NEWS RELEASE

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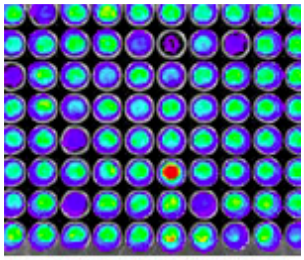
JULY 11, 2006

Penn researchers identify small molecules capable of fighting treatment-resistant tumors

Imaging technology paves way to future individualized cancer treatment

(Philadelphia, PA) - Using a newly developed drug screen, researchers at the **University of Pennsylvania School of Medicine** have discovered small molecule compounds that are able to perform the functions of a gene commonly mutated in many types of cancer. By combining molecular imaging techniques with human cancer cell culture and animal model approaches, the researchers were able to reveal the ability of the compounds to kill human tumor cells. These findings emphasize the growing role of imaging technology in aiding researchers in the development of individualized cancer treatments.



Imaging technology points to small molecules that can fight treatment-resistant tumors

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p53, a tumor suppressor gene, is widely mutated across all types of cancer. In addition to causing aggressive tumor growth, a mutation in the *p53* gene contributes to chemotherapy and radiotherapy resistance. In search of methods to combat treatment-resistant tumors, **Wafik S. El-Deiry, MD, PhD,** Professor in the Departments of Medicine (Hematology/Oncology), Genetics, and Pharmacology,and colleagues employed molecular imaging techniques to evaluate the ability of small molecules to produce normal p53 function in the *p53*-deficient and *p53*-mutant cancer cells. They report their findings in the most recent online issue of the *Proceedings of the National Academy of Sciences*.

In an attempt to defend the body, a normal p53 protein will bind to DNA during periods of cellular stress or damage. The binding of p53 to DNA initiates downstream reactions that keep the stressed cells from multiplying. Under normal conditions, p53 will activate the *p21* gene, causing the cell cycle to freeze, halting cell proliferation; p53 will activate KILLER/DR5, which signals for cell death, or apoptosis. Chemotherapy and radiotherapy set out to deliberately stress tumor cells in hopes of promoting their self-destruction. Unfortunately, mutations to the *p53* gene disrupt the intracellular defense system.

“Mutants of p53 that occur in human cancer fail to bind to DNA or to activate target genes, such as *p21* and *KILLER/DR5*,” explains El-Deiry, who is also the Co-Program Leader of the Radiation Biology Program at the **Abramson Cancer Center** at Penn. “Therefore, when cells are stressed or damaged, p53-mutant cells fail to shutdown and continue to divide uncontrollably.” The development of a drug screen by El-Deiry’s lab allowed the researchers to trace the activity of small molecules in p53-mutant cancer cells.

The small molecule drug screen, developed by El-Deiry’s lab, was created by inserting firefly luciferase, a reporter gene capable of emitting light, into human tumor cells carrying the *p53* mutation, and observing the subsequent response.

“Just as fireflies emit light that we can see with our eyes, the cancer cells were engineered to emit light if a p53-like response was triggered by any of the small molecules that we examined,” explains El-Deiry.

The small molecules screened by El-Deiry’s research group were obtained from the Developmental Therapeutics Program at the National Cancer Institute. The molecules represent many classes of compounds and include both natural and man-made chemicals.

“One by one, we introduced the small molecules to the p53 mutant cancer cells, which possessed the luciferase reporter gene and screened for light emissions,” describes El-Deiry. The light emissions displayed by the live cell imaging instrumentation revealed which molecules were able to achieve p53 responses in the abnormal cancer cells. Further testing exposed the ability of high doses of several groups of the small molecules to kill human cancer cells in cell culture and in mouse models implanted with human tumors.

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Wafik El-Deiry, MD, PhD

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"Our work provides a blueprint for how molecularly targeted therapy can be discovered using new optical imaging technology," states El-Deiry. "This is very important going forward in the era of molecular medicine and individualized therapy for cancer patients."

In the future, El-Deiry plans to continue to explore the therapeutic effects of the small molecule compounds in different types of cancer and to evaluate the potential toxicities of these compounds. Ultimately, El-Deiry's research group hopes to bring new anti-cancer agents to the clinic.

In a review paper published this week in the *Journal of Clinical Oncology*, El-Deiry addresses the importance of molecular imaging in the future of oncologic drug discovery and development.

"With the advancement of molecular imaging, we have the capabilities to develop strategies that will target the molecular alterations in cancer and to closely examine how drugs bind to their respective targets in cancer patients," says El-Deiry. "This will help doctors to understand why anti-cancer drugs work when they do work and fail when they fail." By allowing for better patient selection and treatment monitoring strategies, molecular imaging will likely reduce the future cost of drug development, he predicts.

Study co-authors of the *PNAS* paper are Wenge Wang and Seok-Hyun Kim, both from Penn. These studies were funded in part by the National Cancer Institute Network for Translational Research in Optical Imaging and the National Institutes of Health. Co-authors of the *Journal of Clinical Oncology* review are Caroline C. Sigman, from CCS Associates (Mountain View, CA), and Gary J. Kelloff, from the National Institutes of Health.

This release and related image can also be seen at: www.uphs.upenn.edu/news .

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*The **Abramson Cancer Center of the University of Pennsylvania** was established in 1973 as a center of excellence in cancer research, patient care, education and outreach. Today, the Abramson Cancer Center ranks as one of the nation's best in cancer care, according to US News and World Report, and is one of the top five in National Cancer Institute (NCI) funding. It is one of only 39 NCI-designated comprehensive cancer centers in the United States. Home to one of the largest clinical and research programs in the world, the Abramson Cancer Center of the University of Pennsylvania has 275 active cancer researchers and 250 Penn physicians involved in cancer prevention, diagnosis and treatment.*

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Penn's School of Medicine is ranked #2 in the nation for receipt of NIH research funds; and ranked #3 in the nation in U.S. News & World Report's most recent ranking of top research-oriented medical schools. Supporting 1,400 fulltime faculty and 700 students, the School of Medicine is recognized worldwide for its superior education and training of the next generation of physician-scientists and leaders of academic medicine.

The University of Pennsylvania Health System includes three hospitals, all of which have received numerous national patient-care honors [Hospital of the University of Pennsylvania; Pennsylvania Hospital, the nation's first hospital; and Penn Presbyterian Medical Center]; a faculty practice plan; a primary-care provider network; two multispecialty satellite facilities; and home care and hospice.