INVITED COMMENTARY

Immuno-PET for Tumor Targeting

Monoclonal antibodies are approved for use as diagnostics and therapeutics in a broad range of medical indications including transplantation, cardiology, inflammatory diseases, viral infection, and oncology. Each of these indications utilizes the specificity and avidity of monoclonal antibodies for antigens/receptors for targeting. For oncology, new classes of biologic anticancer agents are predicted to work in only subpopulations of patients, and methods to identify or predict patients who will benefit from a specific therapy, and to optimize therapeutic efficacy, are now recognized as critical factors in the design of early-phase clinical trials (*1*). Monoclonal antibodies face similar hurdles during clinical development. In early-phase clinical trials, radiolabeled antibodies can provide direct evidence of antibody uptake by tumors through gamma camera imaging and can allow essential information on biodistribution, pharmacokinetics, and dosimetry to be derived (*2*). Because of tissue attenuation of photons, corroborative biopsy analysis through radioactive counting and autoradiography further substantiates the quantitative characteristics of uptake. Such trials are technically challenging but provide information that can dramatically alter the development of the immunoconjugate, including predicting toxicities and aiding in the selection of dosages of antibodies for optimal tumor targeting. The demonstration of in vivo tumor uptake of antibodies also provides the impetus to search for ways to optimally use the immunoconjugate in the clinic, including the delivery of isotopes, drugs, or toxins to tumor, using immune effector function through Fc regions or through antibody/receptor interactions on tumor cells, leading to alteration in downstream signaling events with resulting changes in proliferation, angiogenesis, and apoptosis (e.g., erbB1 and erbB2 receptors) (*3*).

The advantages of combining antibodies and PET (immuno-PET) have previously been demonstrated (*4*,*5*). With minimal tissue attenuation and high-resolution imaging capability, the quantitative aspects of immuno-PET over gamma camera imaging permit improved characterization of antibody uptake in vivo. Although immuno-PET has the potential to supersede gamma camera imaging/biopsy-based studies that are often laborious to conduct, the availability of PET isotopes suitable for immuno-PET, and the optimization of labeling strategies, have hampered the development of this approach. Verel et al. (*6*), in this issue of *The Journal of Nuclear Medicine,* rightly allude to a limited choice of longer-lived PET isotopes that are compatible with the pharmacokinetics and distribution of intact antibodies. Apart from half-life, the in vivo behavior of the immunoconjugate is highly dependent on the stability, cellular trafficking, and catabolic pathway of the radiolabeled construct. ^{124}I-HuMV833, an anti–vascular endothelial growth factor antibody, was found to have markedly variable antibody distribution and clearance in a clinical study (*7*). The often-noted choice of radiohalogen compared with radiometals for labeling antibodies (*8*,*9*) is also highly applicable to PET isotopes. ^{124}I linked directly to antibody via tyrosine residues can be expected to have lower tumor retention in antigen systems that are rapidly and extensively routed to lysosomes. Lysosomal degradation of immunoconjugates leads to loss of iodotyrosine but accumulation of radiometals. The exception is when the antigen/antibody complex is either internalized slowly or compartmentalized in such a way that it is kept away from routing to lysosomes for a prolonged period (*10*). In that instance, radiohalogen (direct label) may give satisfactory tumor uptake, but invariably, radiometals may be preferred (*11*). Loss of directly conjugated radiohalogens can be minimized through improved design of residualizing ligands such as diethylenetriaminepentaacetic acid (DTPA) peptides (*12*). Radioimmunoconjugates can therefore be prepared with high labeling efficiencies and high specific activities and with tumor uptake values and therapeutic efficacy comparable to those of radiometal conjugates.

A possible solution to the search for a longer-lived metallic PET isotope in the form of ^{89}Zr for labeling antibodies is described by Verel et al. (*6*). The major breakthrough comes in the ability to isolate ^{89}Zr in high specific activities after irradiation of a low-cost target. Production of isotope in remote facilities can be contemplated, as shipment is possible given the high specific activity and 3.27-d decay half-life of ^{89}Zr. Another important achievement is the preparation of esterified bifunctional metal ion chelator (BFMC) precursors that can be linked to antibody via a stable amide bond. The preparation of stable ^{89}Zr-immunoconjugates is an important achievement, as minimal manipulation of antibody during conjugation with BFMC is advantageous over methods that require more extensive steps. Although clinical immunogenicity of chelate on immunoconjugates has not been exhaustively explored, dodecanetetraacetic acid–based chelates have been implicated, but the immunogenicity is probably at-

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tributable to the carrier protein rather than the chelate itself (*13*). No definitive evidence of immunogenicity of DTPA-based chelates in humans has so far been reported.

A foreseeable limitation of ^{89}Zr is the concomitant high gamma emissions at 909 keV (99.9% abundance), which may limit the radioactive dose that can be administered and affect image quality and quantitative aspects of the imaging (*4*). Finally, to use ^{89}Zr-conjugates as a surrogate for therapeutic isotopes such as ^{90}Y (half-life, 2.67 d) for dosimetry analysis, it will be necessary to demonstrate in preclinical models comparability in the antibody distribution, tumor uptake, and dosimetric characteristics of the 2 radioimmunoconjugates. The lack of availability of cyclotrons with sufficient energy for isotope production together with the high demand on PET cameras has limited the wider use of immuno-PET to date. Molecular evidence of tumor targeting in vivo is essential in antibody development for clinical use in oncology. Better estimates of radiation-absorbed dose can also aid in treatment planning during radioimmunotherapy. Several factors need to be considered when one is presented with a choice between radiohalogens or radiometals for labeling antibodies for tumor targeting.

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