PET-6

IMPACT OF PET-CT IN NEW ERA OF MEDICINE

History and Developments

Positron Emission Tomography (PET) is a relatively recent technology, but the principle has been understood for half a century. The first commercial PET scanners were developed in the late 1960's and used analog electronics to generate tomographic ("sliced") images. The Royal Adelaide Hospital (RAH) investigated this technology in 1968 for bone scanning, but found it too slow and inefficient for clinical use, and difficult to source the isotope.

In the late 1970's more sensitive detectors and tomographic capabilities began to appear. These scanners were still limited to single regions, but improvements continued, with better resolution, and movement from the research area to clinical use.By the mid-1990's, PET had become an important diagnostic tool for medical diagnosis and for dynamic studies of human metabolism. Australia established its first PET facilities, including cyclotrons, in 1992 at the Royal Prince Alfred Hospital, Sydney and Austin Hospital Melbourne. In March 2005 a PET scanner with integral CT was installed at the RAH.

Working and Description of various imaging modalities

Positron emission tomography (PET) is a nuclear medicine imaging technique which produces a three-dimensional image or map of functional processes in the body. The system detects pairs of gamma rays emitted indirectly by a positron-emitting radionuclide (tracer), which is introduced into the body on a biologically active molecule. Images of tracer concentration in 3-dimensional space within the body are then reconstructed by computer analysis. In modern scanners, this reconstruction is often accomplished with the aid of a CT X-ray scan performed on the patient during the same session, in the same machine. To conduct the scan, a short-lived radioactive tracer isotope, which decays by emitting a positron, which also has been chemically incorporated into a biologically active molecule, is injected into into blood circulation. There is a waiting period while the active molecule becomes concentrated in tissues of interest; then the research subject or patient is placed in the imaging scanner. The molecule most commonly used for this purpose is fluorodeoxyglucose (FDG), a sugar, for which the waiting period is typically an hour and the concentrations of tracer imaged then give tissue metabolic activity, in terms of regional glucose uptake.

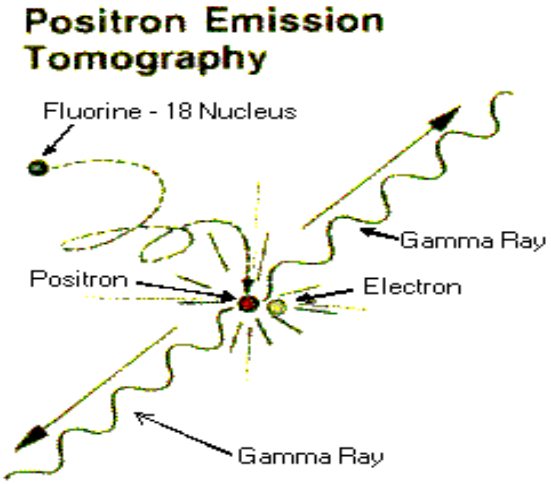
As the radioisotope undergoes positron emission decay (also known as positive beta decay), it emits a positron, the antimatter counterpart of an electron. After travelling up to a few millimeters the positron encounters and annihilates with an electron, producing a pair of annihilation (gamma) photons moving in opposite directions. These are detected when they reach a scintillator material in the scanning device, creating a burst of light which is detected by photomultiplier tubes or silicon avalanche photodiodes (Si APD). The technique depends on simultaneous or coincident detection of the pair of photons; photons which do not arrive in pairs (i.e., within a few nanoseconds) are ignored.

Events

1. Localization of the positron annihilation:

The most significant fraction of electron-positron decays result in two 511 keV gamma photons being emitted at almost 180 degrees to each other; hence it is possible to localize their source along a straight line of coincidence (also called formally the line of response or LOR). In practice the LOR has a finite width as the emitted photons are not exactly 180 degrees apart. If the recovery time of detectors is in the picosecond range rather than the 10's of nanosecond range, it is possible to calculate the single point on the LOR at which an annihilation event originated,

by measuring the "time of flight" of the two photons. This technology is not yet common, but it is available on some new systems.



Radionuclides:

Radionuclides used in PET scanning are typically isotopes with short half lives such as carbon-11 (~20 min), nitrogen-13 (~10 min), oxygen-15 (~2 min), and fluorine-18 (~110 min). These radionuclides are incorporated either into compounds normally used by the body such as glucose (or glucose analogues), water or ammonia, or into molecules that bind to receptors or other sites of drug action. Such labelled compounds are known as radiotracers. It is important to recognize that PET technology can be used to trace the biologic pathway of any compound in living humans (and many other species as well), provided it can be radiolabeled with a PET isotope. Due to the short half lives of most radioisotopes, the radiotracers must be produced using a cyclotron and radiochemistry laboratories that are in close proximity to the PET imaging facility. The half life of fluorine-18 is long enough such that fluorine-18 labeled radiotracers can be manufactured commercially at an offsite location. Because the half-life of F-18 is about two hours, the prepared dose of a radiopharmaceutical bearing this radionuclide will undergo multiple half-lives of decay during the working day. This necessitates frequent recalibration of the remaining dose (determination of activity per unit volume) and careful planning with respect to patient scheduling.

2. Image reconstruction:

More commonly, a technique much like the reconstruction of computed tomography (CT) and single photon emission computed tomography (SPECT) data is used, although the data set collected in PET is much poorer than CT, so reconstruction techniques are more difficult. Using statistics collected from tens-of-thousands of coincidence events, a set of simultaneous equations for the total activity of each parcel of tissue along many LORs can be solved by a number of techniques, and thus a map of radioactivities as a function of location for parcels or bits of tissue (also called voxels), may be constructed and plotted. The resulting map shows the tissues in which the molecular probe has become concentrated, and can be interpreted by a nuclear medicine physician or radiologist in the context of the patient's diagnosis and treatment plan. The raw data collected by a PET scanner are a list of 'coincidence events' representing near-simultaneous detection of annihilation photons by a pair of detectors. Each coincidence event represents a line in space connecting the two detectors along which the positron emission occurred. Coincidence events can be grouped into projections images, called sinograms. The sinograms are sorted by the angle of each view and tilt, the latter in 3D case images. The sinogram images are analogous to the projections captured by computed tomography (CT) scanners, and can be reconstructed in a similar way. However, the statistics of the data is much worse than those obtained through transmission tomography. A normal PET data set has millions of counts for the whole acquisition, while the CT can reach a few billion counts. As such, PET data suffer from scatter and random events much more dramatically than CT data does. In practice, considerable pre-processing of the data is required - correction for random coincidences, estimation and subtraction of scattered photons, detector dead-time correction (after the detection of a photon, the detector must "cool down" again) and detector-sensitivity correction (for both inherent detector sensitivity and changes in sensitivity due to angle of incidence). Filtered back projection (FBP) has been frequently used to reconstruct images from the projections. This algorithm has the advantage of being simple while having a low requirement for computing resources. However, shot noise in the raw data is prominent in the reconstructed images and areas of high tracer uptake tend to form streaks across the image. Iterative expectation-maximization algorithms are now the preferred method of reconstruction. The advantage is a better noise profile and resistance to the streak artifacts common with FBP, but the disadvantage is higher computer resource requirements.

3. Fusion of PET with CT and MRI:

PET scans are increasingly read alongside CT or magnetic resonance imaging (MRI) scans, the combination ("co-registration" or, “fusion”) giving both anatomic and metabolic information (i.e.,

what the structure is, and what it is doing biochemically). Oncologists were often frustrated in trying to match PET images with CT images to determine the precise location of a tumor in relation to an organ or the spinal column. They had little choice other than to "eyeball" the two separate images and make an educated guess as to the tumor's exact location - until 1992, when engineer Ron Nutt and physicist David Townsend came up with the idea of combining a PET and CT into one machine.

After working on their combined PET and CT concept for three years, Nutt and Townsend received a grant from the National Cancer Institute. This enabled the completion of a prototype machine, which was installed at the University of Pittsburgh medical center in 1998. The pair designed the machine to be more patient-friendly by making the diameter of the PET/CT tunnel 28 inches, far more spacious than the typical MRI tunnels.Time Magazine honored PET/CT as the "Medical Science Invention of the Year" in 2000, noting that the PET/CT scanner has "provided medicine with a powerful new diagnostic tool."

Because PET imaging is most useful in combination with anatomical imaging, such as CT, modern PET scanners are now available with integrated high-end multi-detector-row CT scanners. Because the two scans can be performed in immediate sequence during the same session, with the patient not changing position between the two types of scans, the two sets of images are more-precisely registered, so that areas of abnormality on the PET imaging can be more perfectly correlated with anatomy on the CT images. This is very useful in showing detailed views of moving organs or structures with higher amounts of anatomical variation, such as are more likely to occur outside the brain.

The most critical components of a PET camera are the detectors . In some cases these are similar to those used in single-photon imaging: large crystals of sodium-iodide coupled to many photo-multiplier tubes (PMTs). In these detectors a rectangular bundle of crystals, a block, is optically coupled to several PMTs. When a photon interacts in the crystal, electrons are moved from the valence band to the conduction band. These electrons return to the valence band at impurities in the crystal, emitting light in the process. Since the impurities usually have metastable excited states, the light output decays exponentially at a rate characteristic of the crystal. The ideal crystal has high density so that a large fraction of incident photons scintillate, high light output for positioning accuracy, fast rise-time for accurate timing, and a short decay time so that high counting rates can be handled. Most current scanners use bismuth-germanate (BGO), which generates approximately 2500 light photons per 511 keV photon, and has a

decay time (i.e., time-constant) of 300 ns. One such block, for example, couples a 7x8 array of BGO crystals to four PMTs where each crystal is 3.3 mm wide in the transverse plane, 6.25 mm wide in the axial dimension, and 30 mm deep. The block is fabricated in such a way that the amount of light collected by each PMT varies uniquely depending on the crystal in which the scintillation occurred. Hence integrals of the PMT outputs can be decoded to yield the position of each scintillation. The sum of the integrated PMT outputs is proportional to the energy deposited in the crystal.

If the data are acquired in the slice-collimated (2D) mode, the lines-of-response connecting crystals can be binned into sets of parallel projections at evenly spaced angles as shown in figure. Two characteristics are evident. First, samples are unevenly spaced, with finer sampling at the edges of the field-of-view than at the center. Second, the samples along the heavy solid line at angles one and three are offset by one-half of the detector spacing from samples at angle two. Therefore, adjacent parallel projections can be combined to yield one-half the number of projection angles with a sampling distance of one-half the detector width. A typical block might have 3.3 mm thick crystals, so the resulting sampling distance would be 1.65 mm.

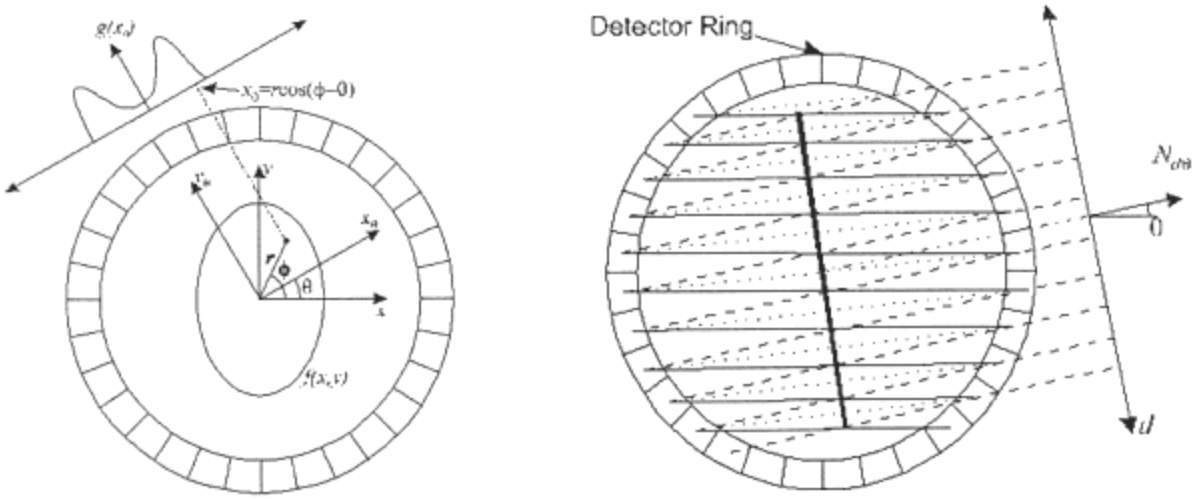
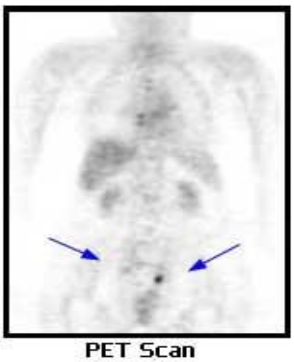


Figure: Projection geometry (left) and sampling pattern in the transaxial plane for a PET scanner (right). Each segment in the detector ring represents one crystal. The solid lines show the parallel projections for the first angle, the dotted lines for the second angle, and the dashed lines for the third angle.

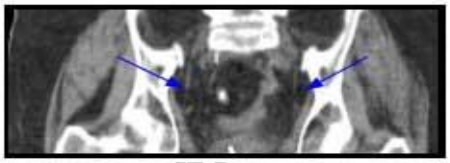
The Nyquist criterion is usually stated in medical imaging applications as requiring that the sampling distance are one-half the spatial resolution expressed as the full-width-at-half-maximum (FWHM). Hence, this block would support a spatial resolution of 3.3 mm. In fact, a

scanner with this crystal size has a measured resolution that is somewhat worse, varying from 3.6 mm at the center of the field-of-view to 5.0 mm at 20 cm from the center. This occurs because scintillations usually consist of one or more Compton interactions followed by photoelectric absorption (assuming the photon is not scattered out of the crystal). Since a 511 keV photon travels on average 7.5 mm in BGO before interacting, the light output is spatially distributed, especially at large radial distances where it is often distributed across two crystals.

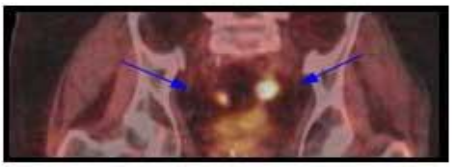
The best obtainable resolution is termed the intrinsic resolution. This resolution is rarely achieved in practice because unfiltered images are usually very noisy. Although current scanners have intrinsic resolutions of less than 5 mm, the final resolution of the image is usually greater than 8 mm because the reconstruction algorithms trade-off resolution for reduced image variance. This final resolution is called the reconstructed resolution. Therefore, the resolution of PET images as they are typically used is not determined by the detectors, but by the degree to which resolution must be degraded to achieve an acceptable image variance. Since the variance is determined by the numbers of counts that can be collected during the scan, the constraints that govern the clinically useful resolution of PET images are the dosage of the radio-pharmaceutical, the duration of the scan, the sensitivity of the scanner, and the count-rate capability of the scanner.



PET Scan



CT Scan



PET/CT Scan

4. Attenuation correction:

As different LORs must traverse different thicknesses of tissue, the photons are attenuated differentially. The result is that structures deep in the body are reconstructed as having falsely low tracer uptake. Contemporary scanners can estimate attenuation using integrated x-ray CT equipment, however earlier equipment offered a crude form of CT using a gamma ray (positron emitting) source and the PET detectors. While attenuation corrected images are generally more faithful representations, the correction process is itself susceptible to significant artifacts. As a result, both corrected and uncorrected images are always reconstructed and read together.

5. 2D/3D reconstruction:

Early PET scanners had only a single ring of detectors, hence the acquisition of data and subsequent reconstruction was restricted to a single transverse plane. More modern scanners now include multiple rings, essentially forming a cylinder of detectors. There are two approaches to reconstructing data from such a scanner: 1) treat each ring as a separate entity, so that only coincidences within a ring are detected, the image from each ring can then be

reconstructed individually (2D reconstruction), or 2) allow coincidences to be detected between rings as well as within rings, then reconstruct the entire volume together (3D). 3D techniques have better sensitivity (because more coincidences are detected and used) and therefore less noise, but are more sensitive to the effects of scatter and random coincidences, as well as requiring correspondingly greater computer resources. PET is both a medical and research tool. It is used heavily in clinical oncology (medical imaging of tumors and the search for metastases), and for clinical diagnosis of certain diffuse brain diseases such as those causing various types of dementias. PET is also an important research tool to map normal human brain and heart function. This is particularly valuable in cancer research, as it results in an increase in the statistical quality of the data (subjects can act as their own control) and substantially reduces the numbers of animals required for a given study.

While some imaging scans such as CT and MRI isolate organic anatomic changes in the body, PET scanners, like SPECT are capable of detecting areas of molecular biology detail (even prior to anatomic change). The PET scanner does this via the use of radiolabelled molecular probes that have different rates of uptake, depending on the type and function of tissue involved. The changing of regional blood flow in various anatomic structures (as a measure of the injected positron emitter) can be visualized and relatively quantified with a PET scan.

PET imaging is best performed using a dedicated PET scanner. However, it is possible to acquire PET images using a conventional dual-head gamma camera fitted with a coincidence detector. The quality of gamma-camera PET is considerably lower, and acquisition is slower. However, for institutions with low demand for PET, this may allow on-site imaging, instead of referring patients to another center, or relying on a visit by a mobile scanner.

Factors Affecting PET

1. Attenuation
2. Random Coincidences
3. Scatter Coincidences
4. Spatial Resolution
5. Sensitivity

PET is a valuable technique for some diseases and disorders, because it is possible to target the radio-chemicals used for particular bodily functions.

1. Oncology: PET scanning with the tracer fluorine-18 (F-18) fluorodeoxyglucose (FDG), called FDG-PET, is widely used in clinical oncology. This tracer is a glucose analog that is taken up by glucose-using cells and phosphorylated by hexokinase (whose mitochondrial form is greatly elevated in rapidly-growing malignant tumours). A typical dose of FDG used in an oncological scan is 200-400 MBq for an adult human. Because the oxygen atom which is replaced by F-18 to generate FDG is required for the next step in glucose metabolism in all cells, no further reactions occur in FDG. Furthermore, most tissues (with the notable exception of liver and kidneys) cannot remove the phosphate added by hexokinase. This means that FDG is trapped in any cell which takes it up, until it decays, since phosphorylated sugars, due to their ionic charge, cannot exit from the cell. This results in intense radiolabeling of tissues with high glucose uptake, such as the brain, the liver, and most cancers. As a result, FDG-PET can be used for diagnosis, staging, and monitoring treatment of cancers, particularly in Hodgkin's disease, non Hodgkin's lymphoma, and lung cancer. Many other types of solid tumors will be found to be very highly labeled on a case-by-case basis-- a fact which becomes especially useful in searching for tumor metastasis, or for recurrence after a known highly-active primary tumor is removed. Because individual PET scans are more expensive than "conventional" imaging with computed tomography (CT) and magnetic resonance imaging (MRI), expansion of FDG-PET in cost-constrained health services will depend on proper health technology assessment; this problem is a difficult one because structural and functional imaging often cannot be directly compared, as they provide different information. Oncology scans using FDG make up over 90% of all PET scans in current practice.
2. PET scan of the human brain.

   Neurology: PET neuroimaging is based on an assumption that areas of high radioactivity are associated with brain activity. What is actually measured indirectly is the flow of blood to different parts of the brain, which is generally believed to be correlated, and has been measured using the tracer oxygen-15. However, because of its 2-minute half-life O-15 must be piped directly from a medical cyclotron for such uses, and this is difficult. In practice, since the brain is normally a rapid user of glucose, and since brain pathologies such as Alzheimer's disease greatly decrease brain metabolism of both glucose and oxygen in tandem, standard FDG-PET of the brain, which measures regional glucose use, may also be successfully used to differentiate Alzheimer's disease

from other dementing processes, and also to make early diagnosis of Alzheimer's disease. The advantage of FDG-PET for these uses is its much wider availability. PET imaging with FDG can also be used for localization of seizure focus: A seizure focus will appear as hypometabolic during an interictal scan. Several radiotracers (i.e. radioligands) have been developed for PET that are ligands for specific neuroreceptor subtypes such as [^{11}C] raclopride and [^{18}F] fallypride for dopamine D2/D3 receptors, [^{11}C]McN 5652 and [^{11}C]DASB for serotonin transporters, or enzyme substrates (e.g. 6-FDOPA for the AADC enzyme). These agents permit the visualization of neuroreceptor pools in the context of a plurality of neuropsychiatric and neurologic illnesses. A novel probe developed at the University of Pittsburgh termed PIB (Pittsburgh Compound-B) permits the visualization of amyloid plaques in the brains of Alzheimer's patients. This technology could assist clinicians in making a positive clinical diagnosis of AD pre-mortem and aid in the development of novel anti-amyloid therapies.

3. Cardiology, atherosclerosis and vascular disease study: In clinical cardiology, FDG-PET can identify so-called "hibernating myocardium", but its cost-effectiveness in this role versus SPECT is unclear. Recently, a role has been suggested for FDG-PET imaging of atherosclerosis to detect patients at risk of stroke [2].
4. Neuropsychology / Cognitive neuroscience: To examine links between specific psychological processes or disorders and brain activity.
5. Psychiatry: Numerous compounds that bind selectively to neuroreceptors of interest in biological psychiatry have been radiolabeled with C-11 or F-18. Radioligands that bind to dopamine receptors (D1,D2, reuptake transporter), serotonin receptors (5HT1A, 5HT2A, reuptake transporter) opioid receptors (mu) and other sites have been used successfully in studies with human subjects. Studies have been performed examining the state of these receptors in patients compared to healthy controls in schizophrenia, substance abuse, mood disorders and other psychiatric conditions.
6. Pharmacology: In pre-clinical trials, it is possible to radiolabel a new drug and inject it into animals. The uptake of the drug, the tissues in which it concentrates, and its eventual elimination, can be monitored far more quickly and cost effectively than the older technique of killing and dissecting the animals to discover the same information. PET scanners for rats and non-human primates are marketed for this purpose. The technique is still generally too expensive for the veterinary medicine market, however, so very few pet PET scans are done. Drug occupancy at the purported site of action can

also be inferred indirectly by competition studies between unlabeled drug and radiolabeled compounds known apriori to bind with specificity to the site.

Safety

PET scanning is non-invasive, but it does involve exposure to ionizing radiation. The total dose of radiation is small, however, usually around 7 mSv. This can be compared to 2.2 mSv average annual background radiation in the UK, 0.02 mSv for a chest x-ray, up to 8 mSv for a CT scan of the chest, 2-6 mSv per annum for aircrew (data from UK National Radiological Protection Board). Patients with small children may be advised to limit proximity to them for several hours following the completion of the test.

Limitations

The minimization of radiation dose to the subject is an attractive feature of the use of short-lived radionuclides. Besides its established role as a diagnostic technique, PET has an expanding role as a method to assess the response to therapy, in particular, cancer therapy where the risk to the patient from lack of knowledge about disease progress is much greater than the risk from the test radiation.

Limitations to the widespread use of PET arise from the high costs of cyclotrons needed to produce the short-lived radionuclides for PET scanning and the need for specially adapted on-site chemical synthesis apparatus to produce the radiopharmaceuticals. Few hospitals and universities are capable of maintaining such systems, and most clinical PET is supported by third-party suppliers of radiotracers which can supply many sites simultaneously. This limitation restricts clinical PET primarily to the use of tracers labelled with F-18, which has a half life of 110 minutes and can be transported a reasonable distance before use, or to rubidium-82, which can be created in a portable generator and is used for myocardial perfusion studies. Nevertheless, in recent years a few on-site cyclotrons with integrated shielding and hot labs have begun to accompany PET units to remote hospitals. The presence of the small on-site cyclotron promises to expand in the future as the cyclotrons shrink in response to the high cost of isotope transportation to remote PET machines

Quality Control Tests

1. Daily Tests

2. Uniformity of the image is checked daily using a elictical filled with a positron emitter
3. Weekly Tests
4. Spatial Resolution is checked for by service personnel by periodically using the line spread functions
5. Center of Rotation is checked so that there are no deviations from the proper alignment.

Future Perspectives

A noninvasive, clinically applicable method of imaging the expression of successful gene transduction in target tissue or specific organs of the body would be of considerable value for monitoring and evaluating gene therapy in human subjects. PET imaging could define the location, magnitude, and persistence of gene expression over time. Targeting of gene therapy to a particular tissue (e.g., tumor) or specific organs of the body is an increasingly active area of research. Several important issues for clinical optimization of gene therapy remain unresolved in many current clinical protocols: (a) Has gene transduction or transfection been successful? (b) Is the distribution of the transduced or transfected gene localized to the target organ or to target tissue, and is the distribution in the target optimal? (c) Is the level of transgene expression in the target organ or tissue sufficient to result in a therapeutic effect? (d) Does the transduced or transfected gene localize to any organ or tissue at sufficient levels to induce unwanted toxicity? (e) In the case of combined prodrug and gene therapy protocols, when is transgene expression at a maximum, and when is the optimal time to initiate treatment with the prodrug? (f) How long does transgene expression persist in the target and other tissues?

Noninvasive-imaging techniques using selected reporter gene and reporter probe combinations will provide a practical and clinically useful way to identify successful gene transduction and expression in patients undergoing gene therapy. One could argue that biopsies of target tissue or blood sampling and analysis of transgene expression, or assay for secretable marker (e.g., carcinoembryonic antigen) could be performed and that imaging is not critical. However, imaging provides some clear advantages, including (a) the ability to repeatedly assess gene expression over time, especially when multiple sequential biopsies are not feasible; (b) the absence of any perturbation of the underlying tissue, which occurs with biopsy procedures; and (c) the ability to obtain 3D spatial information in the entire body as well as target organs and tumors, which could be of considerable value in addressing toxicity issues.

HSV1-*tk* has the advantage of being both a therapeutic gene (combined with ganciclovir treatment) and a reporter gene (using an appropriate radiolabeled probe, such as FIAU or FHBG). This combination allows for direct imaging of the therapeutic gene product (HSV1-TK) and can be used to define the location, magnitude, and duration of HSV1-*tk* gene expression. Experimental validation of this approach has been demonstrated in animal models of colorectal metastases to the liver treated either with adenovirus-mediated HSV1-*tk* gene transfer and ganciclovir (suicide gene therapy) or with conditionally replicating, oncolytic herpes viruses that constitutively express the HSV1-*tk* gene. However, most therapeutic genes do not lend themselves to direct imaging of their transgene product. Furthermore, the development and validation of a new probe and a new imaging paradigm specific to each therapeutic transgene of interest would be a very costly and time-consuming endeavor. Many therapeutic gene products do not readily lend themselves to radionuclide assessment, and it may not even be possible in some cases. It is therefore more reasonable to consider alternative strategies for indirect imaging of therapeutic gene expression that use established reporter gene–reporter probe combinations.

Recommended Readings

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