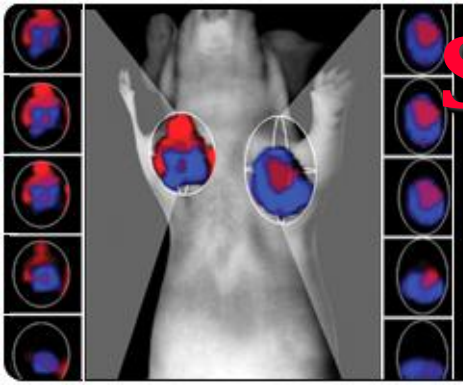

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