

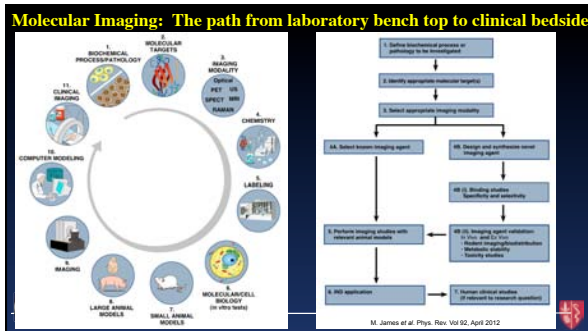
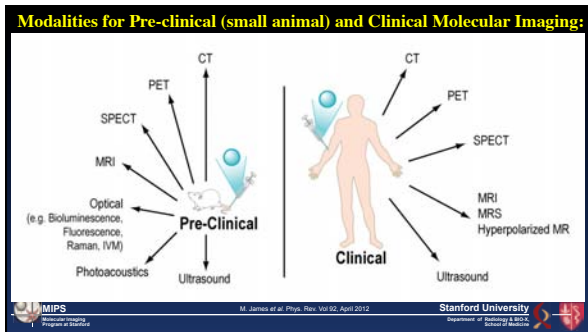


Definition of Molecular Imaging

A biomedical imaging technology that enables one to visualize, quantify, and characterize molecular pathways and signatures of disease in living subjects





Molecular Imaging Modalities and Technologies

Outline of talk

- Introduction to Molecular Imaging
- Brief review of Molecular Imaging modalities and technologies
- Multi-modality systems
- Molecular Imaging Contrast Agents
- Summary

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Imaging has exploited a wide range of the electromagnetic spectrum

Radio Microwave Infrared Visible Ultraviolet X-Rays Gamma Rays & annihilation photons

The electromagnetic spectrum stretches from radio waves to gamma rays.

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Optical Imaging Modality 1: Bioluminescence

A Control CCD Camera
Mouse containing cells expressing/secreting luciferase
D-Luciferin, Coelenterazine

B Before Treatment, After Treatment with CXCR4 1hr, 24hr

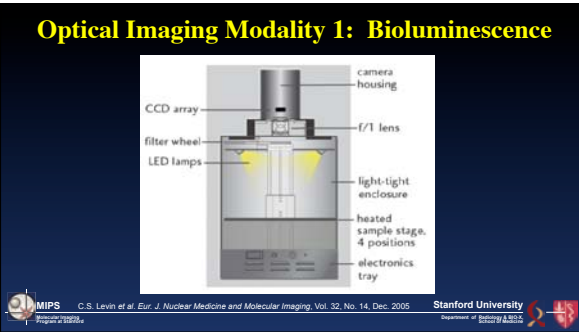
Key Strengths

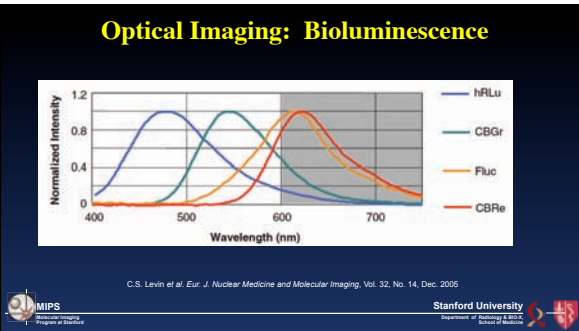
- Relatively inexpensive
- Excellent sensitivity
- Good temporal resolution
- User friendly
- Multiplexing capabilities
- No endogenous bioluminescence

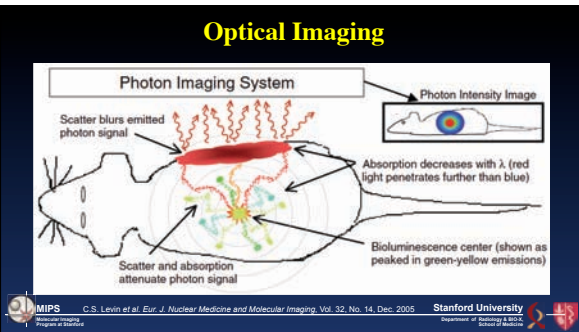
Key Limitations

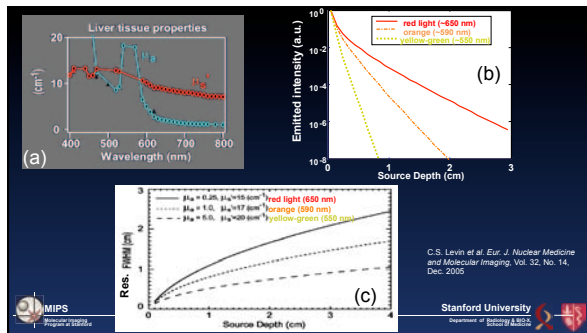
- Limited depth of penetration
- Poor spatial resolution at greater depths
- Images are relatively surface-weighted
- Substrate and enzymatic co-factors required
- Tomography challenging
- Clinical translation very limited

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Optical Imaging: Fluorescence

A

Excitation Light
Emission Light
CCD Camera
Fluorescent Protein

B

Pre-treatment
Post-treatment

Key Strengths

- Relatively inexpensive
- User friendly
- Multiplexing capabilities

Key Limitations

- Limited depth of penetration
- Poor spatial resolution at greater depths
- Surface weighted images
- Autofluorescence

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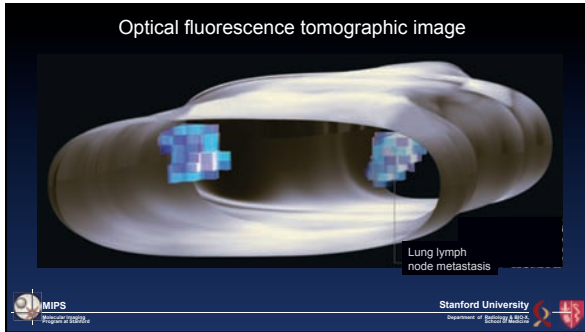
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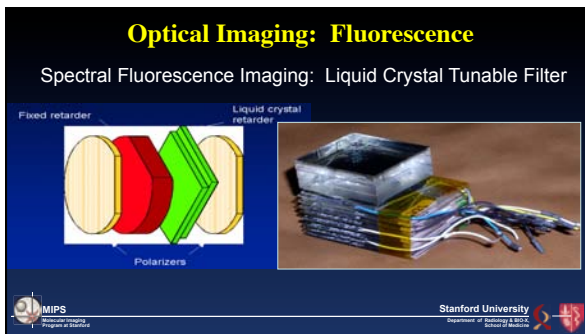
Optical Imaging: Fluorescence

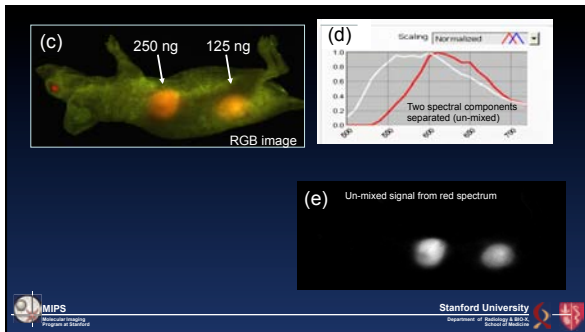
Tomographic imaging system

CCD Camera
Lenses
Filter Wheel
Microscope Incorporated in Imaging Component
X-Y Stage
Laser (excitation)
2 - 4 Channel
Lenses (SOPWA)
SOP (SOP)

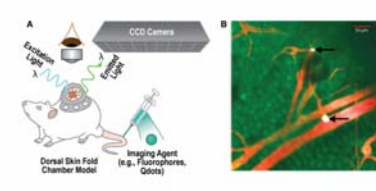
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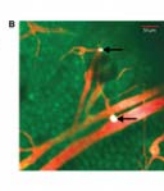




Optical Imaging: Intra-vital microscopy



A Dorsal Skin Fold Chamber Model
Imaging Agent (e.g., Fluorophores, Gobeis)



B

Key Strengths

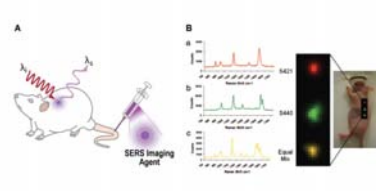
- Excellent spatial resolution
- Multiplexing capabilities
- Dynamic information about microscopic cellular events (real-time imaging)
- Yields quantitative measures of cell size and motility

Key Limitations

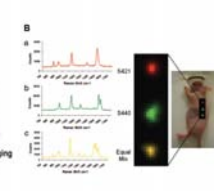
- Poor depth of penetration
- Small field of view
- Can require multiple laser excitations
- Longitudinal studies can be challenging
- Animal models are limited

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Optical Imaging: Raman Scattering



A SERS Imaging Agent



B

Key Strengths

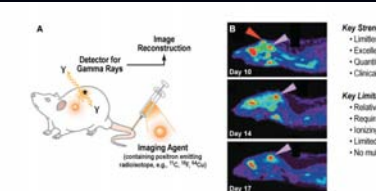
- High sensitivity
- Significant multiplexing capabilities
- Sustainable signal over long periods (longitudinal studies possible)
- Can detect endogenous molecular information without need for imaging agent
- Clinical utility in limited applications

Key Limitations

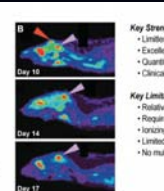
- Poor depth of penetration
- Tomography challenging
- Imaging large fields of view challenging

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Radionuclide Imaging: Positron Emission Tomography (PET)



A Detector for Gamma Rays
Imaging Agent (emitting positron emitting radionuclide, e.g., ¹⁸F, ¹¹C, ¹⁵O)



B Day 13
Day 14
Day 17

Key Strengths

- Limitless depth of penetration
- Excellent sensitivity
- Quantitative data
- Clinical utility

Key Limitations

- Relatively expensive
- Requires cyclotron/generator
- Ionizing radiation
- Limited spatial resolution
- No multiplexing

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Radionuclide Imaging: PET

LSO Array Technology
400 crystals, each 1.5x1.5x10

LSO Array
Tapered Light Guide
PSPMT

511 keV photon imaging detector

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Radionuclide Imaging: Single Photon Emission Computed Tomography (SPECT)

A Image Reconstruction
Detector for Gamma Rays
Imaging Agent (emitting gamma emitter, e.g., ^{99m}Tc , ^{111}In , ^{125}I)

B Coronal Sagittal
4 hours p.i.

Key Strengths

- Limitless depth of penetration
- Excellent sensitivity
- Multiplexing capabilities
- Clinical utility

Key Limitations

- Relatively expensive
- Ionizing radiation
- Limited spatial resolution
- Lack of attenuation correction (therefore only semi-quantitative)

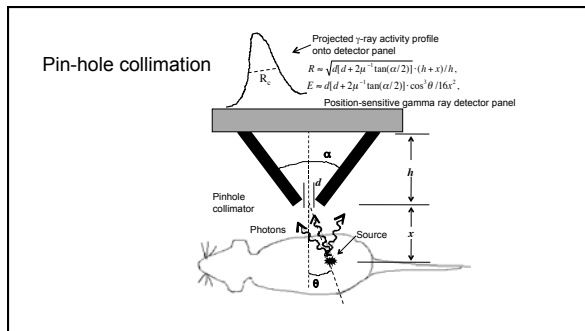
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Radionuclide Imaging: SPECT

Parallel-hole collimator

Pin-hole collimator

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Ultrasound

A

B

Key Strengths

- Relatively inexpensive
- Quantitative data
- No ionizing radiation
- Good temporal resolution
- Excellent sensitivity with microbubbles
- Clinical utility

Key Limitations

- Limited depth of penetration
- Primarily anatomical information
- No multiplexing
- Limited molecular imaging applications
- Limited to imaging soft-tissues only (no bone or air structures)
- Coupling of instrument to subject

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Photoacoustic Imaging (optical + ultrasound)

A

B

Key Strengths

- Superior depth of penetration (compared to most optical techniques)
- Relatively inexpensive
- Good temporal resolution
- Can detect endogenous molecular information
- Clinically translatable

Key Limitations

- Limited to imaging soft-tissues only (no bone or air structures)
- No multiplexing
- Coupling of instrument to subject

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Magnetic Resonance Imaging (MRI)

A Magnetic Field Direction
Radio Frequency Coil
Magnet
Gradient Coils
I.V.
Imaging Agent (e.g., SPIOs, Gd-based agent, hyperpolarized agent)

B No imaging agent
Mouse head
Non-targeted
Targeted

Key Strengths

- Limitless depth of penetration
- High spatial resolution
- Quantitative data
- No ionizing radiation
- Clinical utility


Key Limitations

- Poor sensitivity (requires large mass of imaging agent)
- Relatively expensive
- Relatively poor temporal resolution

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RF transmit/receive coils for high res MRI

Solenoid design
Bird-cage design



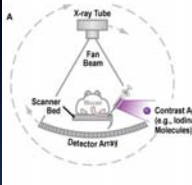
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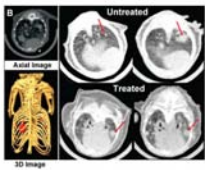
Gradient coils for hi res MRI



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X-ray Computed Tomography (CT)






Key Strengths

- Unlimited depth of penetration
- High spatial resolution
- Good temporal resolution
- Clinical utility

Key Limitations

- Poor sensitivity (requires large mass of imaging agent)
- Primarily anatomical information
- Limited soft tissue resolution
- Limited molecular imaging applications
- Ionizing radiation



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Table 1. Features of available and emerging imaging modalities

Modality	Temporal Resolution	Spatial Resolution	Depth of Penetration	Sensitivity	Multi-channel Capability	Cost	Safety Profile	Used Clinically
Computed tomography (CT)	Minutes	50-200 μm (practical) 0.2-1 mm (intrinsic)	Unlimited	ND	Could be possible	\$\$\$	Ionizing radiation	Yes
Magnetic resonance imaging (MRI)	Minutes/hours	25-100 μm (practical) ~1 mm (intrinsic)	Unlimited	10^{-8} to 10^{-6} M	No	\$\$\$	No ionizing radiation	Yes
Positron emission tomography (PET)	Seconds/minutes	1-3 mm (practical) 5-7 mm (intrinsic)	Unlimited	10^{-11} to 10^{-10} M	No	\$\$\$	Ionizing radiation	Yes
Single photon emission tomography (SPECT)	Minutes	1-2 mm (practical) 8-10 mm (intrinsic)	Unlimited	10^{-10} to 10^{-11} M	Yes	\$\$	Ionizing radiation	Yes
Ultrasound (US)	Seconds/minutes	0.1-0.2 mm for superficial applications 1-2 mm for deeper (few cm depth) applications	mm/cm	Buoyant when microbubbles are used (10^{-10} M)	No/yes	\$	Good safety profile	Yes
Optical fluorescence imaging	Seconds/minutes	2-3 mm	<1 cm	10^{-16} to 10^{-10} M	Yes	\$	Good safety profile but depends on fluorophore used and tissue needed	Emerging clinical utility (see text)
Optical bioluminescence imaging	Seconds/minutes	3-5 mm	1-2 cm	10^{-16} to 10^{-11} M	Yes	\$	Good safety profile	Low potential for clinical translation (see text)
Surface-enhanced Raman scattering (SERS) imaging	Minutes/days	mm	<5 mm	10^{-18} to 10^{-10} M	Yes	ND	ND	Limited clinical applications (see text)
Photoacoustic imaging (PAI)	Seconds/minutes	~10 μm to 1 mm	5 mm to 5 cm	ND	Yes	\$	Good safety profile but depends on imaging agent used and tissue needed	Clinically
Intravital microscopy (IVM)	Seconds/days	1-10 μm	<700 μm	10^{-16} to 10^{-11} M	Yes	\$\$	ND	ND

ND, Not determined.



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Molecular Imaging Modalities and Technologies

Outline of talk

- Introduction to Molecular Imaging
- Brief review of Molecular Imaging modalities and technologies
- **Multi-modality systems**
- Molecular Imaging Contrast Agents
- Summary



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Multi-Modality Imaging: PET/CT

Siemens Biograph PET System Specifications	
Detector diameter	56 cm
Block size	17 cm
Transaxial FOV	51 cm
Radial FOV	17 cm
Number of detector modules	20
Number of PET channels	20,000
CT module diameter	110 cm (100 cm)
Peak photon sensitivity	10%
Resolution at CTFOV	4.4 mm
Average axial resolution	10% of SPECT
Gamma dose reduction	50% PET/CT
Reconstruction algorithms	3D PET/CT, 3D PET/CT, 3D PET/CT

Table 1.

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Table 2.

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Multi-Modality Imaging: PET/CT fused images

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Dual Modality Imaging: SPECT/CT

- SPECT images and CT images acquired sequentially and coregistered

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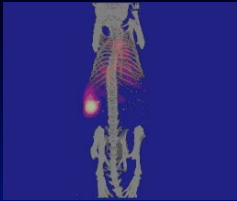
Courtesy of Gamma Medica, Inc.

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Sample CT/SPECT Fused Images

¹¹¹In Herceptin® in Xenograft Tumor Mouse

- 100 uCi of ¹¹¹In tagged Herceptin® injected
- 21 hr. post-injection scan
- 50 uCi detected in animal afterwards
- CT image has been segmented to show skeletal structures
- High uptake in the tumor as well as low uptake in heart and liver are observed.

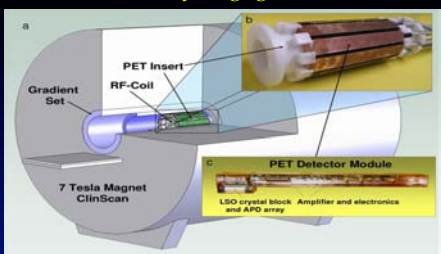


Courtesy of S. P. Williams, Ph.D., Genentech, Inc. and Gamma Medica

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Multi-Modality Imaging: PET/MRI

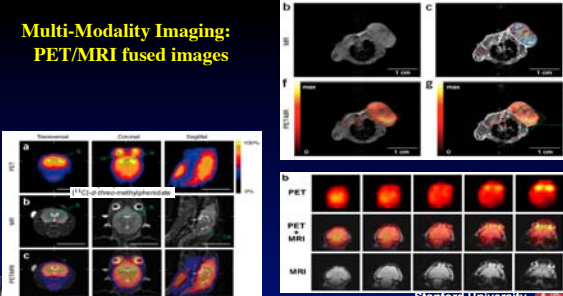


Judenhofer, Nature Medicine, 2008

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Multi-Modality Imaging: PET/MRI fused images



Judenhofer, Nature Medicine, 2008

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Types of Molecular Imaging Contrast Agents

Small Molecule: ^{125}I -FDG (~0.2 kDa)
 Peptide: EGF (~5.5 kDa)
 Aptamer: Molecular Beacon (10 kDa)
 Minibody: Minibody (80 kDa)
 Antibody: Antibody (165 kDa)
 Nanoparticle: SWNT with targeted peptides (~100 nm)

Size (nm) scale: 0 to 1000 nm

Legend: Quencher (green), Donor (red), Fluorophore (orange)

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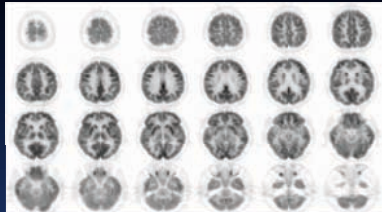
Example Molecular Imaging Contrast Agent: Fluorodeoxyglucose (FDG)

Glucose Transporter
 HKM
 Glycolysis
 ^{125}I -FDG
 ^{125}I -FDG-6- P_0_4


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^{18}F -Fluorodeoxyglucose (FDG)-PET

Neurological disorders



Oncology



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Clinical Translation of Imaging Probes/Techniques



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Summary

- Molecular Imaging is distinguished by being able to measure the fundamental mechanisms of disease on the cellular and molecular level using measurements from outside the body
- Lots of instrumentation research are going on to improve system parameters such as spatial resolution and signal sensitivity
- There is no perfect imaging modality---depends on the basic biology question you are asking
- Multi-modality systems enable multiple parameters to be measured in the same imaging session
- Molecular imaging contrast agents enable amplification of the basic imaging signal. Also an active field of research.