Scientific STAND OUT

Anna Wu

Scanning for the Future of Cancer Therapy

Anna Wu went into science because she likes to figure out how things work. Her focus now is on the cancer cell.

An associate professor of molecular and medical pharmacology, a member of the Crump Institute for Molecular Imaging and a Jonsson Comprehensive Cancer Center scientist, Wu is studying how to better determine exactly what cancers are doing in the human body and what proteins might be sitting on the cancer cell's surface that make the disease behave in certain ways.

Wu's research focus is developing radio-labeled antibodies for cancer imaging and ultimately, for new, leading-edge treatments.

It's a complicated process.

First Wu engineers an antibody so it will bind with specific proteins that sit on the surface of cancer cells. Then she puts a radioactive tag on the antibody so that it can be imaged once the antibody reaches the cancer cells. Under positron emission tomography (PET) scanning, the cancer sites literally light up. The PET scan pinpoints where the cancer is inside the body—the primary tumor and any metastases—and details how the cancer is functioning biologically.

"We could potentially detect the spread of disease and evaluate the tumor sites in a patient without having to do a biopsy," said Wu, who earned a doctorate degree in molecular biophysics and biochemistry from Yale University after graduating from Harvard University with a degree in biochemical sciences. "We're hoping that engineering antibodies for use in imaging will tell us more about the protein expression of tumors."

Such information could be vital when planning treatment strategies, said Wu, co-director of the Tumor Immunology Program Area at the cancer center.

"If we can evaluate the disease and understand our target better, we can choose our therapies better," she said.

Wu also hopes to develop new therapeutic strategies. Ultimately, she would like to be able to attach a toxic radioactive atom to the antibody. The radioactive atom would deliver a deadly radiation dose once the antibody reaches the malignant cell.

"The immediate goal is imaging," Wu said. "The end goal is therapy."

Wu, who heads the biomolecular targeting laboratory at the Crump Institute, has been working with antibodies since the early 1990s. In 1998, she took a yearlong sabbatical from her post at the Beckman Research Institute at City of Hope to work with UCLA researchers in the Crump Institute. Her experience at UCLA led to her focus on imaging research. She was recruited to the UCLA faculty in 2002, where her work continues to expand.

"We're working to develop a whole new class of PET tracers that can tell us more about what a tumor looks like, not just that it's growing fast, but what's on the surface of the cells that we can possibly target," she said.

Wu currently is conducting her research in mice, but the theories will be tested in humans eventually. Taking her laboratory findings and seeing them at work in a clinical setting is an exciting prospect.

"I really wanted to do something that was translational, that was directly applicable to patients," Wu said. "It's so rewarding to have a project that's worthy of evaluation in a patient. Hopefully, these approaches will make a difference."

In addition to her laboratory work, Wu has been active with local cancer support groups and for several years taught basic science with Project LEAD, a course developed by the National Breast Cancer Coalition to help activists influence research and public policy.

She recently completed a three-year term on the 15-member council for the California Breast Cancer Research Program, which administers tens of millions of dollars in funding for breast cancer research. The council, made up of survivors, advocates, activists, scientists and clinicians, sets the objectives, strategies and priorities for the research program and makes funding recommendations for research projects. Wu served as chair of the council during the last year of her term.

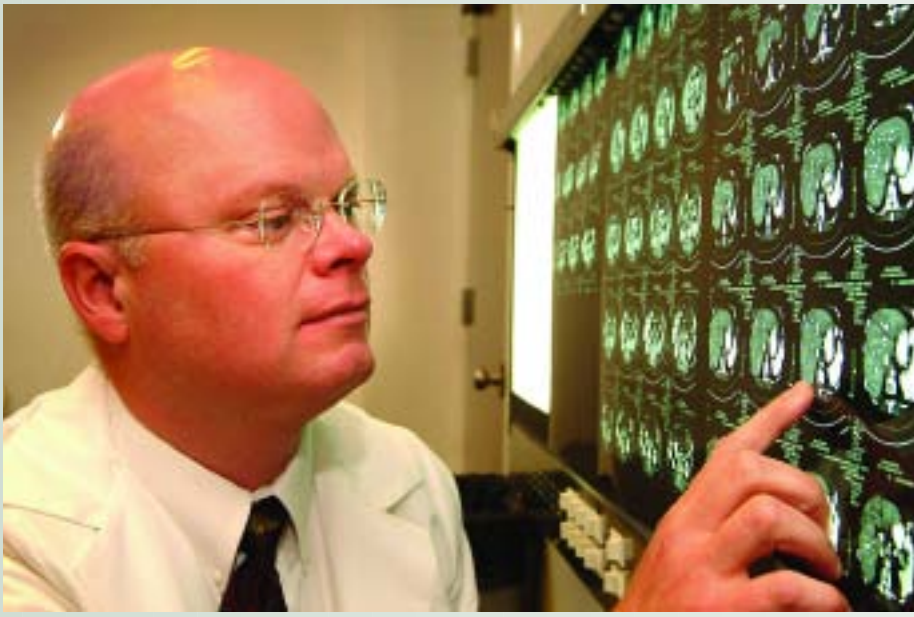
But her real passion is her quest to translate her research into better care for cancer patients.

"We need a better understanding of what's happening in our animal models, and in people," Wu said. "Before, we were limited to our test tubes and Petri dishes. But these new, non-invasive imaging approaches give us a new window, literally, for observing cancer in living mice.

"If we can see what's going on, we can be smarter with our interventions." ✯

Scientific STAND OUT

Dr. Mark Pegram



Targeting Therapies—Treating Cancers Without Chemotherapy

Treating cancer without chemotherapy wasn't something Dr. Mark Pegram imagined he would ever be doing, even as recently as five years ago.

But Pegram, an oncologist, researcher and director of the Women's Cancers Program Area at UCLA's Jonsson Comprehensive Cancer Center, is conducting several clinical trials that do just that—use molecularly targeted therapies alone and in combination to fight cancer.

"Five years ago this, would have been a dream," said Pegram, an associate professor of hematology/oncology. "But it's a dream come true. We now have the clinical tools necessary to think about treating cancer without chemotherapy."

Pegram is leading a host of open or soon-to-be open studies using targeted therapies, agents designed to attack what is broken in a cancer cell. His arsenal includes antibodies that block cell growth signals, inhibitors that interrupt the formation of the independent blood supply that tumors need to grow and spread, and a drug that tricks an enzyme that aids cancer in resisting chemotherapy.

In addition to the studies, Pegram sees patients in the clinic and conducts research in his lab. Things move fast in cancer research and you have to work to keep up.

"The pace of discovery so rapid, there's so much to be done," Pegram said.

Studies have demonstrated a close link in breast cancer between amplification of a gene called HER-2/neu and angiogenesis—the process by which a tumor develops an independent blood supply. Pegram is pairing the drug Herceptin, which targets HER-2 over-expression, with Avastin, a drug designed to cut off the independent blood supply. He just completed a Phase I study of the two humanized antibodies in patients with advanced breast cancer.

The combination of the targeted therapies is a safer alternative to chemotherapy and its accompanying toxicity, Pegram said.

"We've seen some wonderful responses, even in a Phase I study where you don't expect to see responders," Pegram said. A Phase II study of the combination therapy currently is underway.

Another study is examining a new generation of HER-2 inhibitor, a small molecule called a tyrosine kinase inhibitor in the same broad family as the leukemia pill Gleevec. Also in pill form, the inhibitor, called GW572016 (lapatinib), blocks HER-2 activation using a different mechanism than Herceptin. Early Phase I and II studies showed good results in breast cancer patients who did not respond to Herceptin and chemotherapy, Pegram said. Phase II and III studies are underway. If successful, they could pave the way for approval of the drug.

Because Herceptin and GW572016 both block HER-2 but work differently, Pegram has launched a Phase I study pairing the two. Preclinical data indicate that the two have a synergistic effect, meaning each makes the other more effective.

Pegram also will conduct a Phase I study with M.D. Anderson Cancer Center on SMS 599626, a compound that is closely related to GW572016. UCLA was selected as one of two sites nationwide because of Pegram's interest in this area, and because of the excellent reputation of the cancer center's clinical/translational research team.

"I'm fortunate to work with such a committed group, the research coordinators and nurses, data managers and staff involved in the execution of often complex early phase clinical research studies," Pegram said.

UCLA is the only site in the world testing a humanized antibody called Therex, which targets the MUC 1 protein found in about 90 percent of breast cancers. Doses of the drug are individualized for each patient. So far, patients are tolerating the treatment very well, Pegram said.

Finally, Pegram is studying a drug that uses the "Trojan horse" approach to cancer treatment. The drug, NB1011, tricks an enzyme that resists chemotherapy in colorectal cancer patients. Like the Trojan horse, NB1011 appears harmless as it enters a diseased cell, but is converted into a deadly toxin by the enzyme. The Phase I study is completed, and a Phase II study is planned.

The clinical trials of NB1011 are based on work Pegram did in his lab, an excellent example of the investigator-initiated translational research being done at the Jonsson Cancer Center.

"Patients are attracted to novel combinations of biologic therapies," Pegram said. "And it's all about the patients. I've learned so much from my patients and their families. Their courage, their sacrifice and their determination motivate me to work as quickly as possible to get answers." ✯

For more information on clinical trials available at UCLA's Jonsson Cancer Center, call our toll-free hotline at ***888-798-0719****.*

Dr. Nori Kasahara

Scientific STAND OUT

Developing a Stealth Virus for Gene Therapy

Like a tiny assassin, it invades the cancer cell. It's outwardly kind to the host cell, while craftily invading its genome so that the daughter cells to come all have a copy of the intruder in their DNA. As the cell divides, it begins to spread throughout the tumor cell by cell. It doesn't cause much damage initially so as not to attract an immune response.

Quickly and quietly, it seeds the tumor with a suicide gene that later can be triggered to kill the cancer—all before the body recognizes what's happening and has a chance to react.

Call it the stealth virus. Call it the ideal gene therapy. Call it Nori Kasahara's life's work.

A cancer researcher and an associate professor of digestive diseases, Kasahara has worked for decades to design the perfect virus delivery system for gene therapy. The idea is relatively new. The first paper to prove that viruses can be used as gene delivery vehicles was published in 1983. Prior to that, researchers were literally "mashing up DNA and throwing it on cells, hoping it would stick," said Kasahara, who was recruited to UCLA in 2003.

Just a year before that ground-breaking paper, researchers attending the Banbury Conference in New York were told that gene therapy would not happen in their lifetimes. A lot has changed since then, and Kasahara is among those leading the charge.

"It turns out that viruses have evolved into very efficient mechanisms for getting their genes into our cells," said Kasahara, director of the Molecular Biology and Vector Core at UCLA's Jonsson Comprehensive Cancer Center and UCLA's CURE: Digestive Disease Research Center. "We want to take advantage of that to get the genes we want into our cells."

Genes, perhaps, that can kill cancer cells one a time, a sort of intracellular chemotherapy, selectively targeting malignant cells and sparing healthy ones.

The first attempts at gene therapy employed retroviruses that were stripped of their ability to replicate, a requirement of the U.S. Food & Drug Administration to ensure safety.

The virus genes were then replaced with therapeutic genes aimed at treating cancers and other diseases.

The concept proved successful in the Petri dish and worked adequately in animals. A swell of enthusiasm greeted the hundreds of gene therapy clinical trials that followed. But the experimental therapy proved inefficient in humans and enthusiasm soon turned into skepticism. Then, a teenaged gene therapy patient being treated for a liver disorder died. The high-profile case resulted in the closure of many gene therapy studies.

The problem was this: The old method of gene therapy—using the stripped down, non-replicating viruses—required matching the virus head-to-head with the cancer cells as the virus invaded only one cell at a time. It was nearly impossible to provide enough of it to fight the seemingly endless numbers of cancer cells without inducing toxicity.

"In humans, you need to make enough virus to enter a billion cancer cells," Kasahara said. "Even in the most advanced trials at that time, we couldn't do that."

Enter the stealth virus.

Then a researcher at the University of Southern California, Kasahara decided that maybe the viruses didn't have to be so crippled. Maybe this would work better if the viruses were allowed to replicate.

"We wanted to try to give back the natural and most powerful attribute of the virus, its ability to spread," he said.

Kasahara's team created a gene therapy tool called a replication competent retrovirus, or RCR, that is efficient in spreading in tumors, but does not invade normal cells, which don't divide. The RCR can carry therapeutic genes to treat or kill the cancer.

The key, Kasahara said, is in the replication.

"Now, every tumor cell the virus gets into itself becomes a virus producer," he said. "It gets into the tumor cell genome and makes more copies of itself."

As the tumor cells divide, the virus infects the next cell. And the next. Simple. Brilliant.

And Kasahara proved it works in the lab. In animal studies, the RCR spreads within the tumor but does not go into normal tissues nearby.

Encouraged, Kasahara has spearheaded the creation of an international consortium led by UCLA. The consortium will prepare clinical-grade RCR for testing in human subjects. Discussions already are underway with the FDA to initiate clinical trials, but the virus must first be tested and re-tested in laboratory models to ensure it will be safe for humans.

Kasahara hopes to launch human testing in three years. The first trials would be in patients with glioblastoma, an incredibly difficult to treat brain cancer that kills the majority of those who get it. He also hopes to open trials for patients with head and neck cancers. It's likely that gene therapy will be paired with conventional therapy.

"If we've learned anything, it's that one single agent won't work," he said. "The best regimens work in combination. ✯

Tim Solberg

Scientific STAND OUT

Developing a Better Way to Deliver Radiation Therapy

Medical physicist Tim Solberg wants to change the way cancer patients receive radiation treatment.

The plan is simple: Use precision targeting to deliver higher doses in fewer treatments for improved outcomes at a lesser cost.

It's not a pipe dream. Solberg believes researchers will be able to do just that very soon by marrying the most advanced radiation delivery technologies with leading-edge imaging, providing patients with a more effective and much shorter course of treatment.

With conventional radiation therapy, cancer patients must undergo daily treatments for six to eight weeks.

"We break up the radiation into small pieces to try to spare the normal body structures that are unavoidably exposed during treatment," he said.

Solberg believes there's a better way.

"If we can be more precise in our targeting, we can give a higher dose fewer times and achieve a better outcome."

Solberg and other Jonsson Comprehensive Cancer Center researchers currently are using stereotactic radiosurgery, a more focused delivery system for radiation, to treat some brain cancer patients.

"Radiosurgery is a perfect paradigm for how all radiotherapy may be performed in the future," said Solberg, a cancer researcher, professor, vice chairman in radiation oncology and director of medical physics at UCLA.

But other areas of the body present significant challenges. Lung tumors, for example, are difficult to target precisely because the tumor moves as the patient breathes. The solution may be image-guided radiotherapy. Solberg wants to test powerful imaging modalities with radiotherapy, providing greater precision than has yet been achieved.

Intensity modulated radiotherapy, or IMRT, is the most advanced focused delivery technology available now. IMRT puts the radiation dose only where the oncologists want it, keeping the damaging beams away from healthy tissue. IMRT works by shaping the radiation into three dimensions, allowing technicians to target the changing contour of the tumor from any angle. It allows higher doses of radiation to the tumor with less damage to surrounding tissues. UCLA is a national leader in IMRT, Solberg said.

However, Solberg's team quickly recognized that the application of a focused radiotherapy approach such as IMRT can be counterproductive without an equally accurate understanding of the dynamic nature of a patient's anatomy.

That provided the motivation for integrating state-of-the-art imaging technology within the treatment room.

To account for anatomical changes caused by basic physiologic functions, a patient placed on a treatment table can now have their tumor imaged directly, both before and during treatment, using a variety of imaging technologies.

For Solberg, lung cancer is the Holy Grail.

"We don't do well with radiotherapy in lung cancer, and there aren't a lot of options for patients," he said. "From a targeting point of view, we know lung tumors move, and that motion severely limits the efficacy of radiotherapy."

The answer: Respiratory-correlated CT scanning that shows radiation oncologists where the tumor is at every point during treatment.

"We'll be able to see the lung tumor moving, see its shape changing as a patient breathes, and we can redesign the delivery paradigms to account for the changes," Solberg said.

Moving from the anatomical to the cellular perspective, the use of molecular imaging technologies will provide radiation oncologists with additional information for designing focused therapies.

"Visualization of the anatomy is only half the picture," Solberg said. "In prostate cancer, for example, you can see the prostate gland on CT and MRI, but you don't see cancer within the prostate. With molecular imaging technology, we can see the actual cancer better. Now, we treat the whole prostate when we might not have to."

Magnetic resonance spectroscopy (MRS) and positron emission tomography (PET) may provide the cancer-specific information that will enable radiotherapy targeting at the molecular scale.

The final step involves combining the anatomical and molecular information. Solberg believes that respiratory-correlated CT combined with PET scanning holds significant promise for lung cancer patients. Similarly, the use of in-room imaging may provide better patient set-up for guiding MRS-targeted radiotherapy of prostate cancer patients.

It will be one to two years until these sophisticated anatomical and molecular imaging techniques can be combined. To be successful in image-guided radiotherapy, an institution needs the technology and the expertise—people who understand the technology and can implement it. The resources available at UCLA are without rival, Solberg said.

"Everything is converging at the right time for us, the imaging and delivery techniques and computer technology," said Solberg. "The timing is perfect." ✯