Molecular Imaging in Cancer
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Science **312**, 1168 (2006);
DOI: 10.1126/science.1125949

investigators in cancer research and treatment centers, in partnerships with oncology drug companies, worked together on interactive trials that stored data prospectively from all patients being treated with a new drug, even after gaining FDA approval. Doing so would essentially create an evidence-based system where the next patient to be treated would have a better chance of receiving the optimal treatment because of information in the database about all previously treated patients.

Developing such a model of comprehensive oncology health care could potentially blur some of the current distinctions between academic groups, hospital care, government approvals, and the pharmaceutical industry. It will be enabled by reexamining the privacy issues around current HIPPA (Health Insurance Portability and Accountability Act) regulations and the manner in which academic centers sometimes structure their rights to intellectual property. It will require companies to search for ways to identify precompetitive projects and to collaborate. Focused projects run by coordinated partnerships between comprehensive cancer centers, industry, and the government might be very effective. There are many issues to tackle, but there are also real signs that all who might need to be at this table are eager to begin working together. Recent efforts by the FDA suggest the time is ripe for sending out these invitations (*24*).

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24 March 2006; accepted 20 April 2006
10.1126/science.1125948

PERSPECTIVE

Molecular Imaging in Cancer

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Medical imaging technologies have undergone explosive growth over the past few decades and now play a central role in clinical oncology. But the truly transformative power of imaging in the clinical management of cancer patients lies ahead. Today, imaging is at a crossroads, with molecularly targeted imaging agents expected to broadly expand the capabilities of conventional anatomical imaging methods. Molecular imaging will allow clinicians to not only see where a tumor is located in the body, but also to visualize the expression and activity of specific molecules (e.g., proteases and protein kinases) and biological processes (e.g., apoptosis, angiogenesis, and metastasis) that influence tumor behavior and/or response to therapy. This information is expected to have a major impact on cancer detection, individualized treatment, and drug development, as well as our understanding of how cancer arises.

Modern clinical cancer treatments require precise positional information. Where is the tumor located? How large is it? Is it confined, or has it spread to lymph nodes? Does it involve any critical anatomical structures that would alter the treatment strategy? These questions are being answered, at ever-increasing spatial resolution, through the application of traditional anatomical imaging methods such as computed x-ray tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US). Although these methods still represent the mainstay of clinical imaging, it has become clear that the acquisition of molecular and physiological information by nuclear magnetic resonance and optical imaging technologies could vastly enhance our ability to fight cancer (*1*–*3*).

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Emerging genomic and proteomic technologies have the potential to transform the way in which cancer is clinically managed. Molecular imaging is poised to play a central role in this transformation, because it will allow the integration of molecular and physiological information specific to each patient with anatomical information obtained by conventional imaging methods. The hope is that clinical molecular imaging will one day be used to achieve the following: (i) the detection of molecular or physiological alterations that signal the presence of cancer when it is still at a curable stage, (ii) the ability to evaluate and adjust treatment protocols in real time, and (iii) the ability to streamline the cancer drug development process.

Molecular Imaging and Cancer Detection

There is tremendous incentive for developing technologies that detect cancer at its earliest stages. In most cases, detection of stage 1 cancers is associated with a >90% 5-year survival rate (*4*). When lesions are detected even earlier (at the premalignant stage), treatment is often curative. Conventional anatomic imaging techniques typically detect cancers when they are a centimeter or greater in diameter, at which point they already consist of $>10^9$ cells (including circulating and microscopic metastatic deposits). Molecular imaging is expected to play an important role in this setting, because it will allow sensitive and specific monitoring of key molecular targets and host responses associated with early events in carcinogenesis. In lung cancer, for example, potential molecular targets include activated oncogenes such as *KRAS* (*5*), as well as proteins whose expression or activity is consistently altered in tumor cells versus normal cells. An optical probe activated by cathepsins, a family of cysteine proteases that are overexpressed in lung tumors, has been used in mouse models to detect tumors as small as 1 mm in diameter (*6*). Similar fluorescent-based imaging agents can be used in conjunction with endoscopic confocal microscopy for the detection of microscopic epithelial precancerous lesions that elude conventional imaging methods (*7*–*9*). Endoscopic confocal microscopy produces high-magnification cross-sectional images of the gastrointestinal epithelium and could one day permit in vivo characterization of tumors without the need for multiple excisional biopsies. Figure 1, A to F, shows an application of this imaging technology in mice.

Other imaging technologies can provide information important for the staging and restaging of cancers. For example, magnetic nanoparticles targeted to macrophages in lymph nodes have been used to detect nodal metastases in patients with clinically occult cancers. Because of the exquisite spatial resolution of MRI, millimeter-sized metastases are detectable in nonenlarged

lymph nodes (*10*), a size which is beyond the detection threshold of many other imaging techniques (Fig. 1, G to I). This approach has already been validated for a number of genitourinary malignancies, as well as head and neck cancer and breast cancer.

Positron emission tomography (PET) imaging has emerged as a clinical cornerstone in cancer staging and restaging for a number of malignancies and is one of the few molecular imaging technologies approved by the Food and Drug Administration (FDA) (*1*). The most frequently used PET agent (>90% of all cancer-related scans) is [^{18}F]fluorodeoxyglucose (FDG), a glucose analog that is selectively taken up by cells with a high rate of glucose metabolism, which is a distinguishing feature of malignant cells (*11*). FDG-PET imaging has been approved for staging of breast cancer, colorectal cancer, esophageal cancer, head and neck cancer, non–small cell lung cancers, melanoma, and lymphoma (*1*, *11*, *12*).

Molecular Imaging and Cancer Treatment

FDG-PET imaging is also a valuable clinical tool for predicting tumor response to therapy and patient survival (*13*). The technique (Fig. 2 shows examples of specific applications) is particularly well established for lymphoma, gastrointestinal stromal tumors (GISTs), esophageal carcinomas, head and neck cancer, and ovarian cancer. In one recent prospective study of patients with advanced ovarian cancer, sequential FDG-PET imaging was reported to be a more accurate predictor of response to neoadjuvant chemotherapy than other clinical or histopathologic criteria, including changes in serum levels of the tumor marker CA-125 (*14*).

Whereas FDG-PET imaging has been successful for tumor staging and therapy assessment, there has been a continued search for imaging agents that more specifically monitor tumor cell growth and cell death as a means to follow treatment response. This search has driven the development of radiolabeled nucleoside analogs such as thymidine compounds, which, because they are incorporated into DNA, may serve as useful markers of cell proliferation. Such agents are now being tested in clinical trials. Radiolabeled monoclonal antibodies against tumor-specific antigens such as Her2 and carcinoembryonic antigen are also being explored, but these tracers can produce high background signals because of their slow clearance from the blood (*11*). Smaller engineered antibody fragments (minibodies and diabodies) may improve the signal-to-noise ratio because they are cleared more rapidly, but they may also have a reduced affinity for the target antigen. Other targeted radiolabeled imaging agents include proteins such as annexin-V (to measure cell death), nanoparticles targeted to avß3 or VCAM-1 (to measure angiogenesis), and peptides or small molecules including dihydrotestosterone, estrogen, and protein kinase inhibitors.

Molecular Imaging and Cancer Drug Development

The development of new cancer therapeutics is expensive, time-consuming, and often requires vast numbers of patients. These factors all contribute to the final cost of the therapies once they are approved for clinical use (*15*). On average, it takes 10 to 12 years to take a new drug from discovery to regulatory approval at costs that can exceed $880 million (*16*). In addition, many newer drugs (cytotoxic, cytostatic, and molecularly targeted) are often efficacious only in subgroups of patients (*17*), whereas others—despite robust scientific rationale and promising preclinical results—have failed to show efficacy in clinical trials (*18*). Reducing the number and cost of failed projects would benefit the pharmaceutical industry, the health care system, and, most importantly, the patient.

Molecular imaging has the potential to improve the efficiency and cost-effectiveness of drug development programs. Imaging-based biomarkers (specific molecular targets or biological cancer processes) can be used in all phases of the cancer drug development process, from target discovery and validation to the pivotal clinical trials that precede drug approval (*19*). Genetic reporter strategies involving bioluminescence and fluorescent-tagged proteins have been especially valuable for the study of cancer biology and preclinical drug evaluation in mouse models (*20*–*24*). For example, these types of imaging approaches have recently been used to test the antitumor efficacy of epothilones, drugs that disrupt mitosis (*25*), as well as novel constructs of tumor necrosis factor–related apoptosis-inducing ligand (TRAIL), a protein that induces tumor cell apoptosis (*26*). Although the reporter gene strategy cannot be directly translated into the clinic, high-resolution mouse imaging with injectable imaging agents can provide an important window into the effect of drugs on specific targets (*2*, *19*, *23*).

Molecular imaging can help identify new efficacy endpoints that are more easily monitored than currently used endpoints, such as histological analyses of tumor biopsies. For example, steady-state imaging of tumor blood flow can be obtained within minutes in living mice, whereas CD31

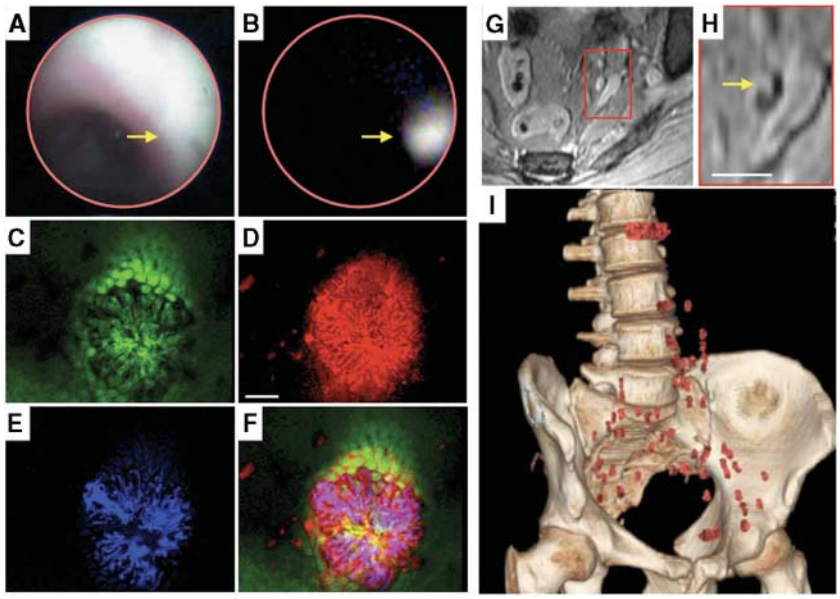

Fig. 1. Molecular imaging used for early detection of cancer in mice and humans. Dysplastic colonic adenoma in *Apc*$^{Min/-}$ mice imaged by fiberoptic endoscopy (**A** and **B**) and endomicroscopy (**C** to **F**). The 2-mm lesion is not detectable by regular colonoscopy (A) but becomes readily apparent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

microvascular density measurements are slower and more labor intensive. Furthermore, because molecular imaging is noninvasive, in the preclinical setting it allows for longitudinal studies in a single animal, which can reduce the number of animals required for an experiment without compromising statistical significance. In the clinical setting, molecular imaging endpoints could be used to identify the most appropriate patient populations in which to test new drugs.

Imaging of cancer drugs that have been labeled with ^{11}C or ^{18}F can facilitate clinical pharmacokinetic and pharmacodynamic assessments, as well as dosing and comparative efficacy studies of different lead compounds. In particular, microdosing studies (defined as 1% of the therapeutic dose, which typically has negligible toxicities in patients) have been advocated as a way to quickly obtain data on drug absorption, distribution, metabolism, excretion, and toxicity (*27*–*29*).

Impediments to Progress

Despite many recent advances in the field, there are still relatively few molecular imaging agents in the clinic. This can be attributed to several factors. First, as is the case with new cancer therapeutics, the attrition rate for new imaging agents is high. Fewer than 25% of new imaging agents survive rigorous preclinical testing in animal models. Suboptimal pharmacokinetics is one of the major reasons for failure. To be successful, imaging agents must display exquisite affinity for their molecular/biological targets, efficiently gain access to these targets, show minimal nonspecific uptake or retention (a major factor contributing to low target-to-background ratios), and have sufficiently long half-lives to be detectable/functional at trace concentrations (*20*). Designing a single imaging agent with all of these features is challenging. Recent efforts to boost target-to-background ratios have used sophisticated chemical signal amplification strategies with some success.

A second factor impeding progress is the regulatory hurdles that preclude rapid translation of molecular imaging technologies from the laboratory to the clinic. This problem has been recognized by the FDA, which has recently released newer, less-stringent criteria for exploratory investigational new drug (IND) studies (*30*). Such studies involve very limited human exposure and have no therapeutic or diagnostic intent. Nevertheless, the revised facilitating guidelines largely apply to isotope-based PET imaging agents and microdosing studies and do not address the use of diagnostic doses to test efficacy for particularly promising fluorescent or MRI agents. Basic fluorochrome structures such as indocyanine green have already been used safely for human breast imaging and other clinical applications (*31*), and, as mentioned above, nanoparticles detectable by MRI have been used to locate submillimeter lymph node metastases in patients with prostate cancer (*10*). Newer, molecularly targeted imaging agents based on the above will be particularly useful in settings where repeated or higher resolution imaging is necessary—for example, in efforts aimed at early detection of cancer.

A third factor impeding the clinical development of molecular imaging agents is economics. The development of an imaging agent currently costs 50 to 100 million dollars, and reimbursement levels from the Centers for Medicare and Medicaid Services for imaging studies are often lower than those for therapeutic drugs. Consequently, the pharmaceutical industry and venture capitalists have been reluctant to invest unless widespread clinical applications are immediately evident. The fact that there are so many competing imaging modalities and that these modalities are all evolving at such a rapid pace (which limits the window of marketability) has also served to diminish investor interest. Another economic consideration relates to the general problem of rising health care costs, which some feel would be exacerbated by the implementation of molecular imaging technologies into patient care. In fact, molecular imaging—if used appropriately—can potentially reduce health care costs. The average cost of new molecularly targeted cancer treatments has increased from about $20,000 per patient per year to ~$100,000 per patient per year (*32*). When such drugs are given as combination therapies (e.g., Avastin, Erbitux, and Eloxatin), the yearly cost can reach multiple hundreds of thousands of dollars per patient. Because molecular imaging techniques can help clinicians match specific therapies to the patient populations which are most likely to respond, they may lower costs by reducing the number of patients eligible for a given treatment combination. In addition, in some settings, molecular imaging techniques may eliminate costly surgical procedures altogether (*10*). In preliminary studies, FDG-PET imaging has been shown to have a high benefit/cost ratio for cancer staging (*1*, *33*).

A final impediment to progress, but one that is likely the easiest to overcome, is that the discovery of imaging agents is a complex multidisciplinary effort. It requires an infrastructure of experts from research fields as diverse as genomics, proteomics, chemical biology, engineering, image computation, and clinical trial design. Although such infrastructures are commonplace in large pharmaceutical companies, there are only a handful of academic centers in the world that have such a collection of experts or have access to appropriate resources.

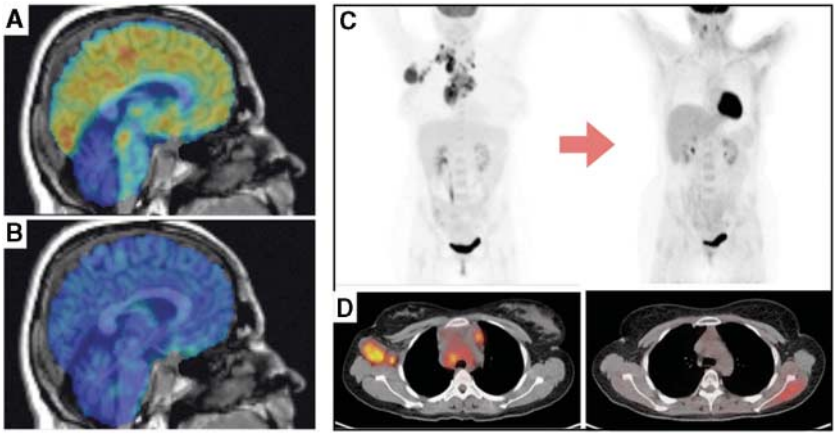

Fig. 2. Molecular imaging used for monitoring of patient response to therapy. (**A**) PET scan of brain substance P (neurokinin-1 receptor) using ^{18}F–substance-P antagonist–receptor quantifier (SPA-RQ) superimposed onto an MRI scan. (**B**) PET scan after receptor blockade with Aprepitant, a neurokinin-1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

Near-Term Needs and Opportunities

What's needed to catalyze the field of molecular imaging in cancer and drive imaging agents into the clinic at a faster pace? Of utmost importance is the need to discover and validate new biomarkers optimally suited for cancer imaging, particularly those with amplification potential such as internalizing cell-surface receptors, enzymes, and abundant nonprotein targets (e.g., growth factor receptors). Recent technological developments that may hasten the biomarker discovery process are: "imaging filters" to screen existing databases for targets ideally suited for imaging, newer conjugation chemistries such as "click chemistry" (*34*), and the use of yeast/phage surface display to identify recombinant antibodies/peptides (*35*). There is also a pressing need for the synthesis of new imaging agents. There is an opportunity to

apply combinatorial methods, chemical biology, synthetic small molecule compounds, and newer nanomaterials as scaffolds to improve pharmacological behavior (*36*, *37*). The continued development of "smart" imaging reagents, whose signal depends on specific biochemical activities, also remains a top priority. For example, small-molecule prodrugs that change their imaging signal upon target interaction have been shown to dramatically boost target-to-background ratios in vivo (*38*, *39*). Additional opportunities exist for the development of fluorescence-based imaging agents, one of the most important growth areas in molecular imaging. Fluorochromes such as indocyanines are inexpensive, stable, involve no radiation, and have been used safely for the past 20 years. Just as in the in vitro setting where they have been key tools in both genomics and proteomics, fluorochromes can be uniquely converted into sensing agents in vivo (*40*). Continuing improvements in instrumentation including high–spatial resolution endomicroscopy, near-infrared intraoperative reflectance imaging, and fluorescence tomography will also be important. The latter technology is of particular interest because it allows accurate in vivo quantitation of near-infrared fluorochrome, which is important to differentiate target binding from pharmacokinetics (*41*).

Given the remarkable parallel progress in other research areas—including our deepening understanding of the molecular basis of human cancer, continued refinements of mouse tumor models, and advances in imaging instrumentation—we can be optimistic that molecular imaging will contribute in many important ways to the improved care of cancer patients.

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43. The author is a founder of and holds shares of stock in VisEn Medical, a company that is developing experimental imaging technologies. The author thanks U. Mahmood, M. Harisinghani, and R. Hargreaves for figures and all members of the Center for Molecular Imaging Research for many helpful discussions.

10.1126/science.1125949

PERSPECTIVE

Antiangiogenic Therapy: A Universal Chemosensitization Strategy for Cancer?

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For more than 50 years, a major goal of research in cancer therapeutics has been to develop universally effective agents that render cancer cells more sensitive to cytotoxic chemotherapy without substantially increasing toxicity to normal cells. The results of recent clinical trials indicate that certain antiangiogenic drugs may produce this long-sought effect. Here, I describe three distinct mechanisms that may help to explain the chemosensitizing activity of these drugs: normalizing tumor vasculature, preventing rapid tumor cell repopulation, and augmenting the antivascular effects of chemotherapy. I then discuss how these potential mechanisms might be exploited to maximize therapeutic efficacy.

In 1971, Judah Folkman first articulated the concept behind what he called "antiangiogenic" drugs: Because progressive tumor growth is dependent on a blood supply, he proposed that treatment with drugs that prevent the formation of tumor blood vessels might be able to constrain cancer for prolonged periods (*1*). Over the next three decades, roughly 10,000 research papers on angiogenesis were published, culminating in a recent report of the first large-scale clinical success of an antiangiogenic drug for cancer treatment (*2*). In this phase III trial, patients with metastatic colorectal cancer who had been treated with a combination of conventional cytotoxic chemotherapy plus bevacizumab, a humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF), showed prolonged survival compared with patients treated with chemotherapy alone (*2*). The combination of bevacizumab (Avastin) and chemotherapy is now approved in the United States and many other countries as a first-line treatment for colorectal cancer. Subsequent phase III trials with bevacizumab and chemotherapy in breast and non–small cell lung cancer have produced similarly promising results (Table 1). In addition, two small-molecule antiangiogenic drugs, SU11248/sunitinib (Sutent) and BAY-43-9006/sorafenib (Nexavar), have been approved as monotherapies for kidney cancer (*3*). Bevacizumab has also shown activity as a monotherapy in kidney cancer (*4*).

These clinical trial results and some others—e.g., in ovarian and pancreatic cancer (*5*, *6*)—underscore the expanding range of tumor types that respond to this class of drugs (Table 1). Although the survival benefits conferred are modest [generally between 2 and 5 months in the completed phase III bevacizumab trials (Table 1)], the results nonetheless represent one

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