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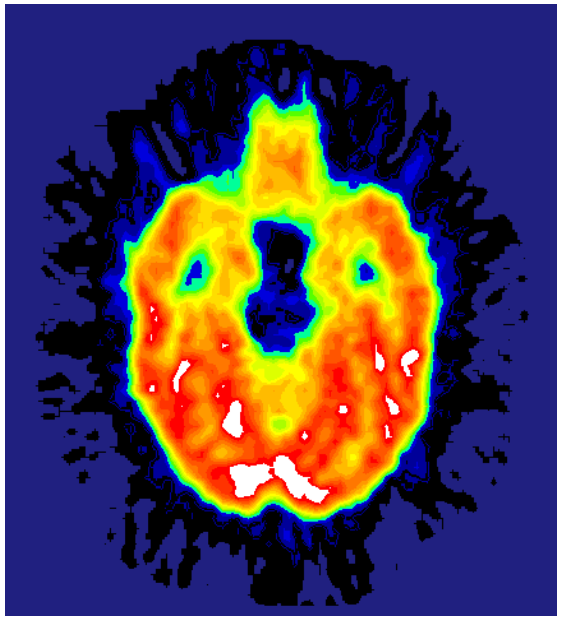
MARKET FORESIGHTING

Molecular imaging

March 2006



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Why is ITI Life Sciences Interested in Molecular Imaging?

ITI's mission is to be a catalyst for growth and sustainability of the Life Science Industry in Scotland.

ITI Life Science conducts foresighting to identify commercially attractive areas that can be exploited through technical innovation and the generation of protectable intellectual assets.

ITI's previously released environmental scan on the medtech sector identified molecular imaging as a key area for innovation with significant market opportunities.

This report is one of a series of foresighting documents (stem cells, biomarkers, cell-based assays, nanotechnology, liquid biofuels and next generation mab technologies) that help ITI define and prioritise strategic funding in order to best meet the ITI Mission.

Initial findings

Initial findings (1)

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Focus on Functionality

Molecular imaging represents a paradigm shift in the focus of medical imaging from the visualisation of anatomy and physiology to the study of metabolic and physiological processes, often in real time.

While current imaging modalities have been in development since the 1970s, incremental technical improvements alongside the more recent innovations in molecular medicine, and a move towards personalised medicine have placed molecular imaging centre stage.

The development and application of multiple imaging modalities in tandem, has been a key driver in addressing the limitations of stand alone imaging technologies.

The Application of Molecular Imaging as a Diagnostic Tool is Immense

Whilst molecular imaging can simply complement existing diagnostics its real potential is in its ability to detect disease where previously there was no way of achieving this (e.g. Alzheimer's) or to allow for an earlier diagnosis (tumour infancy or vulnerable plaque). Molecular imaging is also being used to better evaluate treatment response particularly in cancer therapy.

Initial findings (2)

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Molecular Imaging Fits with the Drive to Streamline Preclinical R&D

From an R&D perspective, molecular imaging is helping pharmaceutical and biotech companies gather the information they need to make cost saving decisions earlier.

Moreover, as for the clinical diagnostic setting, molecular imaging can be used to evaluate the impact of a compound on disease, and for example to study the underlying cause of drug resistance.

Molecular imaging is one of the key tools underpinning the drive towards translational research. Molecular imaging protocols can be incorporated within animal studies and exploratory human studies to secure proof of concept for a target or compound and to assist further optimisation.

A Number of Challenges Remain

There are a lack of commercially available imaging agents largely due to a poorly defined and onerous regulatory path. Consequently the costs of developing new tracers far outweighs the returns dissuading companies from investing in tracer development. However, new collaborative business models designed to mitigate against these issues are emerging typified by GE's deals with Lilly and Roche.

Initial findings (3)

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Significant financial commitment limits participation to firms with large pockets. The market is dominated by a handful of multinationals which arguably dissuades new entrants.

Reimbursement continues to be a major obstacle. The application of imaging more broadly requires robust data demonstrating the clinical and cost benefits of applying the technology to different conditions.

Molecular Imaging is an Attractive Area for ITI Life Sciences

Molecular imaging is particularly attractive to ITI as it presents the opportunity to commercialise valuable know how and tools currently resident to a large extent within academia.

While Scotland has the necessary building blocks (infrastructure, skills and know-how) to exploit molecular imaging, Scotland lacks appropriate commercial vehicles at present.

ITI believes that the preclinical animal market is an exciting near-term opportunity which circumvents some of the regulatory and cost hurdles previously outlined. Moreover, the use of discarded compounds for which safety data exists may help to reduce the cost of developing tracers.

INTRODUCTION:
WHAT IS MOLECULAR IMAGING?

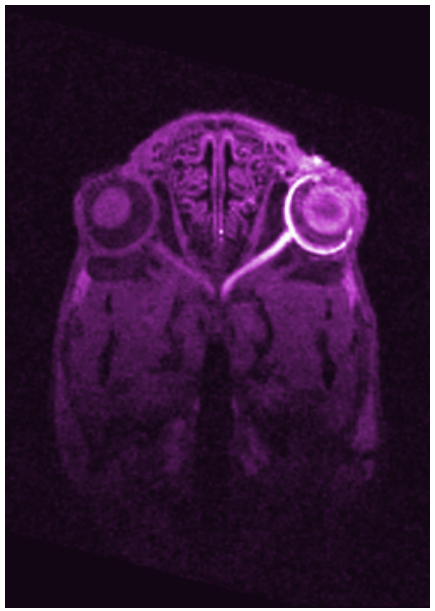
Defining Molecular Imaging

Molecular imaging is an interdisciplinary field focused on the non invasive measurement and characterisation of biological, cellular, and molecular processes as they occur in living organisms.

Molecular imaging encompasses a range of technologies that will converge and align with clinical radiology practise and drug R&D over the coming years as molecular medicine develops. Much of the innovation has stemmed from applying the technologies to oncology, CNS and cardiovascular disease. However, this does not preclude the use of molecular imaging modalities in other areas such as stem cell tracking, drug delivery and other disease states.

The term “molecular imaging” currently incorporates a range of applications including:

- Imaging of specific molecules present in a living system.
- The use of externally added targeted or activatable reporter agents to sense specific molecular targets or cellular processes.
- Application of labelled or natural substrates to observe specific pathways.
- The introduction of genes which can be detected when expressed in the cell.



Manganese Enhanced MRI of the Optic Visual Pathway and Optic Nerve Injury in Adult Rats.

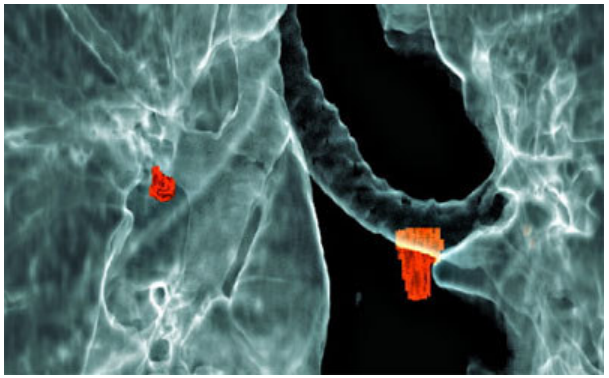
Molecular Imaging is Impacting Now

Regardless of modality, the underlying concept is based on the nuclear medicine tracer principle developed by George de Hevesy. He was awarded the 1943 Nobel Prize in chemistry for discovering that molecules labeled with a radioisotope can be followed as they pass through an organism or as they contribute to complex biochemical processes.

Molecular imaging represents a paradigmic shift in the focus of medical imaging from anatomy and physiology to the study of metabolic and physiological processes, often in real time.

Identifying early markers of therapeutic success is key from a diagnostic and drug development perspective. Early identification of disease provides the opportunity for early intervention to improve clinical outcomes and cost of therapy. Large pharmaceutical companies are now using molecular imaging technology to inform earlier decision making which can increase efficiency and reduce costs.

From a drug delivery perspective, because the cellular processes imaged by the probes are often the same processes that a therapeutic can target, a diagnostic imaging agent could be equipped to deliver a therapeutic compound directly to a diseased site.



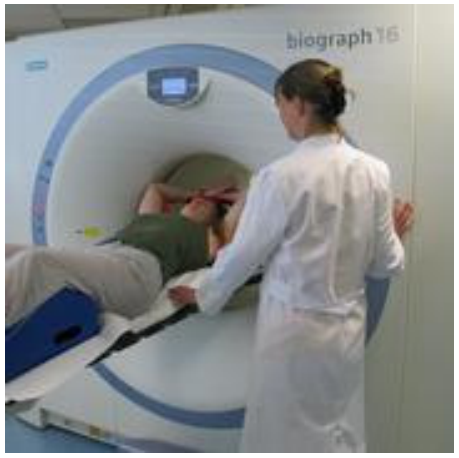
Orange areas of a PET/CT image indicate the uptake of ^{18}F-fluoro-2-deoxy-D-glucose in a primary cancer lesion and a lymph node.

Current Imaging Modalities

The rapid advancement of molecular imaging is partly due to new technology, but also stems from a re-packaging of long-established methods. The field of molecular imaging is still at a relatively early stage of the technology curve based on its potential applications.

So far, the bulk of clinical imaging is performed using a relatively small number of stand alone modalities including:

- Computed Tomography (CT)
- Magnetic Resonance Imaging (MRI)
- Positron Emission Tomography (PET)
- Single Positron Emission Computed Tomography (SPECT)
- Optical imaging



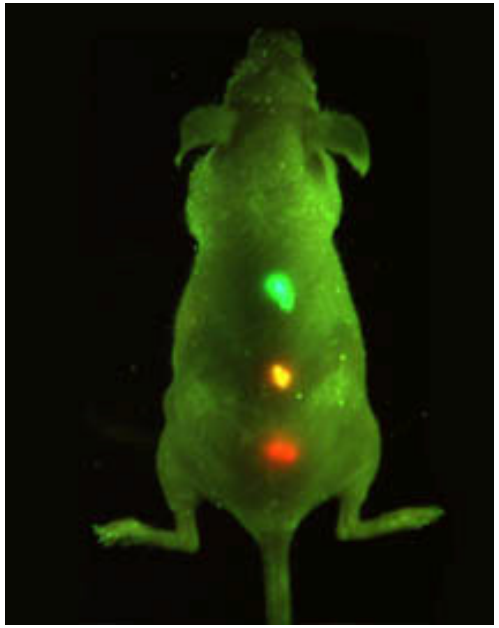
A dual PET/CT scanner.

As a rapidly evolving area, combinations of modalities or fusion approaches such as PET/CT have been adapted for use and are now commercially available.

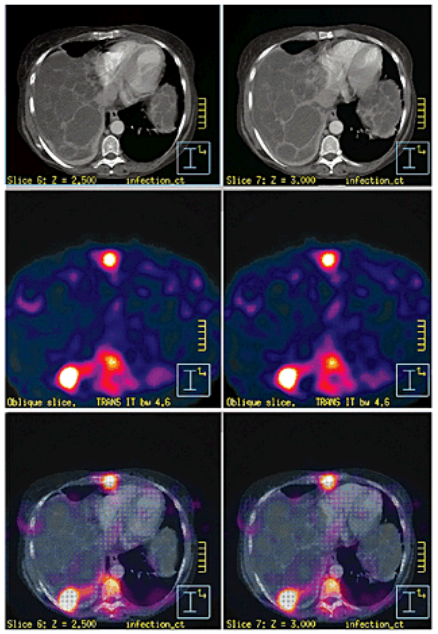
Over time, visualisation at the molecular level will become possible. Since over 75% of the drugs on the market today target membrane-bound proteins, *in situ* visualisation on a cellular level will bring significant improvements to conventional proteomics analysis though identifying protein networks crucial in biological processes.

Within healthcare, molecular imaging has two main applications:

R&D tool

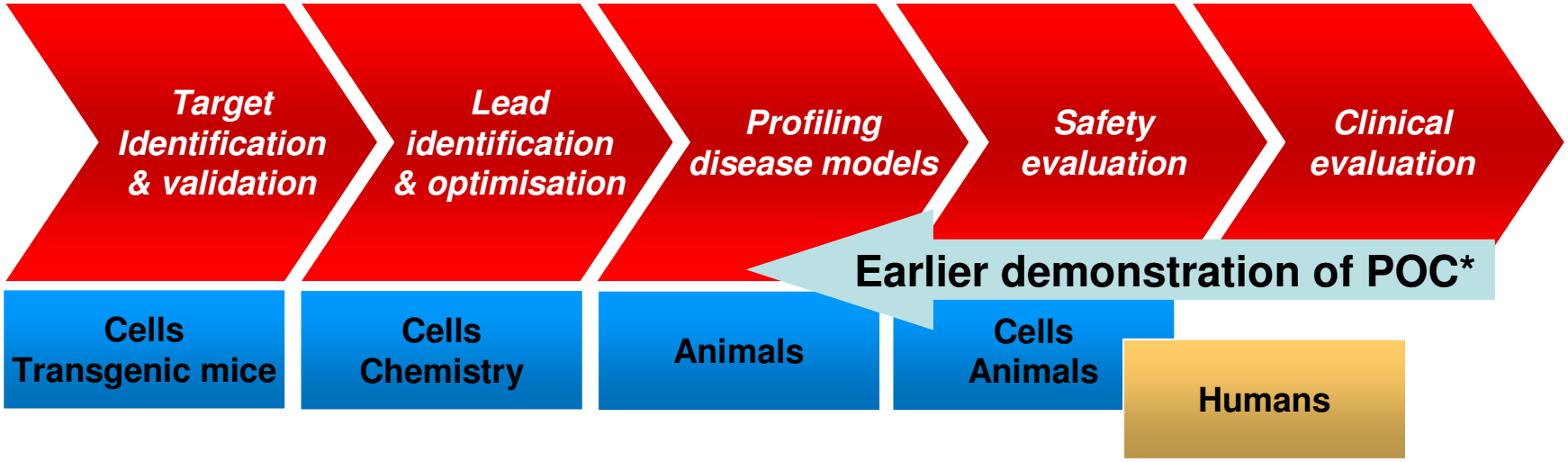


Clinical diagnosis



R&D Tool: Molecular Imaging can Help Deliver Cost Savings in Preclinical Testing

It typically takes 12-15 years to bring a drug to the market at a cost in excess of $1 billion. 80% of these costs are spent on clinical trials and development. Only around 10% of compounds tested in costly clinical trials eventually become a new drug.



Molecular imaging can help shift costs upstream or reduce time lines resulting in significant R&D cost savings.

According to the FDA, even a small improvement in the ability to predict failures could save $100 million in development costs per drug. Despite the significant additional costs to an R&D project in the region of $5000 per PET scan (for example) this is trivial if it allows a company to avoid an unsuccessful multimillion dollar clinical trial later.

*POC: Proof of concept.

…and Provide Early Evidence of Efficacy

Looking for early evidence that imatinib mesylate (*Gleevec/Glivec*) was effective in patients with inoperable gastrointestinal stromal tumours (GIST), Novartis used PET imaging to visualize changes in the tumour.

In a Phase I study a correlation was observed between metabolic changes exhibited within the tumour (probed using FDG) and subsequent alterations in the anatomical structure of the tumour, which became apparent only months after treatment. Furthermore, patients whose tumours didn't exhibit a metabolic change ultimately didn't respond to the drug.

Results suggested that Novartis could use molecular imaging to get a faster determination of *Gleevec*'s benefits, within days or even hours and possibly even to select which patients would be most likely to respond to therapy.

Such applications of molecular imaging are expected to become more widespread, as evidenced by the FDA's Critical Path initiative and outlined on the following slides.

It's All in the Application

Importantly, molecular imaging lets drug developers and researchers study a disease in its native microenvironment. The key is choosing the right application or more importantly, the right combination of applications based on a range of critical factors including:

- Cost
- Time
- Spatial resolution
- Sensitivity
- Depth probing ability
- Quantification potential
- Knowledge/familiarity of practitioners with the modality

Many tools have not been commercially available or robust enough for the pharmaceutical industry in the past 5 years, but molecular imaging is now more commonly used to assist preclinical decision making.

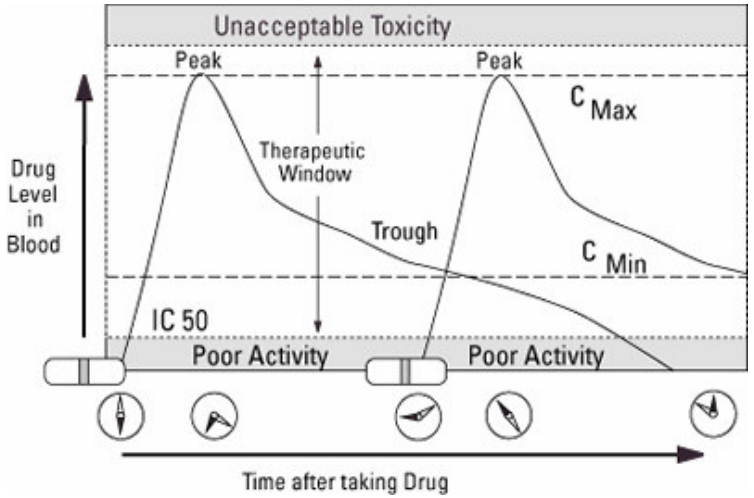
Imaging can provide proof that compounds are hitting the right receptor, and if indeed the receptor is the right target in the first place, at the right dose. In this regard, molecular imaging is becoming a key part of many commercial due diligence exercises.

From a clinical perspective, the correlation of image results with clinical experience remains one of the main challenges going forward.

Molecular Imaging Impacts on Regulation and Future Costs of Therapy

Ultimately molecular imaging approaches may serve as surrogate markers in predicting which treatments individual patients are most responsive to, which fits elegantly with the drive for a more personalised approach to medicine.
From a regulatory perspective, molecular imaging of markers sits well with the FDA's long-standing interest in use of pharmacokinetic (PK) and pharmacodynamic (PD) principles for regulatory decision-making.

Molecular tags could be located through molecular imaging to analyse PK or PD directly at level of drug target, rather than indirectly via plasma concentrations and/or downstream effect indicators.



The ups and downs of a therapeutic window as observed using standard PK data.

Paradoxically, disease-specific targeted agents are likely to be less profitable due to greater market segmentation creating greater risk to developers. Moreover, development costs may be as high as therapeutic agents but revenues are limited by the lower frequency of performed procedures and lower margins compared with therapeutics. This has resulted in an under investment in the pipeline of molecular tracers, slowing the progress of molecular imaging.

Molecular Imaging is Seen as a Key Driver Addressing Poor Productivity

The list of promising biomarkers in need of qualification is long, especially in oncology. The potential for molecular imaging approaches to serve as surrogate markers requires a new regulatory approach by stakeholders to give clarity on the framework and standards required for R&D.

In March 2004, the FDA released a report addressing the recent slowdown in innovative medical therapies submitted to the FDA for approval, titled *Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products*. The report describes the urgent need to modernize and streamline the medical product development process (www.fda.gov/oc/initiatives/criticalpath/).

Through this Initiative, the FDA identified Critical Path Opportunities that include molecular imaging as a way to improve the accuracy of the tests used to predict the safety and efficacy.

The Critical Path Report and Opportunities List

The purpose of the Opportunities List (March, 2006) is to provide concrete focus for public and private efforts and investments in new tools that could revolutionize product development by 2010, and to encourage others to undertake such work in their areas of interest.

The FDA has recognised the potential of molecular imaging by giving guidance to what it recognises as key issues for implementation including:

- Performance standards for imaging displays. Common criteria is needed to assess the performance of multi-dimensional modalities to enhance the understanding and confidence in imaging results through dynamic volumetric image sets.

- Use of imaging as a product development tool. A lack of standard protocols makes it difficult to compare imaging results across trials, and even within an individual trial. Additionally, it is difficult to compile data needed to demonstrate correlation with clinical course which is key for biomarker discovery, particularly for a wide array of conditions.

MARKET DYNAMICS

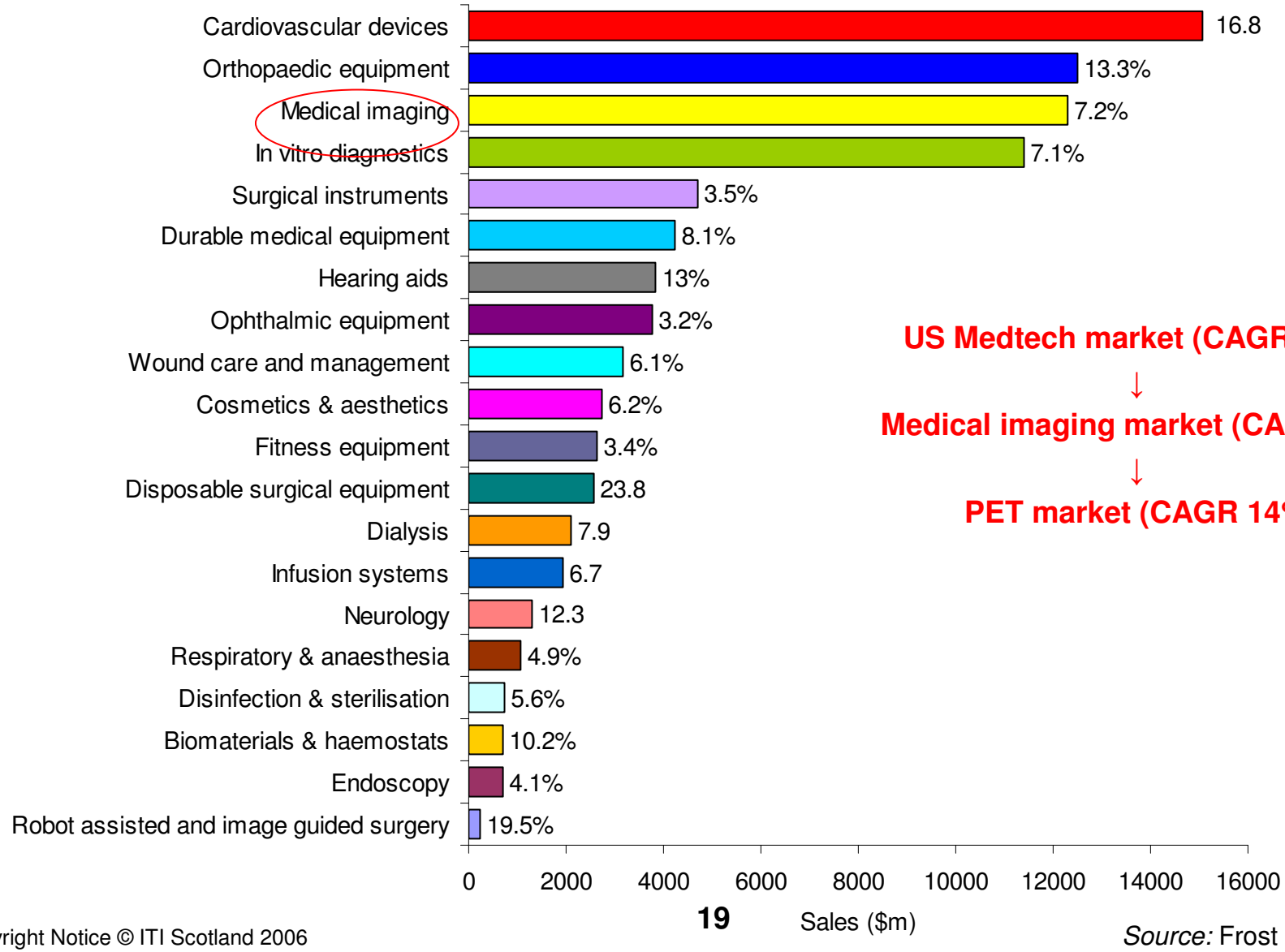
Medical Imaging is Now Firmly Established as an Integral Part of Modern Healthcare….

This is clearly demonstrated by the fact that in 2004 more than 300 million medical imaging procedures were performed in the US alone.

Now valued at over $20 billion per year worldwide, the diagnostic imaging market* is continuing to grow and change as technological advances and product innovations are introduced to meet the demands of a rapidly aging population.

*This includes molecular imaging, and non-molecular imaging modalities including X-ray and IT services.

Must Dig Deeper to Reveal Market Dynamics



US Medtech market (CAGR 10%)

↓

Medical imaging market (CAGR 7%)

↓

PET market (CAGR 14%)

Source: Frost & Sullivan, 2004

Revenues Split by Modality and Imaging Agents

Instruments

PET and PET/CT is predicted to be the fastest growing US modality, reflecting a general trend.

US REVENUES ($m)	2004	2005	2006	2007	2008	2009
Ultrasound	1,355	1,441	1,526	1,611	1,700	1,791
SPECT and SPECT/CT	439	453	467	483	503	517
MRI	1,760	1,828	1,893	1,937	1,961	1,969
PET and PET/CT	826	1,010	1,213	1,383	1,519	1,655
TOTAL	4,380	4,732	5,099	5,414	5,683	5,932

Markets for established modalities are at a fairly mature stage, with fusion modalities like PET/CT driving modest growth. A limited buyer population linked to cost barriers for smaller organisations also prohibits higher uptake.

Imaging agents

US imaging agent sales are expected to reach 60% of global sales by 2009.

$m	2004	2005	2006	2007	2008	2009
World	3,930	4,170	4,350	4,560	4,810	5,200
US	2,070	2,130	2,150	2,770	2,920	3,110

Source: Kalorama

Incremental Change in Imaging Technology is Driving Progress

Imaging IT

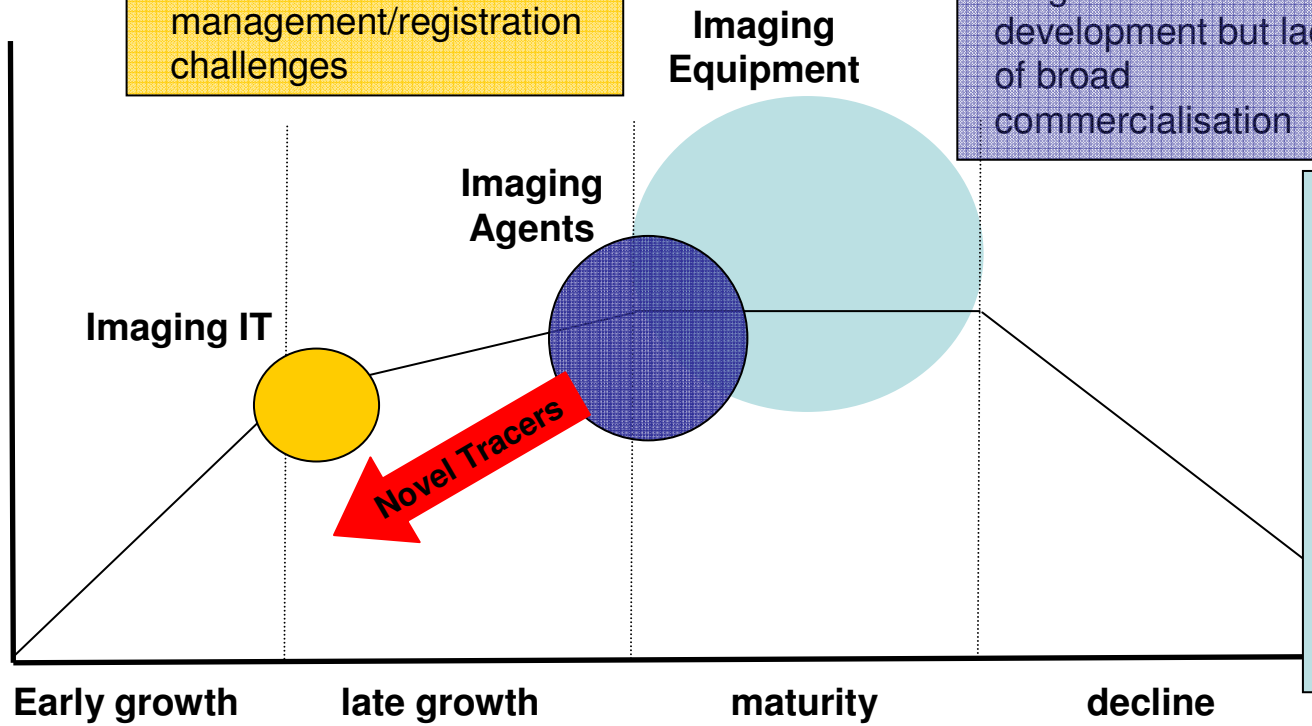
- Demand for IT solutions is driven by new applications of imaging technology and data management/registration challenges

Imaging Agents

- Current tracers consolidate position due to lack of new market entrants
- Large focus on tracer development but lack of broad commercialisation

Novel Tracers

- Likely to exhibit rapid growth (start of life-cycle)
- Market for novel tracers likely to be as large if not larger than the established tracer market



Imaging equipment

- Innovation is based on upgrading/combining current modalities
- Few equipment vendors
- Pace of incremental change is rapid
- No novel modalities are entering the market

Note: bubble size reflects relative market size

The Relatively Flat Market Masks the Underlying Dynamics

Market forecasts for PET and PET/CT and similarly SPECT and SPECT/CT mask the almost 100% shift from single to dual modality systems since 2001.

Constraints on capital funds in the imaging industry have made the modalities market ever more competitive. Mirroring more recent business model shifts in the IT industry, whereby flat hardware margins are offset against more attractive “total solutions and services” models, there is a trend towards providing leasing of medical imaging equipment and bolt-ons.

On the provider side, this has created a tendency towards the leasing of equipment among public hospitals.

These packages can help providers either by allowing them to lease equipment or by enabling them to buy the same outright, given that workable rates are provided.

Additionally, it is too soon to know the scale of revenues from the application of molecular imaging within pharma R&D. Consequently, revenue forecasts for modalities such as PET/CT are likely to be conservative, missing the potential upside from pharma imaging.

Drivers for Molecular Imaging Adoption

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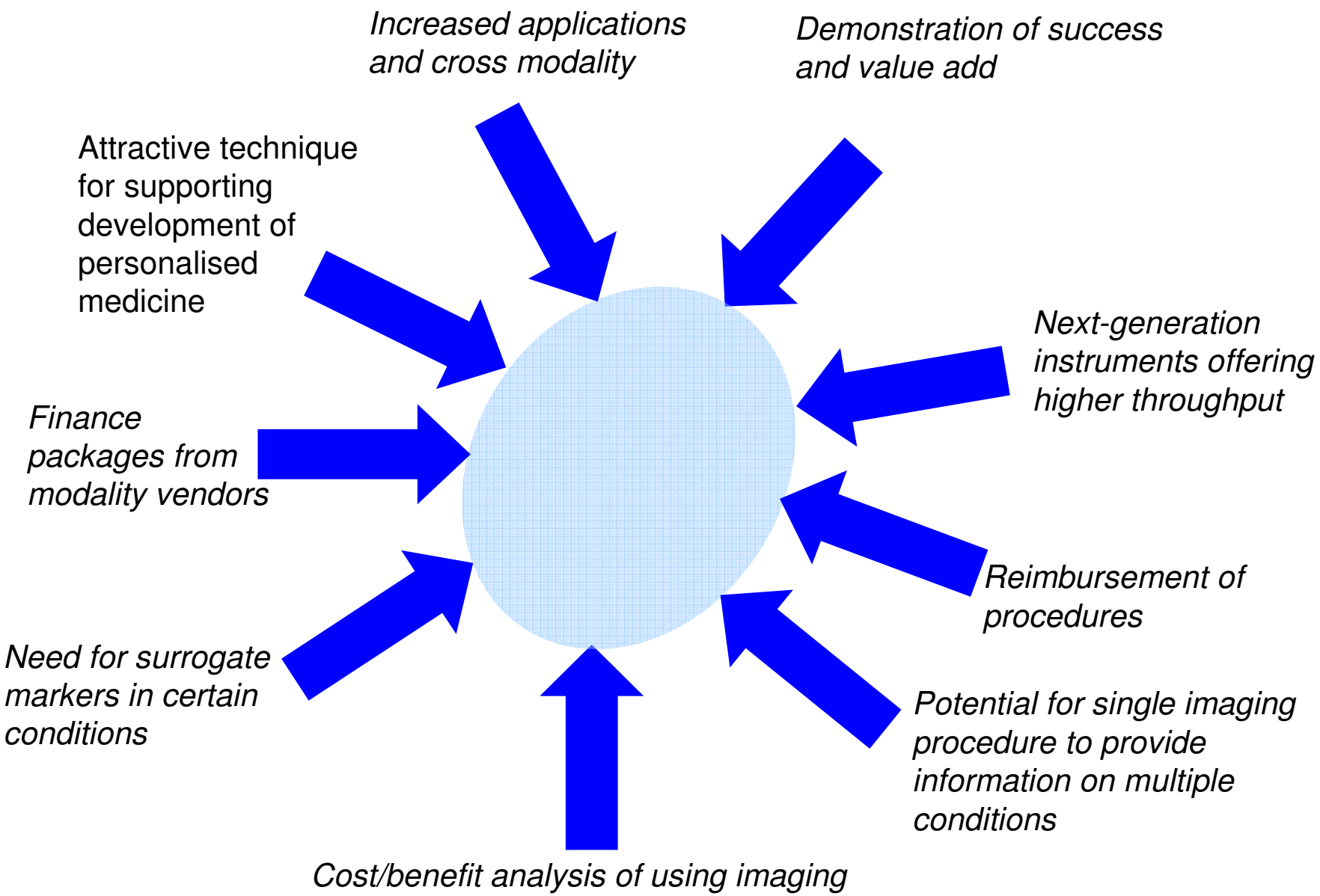
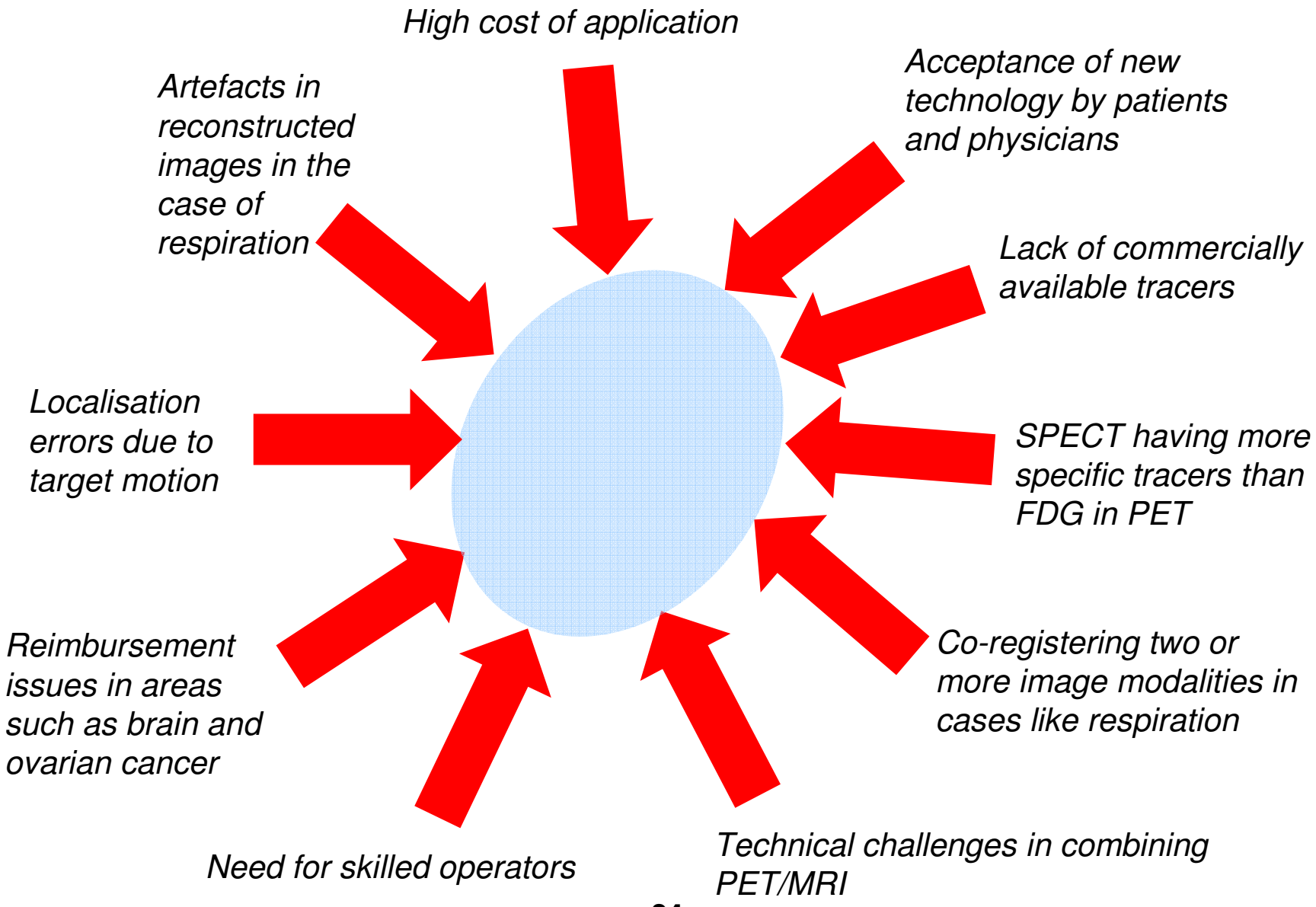


Challenges for Adoption



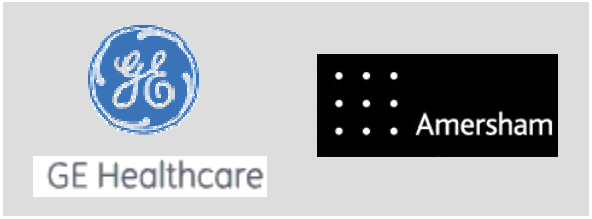
Significant Deal Making Activity - Both in M&A and Collaborations (1)

- The significant upfront and running costs for a molecular imaging capability as well as the need for highly skilled personnel is causing many pharma and biotech companies to consider partnerships and outsourcing rather than developing in-house capabilities.
- Companies such as GSK believe that the only way to ensure you are at the cutting edge is to collaborate with academia. However, this must be balanced with arguably less flexibility and control over timelines. One compromise may be collaborations where the industrial partner places dedicated staff into the academic facility:

  - GSK is investing £46m in the clinical-imaging centre at Imperial's Hammersmith Hospital campus, London. The centre is due to open in 2006
    - The centre will have dedicated resources for MRI and PET together with an advanced radiochemistry development facility and optical imaging, all in a context supporting patient-related studies.
    - Research will focus on cancer, stroke, neurological diseases such as Parkinson's and multiple sclerosis and psychiatric diseases

Significant Deal Making Activity - Both M&A and Collaborations (2)

- Similarly, medtech companies have entered into collaborations with pharma to gain access to molecules that could form the basis of molecular tracers. Additional deals are designed to furnish vendors with components such as IT, software or instrument components enabling them to provide more complete and integrated offerings (solution provision)
- In this regard General Electric has added to its core instrument business by acquiring Amersham (access to contrast agents) and through partnerships with pharma companies such as Eli Lilly and Roche (both in Alzheimer's disease area)
- Similar networks exist for other instrument makers such as Philips (e.g. alliance with Kereos for molecular imaging agents) and Siemens (acquired CTI Molecular Imaging)



Partners monitor impact of a Roche compound on beta amyloid plaques using a GE PET imaging agent.

GE Healthcare can screen Lilly's libraries for targets

CURRENT IMAGING MODALITIES:

OPTICAL IMAGING
CT
PET
SPECT
MRI

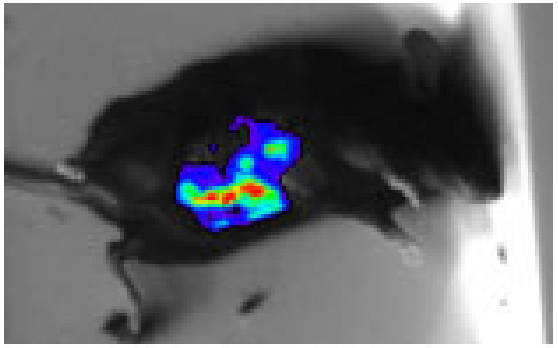
OPTICAL IMAGING

Optical Imaging Via Visible Light

Optical imaging is based on detecting the transmission of light largely using bioluminescent (luciferase-based) or fluorescent (GFP-based) markers in reporter assays.

Molecular probes can be deployed as imaging agents in the detection of disease or as surrogate biomarkers of therapeutic success.

A light emitting reporter is tagged onto the promoter genes or proteins in living animals. Researchers create a transcriptional fusion with a promoter of interest or a translational fusion to create protein/reporter chimeras which can be used as a model to study modulation of the target in response to therapeutic candidates.



A mouse with intraperitoneal carcinomatosis from a colon cancer cell line. Areas of tumour growth are imaged using a vaccinia virus expressing luciferase. The vaccinia virus will traffic specifically to sites of actively growing tumour.

Characteristics of Optical Imaging

Optical imaging has many advantages over the clinically-proven modalities in the preclinical setting:

- Easy to use
- Low cost
- Low background noise
- Allows for multiplexing
- Radioactive probes are not required
- High throughput

- Non-invasive procedure:
  - Each animal acts as own control
  - Inter-individual variance is reduced
  - Fewer animals required to achieve statistical significance
  - Study of models for chronic disease
  - Tissue is analysed in its host environment
  - Animals don't need to be sacrificed

However, *In vivo* reporter assays are not yet suitable to replace efficacy assays and use is limited to animals as the incorporation of genetic labels cannot easily be translated into use in humans. Use is more suited to more superficial targets although the longer wavelengths such as the infra-red range can be used for detection through a whole mouse.

Imaging is largely constrained by specificity of molecular probes for target tissues. A longstanding goal of bioluminescence is to have several probes with distinct long-wavelength emissions for multiple target imaging.

Near-infrared (NIR) Fluorescence Imaging

Through NIR, absorbed light excites a fluorescent molecule within biological tissue which fluoresces at a longer wavelength than transmitted light (through a Stokes shift).

In the NIR range, biological tissue is not very fluorescent, but some tissues do exhibit some auto fluorescence causing problematic background noise which can be reduced to some extent by NIR filtering. Significantly, an exogenous contrast agent is required to improve the signal to noise ratio of an image.

These can be divided into two categories:

- Organic fluorophores
- Inorganic fluorescent semiconductor nanocrystals (quantum dots)

Organic fluorophores have been used in NIR imaging for many years. They are typically 1,200 Daltons or less in size with varying toxicity and biodistribution. Clearing time is typically in minutes through renal filtration.

Some drawbacks to using organic fluorophores is the difficulty in controlling their excitation and emission wavelengths, hydrophobia, molecular stability, low quantum yields, and photobleaching (loss of fluorescence) which has limited their sensitivity to detection.

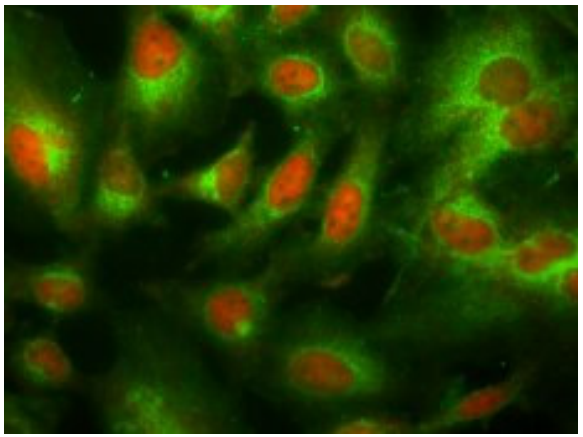
Quantum Dots Hold Great Promise for *In vivo* Molecular Imaging

Quantum dots are nanometer (10-9 meter) scale particles that absorb light which is re-emitted as fluorescence. Quantum dots have the potential to solve many of the problems associated with organic fluorophores.

They are typically made from semiconductor crystals of cadmium selenide encased in a zinc sulfide shell which allows tuning of fluorescence within a narrow bandwidth enabling multi coloured quantum dots.

Because exposure to cadmium could be hazardous, quantum dots have not found their way into clinical use, but have been used as markers to tag particles of interest for use in animal studies.

A number of unique properties such as high quantum yields, large molar extinction coefficients and high photostability make quantum dots attractive for use in biological imaging. However, safety concerns remain particularly if quantum dots are able to cross the blood brain barrier and enter the CNS.



Phosphorylated p42/44 MAP kinse (Erk) (red) and phosphorylated EGF receptor (green) in HeLa cells. Qdot 655 anti-rabbit and Qdot 565 anti mouse secondary antibody conjugates from QuantumDot Corporation were used.

Self Imaging Quantum Dots

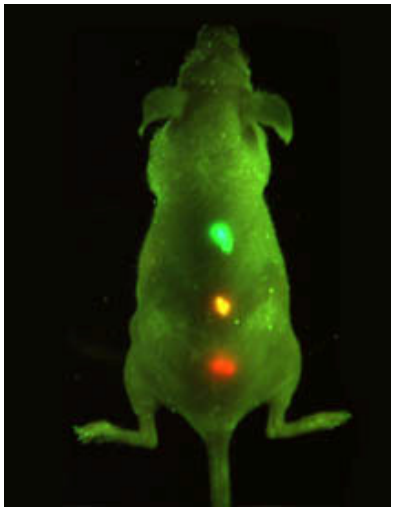
Ideally, a quantum dot would emit light without external illumination, but it has been unclear as to whether quantum dots could operate using a principle of bioluminescence resonance energy transfer (BRET) where a light emitting protein (such as luciferase) transfers energy to a fluorescent protein in close proximity.

The use of current quantum dot technology for *in vivo* imaging is limited due to their dependence on external illumination sources to fluoresce, resulting in background emission (via endogenous chromophores such as collagens, porphyrins and flavins), and some non localised fluorescence.

Recent work published in Nature Biotechnology (Min Kyung So *et. al,* 2006), presented quantum dot conjugates which luminesce *in vivo* by BRET without external excitation.

Compared to existing quantum dots, the self imaging conjugates display greatly enhanced sensitivity in small animal imaging, and could open up new avenues for molecular imaging.

These areas include highly sensitive *in vitro* assays, *in vivo* cell trafficking studies, multiplexed imaging, and the design of biosensors with BRET emission modulated by specific biological interactions.



Imaging of quantum dots in live mice with human prostate cancers. The dots accumulate in the tumours in sufficient numbers large enough to be visible in ultraviolet light under a microscope.

COMPUTED TOMOGRAPHY (CT)

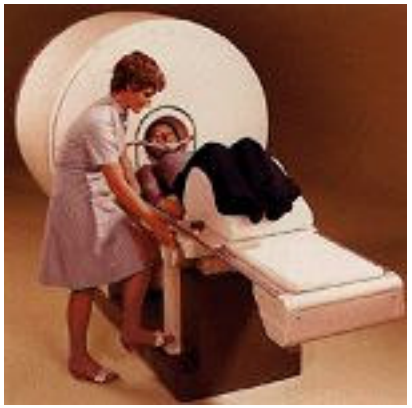
What is CT?

Originally invented in 1972, CT uses an x-ray tube with a series of detectors that enable radiologists to obtain a cross-sectional image of the body. The x-ray tube and its detectors revolve around the body, taking a large number of readings from various angles. These readings are then reconstituted by computer to form the desired cross-sectional image.

With traditional, single-slice CT, the patient table (where the patient lies during the procedure) is moved incrementally to allow the revolving x-ray tube to obtain sufficient slices to reconstruct an image for a complete part of the body.

CT scanning has the ability to image a combination of soft tissue, bone and blood vessels. CT imaging of the head and brain can detect tumours, blood clots, blood vessel defects, enlarged ventricles and image other abnormalities including nerves or eye muscles. CT images are also used as a basis for planning radiotherapy cancer treatment.

CT imaging provides good soft tissue resolution (contrast) as well as high spatial resolution. This enables the use of CT in orthopaedic medicine and imaging of bony structures such as prolapses of vertebral discs, complex joints like the shoulder or hip, and fractures.



The original “Siretom” dedicated head CT scanner c.1974.

The Market for CT is Fast Becoming a Replacement Market as the Modality Matures

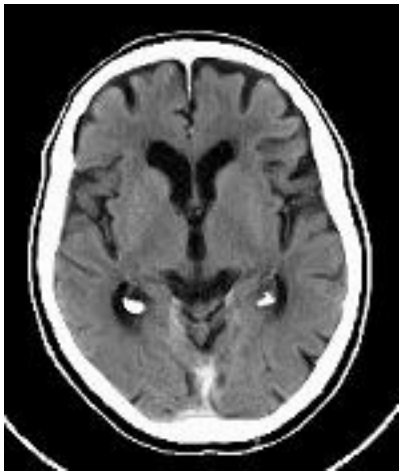
The increasing use of cardiac CT, however, is poised to open up the market to new segments where it will be used by cardiologists as well as radiologists.

This move will bring cost benefits as early CT screenings will remove the need to perform invasive and higher risk cath-lab procedures (cardiac catheterisation). In addition, the possibility of eliminating cardiac catheterization for many patients will win over insurers since it eliminates the need for various individuals to undergo this procedure and is less time consuming.

There is a degree of competition from MRI, but if cardiologists are going to forego an immediate referral for lucrative cath-lab procedures, it is more likely that they will opt for CT that is presently cheaper and more widely reimbursed than MRI.

Indeed, there are encouraging signs coming from the United States that the health care payers are becoming more receptive towards reimbursing 64 slice CT.

The major disadvantage of CT is its use of ionising radiation, which can be harmful in large doses.



Axial CT image of a normal brain using a state-of-the-art CT system and a 512 x 512 matrix image.

Multislice CT is a Major Innovation Area

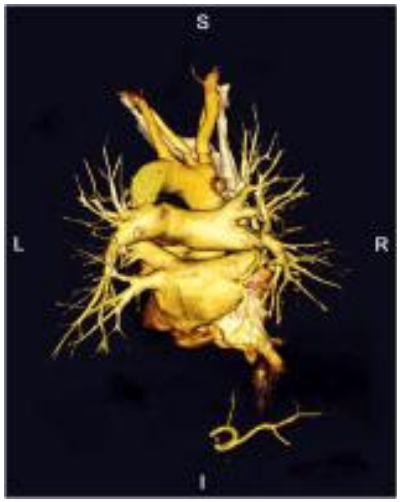
Advances in multi-slice CT have enabled a greater number of cross-sectional slices to be obtained in a shorter space of time.

It has helped make CT an ever more effective imaging modality for both thoracic and cardiac imaging, with a high-quality image of the whole chest or heart now obtainable within a fraction of the time.

The most exiting development in CT, has been 64-slice CT systems which have represented a quantum leap over conventional 16-slice technology, revolutionising imaging of the heart, coronary blood vessels and peripheral circulation.

While 16-slice scanners allowed imaging within 25 seconds, 64-slice enables scanning in 5 to 13 seconds. Additionally, higher resolution now provides images with clarity unheard of a few years ago. Clinicians can now see a patient's heart, blood vessels, and surrounding structures in sufficient detail to diagnose and begin management of coronary artery disease in its early stages, reducing the need for riskier invasive procedures.

Cardiac CT, as well as CT angiography (to scan blood vessels), are already feasible with 16 slice CT, but the increased capability and faster scan times of 64 slice CT is making this a more widespread procedure. 64 slice CT will also make CT the near equivalent of MRI for studying cardiac abnormalities, as the scope of CT moves beyond radiologists to cardiologists.



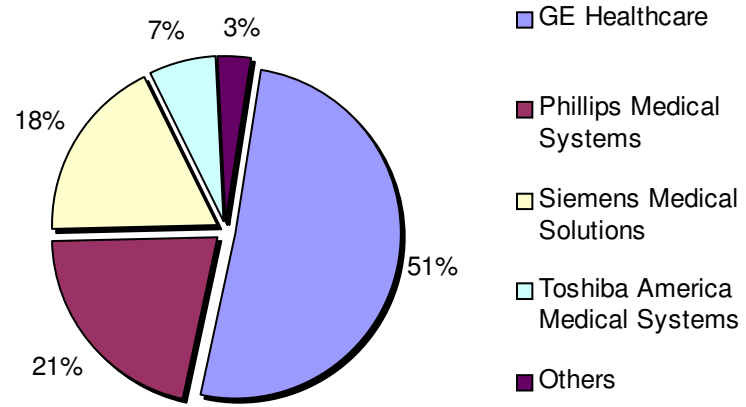
Multislice CT image of the heart

The 64-slice Market

With millions of CT scans conducted annually in the US alone, the market for CT scans is considerable and has been driven by the release of scanners able to deliver a greater number of cross-sectional slices.

In 2004, US sales of CT systems generated over $1.2bn, with a modest CAGR of 3.3% forecast up to 2009.

US CT market share by supplier, August 2005.



Source: medtech insight

Competitors in the 64-slice market

Company	Product	Specifications
GE Healthcare	Lightspeed VCT	64 x 0.625 mm data channels, 40 mm detector length, 0.35 s gantry speed
Phillips Medical Systems	Brilliance 64-Slice	64 x 0.625 mm data channels, 40 mm detector length, 0.40 s gantry speed
Siemens Medical Solutions	Somatom Sensation 64	64 x 0.6 mm data channels, 28.8 mm detector length, 0.33 s gantry speed
Toshiba America Medical Systems	Aquilon 64	64 x 0.5 mm data channels, 32 mm detector length, 0.40 s gantry speed

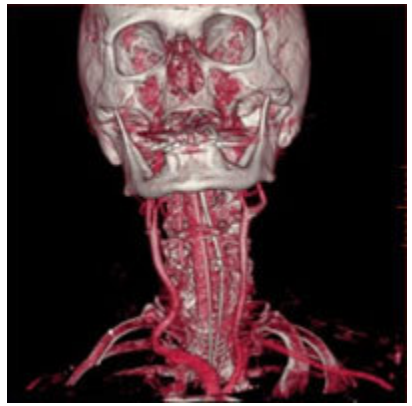
Breaking the "Slice Barrier"

64-slice will likely be superseded by 256-slice technology in the next two years reflecting the rapid pace of progress in this area. Several of the major manufacturers are making incremental improvements while others are taking a more radical approach.

Phillips is developing a new detector design based on "nano-panel" technology. According to Phillips, the technology is based on tiles that can be integrated into panels of any size, will allow the construction of detectors of any slice width that could image an entire organ in a single gantry rotation.

Siemens Medical have introduced the first dual source CT which is faster than existing CT technology, thereby cutting patient exposure to radiation by c.50%. The device will enable imaging of patients with arrhythmias without using beta blockers to slow the heart rate, with the first installation in October 2005.

GE Healthcare's Lightspeed VCT is the fastest selling product in the firm's history, with heart images possible within 5 heart beats (500 were sold by Nov 2005). GE are currently collaborating to compare cardiac CT with invasive angiography, in infants with heart defects, and diagnosis of strokes.



LightSpeed VCT image of the carotid arteries that supply blood to the brain and internal parts of the head.

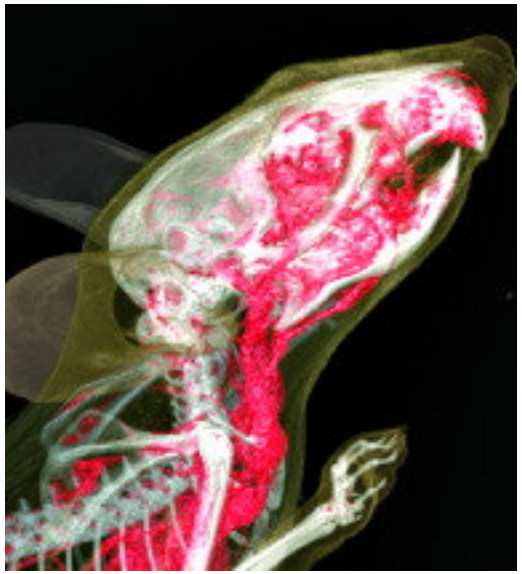
Low-cost and Portable Scanners are Needed

In response to market pull, a number of low-cost CT scanners are in development.

GE is developing Brightspeed CT scanners as a less expensive alternative to its Lightspeed technology, but with 4, 8, and 16-slice configurations for community hospitals and out-patient centres.

An emerging competitor, Neurologica, is developing a cordless, wireless, 29 inch long CereTom multislice CT scanner for head and neck applications at the patient's bedside. Images are sent wirelessly to a computer for analysis.

Approved in 2005 by the FDA, CereTom has broader applications in the emergency room, operating theatres, interventional suites, and medical clinics. Neurologica also plans to expand into orthopaedic and dental applications.



A normal mouse reveals its vasculature with microCT contrast agent Fenestra (Alerion, USA). Bone, vessels, and skin are gray, red, and brown, respectively.

Whole Body CT

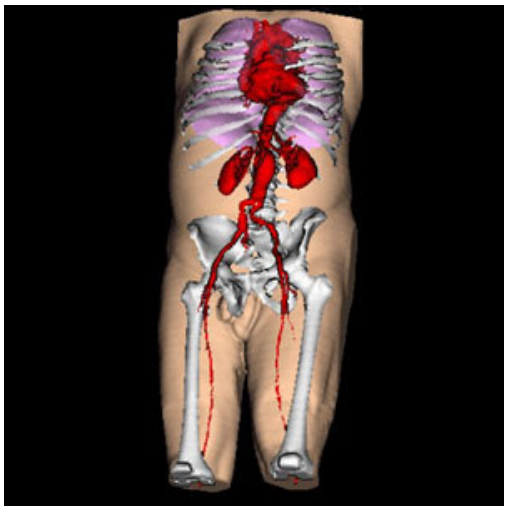
The performance of whole body CT scans has attracted controversy in two respects. Firstly, there is increased concern that doses of ionizing radiation received by patients during the procedure is proving too high.

There is a feeling that as the number of CT slices increase, there is also an increase in dosage levels (though it must be stated that more slices equate to faster scan times, and therefore less time spent exposed to this radiation).

Health care authorities are becoming more watchful of this, with the Spanish authorities now stipulating that dose levels be stated for every public tender for CT.

Second, there is some question within the medical community concerning the reliability of clinical data obtained during this procedure.

This is becoming a greater issue as advances in MRI are now providing a speedy and non-ionizing alternative to this whole body procedure, with clinical studies now vouching for the reliability and effectiveness of whole-body MRI.



A whole body CT scan from Phillips Medical.

IT Solutions to Address Image Overload

With the benefit of increased clinical information obtainable from multi-slice CT comes increased workload for radiologists.

Whereas this can be a source of resistance from health care professionals, advances in computer aided design (CAD) and computer assisted reader (CAR) software are eliminating this problem.

CAR, in particular, is popular within the industry as it is seen as a second pair of eyes assisting the radiologists.

On the other hand, CAD, with its higher levels of automation, does meet with resistance in some circles as it is perceived as endangering the jobs of some radiologists (a perception that appears to be unfounded given the seeming lack of radiologists across Europe).

Overall, these technologies are helping multi-slice CT consolidate its position within the market.

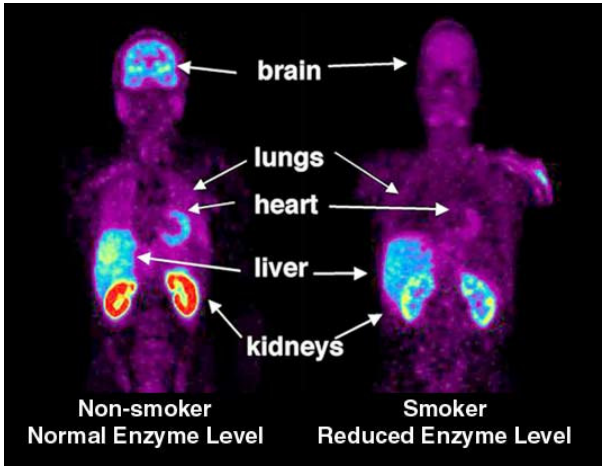
Taking Imaging to the Next Level – Functional Imaging

Molecular imaging is becoming a valuable tool in clinical trials to gain a better understanding of how developmental candidates actually work in patients.

Nuclear modalities including PET and SPECT take imaging to another level to investigate the function of organs and molecular pathways in a non-invasive manner, with the aim of predicting efficacy as early as possible.

For the last 20 years, PET has largely flourished in academic studies of glucose metabolism, but is now emerging as a significant tool for drug development companies not just in the clinic, but also for use in animal studies using microPET.

So far, *in vivo* imaging in preclinical research has largely required anaesthesia, but real time optical technology is being developed to allow imaging on fully conscious animals opening up new opportunities in studying CNS pathologies where weak signals have traditionally caused complexity.

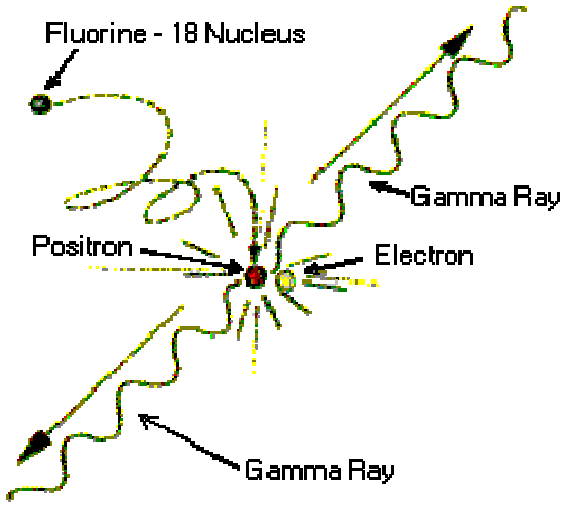


Using PET to study the effects of smoking.

POSITRON EMISSION TOMOGRAPHY (PET)

What is PET?

PET is based on the decay of a radioisotope which emits a positron and annihilates with an electron to produce two high energy photons which propagate in nearly opposite directions.



Photons are detected using a cylindrical ring of scintillation crystals such as bismuth-germinate (BGO), or novel crystals (such as those developed by Photonic Materials Ltd in Scotland) arranged into an array. When the photons travel through a crystal they interact with electrons ultimately resulting in the emitting light.

The light decays exponentially at a rate characteristic of each crystal in the array, thus the output can be decoded to reveal in which crystal the emission occurred. The first PET scanner was introduced in 1975.

For PET imaging, image reconstruction is performed using successive summation of detected positron emission events using a positron emitting isotope such as ^{11}C, ^{18}F, ^{13}N, ^{15}O, ^{64}Cu, ^{84}Ga.

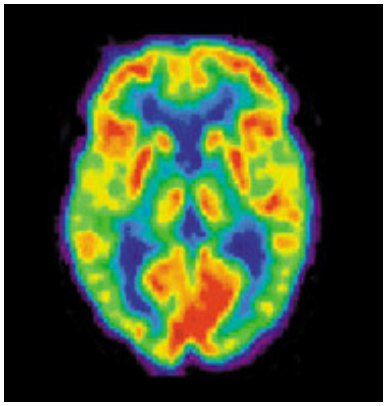
Applications of PET (1)

PET is becoming a major tool in drug development, especially in oncology since it can track the *in vivo* performance of new therapeutics. PET is particularly applicable to measuring perfusion, diffusion, permeability, blood oxygenation and glucose metabolism. MicroPET has been used for the last 5 years in animal studies through pharma collaborations with academia, bridging the gap between animal and human comparisons.

A typical PET scanner.

PET allows examination of the heart, brain and other organs by showing the chemical functioning of an organ or tissue unlike x-ray, CT or MRI which only shows body structure.

PET can be used in coronary artery disease to determine whether a patient will benefit from coronary artery bypass surgery, in tumours to differentiate malignant from benign, as well as showing spreading of malignant tumours, and in brain disease to identify seizures or evaluate degenerative brain diseases such as Parkinson's, Alzheimer's, and stroke.



A PET image of healthy human brain.

Applications of PET (2)

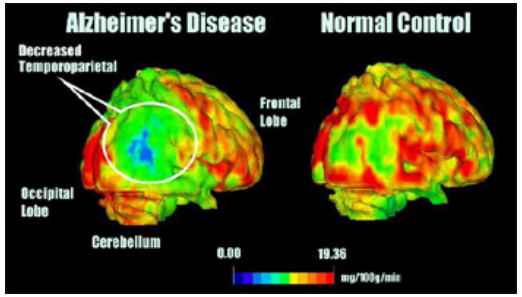
PET can help physicians effectively pinpoint the source of cancer, because many cancer cells are highly metabolic and therefore take up more of the radioactive glucose (FDG) injected in the patient prior to examination.

The areas of high glucose uptake are displayed in the scan imagery, as opposed to the anatomical imagery of CT or MRI, which cannot detect active, viable tumours.

A PET scan can be used in early diagnosis, assisting physicians in determining the best method for treatment. A whole body PET scan may detect whether cancer is isolated to one specific area or has spread to other organs (metastasised) before a treatment plan is determined.

Additionally, greater reimbursement for the procedures is another major factor behind the increasing installation of PET scanners. Equally as important is the need for extensive integration with other modalities and associated documentation and quality control.

Stand alone PET scanners are seeing a decline in sales due to the high adoption of hybrid PET-CT scanners.



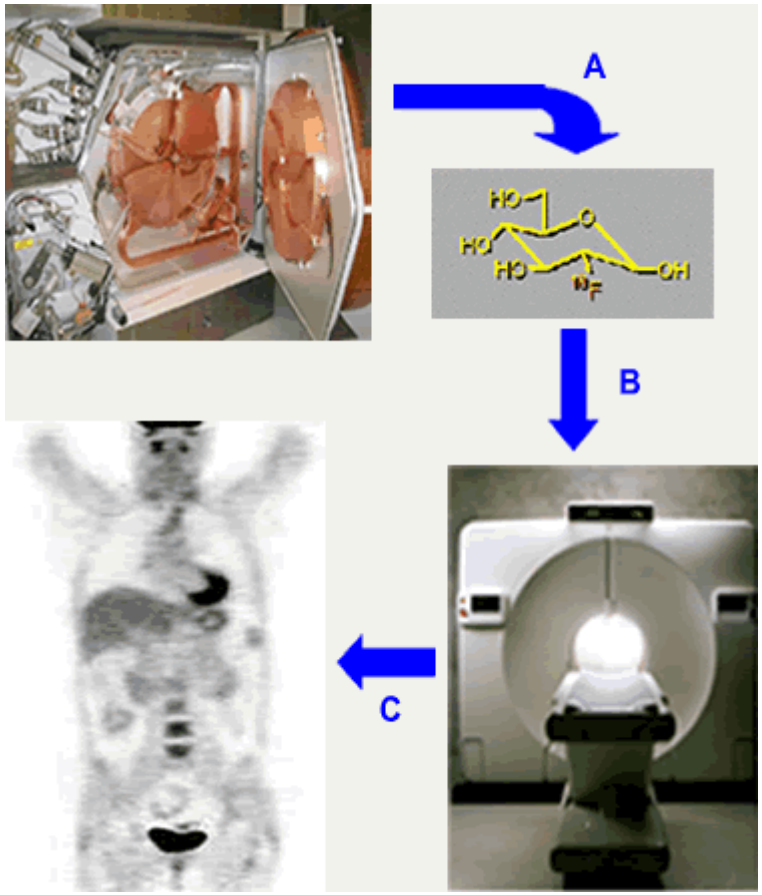
A PET scan used to observe Alzheimer's disease.

There are Few Commercially Available PET Tracers

From its inception, one of the great strengths of PET was the richness of the compounds that could be labeled with short-lived positron-emitting biomolecules.

Presently, FDG is still the only radiopharmaceutical widely used and reimbursed for clinical imaging, with ^{82}Rb on a much smaller scale for myocardial imaging. There are many more PET radiopharmaceuticals available in the research domain, primarily for brain studies.

It is important for the future of PET that the current situation evolves so that other tracers such as **31[^{18}F]-fluoro-31-deoxythmidine** (FLT), ^{11}C-acetate, ^{18}F-choline, amino acid tracers, monoclonal antibodies/fragments and possibly a hypoxia-imaging agent such as ^{18}F-miso or ^{64}Cu-ATSM become available clinically.



PET Imaging via FDG.

A. A isotope of fluorine (fluorine 18) is made in a cyclotron and is chemically inserted into deoxyglucose.

B. FDG is injected into the patient who is then scanned via PET.

C. An image showing the localisation of F18 is formed.

Desirable Properties of an Imaging Agent

In the search for new tracers, a range of characteristics are desirable including:

- Small
  - Fast kinetics leads to images within hours.
- High affinity and specificity
  - Superior contrast
  - Shorter clinical protocols
- Fast and efficient production
  - Chemical synthesis
  - Easy radio labelling
  - Possibility to distribute as a kit
- Safety

Thymidine Kinase Tracers

Targeted nuclear agents can also report on gene expression, for example by targeting a gene-transcribed extracellular protein or by detecting expression of a reporter gene such as herpes simplex virus thymidine kinase (HSV-Tk).

Optical imaging through bioluminescence currently remains a more sensitive imaging modality in this area although PET is used.

In mammalian cells, exogenous HSV-Tk phosphorylates acycloguanosine residues, generating biological signal amplification when the phosphorylated radioisotopes are intracellularly trapped.

Further improvements in PET imaging of gene expression are expected with modified reporter genes encoding highly active mutant thymidine kinases and substrates with improved biological behavior. Some of these paradigms have already been tested in clinical trials.

Antibody Fragment Tracers

For *in vivo* applications using whole antibodies, a long serum half-life results in poor signal to noise ratios for imaging.

Smaller fragments such as diabodies and minibodies, reach their maximum tumour uptakes within 1 to 6 h of administration. Because of rapid blood clearance, tumour to blood ratios increase steadily over time and reach high values 9>20:1) by 24 h, making these fragments promising candidates for imaging.

Clinical imaging studies have been conducted using tumour targeting scFv dimers (diabodies) and minibodies. A ^{123}I labelled anti-CEA minibody has been used to visualise colorectal tumours including lesions not visible through CT scanning.

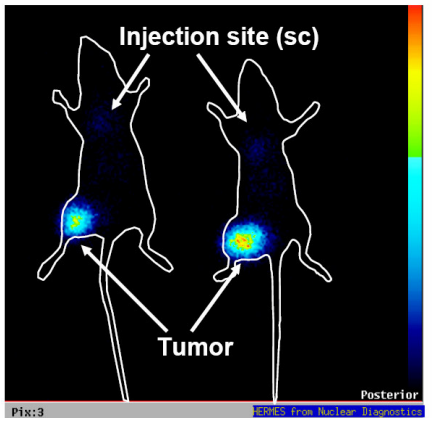
Cost of using labelled antibodies may be a barrier compared to using FDG or labelled small molecules.

Use of a Molecular Scaffold with Antibody Properties for Molecular Imaging

A number of companies are exploring the use of molecules mimicking certain characteristics of antibodies such as specific recognition and high affinity but that are easier to produce, more stable, don't infringe mab IP and easily engineered to create novel tracers.

One such example are the so-called Affibodies being developed by Swedish company Affibody.

These molecules are affinity proteins engineered on a three-helix bundle Protein A domain scaffold. Affibody is currently evaluating radiolabelled affibodies in animal models.



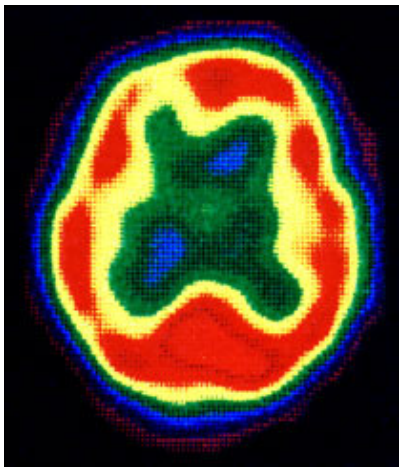
Tumour imaging following injection of labelled affibody.

SINGLE POSITRON EMISSION COMPUTED TOMOGRAPHY (SPECT)

What is SPECT?

A SPECT scan is a nuclear imaging procedure which observes blood flow to tissue and organs. Areas of increased blood flow take up more radioactive tracer as observed in increased brain activity for example.

SPECT is a technique similar to PET. However, the radioactive substances used in SPECT (^{133}Xe, ^{99}Tc, ^{123}I) have longer decay times than those used in PET, and emit single instead of double gamma rays requiring a different detection architecture.



SPECT scan of a human brain

Its images have less sensitivity and are less detailed than PET images, but the SPECT technique is less expensive than PET. Moreover, SPECT centers are more accessible than PET centers because they do not have to be located near a particle accelerator (cyclotron).

SPECT scanning is useful for pre-surgical evaluation of medially uncontrolled seizures, diagnosing stress fractures in the spine, and blood-deprived (ischemic) areas of the brain following a stroke or tumour.

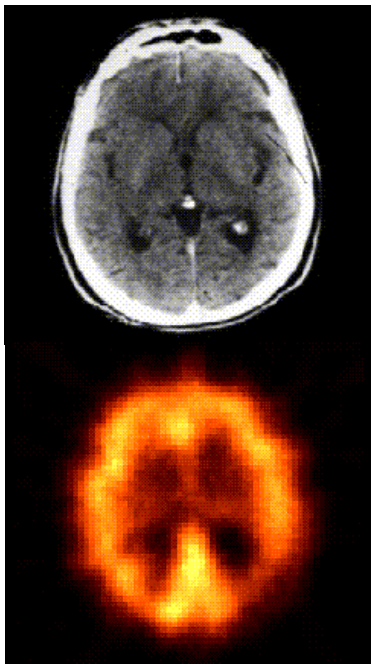
SPECT vs PET

The two techniques usually generate a set of transverse slices at approximately the same orientation in three-dimensional space; however, slice thickness, slice position and spatial resolution are different, and direct comparisons between modalities is difficult.

SPECT imaging offers certain advantages over PET in that many SPECT agents have more specific targeting capabilities than FDG agents. Several SPECT tracers incorporate antibody and peptide formulations that can be targeted to specific tissue receptors, allowing one to discriminate healthy from diseased tissue with a high confidence level.

However, the more specific the targeting agent, the more difficult it is to interpret its position anatomically, since there are fewer landmarks.

This can make it difficult for the average physician to interpret certain SPECT images.

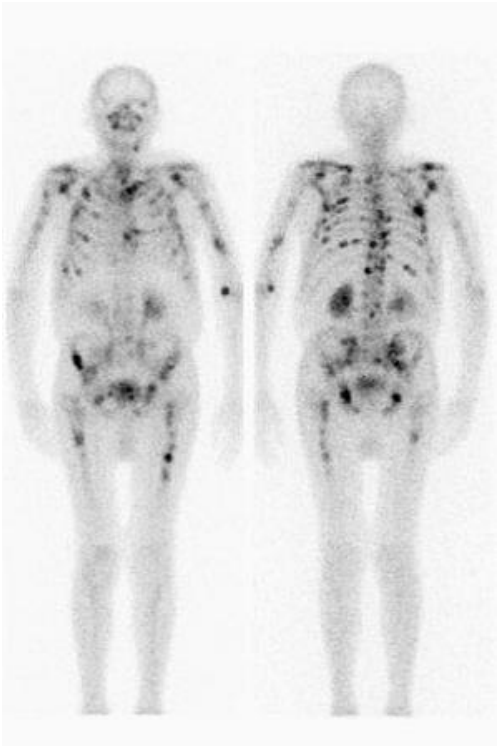


SPECT Vs CT. Typical slices from CT (top) and SPECT (bottom). For CT, slice thickness is much greater than pixel size in a tranverse slice; hence the reconstructed coronal and sagittal sections exhibit poor spatial resolution, despite the high level of detail visible in transverse sections. For SPECT, spatial resolution is uniformly poor and the edges of features are ill-defined.

SPECT Applications

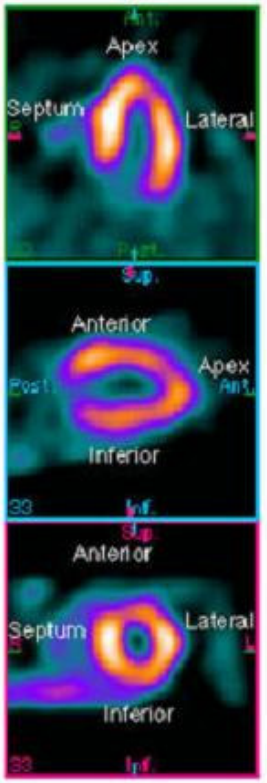
Bone scans

Bone scans are typically performed in order to assess bone growth and to look for bone tumours. The tumours are the dark areas seen in the picture opposite.



Heart imaging

Myocardial scan taken under stress. Regions of the heart that are not being perfused will display as cooler regions.



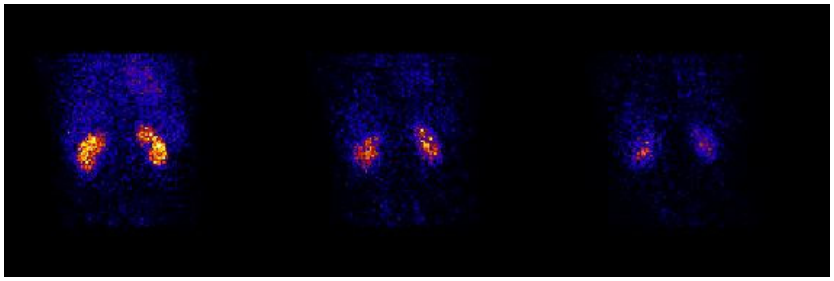
Vertical long axis

Horizontal long axis

Short axis

Kidney imaging

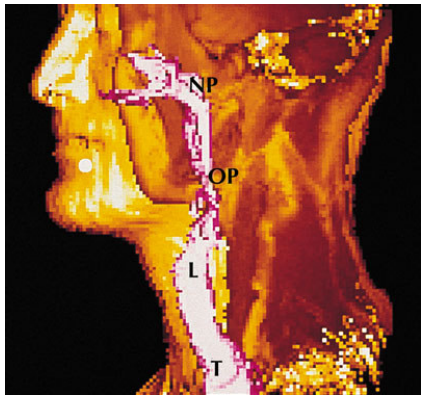
A renal planar scan using MAG3 tracer (a glucose analogue).



MAGNETIC RESONANCE IMAGING (MRI)

What is MRI?

First constructed in 1977, MRI scanners measure changes in nuclear magnetic resonance (NMR) allowing a more sophisticated visualisation of soft tissue than CT, hence its application in brain studies, and musculoskeletal and gastrointestinal systems.



MRI of head and neck

MRI relies on the way that hydrogen atoms, which make up nearly two-thirds of the human body, absorb and then give off magnetic energy, and respond to changes in magnetic fields. Computerised images are calculated from variations in how this energy is absorbed and emitted across the body. As very little energy is involved, the normal biochemistry of the body is completely unaffected.

MRI has the advantage of not exposing the patient to any non-ionising radiation and is also non-invasive.

MRI can image the body in various planes and can differentiate between tissues by recognising their physical and biochemical properties. This provides benefits in that MRI can detect tissues surrounded by bone, such as those which comprise the spinal cord.

MRI Agents

MRI agents have largely been based on either superparamagnetic iron oxide nanoparticles or gadolinium chelates.

Although these agents vary in size (10 to 300 nm), dispersion (monocrystalline, polycrystalline), surface coating (eg, dextran, carboxy dextran, carboxymethyl dextran, starch), and magnetic properties, only a few leading preparations have utility as clinical imaging agents, targeting agents, or sensors.

Efficient targeting often requires strategies such as caging of the dextran coat, which otherwise exists in an equilibrium of free and bound states surrounding the iron oxide core. Dextran-caging has been achieved by cross-linking the coating and resultant particles (cross-linked iron oxide, CLIO) have already been used as a platform to target receptors, enzymes, integrins, and specific cells.

Activatable smart agents have recently been developed for MRI and are generally based on one of two chemical principles: **(1)** enzymatic conversion of paramagnetic compounds or **(2)** assembly-disassembly of paramagnetic substrates or nanoparticles.

One of the Key Drawbacks of MRI Agents is Sensitivity

To illustrate this, consider a compound of molecular mass 500 administered at 1mg/kg and evenly distributed throughout the body.

- This would result approximately in a 2μM tissue concentration (ignoring drug elimination).
- Unfortunately, *in vivo* MR techniques can at best detect substances in mM concentrations.

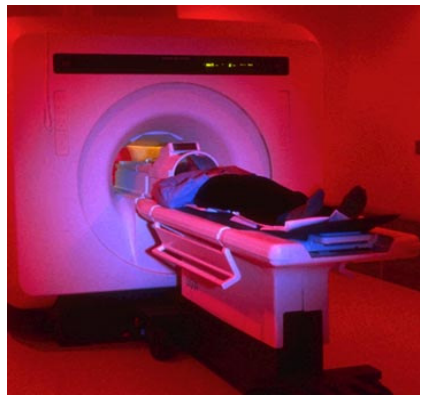
Development of probes for targeted imaging could address this issue:

- EPIX Pharmaceuticals and Schering AG recently received EMEA approval for the first targeted contrast agent for vascular imaging (known as MR angiography). The product, Vasovist, is a small molecule that binds non-covalently and reversibly to serum albumin.
- UniQuest Pty Limited is working with University of Queensland to commercialize a contrast agent that couples gadolinium with known disease specific biomarkers.

Alternatively the modality should be combined with optical imaging or PET.

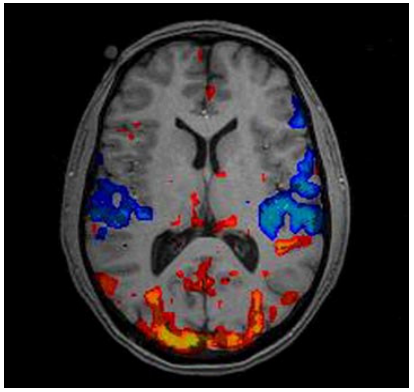
MRI Application (1)

MRI is adept at localising and staging diseases of the central nervous, musculoskeletal and cardiovascular systems. Alongside CT, it also serves as an effective brain imaging modality. With MRI, spatial resolution is greatly improved from millimeters to micrometers and both physiological and anatomical information may be extracted simultaneously.



MRI has also demonstrated promise in understanding the effects of therapies on cartilage and joint soft tissue for rheumatoid arthritis and osteoarthritis.

MRI's drawbacks include its susceptibility to reduced image quality for the chest and abdomen brought about by respiratory and cardiac motion, as well as offering slower patient throughput when compared to CT. Wider and open bore MRI machines with improved signal-to-noise ratios are new features developed to reduce the common patient complaints of claustrophobia and noise when undergoing an MRI procedure.

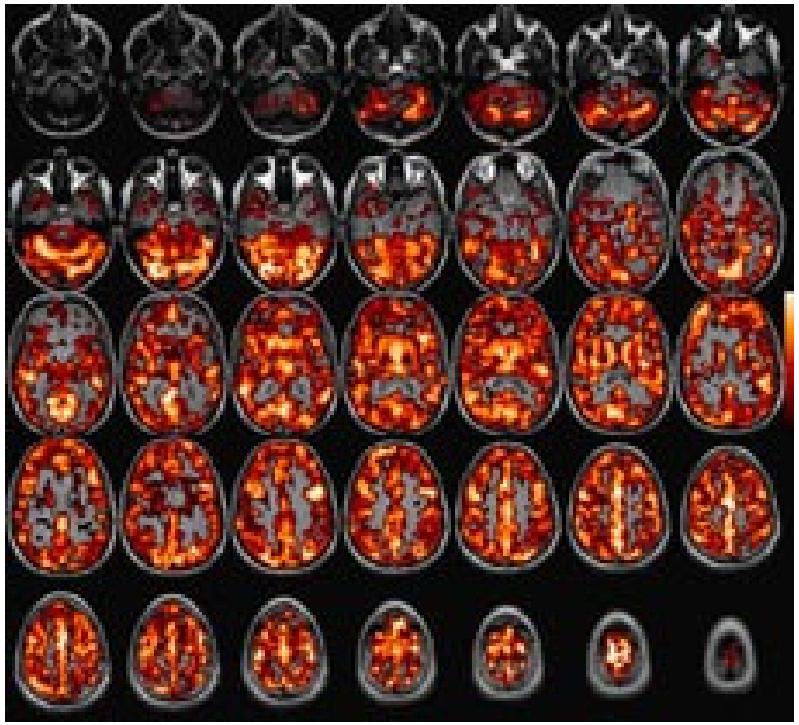


Using fMRI to measure blood flow through the brain.

Functional MRI (fMRI) as a modality to measure haemodynamic response, has evolved since the 1990s as a cheaper, simpler and more sensitive modality than PET. In 2003, there were approximately 10,000 MRI units worldwide, and approximately 75 million MRI scans per year performed.

MRI Application (2)

Stanford's 3T MRI system shows the global response to holding one's breath for 15 seconds. The entire gray matter volume is activated in each subject by the breath-holding task.



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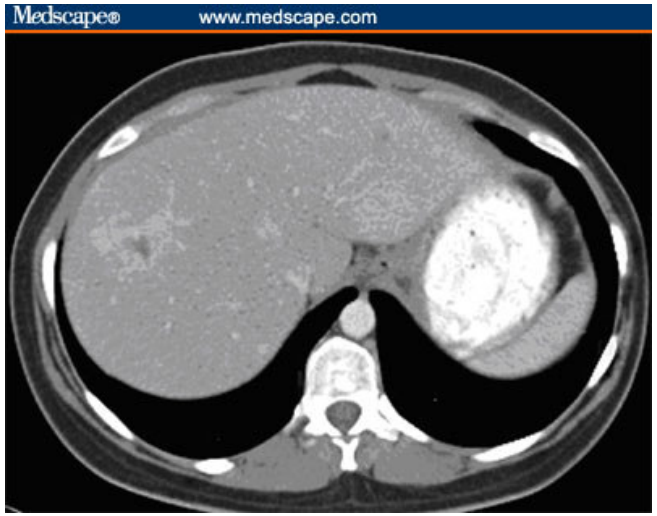

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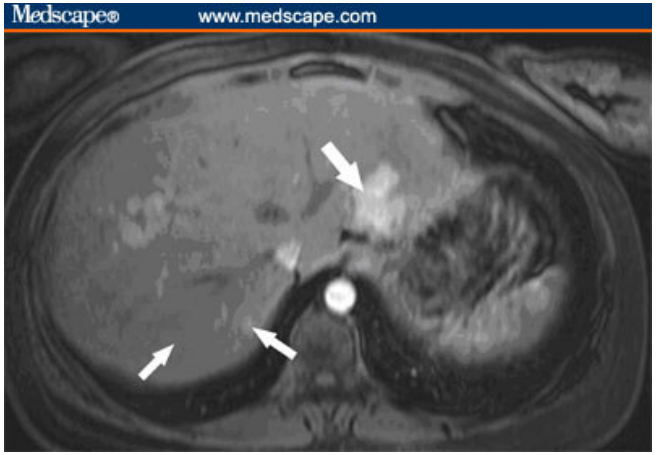


Hypervascular liver metastases from neuroendocrine tumour. (A) High-quality (16-row multidetector) CT and (B) postcontrast MR images. Many more small, bright-appearing tumours are present on MRI (arrows, B) than on CT.

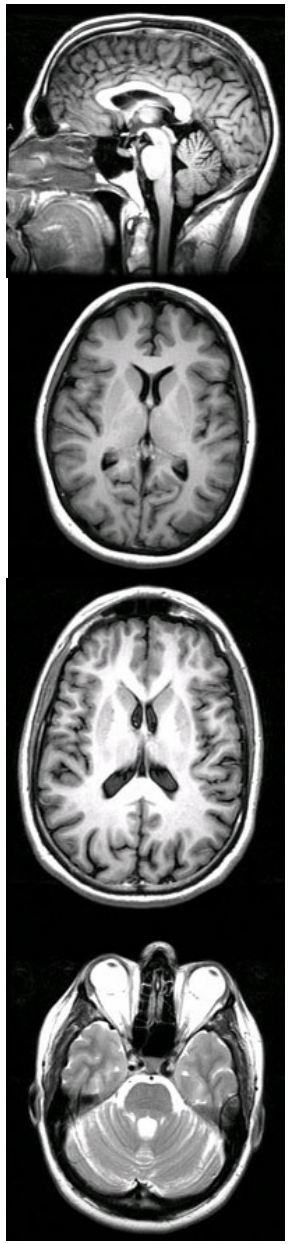
Whole Body MRI

Whereas in the past, MRI has been deemed to be limited due to its comparatively slower speed and higher cost per procedure than CT, current MRI systems feature the capability to screen the entire body in 15 minutes whilst still retaining high image quality and sensitivity to detect disease.

In fact, tests have shown that MRI is superior for the examination of some specific regions such as the head, abdomen and pelvis. This points to favorable growth for MRI within a medical community that has begun to cast doubt on some of the findings obtained from whole-body CT.

Inaccurate findings from CT can necessitate additional procedures, sometimes even including surgery. Concerns voiced over the radiation dosage that patients are subjected to during a CT examination will also boost the profile of MRI for this procedure.

The desire to avoid extra costs for providers and the added risks for the patient points the way to further growth in whole-body MRI procedures.



Images from The 3T whole-body MRI scanner (Signa 3.0T GE Medical Systems).

APPLICATION OF FUSION TECHNOLOGY: MOLECULAR IMAGING THROUGH MULTIPLE MODALITIES

The Significance of Fusion Technology

The significance of functional images has long been recognized, since the days of hand-drawn neck outlines on the early nuclear medicine thyroid scans. With the advent of digital imaging, a more rigorous approach to combining anatomy and function became possible by using software to align the two image sets.

Despite receiving little attention clinically, software registration algorithms for aligning image sets acquired by two different modalities have evolved in the past decade from simple matching procedures to complex nonlinear warping techniques.

Outside of the brain however, software registration has had only limited success and is still not widely used clinically.

Difficulties include:

- Allowing for inconsistent patient positioning between the different scanners (where fused modalities are not in same scanning unit).
- Uncontrolled internal organ movement.
- Co-registration of the whole body remains problematic and validation of the techniques remains a challenge.

Challenges for Multi Modality Vendors

The obvious advantages and attractions of fusion technology also bring with them challenges among providers keen to evaluate these opportunities.

This has created growth in both multi-modality deals and in deals allowing a single vendor to offer a total fusion solution that removes the need for the buyer to deal with multiple vendors. Vendors that fail to treat their offering as a comprehensive solution with the necessary peripherals, software and connectivity face the danger of missing out on the larger, more involved tenders that these workflow improvements have made increasingly common.

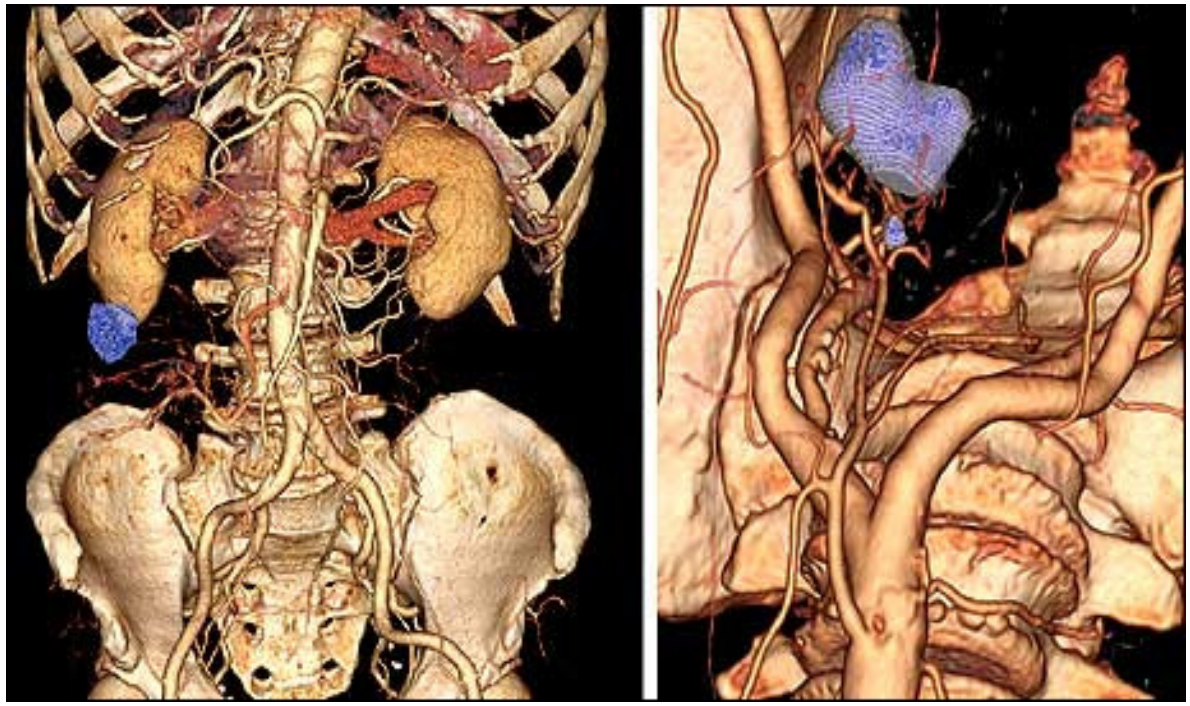
Key factors include:

- Trend towards multi-modality deals.
- Large public tenders challenge market stability.
- Customer education and knowledge development.
- Lack of radiologists.
- Trend towards provider leasing of medical imaging equipment.
- Price erosion and price sensitivity.

Dual Modality Molecular Imaging in Surgery

The images below give an example of the use of dual modality molecular imaging in tumour visualisation prior to surgery.

The fused volume rendering of a PET/CT angiography (left) provides vascular and metabolic visualization for surgical planning. In the zoomed view (right), the surgeon is able to better understand the blood supply and vascular involvement of the tumour in advance of surgery. Both colon cancer scans shown here were captured with GE Healthcare's Discovery PET/CT at the National Cancer Center in East Japan.



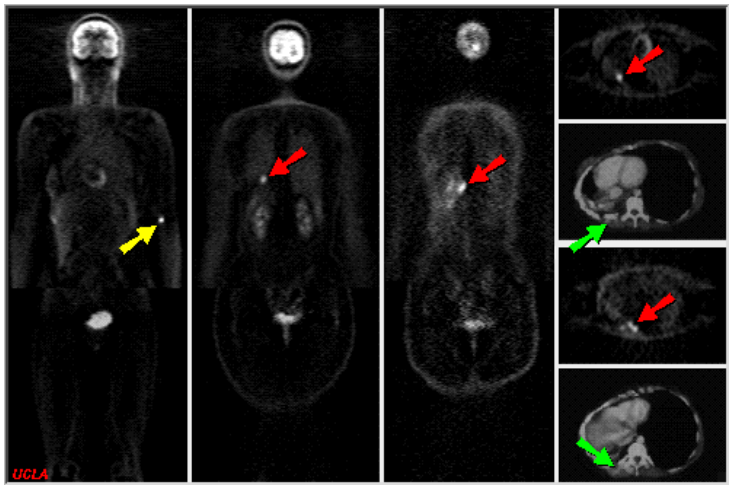
Dual Modality Molecular Imaging Supporting Radiotherapy

As the radiologists are faced with the challenge to achieve very conformal dose distributions while trying to improve local control through dose escalation, the precise location of the target volume and clinical structures are critical.

Through dual modality imaging, it becomes easier to spot the exact location of a tumour, the extent of the disease, and the functional areas to be avoided during the radiation treatment.

Metabolic information can be obtained using a PET/SPECT scanner and anatomic information using a CT/MRI.

Also, detection of unanticipated malignant lesions has a significant clinical impact on healthy individuals and also patients with known malignant disease. In patients with known cancer, work-ups often focus on the patient's primary disease, and incidental coexistence of another primary malignant lesion can be missed.



Fusion imaging in practice. The CT-scan of the chest confirms the presence of a mass in the right chest wall (green arrows). Whole-body FDG-PET confirms hyper metabolism of the mass (red arrows), highly suspicious for recurrence of tumour. Note that the increased activity seen in the arm (yellow arrow) is the injection site; this should not be confused with abnormal uptake.

PET/CT

The Significance of PET/CT

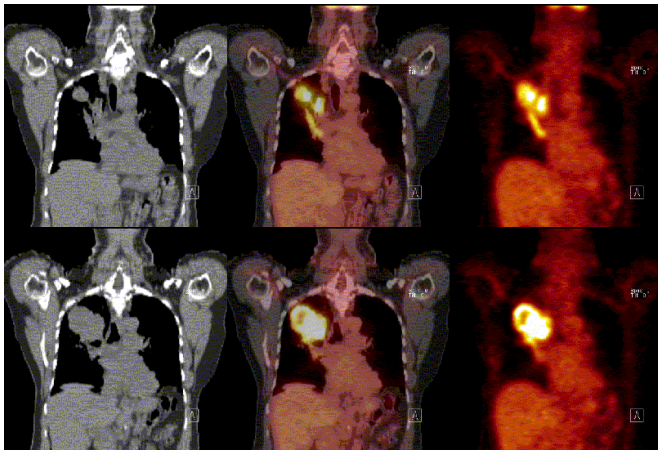
The introduction of high-resolution PET/CT into clinical practice will allow functional imaging to identify early disease well before any anatomical manifestation.

Siemens suggests there has been an almost 100% shift from PET-only to PET/CT systems since 2001, driven by applications in oncology.

Several studies have shown that PET and CT, when evaluated together, increased the diagnostic accuracy of both tests. PET/CT uses various technologies including the CT detector with lutetium oxy-ortho-silicate (LSO) crystal technology that reduces emission scans to 2 to 3 minutes per bed position, providing better attenuation correction.

LSO has a higher light output and a shorter scintillation decay time resulting in improved count rate capabilities. Thus, high FDG doses can be injected and images can be acquired in the three-dimensional mode resulting in improved spatial resolution. This allows for the completion of whole-body PET/CT studies in less than five minutes.

Uptake of this combination has been rapid, particularly within the oncology setting and cardiology appears poised to follow oncology with the development of machines that fuse PET and CT.



Using PET/CT coronal to analyse non-small cell lung cancer of the right upper lobe with pulmonary vein extension in a 68-year-old female with right upper lobe mass.

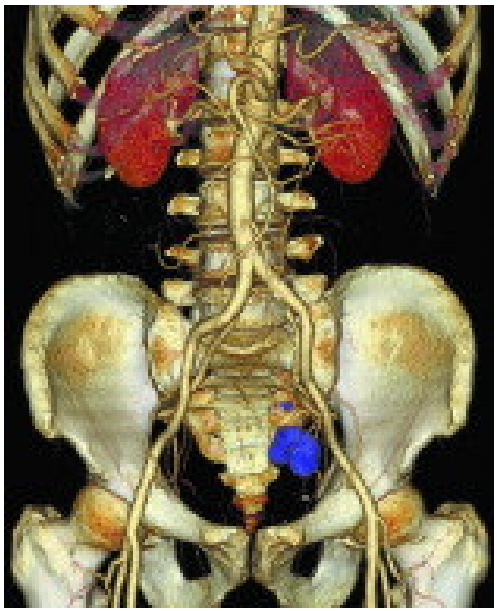
PET/CT in Oncology

Combined PET/CT brings greater accuracy, certainty, improved guided biopsy methods, better treatment planning and response evaluation. Exact anatomical localization of metabolic abnormalities also helps to characterize lesions.

PET/CT is useful in localizing and characterizing incidentally detected lesions in the gastrointestinal tract and adrenal glands. In the case of lung cancer PET/CT has precisely localized the sites of increased FDG uptake.

Studies have reported that PET/CT better predicts the stage of diseases in patients with non-small cell lung carcinoma (NSCLC). Radiation targeting with fused PET/CT images may also result in alterations in radiation therapy planning in patients with NSCLC compared with CT alone.

PET/CT has also shown better sensitivity and specificity in distinguishing benign and malignant abnormalities in the case of thyroid cancer and rectal and colorectal cancer. In difficult clinical situations, such as diagnosis of recurrent ovarian cancer, PET/CT has been found to have an advantage over cross-sectional imaging with higher sensitivity and specificity.



A Colon cancer scan captured by GE's PET/CT and the imaging agent FDG. The fused volume rendering of a PET/CT angiography provides both vascular and metabolic information.

Key Advantages and Limitations of PET/CT

PET/CT advantages include:

- PET/CT offers more accurate localization of FDG uptake.
- Distinction of pathological from physiologic uptake.
- Improvements in monitoring treatment by identifying false positives.
- PET/CT is found to be useful in the initial staging of lung cancer.

PET/CT limitations include:

- Artifacts induced by patient or respiratory motion.
- Respiratory or patient motion induces artifacts on CT and thus, PET/CT images.
- It may not be possible to get a perfect match between PET and CT.
- PET/CT is sometimes inaccurate in localizing the lesions.

PET/MRI

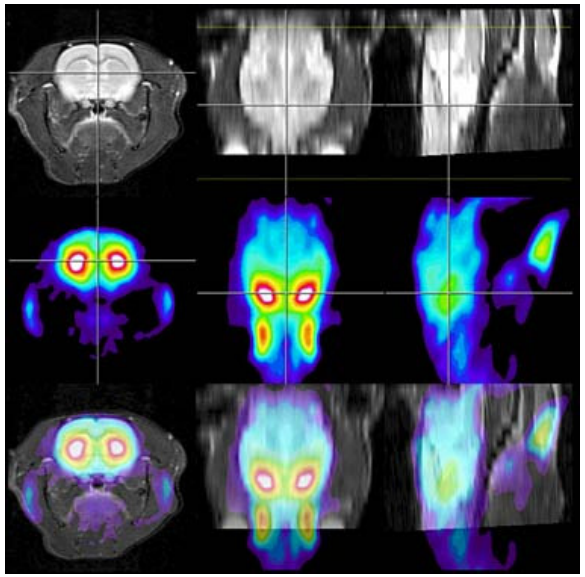
Significance of PET/MRI

Combined PET/MRI scans can provide complimentary data about structure and function and thus has an important role in both clinical and small animal imaging.

Combining PET with MRI technology becomes more challenging due to the strong magnetic fields associated with MRI. Fitting a PET scanner within the small bore of an MRI unit and then getting it to work in a fairly strong magnetic field would be a major challenge.

Nevertheless, significant progress has been made resulting in the design of a prototype small animal PET scanner with lutetium oxy-ortho-silicate (LSO): Cedetector blocks coupled to three multi-channels photo multipliers via optical fibers so that the PET detector can be operated within a conventional MRI system.

Although a number of challenges will have to be met before such a system is scaled up for human studies, it is certainly possible that it may become a reality within the next few years.



Overlay of PET and MRI images.

A. MRI images of a rat brain (axial, multi-slice 256 sq x 16 acquisition, coronal/sagittal views are interpolated).

B. PET imaging of 18F-labeled specific ligand for the dopamin-transport protein. Compound accumulates in brain areas with a high level of dopamin containing neurons.

C. Overlay in all three major directions.

PET/MRI in Oncology

Whole-body PET scanning with FDG can identify areas of cancerous involvement and distinguish malignant from benign lesions and therefore plays an important role in the diagnosis and management of patients with cancer.

PET is limited in its ability to visualize anatomical structures. Whole-body MRI is a promising diagnostic modality for the diagnosis and management of patients with cancer because of its high anatomical resolution.

Whole-body PET and whole-body MRI allow evaluation of both the primary tumour and for the presence of metastasis at the same time.

Going forward, hybrid PET/MRI could become a significant diagnostic modality in cancer applications including pancreatic cancer and cancer screening.

Studies have shown that digitally performed PET/MRI coregistration can increase information on tumour characterization in most cases.

PET/MRI in Neurology

Therapeutic trials in neurological disorders such as Parkinson's and Alzheimer's rely on symptomatic endpoints observed over many years to evaluate progression.

Functional imaging involving PET/MRI may provide a biomarker to assess more subtle changes in disease progression.

The combination of PET and MRI has been used to look inside the living brain to:

- Ascertain the relationship between specific areas of the brain and what function they serve
- Locate the areas of the brain that are affected by neurological disorders
- Develop new strategies to treat disorders.

SPECT/CT

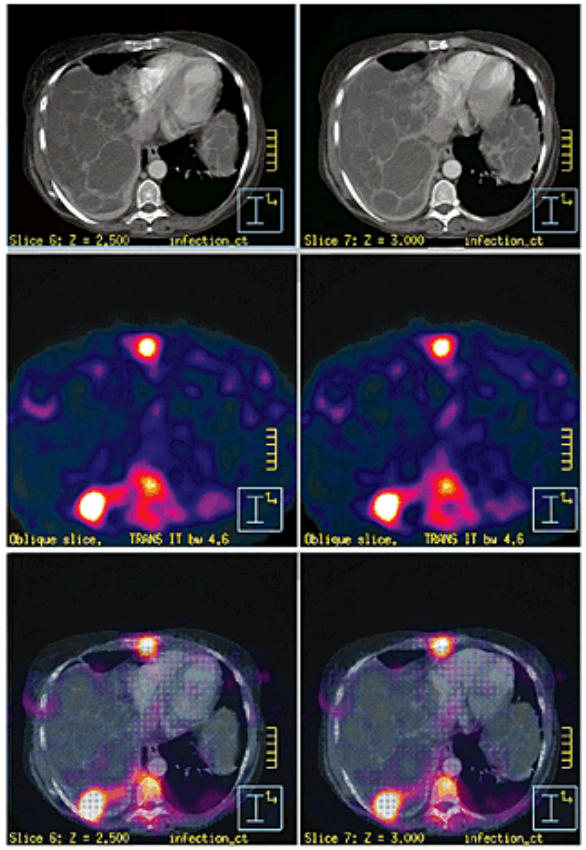
SPECT/CT to Emulate PET/CT?

SPECT/CT has been introduced recently with the expectation that it will emulate PET/CT success as a hybrid imaging modality. The addition of CT may provide a new springboard for SPECT in nuclear cardiology as well as other functional studies.

Combined SPECT with the high-powered CT scanners has found its application in a number of new research and clinical arenas from *in vivo* small animal studies to CT angiography.

By combining high-speed CT scanners with SPECT's definition of disease processes, anatomical mapping and localization can be enhanced.

Most significantly, CT correction greatly reduces the problems of distortion and degradation that typically occur with radionuclide-based methods.



A gallium study on a 64-year-old man with polycystic disease uses SPECT/CT to show the identified cyst in the dome of the liver (**A**: CT image, **B**: SPECT, **C**: SPECT/CT overlay).

Application of SPECT/CT

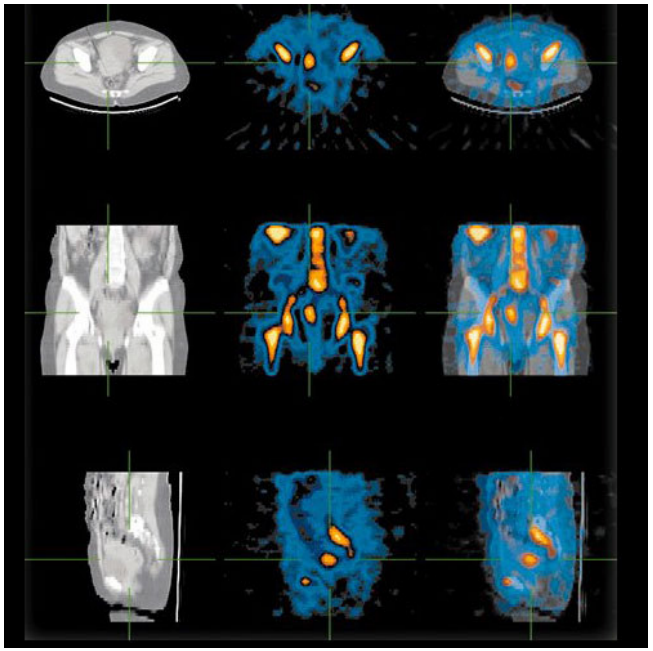
New tracers already under testing specifically target cancers of the brain, thyroid, prostate, breast, lung, ovaries, kidneys, and liver, as well as heart and bone diseases and defects.

The newly developed SPECT tracers are target-specific, attracted only to the tissues they've been designed to find. This enables the physicians to swiftly and precisely observe particular disease processes.

The radioisotopes used have long half-lives that enables monitoring of tissue changes over time. This further strengthens the ability to narrow down the characteristics of a specific disease process.

SPECT/CT helps in identifying ischemia or infarct. It is also useful in reimaging the response to therapy to be able to pick the right drug at the right dose, and to adjust it as needed, to maximize the effects and outcome for that particular patient.

SPECT/CT has been useful in supporting the treatment of non-Hodgkin's lymphoma patients.



SPECT/CT analysis of Non-Hodgkin's Lymphoma. 53 year old female with High Grade Non-Hodgkin's lymphoma of the cervix, after biopsy and partial removal of the tumour. Imaging shows an area of abnormal uptake in the right pelvis. **A:** CT, **B:** SPECT. The combined image **(C)** shows this uptake to be located in the lymphoma in the cervix.

SPECT/CT in Oncology

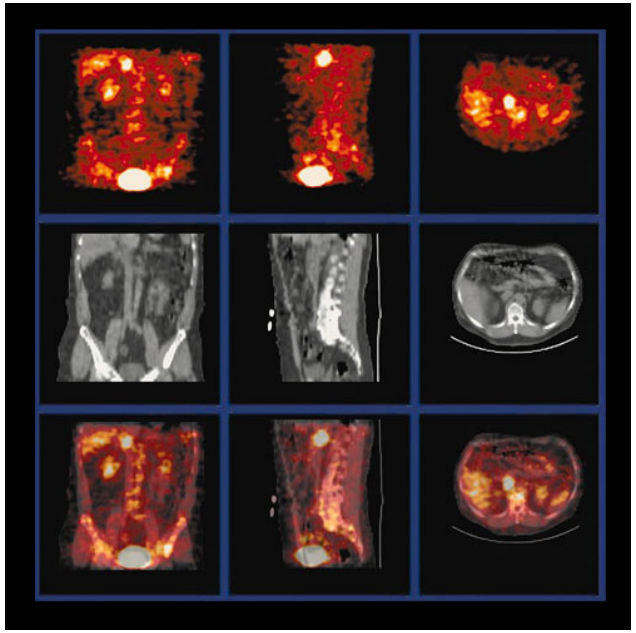
Although SPECT/CT has its applications in oncology, the number of procedures with targeted agents such as Octreoscan (^{111}I labelled peptide) for imaging endocrine tumours, ProstaScint for prostate imaging and NeoTect for lung imaging, has been limited, contrary to expectations of developers.

In addition, PET/CT has pre-empted many oncology SPECT procedures because of the universal nature of FDG and the strong referral patterns established through radiology.

Although there is an opening for SPECT/CT in oncology, there is little justification to make the investment without other higher procedure- volume prospects such as cardiology and areas of general nuclear medicine referenced earlier.

SPECT has had limited application in neurology.

However, there are SPECT agents emerging for imaging Parkinson's disease that could be augmented with CT to improve diagnostic accuracy.



SPECT/CT analysis of colorectal cancer. Co-registration of the functional imaging with the anatomic map, allows focused patient management for the treatment of melanoma in the right adrenal gland.

A: SPECT, **B:**CT, **C:** overlay confirms suspicion of active disease.

SPECT/MRI

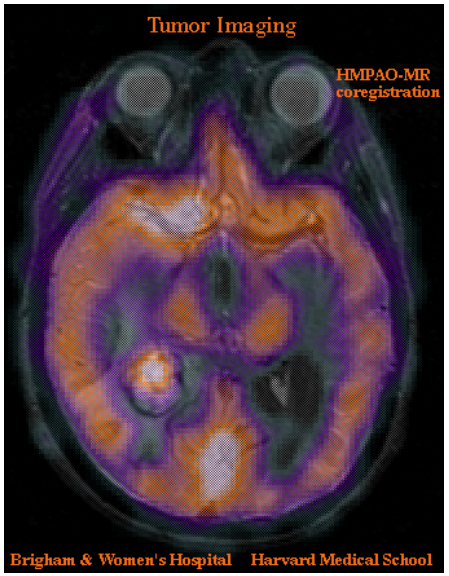
SPECT/MRI

Due to the lack of detailed anatomical information in SPECT images, many studies have combined the use of SPECT and MRI images.

Combining SPECT with MRI addresses some clinical challenges including:

- Improving the reliability and value of SPECT imaging.
- Gathering tissue boundary and volumetric information from brain MRI and validating the reliability of the process.
- More accurate identification of area(s) causing epilepsy prior to surgery.

The clinical benefits of registered SPECT and MRI are in epilepsy, brain tumour, herpes simplex encephalitis, and cerebral infarction.



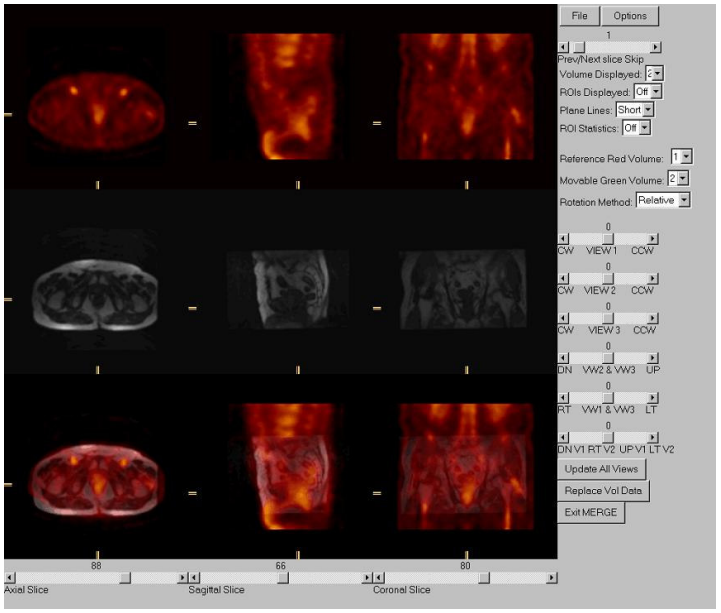
Tumour imaging with SPECT/MRI.

SPECT/MRI in Oncology

The MRI/SPECT fusion made it possible to more accurately identify the location of tumour recurrence as well as determine the area for spectroscopic MRI analysis and for stereotactic biopsy and radiotherapy.

Fused SPECT/MRI images have been used for the diagnosis of recurrent cerebral gliomas. SPECT when used with iodine-131 alpha-methyl tyrosine, a substitute for the more costly Iodine-123, has been justified in view of the nature of the diagnostic problem and also because of the possibility of iodine-131 application on a larger scale.

The importance of applying MRI/SPECT fusion in abdominal and thoracic areas has been recognized, leading to radionuclide therapy for cancer.



SPECT/MRI analysis of prostate cancer. A graphical user interface (GUI) designed in-house is used to manually align the SPECT images (red, top row) with MRI images (middle row), overlaid in the bottom row.

MOLECULAR IMAGING IN SCOTLAND

Current Scottish Academic Expertise

A number of highly skilled research groups exist within Scotland, but to date, there has been limited commercialisation of this know-how.

A range of PET/SPECT tracers are currently in development within academia (mainly for internal use).

Imaging capacity exists and plans are in place for PET/cyclotron facilities at Dundee, Edinburgh and Glasgow, although it is unclear if Scotland needs 4 similar cyclotrons.

SINAPSE: a joint Strategic Research Development Grant (SRDG) bid is proposed for the pooling of brain imaging research resources in Scotland.

Aberdeen

PET/Cyclotron

1.5T MRI

Imaging Science

Dundee

1.5T MRI

Edinburgh

SHEFC 1.5T MRI

Brain SPECT

Imaging science

Glasgow

3T & 1.5T MRI

Brain SPECT

7T small bore MRI

microSPECT

Imaging Science

Scottish Commercialisation Experience - PharmaImaging

The contract research organisation PharmaImaging Group (Livingston) was funded in 2003 through a £15 million combined public (Scottish Executive, Scottish Enterprise) and private sector (GE Medical Systems, Schering) investment package but fell into administration in 2004.

The business model outlined the ambitious plans for the new organisation, which had a number of attractive features:

- The Eliburn Clinic was to operate an all-new, purpose-designed diagnostic imaging centre giving patients access to the latest PET/CT, SPECT, MRI and ultrasound scanning technologies;
- PharmaImaging Limited, the company's contract clinical research arm, intended to provide a comprehensive imaging-based clinical trials service for pharmaceutical companies' drugs.
- PPR Limited (Pharma PET Radiopharmaceuticals) was to manufacture for Schering the radio-pharmaceutical drug Flucis® (FDG) for PET imaging.

Many of the skills and know how behind this venture remain within Scotland and could be tapped into to create new value add opportunities.

Scottish Commercialisation Experience - Photonic Materials

Photonic Materials (Strathclyde Business Park) was founded in 1999 with the vision of developing a differentiated crystal manufacturing solution in the telecoms industry.

Partly due to a collapsing telecoms market in 2002, Photonic Materials repositioned itself in medical imaging, focusing on novel crystals for detectors in PET scanners, alongside oil well imaging.

To date the company has received c.£15m in funding from 3i plc, Scottish Equity Partners, Royal Bank of Scotland Equity Finance and Intel Capital.

Key crystals in development:

Their aim is to manufacture crystals which improve image quality and reduce scan times. The company has developed technology to cost effectively manufacture the following crystals:

- Lutetium Yttrium Orthosilicate (LYSO).
- Lutetium Aluminium Perovskite (LuAP).

NEXT STEPS

ITI Keen to Initiate Dialogue with Interested Parties

Our initial findings suggest that the following opportunities exist :

Tracer development: Exploitation of current tracers in other applications and the development of novel tracers. A variety of technologies including antibody fragments, quantum dots, amino acids and other biological molecules could be leveraged to develop novel tracers and potentially targeted tracers to molecular imaging.

Technological Innovations in: New modalities as stand alone or bolt on applications. Improving performance of current modalities, particularly in combining modalities for improved R&D efficiency or clinical diagnosis.

ITI Life Sciences would very much welcome dialogue with those keen to discuss any aspect of this report or their own interest in the molecular imaging field. We would particularly welcome enquiries from those keen to discuss exciting projects that are aligned with the findings of this report.

To arrange a discussion, please contact ITI Life Sciences at:

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