1994

OncoLog Volume 38, Number 01 January-March 1994

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January–March, 1994
Volume 39, Number 1

THE UNIVERSITY OF TEXAS
MD ANDERSON
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MD Anderson Oncolog

Survival time doubled in experimental studies

Liposomal muramyl tripeptide kills bone cancer cells by stimulating the immune system

Lab to Clinic

Eugenie Kleinerman is a professor of cell biology and pediatrics in the Department of Cell Biology

Until Eugenie Kleinerman, M.D., professor of cell biology and pediatrics at The University of Texas M. D. Anderson Cancer Center, began treating bone cancer patients with liposomal muramyl tripeptide (MTP), the choice of therapies for relapsed bone cancer was limited. The disease, which is most common among teenagers, can be treated with chemotherapy, but it quickly spreads to the lungs. If the lung metastases are refractory to chemotherapy, they usually kill the patients in less than five months. Liposomal MTP treatment, however, has more than doubled survival time, is well tolerated by patients, and can often be administered by private physicians outside of cancer centers.

The new therapy is the cumulation of more than 10 years of research at M. D. Anderson Cancer Center. Kleinerman credits Isaiah Fidler, D.V.M., chairman of cell biology at M. D. Anderson, with sparking her interest in liposomal MTP in 1982. "I heard him give a lecture at the annual meeting of the American Association for Cancer Research about his mouse model using liposomal MTP, and it was like a light bulb went on, and I said, 'That would work for osteosarcoma.' At the time I was a fellow at the National Cancer Institute. Being a pediatrician, I was interested in pediatric cancers, and one of the problems with bone cancer is that it metastasizes to the lung. Fidler had injected mice intravenously with MTP and gotten uptake in the lung. It struck me that if we could get MTP delivery to the lung we could turn on the pulmonary macrophages and eradicate the remaining tumor cells." (See box, "How liposomal MTP works.")

Despite her excitement, Kleinerman already had a research project, and it was difficult for her as a junior faculty member to initiate another, more speculative project. Some of her peers were not enthusiastic about her idea, either. At the time, biologically based therapies were uncommon, and osteosarcoma was not as high a priority as lung or breast cancer. "It took me about a month to get up enough nerve to speak to Fidler about my idea," she said. But Fidler encouraged Kleinerman's interest in treating osteosarcoma patients with MTP. They began a collaborative study, and eventually Kleinerman came to M. D. Anderson. "The pediatric department here was very receptive to my ideas and very receptive to my having a joint appointment in cell biology, treating patients, and moving my bench findings into the clinic," she said.

So far, Kleinerman and her colleagues have treated about 50 patients with liposomal MTP for pulmonary metastases refractory to chemotherapy. The first 16 patients were infused with liposomal MTP for one hour twice weekly for 12 weeks and then once a week for another 12 weeks. These patients have lived twice as long as untreated patients. Some are alive three years after treatment, including one former pediatric osteosarcoma patient who is now nearly through college.

In addition to being effective, the treatment was easy to administer and so relatively inexpensive. The patients did not have to travel to a cancer center to be treated—they could receive

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MTP in an outpatient clinic or even in their family doctor's office. Kleinerman explained, "It took about half a day to train someone to administer the drug. And we had absolutely no problems, whether it was at a cancer center, the home oncologist's office, or a general practitioner's office." And MTP was well tolerated by the patients. "Patients generally liked the therapy. Some asked to be on the regimen longer," said Kleinerman. The few side effects, which included fever, chills, and muscle aches, generally lasted less than a day after administration and did not prevent the patients from working or attending school.

The encouraging results from Kleinerman's initial study have led to a unique national trial combining liposomal MTP and chemotherapy to treat newly diagnosed osteosarcoma. Two large cooperative groups, the Children's Cancer Study Group (CCG) and the Pediatric Oncology Group (POG), will collaborate in treating 500 patients across the country. "It is very unusual for the two groups to get together to do a study, but both are excited about the potential of this agent, and so they agreed to combine resources. By collaborating, we'll get the study done much faster," said Kleinerman. Some patients will be treated at M. D. Anderson, which will be the only institution in the country to thoroughly study the patients' immune systems, to better characterize how MTP kills cancer cells. "I strongly encourage physicians in CCG and POG who have patients with osteosarcoma to put them on the protocol," said Kleinerman. Because the protocol combines chemotherapy and liposomal MTP administration, patients will be treated at cancer centers, but the possibility of outpatient treatment still exists. "If the doctors feel comfortable giving chemotherapy, I think they can certainly be trained to give MTP. If they are not part of CCG or POG, and they want to refer patients to M. D. Anderson, we would be extremely grateful. We have worked very hard to keep referring physicians involved and up-to-date on what is happening. Some have even written scientific papers with us."

The MTP trial will take three to five years, but

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How liposomal MTP works

MTP induces a patient's own immune system to kill tumors. The drug is a synthetic analog of a molecule contained in a mycobacterium. This molecule, which is the smallest part of the mycobacterium to produce an immune response in patients, was selected because of its effect on macrophages, the specialized immune cells that rid the body of foreign objects. If MTP is taken up by macrophages, it transforms them into killer cells that specifically destroy tumor cells.

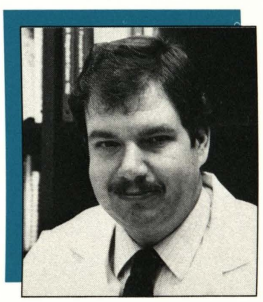
But in its unmodified form, MTP is degraded by the kidney in about one hour, before it can be taken up by the macrophages. In 1982, Isaiah Fidler, D.V.M., chairman of cell biology at M. D. Anderson, first demonstrated that MTP administered to mice in liposomes (small hollow spheres of lipid bilayers much like the membrane of a cell) is active long enough to produce killer cells. In the macrophages, MTP is gradually released from the liposomes ("like a time capsule," said Kleinerman) and is active for about eight hours.

The body's rapid and selective response to liposomal MTP targets the drug to the liver, spleen, and lungs, but it prevents the drug from reaching other organs. Demitrios Papahadjopoulous of the University of California at San Francisco and Theresa M. Allen of the University of Alberta have changed the composition of standard liposomes to develop Stealth™ liposomes—chemically altered liposomes that better avoid degradation and so stimulate killer-cell production longer. Such improvements in liposome technology may not only make MTP treatment of osteosarcoma more effective—they may also enable MTP to reach other organs and thus be effective against other kinds of cancer. An oral preparation of MTP, which would be even easier to administer than liposomal MTP, is also being developed.

Garlic may contain compounds that prevent esophageal and colon tumors

Researcher studies the chemopreventive power of garlic

Cancer Prevention



Michael J. Wargovich is an associate professor of medicine in the Department of Gastrointestinal Medical Oncology and Digestive Diseases

"Our apothecary's shop is our garden full of pot-herbs, and our doctor is a clove of garlic," an anonymous author wrote in 1615. Modern science tends to dismiss such folk remedies as superstition, but in the case of garlic, this Renaissance writer's beliefs may have a solid scientific foundation. Recent studies have suggested that garlic might be helpful in curing various skin diseases, in lowering blood pressure, and in inhibiting platelet aggregation, possibly reducing the risk of heart attack. To the centuries-old lore of the power of garlic as an antibiotic, Michael J. Wargovich, Ph.D., associate professor of medicine at M. D. Anderson Cancer Center, has added data showing garlic's effectiveness in preventing the development of esophageal and colon cancer in rodents. Other laboratories have shown garlic to be active against mammary cancer, skin cancer, and lung cancer in rats.

Because of these results in animals, and because it is a natural, edible substance, garlic is promising for cancer prevention in humans, said Wargovich, whose laboratory is one of the National Cancer Institute's primary screening laboratories for potential colon cancer chemopreventives. The search for compounds that prevent cancer has intensified with the mounting evidence that many types of cancer are caused or triggered by factors relating to lifestyle and environment. One of two basic scientists who work alongside clinicians in the Department of Gastrointestinal Medical Oncology and Digestive Diseases, Wargovich is working on several projects with the hope of showing that chemopreventive agents are available on a grocery shelf.

Garlic extract prevents esophageal and colon tumors in rodents

Wargovich encountered garlic's chemopreventive properties almost 10 years ago, during a postdoctoral fellowship at the Ludwig Institute in Toronto, where he developed an assay system for determining whether various compounds could suppress the DNA-damaging effects of carcinogenic agents. When researchers at New York University later found that garlic and onion oils inhibited tumor formation in a skin carcinogenesis assay, Wargovich tried the garlic oil in his system and was intrigued to find minor suppression of damage to mouse nuclei.

He set out to discover which of the 60 to 100 chemicals in garlic had led to the inhibition and found that most of the preliminary work had already been done. Since garlic has been used for centuries as a flavoring agent, the food industry already had isolated 20 to 40 of its chemical components. Wargovich's laboratory bought samples of 13 of them and began systematically testing them in the colon carcinogen assay.

"Right away, we came up with an extremely active substance that to this day is one of the most powerful anticarcinogens around," Wargovich said. The compound was diallyl sulfide (DAS), "notorious for its odor," he said; "it smells pretty awful in the laboratory." Wargovich demonstrated that DAS inhibits the formation of 1,2-dimethylhydrazine (DMH)-induced colon tumors in mice. He continued his experiments after coming to M. D. Anderson in 1984 and found that the amount of tumor inhibition correlates linearly with the dose of DAS administered. "I began thinking that DAS might be helpful in other sites along the digestive tract," Wargovich said. He undertook a study of nitrosomethylbenzylamine (NMBA)-induced esophageal tumors in the rat and found that DAS completely inhibited the tumors from developing.

Will these results in mice and rats translate into prevention of cancers in man? Wargovich is optimistic. He noted that the types of tumors induced by DMH and NMBA in rodents are similar to colon tumors and squamous cell esophageal cancers seen in humans. However, several challenges remain in developing DAS for use by man, he said. First, little is known about DAS's distribution around the body. Second, because of DAS's distinctive odor and taste, it would be difficult to do a blind clinical trial; however, one solution to

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"Sure, eat more garlic, but don't go overboard, because it can have toxic effects"

that problem would be to give control subjects lower, noneffective doses of the compound.

A third drawback of DAS is that because it is lipid soluble, it breaks down when heated. "If you smell garlic cooking in your kitchen, you've destroyed a lot of the compounds that we think are cancer preventive," Wargovich said. Because people are hesitant to eat a lot of raw garlic, his laboratory is investigating some of its water-soluble components, which persist during limited heating and are far less smelly. "We're trying to find a potential chemopreventive agent that's palatable," he said. One water-soluble compound that he has found effective in inhibiting DMH-induced colon tumors in mice is *S*-allyl-cysteine (SAC). Although larger doses of SAC than of DAS are required for inhibition, SAC seems to be less toxic.

Garlic targets enzyme systems in the liver

The key to garlic's effectiveness in these experiments may not lie in its direct effects on the colon and esophagus, but rather in preliminary biochemical reactions in the liver. Evidence suggests that garlic affects two liver enzyme systems that could be responsible for the anticarcinogenic effects, Wargovich said. The first involves a form of cytochrome P450 that, in metabolizing DMH and NMBA, activates these carcinogens. DAS has been shown to inhibit this enzyme system. The second enzyme system involves the liver's detoxification pathway. Wargovich has shown that DAS boosts the activity of glutathione S-transferase, which joins foreign substances (such as DMH and NMBA) with glutathione, forming complexes that are excreted from the liver in bile.

Last year, Wargovich and his colleagues found that carcinogenesis in the rat esophagus is inhibited if DAS is administered before, but not after, NMBA. This result further supported the idea that DAS modifies the metabolic activation of NMBA or increases detoxification activity. In this study, Wargovich also noted that DAS does not itself promote the production of esophageal tumors. This observation was encouraging because a number of promising agents that block the early phases of carcinogenesis in one organ have been found after chronic testing to promote tumorigenesis in another organ and thus cannot be used in man.

Most data suggest that the detoxification pathway is responsible for the preventive effects Wargovich has observed, he said. "That's good in that we are exposed daily through breathing and food to an array of environmental carcinogens," he said. However, if garlic increases the detoxification activity in the liver, other medications and analgesics are probably excreted along with the carcinogens. The liver doesn't recognize the difference between a drug and a poison; both types of chemicals are treated the same way, Wargovich said.

Wargovich has been collaborating on this research with Wakunaga Pharmaceutical Company, which sells over-the-counter garlic preparations in Japan. Whereas Asians have been using garlic medicinally for centuries, Wargovich noted, "in this country, we're a little behind in using foods and herbs for medication."

Wargovich and Wakunaga researchers have proposed the first clinical trial of these garlic derivatives. Since they are beginning to understand how DAS and SAC work, they plan to target people who would benefit most from them—those who are exposed to high levels of carcinogens in their lifestyle. Levels of glutathione S-transferase are lower in Japanese smokers than in nonsmokers; the trial would reveal whether garlic compounds can boost the levels of this enzyme in smokers, thereby restoring the protective detoxifying function of the liver. Successful results from this and other trials could lead to new chemoprevention regimens for people at high risk of developing cancer.

Anticarcinogenic "designer foods" are a possibility

Wargovich is often asked whether his results mean people should start eating lots of garlic. "My answer is, sure, eat more garlic," he said. "But don't go overboard, because it can have toxic effects." Since garlic is a good antibiotic, too much can wreak havoc on the gastrointestinal system. Wargovich also noted that researchers

haven't pinpointed a single food that will prevent cancer. "It is likely that a mixed diet with a lot of different chemopreventive agents (e.g., fresh fruits and vegetables) will be most effective," he said. (Other potential chemopreventive compounds Wargovich is studying are aspirin and calcium.) Only limited experimentation has been done with combinations of chemopreventive agents (e.g., garlic and citrus fruits), but in almost every case, he said, the combination has been more effective in inhibiting carcinogenesis than has any single agent.

A project that Wargovich is working on with Dr. Leonard Pike, head of the Vegetable Improvement Center at Texas A&M, aims to create a "designer food" that is enriched in chemopreventive agents and is palatable. This idea combines 1990s technology with an old approach. "The major diseases in this country were conquered by supplementation—putting vitamins in bread, iodine in salt," Wargovich noted. However, one question that is raised by such supplementation is where the Food and Drug Administration draws the line between a food and a drug.

Pike spent 10 years breeding the sulfur compounds out of onions, resulting in the Texas 1015 supersweet onion, which has been very popular. Using traditional breeding methods, just as the 19th-century botanist Gregor Mendel did, Pike will try to develop a garlicky-tasting onion that is rich in the chemopreventive agents Wargovich has been studying. "Plant geneticists have long bred crops for color, size, and marketability," Wargovich said. "Now they are breeding crops for health benefits." ■

—Sunita Patterson

Physicians who desire additional information may write Dr. Wargovich, Department of Gastrointestinal Medical Oncology and Digestive Diseases, Box 78, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030, or call (713) 792-7493.

MTP

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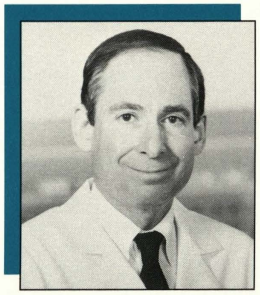
because the disease-free survival time for untreated patients is so short, Kleinerman anticipates that the success or failure of the treatment can be estimated in a year or two. If liposomal MTP is effective against primary osteosarcoma, it may be administered with other therapies or for longer periods of time than in the initial study.

Liposomal MTP may also be used to treat other cancers. Because her laboratory studies showed that liposomal MTP is taken up by the liver, spleen, and lungs, Kleinerman believes that liposomal MTP may be effective against other cancers that affect these organs, including colon cancer, which frequently metastasizes to the liver. A small pilot study of 20 patients at M. D. Anderson also showed that liposomal MTP is successful in treating melanoma. Unfortunately, there is a limited amount of liposomal MTP available, and it is being reserved for those patients who participate in the national osteosarcoma trial. For osteosarcoma patients who cannot be treated with MTP or are not cured by it, Kleinerman is exploring another biologically based therapy. "We're combining interleukin-1 with a common chemotherapeutic agent, VP16 [etoposide]. We found in the laboratory that cells that are resistant to VP16 can be made sensitive if you combine interleukin-1 with VP16," she explained. As in her MTP study, she is carefully considering the most effective way to use the drug, to maximize its biological effect while minimizing the cost and the disruption to patients' lives. "I think this is the way we're going to have to go in cancer treatment—managed care. We're going to have to start looking for therapies that are more cost effective, that don't take people away from home, so that they can continue working and going to school," she emphasized. ■

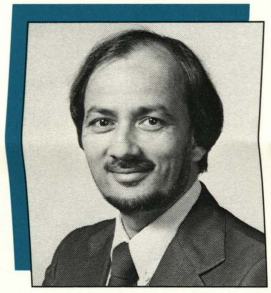
—Maureen E. Goode

Physicians who desire additional information may write Dr. Kleinerman, Department of Cell Biology, Box 173, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, or call (713) 792-8110.

"Our patients come to us now asking for the gene therapy they've heard about on television"



Jack Roth is chairman of the Department of Cardiovascular and Thoracic Surgery



Sewa Legha is chief of the Melanoma Section of the Department of Medical Oncology

Gene Therapy

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tors using these approaches experimentally to treat melanoma are looking for an alternative to conventional immunotherapeutic treatment, which, although effective in some patients, is extremely toxic. They hope that the new therapies will allow local, rather than systemic, administration of larger and more effective doses of the standard chemotherapy or radiotherapy without the often intolerable side effects of those therapies.

Chemoprotection: a second approach

These are also the hopes of a team of scientists at M. D. Anderson who are investigating a second gene therapy approach called "chemoprotection." The team, led by Albert B. Deisseroth, M.D., Ph.D., Chairman of the Department of Hematology, is investigating the application of gene therapy in protecting normal cells and tissues from the often ravaging effects of chemotherapy and radiotherapy. As Deisseroth pointed out, "Over the past 50 years, the limiting factor in our ability to effectively treat patients with solid tumors has been the damage that the treatment causes to normal cells. The goal of chemoprotection is to save lives by allowing patients to benefit more from these standard treatments."

A third approach "corrects" genetic defects

Jack A. Roth, M.D., Chairman of the Department of Thoracic and Cardiovascular Surgery at M. D. Anderson, has taken a third and very different approach by attempting to correct the genetic defects that cause the cancer. This approach, called "replacement," comprises two different strategies. In one, the objective is to correct a mutation that prompts a proto-oncogene, a gene that controls cell growth and division, to go awry and become an oncogene, a gene that allows the uncontrolled cell proliferation that leads to the development of tumors. Roth's team uses a complementary "antisense," or mirror-image, strand of RNA that incapacitates the cancer-causing oncogene by forming a duplex with it. The second strategy is to replace defective tumor suppressor genes, genes that would otherwise block the effects of oncogenes, with functioning ones by administering them directly to the tumor cells.

Both chemoprotection and replacement have been successfully applied in laboratory experiments. The chemoprotection approach has undergone extensive testing in human ovarian cancer cell cultures and in cancerous mice at the National Institutes of Health (NIH). Likewise, in work done at M. D. Anderson by Roth's team, replacement strategies have been shown to work in lung cancer cell cultures and in mice in which lung tumors had been induced. The NIH Recombinant DNA Advisory Committee, which must approve all U.S. human gene therapy protocols, recently gave both teams the go-ahead to try these therapies as phase I (dose and toxicity) studies in human cancer patients in whom other therapies were ineffective. The chemoprotection team's first clinical trial, scheduled to begin this winter, will take normal bone marrow cells from patients with advanced ovarian tumors. The cells will be altered with a gene that will help them resist the damaging effects of paclitaxel (Taxol®), an agent known to be effective against ovarian tumors at an intolerably high dose. After the altered cells are returned to the patients, the patients will receive progressively higher doses of paclitaxel, which Deisseroth hopes will destroy their tumors while leaving their bone marrow unharmed. Bone marrow cells were chosen for the treatment because they are the most sensitive in the body to the toxic effects of chemotherapy. Roth's team's study will encompass both replacement strategies in lung cancer patients.

Therapies still highly experimental

Both investigators cautioned, however, that these therapies are still in extremely early experimental stages, that they are being used only on a few patients, and that the outcomes are uncertain. Although hopes are high, of course, Roth said it is too early to talk of "cures." For example, the technology that allows delivery of foreign

"The goal of chemoprotection is to save lives by allowing patients to benefit more from these standard treatments"

genes into living human cells has not yet been perfected. Therapeutic genes are usually delivered through recombinant retroviruses that are designed to "infect" cells, get into the nuclear DNA, and insert the gene into the genome (the individual's complete genetic material) so that it can perform its intended function. He is quick to mention that the retroviruses have been "safety modified" to not cause disease.

Integrational mutagenesis a theoretical possibility

Although the outcomes in animal studies suggest that the incorporation of the foreign gene into the cell's DNA has no effect on the host other than the desired one, there is as yet no way to ascertain this specificity. Deisseroth admitted that there is a theoretical possibility of "integrational mutagenesis," in which the introduced gene positions itself improperly and causes dysregulation in the cell's function, which may develop into a second tumor. He discounted the possibility as being much less likely than a second tumor or a fatal toxic reaction in a patient receiving a standard therapeutic modality. Although he agreed that the outcomes of human gene therapy are unknown, he believes that its use poses no ethical dilemma. He pointed out that the prognosis of patients who are to receive these experimental therapies is poor and that the chemoprotection protocol is a next logical step, given the efficacy of the available treatments.

Sewa Legha, M.D., chief of the Melanoma Section in the Department of Medical Oncology, is head of M. D. Anderson's Institutional Review Board (IRB), which is responsible for reviewing, on behalf of the institution, the scientific merit, ethics, safety, and other aspects of clinical protocols implemented at M. D. Anderson. He emphasized that these therapies, because they do not tamper with reproductive cells, do not result in the "genetically altered" humans that some critics fear will result from gene therapy. Legha said that most scientists working in the field of genetics now believe that the fears of genetic manipulation that arose 20 years ago when the recombinant DNA technology was new do not apply to modern gene therapy, which affects only the patient treated, not his offspring; the effects last only as long as the patient lives.

Although he is enthusiastic about the possibilities for gene therapy in his own area of clinical expertise, Legha agreed that the day when we can offer gene therapy cures is still far off. He cited the extensive work that must be done and the problems that must be overcome before gene therapy can become reality. First, the genetic abnormality must be identified. This is part of the purpose of the international Human Genome Project, which by "mapping" the normal human genome will provide a baseline with which to compare genetic abnormalities. Only when the genetic abnormality responsible for a disease is identified can a specific gene therapy be developed.

For now, best hope for most patients is standard therapy

Legha said, "Our patients come to us now asking for the gene therapy they've heard about on television. Naturally enough, they don't want the standard therapies, which may have undesirable side effects, but the gene therapy that they believe will cure them. We explain that the gene therapy is entirely experimental and that they are not eligible for the protocol. We tell them we have treatments that are tested and more effective, but gene therapy, with its potential for cure, is so intuitively attractive that sometimes they don't want to listen. For now, however, their best bet is to start with the standard therapies or the more widely accepted experimental therapies."

—KATHRYN L. HALE

Physicians who desire additional information may write Drs. Roth, Deisseroth, or Legha at the Departments of Thoracic and Cardiovascular Surgery (Roth), Hematology (Deisseroth), or Medical Oncology (Legha), The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, Texas 77030, or call (713) 792-6932 (Roth), 792-8750 (Deisseroth), or 792-2921 (Legha).

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Published quarterly by the Department of Scientific Publications, Division of Academic Affairs, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030.

Made possible by a gift from the late Mrs. Harry C. Wiess.

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Therapies still experimental, caution researchers

Gene therapy at M. D. Anderson

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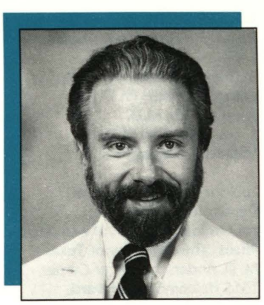

Albert Deisseroth is chairman of the Department of Hematology

Gene therapy. You may have heard about it on the television or radio, seen it in the newspapers. It's being compared to vaccines and antibiotics as the next great discovery in medicine. You may even have had patients ask about it, for themselves or for a family member. What does gene therapy mean, and what are its implications for curing diseases and caring for patients?

The term "gene therapy" encompasses a number of different therapeutic strategies, but all involve the introduction of an exogenous gene to stimulate a desired response in the body. The diseases it targets have only two things in common: they are all serious, and they are all caused, at least in part, by a defective, mutated, or missing human gene that disables the body's natural protection against disease. The obvious targets are hereditary diseases, notably cystic fibrosis, various enzyme deficiencies, and hemophilia, but gene therapies are also being tried in immunodeficiency diseases, heart disease, and neurological disorders such as Parkinson's and Alzheimer's diseases. Here at M. D. Anderson Cancer Center, of course, gene therapies are being investigated for their effects on neoplastic diseases. Cancer researchers have long searched for new methods of treating those cancer patients not cured by the "standard therapies," that is, surgery, radiotherapy, and chemotherapy. Gene therapy, still in very early experimental stages, may provide alternatives for those patients.

Gene therapies for cancer work in one of three fundamental ways. One approach works with the body's natural immune system to enhance the body's ability to fight the growing cancer. The therapy may, for example, stimulate the immune system to produce large quantities of endogenous cancer-killing substances or alter the cancer cells so that the immune system can more efficiently recognize and attack them. Investiga-

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