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EDITORIAL

Radiolabeled Antibodies to Oncogene-Encoded Molecules for Tumor Imaging and Therapy

The article by Bakir et al. in this issue of *The Journal of Nuclear Medicine* (*1*) demonstrates that a monoclonal antibody (Mab), ICR12, to a protein encoded by the c-erb B2 proto-oncogene, after radiolabeling with ^{124}I localized selectively to c-erb B2 expressing human tumors grows in nude mice. The localization could be detected by positron emission tomography (PET). The specific Mab localized 3-4 times better than a control Mab to tumor and there was up to 12% of the injected dose of ICR12 per gram of tumor tissue. The degree of tumor uptake, as well as the selectivity of specific, versus control antibody was comparable with data reported from similar studies with other antibodies using radioisotopes such as ^{125}I, ^{131}I or ^{111}In (*2*). As emphasized by the authors, the data suggest that ^{124}I-labeled ICR12 will be clinically useful for the diagnostic imaging of some breast carcinomas as well as other neoplasms which overexpress the c-erb B2 proto-oncogene product, and it is likely that the PET scanning technology will have advantages over conventional scintigraphy. A study by De Santes et al. (*3*) describes somewhat similar findings, but using different Mabs and ^{131}I instead of ^{124}I (and PET scanning).

An attractive feature of the work performed by Bakir et al. (and by De Santes et al.) is that the target molecule, p185, is encoded by a proto-oncogene. This has an advantage over tumor-associated differentiation antigens, which are the tumor markers most commonly used so far since the expression of p185 is not only higher in neoplasms than in normal tissues (which is true also for tumor-associated differentiation antigens), but is more intimately associated with the neoplastic state (*4*). Interestingly, overexpression of c-erb B2 correlates with a decreased sensitivity to treatment with hormones or chemotherapeutic drugs (*5,6*). This suggests that diagnostic imaging of tumors using Mabs such as ICR12 may be informative with respect to how aggressive the therapy should be and hence offers an advantage over imaging with Mabs to antigens whose expression does not correlate with prognosis. Furthermore, it may be possible to treat those tumors which can bind anti-p185 Mab by using it as a vehicle to deliver a large dose of radioisotope, and there are reasons to hope that p185 would be less likely to be lost from the cancer cells than antigens which are not encoded by an oncogene. The present study also suggests that certain antigens encoded by other oncogenes, for example, by mutated ras p21, or by mutated suppressor genes, could also prove useful as markers for in vivo diagnostics and perhaps even as therapeutic targets.

While the idea of using antibodies as "magic bullets" for tumor targeting was postulated a century ago by Paul Ehrlich, it has not been until fairly recently that by using Mab technology, antigens have been identified which are both expressed more in tumors than in most normal tissues and are lacking from critical cells such as hematopoetic stem cells. Some encouraging therapeutic findings have been already obtained with lymphomas where complete tumor regressions have been seen in patients given radiolabeled antibodies to tumor-associated differentiation antigens (*7,8*). While similar success has not been achieved when using Mabs to deliver radioisotopes to carcinomas, some provocative data have been obtained quite recently using an anti-carcinoma Mab, L6, to deliver ^{131}I to a small group of patients with breast carcinoma (*9*). Therapeutic studies in man in which anti-cancer drugs or toxins have been delivered via Mabs

Received Aug. 25, 1992; accepted Aug. 25, 1992.

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have so far yielded mostly disappointing results. This may, however, have been due to the use of Mabs with insufficient selectivity for tumor versus critical normal target tissues as well as to a failure to select Mabs which easily internalize drugs or toxins into cancer cells, since complete cures of established tumors can be regularly accomplished in animal models by using conjugates between internalizing antibodies and the anticancer drug adriamycin (*10*). Internalizing Mabs to oncogene-encoded cellular products of high tumor selectivity are of particular interest.

Bakir et al. have accomplished an important early step towards employing p185 as a diagnostic marker by showing that human tumor cells expressing p185 can bind sufficient amounts of ^{124}I-labeled Mab for tumor detection in nude mice via PET scanning. The next step, which is substantially more difficult, is to find out whether a similarly radiolabeled ICR12 will localize to p185 positive tumor cells also in man. While localization of radiolabeled Mabs has been demonstrated in man (*2*), fractions of 1% of the injected dose, rather than 12%, have been detected in tumor, at the very best. Therefore, it will not be until radiolabeled ICR12 (and similar Mabs) have entered human trials and the amount of relative uptake in tumor versus normal tissues is known, that one will get a feeling about diagnostic and therapeutic potentials. Personally, we like to be optimistic.

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