

## Molecular Imaging

This tutorial will define what is currently considered molecular imaging. It will provide history and an overview, discuss the goals and the advantages of molecular imaging. It will clarify what is and is not molecular imaging, and give examples of different imaging case studies. It will also discuss MRI, Optical Imaging, SPECT and PET imaging, and how they relate to molecular imaging.

### **Molecular Imaging: Definition, Overview and Goals**

- Definition as published in Eur J Nucl Med: Molecular imaging has its roots in nuclear medicine and in many ways is a direct extension of this discipline. Nuclear Medicine has always focused on patient management through the use of injected radiolabeled tracers in conjunction with imaging technology.
- Definition as published in Genes & Dev: Molecular imaging is the visual representation, characterization, and quantification of biological processes at the cellular and subcellular levels within intact living organisms. The images obtained reflect cellular and molecular pathways and *in vivo* mechanisms of disease present within the natural physiological environment.
- Definition according to the American College of Radiology: Molecular imaging is the spatially localized and/or temporally resolved sensing of molecular and cellular processes *in vivo*.

## Overview of Molecular Imaging

- Development of the first microscope in the late sixteenth century led to a keen interest in observations of structure of tissues and organs. This interest in organ structure and function has driven advances in biology ever since.
- Molecular imaging originated from the field of radiopharmacology due to the need to better understand the fundamental molecular pathways inside organisms in a noninvasive manner. Molecular imaging unites molecular biology and in vivo imaging and enables the visualization of cellular function and the follow-up of the molecular process in living organisms without perturbing them.
- Molecular Imaging is multidisciplinary and involves utilization of a variety of imaging techniques. One must have an in-depth knowledge of cellular and molecular biology, chemistry and radiochemistry, pharmacology, physiology and medicine, medical physics, mathematics, computer science, and related topics. It extends observations in living subjects to a more meaningful dimension.
- There are very few studies performed in Nuclear Medicine which are not examples of molecular imaging. The underlying principles of molecular imaging have been extended to other imaging modalities such as optical imaging and magnetic resonance imaging (MRI). Molecular imaging probes can now also be developed by taking advantage of the rapidly increasing knowledge of available cellular/molecular targets.
- Molecular imaging has evolved very rapidly since 1995 through the integration of cell biology, molecular biology and diagnostic imaging. The present rapid pace of advancements in biotechnology and functional genomics is resulting in parallel progress in molecular imaging innovations and applications. The development, validation, and application of these novel imaging techniques in living subjects should further enhance our understanding of disease mechanisms and go hand in hand with the development of molecular medicine.

## **Molecular Imaging: Goals**

- to develop noninvasive in vivo imaging methods that reflect specific cellular and molecular processes, for example, gene expression, or more complex molecular interactions such as protein–protein interactions
- to monitor multiple molecular events near-simultaneously
- to follow trafficking and targeting of cells
- to optimize drug and gene therapy
- to image drug effects at a molecular and cellular level
- to assess disease progression at a molecular pathological level; and
- to create the possibility of achieving all of the above goals of imaging in a rapid, reproducible, and quantitative manner, resulting in the ability to monitor time-dependent experimental, developmental, environmental, and therapeutic influences on gene products in the same animal or patient.

## **MOLECULAR IMAGING: Advantages and Examples**

### **ADVANTAGES: Molecular Imaging**

- Molecular imaging studies permit the evaluation of biological pathways.
- Molecular imaging permits both the temporal and the spatial biodistribution of a molecular probe and related biological processes to be determined in a more meaningful manner throughout an intact living subject.
- it eliminates the need to kill small animals as part of their phenotype determination
- by repetitive imaging it is possible to investigate mutants that are otherwise difficult to interpret with data taken at a single time point
- it allows concomitant visual and analytical biological phenotyping of animals; and
- it allows the researcher to exercise options of multiple imaging strategies (e.g., by using different imaging probes or modalities)

## Which are/are not examples of molecular imaging?

Tc-MAA for pulmonary perfusion studies

Tc-RBCs for Blood Pool Imaging

Tc-MDP for Bone Scan

Tc-Mebrofenin for Hepatobiliary Scan

Tc-Sulfur Colloid for Live Scan

I-123 mIBG for Neuroendocrine Tumor Imaging

Rb-82 Ion for Myocardial Perfusion Study

I-131 NaI for Therapy of Hyperthyroidism

Y-90 Zevalin for Therapy of NHL

In-111 Octreoscan for Imaging Carcinoid

## Red shows the ones that qualify as examples of Molecular Imaging

- Tc-MAA for pulmonary perfusion studies
- Tc-RBCs for Blood Pool Imaging
- **Tc-MDP for Bone Scan**
- **Tc-Mebrofenin for Hepatobiliary Scan**
- Tc-Sulfur Colloid for Live Scan
- **I-123 mIBG for Neuroendocrine Tumor Imaging**
- **Rb-82 Ion for Myocardial Perfusion Study**
- **I-131 NaI for Therapy of Hyperthyroidism**
- **I-131 Bexxar for Therapy of NHL**
- **In-111 Octreoscan for Imaging Carcinoid**

## **How Do You Know That Tc-MAA for pulmonary perfusion studies, Tc-RBCs for Blood Pool Imaging, and Tc-Sulfur Colloid for Live Scan Are NOT Examples of Molecular Imaging?**

When one uses Tc-MAA for pulmonary perfusion studies, the chemical formula of the molecule is irrelevant. Any compound in the physical form of macroaggregates (large particles in the range of 10 – 90  $\mu\text{m}$ ) will occlude capillaries (example: Tc-macroaggregates of oatmeal). We are therefore not working on a molecular level with a mechanism of localization that requires a particular molecule for a particular receptor site, but rather one that requires a particular particle size range.

Similar to the use of Tc-MAA for lung imaging, when one injects Tc-SC for RES imaging studies, the chemical formula of the molecule is irrelevant. Any compound in the physical form of microaggregates (small particles in the range of 0.1 – 2.0  $\mu\text{m}$ ) will be phagocytized by Kupffer cells in the reticuloendothelial system (example: Tc-microaggregated human serum albumin). As before, we are not working on a molecular level with a mechanism of localization that requires a particular molecule for a particular receptor site, but rather one that requires a particular particle size range.

The use of Tc- RBC for visualization of the blood pool is technically not molecular imaging because RBCs are not molecules, but rather cells. While one could make the argument that we are forming the molecule Tc-hemoglobin within the red cells, thereby radiolabeling a part of the body, the imaging was not performed following the injection of the molecule Tc-hemoglobin.

### **Functional Studies:**

The Bottom Line: Uptake, distribution, and clearance of a radioactive drug are based upon organ function rather than tissue density. Working on a molecular level results in earlier detection of certain diseases than with other imaging modalities.

### **Examples of Earlier Detection of Disease**

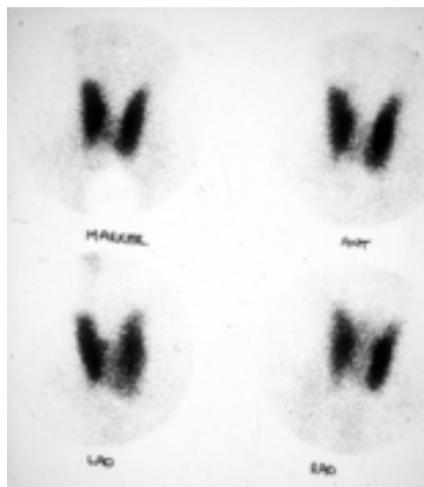
- Bone scan detects metastases earlier than X-rays: more sensitive, but less specific
- I-123 mIBG detects pheochromocytoma metastatic to lymph nodes that cannot be visualized on a CT scan

## EXAMPLES: Molecular Imaging

Imaging of neuroendocrine tumors with I-123 mIBG identifies lymph nodes containing metastatic pheochromocytoma long before they appear on CT scans. This patient had only 1 tumor (arrow) evident on a CT scan.

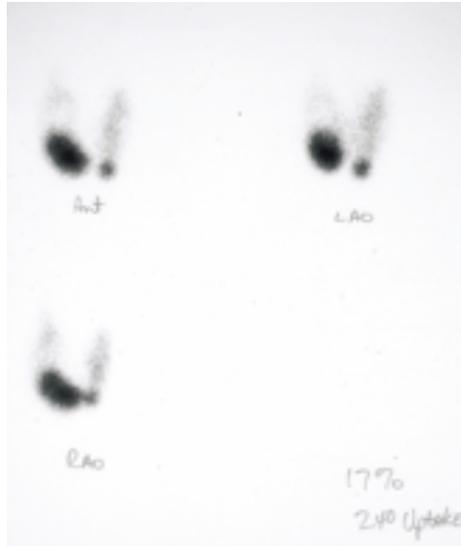


Imaging of hyperthyroidism (Graves' disease) using I-123 NaI.  
Note uniformity of uptake with no hot spots or cold spots

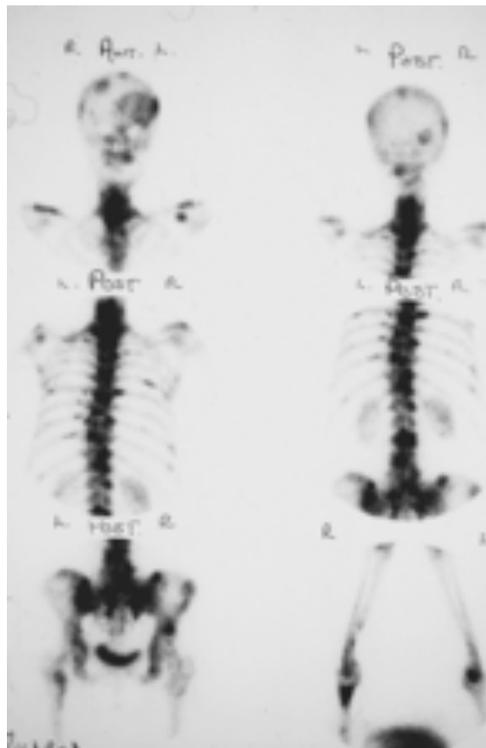


## Imaging of hot nodules using I-123 NaI.

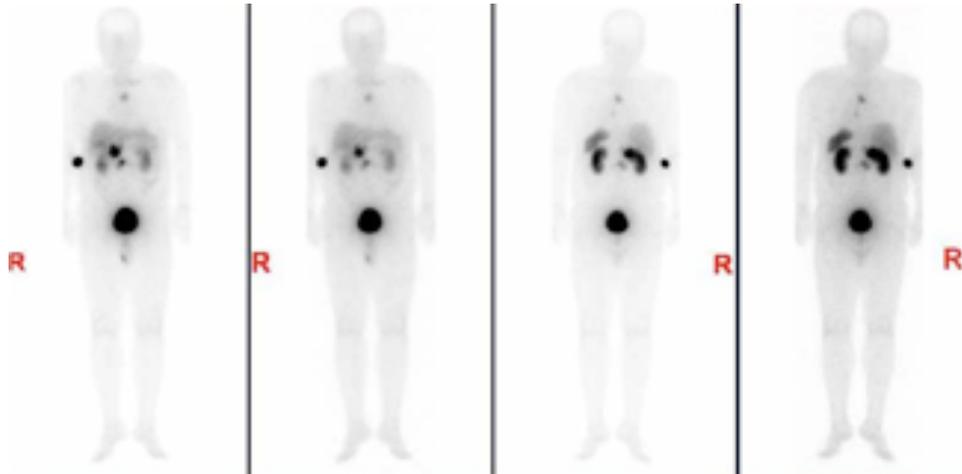
Note suppression of uptake in the remainder of the thyroid gland.



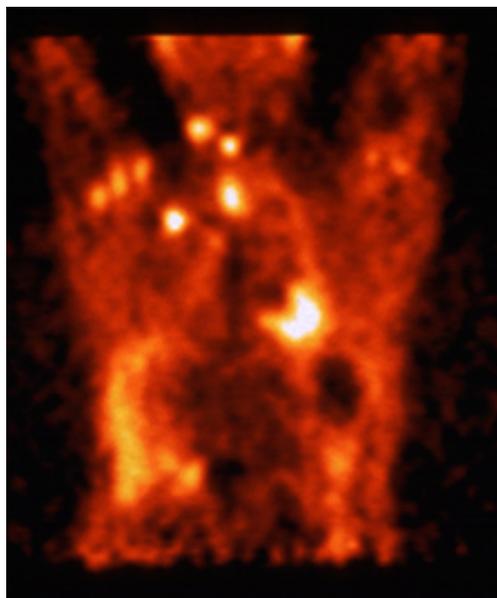
Skeletal imaging with Tc-99m MDP or another labeled phosphate analog provides planar and/or tomographic images of bony metastases months or years before they can be identified by any other imaging modality. It traces phosphate uptake by hydroxyapatite molecules in bone tissue.



In-111 Octreoscan Study positive for liver metastases. The tumor has somatostatin receptor sites which readily take up this somatostatin analog.



Following injection of F-18 FDG, a sugar analog, a PET scan can reveal the presence of breast cancer cells in specific areas of the body, in particular, lymph nodes that have not yet changed size or shape. These tumors are frequently missed by other imaging modalities since molecular changes predate structural changes. This is a breast cancer patient with a normal CT scan.



Prostate Cancer imaging with In-111 ProstaScint involves a radiolabeled antibody specific for a tumor membrane surface antigen on prostate cancer cells. The resulting antigen-antibody complex is precipitated at the tumor site and permits external detection of both primary and metastatic disease. Although disliked by patients, this is considered to be the best diagnostic procedure available for detecting recurrent prostate cancer. This is a Whole Body ProstaScint Scan of a Patient with Rising PSA while undergoing Hormonal Therapy. ProstaScint activity in a left supraclavicular lymph node and in many central abdominal lymph nodes (arrows) indicates a high likelihood of metastatic disease and hormone resistant.



Bone Imaging with F-18 NaF provides excellent quality images of bony metastases by tracing the absorption of fluoride ion by bone tissue, with preferential uptake in metastases. F-18 NaF PET scans have improved anatomic detail compared with conventional gamma camera systems, with higher accuracy in detecting both osteolytic and osteoblastic metastases. They have a greater differentiation rate of benign versus malignant lesions and improved ability to identify the extent of bone metastases.



## Overview of Molecular Imaging

- Advancements in this field are applicable to the diagnosis of oncologic, endocrine, neurological and cardiovascular diseases. This technique also improves treatment options of certain diseases by optimizing the testing of chemotherapeutics and other medications..
  - Molecular imaging is expected to have a major economic impact due to earlier and more precise diagnosis. For example, a PET scan saves the patient or his insurance company thousands of dollars by eliminating unnecessary biopsies and surgeries.
- ### Molecular and functional Imaging
- Molecular imaging differs from traditional radiographic imaging, which focuses on anatomy; molecular imaging literally operates at the molecular level and therefore permits evaluation of metabolic pathways. The radiotracers injected into patients produce images reflective of molecular changes within an internal organ. This is very different than imaging based on the density of bone, muscle, and fat.
  - Molecular imaging permits early detection and treatment of disease and basic pharmaceutical development. Furthermore, molecular imaging permits quantitative evaluation of uptake in an internal organ or tumor.
  - Molecular imaging may help to identify a disease before there are symptoms.
  - There are many different modalities that can be used for noninvasive molecular imaging. Each has its different strengths and weaknesses and some are more adept at imaging multiple targets than others.



## MOLECULAR IMAGING: Imaging Modalities

### Magnetic resonance imaging (MRI)

- Advantage: very high spatial resolution and is very adept at morphological imaging and functional imaging.
- Disadvantage: MRI has a sensitivity of around  $10^{-3}$  mol/L to  $10^{-5}$  mol/L which, compared to other types of imaging, can be very limiting. This problem stems from the fact that the difference between number of atoms in the high energy state and the low energy state is very small. For example, at 1.5 Tesla, the difference between high and low energy states is approximately 9 molecules per 2 million. Efforts are underway to increase MR sensitivity.

### Optical imaging

- There are a number of approaches used for optical imaging. The various methods depend upon fluorescence, bioluminescence, absorption or reflectance as the source of contrast. Unlike radioactive tracers, optical imaging does not have safety issues to consider.
- The downside of optical imaging is the lack of penetration depth, especially when working at visible wavelengths. Depth of penetration is related to the absorption and scattering of light, which is primarily a function of the wavelength of the excitation source.
- Fluorescent probes and labels are an important tool for optical imaging. Several studies have demonstrated the use of infrared dye-labeled probes in optical imaging.

### Single photon emission computed tomography (SPECT)

- The main purpose of SPECT when used in brain imaging is to measure the regional cerebral blood flow (rCBF). The development of computed tomography in the 1970s allowed mapping of the distribution of the radioisotopes in the brain, and led to the technique now called SPECT.
- The imaging agent used in SPECT emits non-coincident gamma rays, as opposed to the coincident gamma rays associated with positron emitters (such as F-18) used in PET. There are a range of radiotracers (such as Tc-99m, In-111, I-123, Tl-201) that can be used in SPECT, depending on the specific application.
- Xenon (Xe-133) gas is one such radiotracer. It has been shown to be valuable for diagnostic inhalation studies for the evaluation of pulmonary function and may also be used to assess rCBF.

### Positron emission tomography (PET)

- PET imaging employs positron emitting isotope. These positrons annihilate nearby electrons, emitting two 511 keV photons at an angle of 180 degrees to each other. These photons are then detected by the scanner based on coincident collisions in the detector.
- PET radioisotopes include C-11, N-13, O-15, F-18, Cu-64, Cu-62, I-124, Br-76, Rb-82 and Ga-68. F-18 FDG is the most used PET Radiopharmaceutical worldwide. One of the major disadvantages of PET is that the radiotracers must be made with a cyclotron. Since each of these radionuclides typically has a half life measured in minutes or hours, the cyclotron has to be in very close proximity to

the imaging facility. This significantly increases the cost of PET radionuclides, compared to that of Tc99m, which is generator-produced.

- PET imaging does have many advantages though, since it often detects disease missed by other modalities. In addition, it operates at molar concentrations as low as picomolar.



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