Bioimage Informatics

Lecture 23, Spring 2012

Emerging Applications: Molecular Imaging

Outline

- Overview of molecular imaging
- Molecular imaging modalities
- Molecular imaging applications
- Discussion & future directions

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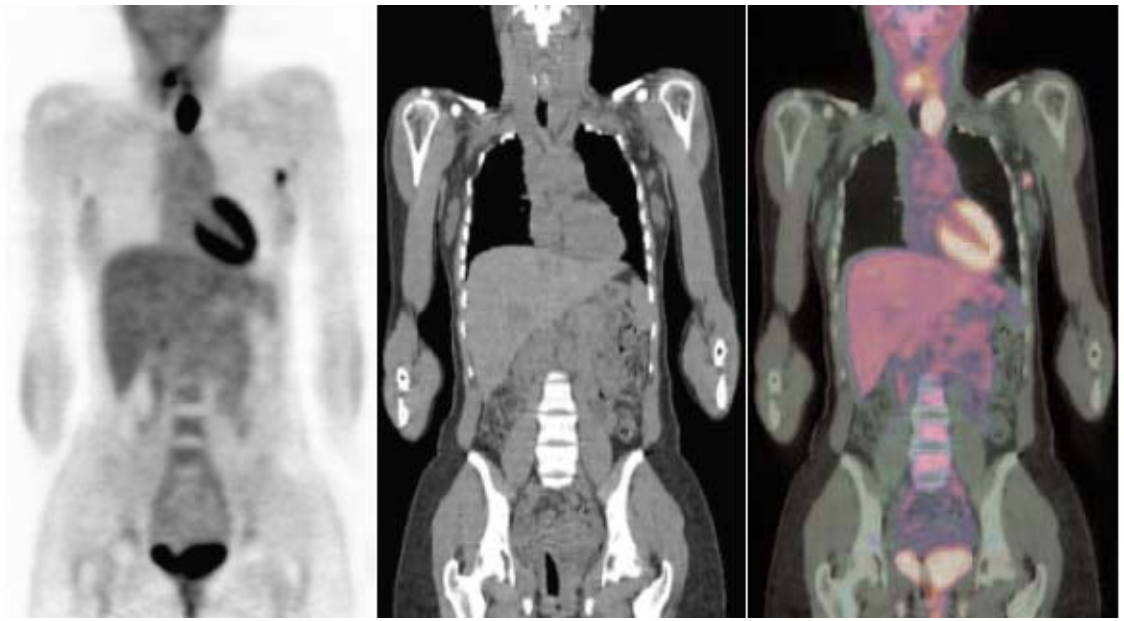
Molecular Imaging: an Example



http://www.medical.siemens.com/siemens/zh_TW/rg_marcom_FBAs/files/brochures/Jan_Grimm_Molecular_Imaging.pdf

- Human or animal models; Imaging with molecular specificity.
  FDG: 18F-fluorodeoxyglucose
- Molecular imaging is a convergence of medical imaging and biological imaging, especially in developing and applying specific molecular probes.
- Molecular imaging focuses on disease applications.

Overview of Molecular Imaging (I)

- Molecular imaging is considered as a new development of radiology. It aims to visualize processes of interest at the cellular and molecular level within living subjects, especially humans.

- Traditionally, medical imaging mainly focuses on morphological, anatomical, and/or physiological changes.

- But it is often too late when these changes become detectable.

- The main driving force of molecular imaging is the radiology community.
    - Early detection
    - Direct monitoring of disease progression
    - Direct monitoring of treatment outcomes

Overview of Molecular Imaging (II)

- Definition 1: Molecular imaging is the in-vivo characterization and measurement of biological processes at the cellular and molecular level.

  R. Weissleder & U. Mahmood, Molecular imaging, *Radiology*, 219:316-333, 2001.

- Definition 2: Molecular imaging techniques directly or indirectly monitor and record the spatiotemporal distribution of molecular or cellular processes for biochemical, biological, diagnostic, or therapeutic applications.

  ML Thakur, BC Lentle, SNM; Radiological Society of North America (RSNA). Joint SNM/RSNA Molecular Imaging Summit Statement. *J. Nucl. Med* 46:11N–13N, 2005.

Overview of Molecular Imaging (III)

- Basic elements of molecular imaging

  - Molecular probes: high-sensitivity, high-specificity.

  - Signal amplification strategy.

    Example 1) DNA→ mRNA → Protein

    Example 2) By accumulation

  - Signal collection strategy→ modality selection.

Overview of Molecular Imaging (IV)

- Molecular imaging modalities
  - PET, SPECT, CT, MRI, Ultrasound, Optical Imaging
  - These modalities are often used in combination with specific molecular tracers.
- Applications
  - Cancer
  - Cardiovascular diseases
  - Neurological disease
- Research in molecular imaging became well publicized in the late 1990s.
- Most of the molecular imaging programs in the US are established after 2005. H. J. Otero et al, Molecular imaging programs in the US, *Academic Radiology*, vol. 14, pp. 125-131, 2007.

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Overview of Different Imaging Modalities (I)

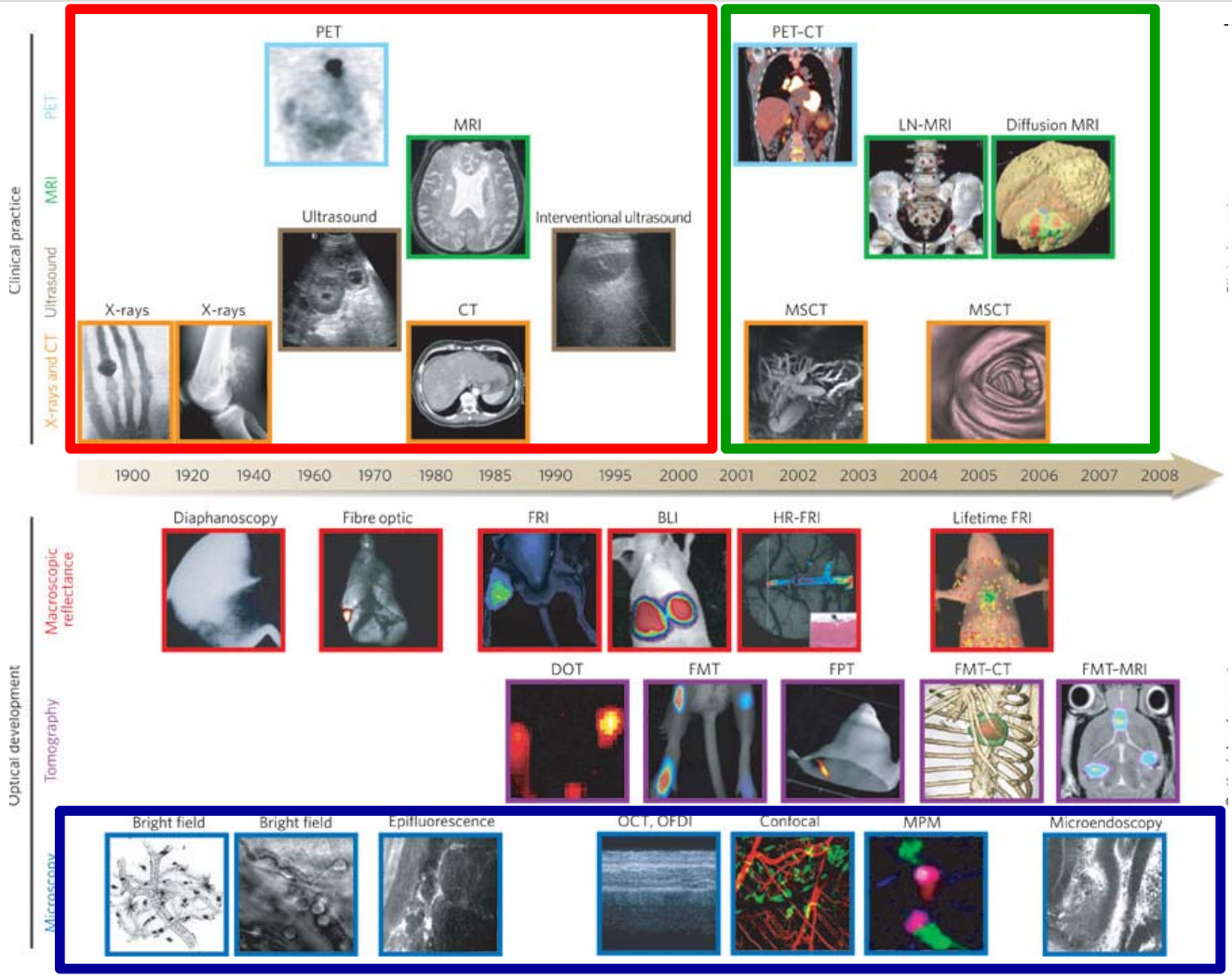
Table 1 | Overview of imaging systems

Technique	Resolution*	Depth	Time†	Quantitative‡	Multi-channel	Imaging agents	Target	Cost*§	Main small-animal use	Clinical use
MRI	10–100 μm	No limit	Minutes to hours	Yes	No	Paramagnetic chelates, magnetic particles	Anatomical, physiological, molecular	$$$	Versatile imaging modality with high soft-tissue contrast	Yes
CT	50 μm	No limit	Minutes	Yes	No	Iodinated molecules	Anatomical, physiological	$$	Imaging lungs and bone	Yes
Ultrasound	50 μm	cm	Seconds to minutes	Yes	No	Microbubbles	Anatomical, physiological	$$	Vascular and interventional imaging‖	Yes
PET	1–2 mm	No limit	Minutes to hours	Yes	No	^{18}F-, ^{64}Cu- or ^{11}C-labelled compounds	Physiological, molecular	$$$	Versatile imaging modality with many tracers	Yes
SPECT	1–2 mm	No limit	Minutes to hours	Yes	No	^{99m}Tc- or ^{111}In-labelled compounds	Physiological, molecular	$$	Imaging labelled antibodies, proteins and peptides	Yes
Fluorescence reflectance imaging	2–3 mm	<1 cm	Seconds to minutes	No	Yes	Photoproteins, fluorochromes	Physiological, molecular	$	Rapid screening of molecular events in surface-based disease	Yes
FMT	1 mm	<10 cm	Minutes to hours	Yes	Yes	Near-infrared fluorochromes	Physiological, molecular	$$	Quantitative imaging of fluorochrome reporters	In development
Bioluminescence imaging	Several mm	cm	Minutes	No	Yes	Luciferins	Molecular	$$	Gene expression, cell and bacterium tracking	No
Intravital microscopy¶	1 μm	<400–800 μm	Seconds to hours	No	Yes	Photoproteins, fluorochromes	Anatomical, physiological, molecular	$$$	All of the above at higher resolutions but limited depths and coverage	In development#

*For high-resolution, small-animal imaging systems. (Clinical imaging systems differ.) †Time for image acquisition. ‡Quantitative here means inherently quantitative. All approaches allow relative quantification. §Cost is based on purchase price of imaging systems in the United States: $, <US$100,000; $$, US$100,000–300,000; $$$, >US$300,000. ‖Interventional means used for interventional procedures such as biopsies or injection of cells under ultrasound guidance. ¶Laser-scanning confocal or multiphoton microscopy. #For microendoscopy and skin imaging. (Table adapted, with permission, from ref. 85.)

R. Weissleder, MJ Pittet, Imaging in the era of molecular oncology, *Nature*. 2008 Apr 3;452(7187):580-9.

Overview of Different Imaging Modalities (II)



R. Weissleder, MJ Pittet, Imaging in the era of molecular oncology, *Nature*. 2008 Apr 3;452(7187):580-9.

Overview of Different Imaging Modalities (III)

Table 1
Attributes of Molecular Imaging Modalities (1,2)

Modality	Sensitivity	Spatial Resolution	Temporal Resolution	Penetration Depth	Cost
SPECT	Medium	Low	Low	High	Medium
PET	High	Low	Low	High	High
MR imaging	Low	High	High	High	High
US	Medium	Medium	High	Medium	Low
Optical imaging	High	Low	High	Low	Low

Wang et al, Molecular imaging: a primer for interventionists and imagers, J. Vasc. Interv. Radiol. 2006, 17:1405-1423.

Penetration Depth of Fluorescence Imaging Techniques

- Widefield fluorescence microscopy (epifluorescence)
  - Several hundred nanometers to a few microns
- Confocal fluorescence microscopy
  - Several hundred nanometers to tens of microns
- Multi-photon microscopy
  - Up to a few hundred microns
- In most cases these techniques are not applicable to imaging deep into tissues and organs.

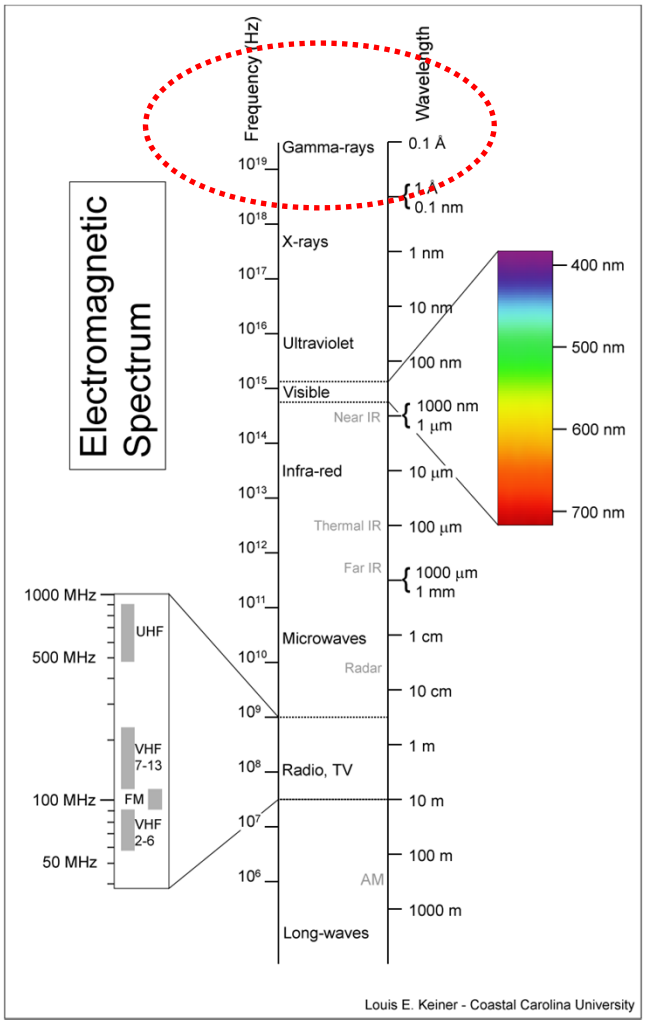
Photon Energy

- Energy of a photon: Planck's law

$$E = h\nu = h\frac{c}{\lambda}$$

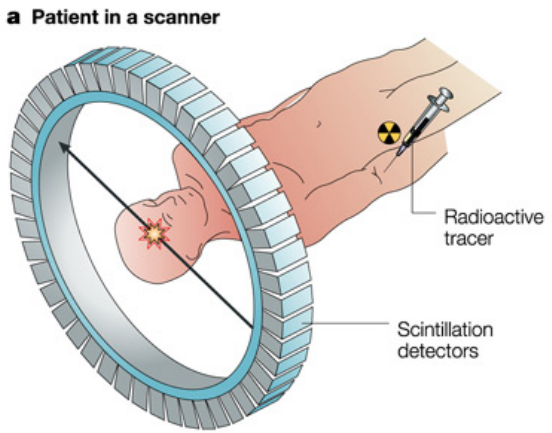
h: Planck's constant; 6.626×10^{-34}J·s
v: frequency of light;
λ: wavelength of light
c: speed of light
energy of a photon =
3.973×10^{-19}J at 500nm

- Shorter waves have higher energy.



Positron Emission Tomography (PET) (I)

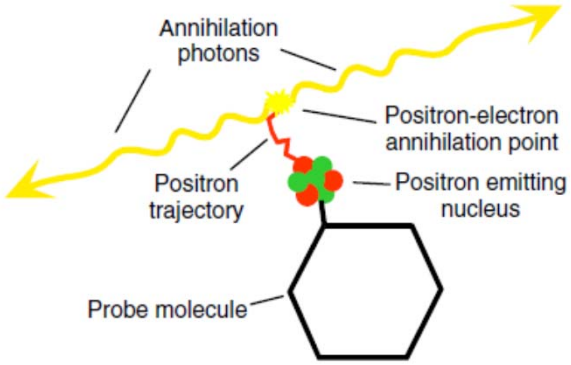
- A 3D/4D nuclear medicine imaging modality that detects positron emissions from short-lived radioactive tracer molecules (e.g. isotopes such as ^{18}F, ^{11}C, ^{13}N, ^{15}O, ^{124}I).
- Injection into blood circulation is often used to incorporate tracer molecules.
- PET has low spatial-temporal resolution and is therefore usually combined with CT.

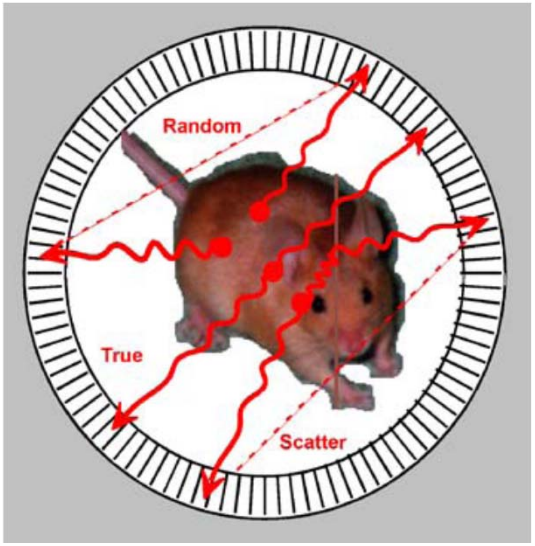


West CM, Jones T, Price P **The potential of positron-emission tomography to study anticancer-drug resistance.** Nat Rev Cancer. 2004 Jun;4(6):457-69.

Positron Emission Tomography (PET) (II)

- A positron has the same mass as an electron but the opposite charge.
- Positron-electron annihilation generates a pair of Gamma-ray photons.
- Hundreds of imaging probes available.
- Probe molecules are located through “true” events whereas “random” and “scatter” events generate background noise.





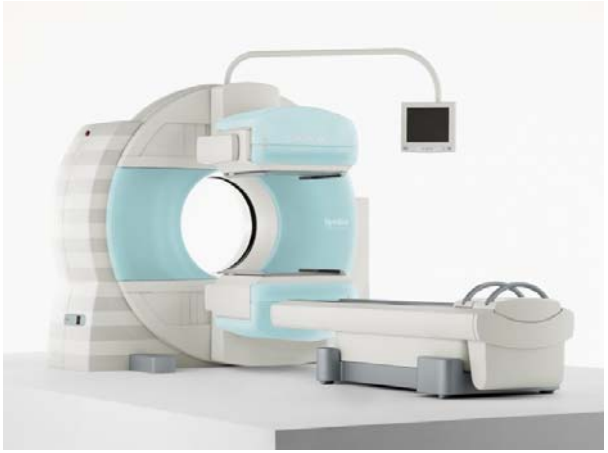
C.S. Levin, Primer on molecular imaging technology, *Eur J Nucl Med Mol Imaging* (2005) 32:S325–S345

Positron Emission Tomography (PET) (III)

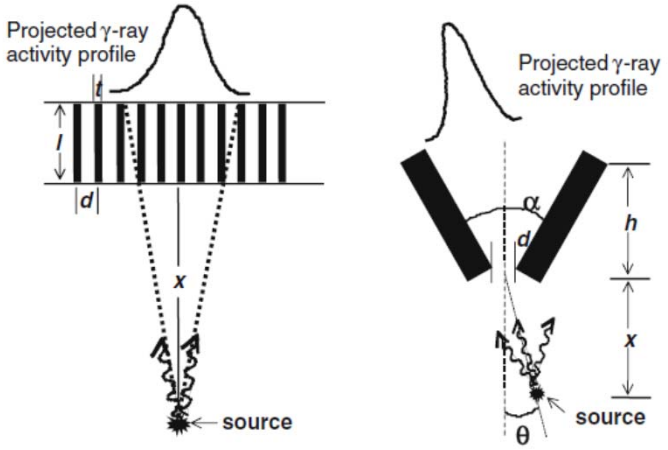
- Short-lived radioactive tracers must be freshly prepared using cyclotron.
  - Carbon-11: ~ 20 minutes
  - Fluorine-18: ~110 minutes
- Any compound that can be conjugated with the tracers can be imaging using PET.
- Resolution: typically on the scale of a few millimeters

Single Photon Emission Computed Tomography (SPECT)

- Similar to PET in the using of gamma rays.
- Comparison with PET.
  - SPECT tracers directly generate gamma rays
  - PET requires positron
- Resolution: slightly lower than PET; at millimeter level.
- Substantially lower cost in comparison to PET because SPECT uses cheaper isotopes.



SPECT from Siemens



C.S. Levin, Primer on molecular imaging technology, *Eur J Nucl Med Mol Imaging* (2005) 32:S325–S345

PET vs SPECT

- Sensitivity
  - PET generally has substantially higher sensitivity.
- Imaging duration
  - SPECT can provide much longer imaging window due to the longer half-life of tracers.
- Temporal resolution
  - PET has intrinsic advantages
- Cost
  - SPECT has substantially lower cost.

Imaging modality	Form of energy used	Spatial resolution (mm)	Acquisition time per frame (s)	Molecular probe mass required (ng)	Molecular sensitivity (mol/l)	Tissue penetration depth (mm)	Mainly small animal or clinical?	Signal quantification capabilities	Cost (equipment and usage)
PET	Annihilation photons	1–4 (animal), 6–10 (clinical)	1–300	1–100	10^{-11} – 10^{-12}	>300	Both	High	High
SPECT	Gamma rays	0.5–5 (animal), 7–15 (clinical)	60–2,000	1–100	10^{-10} – 10^{-11}	>300	Both	Medium–high	Medium–high

A. Rahmim & H. Zaidi, PET versus SPECT: strengths, limitations and challenges, *Nuclear Medicine*, 29:193-207, 2008.

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Applications (I): Cancer Detection in Mouse Models

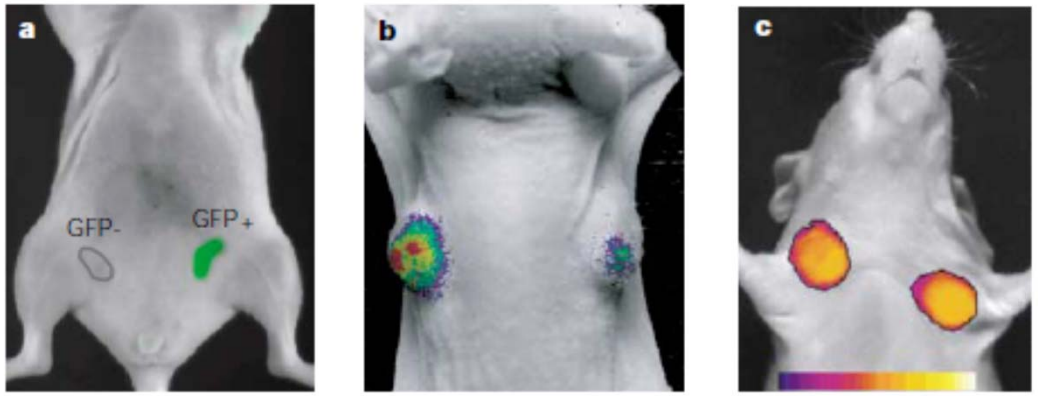
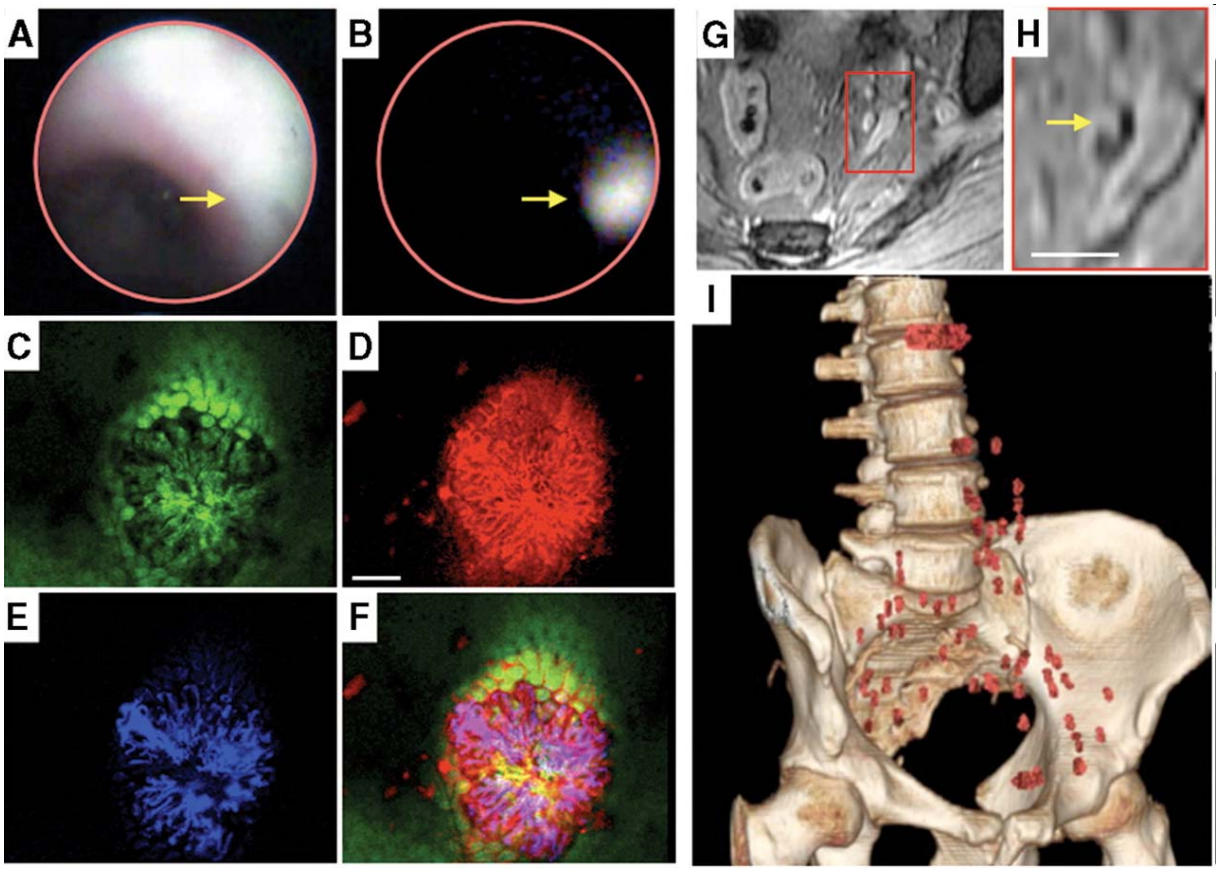


Figure 2 | **Optical imaging.** Fluorescent and bioluminescent signals emanating from superficial structures such as surface-implanted tumours can be imaged with sensitive charge-coupled device cameras. **a** | Fluorescence imaging in the visible light range (400–600 nm) can be used to detect green fluorescent protein (GFP) expressed by the right, but not by the left, tumour. **b** | Bilateral chest tumours expressing transgenic luciferase and imaged with a photon-counting camera after intraperitoneal injection of luciferin. The tumour on the left expresses higher levels of luciferase, indicated by areas of red, yellow and green colouration, than the tumour on the right. **c** | Near-infrared (NIR) fluorescence imaging (700–900 nm) can be used to image deeper tumours than can fluorescence imaging in the visible light range[53]. This example shows matrix metalloproteinase 2 (MMP-2) enzyme levels in bilaterally implanted breast tumours using an NIR fluorescence probe coupled to an MMP-2 substrate[58]. (Image in **a** courtesy of U. Mahmmod, MGH CMIR, Boston, USA; image in **b** courtesy of Y. Saeki and V. Ntziachristos, MGH CMIR, Boston, USA.)

R. Weissleder, Scaling down imaging: molecular mapping of cancer in mice, *Nature Review Cancer*. 2002 2: 1-8.

Applications (II): Cancer Detection in Human



R. Weissleder, Molecular imaging in Cancer, *Science*. 2006 312:1168-1171.

Fig. 1. Molecular imaging used for early detection of cancer in mice and humans. Dysplastic colonic adenoma in $Apc^{Min/-}$ mice imaged by fiberoptic endoscopy (**A** and **B**) and endomicroscopy (**C** to **F**). The 2-mm lesion is not detectable by regular colonoscopy (A) but becomes readily apparent by imaging cathepsin protease activity in the near infrared channel (B). Arrows indicate location of adenoma. [(C) to (F)] show that endomicroscopy of an adenomatous lesion in a living mouse provides cellular resolution of this early lesion (C), cathepsin expression (D) (scale bar, 1 mm), and microvascularity (E). (F) is a merged image. (**G** and **H**) MRI of a human male pelvis showing prostate cancer metastasis. (G) shows an axial MRI of the pelvis. The square highlights a region of nonenlarged lymph nodes and vessels. Magnetic nanoparticles with affinity for lymph node macrophages were administered systemically to detect intranodal metastases. (H) is a magnified region after nanoparticle administration, which shows 1.3-mm micrometastases in a 4 × 7 mm lymph node. Scale bar, 10 mm. Arrow points to micrometastases within dark lymph node. (**I**) Reconstruction of lymph node metastases detected in 34 patients by the above technique. The extensive, unpredictable spread of prostate cancer to these nodes (red) is one of the reasons that imaging in individual patients is so important.

Applications (III): Therapy Response Monitoring

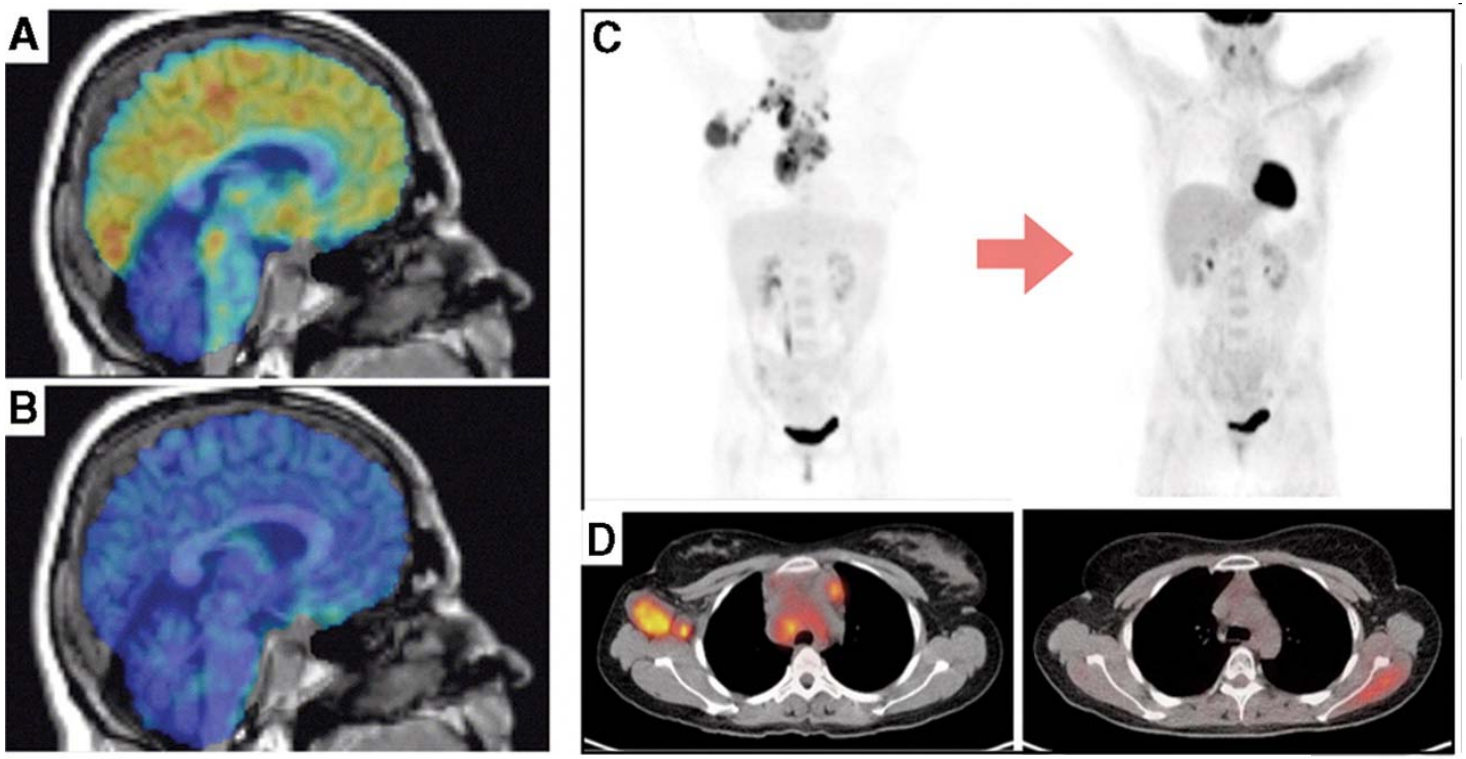


Fig. 2. Molecular imaging used for monitoring of patient response to therapy. (**A**) PET scan of brain substance P (neurokinin-1 receptor) using ^{18}F–substance-P antagonist–receptor quantifier (SPA-RQ) superimposed onto an MRI scan. (**B**) PET scan after receptor blockade with Aprepitant, a neurokinin-1 receptor antagonist. Blue indicates low levels of tracer binding; yellow and orange indicate high levels of tracer binding. The study shown here assessed the efficacy of Aprepitant as a treatment for depression; however, the drug is also used to treat cancer patients for chemotherapy-induced nausea. Panels (A) and (B) are reprinted with permission from (*42*) with permission from the Society of Biological Psychiatry. (**C**) FDG-PET scan of a patient with lymphoma before (left) and after (right) treatment. (**D**) Corresponding axial PET-CT axial sections show a decrease in FDG activity (yellow red) in axilla and mediastinum.

R. Weissleder, Molecular imaging in Cancer, *Science*. 2006 312:1168-1171.

Application (IV): Drug Development

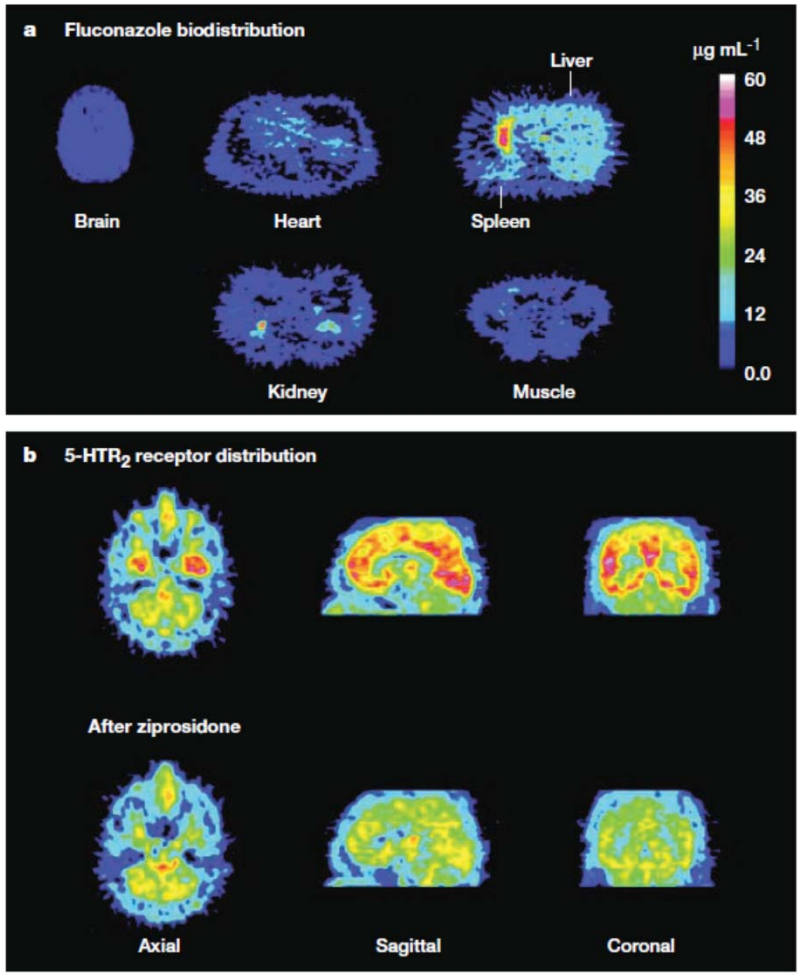


Figure 3 | **Imaging drug pharmacokinetics and pharmacodynamics. a** | Representative positron emission tomography (PET) images of human subjects injected with ^{18}F-fluconazole. Images are displayed with a common colour scale (μg ml^{-1} tissue; reprinted with permission from REF. 35 © (1993) American Society for Microbiology). **b** | Axial, sagittal and coronal images of a healthy volunteer injected with the $5HT_2$ ligand ^{18}F-setoperone to image serotonin ($5HT_2$) receptor occupancy. The top row is before and the bottom row after administration of 40 mg of oral ziprosidone, an antipsychotic agent with high affinity for serotonin and dopamine receptors. Fitting of cortical data was used to determine binding constants and receptor occupancy. Reprinted with permission from REF. 32 © (1996) American Society for Pharmacology and Experimental Therapeutics.

R. Weissleder, Molecular imaging in drug discovery & development, *Nature Review Drug Discovery*. 2003 2: 123-131.

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Discussion & Future Directions

- Molecular imaging is the integration of specific molecular tagging with medical imaging modalities.
- It represents the future of medical imaging.
- A critical challenge is the development of specific molecular tags.
- Computational image analysis plays essential roles in many aspects of molecular imaging.

General References

[1] R. Weissleder & U. Mahmood, Molecular imaging, *Radiology*, 219:316-333, 2001.

[2] R. Weissleder, Molecular imaging in drug discovery & development, *Nature Review Drug Discovery*. 2: 123-131, 2003.

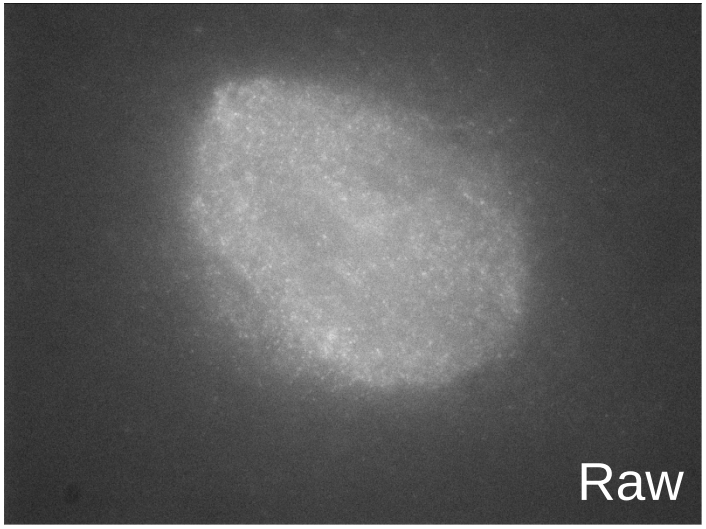
[3] R. Weissleder, Molecular imaging in Cancer, *Science*. 312:1168-1171, 2006.

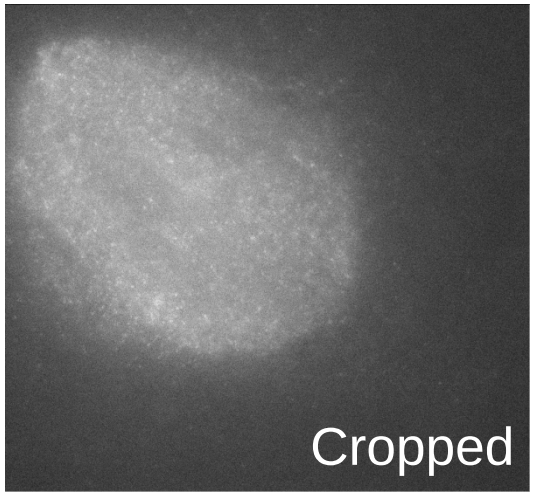
[4] C.S. Levin, Primer on molecular imaging technology, *Eur. J. Nucl. Med. Mol. Imaging*, 32:S325–S345, 2005.

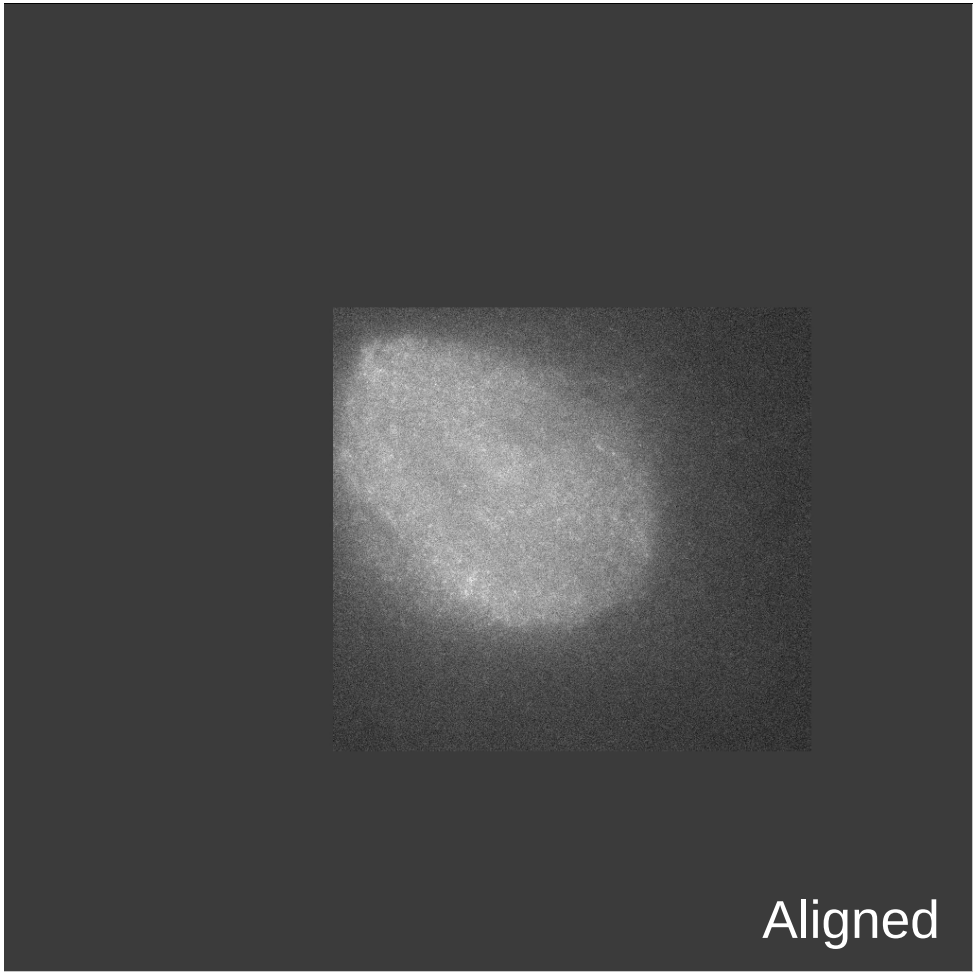
[5] Wang et al, Molecular imaging: a primer for interventionists and imagers, *J. Vasc. Interv. Radiol.* 17:1405-1423, 2006

[6] ML Thakur, BC Lentle, SNM; Radiological Society of North America (RSNA). Joint SNM/RSNA Molecular Imaging Summit Statement. *J. Nucl. Med.* 46:11N–13N 42N, 2005.

Image Alignment Demo #1

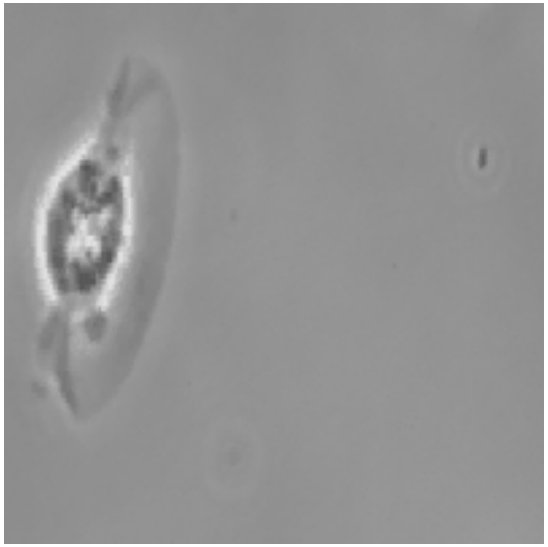






Yang *et al*, *Journal of Cell Biology*, 182:631-639, 2008.

Image Alignment Demo #2



Wilson et al, *Nature*, 465:373-377, 2010.

Questions?