Measuring Oncogenic Signaling Pathways in Cancer with PET: An Emerging Paradigm from Studies in Castration-Resistant Prostate Cancer

Michael J. Evans

ABSTRACT

As parallel advances in cancer biology and drug development continue to elevate the role of targeted therapies in oncology, the need for imaging biomarkers that systematically measure the biology associated with therapeutic intervention has become more urgent. Although the molecular imaging community has a commitment to develop technologies to this end, few investigational radiotracers directly measure the biology of common oncogenic signaling pathways often addressed by targeted therapies. Visible progress has been achieved with a handful of radiotracers rationally designed to intercalate the pathobiology of prostate cancer, a molecularly heterogeneous disease nevertheless broadly defined by a fairly small repertoire of recurrent oncogenic lesions.

Significance: That variable treatment responses or emergent resistance phenotypes are often documented in humans argues strongly for diagnostic technologies that can be realistically applied post-therapy to capture the dynamic patterns of disease response. The purpose of this review is to describe a collection of radiotracers developed to measure the pathobiology of prostate cancer for improved treatment monitoring, placing particular emphasis on the biologic rationale for their preparation. A chronologic description of radiotracer development programs is outlined, primarily to stress how an ongoing dialectic between earlier and more contemporary imaging technologies has accelerated discovery.

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INTRODUCTION

On theoretical and practical grounds, a mandate for new imaging biomarkers that measure the output of oncogenic signaling pathways can be sensibly justified. As the oncology community now routinely advances targeted therapies alongside cytotoxic therapies into the clinic, it seems logical that cognate imaging biomarkers should complement this development by measuring those molecular events immediately impacted by targeted therapies, rather than reporting a symptom of overall tumor burden or health. Disappointingly (and for unclear reasons), in only a few settings have imaging biomarkers whose biology is distally related to the pharmacology of a targeted therapy impacted the approval process and patient care (vide infra). Nevertheless, regulatory agencies remain highly motivated to conditionally reshape drug approval criteria on the basis of any biomarker “reasonably likely to predict” clinical benefit (1, 2). With these considerations in mind, there seem to be ample opportunities for carefully designed imaging tools to streamline the clinical evaluation of experimental therapies.

One example of a malignancy that seems primed to benefit from the application of radiotracers measuring oncogenic signaling pathways is castration-resistant prostate cancer (CRPC), the most advanced and fatal form of the disease. Indeed, many years of work have defined several oncogenic events that, in some permutation, drive the lethality of CRPC (ref. 3; Fig. 1). Two of the most frequently annotated phenomena—reactivation of androgen receptor (AR) signaling (4) and aberrant phosphoinositide 3-kinase (PI3K) pathway signaling (5, 6)—are readily addressable by targeted therapies, some of which have or are undergoing clinical evaluation in CRPC (7, 8). Notably, 2 agents targeting the AR signaling axis—abiraterone acetate (9) and MDV3100 (10)—extended survival in clinical trials, pointing to the substantial progress that has...
been made in comprehending the molecular determinants of CRPC. Moreover, that neither drug has been uniformly effective in the patient populations studied to date further supports a need to develop biomarkers that identify upfront the patients most likely to respond to therapy, and/or more clearly indicate a molecular tumor response posttherapy.

Also (beyond invoking overall survival), defining responsive versus resistant subpopulations has been challenging for patients with CRPC. As distant prostate cancer metastases largely deposit in the bone, assessing objective response rates with radiologic criteria (e.g., Response Evaluation Criteria in Solid Tumors [RECIST]) is essentially ineffective (11). Appreciating this, oversight bodies such as the Prostate Cancer Clinical Trials Consortium have promulgated more standardized criteria to interpret tumor progression in clinical trials with bone scans [i.e., ^{99m}Tc-MDP, and more recently, ^{18}F-NaF (12)]. Although very accessible, this technology has several limitations (13). Most notably, it has been empirically shown that radiographic responses can lag tumor responses to targeted therapies by months or even years. This phenomenon is rationalized on the basis of the mechanism of radionuclide localization to osteoblastic lesions. In both cases, the radiotracers target normal skeletal foci actively undergoing repair, rather than targeting the tumor itself, and normal bone healing can persist long after ablation of a nearby tumor. Consequently, even partial resolution of a bone scan is uncommon for therapies known to extend overall survival.

Into this vacuum, several groups have attempted to establish a role for positron emission tomography (PET) in the management of CRPC, owing to its sensitivity, noninvasiveness, and quantitative properties (14). Particular emphasis has been placed on small-molecule radiotracers that might reveal a whole-body assessment of a “metabolic tumor phenotype” (e.g., ^{18}F-FDG, ^{18}F-FACBC, ^{11}C-methionine, ^{11}C-acetate, and ^{11}C-choline). A thorough discussion of these approaches is beyond the scope of this review, and several high-quality treatments in the literature can be found elsewhere (15, 16). However, that none of these radiotracers have been adopted into widespread clinical use for treatment monitoring underscores their shortcomings. Principally (although their respective mechanisms of tumor uptake are generally well characterized), that the deeper biologic basis of their avidity for CRPC is not understood limits the hypotheses that one can reasonably advance to establish their clinical usefulness. Consequently, that many otherwise useful radiotracers cannot be cross-applied to CRPC for similar gains has elevated the criteria for radiotracer design.

The Biomarker Landscape and the Emergence of Molecular Imaging in Oncology

Before discussing the investigational radiotracers that are the topic of this review, the broader setting of biomarker development should be described to establish the context for their preparation. Generally, biomarkers can be defined according to the timing, and in turn, the purpose of their application (17). For instance, those assayed from treatment-naïve patients are intended to detect subclinical disease early, distinguish aggressive from indolent disease, or sort patient populations according to those most likely to respond to a given systemic therapy (screening, prognostic, or predictive biomarkers, respectively). Posttherapy, biomarkers can be immediately applied to interpret the extent of target inhibition (pharmacodynamic biomarkers), or at early and intermediate intervals to assess tumor response parameters that could indicate an eventual increase in overall survival (clinical or surrogate endpoints).

Beyond disease staging, an obvious clinical use for functional imaging biomarkers pretherapy has not yet been realized, and more visible progress establishing a role for molecular imaging in oncology has been shown post therapy. The first milestone (even predating the term “molecular imaging”) was the appreciation that a radiotracer measuring an aspect of tumor health could unambiguously show cancer cell death posttherapy (and point to an eventual increase in overall survival), even when anatomical imaging did not.
necessarily depict a convincing regression in a mass once known to bear a cancerous lesion. Initially with 67Ga-citrate single-photon emission computed tomography (SPECT) postcyotoxic chemotherapy in lymphomas (18) and more recently with 18F-FDG PET after targeted therapies in lung cancer, gastrointestinal stromal tumors, or glioblastoma (19–21), these precedents established and continue to support a unique virtue for monitoring tumor response with a functional imaging biomarker.

Although it is quite encouraging that radiotracers reflective of clinical outcome can be empirically identified and validated without much prior appreciation of a functional relationship to the drug target, the phenomenologic nature of these correlations makes it challenging to extract ubiquitous lessons that might instruct future radiotracer design. Indeed, of the many investigational radiotracers developed to monitor an aspect of tumor health to date, only a few have been shown in any context to clearly outperform the current gold standard of tumor health. This is not to say that radiotracers cannot be rationally engineered to noninvasively assay the immediate biologic properties of a given target protein.

Many groups have contributed to a general model showing that radiotracers imitating the pharmacology of an endogenous substrate, ligand, or a synthetic drug can serve as powerful pharmacodynamic biomarkers (24, 25). The model extends from the premise that a competition between radiotracer and a large excess of cold drug for binding to a mutual target protein can be exploited to interpret the extent of target blockade by drug. One prominent example is 16α-[18F] fluoro-17β-estradiol, a radiolabeled version of the endogenous female sex hormone, which has been effectively used to annotate estrogen receptor status in breast cancer patients, as well as to titrate the dose of antiestrogen therapies (26, 27).

As will be discussed in the following section, there are documented shortcomings to this approach, and a complementary model has advocated evaluating inhibition more directly by measuring the downstream biology of the target. A seminal example was the use of a radiolabeled F(ab′)2 derivative of trastuzumab [a monoclonal antibody (mAb) to the receptor tyrosine kinase HER2] to interpret the impact of a dose of an inhibitor for the molecular chaperone HSP90 (28). Because HSP90 prevents HER2 degradation, the authors showed that the downregulation of HER2 induced by HSP90 inhibition could be monitored by PET to quantify the extent of target inhibition in vivo. Beyond the immediate clinical significance of these findings, this study helped to establish a paradigm that has since been invoked repeatedly to develop pharmacodynamic imaging biomarkers for unrelated targets and malignancies (29, 30).

Because the potential for carefully designed radiotracers to broadly impact clinical practice is now very clear, I would submit that one of the next major frontiers for the molecular imaging community is to apply the aforementioned concepts to more systematically develop biomarkers matched to the pathobiology of validated oncogenic drivers in cancer. In the following sections, several investigational radiotracers engineered to address this end in CRPC will be described, with a particular emphasis on the biologic rationale for their preparation and the unmet need that warranted their development. The technologies will be outlined in chronologic order of discovery to emphasize how the lessons imparted by earlier technologies have empowered the development of newer radiotracers.

18F-16β-Fluoro-5α-Dihydrotestosterone, a Radioligand Designed to Quantify AR Occupancy by Antiandrogens

The merit of inhibiting AR signaling in prostate cancer has been understood for decades (7), and the favorable results from 2 recent trials treating CRPC with highly potent AR inhibitors underscore the importance of AR in all stages of the disease. Although the clinical successes of the antiandrogen MDV3100 and the androgen biosynthesis inhibitor abiraterone acetate represent a milestone for the field, approximately 50% of patients fail to respond to either therapy. At least 2 hypotheses could account for this phenomenon. First, a patient’s disease may bear biologic features that preclude response to even complete AR inhibition. Second, the dose of drug may be insufficient to impair AR signaling to the extent required to observe survival benefit.

The second hypothesis relates to the pharmacodynamic properties of the drug dose, and for antiandrogen therapies understanding the extent to which drug binds AR could be greatly insightful. Exploring on previous observations con- ferred by researchers at Washington University in St. Louis (31–33), researchers at Memorial Sloan-Kettering Cancer Center (MSKCC) showed that 18F-16β-fluoro-5α-dihydrotestosterone (18F-FDHT), a radiolabeled form of dihydrotestosterone that binds AR in prostate cancer lesions (34–36), can be used in line with antiandrogen therapy to assess the extent of receptor blockade by drug (Fig. 2A). A pilot study was conducted with 22 patients enrolled in the phase I/II portion of the MDV3100 trial to assess drug pharmacodynamics (10). Before beginning therapy, patients received an 18F-FDHT scan, and 4 weeks postinitiation, a follow-up scan. Regardless of dose, possetherapy 18F-FDHT maximum standardized uptake values (SUVmax) almost uniformly declined (21 of 22 patients), strongly suggesting that MDV3100 effectively binds AR in vivo.

Whereas these data clearly support the continued use of 18F-FDHT to interpret dose selection for antiandrogens in patients, it is interesting to note that the 18F-FDHT “responses” did not overlap well with other conventional indicators of biologic tumor response (ref. 37; Fig. 2B). Over the same time frame, approximately 40% of patients (9 of 22) profiled with 18F-FDHT showed rising 18F-FDG values, suggesting that tumor health was unaffected by MDV3100. Moreover, a nonoverlapping group of patients comprising approximately 40% of the cohort (9 of 22) had stable or rising serum values of prostate-specific antigen (PSA), which is encoded by an AR target gene, suggesting that AR function was not inhibited.

These observations raise the possibility that, in some contexts, engaging AR with an antiandrogen does not necessarily result in tumor response or AR inhibition. Indeed, symptoms of this phenomenon have been observed sporadically for many years. For instance, it is well known that in preclinical prostate cancer models bearing AR overexpression, the antiandrogen bicalutamide paradoxically acts as an agonist...
for AR [an effect that \(^{18}\)F-FDHT PET would not distinguish from authentic antagonism (4)]. More speculatively, PSA levels have been shown to occasionally decline after suspension of antiandrogen therapy in patients (i.e., “flutamide withdrawal syndrome”), perhaps recapitulating this preclinical observation in vivo (38).

Although further research is required to establish the diagnostic value of posttherapy declines in \(^{18}\)F-FDHT, the lessons from the proof-of-concept studies stress that there is a need to measure AR signaling output directly. Indeed, beyond the issues discussed above, it seems unlikely that \(^{18}\)F-FDHT PET would bear any meaningful information about the pharmacology of androgen biosynthesis inhibitors, as these drugs inhibit AR function without physically binding the receptor. As an aside, it is also well appreciated that \(^{18}\)F-FDHT is quite unstable in vivo—significant metabolism occurs within minutes postinjection—further underscoring a need for second-generation radiotracers targeting this oncogene (34). Consequently, the next 2 sections will describe 2 preclinical efforts to noninvasively measure AR signaling output itself.

\(^{89}\)Zr-J591, a Radiotracer Designed to Measure AR Pathway Signaling by Quantifying Relative Changes in the Expression of Prostate-Specific Membrane Antigen

The rationale for developing an imaging biomarker reflective of AR pathway signaling also borrows heavily from insights garnered by studying serum levels of secreted proteins encoded by AR target genes. AR-regulated kallikreins—most notably, PSA—have been measured exhaustively in patient serum to screen for disease onset, develop prognoses, and monitor treatment response (39, 40). Although useful, the shortcomings of this approach are well documented, and in principle, an imaging biomarker reflective of AR signaling could supplement these limitations. For example, circulating PSA levels are a depiction not only of changes in AR transcription but also of secretion into pericellular space and leakage into the serum—2 processes that are poorly understood and not necessarily AR regulated. It is also well documented that only a very small fraction of the total PSA produced in the prostate escapes into the serum (41), suggesting that a posttranslational step (rather than AR-driven transcriptional changes per se) may be rate-limiting to PSA accumulation in the blood. Alternatively, measuring a gene with fewer degrees of freedom between AR transcription and expression (i.e., imaging a cell surface antigen) could confer more faithful measurements of AR signaling.

A further complication is that radiographic responses to androgen deprivation therapy in a patient can be mixed, with some lesions shrinking whereas others are stable or expanding, perhaps a reflection of the heterogeneity of metastatic lesions even within the same patient. Indeed, the recent work imaging patients with \(^{18}\)F-FDG and \(^{18}\)F-FDHT has revealed a highly diverse array of radiotracer uptake among CRPC lesions (37). By extension, the differential sensitivity of metastatic lesions to androgen deprivation therapy could be rationalized by different levels of AR inhibition. Because a serum biomarker reflects an average across all lesions, it would not inform as to whether AR inhibition varies at different sites, whereas an appropriately designed imaging biomarker could likely capture this behavior.

Among the genes shown to be regulated by AR, the gene encoding prostate-specific membrane antigen (PSMA) emerged as an immediately attractive candidate biomarker, owing to the large repertoire of tools available to image this protein, including reagents already cleared for clinical use.
Capitalizing on this information, Evans and colleagues showed in vitro and in vivo that androgens repress PSMA expression in multiple prostate cancer models, whereas antiandrogens upregulate expression (47). Genetic ablation of AR with siRNA in vitro confirmed that these phenomena are AR mediated. The expression changes were also substantial enough to be quantitatively measured in vivo in human prostate cancer xenograft models through PET imaging with a radiolabeled version of a fully humanized antibody to PSMA, 64Cu-labeled J591 (48).

In parallel, Holland and colleagues found that altering the radiolabeling strategy by appending zirconium-89 to J591 resulted in unprecedented tumor contrast ratios (>20:1 compared with muscle) in prostate cancer models (49). Moreover, because the half-life of zirconium-89 is long (t1/2 ~ 78 hours), images could be acquired up to 144 hours after injection of 89Zr-J591. Both the tumor contrast and the magnitude of radiotracer uptake in the tumor improved continuously over time, likely due to antibody clearance from blood circulation and normal tissues. Collectively, these findings have motivated an ongoing clinical trial at MSKCC to evaluate 89Zr-J591 for prostate cancer diagnosis and treatment monitoring, and at time of press, first-in-human studies had commenced.

89Zr-5A10, a Radiotracer Designed to Measure AR Pathway Signaling by Quantifying Relative Changes in the Expression of Free PSA

Although 89Zr-J591 is an attractive lead agent, PSMA expression is not prostate specific, the mechanism of AR repression of PSMA is not defined, and the clinical impact of AR-directed therapy on PSMA expression remains to be determined. In this regard, a radiotracer that targets a more thoroughly validated clinical biomarker of AR status could be a sensible alternative pending the outcome of the 89Zr-J591 trial. Appreciating this, Ulmert and colleagues recently disclosed a strategy to measure AR status by targeting PSA with an antibody-based radiotracer (50).

As a secreted protein, PSA is admittedly not an obvious imaging target, and one could reasonably argue that circulating antigens could confound tumor imaging by sequestering the radiotracer in serum. As serum PSA overwhelmingly exists in complexes with serpins (e.g., alpha-1 antichymotrypsin), the authors overcame this challenge by radiolabeling a monoclonal antibody (5A10) specifically reactive with uncomplexed or “free” PSA (Fig. 4A and B). Because of limited access to serpins, the tumor microenvironment is enriched in free PSA, and on this basis, it was hypothesized that the radiotracer would accumulate at or within a tumor cell. Consistent with this expectation, 89Zr-labeled 5A10 localized to multiple prostate cancer tumors in an AR- and PSA-dependent manner and effectively measured changes in PSA expression triggered by MDV3100 treatment. Moreover, 89Zr-5A10 readily detected osseous prostate cancer lesions and was not cross-reactive with the nonmalignant conditions that score on traditional bone scans. This data effectively established proof-of-concept, and pending the humanization of 5A10, the ultimate clinical utility of this strategy can be assessed.

One additional advantage to developing a radiotracer targeting a secreted protein is that any knowledge highlighting a shortcoming of the serum measurement provides an obvious clinical scenario to determine whether the imaging tool can reveal any new and useful information. Indeed, the greatest hurdle to the approval of investigational radiotracers is showing a clear clinical utility to regulatory agencies, and the attrition rate is currently high. As there are many partially flawed serum biomarkers in oncology [e.g., CA125 for ovarian cancer (51),...
Figure 4. Noninvasively measuring AR signaling pathway output with a radiotracer targeting free PSA. A, a schematic representation of the relationship between AR activity and PSA expression and the strategy to exploit this relationship for PET imaging. The kallikrein PSA is encoded by an AR target gene (KLK3) and has a complicated posttranscriptional lifetime. The gene is expressed as a catalytically inactive proenzyme ("pro" PSA) and is activated by the proteolytic activity of human kallikrein 2 (hK2). The pool of PSA with an unobscured catalytic cleft is referred to as "free" PSA and can be secreted into extracellular space. Through an undefined mechanism, a small portion of free PSA will leak into the bloodstream, whereupon it is rapidly and irreversibly complexed with serpins (e.g., alpha-1 antichymotrypsin). To target tumor-associated PSA, an antibody that specifically recognizes free PSA was radiolabeled (89Zr-5A10). The color bar at the bottom highlights the gradient of PSA concentrations in the various tissue compartments, further underscoring the usefulness of targeting tumor-associated PSA species for imaging. B, a schematic representation showing how 89Zr-5A10 PET can inform on the in vivo pharmacology of androgen deprivation therapies. The model was derived from that established with J591 PET.
Imaging Oncogene Signaling with PET

[Figure 5. Noninvasively measuring MYC signaling with a radiotracer targeting TFRC. A schematic representation of the relationship between MYC activity and TFRC expression and the strategy to exploit this relationship for PET imaging. TFRC is a validated MYC target gene in many cancers, including prostate cancer. The soluble ligand of TFRC, the serum protein transferrin (Tf), was radiolabeled to target the relative changes in TFRC expression that occur with fluctuations in MYC signaling.]

carcinoembryonic antigen for colorectal cancer (52), and carbonic anhydrase-9 for renal cell carcinoma (53)], this paradigm may be useful to substantiate the approval of other radiotracers.

\[\text{Zr-Transferrin, a Radiotracer Designed to Measure Aberrant MYC Signaling by Quantifying Relative Changes in the Expression of the Transferrin Receptor}\]

The previous sections have dealt with technologies designed to measure dimensions of the AR signaling axis. Several other oncogenic signaling events are known to drive prostate cancer, suggesting that a panel of biomarkers may be required to comprehensively manage the disease. One important oncogenic driver of prostate cancer is the transcription factor MYC. Through analysis of biopsies from early stages of disease, most estimates indicate that pathologic activation of MYC occurs in approximately 30% of prostate cancers, and MYC copy number alterations are known to correlate with poor clinical outcome (54, 55). Moreover, in genetically engineered mouse models, prostate-specific MYC overexpression leads to invasive adenocarcinoma (56). Nevertheless, very little is known about the role of MYC in clinical disease beyond what can be inferred from biopsy, and in particular, the impact of aberrant MYC activity on therapeutic intervention in CRPC is entirely unknown.

These observations argue strongly for a noninvasive biomarker of MYC status, and the model invoked for AR provided Holland and colleagues with a clear avenue for radiotracer development (57). Among the target genes regulated by MYC, the transferrin receptor (TFRC) emerged as an obvious candidate (58), owing to several decades of work showing that transferrin (the serum ligand for TFRC) is a versatile scaffold for radionuclides (Fig. 5; refs. 59–61). Appreciating the quality of previously published work with Zr-labeled biomolecules (62, 63), the authors prepared Zr-transferrin (Zr-Tf) and evaluated the properties of the radiotracer in preclinical models of MYC-driven prostate cancer.

Unlike previous strategies (60, 64) to image TFRC expression levels (e.g., Ga-citrate), Zr-Tf produced high-contrast PET images with exceptional resolution and low uptake in normal tissues. The radiotracer sensitively measured treatment-induced changes in MYC and TFRC expression in MycCaP tumors, a murine prostate cancer model bearing an androgen-regulated, inducible MYC allele (65). The superior pharmacokinetic properties of Zr-Tf also allowed the detection of spontaneously developing prostate cancer in a transgenic MYC prostate cancer model (56). Notably, Zr-Tf detected regions of aberrant MYC signaling independent of the histopathologic stage of disease, imaging foci that appeared well before histologic or anatomic evidence of adenocarcinoma.

Although this work is of immediate relevance to the mouse modeling community (PET imaging of prostate cancer with common radiotracers such as FDG is not useful because the prostate is obscured by bladder accumulation of radiotracer), Zr-Tf could also become a powerful imaging biomarker in man for cancer detection and for assessing response to therapy. Particularly in light of recent reports showing that JQ1—an inhibitor of the epigenetic protein BRD4—exerts its antitumor effects by downregulating MYC, this radiotracer may be suitable for monitoring response to this promising new therapy (66–68). Finally, TFRC is also regulated by MYC in other cancers, including lymphoma (69) and breast (70), which may further broaden the significance of this technology.
Emerging Themes and Concluding Remarks

As the oncology community continues to substantiate the hypothesis that many cancers can be managed with cleaner pharmacologic agents targeting disease-specific molecular aberrations, the molecular imaging community is positioned to serve as a powerful foil to accelerate discovery and streamline the clinical evaluation of experimental therapeutics. At the forefront, many years of work deconstructing the molecular determinants of CRPC have facilitated the rational design of several novel radiotracers to address the pathobiology of 2 highly visible oncogenes. The radiotracers described herein are most obviously applied as pharmacodynamic biomarkers or early and intermediate response indicators, although one could reasonably imagine extending this paradigm to other classes of biomarkers. The promise of this proof-of-concept work can be summarized into a handful of themes that will hopefully empower future radiotracer development programs for CRPC and other malignancies:

1. Favoring biologic events directly impacted by oncogenic signaling pathways may enhance the informational content of PET scans. The sporadic success of radiotracers targeting gross tumor properties, the complications associated with interpreting the multiple equilibria that govern ambient serum biomarker concentrations, and the inspiring example set with pharmacodynamic imaging biomarkers argue for developing imaging biomarkers derived from molecular events more immediately affected by oncogene activity to evaluate targeted therapies.

2. Mining transcriptional profiling data is a highly effective approach to triage candidate imaging biomarkers. The examples presented herein primarily focus on exploiting imaging biomarkers target genes whose expression is driven by oncogenic transcription factors. This model draws on previous insights garnered principally from studying secreted biomarkers in oncology and should scale well to other oncogenic signaling pathways. One particularly attractive aspect of this approach is that it capitalizes on the wealth of expression data publicly available from preclinical models and clinical specimens, providing an extensive list of genes that can be cross-referenced over many independently derived data sets to improve confidence in target selection.

3. Deliberately targeting an “imageable” form of a serum biomarker could more clearly define a unique clinical utility for investigational imaging agents. For several serum biomarkers used in the management of cancer, a vast body of epidemiologic data has clearly highlighted virtues and shortcomings. Given the challenges associated with showing a clear clinical use for investigational radiotracers, attention from the imaging community should be paid, where appropriate, to targets bearing a strong epidemiologic history to more readily highlight the unique virtues of an imaging tool.

Although the data summarized in this review make a case for a philosophy of de novo radiotracer design from carefully curated imaging targets, it is worth noting that this approach is not the only manner in which to discover imaging biomarkers reflective of aberrant oncogenic signaling. For instance, in a highly instructive study, Palaskas and colleagues analyzed the molecular basis of $^{18}$F-FDG avidity in breast cancer biopsies with an annotated PET history (70). An unbiased survey of transcriptional changes identified a genetic signature indicative of elevated MYC activity in basal-like breast cancer tissues that were avid for $^{18}$F-FDG, and immunohistochemical analysis of patient tissue showed a strong correlation between MYC overexpression and high $^{18}$F-FDG SUV$_{max}$ values. These findings raise the possibility that other radiotracers engineered to measure a general property of tumor health may in some contexts be ascribed to readily interpretable oncogenic events. In this regard, retrospectively defining the pathobiologic events that drive the upregulation of the machinery responsible for retaining a radiotracer or within a tumor cell could be a highly attractive and expedient approach to expand the clinical use of an investigational radiotracer, particularly among those for which successful feasibility studies in humans have already been conducted.

Moving forward, one outstanding concern for the oncology and molecular imaging communities should be the logic of continuing to argue that a single radiotracer can emerge as an instructive endpoint in clinical trials. Indeed, the documented molecular heterogeneity of some cancers (71) as well as the fact that oncogenes such as AR or MYC can regulate hundreds of genes (72, 73) should continue to raise doubts as to whether, even for a single oncogene, one cognate imaging biomarker may be broadly applicable to patient populations. Speaking to this point, many promising predictive biomarkers constitute molecular signatures derived from a panel of genetic events, rather than a single “smoking gun” event per se (74). In this regard (and despite the remarkable precedent established with $^{68}$Ga-citrate and $^{18}$F-FDG), the clinical merit of documenting tumor response to therapy with an imaging biomarker must be continuously reevaluated. Ultimately, molecular imaging tools will almost certainly be best invoked as one of many endpoints in clinical trials, combining their considerable virtues with other emerging noninvasive technologies (e.g., profiling circulating tumor cells in patient serum; ref. 75) that might supplement their shortcomings.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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