

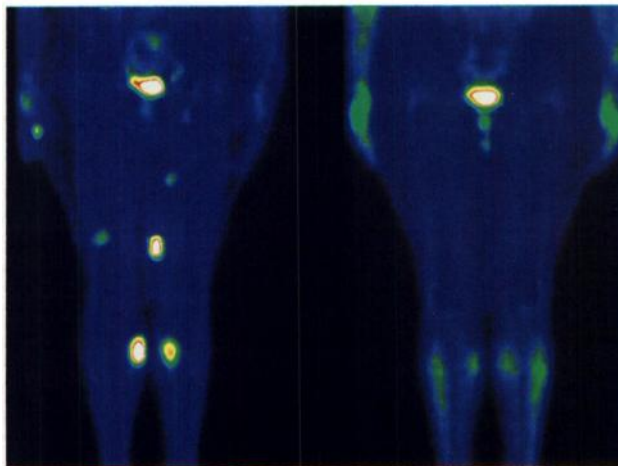
Emerging Radiolabeled Therapies Hold Promise for Treatment of Cancer

As more monoclonal imaging agents receive FDA approval, researchers are turning toward radiolabeled therapeutic monoclonals and peptides to see if they will be effective in the treatment of cancer and other diseases.

Once the darling of the oncology world, monoclonal antibodies have received a somewhat mixed reception in recent years. About a decade ago, researchers envisioned that monoclonal antibodies would usher in a new generation of therapeutic agents that packed the same punch as existing agents without the toxic side effects. A few years later, though, researchers became less enthusiastic as they failed to achieve good clinical results with monoclonals against solid tumors.

Recently, however, enthusiasm for this therapeutic approach has increased. Several companies in the U.S. and Europe are currently testing monoclonal therapies in clinical trials—particularly with non-Hodgkin's lymphoma—although none has yet received approval by the Food and Drug Administration (FDA). One pharmaceutical company, Immunomedics, Inc., in Newark, NJ, is conducting Phase I/II trials with monoclonal therapies for non-Hodgkin's lymphoma and colorectal cancer to complement its monoclonal imaging agents for non-Hodgkin's lymphoma (LymphoScan) and colorectal cancer (CEA-Scan).

"We usually match an imaging agent with a therapeutic because we think each helps the other in the approach to diagnosing and treating the patient," said David M. Goldenberg, ScD, MD, chairman and founder of Immunomedics. Other pharmaceutical companies are taking the same approach and are using nuclear imaging to tailor the therapeutic dose to the patient to yield the highest possible efficacy with the lowest toxicity. With the ^{131}I anti-B1 antibody for non-Hodgkin's lymphoma (manufactured by Coulter Pharmaceutical, Inc., Palo Alto, CA), for instance, researchers inject a small dose (5 mCi) of the therapeutic antibody and perform a whole body scan one hour later to mea-



Sequential FDG-PET scans of a patient with non-Hodgkin's lymphoma that responded poorly to standard chemotherapy. (Left) This PET scan is of the lower half of the body and was obtained two days before radiolimmunotherapy was administered. It shows several foci of intense FDG uptake in subcutaneous nodules of non-Hodgkin's lymphoma. (Right) This PET scan was obtained 34 days after the patient was treated with 97.9 mCi ^{131}I anti-B1 antibody. Nearly complete resolution of the tumor foci is seen. Activity in the upper midline is excreted FDG in the bladder. This patient ultimately had a complete response to treatment with no toxicity.

sure uptake. Two additional scans are performed about three and six days later to measure clearance. "This is one of the first therapies in nuclear medicine where the physician can actually use patient-specific scan data to plan that individual patient's treatment," said Richard Wahl, MD, a professor of radiology at the University of Michigan, Ann Arbor, and coauthor of the ^{131}I anti-B1 antibody studies.

If the trend in monoclonal imaging agents is any indication, radiolabeled monoclonal antibody therapies will be approved for the treatment of cancer within the next few years. In covering this giant research area, *Newsline* chose to focus on those clinical trials that are furthest along the route toward FDA approval. (Note: None of these therapies has yet been tested in randomized, controlled clinical trials.) In addition, there are dozens of other intriguing trials in the preclinical or Phase I (dose escalation) stage that may prove to be promising in the years ahead.

Clinical Trials for Non-Hodgkin's Lymphoma

Researchers predict that the first radiolabeled therapeutic monoclonal antibody to receive FDA approval will be the ^{131}I anti-B1 antibody (Bexxar)

developed by Coulter for the treatment of non-Hodgkin's lymphoma. Coulter is currently enrolling 60 patients in a Phase III multicenter trial and hopes to file for FDA approval by fall 1998, according to George Tidmarsh, MD, PhD, vice president of clinical development at Coulter.

The results from Phase I and II trials were promising: A 1993 *New England Journal of Medicine* article (*N Engl J Med* 1993;329:459-465) reported that 9 patients with non-Hodgkin's lymphoma in whom primary chemotherapy had failed were treated with Bexxar. Six of the 9 patients had substantial tumor responses, and 4 of those 6 had complete remissions. In a follow-up 1996 study involving the original 9 patients and an additional 28 patients, 79% of patients who received a radioimmunotherapeutic dose achieved either a complete or partial response, and 50% achieved complete remission (*J Clin Oncol* 1996;14:1974-1981). The monoclonal antibody works by binding to the CD20 antigen found on lymphoma cells as well as on normal B cells. According to Wahl, although B-cell, platelet, and white blood cell counts are lowered by the therapy, the levels gradually return to normal, so side effects are generally minimal.

Although patients are still being tracked for recurrences, Wahl said that so far complete remissions have averaged a median of 19 months, which is longer than what would be expected with traditional chemotherapy treatments. "My oncology colleague, Dr. Mark Kaminski, and I have also conducted a Phase II trial using the monoclonal antibody as a first course of treatment for previously untreated B-cell lymphoma patients," said Wahl. "Every one of the first 17 patients responded to the treatment with modest toxicity." Usually, patients receive conventional chemotherapy administered over four to eight months as compared to the two doses—one dosimetric and one therapeutic—of the radiolabeled monoclonal antibody.

A total of four monoclonal antibodies for non-Hodgkin's lymphoma are currently in clinical trials: Coulter has a high-dose form of its anti-B1 antibody in trials as well as Bexxar. Immunomedics is testing LL2, a humanized antibody that researchers claim is less likely to cause a human antimouse antibody (HAMA) response, in which antibodies are made in reaction to the mouse antibody found in most monoclonals. Alphatherapeutics in Tustin, CA, is testing its Lym-1 in trials as well.

Other monoclonal antibody researchers are excited by the results from these early trials: "These antibodies appear to be very effective in people with low-grade lymphoma who have failed chemotherapy," said Steven Larson, MD, chief of nuclear medicine at Memorial Sloan-Kettering Cancer Center in New York. "Within the next few years, I think

we'll see several therapeutic agents popping out of the FDA pipeline."

From Brain Tumors to Bone Marrow Transplants

One area in which monoclonal antibody therapies could become the first line of treatment after surgery is for the treatment of malignant gliomas. R. Edward Coleman, MD, a professor of radiology at Duke University Medical Center in Durham, NC, and his colleagues are conducting a Phase II trial using ¹³¹I-labeled anti-tenascin monoclonal antibody 81C6 in patients with a glioma-type brain tumor such as glioblastoma multiforme. Researchers administer the monoclonal antibody directly to the

Clinical Use of Monoclonal Imaging Agents

The trend toward developing monoclonal antibody and peptide therapeutics closely mirrors the development of these imaging agents. Although no monoclonal antibody or peptide therapies have yet received FDA approval, several imaging agents have received FDA approval in recent years. Thus, many companies are now developing therapeutic agents to treat those cancers they can successfully image.

- **Colorectal cancer:** OncoScint, manufactured by Cytogen, was the first monoclonal imaging agent to receive FDA approval (December 1992) for imaging colorectal cancer. In 1996 OncoScint received an FDA-approved label change to include multiple imaging injections in patients with a negative HAMA level. Immunomedics' CEA-Scan received FDA approval in 1996 for colorectal cancer imaging. CEA-Scan was approved for a single use only—Immunomedics, however, has filed additional data with the FDA to have that restriction removed—and must be used in conjunction with a CT scan to confirm metastases.

- **Small-cell lung cancer:** In February 1997, DuPont Merck received FDA approval for Verluma, a technetium-labeled monoclonal antibody for the staging of small-cell lung cancer. The test is used to detect distant metastases in both bones and soft-tissue organs such as the liver. Patients who are not found to have extensive disease still have to undergo traditional tests such as bone scans.

- **Prostate cancer:** Cytogen's ProstaScint received FDA approval in fall 1996 for prostate cancer imaging. It is used for two groups of patients: those suspected of having lymph node metastases presurgically and those suspected of having a postsurgical recurrence.

- **Neuroendocrine tumors:** Octreoscan, manufactured by Mallinckrodt Medical, Inc., in St. Louis, MO, is a peptide imaging agent used to diagnose neuroendocrine tumors. It received FDA approval for this use several years ago. The radiopharmaceutical targets somatostatin receptors on tumor cells.

tumor through a reservoir system placed into the tumor during surgery. "The antibody is designed to react with tenascin, an extracellular matrix protein ubiquitous in gliomas," said Coleman. "Once this reaction occurs, the radionuclide is delivered to the cancer cells and destroys them."

In Phase I trials (not designed to look at effectiveness), 4 of 5 patients with recurrent gliomas had partial responses to the therapy. "The mean survival
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Cancer Treatment

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for patients was longer than for those on other experimental therapies," Coleman said. The results were so promising that the research team changed the protocol for its Phase II trials and is using the antibody on newly diagnosed patients as a first line of therapy after surgery. So far, 12 patients have been treated with the antibody, after which they were treated with external beam therapy, a conventional but not highly effective treatment for gliomas. A total of 30 to 50 patients will be treated in the Phase II trial before results are published.

For those patients who suffer relapses of non-Hodgkin's lymphoma or have advanced leukemia, monoclonal antibody therapies may offer some hope for prolonged survival. Researchers at the University of Washington and Fred Hutchinson Cancer Center in Seattle are administering a high-dose form of the ^{131}I anti-CD20 monoclonal antibody followed by bone marrow transplantation in patients with recurrent lymphomas. Patients receive a therapeutic dose on the order of 300-800 mCi—about 5 to 6 times higher than the standard dose being tested in newly diagnosed patients.

In Phase II trials, 17 of 21 patients had complete remissions of their lymphomas, and half of those are still disease-free after a median follow-up of four years, according to study leader Oliver Press, MD, PhD, a professor of medicine and biological structure at the University of Washington. "We also see less toxicity with the antibody," said Press. "We're now planning on combining the antibody with conventional high-dose chemotherapy to see how much that adds to the toxicity."

In other research, scientists are developing a bone marrow transplant regimen for acute leukemia using the ^{131}I -labeled anti-CD45 antibody. In a Phase I/II trial in which 15 patients in remission were given a combination of the antibody and the chemotherapy drugs busulfan and cyclophosphamide, 85% of patients achieved disease-free survival for as long as 30 months. This compares to a 50% to 60% survival rate for those receiving just the high-dose chemotherapy. "If a Phase III comparison of chemotherapy versus chemotherapy plus antibody shows that the addition of the antibody reduces recurrence rates, this could become a first line of therapy for leukemia patients," said study leader Dana Matthews, MD, an assistant professor in the department of pediatrics at the University of Washington.

A Look into the Future

Predicting which experimental therapies will prove promising enough to be submitted for FDA approval is an impossible task. Here, though, are some intriguing areas of research currently in Phase I trials or in the preclinical stage. (Note that none has yet been tested for efficacy in humans.)

- **Peptides:** Diatide, Inc., a biopharmaceutical company in Londonderry, NH, recently received a National Institutes of Health grant to study the effectiveness of a compound composed of Fibrolyse, a clot-dissolving enzyme, and P734, a synthetic peptide, for the treatment of arterial thrombosis, a major cause of heart attack and stroke. Diatide researchers will study the compound in animals to determine if it eventually can be tested in patients with arterial thrombus for whom conventional treatments are ineffective or who have early reocclusion of the blood vessels.

Immunomedics is testing somatostatin receptor-targeting peptides in animal studies for the treatment of neuroendocrine tumors. Coulter is planning to begin Phase I trials of a tumor-activated peptide (whose name has not yet been released) coupled with the chemotherapy drug doxorubicin to see if the peptide enhances the effectiveness of chemotherapy in a variety of cancers such as breast cancer.

- **Other indications for established therapeutics:** Cytogen is currently conducting a Phase I trial using ^{153}Sm -EDTMP to determine if it alleviates joint pain in patients with refractory rheumatoid arthritis. The radiopharmaceutical is also being investigated for prevention of bone metastases, treatment of primary bone tumors and alleviation of bone cancer pain in children.

Coleman and his research team are beginning a Phase I trial to see if ^{131}I -MIBG therapy is effective against neuroendocrine tumors. A group of researchers from Holland are studying high-dose radiolabeled octreotide for neuroendocrine tumors.

- **Unnamed antibodies:** Larson and his team at Memorial-Sloan Kettering are currently conducting Phase I trials for the M-195 antibody radiolabeled with ^{90}Y and ^{213}Bi for the treatment of leukemia. Other researchers are studying the 3-F8 antibody as an experimental therapy for neuroblastoma in children.

—Deborah Kotz

Note: Many of the researchers interviewed for this article hold patents on the therapeutics they are investigating. They may also serve as consultants to pharmaceutical companies marketing the therapeutics.

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