News
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*****Cancer immunology researcher at UTHSCD named to National Academy of Sciences.

DALLAS -- Scientists have different motivations, says Dr. Jonathan Uhr. "Most of us don't know why we're so driven to find the answers. But the net result is the same thing. If we're ambitious enough and driven enough, we just work until we get the answer."

Uhr, chairman of the Department of Microbiology at The University of Texas Health Science Center at Dallas, is a pioneer immunology researcher who is driven to get an answer in cancer treatment.

In recognition of Uhr's contributions in immunology, he was elected to membership in the National Academy of Sciences May 1. The academy of 1,428 distinguished scientists and engineers is the nation's top scientific advisory group, serving as official advisor to the federal government. Of the 60 newly elected members, Uhr is the only Texan. He is the sixth member elected from UTHSCD.

"One of the greatest advances in biology in the last two decades is the discovery of how lymphocytes differentiate and make antibodies," says Dr. Michael Brown, director of the Center for Genetic Diseases at UTHSCD and also a member of NAS. "Dr. Uhr was a pioneer in learning the sequence of events that make that happen."

Uhr in collaboration with Dr. Ellen Vitetta discovered that a lymphocyte (a type of white blood cell) synthesizes a form of antibody that stays on its cell surface. When the antibody recognizes an antigen, the lymphocyte is stimulated to divide. The new cells then secrete the antibody to fight the antigen.

"Dr. Uhr has also built up one of the top two or three microbiology departments in the world at the health science center," says Brown. "He has brought in a number of other scientists who are absolutely front rank. Not only his and Ellen Vitetta's work, but also that of Don Capra, Jim Forman and Phil Tucker are really exciting."

"After working with him for 15 years, I think his greatest strength in science is his tremendous intuition for areas that are important and ready for scientific attack -- he has a 'nose for science,'" says Vitetta, professor of Microbiology at UTHSCD. "He has a tremendous ability to motivate and guide people who work with him. He's enthusiastic and optimistic."

Uhr is currently working with Vitetta to use antibodies to target toxins to tumor cells.

"Conventional chemotherapy can work, but there are so many side effects," says Uhr. "The drugs attack rapidly dividing cells, and they can't distinguish among rapidly dividing cells. Besides attacking the tumor, they attack the gastrointestinal lining, hair follicles and blood cells. You have to kill many normal cells to kill tumor cells, and that's a heavy price to pay. It limits the amount of chemotherapy you can do."

When Uhr and Vitetta started, the idea was to use antibodies as carriers for substances so toxic that if one molecule penetrated a cell, it would kill the cell. Because of their work it is now possible to make antibodies relatively tumor-specific.

Within the last five or six years techniques have been developed for preparing purified antibodies against tumor cells. And the immunologists realized they could test the old idea of targeting poisons with antibodies -- a new type of anti-cancer treatment.

"At the time we started six years ago, there was not an ideal animal tumor model to study," says Uhr. "Then in 1977 an elderly mouse at Stanford developed a special type of leukemia that had not been described before. It was a perfect leukemia for us to use. The

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leukemia (malignant white blood cells) had a molecule on the surface that was not present on normal cells to which we could make antibodies.

"This was the first B cell leukemia described in mice. We finally talked our friends at Stanford into sending three animals. They arrived at D-FW Airport on a day when everything was iced in. No delivery trucks were running, and we knew that the mice wouldn't survive at the airport, and we probably couldn't talk Stanford into sending any more. So Ellen Vitetta and I drove out there, skidded our way out over the overpasses and picked up three shivering, sick-looking mice. We brought them in and transferred their leukemia to other mice immediately.

"We promptly made special antibodies. And the next decision was what poison to use. Ricin is a highly poisonous plant toxin with two parts: one is the poison, and one binds to all cells. We took the latter part off and replaced it with an antibody."

The antibody-ricin combination became a biological missile. The antibody would direct the hybrid molecule to the tumor cell, and the ricin would kill it.

"The idea was very simple," says Uhr. "But the testing of the idea is not. Fifteen or 20 people have been working on it full time for the last six years. Significant progress has been made, but we have a long way to go."

Test-tube studies indicate the researchers can kill unwanted cells in bone marrow, including human bone marrow.

Bone marrow transplant is a rescue technique used to save a patient's life following treatments with high doses of radiation and chemotherapy. "The combined treatment is drastic," says Uhr. Patients with certain advanced cancers are given supralethal doses of radiation and drugs to wipe out all of their rapidly reproducing cells. The treatment kills both normal and cancerous blood cells. To replace the normal ones, the patient is then given a bone marrow transplant."

All the cells necessary to repopulate the patient's blood cells are made in the marrow. Because of tissue rejection problems, the trend has been to give patients their own saved marrow instead of marrow from a donor. But with this technique there is the danger of reintroducing some of the cancerous cells.

When it is suspected that a cancer patient in remission might relapse, bone marrow is taken and frozen. If the cancer recurs, they are treated with supralethal doses of radiation and drugs. Then the saved marrow is reintroduced. But if there are any cancer cells left in this marrow, the cancer could recur.

"We have evidence we can wipe out tumor cells in the bone marrow outside the body by treating it with an immunotoxin (antibody-ricin combination) specific to tumor cells," says Uhr. His group has accomplished this in diseased mice marrow. Human trials have yet to be done.

"Another variation of this kind of treatment would be to give the patient bone marrow from a sibling matched for tissue type (transplantation antigens)," says the researcher. "Even though donor and recipient are matched, a large number of patients die from graft versus host disease (the patient's immune system attacks the new cells as foreign). But there's evidence graft versus host disease can be inhibited by killing a certain kind of lymphocyte in the bone marrow that's not necessary to the patient's recovery. We're working with the Seattle bone marrow transplant group and hope to initiate this latter approach soon.

"In addition, there's evidence in the mouse that we can produce excellent results in treating advanced leukemia by injecting the immunotoxin directly into the animal's bloodstream. Mice with a tumor that is 20 percent of their body weight have been treated with radiation and immunotoxin and followed for six months (a long time in the life of a mouse). They have been disease-free.

"We have examined their tissues, and they're not completely free of tumor cells. But we believe they're reduced to such a minute number that the immune system can hold them in check. There's every reason to believe that this could happen in the human. Once you develop a tumor, the immune response plays a significant role in the outcome."

However, the researchers do not depend upon this natural immune response, which usually is a weak one. "We improve upon nature by creating immunotoxins in a test tube and giving them to the patients; in other words, we give them a highly potent artificial immunity.

We're developing agents for the same type of human tumors and taking steps toward trials in humans.

"You know, there's a price you pay for this kind of story. I received about 300 calls and letters from the Reader's Digest story (two years ago), and they're still coming in. I thought I wouldn't talk personally to each caller, but I had to -- their stories were heart-rending, and they appreciated having someone listen to them even though I could not offer direct help."

Both Uhr's parents died of cancer. He knows that patients grasp at straws, but his research is at the basic science level. It may be several years before these therapies are tested sufficiently to be used in human patients.

In addition to the scientific work "the amount of time that has to be spent preparing grant applications and progress reports to the government is almost as formidable as testing. It takes about 30 percent of my time. And no one else can do it for me." Private support is increasingly important to the research.

Uhr also spends a great deal of time on departmental affairs.

"Dr. Uhr reads every paper that goes out of the department," says Vitetta. "The faculty is highly dependent on his advice because they know that he cares and that he has excellent judgment."

Uhr stresses the importance of communicating research. "There are very few who write or speak as well as those he's trained," says Vitetta.

"Of all the people I know in science, I think he most of all gets enjoyment out of scientific discoveries whether or not they're his own. So people come to him for guidance.

"He's never lost his sense of humor. He still acts in the plays at the Christmas parties and enjoys them as much as anyone else."

Sometime Uhr becomes so preoccupied with a scientific problem that he loses track of what he's doing. Vitetta recalls her first visit to his office 15 years ago. "I was sitting in his office totally terrified and timidly discussing what I would do. He suddenly got up, packed his briefcase, turned out the light, walked out and locked the door. There I sat in a dark, locked office." He simply had something else on his mind and left.

Several of Uhr's students have become department chairmen and senior faculty at well-known institutions.

One student who worked in Uhr's lab when he was just beginning as a teacher was Dr. Matthew Scharff. Scharff is now professor of Cell Biology, Harry Eagle Professor of Cancer Research and associate director of the Cancer Center at Albert Einstein College of Medicine. He was elected to NAS several years ago.

Says Scharff: "It was a lovely way to learn science. It was interesting and stimulating, and we had a lot of fun. When an observation arises, Dr. Uhr is absolutely terrific at projecting where it's going to go and devising experiments to get there. I learned a lot from him about how to do experiments."

Once Scharff and Uhr went out to play tennis, and Scharff won. "Dr. Uhr refused to play me again till he had had three tennis lessons. Then I never beat him again."

In addition to chairing the Department of Microbiology, Uhr is professor of Microbiology and of Internal Medicine and the first holder of the Mary Nell and Ralph B. Rogers Professorship in Immunology.

He serves as president of the American Association of Immunologists, consultant to the Howard Hughes Medical Institute and member of the editorial boards of Cellular Immunology and Immunological Reviews. He is also a member of the U.S.-Japan Panel of the Cooperative Science Program in Immunology and the U.S. representative to the International Union of Immunological Societies. He served as program chairman of the First International Congress of Immunology in 1971 and has served on many other professional committees and editorial boards. He has published more than 250 scientific papers in the field of immunology.

Uhr received his M.D. from New York University School of Medicine. After completing an internship and residencies in pathology and medicine at Mount Sinai Hospital, he joined the faculty at NYU School of Medicine. There he also directed the Irvington House Institute for

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Rheumatic Fever and Allied Diseases. He came to UTHSCD as professor and department chairman in 1972.

Other scientists at UTHSCD who have been elected to the NAS besides Uhr and Brown are: Dr. Samuel M. McCann, chairman of the Department of Physiology; Dr. Jean D. Wilson, professor of Internal Medicine; Dr. Joseph L. Goldstein, chairman of the Department of Molecular Genetics, and Dr. Ronald Estabrook, Virginia Lazenby O'Hara Professor of Biochemistry.

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