

Gene “survivin”

inhibits cell death



Dr. Dario Altieri, professor of pathology, is part of a team credited with discovering survivin, a gene that inhibits the programmed death of cells.

THE YALE CANCER CENTER scientists who identified a gene that enables cancer cells to evade one of the body’s mechanisms for weeding out mutations have refined their understanding of the gene and suggested potential new avenues for cancer treatment.

Their findings, published in the journal *Nature*, show that the gene, called survivin, is concentrated on the mitotic spindle, a cell component that is central to the process of cell division. “Survivin was absolutely undetectable in normal tissues, but we found it over-expressed in all the most common human cancers,” says Dario C. Altieri, M.D., professor of pathology and leader of the study. Survivin inhibits apoptosis, the programmed death of cells, thereby allowing mutated cells to survive.

Because it is present at mitosis, or cell reproduction, the gene may also be the link between two processes researchers have long believed were connected, apoptosis and cell cycle regulation. In normal tissue, survivin is expressed only during the development of the embryo and fetus, where it is believed to play a role in controlling apoptosis to maintain a state of equilibrium within the body and organ and tissue development.

In their recent findings, Altieri and his colleagues built on their earlier discovery and cloning of survivin. “We are providing some mechanistic implications for why cancer cells might have selected this particular gene for survival,” says Altieri, who collaborated on the project with researchers at the S. Raffaele Scientific Institute in Milan. The next step is to identify survivin antagonists that would increase the effectiveness of chemotherapy by removing survivin’s protective function on the mitotic apparatus.

Zahn and Crapple join board

The Yale Cancer Center’s Director’s Advisory Board has two new members. **Paula Zahn**, a resident of New York and Connecticut, is a news anchor with the Fox Television Network. **George Crapple** of Greenwich is vice chairman, co-chief executive officer and a director of Millburn Ridgefield Corporation, a financial management and investment firm. The Director’s Advisory Board is charged with raising public awareness of the role of the Cancer Center and expanding fundraising opportunities.



Paula Zahn



George Crapple

Cancer cure: hope or hype?

YOU COULDN’T HELP but have heard about it...and if you were a cancer patient, or close to someone who is, you couldn’t help but have experienced a strong—if fleeting—burst of hope.

The cancer “breakthrough” story that dominated the news just over a year ago sent the public as well as cancer researchers and clinicians abuzz with questions and commentary. A front-page *The New York Times* story suggested that two molecules, angiostatin and endostatin, would cure cancer in two years. Research had shown the two compounds to be potent anti-cancer agents in mice.

Largely overlooked in the brouhaha was the fact that about 20 similar drugs, angiogenesis inhibitors, have already begun testing in humans. Anti-angiogenesis research is hardly new. The approach seeks to kill cancerous tumors by blocking the growth of blood vessels that supply oxygen and nutrients to the tumors.

Yale Cancer Center member Craig Crews, Ph.D. has been doing similar work here, contrib-

uting to major advances in the field. Two years ago his research team identified one of the specific enzymes necessary for the complex task of blood vessel construction. More recently, Crews joined Cornell biochemists in unveiling the three-dimensional chemical structure of a key protein that is the target of TNP-470, an experimental drug that shows promise for starving cancerous tumors.

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What's New

The National Cancer Institute has awarded a five-year, \$6.5 million grant to a program headed by **Daniel DiMaio**, M.D., Ph.D., professor of genetics and director of the Cancer Center's Molecular Virology Research Program. The main focus of the research project is the use of molecular approaches to explore the contribution of viral gene products and cellular mutagenesis to oncogenic transformation, the process by which a normal cell is converted into a tumor cell.

YCC Director **Vincent T. DeVita, Jr.**, M.D. will be the featured speaker at a fashion show and luncheon hosted by the Breast Cancer Alliance in Greenwich on October 15. Proceeds from the annual event will benefit breast cancer research conducted at the Cancer Center by **Michael DiGiovanna**, M.D.

YCC member **Bruce Haffty**, M.D., associate professor of therapeutic radiology, was selected for *Good Housekeeping* magazine's list of "The 318 Top Cancer Specialists for Women." The physicians were nominated by department chairs and section chiefs in surgical, medical and radiation oncology at major medical centers across the country.

The Yale School of Nursing is set to open an oncology nurse practitioner master's specialty to prepare advanced practice nurses to provide comprehensive care and support to cancer patients and families. The first students will be admitted in fall of 1999 and will study under the direction of Yale Cancer Center member and professor of nursing **M. Tish Knopf**, Ph.D.



YCC member **Ira Mellman**, Ph.D., professor of cell biology and immunology, has been appointed editor-in-chief of the *Journal Cell Biology*.

Linda Mowad, project director of the Cancer Information Service New England Region, was elected secretary for the American Cancer Society New England Board of Directors.

Radiation therapy: directed doses

IT'S CALLED Intensity Modulated Radiation Therapy (IMRT), and it involves delivering defined doses of radiation to tumors from different angles. It differs from conventional radiation therapy in that it allows for more precise dose distributions, increasing the dose to the tumor itself while at the same time avoiding unnecessary radiation to critical body structures.

"The overall goal is to achieve more uncomplicated cures," says Jonathan Knisely, M.D., assistant professor of radiation therapy at the Yale School of Medicine. "While there have been no studies showing that this type of treatment results in fewer side effects, my personal observation has been that it does."

Although new to the Yale Cancer Center, IMRT has been in use elsewhere for several years. "Patients like the idea of having the radiation more closely conformed to where the problem is," says Knisely. "It's a more attractive option, though we can't guarantee better results than those achieved with conventional radiation therapy."

Using an attachment to the linear accelerator, radiation is delivered at the best angles and at the optimal intensities to the tumor site. The settings are determined with precision accuracy by a computer program, which instructs the dose-delivering components to open and close as the device arcs around the body. The calculations are based on CT scans and/or ultrasound pictures of the affected area.

Size, shape and location of the tumor are important factors in determining whether a patient is a good candidate for IMRT. It is used most commonly to treat brain tumors whose proximity to sensitive brain tissue and structures would make conventional radiation therapy more difficult. It is also considered in cases where surgery is not an option, such as when removal of a tumor located on or near the optic nerve carries the risk of blindness.

In addition to brain tumors, IMRT is also useful in treating head and neck cancer and prostate cancer. It's a highly specialized treatment, says Knisely, one that will never replace conventional radiation altogether.



Shirley Peak is one of the first patients to benefit from intensity modulated radiation therapy (IMRT) at the Yale Cancer Center. Peak, who is being treated for a brain tumor by Dr. Jonathan Knisely, travels daily from Marlborough, Connecticut for her 15-minute treatment. The mask over her face restricts head movement, helping to ensure exact dosage measurements.

In My Steps

More than 60 doctors, nurses and other health care professionals from throughout the Cancer Center got a virtual taste of cancer related fatigue as part of an education and awareness program sponsored by Ortho Biotech Pharmaceuticals. The program, called "In My Steps," features interactive computer technology that "walks" caregivers through some of the simple daily tasks made difficult by the debilitating fatigue suffered by nearly 75 percent of all cancer patients. Participants, including Dr. Michael DiGiovanna (left) reported an increased understanding of the difficulties faced by patients coping with fatigue.



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A Comprehensive Cancer Center designated by the National Cancer Institute

Luncheon benefit for Dr. Mel's Fund

A benefit kick-off luncheon for the newly established Dr. Mel Goldstein Multiple Myeloma Research Fund at Yale Cancer Center will be held on Friday, September 17. News Channel 8's Dr. Mel, a YCC patient and friend, is donating all profits from his new book, "The Complete Idiots Guide to the Weather," to the fund. The luncheon will be held at the New Haven Lawn Club. The ticket price of \$50 will include lunch and the book, a compendium chock full of information on meteorology for the layman. For information please call R.J. Julia Booksellers at 203-245-3959.

Celebrating survival

NEARLY 300 CANCER PATIENTS, survivors and family members took part in the Yale Cancer Center's observance of National Cancer Survivors Day in June. The emcee for the event, Channel 8 Meteorologist Dr. Mel Goldstein, himself a survivor of multiple myeloma, delivered on his promise of blue skies and warm weather for the outdoor luncheon ceremony.

Highlighting the event was the Connecticut dedication of the new Prostate Cancer Awareness Stamp, the third cancer-related stamp to be issued by the U.S. Postal Service. This newest stamp bears the message, "Annual Check-ups and Tests," and promotes the importance of early detection and treatment. As a result of its active role in calling public attention to cancer, the Postal Service received a special award from the Cancer Center.

Participants were enthusiastic about the workshops offered during the day. Sessions on such topics as Enhancing your Lifestyle through Exercise and Nutrition, Cancer Genetics, Surfing the Net for Cancer Information, Reflexology and Massage and Reiki appeared to fill an unmet need for information on living with cancer experienced by virtually all survivors.

"I wish I went to Reiki while caring for my late spouse," wrote one participant on the program evaluation form. "What an incredible, uplifting session," wrote another of the workshop on Life After Cancer Treatment. Such comments and the demeanor of those attending made it clear that they came away having achieved the sentiment expressed in the theme of the day: "Renewing the Spirit: for those who have been touched by cancer."



Jo Saunders, Connecticut district manager for the United States Postal Service, (second from left) joins cancer survivors David Koch, Steve Corman and Mary McCarthy in unveiling the Prostate Cancer Awareness Stamp.

Yale-New Haven Hospital social workers Eileen Kane and Alicia Genovese demonstrate the techniques involved in Reiki, the ancient art of therapeutic touch, during a workshop for cancer survivors.



Tobacco settlement in Connecticut

During a special session of the General Assembly, Connecticut lawmakers approved spending \$5 million on anti-smoking programs over the next two years and donating an additional \$40 million to a trust fund, whose interest will go toward programs to combat smoking. The money comes from the \$300 million Connecticut is expected to receive over the next two years as part of a national settlement between tobacco companies and 46 states. The bulk of the \$300 million will be incorporated into the state budget and used for a variety of purposes.

While the \$45 million total represents only 15 percent of the state's share of the tobacco settlement, the legislative agreement represents a victory of sorts for anti-smoking advocates. Initial proposals from both Governor John Rowland and the legislature's appropriations committee would have earmarked only about \$500,000 for tobacco prevention and cessation programs. Still, Connecticut remains near the bottom among the states in per capita spending on tobacco programs—\$1.56 per resident. Neighboring Massachusetts has allocated \$9.72 per resident.

Calling the outcome a "mixed victory," YCC Associate Director for Cancer Prevention and Control, Susan Mayne, Ph.D. says public health advocates are disappointed at the lack of a clear tobacco prevention and control plan for the State of Connecticut. "Our goal was to secure funding for a plan that would identify the most critical targets in our state, and then seek proposals to address those needs. As it now stands, there is no money for planning, and no assurance that the \$45 million earmarked will be spent on data-driven public health priorities."

Just how the money will be allocated is still undecided. Under the legislation, the \$40 million tobacco trust fund will be controlled by a special board appointed by the Governor and legislative leaders. Mayne says the Yale Cancer Center will remain involved, working with state officials to ensure that the trust fund is responsibly administered. We will also continue to seek state and national funding for a comprehensive cancer prevention and control plan for the state.

Five-a-day for better health

HOW MANY FRUITS and vegetables do you eat each day? What prevents you from eating more? Would you be willing to eat more? Those are some of the questions being asked of selected callers to the Cancer Information Service (CIS) as part of a nationwide study designed to promote a balanced diet for better health.

The 5-A-Day intervention study is a sequel to an earlier study, in which callers received verbal messages as well as written materials explaining the benefits of eating at least five servings of fruits and vegetables a day. That research revealed that the CIS, through proactive educational efforts, can have a positive impact on increasing fruit and vegetable consumption. The new project builds on those results, testing whether printed materials *tailored* to individual study participants will be even more effective.

Callers must meet specific criteria to be eligible for the study. They must be at least 18 years old, not a cancer patient in treatment or awaiting treatment, not severely distressed or terminally ill, and not on a physician-prescribed diet that limits fruit and vegetable consumption. Participants are then selected at random by a special computer program based on demographic information.

The initial telephone intervention consists of a seven-minute interview assessing the caller's fruit and vegetable consumption. The information specialist then explains the importance of eating at least five servings of fruits and vegetables every day, and asks the caller for a commitment to eat more. Within a few days, participants are sent a personalized packet of educational materials, prepared through a centralized computer clearinghouse. Follow-up phone interviews, conducted at three and 12 months after enrollment, determine how participants are doing—if they have, in fact, increased the number of fruits and vegetables they consume, and if not, what barriers they are facing.

5-a-day for better health

“Callers are responding very well so far,” notes CIS Project Director Linda Mowad. “Very few have refused to take part. The information specialists also feel like they are helping callers and the community at large, while at the same time participating in an important research project. Being on the front lines of this study, they have tremendous input into its implementation and design.”

Research has shown that a diet rich in fruits and vegetables can significantly reduce the risk of cancer, particularly cancers of the oral cavity, esophagus, pharynx, larynx, stomach, pancreas, colon, rectum, lung, bladder, endometrium, cervix and ovary. The evidence is stronger for vegetable than for fruit consumption, though a wide variety of both are advised.

Jerrienne Heimendinger is the principal investigator on the project. She believes the CIS is an ideal vehicle for this type of research. “People who call the CIS are already motivated and appreciate the service,” she explains. “Often the callers engage in extended conversation and establish a rapport with the information specialists, making it easier to collect information. This is a wonderful way to acquire research subjects.”

A total of 3,200 callers – through CIS offices at Yale, New York City, Texas, Northern California, Wisconsin and West Virginia – will be enrolled in the intervention study, with accrual continuing throughout the summer. The results are expected to be published in the winter of 2001.



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Cancer cure: hope or hype?

“The beauty of these medications is that they all block the same basic mechanism – blood vessel growth – which makes them effective against a wide range of tumors, including lung, brain, prostate and breast tumors,” says Crews, assistant professor of molecular, cellular and development biology. “They also appear to be far less toxic to patients than radiation or chemotherapy.”

Given the promising outcome of the endostatin and angiostatin experiments, meanwhile, the National Cancer Institute moved quickly to confirm the results and prepare the compounds for studies in people. Preliminary results indicate that in some treatment groups, murine endostatin shows slight delays in the growth of lung tumors in mice. Other studies showed delay in tumor growth using the human version of endostatin in mice. However, to date,

NCI studies have not produced the marked regression of these tumors in mice that were initially reported.

The result of such media hype, unfortunately, has been to mislead a public that hears part of a story and becomes filled with false hope. Difficult for most to grasp is the translational process of moving from animal research to use in humans, and the time required to attain a new drug that’s approved for clinical use.

As Yale Cancer Center Director Vincent T. DeVita, Jr., M.D. told the *New Haven Register*: “Animal models have never predicted humans one-to-one. One drug or one cure is unlikely. It seems likely that we’ll have to bang the cancer cells on the head from two directions. Anti-angiogenesis drugs may well be one of the two clubs.”

If there is a positive to all this it is that it has acutely focused public attention on cancer research – what it is, where it’s going and the support it requires.

COMING UP

SEPTEMBER 27

The Burger King Cancer Foundation of Metro New York’s second annual Celebrity Classic Golf and Tennis Tournament to benefit the Yale Cancer Center, Columbia Presbyterian Cancer Center and the Cancer Institute of New Jersey. For information, call Judith Winslow at 203-785-2144.

OCTOBER 15

Second annual Richard D. Frisbee III Stem Cell Symposium: “Clinical and Molecular Advances in Immunotherapy and Stem Cell Transplantation” at the Omni Hotel in New Haven. For information, call Dr. Edward Snyder at 203-688-2441.

OCTOBER 17

YNHH Auxiliary Fashion Show at Water’s Edge Resort in Westbrook. Models will include oncology patients and physicians, and the money raised will benefit breast cancer programs. For information, call Janice at 203-688-5717.

OCTOBER 23

Y-ME of Connecticut Breast Cancer Symposium: “Survivorship for the New Millenium” at the Yale School of Medicine. Special guest Dr. Bernie Siegel will speak on “Loving & Laughing & What Gets You Through.” For information call Y-ME of CT at 203-483-8200.

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