UC SANTA BARBARA
THE Current

April 6, 2011
Gail Gallessich

Chemical Engineers at UCSB Design Molecular Probe to Study Disease

Chemical engineers at UC Santa Barbara expect that their new process to create molecular probes may eventually result in the development of new drugs to treat cancer and other illnesses.

Their work, reported in the journal Chemistry & Biology, published by Cell Press, describes a new strategy to build molecular probes to visualize, measure, and learn about the activities of enzymes, called proteases, on the surface of cancer cells.

Patrick Daugherty, senior author and professor of chemical engineering at UCSB, explained that the probes are effective at understanding proteases involved in tumor metastasis.

"Tumor metastasis is widely regarded as the cause of death for cancer patients," said Daugherty. "It's not usually the primary tumor that causes death. Metastasis is mediated by proteases, like the one we are studying here. These proteases can enable tumor cells to separate and degrade surrounding tissue, and then migrate to sites distant from the primary tumor. The tumor doesn't just fall apart. There are many events that must occur for a tumor to release cancerous cells into the blood stream that can circulate and end up in other tissues such as liver or bone."

The probes allowed the researchers, for the first time, to measure directly the activity of a protease involved in metastasis. They did this by adding their probe into

a dish of tumor cells. They then measured the activity of this protease that breaks down collagen –– the single most abundant protein (by mass) in the human body.

"We have immediate plans to use similar probes to effectively distinguish metastatic HER2 positive tumors, one of the most commonly used biomarkers of breast cancer," said Daugherty. "A significant fraction of patients have HER2 positive tumors but we don't know which of those tumors is going to metastasize yet. But our ability to make these probes can allow us to identify which of those HER2 positive tumors have the ability to break down that surrounding tissue, to detach from the primary tumor, and to establish a separate tumor somewhere else in the body."

The authors designed the molecular probe to be recognized by a single protease rather than by the many proteases that are present in human tissues. That is half of the probe. The other half of the probe involves an optical technique used to measure activity. This approach relies upon the use of two engineered fluorescent proteins, derived from marine organisms, that absorb and emit light in a process called FRET, or Forster resonance energy transfer.

To prepare the probes, the researchers introduced a gene that encodes the probe into the bacteria E. coli. Then they produced and purified significant quantities of the probe. All of the information needed for the probe is encoded by a DNA sequence. The probes are easy and inexpensive to produce, as well as easily shared with other researchers.

In addition to studying cancer, similarly constructed probes have ramifications for studying Alzheimer's disease, arthritis and connective tissue diseases, bacterial infections, viruses, and many other diseases.

"The fact that you can generalize the concept, and the way you make these probes, to many systems, makes it attractive," said Daugherty. "We happen to study the activity of this protease and a certain type of tumor cells that are derived from cancer patients. But you could apply this to hundreds of molecules and really develop a working understanding of how groups of proteases function together in cell biology."

In individuals with rheumatoid arthritis, for example, there is increased production of proteases, including the one studied by Daugherty's team. This protease mediates collagen breakdown and joint destruction. "If you've got an enzyme that can chew up collagen and you've got lots of collagen in your joints, then you would expect that

you would see more rapid degradation of the joint by those proteases," said Daugherty.

Daugherty's research group has created approximately 25 probes analogous to the one presented in the paper. They are building a panel of about 100 probes and will use this panel to characterize how different proteases function. This investigation could lead to new drug therapies for a variety of diseases.

The first author on the paper is Daugherty's former graduate student, Abeer Jabaiah, who is applying a similar process to another protease involved in tumor metastasis as a postdoctoral fellow in Daugherty's lab.

Funding for this work was provided by the National Institutes of Health through the National Cancer Institute's Center of Cancer Nanotechnology Excellence and the National Heart, Lung, and Blood Institute's Program of Excellence in Nanotechnology.

[RETURN TO TOP]

† Bottom photo: Patrick Daugherty with fluorescence activated cell sorter, the instrument that picks out extremely rare cells that make the molecular probes.

Credit: George Foulsham, Office of Public Affairs, UCSB

Related Links

Patrick Daugherty

About UC Santa Barbara

The University of California, Santa Barbara is a leading research institution that also provides a comprehensive liberal arts learning experience. Our academic community of faculty, students, and staff is characterized by a culture of interdisciplinary collaboration that is responsive to the needs of our multicultural and global society. All of this takes place within a living and learning environment like no other, as we draw inspiration from the beauty and resources of our extraordinary location at the edge of the Pacific Ocean.