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Re:Activity and Protein Levels in Studies of Monoclonal Antibody Imaging

The recent imaging article by Khaw et al. (*1*) is to be recommended for its thoroughness regarding monoclonal antibody research with the nude-mouse model, but there are pertinent questions that the authors fail to discuss. These concern the relatively large amounts of indium-111 and protein given to the animals. It seems that their experiments pertain more to monoclonal-associated radiation therapy than to diagnosis.

Khaw et al. (*1*) report injection of 200 μCi of In-111-labeled antibody into ~20 g of mouse. The activity was attached, in the case of their intact monoclonal 10-3D2, to 20 μg of IgG. If one assumes a 70-kg human and scales these values upward by a factor equal to the ratio of human to mouse masses, rather unacceptable levels of activity and protein are obtained. Amounts approaching a curie of In-111 and 100 mg of mouse-derived protein would probably not be permitted in a human imaging study. A reduction in these levels by approximately two orders of magnitude would be clinically realistic.

The obvious question arises as to the resultant murine biodistributions with such appropriately lowered amounts of activity and tracer. With a relatively small number of antibodies and no sloughing of tumor-associated antigens (*1*), it is possible that the tumor uptake, measured in % injected dose/g, could be significantly increased. On the other hand, if the antigen does enter the circulation to some degree, it is likely that lowering the amount of injected antibody would reduce the injected dose/g lodging in the tumor (*2*). Other opposing effects can occur. In the related therapy situation, Order (*3*) has described prolonging by several days the human tumor retention of a labeled monoclonal IgG by raising the total protein dose to approximately 200 mg. The additional carrier protein appeared to retard sloughing of labeled monoclonal complexes and thus to enhance radiotherapeutic effects. At any rate, it is unclear that if the amounts of In-111 and IgG were reduced, there would be consistency in the levels of tumor uptake and figures of merit reported in the recent article.

Questions regarding dose-level effects on pharmacokinetics are also involved in the conclusions reached by Khaw et al (*1*). Using signal-to-noise criteria, they report optimal BT-20 tumor localization of 10-3D2 at 4 days after i.v. injection in the nude-mouse model. This result might not recur, however, with decreased amounts of activity and protein. In fact, imaging out to 7 days, as reported by these authors, may not even be possible with In-111 levels reduced by a factor of 100.

It seems that drug-dose effects need to be addressed by researchers in monoclonal imaging. One cannot simply assume that the amount of radiopharmaceutical given to a particular species has no effect on the biodistribution. Differential tissue uptake is generally going to be a function of the amount of material injected per unit mass of the animal used in the experiment. Clearly, diagnostic animal research should concern activity levels less than 10 mCi/70 kg or 140 μCi/g—i.e., be equivalent to the maximum human dose levels. Similarly, the amount of protein should be restricted to less than 500 μg/70 kg or 7 ng/g of test animal so as to reduce the likelihood of antimouse antibody production with serial studies. Published reports involving polyclonal (*4*) and monoclonal (*5*) human imaging trials are in good agreement with these limits.

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Reply

My colleagues and I thank Dr. Williams for his thoughtful comments on our article (*1*). We disagree, however, with his suggestion that the concentration of monoclonal antibody and the amount of In-111 reported in our manuscript were excessive, amounting to what he describes as "monoclonal-associated radiation therapy." These quantities were selected for the following reasons: (a) the amount of antigen expected on the surface of the tumor; (b) the physical constraints involved in imaging small animals; (c) the radionuclide used; and (d) the assumption that use of approximately 0.2% murine antibody in a murine model would not interfere with the circulation of the injected antibody.

Dr. Williams suggests that one can extrapolate from the antibody concentration and radiation doses used in our nude-mouse model to those used for a 70-kg patient with mammary carcinoma.