The reference standard by which we monitor tumor progression, tumor response to all forms of therapy, and the emergence of therapy-resistant tumors in the clinic has been alterations in tumor volume as measured by computed tomography (CT) via the use of the Response Evaluation Criteria in Solid Tumors (RECIST) standard (1). RECIST is likely to continue to be the criterion of choice, for the immediate future, in the evaluation of the success or failure of cancer therapy clinical trials. However, molecular imaging techniques that measure tumor metabolic properties and/or expression of tumor-associated gene products are making rapid advances in the identification of tumor lesions, in the stratification of patients for alternative therapies, in the evaluation of tumor response to therapy, and in the identification of emerging resistance of metastases to treatment (2). Currently, the most widely used molecular imaging technique, both to stratify patients for alternative therapies and to monitor for emerging resistance to a therapeutic regimen, is positron emission tomography (PET) measurement of tumor glucose use by 18F-fluorodeoxyglucose (18F-FDG) uptake. Increased 18F-FDG retention often is indicative of the presence of a tumor, as a consequence of increased tumor glucose use resulting from the Warburg effect in cancer cells (3). In many cases, response to therapy can be rapidly (e.g., days) determined by a decrease in 18F-FDG tumor uptake after the initiation of a therapeutic protocol. In contrast, weeks or months are usually required to observe changes in tumor size by RECIST. The now classic differential response to imatinib for gastrointestinal stromal tumors resulting from alternative oncogene drivers (4) is the most well-known example, but a rapid evaluation of response versus resistance has been validated for 18F-FDG uptake by PET for a variety of therapeutic modalities in a number of distinct tumor types (5).

In addition to its use in stratification for therapy, progression by acquired resistance to a therapeutic regimen also can be observed as increased 18F-FDG tumor uptake, often in a subset of previously responding metastases. This “short cut” to identifying emerging resistant metastases was demonstrated dramatically by Flaherty and colleagues (6). They evaluated vemurafenib therapy for V600E BRAF-driven metastatic melanomas by comparing 18F-FDG PET and concurrent CT analyses.

Although PET with 18F-FDG has emerged as a valuable tool in identifying tumor metastases and in monitoring tumor response to therapies in a variety of cancers, some tumors are not 18F-FDG avid. To develop molecular imaging techniques as noninvasive, diagnostic biomarkers for the presence of cancer and to monitor tumor burden in response to therapy, many laboratories are creating ligands, labeled with positron-emitting isotopes, that recognize “receptors” whose levels are either ectopically misexpressed or overexpressed by tumors. Positron-emitting conjugates of growth factors, hormones, lectins, cytokines, and antibodies whose receptor/antigen targets are thought to be differentially expressed on tumor cells are in development and evaluation in a variety of contexts (7).

Prostate cancer is one of those cancers for which 18F-FDG PET analysis is not very useful; these tumors, at least at early stages, are not 18F-FDG avid. Prostate cancer, the second most common cancer in men, has a somewhat unpredictable progression course for many patients after initial diagnosis, ranging from indolent and ultimately not the cause of death for some patients to virulent, rapidly metastasizing, and ultimately fatal consequences within a relatively short time after diagnosis for others.

Because of the wide range of disease progression for these patients and the variety of treatment options available, increases in our ability to identify the presence of metastatic prostate lesions and to monitor their response to alternative therapies are objectives of primary importance and investigation. In these contexts, metabolic positron-emitting probes such as 11C-choline, 11F-labeled choline derivatives (e.g., 11F-fluoroethylcholine), 11C-acetate, 11C-methionine, and fluorinated amino acids have been used, with mixed...
results, to monitor both for the presence of metastatic prostate cancers and for posttherapy cancer recurrence.

Mease (8) recently summarized the literature on radiotracer-based attempts to image prostate cancers; he describes technetium diphosphates, 18F-fluoride, 18F-FDG, 11C-acetate, 11C- and 18F-labeled choline, 11C- and 18F-labeled 1-aminocyclobutane-1-caboxyl acid, radiolabeled androgen receptor (AR) binding compounds, radiolabeled vasoactive intestinal peptides, radiolabeled galactic 3-binding peptide, radiolabeled gastrin-releasing peptide and bombesin, labeled small molecules and oligonucleotides, that bind to prostate-specific membrane antigen (PSMA), and radiolabeled monoclonal antibodies that bind to various PSMA epitopes.

Many investigators have turned to radiolabelled antibodies in attempts both to measure the tumor burden of metastatic prostate cancer with PET and to monitor metastatic prostate tumor responses to alternative therapies. PSMA has been the most widely investigated imaging target; nearly all prostate tumors express this antigen, which is enriched in metastatic, castration-resistant tumors. A number of monoclonal antibodies directed against a variety of epitopes on the PSMA molecule have been generated and used as radiolabeled probes, after intravenous injection, for the detection of prostate cancer metastases.

One radiolabeled PSMA monoclonal antibody [Indium (111) capromab pendetide, trade name ProstaScint] is commercially available and is used to monitor prostate cancer. Results for ProstaScint in monitoring tumor burden and the management of therapy have not resulted in a consensus in the clinical community. Our conclusion is that—at the present time—there is no molecular imaging paradigm for prostate cancer that can reliably and effectively monitor metastatic tumor burden, stratify patients for alternative therapies, predict the likelihood of efficacy for alternative therapies, monitor response to therapy, or rapidly identify lesions that have acquired resistance to therapy.

In this issue of Cancer Discovery, Ulmert and colleagues (9) point out that many of the tumor-associated targets for which radiolabeled ligands have been described have no history as validated biomarkers for disease presence or progression. In contrast, prostate-specific antigen (PSA), a protein whose expression is under the control of the androgen receptor and is unique to the prostate, has a long history as a serum biomarker for the presence of prostate cancer, progression, reoccurrence, and response to therapy—albeit with nearly as long a history of controversy regarding its value in monitoring prostate cancer.

Ulmert and colleagues (9) postulated that a radiolabeled antibody that is able to recognize a form of PSA preferentially sequestered in tumors, but that is unable to recognize the circulating form(s) of PSA, might be able to noninvasively monitor prostate cancer tumor burden. Taking advantage of a large collection of monoclonal antibodies directed against PSA (10), they labeled a monoclonal antibody, 5A10, reported to “recognize an epitope adjacent to the catalytic cleft of PSA” (9) with the positron-emitting isotope $^{89}$Zr. Their studies are based on the assumption that the enzyme is present in the pericellular space in a form available for 5A10 recognition. They suggest that, after secretion, this epitope becomes antibody unavailable, as a consequence of binding to a wide range of serum proteins (e.g., α1-antichymotrypsin, α2 macroglobulin, inter-α-trypsin inhibitor, α1-antitrypsin, protein C inhibitor) that sequester PSA.

Using a combination both of radioactive $^{89}$Zr-labeled 5A10 accumulation in isolated tissues and of noninvasive PET and CT scanning, they demonstrate in a series of murine xenograft model experiments that: (i) the $^{89}$Zr–SA10 probe can image, in a noninvasive fashion, the presence of PSA-positive subcutaneous tumors; (ii) excess cold SA10 antibody can block PSA-positive tumor $^{89}$Zr–SA10 accumulation; (iii) AR-negative/PSA-negative prostate tumor xenografts do not accumulate probe; (iv) elevation of PSA expression in response to androgen treatment of AR-positive xenografts can be measured by increased intratumoral $^{89}$Zr–SA10 accumulation; and (v) antiandrogen-mediated reduction in PSA levels can be monitored noninvasively in xenograft tumors by PET scanning after the intravenous administration of $^{89}$Zr–SA10. Finally, successful therapeutic response of bone metastases, the most common metastatic site for prostate cancer, is particularly difficult to evaluate by structural and/or nuclear medicine imaging techniques. However, osseous xenografts of AR-PSA+ xenografts in hindlimb tibiae could be clearly observed by PET/CT after the intravenous administration of $^{89}$Zr–SA10.

Although the processing that makes intratumoral PSA detectable by $^{89}$Zr–SA10 antibody is not well understood, the experiments suggest that this reagent has great promise for monitoring, in a clinical context, potentially heterogeneous responses of multiple prostate cancer metastases to antiandrogen therapy. By choosing to pursue an imaging approach to a known cancer biomarker, Ulmert and colleagues (9) have developed a reagent that has the potential to move rapidly to clinical application.

There have been substantial advances recently in radiolabeling antibodies with $^{18}$F (11), $^{68}$Ga (12), and $^{89}$Zr (13) for noninvasive nuclear medicine imaging. Parallel advances in molecular engineering of antibody molecules have permitted the creation of targeted imaging molecules with modifiable pharmacokinetic properties, that is, properties that can be tuned to optimize tumor-to-background sensitivity (14). The development of methods to modify pharmacokinetic properties of antibody-based imaging probes and the emerging new technologies to rapidly radiolabel these probes with a variety of PET-emitting isotopes, coupled with the judicious choice of tumor targets—as exemplified by the work of Ulmert and colleagues (9) described here—bodes well both for the future of immunoPET noninvasive tumor imaging technology and for cancer patients in need of new noninvasive biomarker methods to stratify their options for therapy and to evaluate their responses to treatment.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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A Spotlight from Prostate Cancer

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