

Junior Faculty: **Joining the fight against cancer**

By Melanie Rome

Sven de Vos

According to Greek mythology, the bravest hero in the Trojan War, Achilles, had a weak spot, his heel. To this day, people still refer to a weakness or a soft spot as an Achilles heel.

Dr. Sven de Vos, an assistant professor of hematology/oncology, likes to think that he's on a mission to discover the Achilles heel of several types of lymphoma.

The winner of the Society for Hematopathology's Pathologist-in-Training Prize for best presentation at the 2002 United States and Canadian Academy of Pathology meeting, de Vos is fascinated by the complexity of lymphomas and is searching for new and novel approaches to treat the disease.

"I'm mostly interested in identifying the molecular Achilles heels of lymphomas and to exploit such targets with novel, non-chemotherapy treatment approaches," said de Vos, also a Jonsson Comprehensive Cancer Center researcher.

After joining the UCLA faculty in 2002, de Vos opened a Phase II trial of a drug called Velcade, a novel proteasome inhibitor, to treat chemotherapy-refractory diffuse large B-cell lymphoma, the most common form of lymphoma.

de Vos and his team currently are working on two very promising projects. The first focuses on a very aggressive form of non-Hodgkin's lymphoma called mantle cell lymphoma. So far, research has shown that patients with the most aggressive form of mantle cell lymphoma over-express a certain gene called PIM 1.

"PIM 1 is not an innocent bystander," said de Vos. "This is a gene with a history as an oncogene."

Interestingly, de Vos says that the over-expression of the PIM 1 gene also is found in about a third of diffuse large B-cell lymphomas as well.

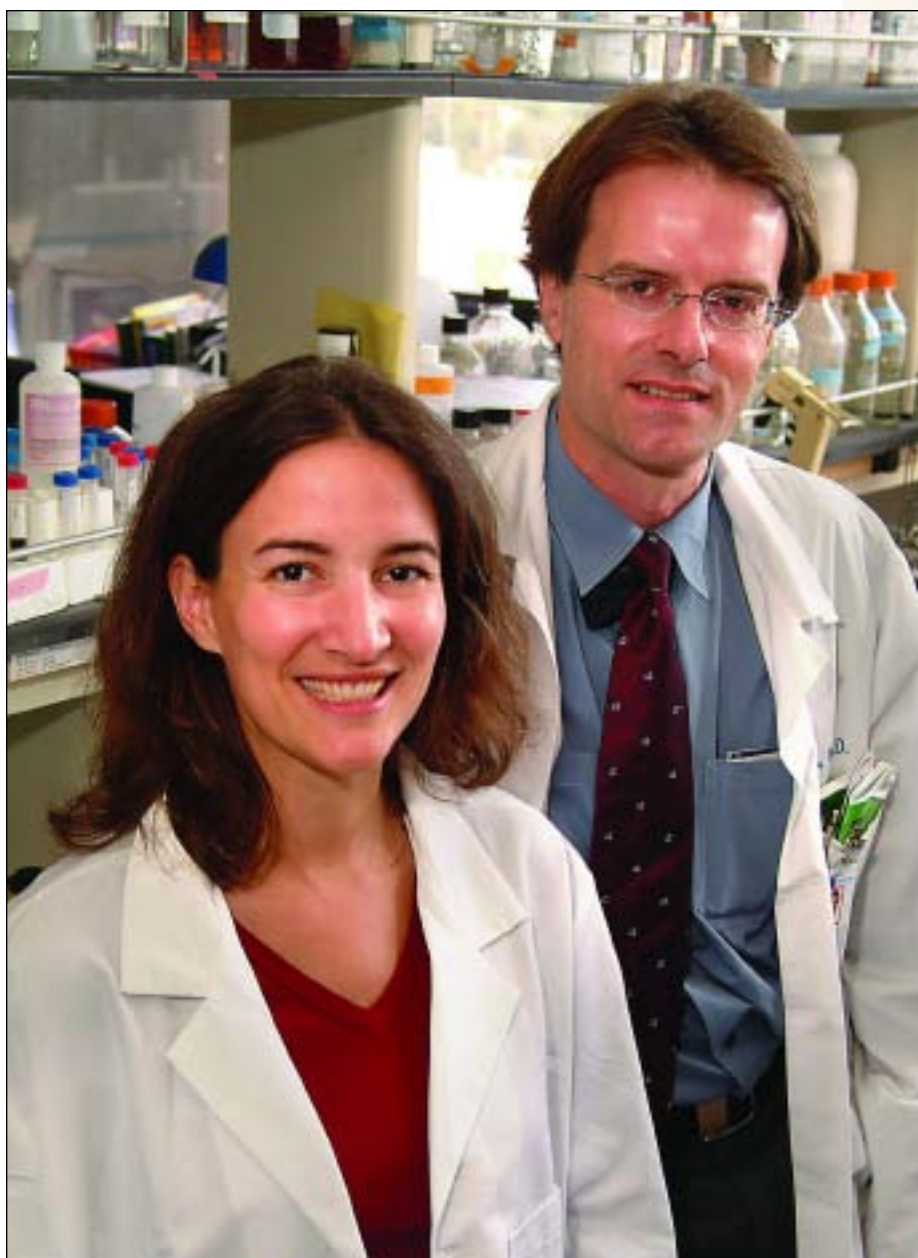
de Vos hypothesizes that the over-expression of the PIM 1 gene in combination with the over-expression of another gene, Cyclin D1, are major factors responsi-

ble for the development of aggressive mantle cell lymphoma. He hopes to prove this theory in upcoming experiments in animal models. If his assumption about the role of the PIM 1 and Cyclin D1 genes proves correct, future experiments will involve attempting to "shut down" these two genes, which de Vos may find are the Achilles heels of mantle cell lymphoma.

de Vos also is participating in a second project involving Epstein-Barr Virus (EBV) positive lymphomas. This is a type of lymphoma uniquely marked by the presence of the EBV genome in the cell's nucleus. de Vos sees the presence of the EBV virus as

the Achilles heel in this type of lymphoma. He says that future experiments and clinical trials will involve treatments targeting the EBV in the lymphoma cells as a means to stop the disease.

EBV has two different life cycles—the productive "lytic" and the non-productive "latent" cycle. Most EBV-positive lymphomas are infected with latent EBV. The proteasome inhibitor Velcade can "switch on" the lytic EBV cycle in EBV-positive lymphomas, initiating the expression of viral thymidine kinase and other viral lytic antigens. The thymidine kinase gene also is known as the suicide gene



used in gene therapy trials against cancer.

A drug called Gancyclovir is then administered and the thymidine kinase converts Gancyclovir to a toxin, which can kill lymphoma cells. Plans for a clinical trial for EBV-positive lymphomas currently are underway, de Vos said.

de Vos, who was born in Germany and completed his residency here, says that after arriving in Los Angeles in 1992, he was

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—Heather Maynard, Ph.D.

greeted by a series of the city’s disasters. First there were the riots, followed by an El Nino winter with two months of rain and flooding. Next came the 1994 Northridge earthquake, followed by the Malibu fires. Despite all of this, de Vos says he likes L.A. very much.

de Vos also is thrilled that his current position encompasses both of his passions, clinical work and research. He especially appreciates being able to work at UCLA.

“UCLA is unique because the university has so many world-class researchers and physicians who are leaders in their field, all in a concentrated area. People here are very collaborative,” says de Vos.

Heather Maynard

In the world of nanotechnology, objects are so small that 10,000 of them could fit on the sharp end of a pin. At this small scale, these same objects tend to take on new chemical and physical properties.

Welcome to the world of scientist and cancer researcher Heather Maynard.

An assistant professor of organic chemistry and a member of UCLA’s California NanoSystems Institute (CNSI), Maynard’s research centers on the creation of minute particles that she hopes will someday be used in the fight against cancer.

As a polymer chemist with a background in both chemistry and biomedical engineering, Maynard makes bioconjugates, compounds that link together man-made and naturally occurring elements. One such bioconjugate may someday be used in the early detection of cancer and as a non-invasive tool to monitor the success of cancer treatments.

According to Maynard, a member of UCLA’s Jonsson Comprehensive Cancer Center, this bioconjugate is part plastic and part sugar. The plastic, not unlike the kind used to make ordinary disposable cups, brings with it structural stability. The sugar has the advantage that it should be recognized by the body as a natural biomolecule. When the sugar biomolecule is attached to a long string of molecules or polymer, the result is a bioconjugate that Maynard hypothesizes may be used to detect certain cancer tumor markers—specifically those markers that signal angiogenesis, the formation of blood vessels that feed the tumors and allow them to grow and spread. Maynard says that it is especially prudent to try and detect these particular tumor markers because the adult body does not normally make new blood vessels, except in the cases of reproduction, wound healing and, of course, cancer. In addition, these markers can be found in urine. With the use of the specially manufactured bio-

conjugate, Maynard hopes that someday cancer can be detected just by conducting a simple urine test.

Maynard says that this particular bioconjugate also has the potential to be used as a means to evaluate the effectiveness of cancer treatments by measuring the levels of tumor markers found in the urine. Such an advance might be a quick way to determine if a patient is responding to cancer therapy.

Maynard also is experimenting with bioconjugates that combine plastics with peptides, another naturally occurring element. She says such bioconjugates might be used in the future to limit the movement of cancer cells by targeting the cells and simultaneously inhibiting tumor cell migration.

For Maynard, her primary goal is to prove that the technology she is developing will be effective. But her overall mission is to create materials that will help mankind.

“I like to talk with the medical doctors and see what’s needed,” said Maynard.

The advantage to working in the CNSI, said Maynard, is the potential for collaboration with other scientists, engineers and doctors.

“When thinking about coming to UCLA, I was excited about the possibility of working with other scientists and engineers to apply the bioconjugates I create to make useful devices and materials,” said Maynard.

Maynard earned a bachelor’s degree in chemistry with honors at the University of North Carolina at Chapel Hill, a master’s degree in materials science at the University of California, Santa Barbara, and a doctorate degree in chemistry at the California Institute of Technology.

Before coming to UCLA, she worked at the Swiss Federal Institute of Technology and the University of Zurich, where she conducted research into angiogenesis as an American Cancer Society postdoctoral fellow. Maynard joined the UCLA faculty in August 2002 as the first Howard Reiss Career Development Chair in chemistry and biochemistry.

When she’s not in the lab, Maynard focuses on less scientific activities—she likes to read poetry and run.

From left: Cancer researchers Heather Maynard and Sven de Vos

Christian Head

When a patient ribs him about his name, which happens at least once a day, this doctor isn't at all bothered. In fact, the head and neck surgeon and cancer researcher thinks it's the perfect ice breaker.

"It helps patients feel more comfortable," said the aptly named Dr. Christian Head, an assistant professor of surgery.

All kidding aside, Head is involved in very serious work. He's helping to find new and more effective treatments for head and neck cancers.

The major risk factors for developing head and neck cancer, which will strike more than 55,000 Americans this year alone, are smoking and drinking, Head said. And, in his experience, patients with these types of cancers usually do both. To make matters worse, the patients that Head treats usually are in the advanced stages of these diseases, when the cancers are much harder to treat. Because of this, the mortality rate is usually around 50%.

Head helps facilitate research on head and neck cancers—cancers of the mouth, tongue, larynx and pharynx—by working to complete the establishment of the UCLA Head and Neck Tissue Bank. With the consent of patients, samples of their cancerous tissue are stored in the tissue bank to be used by researchers studying cancer. Head says that by having such a tissue bank, "we're able to look at the genetic make-up of cancer so that, hopefully, targets for potential cancer treatments can be found."

Head has spent the last 18 months working to develop the tissue bank, specifically trying to increase the number of patients willing to donate samples, as well as creating the tissue bank's infrastructure to better streamline research. The UCLA Head and Neck Tissue Bank is funded in part by UCLA's Jonsson Comprehensive Cancer Center.

Head is also "very excited" about a new partnership between the Jonsson Cancer Center and the Charles R. Drew University of Medicine and Science that will provide leading-edge experimental cancer treatments to an under-served, primarily minority patient population in South Central Los

Angeles. As part of the larger partnership, a pilot grant is funding the establishment of a tissue bank at Drew University and providing money to train research personnel there. Head, who oversees the head and neck component of the partnership, says that UCLA researchers will benefit by having access to minority populations, whose mortality rates for head and neck cancers are twice that of Caucasians.

Using techniques developed by his mentor, Dr. Dennis Slamon, director of Clinical/Translational Research at the cancer center, Head's research is focused on two specific targets for head and neck cancers. Using animal tumor samples, Head is testing drugs that prevent angiogenesis, the formation of blood vessels that feed tumors so they can grow and spread. Tumors cannot grow bigger than a pinhead unless they develop an independent blood supply. Researchers hope that by cutting off or stopping development of that blood supply, cancer growth will be arrested.

Head also hopes to develop new targeted therapies that block cancer cell signaling pathways, resulting in cell death. There are a number of promising new cancer drugs such as Erbitux, which has been demonstrated to improve survival in patients with advanced head and neck cancer. This is one of many new therapeutic agents being investigated in Head's laboratory.

Head says that to him, these areas of research are "fascinating" and represent the "next step" in increasing patient survival rates. In addition to his own research, Head also would like to see UCLA increase the numbers of clinical trials available for head and neck cancers. He currently is working with Dr. Carolyn Britten, an assistant professor of hematology/oncology, to realize this goal.

Even as an undergraduate at the University of Virginia, Head says he knew he wanted to be involved in research. It was during medical school at Ohio State University that he decided to become a head and neck surgeon. After a surgery internship at the University of Maryland in Baltimore, Head says he came to UCLA to be part of "one of the top head and neck programs in the country."

Antoni Ribas

Not unlike the guided imagery used by some cancer patients, Dr. Antoni Ribas pictures the body waging a war against a major enemy—cancer. But Ribas is turning imagery into reality by participating in research in which the body's own immune system is the army fighting this deadly disease.

"Our goal is to train the body's immune system to see that cancer is something bad, so it will fight it," said Ribas, an assistant professor of hematology/oncology and a researcher at UCLA's Jonsson Comprehensive Cancer Center since 2002.

During the last seven years, Ribas and his colleagues have been conducting clinical trials involving one of the most deadly forms of cancer, metastatic melanoma. Results so far have been encouraging and even dramatic in some of the cases. Patients in the trials were given a series of three injections containing laboratory-grown dendritic cells, specialized blood cells that recognize foreign substances and stimulate an immune response to fight invaders (For one patient's success story, see page 12).

"Dendritic cells are like the generals of the body's immune system," Ribas said. "They tell the fighter cells, lymphocytes, what they should be doing."

The dendritic cells were manipulated in the laboratory so that they contain tumor antigens, proteins specific to melanoma. Once injected into the patient's body, these special cells stimulated the patient's immune system to fight the cancer. In about one in 10 cases, the results were dramatic, with the melanoma disappearing within two to three months. According to Ribas, the dendritic cell therapy is similar to how vaccines work to prevent the body from contracting certain diseases.

"We're trying to take the same knowledge and apply it to cancer," he said.

However, nothing is simple in cancer, as the disease occurs within the body whereas viruses and other types of disease generally invade from outside. Further complicating matters is that cancer is not normally a disease fought by the body's immune system.

From left: Cancer researchers Antoni Ribas and Christian Head

Researchers have to find a way to trick the body into fighting cancer.

What excites Ribas about the dendritic cell therapy is the fact that, unlike other forms of cancer treatment, this therapy is not toxic to the body like chemotherapy, radiation and other immunotherapies. The main reason is that dendritic cell vaccines are rationally designed to focus the immune response specifically to a protein present in the cancer, as opposed to a non-specific activation of the immune system.

Ribas and his colleagues have completed

the first phase of another clinical trial for metastatic melanoma involving a monoclonal antibody named CP-675,206, directed against CTLA4, a protein that acts as the main “off” switch for the body’s immune system. Patients were given an antibody to CTLA4 that locks the immune system into the “on” position, thus preventing the immune system from turning itself off. About half of the patients who received the highest dose of the antibody experienced durable regression of the cancer. However, there were some side effects such as diarrhea, skin rash and thyroid gland problems.

In another potentially exciting trial, patients will be given both dendritic cells and the anti-CTLA4 antibody. The rationale is to combine the ability of the dendritic cell vaccines to turn the immune system on specifically against proteins in the can-

cer while using the CTLA4 antibody to prevent the immune system from turning itself off. This may result in a stronger activation of the immune system specifically against the cancer.

Ribas also is involved in two other studies for liver cancer that employ theories similar to those tested in the melanoma trials. Although liver cancer is more prevalent in Asia and East Africa, the number of Americans who develop and die from it is increasing.

Born in Spain where most of his family still resides, Ribas was inspired to pursue his cancer research by his father, also an oncologist. Ribas said his decision to become a doctor was sparked after spending a week in engineering school.

“They filled up the board with numbers and symbols I did not understand, and I thought to myself that medical school has to be easier than this,” said Ribas, who also serves as assistant director of clinical programs in the Human Gene Medicine Program Area at the cancer center.

Ribas attended medical school in Spain, and did post doctoral work in San Diego and at UCLA before joining the UCLA faculty two years ago. ★

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