At first glance, the concept of using radionuclide-labeled monoclonal antibodies to target radioactivity to tumor sites for the detection and possible treatment of malignancies appears quite appealing in terms of its rationale and simplicity. However, as is apparent in Dr. Divgi's comprehensive review of the many clinical studies that have been performed to test this concept, there are a number of complexities that require further study and resolution so that this approach can be optimally and more widely applied in clinical medicine. Although Dr. Divgi touches on many of these issues, some points are worthy of emphasis and further discussion.

Optimal Characteristics of Target Antigens
First, as is evident from his review, a large number of tumor-associated antigens have been explored as potential targets for radioimmunodetection and radiimmunotherapy, in many instances, even for the same disease. The variable results reported using these different targets suggests that, at least in part, the characteristics of the antigen may play a vital role in the success of this modality. However, it is not yet clear what the optimal characteristics of target antigens should be. For example, how specific does the antigen need to be for the tumor, relative to other tissues? One can envision that low degrees of specificity would be counterproductive. On the other hand, however, if the antigen were extremely specific, it is likely that a greater proportion of cells within a tumor might not express that antigen by virtue of the commonly observed phenomenon of antigenic heterogeneity. The decreased antigen expression by tumor cells would potentially limit the number of sites available to attract and retain radiolabeled antibody. This possibility, in turn, raises the issue of the optimal abundance of target antigen on tumor cells. A minimum number of target sites is probably required, but it has yet to be clinically demonstrated that increasing the number of target sites (by upregulating antigen expression via administering interferon-alfa [Intron A, Roferon-A] or interferon-gamma [Actimmune], for instance) results in significantly enhanced tumor targeting or tumor response. The absence of such a finding suggests that other factors may be more important than the number of target sites. One of these other factors may be the stability of expression of the antigen upon binding by antibody. A number of antigens are known to be rapidly shed from the cell surface or internalized into the cell upon engagement by antibody. This antigenic modulation may not only affect the number of available target sites for antibody binding but also (in the case of internalization) result in rapid dehalogenization of antibodies labeled with radioiodine and rapid elimination of radioiodine from the cell [1]. The latter situation results in a decrease in residence time of the radionuclide in the tumor, and thus, less effective radiation.

Finally, a characteristic given little discussion in Dr. Divgi's review is the physiologic function of the antigen. Therapeutically, it may not be enough simply to target more and more radiation to tumor cells to achieve optimal results. An antigen whose binding by antibody may induce cell-cycle arrest, apoptosis, or other events that enhance therapeutic effects may provide a significant advantage over nonfunctional target antigens [2].

Nature of the Monoclonal Antibody
Another issue requiring further study is the nature of the monoclonal antibodies used, such as their...
species of origin (murine vs human), molecular size (intact vs fragments), and affinity for antigen. For instance, while the antigenicity of murine antibodies poses a problem for multiple-use applications, the longer half-life of mouse/human chimeric antibodies or genetically humanized antibodies may increase nonspecific radiation from prolonged retention in the blood. Actually, the use of radiolabeled mouse antibodies in patients with lymphoma (the most successful therapeutic application of this approach found so far) results in the development of antimouse antibodies only rarely (< 20% of patients with B-cell lymphoma), and thus, repetitive use is a definite option for radioimaging or radioimmunotherapy in these patients. Consequently, the impact of introducing humanized antibodies in this setting is uncertain. It should be pointed out that the reason for the difference in the induction of antimouse antibodies between lymphoma patients and patients with other malignancies may not be due solely to the degree of prior immunosuppressive treatment lymphoma patients may have received, as Dr. Divgi suggests, but rather, may relate, in part, to the immunosuppressive nature of the disease itself.

Choice of Radionuclide

Although the choice of radionuclides for diagnostic radiolabeled antibody imaging has broadened considerably in the last few years, iodine-131 remains the gold standard for radioimmunotherapeutic purposes. Other radionuclides, such as the pure beta-emitting radiometal yttrium-90, may have advantages from the standpoint that they do not emit gamma rays and can thus be administered on an outpatient basis (because radiation confinement procedures would be unnecessary), and that they appear to have higher beta-particle energies than iodine-131. However, these radiometals require chelation to attach the radionuclide to the antibody, and as Dr. Divgi points out, the chelates presently used tend to be unstable.

The consequence of detachment of yttrium-90 from the antibody can be deposition of this bone-seeking radiometal in the bone marrow, leading to excessive bone marrow toxicity. This is in contrast to the fate of detached iodine-131, which is harmlessly and rapidly excreted in the urine and gut. Furthermore, the lack of gamma emissions from yttrium-90 makes it difficult to detect problems in biodistribution of the radiolabeled antibody and to estimate the radiation dose delivered to the bone marrow and normal organs, as well as tumors. New chelation techniques are being developed, but some of the conjugates using these new chelators have been reported to be more immunogenic in humans.

Another point worth emphasizing with regard to the choice of radionuclide for therapy has to do with the path length of the energetic particles emitted by particular isotopes. The beta particles emitted from iodine-131, for example, have a path length of almost 1 mm. While this path length results in containment of irradiation to a circumscribed area, it is long enough that many cells within a tumor that are within close proximity to the cell targeted by an iodine-131-labeled antibody can be exposed to radiation from this point source. In turn, other cells targeted within the tumor can become point sources for the irradiation of the above targeted cell, as well as other cells.

The efficiency of this cross-fire effect may be affected by the size of the tumor being targeted. The smaller the tumor, the lesser the opportunity for therapeutic cross-fire and the greater the irradiation of surrounding normal tissue. On the other hand, very short-range alpha particles emitted from some radionuclides may be more ideal for irradiating microscopic tumors and less ideal for larger tumors; in the latter case, antibodies labeled with alpha emitters may be more likely to have an inhomogeneous distribution of radiation within the tumor, with some areas receiving little or no irradiation. Thus, beta emitters may not be the best choice for the treatment of minimal residual disease (adjuvant therapy), and alphaemitters may not be the best choice for the treatment of gross disease, although this hypothesis needs further testing.

Optimal Dose/Dose Schedule

Another issue that requires further study is the optimal dose and dose schedule for radioimmunotherapy. Should dosing follow conventional paradigms in radiotherapy and chemotherapy and use fractionated dosing? Should a single maximally tolerated dose not requiring hematopoietic stem-cell support be used? Should a single ultra-high dose with hematopoietic stem cell support be employed? On what basis should a dose be prescribed—millicuries, millicuries per square meter, calculated radiation dose (cGy) to the whole body, bone marrow, or normal organ determined from a preceding trace-labeled dose, or some other measurement? Various clinical trials are addressing these questions. Ultimately, we may find that the answers vary for different clinical situations, such as tumor type, tumor burden, and type of antibody used.

Disappointing Results in Solid Tumors

Finally, we must face the fact that the results obtained so far from the clinical trials of radioimmunotherapy in solid tumors have been disappointing. This is in stark contrast to the high
response rates and durability of responses obtained with radiolabeled antibodies against B-cell
antigens [3,4]. Thus, while it appears that radioimmunotherapy will likely play a significant role in
the management of lymphomas and leukemias in the near future, such a prospect for solid tumors is
more distant.
Perhaps the lessons learned from the successful application of this therapy in hematopoietic
malignancies will shed light on potential directions for future research to optimize therapy for solid
tumors. In any event, while I concur with Dr. Divgi that the future is bright for the clinical application
of radiolabeled antibodies, we should acknowledge that this field is still early in its development and
that significant advances will come from careful investigations addressing the complex issues
inherent in this approach.

References:

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