Letter to the Editor


We read with interest the report of Sugiyama et al. (1) on the selective growth inhibition of antigen-positive human lung tumor cells by $^{125}$I-labeled monoclonal antibody. The authors demonstrate cell-specific binding as well as antibody-specific inhibition of cell growth. This group previously reported that about 40% of bound antibody was internalized within 30 min after binding (2). The authors attribute the observed growth inhibition of antigen-positive lung tumor cells to the Auger effect associated with $^{125}$I decay and take issue with the findings of numerous investigators, including ourselves, that the therapeutic power of $^{125}$I-mediated cytotoxicity requires nuclear localization.

There is abundant evidence from treating thyrotoxicosis to show that extranuclear $^{125}$I is cytotoxic (3, 4). We speculated in 1985 (5) that the Auger effect could not be used to therapeutic advantage with $^{125}$I-labeled monoclonal antibodies because there was no evidence at that time that monoclonal antibodies underwent nuclear sequestration. It now appears that internalization, but not necessarily nuclear sequestration, does occur (2). In our opinion, however, the cytotoxicity observed by Sugiyama et al. is not related to the Auger effect but simply represents a manifestation of low energy overlap $\gamma$-irradiation.

Conventional MIRD dosimetry trivializes the therapeutic usefulness of Auger-emitting radionuclides such as $^{125}$I (6, 7). Each $^{125}$I disintegration releases some 20 low energy and densely ionizing electrons. Energy deposition decreases exponentially from the site of disintegration. It is reduced 1000-fold at a distance of 10 nm from the site of disintegration. Although Auger electrons contribute only a tiny fraction of the total energy released per disintegration, their exquisite toxicity when associated with nuclear structures is profound and well documented. When localized in the nucleus as iododeoxyuridine (8, 9), iodotamoxifen (10), or iodoestradiol (11), the $D_{27}$ (dose to reduce survival 37%) is 80–100 disintegrations per cell. By comparison, $^{125}$I bound to the cell membrane as iodoconcancavalin A, localized to the cytoplasm as iodoiodohyododamidine (12) or exposed to target cells as iodinated monoclonal antibodies (13, 14) is much less toxic with $D_{27}$ values in excess of 10,000 disintegrations per cell. The radiotoxicity with this latter group of radiopharmaceuticals can be attributed almost exclusively to overlap irradiation from the 35 keV photon released in 70% of $^{125}$I disintegrations. At comparable media concentrations, $^{125}$I as sodium iodide (9) or iodoantipyrine (10), a marker for the intracellular water space, is minimally radiotoxic compared to nuclear $^{125}$I. Because Sugiyama et al. (1) failed to determine the amount of cell-associated radioactivity in their experiments, it is impossible to compare their results with radiotoxicity standards (e.g., $D_{27}$) and statements about the absolute or relative therapeutic efficacy of $^{125}$I versus other radionuclides for monoclonal antibody therapy are conjectural.

Internalization of $^{125}$I-monoclonal antibody as observed by Sugiyama et al. (1) may be irrelevant to the mechanism of toxicity. In Fig. 4 of their report, they demonstrate similar toxicities for antigen-positive and -negative cells exposed to either specific or nonspecific monoclonal antibodies. Assuming that the nonspecific antibody used in these studies is not internalized by the antigen-positive cells, the failure to distinguish major differences in specific and nonspecific antibody-mediated toxicities can best be explained by the long-range effects of the 35 keV product of $^{125}$I decay. This photon has a range of 10 $\mu$m and does not require cellular internalization or nuclear localization for toxicity.

We share with many research groups a keen interest in the interdisciplinary area of antibody-mediated radiotherapy. However, successful therapeutic applications will proceed only after thoughtful experimentation and selection of both the carrier and the radionuclide. Selection of appropriate radionuclides for these studies must be based on careful evaluation of the physical properties, microdosimetry, and behavior in biological systems.

William H. McLaughlin
Michael W. Epperly
William D. Bloomer
Department of Radiation Oncology
University of Pittsburgh - School of Medicine
Joint Radiation Oncology Center
Pittsburgh Cancer Institute
230 Lothrop Street
Pittsburgh, Pennsylvania 15213

References


Received 9/26/88; accepted 7/18/89. 1 To whom correspondence should be addressed.

William H. McLaughlin, Michael W. Epperly and William D. Bloomer


Updated version Access the most recent version of this article at: [http://cancerres.aacrjournals.org/content/49/20/5774.citation](http://cancerres.aacrjournals.org/content/49/20/5774.citation)