Radioimmunoconjugates

Targeting Disease for Diagnosis and Treatment

"This area is going to be one of the future directions in nuclear medicine. If the nuclear medicine community isn't prepared to cope with it, it won't be done, or someone else will do it."

When Edward Harrison was told that the grapefruit-sized tumor in his liver was inoperable and that he should try to live out his remaining 60-90 days as enjoyably as he could, he refused. Unwilling to give up so easily, the then 81-year-old retiree went to physicians at The Johns Hopkins Oncology Center for help. After being treated with 13 cycles of an experimental iodine-131 (^{131}I)-conjugated polyclonal antibody, Mr. Harrison was in complete remission. Today, more than five years later, he is free of disease.

Mr. Harrison and many other cancer patients have benefited from such pioneering efforts, which use radioimmunoconjugates in the treatment and detection of disease. While the Food and Drug Administration (FDA) has yet to give market approval to any radioimmunoconjugate agent, scores of researchers across the United States and worldwide are amassing evidence supporting the role of a variety of radioimmunoconjugates in the treatment and diagnosis of many cancers as well as the detection of heart disease, autoimmune disorders, and infection.

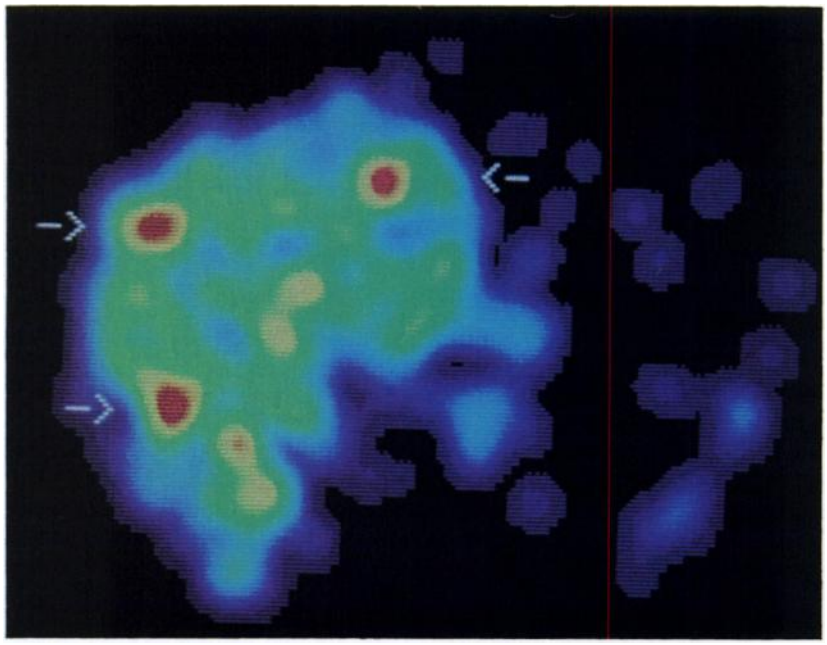
Assessing the status and potential of radioimmunotherapy (RAIT) and radioimmunodetection (RAID), Aldo N. Serafini, MD, professor of radiology and medicine at the University of Miami School of Medicine in Florida, says, "An extensive number of clinical trials have now been conducted in a number of countries using a number of antibodies, with results that indicate that monoclonal antibody techniques promise to be clinically useful tools for the detection of both benign and malignant disorders as well as useful tools for adjuvant therapy in the treatment of cancer. RAIT offers the hope of targeted therapy, and, as such, it should reduce the morbidity associated with the side effects of conventional treatments and improve the survival rate because larger doses of both radioactive and chemotherapeutic agents will reach tumor sites."

David M. Goldenberg, ScD, MD, President of the Center for Molecular Medicine and Immunology in Newark, New Jersey, says, "Monoclonal antibodies for imaging and detecting cancer, myocardial infarction, sites of infection, and fibrin clots have already demonstrated clinical usefulness. Monoclonal antibodies labeled with isotopes for cancer therapy are still finding their role. Therapeutic radioactive monoclonal antibodies probably will have their first successes in radiosensitive tumors, such as lymphomas. But, with the development of appropriate radionuclides and humanized antibodies, monoclonals will eventually gain a significant role in treating solid tumors."

Areas of Application

The use of antibodies labeled with radioisotopes for diagnosis and therapy has steadily progressed over the last decade with improvements in antibodies, radioisotopes, and instrumentation and in the choice of targeted antigens. According to the FDA, "at least 60%" of the 350 to 400 antibody investigational new drug applications involve radioimmunoconjugates. Despite the lack of market approval for radioimmunoconjugates, at least a dozen companies are developing products, and investigators have found widespread clinical applications for their use. Dr. Serafini lists the following indications for RAID: "to detect occult disease in patients with high clinical suspicion; to stage the extent and degree of disease before and after therapy; to reevaluate patients with known disease but new symptoms; to improve the specificity of equivocal findings found using other imaging modalities; to assess the possible role of RAIT; and to assess the viability of tissues in both benign and malignant disorders." Therapy with radioimmunoconjugates is indicated, according to Dr. Serafini, "in the treatment of various solid and hematologic tumors; as an adjuvant to complement other forms of therapy; and to reduce recurrence due to small, undetected residual tumor in the early stages of diseases such as ovarian cancer."

Oncology has been the major focus of radioimmunoconjugates since their early development in the late 1970s by



(Figure 1; Three hour transverse SPECT abdomen image of a ^{99m}Tc-labeled CEA monoclonal antibody targeting multiple liver metastases that are 3-5 mm in diameter, shown with arrows. Courtesy: Center for Molecular Medicine and Immunology.)

Dr. Goldenberg and his coworkers. Over the past few years, researchers have made significant headway into detecting neuroblastoma, cholangiocarcinoma, germ cell tumors, carcinoembryonic antigen (CEA)-producing tumors, and alphafeto-protein (AFP)-producing tumors as well as cancers of the bone, colon, liver, lung, and pancreas.

Pointing to the advantages of functional imaging with radioantibodies over anatomic imaging methods, Dr. Serafini says, "By detecting tumor markers rather than morphological change, RAID can, for example, better differentiate between postsurgical fibrous tissue and tumorous tissue and predict the effectiveness of RAIT to the tumor site."

More specifically, Dr. Serafini says that efforts to detect colorectal and ovarian cancers with radioimmunoconjugates "are detecting disease that computed tomography and magnetic resonance imaging are not finding and are useful to complement those methods." He also notes that the results of studies of lung cancer indicate that RAID "is going to be a useful modality for staging these cancers."

In a novel approach that is applicable to many types of cancer, David A. Goodwin, MD, chief of nuclear medicine at the VA Medical Center, Palo Alto, California, professor of diagnostic imaging at Stanford University School of Medicine, and his colleagues have developed a pretargeted antibody technique for RAID. Dr. Goodwin says the group uses a bispecific conjugate, with a tumor-binding site and a non-covalent hapten or biotin chelate binding site. The technique is performed in three steps, he explains. "In the first step, the researchers let the antibody circulate until it localizes in the tumor," a process that may take up to nine days. "The second step, the chase... removes the antibody from the circulation." This step, which takes about five minutes, is immediately followed by step three, the injection of a radionuclide in the form of a hapten or biotin chelate. Dr. Goodwin notes that because the chelated radionuclide is rapidly diffused through the extracellular material and excreted through the kidneys, imaging one to three hours after radionuclide injection using this technique provides a "much improved target-to-background ratio, on the order of ten to one in blood and three to one in the liver. The tumor is much easier to see."

The group has used the method to visualize human colon tumors and other solid tumors in immunocompromised mice using technetium-99m (^{99m}Tc) for single photon emission computed tomography (SPECT) imaging and gallium-68 (^{68}Ga) for positron emission tomography imaging. Although the group has not applied the pretargeted antibody method to RAIT, Dr. Goodwin says it "looks very promising for therapy because bone marrow uptake is low with this technique." But, as with other RAIT methods, the outcome ultimately "depends on the absolute amount of radionuclide you can get into the tumor."

In cancer therapy, radioimmunoconjugates have been targeted at antigens of melanoma and B- and T-cell lymphomas as well as of liver, gastrointestinal, colorectal, breast, ovarian, pancreas, and prostate cancers.

Gerald C. DeNardo, MD, professor and chief of the section of radiodiagnosis/therapy at the University of California, Davis, (UCD) in Sacramento, points out that "despite the fact that the use of radioantibodies has been in patients with very advanced disease who have failed everything else and are not receiving any other treatments that might improve results, there have been successes. This is very encouraging."

Significant advances are being made in the treatment of lymphomas and leukemias. Carl M. Pinsky, MD, vice president of medical affairs at Immunomedics, Inc., in Warren, New Jersey, notes that "since patients with lymphomas generally have depressed HAMA [human antimouse antibody]

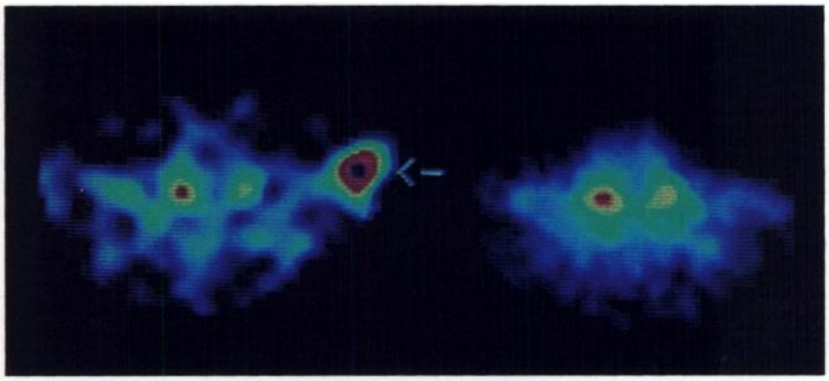
reactions, murine monoclonal antibody radioimmunoconjugates may find their first therapeutic application in this disease."

Indeed, for the past six or seven years, researchers at UCD have treated patients with lymph node cancers, including lymphoma and leukemia, using an ^{131}I-labeled antibody against malignant lymphocytes. Dr. DeNardo says the group has observed a 95% response rate — 70% decrease in tumor size or complete disappearance of the tumor — in more than 40 patients who had failed to respond to chemotherapy or radiation therapy.

Stanley E. Order, MD, ScD, Willard and Lillian Hackerman Professor and director of Radiation Oncology, The Johns Hopkins Oncology Center, Baltimore, Maryland, says 60% of the Hodgkin's disease patients his center treated with a yttrium-90 (^{90}Y)-conjugated antibody achieved remission, and half of those remissions were complete. Dr. Order, who treated Mr. Harrison, says that this work, which improved on the group's results with ^{131}I, "demonstrates that if you make the isotope more powerful, you can achieve a better clinical result."

In another example, Dr. Order notes that he and other researchers at Johns Hopkins have achieved positive results in studies of liver cancer. Through in vitro studies, the group has shown that when cells undergo prolonged exposure to radiation, the cells shift to phases "during which they are more radiosensitive and chemosensitive." Thus, says Dr. Order, "radioantibodies can be combined with chemotherapy and radiation therapy with improved results." In addition, Dr. Order says that five patients other than Mr. Harrison had nonresectable hepatoma, were treated with an ^{131}I radioimmunoconjugate, and "became medically cured or put into remission so that they could be surgically cured. They are all disease-free at five years."

The UCD researchers have started to study RAIT in breast cancer patients. Using an ^{131}I-labeled humanized mouse antibody against adenocarcinoma, over the past year and a half. the group has observed shrinkage of tumors in five patients studied, according to Dr. DeNardo.



(Figure 2; Left, an arrow points to a lymphomatous mass revealed with an ^{131}I-labeled monoclonal antibody, LL2 in a 24-hour transverse SPECT chest image taken during ***radioimmunotherapy. Right, resolution of the site is shown in this 24-hour SPECT image taken one month following therapy. Courtesy: Center for Molecular Medicine and Immunology.)***

Radioimmunoconjugates are also being studied in the detection of a variety of other disease states, including myocardial infarction, vascular thrombi, infections, transplant rejection, and autoimmune diseases, such as arthritis, diabetes, systemic lupus erythematosis, and multiple sclerosis.

The detection of infection is a burgeoning area. Dr. Serafini, who has used indium-lll (^{111}In)-labeled immunoglobulin (Ig) G to detect infections associated with diverse conditions, including abdominal and pelvic abscesses and pulmonary and bone infections, says, "a wide variety of acute and chronic infections can be targeted with specific (murine) and nonspecific (human) antibodies." Dr. Serafini notes that groups in the U.S. and Europe are studying ^{99m}Tc-labeled IgG molecules and ^{111}In- and ^{99m}Tc-labeled antigranulocyte antibodies in infection imaging.

Immunoconjugated Isotopes

RAID and RAIT studies in oncology and other areas have involved an extensive array of radioisotopes, but factors of cost, availability, and ease of use are beginning to narrow the list. "Although the list of usable isotopes is long in both the diagnostic and therapeutic areas, the ones that are going to survive are the ones that are readily available at a competitive cost and that can be clinically used with simple conjugation and kit preparation methods," predicts Dr. Serafini.

The isotopes that have been the focus of RAID studies are ^{99m}Tc, ^{111}In, ^{131}I, iodine-123 (^{123}I), and ^{68}Ga. In RAID, says Dr. Serafini, "For practical purposes, the isotopes that are appropriate are the technetium and indium agents, since other agents are either not readily available or not ideally suited for imaging with currently available instrumentation." Dr. Goldenberg says that "for imaging, clearly the preferred isotope is technetium-99m because of it's relatively low cost and excellent imaging properties." More specifically, according to Dr. Serafini, "isotopes with shorter half-lives, such as technetium-99m, are better suited when combined with fragments, which allow for earlier imaging, whereas longer-lived isotopes, such as ^{111}In, may be better suited as isotopes for whole antibodies, in which targeting of the tissue or tumor may require more than 24

Characteristics of Radionuclides Being Studied in RAID and RAIT

Detection

Nuclide	Half-Life	Principle Radiation(s)/(Energies)
^{99m}Tc	6 hours	γ (140 keV)
^{111}In	3 days	γ (173, 247 keV)
^{131}I	8 hours	β (610 keV, etc.); γ (364 keV, etc.)
^{123}I	13 hours	γ (159 keV)
^{68}Ga	1.1 hours	β^+ (1.9 MeV); γ (511 keV)

Therapy

Nuclide	Half-Life	Principle Radiation(s)/(Energies)
^{131}I	8 days	β (610 keV, etc.); γ (364 keV, etc.)
^{90}Y	64 hours	β (2.3 MeV)
^{67}Cu	61 hours	γ (184, 90 keV); β (570 keV, max.)
^{186}Re	90 hours	γ (140 keV); β (1.1 MeV)
^{188}Re	17 hours	γ (160 keV); β (2.1, 2.0 MeV)
^{125}I	60 hours	I.C. X-ray, Auger (27.35 keV)
^{77}Br	58 hours	γ (240, 520 keV); β^+ (340 keV)
^{119m}Sb	250 days	Auger e^- (20–60 keV)
^{211}At	7 hours	α (5.9 MeV)
^{197}Hg	65 hours	γ (80 keV); Auger e^- (60, 70 keV)

hours." Dr. Serafini further notes that "although ^{123}I has been shown to have good sensitivity for detecting various cancers, it is not readily available, and it is expensive."

In the therapeutic area, researchers are examining an extensive list that includes, copper-67 (^{67}Cu), ^{90}Y, rhenium-186 (^{186}Re), rhenium-188 (^{188}Re), ^{131}I, iodine-125 (^{125}I), bromine-77 (^{77}Br), antimony-119 (^{119}Sb), astatine-211 (^{211}At), and mercury-197 (^{197}Hg). While ^{131}I has been most widely used in RAIT, Dr. Goldenberg selects ^{90}Y, ^{67}Cu, ^{186}Re, ^{188}Re, ^{211}At, and ^{125}I as the alternative isotopes having the most potential. According to Dr. Serafini, ^{131}I's advantages are its low cost, wide availability, and high specific activity, and that it enables physicians to administer a therapeutic dose after a tumor is localized with a diagnostic dose. Dr. DeNardo says that although ^{131}I "probably always will be useful for some kinds of cancer in antibodies," there are disadvantageous "radiation safety aspects" associated with its use, and "in some antibody-tumor systems ^{131}I doesn't stay on the antibody and, therefore, the tumor, as long." Referring to the application of metals, such as ^{90}Y and ^{186}Re, instead of ^{131}I, he says, "The bottom line is you can get more radiation and more treatment to the tumor. But, the other side of the coin is that the metals also stay longer in other places, such as the liver and the bone marrow." He notes, however, that "newer formulations of yttrium hold on to the tumor better," so less goes to the bone marrow. He is also quick to point out that ^{67}Cu, "unlike some of the other metals, does not go to the bone marrow."

The UCD researchers have started pharmacologic studies of ^{67}Cu in humans. Dr. DeNardo, who calls ^{67}Cu "a therapeutic technetium," says, "the quality of the copper-67 images is as good as with ^{99m}Tc, its therapeutic emissions are like ^{131}I, and it tends to stay on the tumor longer than ^{131}I."

What's Holding It Back?

Despite the possibilities, the availability of appropriate isotopes at a low cost for clinical use is one of several factors that needs to be ensured if the field is to progress. To a large degree, researchers have identified the problems and are working on ways to solve them.

"The cost and availability of isotopes and the availability of suitable conjugation techniques enabling administration of appropriate doses are of particular importance to progress in therapy," says Dr. Serafini.

According to Dr. Goldenberg, the problems blocking the advancement of RAIT are: the HAMA response, the lack of stable conjugates, and the low rate of incorporation of antibody into tumor. So progress hinges on the development of "highly selective antibodies that won't result in HAMA, in conjugates that won't degrade or leave the tumor." Noting that these areas are being studied, he says, "Radioimmunotherapy is now where radioimmunodetection was six years ago. We are just at the threshold of getting good results. The next two to five years will bring many agents into clinical trials."

Researchers are working on various ways to prevent the development of HAMAs including using immunosuppressive drugs, removing the immunogenic Fc portion of the antibody by fragmenting antibodies, using humanized or chimeric antibodies with decreasing amounts of murine protein, and increasing a patient's tolerance by injecting first with cold nonspecific antibody and then specific labeled antibodies. According to Dr. Serafini, this process also increases the antibody's specific targeting ability, because the cold antibody binds circulating antigen and enables more radioantibody to reach the target site.

Pointing to progress made in this area, Dr. Serafini says, "Although the HAMA question has been one of con-

cern, both therapeutic and diagnostic studies are being done in which repeated doses are being administered successfully to patients. There are methods to combat the HAMA response, such as to make the patient more tolerant or use human, humanized, or chimeric antibodies. Chimeric and human antibodies will reduce or eliminate these problems."

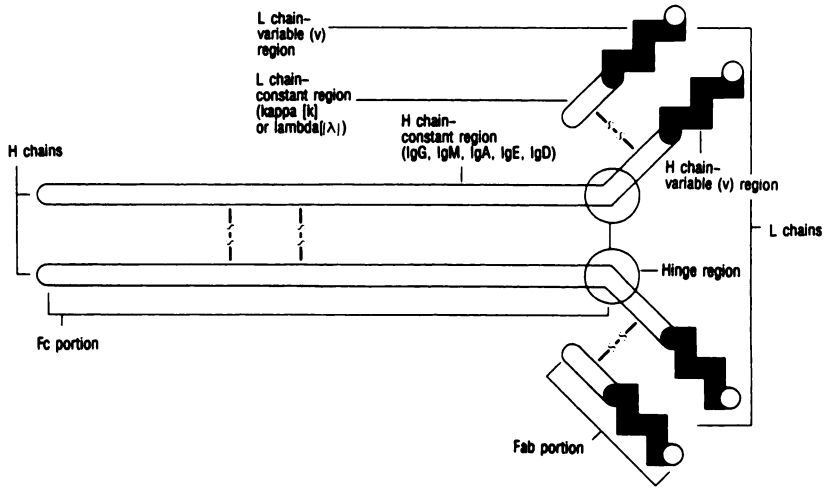
Dr. Goldenberg says efforts center on "making as much of the antibody or targeting molecule human as possible and as small as possible without affecting its targeting ability." Thomas J. McKearn, MD, PhD, executive vice president of Cytogen Corporation in Princeton, New Jersey, also forsees small, humanized antibody-like molecules dominating the field in the near future. He says that Cytogen has developed five whole-antibody or fragment products that use ^{111}In or ^{99m}Tc to image various cancers and a whole-antibody agent that uses ^{90}Y for cancer therapy. These products are in various stages of FDA testing or review. The company is working on "reengineering antibodies—making them more human, less immunogenic—and molecular simplification to reduce the size of the molecule so it can target more efficiently," according to Dr. McKearn. He says the company has developed a thrombus imaging agent in which ^{99m}Tc is conjugated with a targeting peptide sequence, rather than a whole antibody or fragment. Paul Abrams, MD, JD, president and chief executive officer of NeoRx Corporation in Seattle, Washington, says NeoRx is also developing "novel chimeric and humanized constructs that have targeting principles that are based upon antibody targeting principles." The company has developed several ^{99m}Tc-labeled fragment cancer imaging agents that are undergoing FDA review or testing and is studying a ^{186}Re-labeled antibody in the treatment of ovarian cancer.

Further efforts to improve targeting and minimize the HAMA response were discussed during the Third Conference on Radioimmunodetection and Radioimmunotherapy of Cancer, held November 15-17 in Princeton, New Jersey. Presenting some of the latest techniques in an abstract submitted to the Conference, Jeffrey Schlom, PhD, chief of the laboratory of tumor immu-

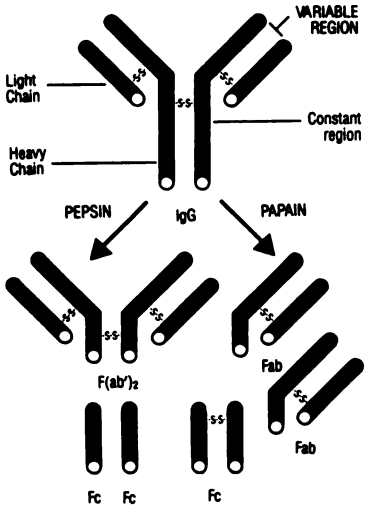
Make-up of IgG and its Fragments

The most common class of antibodies, the immunoglobulin G (IgG) molecule, is made up of four peptide chains, two heavy and two light, which are covalently bonded via a sulfide bridge into the shape of the letter Y. The N-terminal ends of the heavy and light chains are called variable regions because of their varying amino acid sequences. Each antibody molecule has two variable regions, which are where the antibody binds to an antigen. The opposite end of the chains is the constant region to which other molecules of the immune system bind, effecting an immune response.

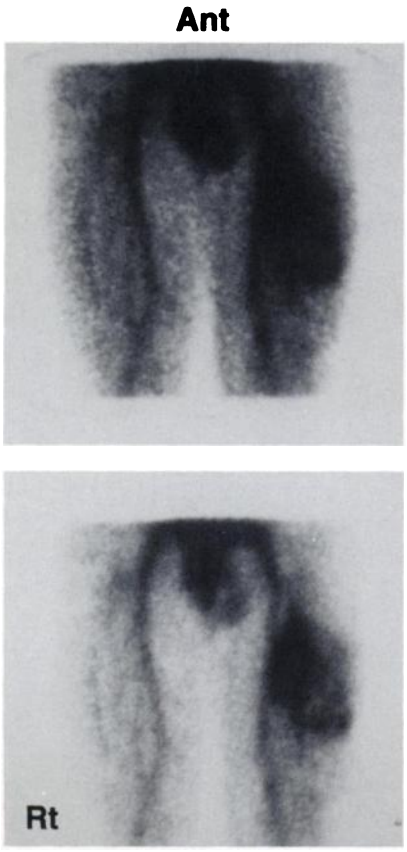
To produce IgG fragments, investigators use one of two methods. Papain digests the whole antibody into two Fab fragments, which are made up of an N-terminal region of a heavy chain bonded to an entire light chain and one Fc fragment made up of the constant regions of the heavy chain. Pepsin cleaves the antibody into $F(ab')_2$, a single fragment made up of the variable region of the bonded heavy chains bonded to the two light chains and two fragments of Fc (see Figures 3 & 4). ■



(Figure 3; Components of the Immunoglobulin molecule. Courtesy: NeoRx Corporation.)



(Figure 4; IgG molecule fragments. Courtesy: NeoRx Corporation.)



(Figure 5; ^{111}In-IgG Scan performed at 6 hours shows intense localization in the left thigh of a 44-year-old male with a history of pain and swelling that was unresponsive to antibiotics. X-ray and pathology confirmed osteomyelitis and cellulitis secondary to staphylococcal aureus infection. Courtesy: A. Serafini, MD, University of Miami.)

nology and biology at the National Cancer Institute, Bethesda, Maryland, noted that recombinant/chimeric Ig molecules, which have human Fc regions, can reduce the HAMA response. Humanizing Igs through complementarity determining region grafting should also reduce the HAMA response, he added. In addition, single chain antigen-binding proteins, novel recombinant proteins expressed in *E. coli*, "are stable in vivo, have an extremely rapid plasma clearance, and can target tumors efficiently." Dr. Schlom also noted that the "availability of recombinant/chimeric Ig forms now makes feasible the use of multiple Ig dosing protocols. Experimental studies have shown that dose fractionation protocols can reduce toxicity and subsequently greatly increase efficacy of [monoclonal antibody]-based tumor therapy." He pointed to studies showing that some biological response modifiers, "can up-regulate the expression of tumor cells but not normal cells." Dr. Schlom predicted that these techniques, "together with second generation higher affinity antibodies, new chelates, and a wider choice of isotopes, offer new approaches that may well lead to more effective [monoclonal antibody]-based diagnostic and therapeutic applications."

However, improving targeting and decreasing immunogenicity are not the only areas that need work. The expense of this technology and the variable sensitivities that have been reported are other negative issues.

Commenting on the varying sensitivities that have been reported by different groups doing RAID, Dr. Serafini says that it's difficult to compare these figures because the researchers used "different antibodies, isotopes, labeling procedures, and methods of imaging." He says that studies need to be done comparing work done with similar methods.

Acknowledging that RAID is time consuming and expensive compared to CT and MRI, Dr. Serafini says that "industry needs to address the specific needs of the cancer patient in order to reduce imaging time. Maybe [manufacturers] should build instruments with dual detectors or ring detectors, which can scan faster and increase throughput," and, thereby, decrease the expense.

According to Dr. Goldenberg, Immunomedics has responded to the need for a simple, rapid, low-cost imaging kit, and is completing Phase III clinical trials of a one-step, five minute ^{99m}Tc-labeling kit for an anti-CEA fragment. Dr. Pinsky says that three-to-five hour planar and SPECT images using this fragment can reveal tumors as small as 0.3-0.5 mm. "Phase III studies have not only demonstrated excellent targeting, but no HAMA responses after the injection of antibody fragment," he notes.

In addition, notes Dr. Serafini, practitioners must address the issue of who will provide this technology. Since it would not be cost effective for every clinical center to have radiolabeling facilities, he argues that the field must decide whether to license a few regional centers to make up radioimmunoconjugates and perform RAID and RAIT or have many centers do RAID and RAIT with commercially supplied radioimmunoconjugates.

Beyond the issue of which centers will provide RAIT and RAID is the question of which specialists will image and treat with radioiantibodies. Dr. DeNardo urges nuclear medicine practitioners to "get in gear now and start learning because this area is going to be one of the future directions in nuclear medicine. If the nuclear medicine community isn't prepared to cope with it, it won't be done, or someone else will do it."

In addition to the scientific issues that need to be ironed out, regulatory reins keep the technology in check. Some in the field have expressed concern that the FDA's pace in approving radioimmunoconjugates is too slow and may hinder progress. Others say the pace reflects FDA's need to satisfy safety and efficacy concerns with this emerging technology. Dr. Serafini says the FDA's slow pace of approving these agents perplexes and worries him because it may have a negative impact on commercially-funded research and overall progress in this area. He predicts that "industry will respond to a much greater degree once they see one of the antibody products approved by the FDA. Now, they're holding back."

Dr. McKearn says, "There is a very widespread concern that staffing needs

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Radioimmunoconjugates

(continued from page 20A)

at the FDA have not been adequately dealt with." Placing the blame on Congress for not appropriating the necessary funds, he adds, "speeding up the review process could be accomplished without compromising safety and efficacy standards, and that would make products available for use more expeditiously."

On the other hand, Dr. Abrams says that since "these are the first products that [FDA] has seen as labeled antibodies or in vivo diagnostic imaging products, they need to satisfy their curiosities and concerns. That is quite appropriate."

Curtis L. Scribner, MD, chief of the hematologic products branch at the FDA, says the FDA's concerns center around the specificity and sensitivity of these agents. "There's no such thing as a truly tumor-specific antibody. The difficulties with radioantibodies as with all radioimaging agents are with the deposition of radioactivity over the normal structures. Radioimmunotherapy," he adds, "takes the cross-reactivity sort of to its extreme."

Despite the problems, he says, "The field of specific antibody targeting to tissues is still a very exciting area, and it holds a lot of promise."

But, as one who knows only too well how radioimmunoconjugates can be of benefit, Mr. Harrison expresses dismay at this untapped promise and the FDA's pace of approval. He says that after he went into remission, he asked Dr. Order, "how soon are you going to get this stuff out on the market? If it was Europe it would have been out yesterday."

Sarah M. Tilyou

Lines from President

(continued from page 26A)

nitrogen-13 ammonia? No individual PET practice can possibly undertake an NDA on its own.

Practitioners of nuclear medicine who make up their own kits for use within an institution for radiopharmaceutical compounding are able to do so under each state's rules of practice of pharmacy and medicine. In fact, that practice is no different from compounding ^{18}FFDG on site for use within an institution. These issues and SNM and ACNP's differences with ICP were discussed, understood, and, to some degree, reconciled. All concerned parties agreed to move forward and keep each other informed. These differences in approach are a source of confusion that blurs the image of nuclear medicine. The questioned jurisdiction of FDA to regulate what SNM and ACNP argue falls under state jurisdiction is the core of the issue.

Questions over turf are fierce. Everyone in the nuclear medicine community knows what they are and what their significance is to the future of nuclear medicine. Physicians have been taught and generally believe that the research of today becomes the clinical practice of tomorrow and that those who perform the research are most likely to be those who will inherit that clinical practice. It doesn't always happen that way. Particularly when the issue of income for physicians, hospitals, and joint venture groups is at stake, monetary incentives seem to overpower the logic that those who do the research to develop a clinical tool have the right and the best credentials to do that clinical work.

The ACR recently supported a landmark study that compared the costs of imaging performed by radiologists versus non-radiologists for a few specific clinical problems in a large population of patients. The costs to the same insurance company were shockingly higher when imaging was done by non-radiologists compared to radiologists. The reasons for the non-radiologists' increased costs were higher charges and higher utilization. Such data may provide a basis for anti-self referral legislation, which would undoubtedly alleviate some nuclear medicine turf conflicts.

Reflections on PET and turf touch only a small segment of the three-dimensional dynamic image of nuclear medicine as a specialty. The more comprehensive image of nuclear medicine that Summit participants saw indicated that the specialty looks good, but it could look better. The group speculated that if nuclear medicine practitioners can protect their turf, the future of the field probably will not be substantially different from the future of medicine in general. All indications are that the future of medicine in this country is not as bright as health professionals would like, but they are working hard to keep the flame glowing.

Summit participants were:
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