EDITORIAL

Progress and Promise

Our understanding of the mechanisms underlying the retention of indium radiolabel in the liver are significantly improved by the work of Kinuya et al. (*1*). Understanding these mechanisms is important because radioactive indium has great potential utility (*2*). Indium-111 decay energies image better than those of ^{131}I and ^{125}I while avoiding the constraints of the half-life of ^{123}I (expense and limited time for accumulation in the targeted lesions). However, the prolonged retention of ^{111}In in normal tissues, especially the liver, reduces the conspicuity of targeted lesions compared to iodinated antibodies (*2*). Even with an improved chelate (SCN-Bz-DTPA), indium-labeled B72.3 detected liver metastases in only one of eight patients with such lesions while ^{131}I-B72.3 depicted liver metastases in four of six patients with these lesions. The observation of much more intense images of the liver with ^{111}In-SCN-Bz-DTPA-B72.3 than with ^{131}I-B72.3, demonstrates that even with the improved chelate, the nonspecific localization of ^{111}In in the liver remains too great for optimal imaging. Clearly, one goal for improved indium chelators is matching or exceeding the tumor-to-liver ratios achieved by iodine labels.

The need to lower indium concentrations in the liver and the need to improve the dosimetry of ^{90}Y (*3*) motivated some previous studies of the metabolism of indium-labeled antibodies. These studies indicate that liver, kidney and tumor (CEA-producing human colonic tumor xenograft, GW-39) remove an indium-containing low molecular weight fraction (LMWF) from antibodies (*3–5*). When the chelator was isothiocyanatobenzl-DTPA SCN-Bz-DTPA (*6,7*) the LMWF has a molecular weight similar to that of DTPA. These studies suggested that the increase of radioactivity in the liver results from retention of the LMWF for antibodies labeled via the SCN-Bz-DTPA chelate.

While this chelate initially showed promise in increasing the conspicuity of liver lesions (*6*), in practice it did not. This situation prompted the development and testing of modified versions of SCN-Bz-DTPA (*7,8*). The modifications to SCN-Bz-DTPA (1M3B, MX, 1M3B, 1B3M and 1B4M) clearly improved its performance. In Roselli's study of these chelates attached to B72.3 targeted against an LS-174T tumor, using the 1B3M-DTPA chelate rather than the SCN-Bz-DTPA chelate increased the tumor-to-liver ratio from 3.99 to 9.96 at 120 hr following injection. In a similar animal model (Table 2), the biodistribution of ^{125}I-B72.3 was compared to ^{111}In-CA-DTPA-B72.3 (*9*) and to ^{111}In chelated to B72.3 via another variant of SCN-Bz-DTPA (*10*) (Table 1). While comparing results from separate studies even in similar models warrants caution, the data in Table 1 argue that new chelators substantially improve the tumor-to-tissue ratios for liver, spleen and kidney over comparable ratios obtained with CA-DTPA (cylic DTPA dianhydride). These data also suggest that the use of the chelator developed by Sumerdon et al. (*11*) and tested by Carney et al. (*10*) and Divgi et al. (*12*) produce tumor-to-tissue ratios comparable to ^{125}I labeling. Determining if the use of the 1B3M-DTPA chelate improves these ratios beyond those obtained by ^{125}I labeling (tumor-to-liver ratios of 5.94 versus 4.85 at 48 hr) requires a dual isotope study comparable to those conducted by Carney et al. (*10*) and Brown et al. (*9*). The data in Table 1 also suggest that the choice of chelator may depend on the region of the body in which lesion detection is most important. For example, while the use of CA-DTPA produces the lowest tumor-to-liver ratio, its use appears to produce higher tumor-to-tissue ratios for heart, muscle and the GI tract which is an important consideration for abdominal imaging beyond the borders of the liver, spleen and kidneys.

The availability of chelates for indium which produce tumor-to-tissue ratios rivaling or exceeding those produced by iodination, clearly warrants comparing their metabolism with that of CA-DTPA. The study of the CA-DTPA, 1B4M and CHX-B chelates conjugated to the T101 monoclonal antibody (Mab), demonstrates clear differences in the metabolism and biodistribution of CA-DTPA and the two newer chelators. Adding the LMWF for CA-DTPA (4.8% ID/g) to the radioactivity probably associated with transferrin (1.1% ID/g) yields 5.9% ID/g which is 3.5 times the comparable sum for the new chelates (1.7% ID/g). The elimination of transchelation to transferrin and the reduced concentration of the LMWF roughly accounts for the difference in liver activity between the new chelates and CA-DTPA (4.5% and 4.1% ID/g versus 8.2% ID/g).

The finding that for all three chelators the urine contained only the 1,500-MW metabolite, supports the conclusion that three chelates share a common primary elimination pathway. Accelerating the diffusion of this metabolite from normal tissues while retaining it in the targeted lesions could improve their conspicuity. Since the main biliary component of radioactivity was intact IgG, finding a chelate which prevents the excretion of intact IgG into the bile either by altering the properties of the conjugate or by increasing the metabolism of the conjugate into chelate and antibody could reduce the activity in the GI tract. Perhaps the faster formation of the LMWF from the CA-DTPA conjugate accounts for the CA-DTPA conjugate's apparent doubling the tumor to GI tract ratio compared to Abbott's variant of the SCN-Bz-DTPA conjugate (Table 1).

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For correspondence or reprints contact: Donald Rauh, MD, PhD, 972 Roelofs Rd, Yardley, PA 19067.

TABLE 1
Tumor-to-Tissue Ratios

	Chelate								
	CA-DTPA[†¶]	SCN-Bz-DTPA[*§]		1B4M-DTPA[*§]		1B3M-DTPA[*§]		Sumerdon chelator	^{125}I[‡]
Tissue	48 hr	48 hr	120 hr	48 hr	120 hr	48 hr	120 hr	48 hr	48 hr
Liver	2.18	3.32	3.99	4.51	5.47	5.94	9.96	4.35	4.85
Spleen	3.48	4.32	4.73	5.53	5.91	5.91	7.00	4.59	5.12
Kidney	3.34	5.69	7.69	4.02	6.43	5.08	8.74	5.12	5.25
Femur	—	11.61	16.29	11.32	17.70	12.88	23.18	—	—
Heart	14.31	—	—	—	—	—	—	2.86	2.85
Lung	6.87	—	—	—	—	—	—	6.41	2.75
G.I. Tract	20.80	—	—	—	—	—	—	10.38	12.89
Muscle	42.22	—	—	—	—	—	—	10.82	10.89
Blood	3.76	1.67	3.15	1.39	2.30	1.75	3.44	1.18	1.06

*HPLC and purification.
†Large s.d.s.
‡After Carney et al.
§After Roselli et al.
¶After Brown et al.

These findings are globally consistent with earlier studies (*3*) but the presentation is not sufficiently detailed to compare the differences in the metabolism in the kidney versus liver found earlier (*3*). More detailed data is required to compare the metabolism of the 1B4M and CHX conjugates in the liver, kidney and tumor with that of SCN-Bz-DTPA.

Having demonstrated that refinements in the SCN-Bz-DTPA family of chelates reduces the radioactive background in the liver which probably increases the detection of liver metastases (*12*), the techniques employed by these and other investigators (*1,3*) can address a number of significant questions:

1. Does the metabolism of the newer chelators differ from that of CA-DTPA or SCN-Bz-DTPA in tumors? For detecting tumors and their metastases, understanding the mechanism of localization in the tumor is as important as understanding the mechanism of localization in other tissues.
2. Is the inferred advantage (Table 1) of CA-DTPA over the SCN-Bz-DTPA class of chelates for detecting metastases in certain tissues (heart, GI tract, muscle) real or an artifact of comparing separate studies?
3. Does coupling the newer chelates with other methods for improving the biodistribution of labeled antibodies (*13,14*) introduce advantageous alterations in the metabolism of the conjugated Mab with a resulting improvement in biodistribution and tumor detection?
4. Do further increases in the lipophilicity of the chelator improve clearance from normal tissues?
5. What differences in the metabolism of the 1B3M chelator (*8*) result in its having a substantially higher tumor uptake than other members of the SCN-Bz-DTPA family of chelators? Does this advantage extend to tumor types other than LS-174T?

TABLE 2
Comparison of Experimental Systems

	Roselli et al.	Carney et al.	Brown et al.
Animal	Athymic mice	Athymic Nu/Wu BALB/c female mice	Athymic nu AF female mice
Age	—	—	4–5 week
Tumor type	LS174T	LS174T	LS174T
Size	0.5–0.8 cm	100–500 mg.	571 ± 498 mg. S.D.
Chelates/antibody	<1	3	—
Labeling Ph	4–6	6.0	—
Other	—	—	Exchange labeling via ^{111}In-EDDA
Immunoreactivity	25%–30%	—	HPLC (TSK-250) removal of free ^{111}In

Since answering these questions involves extensive experimentation, the requisite studies may be carried out at a number of centers. The more similar the system studied, the more easily one can compare results and broaden conclusions. The use of a common referent within the experiments (e.g., ^{125}I-B72.3) could further improve the comparison of results.

Progress in chelator development has improved the biodistribution of Mabs as shown both in Table 1 and by the demonstration of a Mab conjugated with a variant of SCN-Bz-DTPA having more sensitivity in detecting liver metastases than x-ray CT (*12*). These advances suggest that Mabs will eventually fulfill their promise of improving the detection and treatment of tumors and other targeted lesions. Examining the metabolism of conjugates as chelators is improving and comparing the metabolic products of older and newer chelates may speed their evolution.

Donald A. Rauh
Yardley, Pennsylvania

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