Molecular imaging is broadly defined as the characterization and measurement of biologic processes in living animals, model systems, and humans at the cellular and molecular level using remote imaging detectors. With a first draft of the human genome completed and a refined map underway, sequencing of the human genome is expected to lead to new medical therapies, diagnostics, and, ultimately, cures previously not imagined. In this emerging “postgenomic era,” wherein functionality will be added to this vast array of genetic information, opportunity exists for imaging to play a significant role in both basic and translational research, as well as in clinical care for cancer patients. Herein, future objectives are focused on adding functional information through molecular imaging. The goal is to advance patient care and our understanding of medicine through noninvasive in vivo interrogation of the cellular and molecular events mediating normal physiology and pathologic processes. In the future, it is likely that genetic information will become the primary basis for day-to-day management and treatment decisions, and therapies will be individualized to each patient’s biochemical state. Major efforts in clinical imaging will shift from anatomic morphometric characterization to noninvasive analysis of molecular processes in vivo.

Molecular imaging is focused on noninvasive, repetitive monitoring of gene expression in vivo. The target genes can be either endogenous or exogenous genes. To meet the goal of monitoring endogenous genes in vivo, a strategic choice must be made regarding whether it is best to image deoxyribonucleic acid (DNA) per se, messenger ribonucleic acid (mRNA transcripts), the protein product of gene expression, or functional activity of the expressed protein. The best strategy may depend on the biomedical context of the target gene under investigation and the desired endpoint of the clinical application. Similarly, for monitoring exogenous (transgene) gene expression in vivo, as will occur in gene therapy or use of reporter genes, the choice of measuring DNA, mRNA, protein, or function remains fundamental to designing optimal imaging strategies and probes. Ultimately, these choices will be influenced by the characteristics of the biochemical and pathophysiologic pathways under investigation and their potential as imaging targets in vivo. One consideration relates to the number of target molecules and their impact on generating sufficient signal-to-noise for imaging. For example, direct imaging of DNA would require imaging just two molecules per cell, a considerable challenge for remote imaging devices, such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), and optical imaging. Furthermore, any two DNA molecules may not be identical (heterologous polymorphisms). Non-specific and nontarget binding of imaging probes may overwhelm specific signals arising from target DNA. Similarly, mRNA is typically present at only 50 to thousands of molecules per cell and, again, direct imaging approaches requiring one-to-one correlation with the target molecules face considerable challenges. Conversely, proteins can be present at significantly higher levels, perhaps thousands to millions of copies per cell, and thus, direct imaging of proteins is achieved readily. Indeed, as will be seen below, direct molecular imaging of receptor subtypes with radiopharmaceuticals is already a clinical reality. Finally, imaging protein function has the potential for massive signal amplification when the target protein is, for example, an enzyme that can intensify the signal through metabolic conversion or activation of a precursor substrate or transport of a prodrug into an intracellular compartment.

Most (but not necessarily all) molecular imaging approaches make use of image-enhancing or contrast agents that provide molecular specificity to the imaging signal. These agents have inherent physicochemical differences producing their respective image contrast that, in turn, provide advantages or limitations for certain types of molecular imaging queries. In practice, choice of imaging modality and probe usually reduce to choosing between higher spatial resolution and high sensitivity (Figure 36i-1). For example, PET and SPECT agents inherently are synthesized at sufficiently high specific activity to enable use of tracer (nonpharmacologic) concentrations of compound (picomolar) for detecting molecular signals and providing desired levels of image contrast. However, the physics of gamma ray detection result in lower spatial resolution. Conversely, MRI contrast agents that affect water relaxivity inherently provide higher spatial resolution than PET or SPECT imaging. However, because of the indirect nature of enhancement produced by MRI contrast agents, higher concentrations of material, on the order of 10 to 100 micromolar concentrations, generally are necessary to produce sufficient image contrast. These pharmacologic levels of compound result in a stringent standard for MRI contrast agents in regard to clinical risks of toxicity, cross-reactivity, and pharmacodynamic effects of the agents in vivo. Pharmacologic concentrations of contrast agents also may perturb the underlying molecular signal that is being monitored by MRI. Thus, when high sensitivity is desired, tracer technologies will provide advantages for many molecular imaging applications. In contrast, when high spatial resolution is required, MRI may provide the necessary information. Similar tradeoffs could extend to ultrasonogram contrast agents, optical imaging techniques, and even x-ray contrast agents. In addition, fusion imaging strategies are rapidly becoming clinical reality, which enables, for example, the biochemical information contained in PET images to be coregistered with the high spatial information contained in CT images. Because the goal of molecular imaging is to interrogate specific molecular signals, the underlying biomedical question, rather than the technology itself, will drive the choice of imaging agent and technique(s).

Researchers and clinicians already have developed and characterized methods for oncologic imaging of endogenous proteins and their respective functions. This review highlights several significant advances in imaging enzymes (hexokinase, thymidine kinase, β-galactosidase),
receptors (somatostatin receptor subtypes, neurotensin receptor subtypes, αvβ3 integrin), and transporters (MDRI P-glycoprotein, sodium-iodide symporter). In addition, innovative methods to image reporter transgenes (herpes simplex virus 1 thymidine kinase, somatostatin receptor subtype 2, transferrin receptor, luciferase) are under investigation for imaging gene promoter activation and repression, signal-transduction pathways and protein–protein interactions in vivo. The reader is also referred to several recent reviews for additional information.3-5 These examples point to the present and promising future of clinical molecular imaging in the emerging era of molecular medicine.

**CLINICAL MOLECULAR IMAGING TODAY: PET AND SPECT**

**ENZYMES** Positron emission tomography (PET) with 2-(18F)-fluoro-deoxy-d-glucose (FDG) may be characterized as one of the first “molecular imaging” techniques validated by basic cancer research and used in a clinical setting.6 Warburg recognized the increased rates of glycolysis present in tumors more than 70 years ago.7 Hexokinase catalyzes the initial, rate-limiting step in glycolysis, which is phosphorylation of glucose to glucose-6-phosphate. FDG, an analog of glucose, enters cells through the same pathways of facilitated diffusion as glucose, that is, via glucose transporters Glut1 and Glut4, and is subsequently phosphorylated by hexokinase. However, FDG-6-phosphate is not further metabolized significantly and, because it is negatively charged, remains trapped within cells. Imaging of hexokinase activity can be achieved by incorporating 18F into FDG, enabling detection of the trapped, phosphorylated metabolite by PET. Pharmacologic doses of FDG actually inhibit glycolysis in vivo, but imaging with this compound can be performed safely because only tracer amounts are needed for PET. Transport kinetics of FDG across tumor cell membranes can also affect final imaging signal. The importance of transport of FDG has been well shown in the myocardium and skeletal muscle,8,9 and several groups have shown that Glut1 protein levels are increased on the cell surface of many cancer cells.10,11 Imaging of “tumor metabolism” with FDG has an established clinical utility for detection of cancer, staging cancer, particularly for identification of metastatic disease, and guiding therapeutic choices.12-15 FDG–PET has proven value in preoperative staging and assessment of patients with recurrent or residual disease, especially colorectal cancer, head and neck tumors, lymphoma, and melanoma.16-20 FDG–PET also has been validated in the work-up and characterization of indeterminate single pulmonary nodules.21,22

In an alternative approach, investigators have sought more direct measures of tumor progression with a spotlight on cell proliferation, one hallmark of cancer.23 One tactic has been use of radiolabeled thymidine, a method that has been used for years in cell culture and animal studies to assess cell proliferation. Rapidly incorporated into newly synthesized DNA, thymidine analogs radiolabeled with PET isotopes can provide images of tumor cell proliferation. Several 18F-labeled analogs have been synthesized and two compounds show promise, 18F-labeled 3'-deoxy-3'-fluorothymidine (FLT)24 and 1-(2'-fluoro-2'-deoxy-β-d-ribofuranosyl)-thymidine (FMAU).25,26 FLT and FMAU are transported into cells by the nucleoside transporter family and phosphorylated by endogenous thymidine kinase (TK) leading to intracellular trapping of the radiopharmaceuticals. When prepared at high specific activity, each has shown promise as a measure of cell and tumor proliferation.27 Although further studies are needed for validation, a recent clinical trial shows excellent correlation between FLT standard uptake values and independent assessment of proliferation by Ki-67 immunostaining of lung nodules.28

Many cancers show a high content of phosphorylcholine by 31P nuclear magnetic resonance, whereas normal tissues show low or nondetectable levels.29 Choline is thought to be transported into cells by an active transporter mechanism,30 and phosphorylcholine, a product of choline kinase, is the first intermediate in the incorporation and trapping of choline into the phospholipid pool.31 Based on this biochemical pathway and the observation that choline uptake and phosphorylation are increased in tumor cells, choline has been developed as a PET tracer for tumor imaging.32 Several analogs are under investigation, including 11C-choline,32 18F-fluorocholine,31 and 18F-fluoromethylcholine (FCH).33

**RECEPTORS** Several clinically available radio-pharmaceuticals in diagnostic nuclear medicine are illustrations of receptor-targeted molecular imaging.34 For example, somatostatin receptors (SSTRs), while widely distributed throughout the body, are also expressed on many tumors of neuroendocrine origin, such as somatotrophes tumors of the anterior pituitary and pancreatic islet-cell tumors.35-37 In addition, cells and tumors not of neuroendocrine origin, such as lymphocytic subtypes, lymphomas, and breast cancer, also express somatostatin receptors.38-40 The utility of somatostatin itself as a radiopharmaceutical is limited, primarily because of rapid proteolytic degradation of the peptide leading to a short serum half-life of approximately 3 min. Therefore, nonmetabolized SSTR-targeted radiolabeled peptides were developed as radiopharmaceuticals for molecular imaging of cancers expressing SSTR. The best characterized SSTR-targeted agent is an 111In-labeled analog of somatostatin comprising 8-amino acid residues commonly known as octreotide.41,42 In addition, other somatostatin analogs have been labeled with a variety of radionuclides, including 99mTc,43-46 64Cu,47,48 67Ga,49 18F,50 and 86Y51,52 for applications in diagnostic molecular imaging.

Neurotensin (NT) is a 13-amino-acid peptide,53,54 and like other neuropeptides, NT fulfills a dual function of both neurotransmitter/neuro-modulator in the nervous system and local hormone in the periphery through interaction with receptors.55 Neurotensin receptors (NTRs) have been found to be expressed in a majority of pancreatic tumors.56,57 Various nuclides, such as 111In,20TI, and 99mTc, have been incorporated into the active fragment of NT (known as NT(8-13)) through various strategies including bifunctional chelates, such as diethylentriamine pentaacetic acid (DTPA),58 peptide-based chelators,59 and technetium-carbonyl complexes.60,61 These agents are under active clinical evaluation as NTR imaging agents.

Other receptor-targeted peptide-based radiopharmaceuticals include bombesin (BN) analogs62 and vasoactive intestinal peptide (VIP).53,64 The latter, when radiolabeled as 123I-VIP, has been used to image patients with gastrointestinal adenocarcinomas and endocrine tumors.65 Integrin αvβ3 is a transmembrane protein that affects tumor growth, invasion, and metastases. During angiogenesis, αvβ3 is upregulated on activated endothelial cells, making this integrin an important target of new tumor-specific therapies for cancer.66 αvβ3 recognizes a specific conformation of the tripeptide motif arginine-glycine-aspartic acid (RGD). To enable noninvasive imaging of αvβ3, researchers developed radiolabeled cyclic peptides that contain the RGD motif.67 In animal models, high target-to-background accumulation of labeled RGD peptide has been observed with both SPECT and PET radionuclides. Potentially, PET imaging of αvβ3 can quantify receptor density at a tumor site to allow noninvasive monitoring of early treatment effects.

Peptide-based radiopharmaceuticals also have been used for in vivo imaging of phosphatidyserine (PS), a lipid component of cell membranes. PS normally is confined to the inner leaflet of cell plasma membranes, but during apoptosis, PS is exposed on the outer leaflet of cell plasma membranes, a signaling beacon for recognition and phagocytosis of apoptotic cells.68 Because the endogenous polypeptide annexin-V binds to PS with high affinity,69 binding of fluorescently labeled annexin-V is commonly used to detect apoptotic cells in vitro. Recently, annexin-V was labeled with 99mTc, enabling molecular imaging of cell death in animal models and patients in vivo.70-72

**TRANSPORTERS** Sodium-iodide symporter (NIS) is a membrane glycoprotein that uses the transmembrane sodium gradient maintained by the sodium/potassium ATPase to cotransport iodine and sodium into cells. Secondary active transport of iodine by NIS occurs in the thyroid gland, lactating breast epithelium, salivary glands, and gastric mucosa. Thus, these tissues concentrate radioactive isotopes of iodine (such as 123I and 131I) or 99mTc-pertechnetate, which has been used in clinical nuclear medicine for diagnosis and targeted therapy of thyroid gland pathology.74 NIS has been used as a suicide gene for treatment of tumors in animal
models. Viral vectors have been used to transfer the NIS gene to tumor xenografts in mice, inducing specific accumulation of $^{121}$I as detected by imaging and analysis of tumor specimens.\textsuperscript{75,76} Expression of NIS significantly enhanced uptake of $^{131}$I and produced reductions in tumor volume. Expression of functional NIS in mouse models of breast cancer also show specific accumulation of $^{99m}$Tc-pertechnetate.\textsuperscript{74} Immunohistochemistry has shown expression of NIS in 80\% of breast cancer specimens, and Moon and colleagues analyzed uptake of $^{99m}$Tc-pertechnetate in patients with breast cancer, finding accumulation of radiotracer in approximately 20\%.\textsuperscript{77} In these patients, expression of NIS mRNA correlated with positive and negative uptake of $^{99m}$Tc-pertechnetate.

Emergence of multidrug resistance (MDR) is a major obstacle to successful chemotherapy of cancer.\textsuperscript{78} Several of the first characterized mechanisms of MDR include transporter-mediated resistance conferred by increased expression of the transmembrane glycoprotein, P-glycoprotein (Pgp), the product of the $MDR1$ gene\textsuperscript{79,80} and a related membrane glycoprotein, the multidrug resistance protein (MRP1).\textsuperscript{81} Pgp and MRP1 confer resistance to an overlapping array of structurally and functionally unrelated chemotherapeutic agents, toxic xenobiotics and natural product drugs.\textsuperscript{82} Cells in culture exhibiting MDR generally show reduced net drug accumulation and altered intracellular drug distribution.

$MDR1$ Pgp and related transporters have been targets for cancer therapy on two fronts. First, reversal of multidrug resistance in tumor cells by nontoxic agents that block the transport activity of these proteins has been an important target of pharmaceutical development.\textsuperscript{83} When coadministered with a cytotoxic agent, these antagonists, known as MDR modulators, enhance net accumulation of cytotoxic compounds within the tumor cells. Several high-potency modulators discovered by targeted synthesis or combinatorial chemistry in combination with high-throughput screening are now in clinical trials.\textsuperscript{83,84} Second, transgenic expression of the $MDR1$ gene has been explored for hematopoietic cell protection in the context of cancer chemotherapy,\textsuperscript{85,86} wherein Pgp could protect hematopoietic progenitor cells from chemotherapy-induced myelotoxicity.

Noninvasive molecular imaging with a transport substrate serving as a surrogate marker of chemotherapeutic agents has been sought, and several gamma-emitting compounds have been synthesized, validated, and characterized as transport substrates for $MDR1$ Pgp.\textsuperscript{83,87} One of the best characterized is $haxekis$ (2-methoxyisobutyl isonitrile)$^{99m}$Tc(I) ($^{99m}$Tc-sestamibi), a widely available radiopharmaceutical.\textsuperscript{88} Being cationic and modestly hydrophobic, similar to many chemotherapeutic drugs in the MDR phenotype, $^{99m}$Tc-sestamibi accumulates within cells in response to the physiologically negative mitochondrial and plasma membrane potentials.\textsuperscript{89} Thus, cellular accumulation of $^{99m}$Tc-sestamibi into drug-sensitive tumor cells is high and translates into a “hot spot” on scintigraphic images or a slow washout rate from a tumor focus. However, functional $MDR1$ Pgp mediates net outward transport of $^{99m}$Tc-sestamibi from cells, thereby resulting in reduced net accumulation, detected either as a “cold” tumor or as a rapid washout rate from a tumor focus. Many studies have validated $^{99m}$Tc-sestamibi for clinical analysis of MDR with imaging gamma cameras commonly available in nuclear medicine facilities.\textsuperscript{80,89–95} Furthermore, blockade of Pgp-mediated extrusion of $^{99m}$Tc-sestamibi from tissues and tumors has been observed after administration of potent MDR modulators in clinical trials (Figure 36i-2).\textsuperscript{80,91,92} Repetitive, noninvasive identification of transporter-mediated resistance could guide choices of chemotherapeutic agents, guide use of modulating agents, monitor MDR gene therapy, and provide important prognostic information for cancer patients.

**ON THE HORIZON: IMAGING GENE EXPRESSION IN VIVO WITH REPORTER GENES**

Reporter genes are commonly used in molecular biology to monitor expression and/or repression of a gene of interest. Typical reporter genes consist of a chimeric gene linking an endogenous or exogenous gene promoter to an enzyme (luciferase or β-galactosidase) or fluorophore (green fluorescent protein [GFP]). In all cases, the reporter must be introduced into the target cell or tissue by using a variety of methods, including transfection of DNA, transduction with viral vectors, or incorporation into the genome of transgenic animals in the context of cancer research. The reporter gene can then be used to detect activation of an endogenous promoter of interest or exogenous gene as might occur with cancer gene therapy. Ideally, the magnitude and time course of reporter gene activity will parallel the strength and duration of expression of the target endogenous or vector gene. Imaging reporter gene approaches might be used in future gene therapy protocols to address difficult clinical issues pertaining to whether a given vector reached its target, how much gene transfer occurred, and whether the target gene is expressed.

For detection of gene expression and regulation in vivo with PET, researchers have developed and characterized novel imaging reporter systems. Most studies have used either heterologous enzymes such as herpes simplex virus-1 thymidine kinase (HSV1-tk) \textsuperscript{96–98} or receptors such as the dopamine-\textsuperscript{2} \textsuperscript{199,100} or SSTR.\textsuperscript{101,102} The sodium-iodide transporter has also been proposed as an imaging reporter gene.\textsuperscript{103} As compared with direct imaging of small quantities of mRNA, these systems have the potential to provide signal amplification at two biologic levels and thereby increase sensitivity for detecting and localizing gene expression. First, a single mRNA transcript is translated into many copies of a receptor or enzyme. Second, each molecule of an enzyme can catalyze intracellular trapping of a large number of reporter probe molecules, thus theoretically providing greater signal compared to a receptor system that binds a single reporter ligand at a time. However, enzyme systems, as well as receptors, have been used successfully for molecular imaging of gene expression.\textsuperscript{99,100} In addition, while conventional promoter-enhancer elements often are engineered directly upstream of the reporter gene of interest, so-called cis-acting systems, other variants of reporter systems useful for imaging are trans-activating systems.\textsuperscript{104} Trans-activating systems can amplify signals arising from weak primary promoters as the intermediate transcription factor can repetitively transactivate multiple target promoters. These and other reporter strategies may enable direct imaging of gene therapy as well as enable indirect imaging of endogenous gene expression via use of endogenous promoters driving reporter constructs.
The underlying principle driving use of HSV1-tk for therapeutic and imaging applications is its relaxed specificity for phosphorylating nucleoside analogs, such as ganciclovir, compared with endogenous thymidine kinases normally present in mammalian cells. Following active transport of a nucleoside analog across the cell membrane, the agent is selectively phosphorylated by viral thymidine kinase. The monophosphorylated nucleoside is trapped within cells and subsequently converted to a nucleoside triphosphate. These metabolic steps result in trapping of nucleoside analogs such as ganciclovir selectively within cells that express HSV1-tk. In the absence of the viral thymidine analogs, nucleoside analogs are not phosphorylated by native enzymes and do not accumulate within cells. In pharmacologic doses, incorporation of nucleoside analogs into DNA causes cell death. However, tracer amounts of radiolabeled nucleoside analogs are trapped inside cells without causing toxicity, thus enabling repetitive imaging of HSV1-tk activity with SPECT or PET. Radiolabeled nucleoside analogs appropriate for in vivo detection of HSV1-tk have been developed and characterized, including uracil nucleoside derivatives (such as FIAU labeled with $^{124}$I or $^{131}$I) and acycloguanosine derivatives (such as $^{18}$F-FHBG).

To introduce HSV1-tk into animals for imaging, investigators have either transfected tumor cells with HSV1-tk in vitro and subsequently implanted these cells into mice to form tumors or delivered the reporter gene into tissues via adenoviral vectors. Initial imaging studies with HSV1-tk used heterologous viral promoters, such as promoters of early genes in cytomegalovirus, SV40, or Rous sarcoma virus, to drive expression of the reporter. These promoters provide constitutive, high-level amounts of enzyme that likely exceed expression driven by most endogenous mammalian promoters. More recently, investigators have shown the feasibility of imaging constitutive human promoters, such as elongation factor $1\alpha$, or promoters regulated by endogenous transcription factors, such as p53 or nuclear factor of activated T cells.

In another recent advancement, protein–protein interactions were imaged in vivo by PET and fluorescence imaging by using an engineered fusion reporter gene comprising a mutant HSV1-tk and GFP for readout of a tetra-cycline-inducible two-hybrid system (Figure 36i-3). By using PET, interactions between p53 tumor suppressor and the large T antigen (Tag) of SV40 virus were quantitatively visualized in tumor xenografts of HeLa cells containing noninteracting control proteins and interacting p53-TAg proteins. PET reporter gene (HSV1-tk–GFP), but only one domain (Ga14 BD) can bind on its own to specific DNA sequences that regulate activation of the reporter. However, when p53 and Tag proteins interact, the second domain (VP16) is now properly assembled, thereby switching on the reporter gene. The activated reporter can be detected by PET imaging of living mice using the positron-emitting radiopharmaceutical $^{18}$F-FHBG.

While further from immediate clinical utility than nuclear imaging approaches, promising strategies with probes visualized by technologies other than PET and SPECT are under development for imaging gene expression and tumor enzyme activities in vivo. For example, the transferrin receptor has been engineered as an MRI reporter gene, and proof-of-principle studies show the feasibility of imaging transferrin-bound superparamagnetic particles as MR relaxivity probes in vivo. Another approach uses enzymatically activated MR contrast agents generated within target cells to interrogate reporter genes. In one example, $\beta$-galactosidase, the product of the lacZ reporter gene, catalyzes the conversion of a blocked gadolinium-based MR contrast agent from a low-relaxivity complex into a high-relaxivity product. Herein, the cleavable galactopyranose is the blocking group that confers $\beta$-galactosidase enzymatic specificity to the MR imaging probe. While current templates of this class of MR contrast agents cannot permeate cell membranes and thus are not clinically viable at this time, future applications with analogs designed for improved delivery remain possible.

Another interesting approach involves use of activated optical probes or optical beacons. These reagents typically are graft copolymers (methoxy-polyethylene-glycol-derivatized poly-L-lysine) appended with cleavable peptides conjugated between the polymer and near-infrared agents targeted to specific protein–protein interactions in living animals. These may aid the drug-development process.

Transgenic mice that use HSV1-tk as a reporter for upregulation or deletion of a specific gene are also in development. In one recent report, a transgenic mouse was engineered in which the endogenous albumin promoter drove expression of HSV1-tk primarily in the liver. $^{18}$F-FHBG uptake in the liver was shown to correlate with changes in normalized albumin mRNA in response to the protein content of an experimental diet fed to the mice. These data suggested that PET reporter genes enable indirect monitoring of endogenous promoter activity in vivo. Progress in these areas of research will increase greatly the number and types of cancer medicine applications that can be addressed by molecular imaging of gene expression in vivo with PET and SPECT.

**ON THE HORIZON: CLINICAL MOLECULAR IMAGING WITH OPTICAL AND MRI**

While further from immediate clinical utility than nuclear imaging approaches, promising strategies with probes visualized by technologies other than PET and SPECT are under development for imaging gene expression and tumor
fluorescent (NIRF) fluorophores such as tricarbocyanine and indocyanine green dyes. The spectral properties of these dyes produce self-quenching when the fluorophores are coassembled on the polymer. However, upon proteolysis of the intervening target peptide sequence, the fluorophores are released into the surrounding environment, enabling the generation of fluorescence signals. The feasibility of imaging tumor matrix metalloproteinase and cathepsin activities in vivo has been demonstrated.116–118

Bioluminescence enables molecular imaging in vivo by exploiting visible photons emitted by energy-dependent reactions catalyzed by various luciferases.119–121 Derived from a variety of organisms, luciferase genes have been cloned and engineered into expression cassettes as imaging reporter genes. Two of the most commonly used luciferases for molecular imaging applications are brightly (Photinus pyralis) luciferase and coral (Renilla reniformis) luciferase. In firefly luciferase, the substrate luciferin is catalyzed in an adenosine triphosphate (ATP)- and oxygen-dependent reaction into oxyluciferin, thereby emitting a visible photon. In Renilla luciferase, the substrate coelenterazine emits a blue-shifted photon in a short-lived ATP-independent reaction. Luciferase reporters are detected with low-light charge-coupled device cameras and fiberoptic catheters by imaging tissue or whole organ sections. For example, adeno-ovtal vectors engineered to express firefly luciferase enabled whole-body detection of viral particles in living mice.122 In another application, interacting fusion proteins were engineered to drive expression of firefly luciferase in a mouse model of intraperitoneal tumor cells.123 While the clinical safety of luciferin and related substrates may be determined, humanized substrates may be available in the future for optical imaging applications in patients.

SUMMARY

Overall, the goals of molecular imaging in cancer are to translate the expanding body of knowledge obtained from molecular and genomic cancer research into care for patients by integrating the techniques and technologies of the imaging sciences with the power of molecular biology and biochemistry. To achieve these goals in the future, initiatives must encourage the incorporation of molecular cell biology into the design, synthesis, validation, and application of new imaging pharmaceuticals and encourage imaging clinicians, oncologists, researchers, molecular biologists, and chemists to participate in interdisciplinary, cooperative, and integrated programs to develop targeted tools for cancer care.

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