Editorial

Advancements in Therapeutic Nuclear Medicine

Significant advancements in monoclonal antibody techniques for pretargeting make it very likely that radiopharmaceuticals will become an important part of therapy for various cancers. The ability to deliver high radiation doses to tumors with minimal bone marrow toxicity will offer significant therapeutic improvement and prolong lives. In addition to the use of beta particles, alpha particles may soon become a mainstay in therapeutic nuclear medicine. In this issue, *Newsline* is pleased to present a review of current research on the uses of alpha particles ("Alpha Particle Therapy Poised to Become New Line of Cancer Treatment" by Deborah Kotz, page17N) and a summary of one company's research into pretargeting ("Antibody Pretargeted Radiotherapy: A New Approach and a Second Chance" by Alan R. Fritzberg, PhD, of NeoRx Corporation, page 20N).

At a recent meeting sponsored by the Nuclear Medicine Research Council in the Tri-Cities area of Washington State, I was excited to hear a presentation by a representative of Frost & Sullivan, an international marketing and consulting firm based in Mountain View, CA, regarding the significant growth projected in both therapeutic and diagnostic nuclear medicine. This information is very important for nuclear medicine professionals to consider in planning for the future. A portion of the first section of this report is reprinted in this issue of *Newsline* (see "Future of Nuclear Medicine, Part 1: Marketing Research Forecasts," page 27N). Two additional sections of this report, "Assessment of the U.S. Diagnostic Radiopharmaceuticals Market (2001–2020)" and "Assessment of the U.S. Therapeutic Radiopharmaceuticals Market (2001–2020)" will appear in future issues.

Improvements in pretargeting, research using alpha particles and the increasing nuclear medicine diagnostic capabilities in oncology are all reasons that I believe nuclear medicine physicians are well suited to play a major role in caring for oncology patients. Nuclear medicine organizations need to take measures to ensure that we advance our knowledge in dosimetry and radiation biology. It is for these reasons that I challenge the leaders of nuclear medicine organizations to include presentations on dosimetry, radiation biology and oncology at nuclear medicine meetings. I encourage nuclear medicine residency directors to increase the coverage of these subjects in their training programs. In addition, the American Board of Nuclear Medicine might consider including more questions on dosimetry, radiation biology, oncology and therapeutic nuclear medicine in its certification examination. And finally, nuclear medicine practitioners should attend tumor board meetings at their facilities and present advancements as they become available.

—Conrad E. Nagle, MD
Editor, *Newsline*

Alpha Particle Therapy Poised to Become New Line of Cancer Treatment

For more than 15 years, cancer researchers have conceptualized using powerful alpha particles to target cancer cells. The first clinical trials have begun. The question now is: Will it work?

Cancer researchers looking for an extremely potent and highly specific way to target cancer cells are in early clinical trials investigating the use of monoclonal antibodies attached to alpha-emitting radionuclides. Several news items in national magazines and trade publications have already begun to hype alpha emitters, dubbing them "smart bombs" and "magic bullets." Given these high expectations, scientists now face the challenges of testing the efficacy of this new therapy in clinical trials and determining how, if at all, it will come into widespread use in hospitals.

Oncologists are increasingly recognizing the value of harnessing the high energy of alpha particles to destroy cancer cells. The challenge and

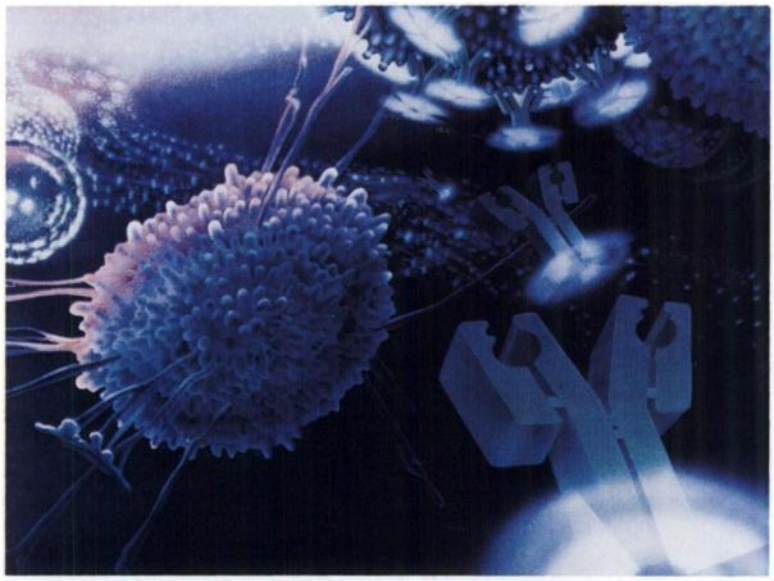

Photo: Robert E. Schenter, PhD

Radioisotope-tagged "smart bullets." Monoclonal antibodies target malignant cells for diagnosis and treatment.

"First, someone had to develop a humanized antibody that could effectively target cancer cells. Then... a way to attach the isotope to the antibody. Lastly... an alpha emitter ... readily available and safe to use."

limiting factor has been the delivery of the alpha particle energy to the cancer cell without toxicity to vital, healthy tissues. Researchers already have been investigating the use of monoclonal antibodies radiolabeled with beta emitters such as ^{90}Y in clinical trials with somewhat successful results in lymphoma, brain tumors and leukemia. But alpha emitters (which include ^{213}Bi, ^{211}At and ^{223}Ra) have a much higher linear energy transfer and a much greater specificity than beta emitters. "It may take as few as 1 or 2 hits by an alpha particle through the nucleus to kill a cancer cell, whereas it may take 2000 to 3000 hits by beta particles," said Darrell Fisher, PhD, a medical physicist who has conducted basic alpha radiobiology studies at Pacific Northwest National Laboratory (PNNL) in Richland, WA. Moreover, alpha particles have a range of 50μ to 70μ compared to a 1-mm to 10-mm range for beta particles. A more targeted range means less toxicity to surrounding healthy tissues.

As compelling as alpha emitters appear to be, oncology researchers have had to wait until advances in pharmacology and chemistry caught up with their dreams. "Before beginning clinical trials, we needed to overcome three major challenges," said David Scheinberg, MD, PhD, chief of leukemia services at Memorial Sloan-Kettering Cancer Center in New York. "First, someone had to develop a humanized antibody that could effectively target cancer cells. Then, we needed a way to attach the isotope to the antibody. Lastly, we had to find a good alpha emitter that is readily available and safe to use in the hospital." Working in collaboration with medical physicists and chemists in various parts of the country, Scheinberg and his colleagues began a Phase I clinical trial of alpha-emitter therapy in leukemia patients in 1996. They were the first—and are still the only—group to have tried alpha-labeled monoclonal antibody treatments in humans. Several other institutions are conducting animal studies and are planning to begin human trials within the next year.

Early Success in Leukemia Patients

In October 1996, Scheinberg and his team began treating patients with relapsed or refractory acute myelogenous leukemia with alpha-emitter therapy. In an abstract presented in December 1997 at the American Society of Hematology meeting (1997 ASH Abstract Book, #2113), researchers reported that no acute toxicities were seen in nine patients who were treated with ^{213}Bi attached to the humanized antibody M195 at doses ranging from 16 mCi to 43 mCi for ^{213}Bi and from 1.6 mg to 4.4 mg for the antibody. Illustrating the amazing specificity of alpha emitters, doses to the targeted cancer sites were 10,000 to 40,000 times higher than the estimated radiation dose to the kidneys or whole body. The absorbed dose ratio between cancer sites in the marrow, liver and spleen and the whole body was 1000-fold greater than what has been observed for beta-emitting nuclides. "We also saw as much as a 70% reduction of leukemia cells in the bone marrow," said Scheinberg. "However, we know we must kill 99% or more of cells to put a patient into remission. So, we'll continue to escalate the doses until we've achieved a complete remission or have reached a toxic level."

The team's radionuclide of choice is ^{213}Bi, mainly because it has an effective chelating agent, which provides a stable link between the alpha emitter and the monoclonal antibody. (Before last year, there were no chelating agents available for ^{225}Ac or ^{223}Ra.) In addition, ^{213}Bi is obtainable through a European supplier of generators and has a short half-life of 45 minutes. "We can inject patients at 9:00 a.m., and by noon they are only minimally radioactive," said Scheinberg.

After patients are injected with the monoclonal antibody radiolabeled with ^{213}Bi, they are scanned with a gamma camera equipped with a high-energy collimator. Spot images of the liver, spleen, kidney, pelvis and vertebrae are taken rather than whole-body images, since each whole-body scan takes up to 20 minutes and the short half-life of ^{213}Bi does not allow for repeat imaging. "Our nuclear physicians get real-time images and continue the scans for 2 hours after the first injection," said Scheinberg. "The scans give us information on biodistribution, pharmacokinetics and dosimetry." For instance, researchers have learned that it takes 6 minutes for the alpha emitter to reach a site of known disease. "It gets there quickly and stays there," Scheinberg said. "We have found no loss through the kidneys or other organs where there could be a potential for toxicity." Patients do experience a mild suppression of marrow progenitor cells for up to a few weeks after treatment, but this does not appear to increase their incidence of infections.

The Challenge of Infiltrating a Solid Tumor

Although alpha emitters have the clear potential to become a treatment for leukemia patients, several research groups are planning upcoming clinical trials to see whether alpha particles can effectively kill solid tumors. Researchers have had discouraging results using monoclonal antibodies radiolabeled with beta emitters in patients with solid tumors. The main reason is the difficulty in getting the antibody to penetrate the malignant mass rapidly enough to deliver the radiation. To circumvent this problem, Mike Zalutsky, PhD, a chemist and professor of radiology, and his colleagues at Duke University Medical Center in Durham, NC, plan to begin clinical trials within

the next few months in which they will administer the monoclonal antibody and alpha emitter directly to the tumor site in brain cancer patients with solid gliomas or neoplastic meningitis. The therapy will be delivered through a reservoir system placed into the tumor during surgery. As reported in an October 1997 *Newsline* article, R. Edward Coleman, MD, a professor of radiology at Duke, has been investigating this system using the beta emitter ^{131}I in brain cancer patients and has achieved good preliminary results (*J Nucl Med* 1997;38(10):23N).

"We are excited to begin trials with alpha emitters because of their limited range of only a few cell diameters," said Zalutsky. "We want to see if we can minimize the destruction of normal brain cells in patients with glioma and avoid damage to the spinal cord in those with neoplastic meningitis." His team will be using ^{211}At as the alpha emitter attached to the monoclonal antibody 81C6, which is designed to react with tenascin, an extracellular matrix protein present in gliomas. Zalutsky said his team chose to use ^{211}At for three main reasons: It has a 7-hour half-life, which gives the monoclonal antibody time to diffuse into the tumor cavity, it has high alpha emissions and it is readily available from the cyclotron on Duke's campus. "I can place an order for a single patient dose and have it delivered to me within the hour," Zalutsky said. At the time of preparation of this article, the Duke researchers were preparing to file an investigational new drug application with the Food and Drug Administration, pending approval by the university's internal review board. According to Zalutsky, once the formal approvals are granted, dose-escalation studies on patients could begin as early as spring 1998.

The reservoir delivery system may work well for brain cancer patients, but what about patients with breast, prostate or other types of solid tumors? Scientists at NeoRx Corporation, a biotechnology company in Seattle, WA, are developing a multistep delivery system for alpha and beta emitters that has shown potential for shrinking lung, breast and colon tumors in animals. (See "Antibody Pretargeted Therapy," page 20N.) The system involves pretargeting the tumor by first injecting a nonradiolabeled monoclonal antibody NR-LU-10 (which recognizes a glycoprotein expressed on most carcinomas) linked to streptavidin. The researchers then wait up to 48 hours until the monoclonal compound is taken up and evenly distributed throughout the tumor. They then inject a clearing agent to remove any remaining antibody-streptavidin circulating in the bloodstream. "Once we know the monoclonal is only concentrated in the tumor, we can inject biotin, which has a high affinity for the streptavidin conjugate, radiolabeled with an alpha particle," said Alan R. Fritzberg, PhD, chief scientist at NeoRx. In recent research in mice using the beta emitter ^{90}Y, NeoRx scientists achieved complete regressions in 80% of breast tumor xenografts and 100% of colon cancer and small-cell lung cancer xenografts.

As for human trials with alpha emitters, preclinical trials during the next year will focus on efficacy and toxicity studies using pretargeted ^{212}Pb (which decays to the alpha emitter ^{212}Bi). If results are promising, Phase I clinical studies may begin in 1999.

Researchers at the National Cancer Institute (NCI) are investigating a similar delivery system using monoclonal antibody fragments instead of whole antibodies in an attempt to create a faster way for monoclonal antibodies to infiltrate solid tumors. They are currently administering antibody fragments linked by genetic engineering to streptavidin conjugate followed by an injection of biotin radiolabeled with ^{212}At in a mouse that displays human T-cell leukemia. Regardless of the delivery system, "it's very difficult to get an intact antibody inside a solid tumor rapidly enough to deliver the alpha particles. The use of antibody fragments or biotin might solve this problem," said Thomas A. Waldmann, MD, chief of the metabolism branch of NCI, who has been directing research with alpha and beta particles.

This delivery method, however, is still in the experimental stages. In fact, chemist Martin Brechbiel, PhD, and his research team at NCI are devoting all their research efforts solely to the task of finding new chelating or linking agents that will draw alpha particles more completely to the antibody fragments. "The biggest challenge of working with alpha particles is finding effective chelating agents," said Fisher, who has been investigating new chelating agents at PNNL. "Researchers are still perfecting the techniques."

Supply Shortage of Some Alpha Emitters

Beyond working out the science of delivering alpha particles to tumor cells, many researchers have experienced a shortage of alpha emitters that are produced in reactors. "The shortage in supply of Ac generators [for the production of ^{213}Bi] has greatly slowed down the speed of our trials," said Scheinberg. "Until now, we were only able to get one generator every 40 days from our supplier in Europe." His group recently finalized a deal with the U.S. Department of Energy (DOE) to begin receiving shipments of Ac generators over the next few months from Oak Ridge National Laboratory in Oak Ridge, TN. Interestingly, the initial source of ^{213}Bi is ^{233}U (a fissile material once produced for nuclear weapons but never used), which is the

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"We want to see if we can minimize the destruction of normal brain cells in patients with glioma and avoid damage to the spinal cord in those with neoplastic meningitis."

ings of government. This 5-day forum, to be held in April 1998, is being coordinated by the SNM-TS as part of HPN's commitment to this project.

Outreach to Chapter Meetings

The Government Relations Office conducted several chapter visits by Robert Carretta, MD, chairman of the Government Relations Committee, in an effort to expand the visibility of the ACNP and SNM's government relations efforts. Chapter visits included those to the Pacific Northwest, Greater New York, Missouri Valley, and Northern and Southern California meetings. Chapters interested in arranging for a government relations speaker at their upcoming meetings should contact David Nichols, Director of Government Relations, at (703) 708-9773.

Political Action Committee

SNM, through the Government Relations Office, is moving forward with the establishment of a political action committee (PAC) by April 1998. This PAC will allow the Society to become more visible in the Congress and assist those members who are legislative friends of nuclear medicine in their reelection campaigns.

Legislative Network

The SNM-TS continues to operate a very successful legislative network. With more than 50 members in the legislative network, spread out among all the chapters of the SNM, the network enables members to keep informed on legislative issues and contact their members of Congress prior to key votes on Capitol Hill. If you are interested in participating in this legislative network or being included as a key contact in our nuclear medicine database, please contact Amanda Sullivan in the Government Relations Office at (703) 708-9773.

For more information on any of these topics, members are encouraged to routinely check the government relations page on the web at www.snm.org or to contact the Government Relations Office at (703) 708-9773.

—David Nichols is the director of the ACNP/SNM government relations office.

Alpha Particle Therapy

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parent of ^{229}Th, which is the parent of ^{225}Ac, which is the parent of ^{213}Bi. The DOE is currently working out plans to use U.S. uranium stockpiles for the production of alpha emitters and other medical isotopes. "This is a swords-to-plowshares story about using bomb-grade materials directly toward the treatment of cancer," said Robert E. Schenter, PhD, deputy site manager for the isotope program at PNNL. Scientists at PNNL are currently producing the beta emitter ^{90}Y and the alpha emitters ^{213}Bi, ^{225}Ac and ^{223}Ra from stored nuclear materials.

Still a Long Way to Go

As promising as alpha emitters seem as a potential treatment for cancer, researchers remain reserved in their enthusiasm. They remember the initial excitement over monoclonal antibodies and the resulting disappointment when that treatment failed to work against solid tumors. While acknowledging that they have made tremendous strides in alpha research over the past decade, researchers know they still have a long way to go.

—Deborah Kotz

Antibody Pretargeted Radiography

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recently initiated to evaluate tumor delivery of ^{212}Pb/^{212}Bi in the pretargeting system.

Initial studies used the gamma-emitting isotopes ^{203}Pb and ^{205}Bi for study of DOTA-biotin stability and pretargeting. The complexes were found to be stable, and pretargeting tumor and normal organ values were similar to those with ^{111}In and ^{90}Y. Then, ^{212}Pb and ^{212}Bi DOTA-biotin were prepared and evaluated. As expected from the results of Mirzadeh et al., about 35% of the biotin binding was lost for the ^{212}Bi from decay of the ^{212}Pb. However, when applied in the pretargeting context with NR-LU-10-SA, both the ^{212}Pb and ^{212}Bi values in tissue resulted in over 20% ID/g in tumor in 15 min, rising to 30% ID/g after 1 hr. Blood values were below 5% ID/g by 15 min, resulting in high tumor-to-blood AUC values. The kidney ^{212}Bi values were increased over the first 3 hr, then diminished, indicating that ^{212}Bi released from circulating forms localized in the kidney, but tumor-targeted radioactivity remained, even following escape from the DOTA chelator.

The preliminary studies of the alpha emitters briefly described establish potential in an efficient targeting system for radionuclides with short half-lives. The pretargeting system provides a means to evaluate the potential of targeted alpha radiotherapy in small and large xenograft tumors as well as metastatic tumor models. Issues for alpha emitters in pretargeting to be addressed in future research include toxicity to normal tissues and efficacy with respect to applicability in micrometastases relevant to adjuvant tumor treatment and the potential for treating established solid tumors.

Note: Pretargeting of ^{212}Pb supported by PHS Grant CA71221.

—Alan R. Fritzberg, PhD, is chief scientist and chairman of the scientific advisory board, NeoRx Corporation, Seattle, WA.