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REPORT TO PHYSICIANS

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OncoLog

Collaboration Between Scientists, Clinicians Moves Apoptosis Studies Forward

by Maureen Goode, Ph.D.

To penetrate the ingenious defenses of cancer cells that often make them resistant to therapy, researchers at The University of Texas M. D. Anderson Cancer Center are investigating the use of synthetic peptides that function as tiny assassins—targeting tumor cells from the inside with lethal accuracy.

These agents, called proteasome inhibitors, have been shown to induce high levels of apoptosis, or programmed cell death, in prostate cancer cells. Now, studies of proteasome inhibitors at M. D. Anderson are moving from the lab to a phase I clinical trial of the synthesized proteasome inhibitor PS-341.

Apoptosis is a normal, genetically controlled cellular process that kills cells in response to certain stimuli. Affected cells are marked by characteristic morphological changes: They shrink, their chromosomes condense, their DNA fragments, and blebs appear on their cell membranes. The study of apoptosis began in the 1970s, when scientists first detected these changes in electron micrographs of rat liver cells.

Research by Associate Professor of Cancer Biology **David J. McConkey, Ph.D.**, *and others into the mechanisms of apoptosis recently led to the first clinical trial of the synthesized proteasome inhibitor PS-341 in patients with prostate cancer.*

David J. McConkey, Ph.D., associate professor in the Department of Cancer Biology at M. D. Anderson, is studying how apoptosis is disrupted during tumor progression, especially in metastatic cells, and how disruptions make cells resistant to therapy.

"Chemotherapeutic agents and other therapeutic strategies induce apoptosis in their tumor targets," he explained. "Tumors that become resistant to treatment appear to have developed mechanisms to resist apoptosis. By identifying those mechanisms, we will identify the interrupter."

(Continued on **next page***)*

Apoptosis Studies Move Forward

(Continued from **page 1***)*

Unlike necrosis, which kills normal cells that have experienced trauma, apoptosis seems to kill only diseased or unwanted cells. Necrotic cells burst and cause inflammation that can damage nearby normal tissue. In contrast, apoptotic cells lose contact with neighboring cells and are removed by the body's scavenging cells before they burst and release possibly harmful contents into the body. This may be the most important characteristic of apoptosis.

"We think apoptosis may have evolved as a way to safely remove large quantities of single cells without inducing an inflammatory response," said Dr. McConkey, who is one of more than 100 researchers at M. D. Anderson studying apoptosis. "Work over the past decade or so has revealed that apoptosis is regulated by an evolutionarily conserved molecular pathway. The original studies were conducted in a nematode worm, *Caenorhabditis elegans.*"

The worm studies revealed that three genes are essential for apoptosis: *ced3*, *ced4*, and *ced9*, the worm version of the human oncogene *bcl2*, which blocks the action of the other two genes to inhibit apoptosis. *bcl2* acts through the caspases, a group of at least 13 of the proteins called proteases. It is the proteases, which control enzymes to produce the characteristic DNA fragmentation seen during apoptosis, that are the focus of Dr. McConkey's studies. Similar research by Timothy J. McDonnell, M.D., Ph.D., an associate professor in the Department of Molecular Pathology, is aimed at determining how *bcl2* and its relatives regulate the responses of prostate cancer cells to therapy.

"We were looking for other proteases involved in apoptosis and happened across one called the proteasome that controls an important survival pathway," Dr. McConkey said. The proteasome is a huge complex of 14 proteases that degrade the proteins that control the transit of the cell through its normal replication cycle.

Preliminary evidence suggested that the proteasome was involved in controlling apoptosis in chronic lymphocytic leukemia cells. Dr. McConkey and colleagues also found high proteasome levels in metastatic and nonmetastatic prostate cancer cells. Treatment with proteasome inhibitors induced high levels of apoptosis in both cell types, even in cells that were engineered to overexpress *bcl2* and should have been resistant to apoptosis.

Proteasome inhibitors are 100 to 1000 times more selective for the proteasome than for the next most common protein they attack. Dr. McConkey and others have shown that proteasome inhibitors can actually inhibit apoptosis in some normal cells, thus improving their survival.

"We have found that treatment of DiFi human colon cancer cells with C225 alone induces apoptosis ..."

– Zhen Fan, M.D., assistant professor, Department of Experimental Therapeutics

The clinical application of these findings is typical of M. D. Anderson collaborations that bring together scientists and clinicians.

"Fortuitously," said Dr. McConkey, "I was at a Grand Rounds where Professor of Pharmacology Robert A. Newman, M.D., described the proteasome inhibitors as a novel class of therapeutic agents that were among the most potent compounds seen in the National Cancer Institute's drug screening tests. This, combined with the activity we had seen against *bcl2* in tumors, suggested that proteasome inhibitors might have therapeutic potency. So, we met with ProScript, the company synthesizing the proteasome inhibitor PS-341."

This led Chairman Christopher J. Logothetis, M.D., and Assistant Professor Christos N. Papandreou, M.D., of the Department of Genitourinary Medical Oncology to organize the first clinical trial of PS-341 in patients with advanced prostate cancer. In this phase I trial, PS-341 is being administered on an outpatient basis by intravenous bolus once a week for four weeks. So far, 21 patients have received the drug.

"In a phase I trial, it's rare to see efficacy," said Dr. Papandreou. However, PS-341 has not only been well tolerated but has also appeared to reduce tumor size.

A research team led by M. D. Anderson President John Mendelsohn, M.D., is also examining apoptosis as a novel approach for cancer therapy. Dr. Mendelsohn and colleagues have pioneered the clinical use of the anti-epidermal growth factor receptor monoclonal antibody C225, which inhibits the proliferation of cancer cells. In the course of their studies, they have also linked C225 to apoptosis.

"We found that C225 induces apoptosis under certain conditions," said Zhen Fan, M.D., assistant professor in the Department of Experimental Therapeutics and a close collaborator with Dr. Mendelsohn on the C225 study. "C225 inhibits the proliferation of many cultured human cancer cells, and, when administered concurrently with chemotherapeutic agents, C225 can kill human tumor xenografts growing on mice."

These results have provided the impetus for ongoing phase II and III clinical trials of C225 combined with chemotherapy or radiation therapy in patients with cancers of the pancreas, colon, and head and neck.

"We have found that treatment of DiFi human colon cancer cells with C225 alone induces apoptosis, which is normally not seen unless C225 is combined with chemotherapy or radiation therapy," Dr. Fan said. "I want to know why these cells are so sensitive to C225 so that we can identify novel molecular targets for therapeutic interventions.

"To successfully treat cancer," he added, "inhibiting growth is not enough." ●

FOR MORE INFORMATION, *contact Dr. McConkey at (713) 792-8591, Dr. Papandreou at (713) 792-2830, or Dr. Fan at (713) 745-3560.*

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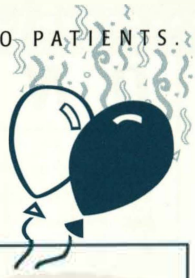
HOUSE•CALL

Make Cancer Prevention Part of Your New Year's Resolutions



Goodbye 1999, hello 2000! Like a clean slate, a new year offers a fresh start and the chance to make up for some of the mistakes and excesses of the previous year. With 1999 winding down and a new millennium approaching, now is the perfect time to consider some New Year's resolutions that can help reduce your chances of developing cancer and increase the odds of detecting cancer at an early, more treatable stage.

1. Get a physical examination.

If you haven't had a recent complete physical examination, make an appointment. The American Cancer Society recommends a cancer-related checkup every three years for persons between 20 and 40 years of age and yearly exams after age 40.

Don't forget to see your dentist regularly, too. Dentists, as well as physicians, find oral cancers.

2. Be sure you've had appropriate cancer screening tests.

Screening tests for specific cancers can detect disease early and save thousands of lives each year. Common tests include mammograms to check for breast cancer, PSA blood tests and digital rectal exams for prostate cancer, and Pap smears for cervical cancer. Ask your doctor what tests you should have this year.

3. Perform regular self-examinations.

Some cancers can be detected by self-examination. Women should perform monthly breast self-exams. Men should do a monthly testicular self-exam. All adults should check their skin regularly for signs of skin cancer. Ask your health professional for instructions and more information.

4. Quit smoking.

About one out of every three cancer deaths and 85% of lung cancers are linked to smoking. Cigarettes, snuff, and chewing tobacco can also cause cancers of the bladder, pancreas, mouth, and throat, as well as other lung diseases, heart disease, and stroke.

Spouses and children of smokers are also at increased risk of developing cancer, and young children of smokers are hospitalized more often for serious lung problems.

Remember, even if you've smoked heavily for years, quitting now can still help reduce your cancer risk.

5. Improve your diet.

About 35% of all cancers may be related to diet. To reduce your cancer risk, increase your consumption of fruits and vegetables (5 to 9 servings a day) and whole-grain foods (6 to 11 servings daily), and reduce your intake of meats and other high-fat foods. A low-fat, plant-based diet is your best protection against almost all cancers.

Also, watch your alcohol consumption. Although moderate alcohol consumption (a maximum of two drinks per day) has been shown to decrease the risk of coronary heart disease in middle-aged adults, drinking has been linked to breast, colon, and liver cancers. Smokers who drink have a greatly increased risk of head and neck cancer.

6. Exercise.

Moderate to vigorous exercise just three or four times a week can help reduce your cancer risk while making you look and feel better. Ask your physician about starting or restarting a regular exercise program.

7. Beware the burning sun.

Overexposure to sunlight can cause skin cancer, the most common—and most preventable—cancer of all. If possible, avoid the sun between 11 a.m. and 4 p.m., when the rays are strongest. If you must be out in the sun, cover up with clothing and sunglasses. Use an SPF 15 or higher sunscreen that protects against both UV-A and UV-B rays. Teach children to be sun-wise, too, and always shield babies from direct sunlight.

8. Don't procrastinate!

It can be hard to make lifestyle changes and all too easy to put off taking greater control of our health. Resolve to prevent cancer today and take the first step toward enjoying better health for many years to come. ●

For more information, contact your physician or contact the M. D. Anderson Information Line:

(800) 392-1611 *within the United States, or*

(713) 792-6161 *in Houston and outside the United States.*

December 1999

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Ushering in New Technologies:
Medical Physicists Focus on IMRT, Ultrasound-Guided Brachytherapy

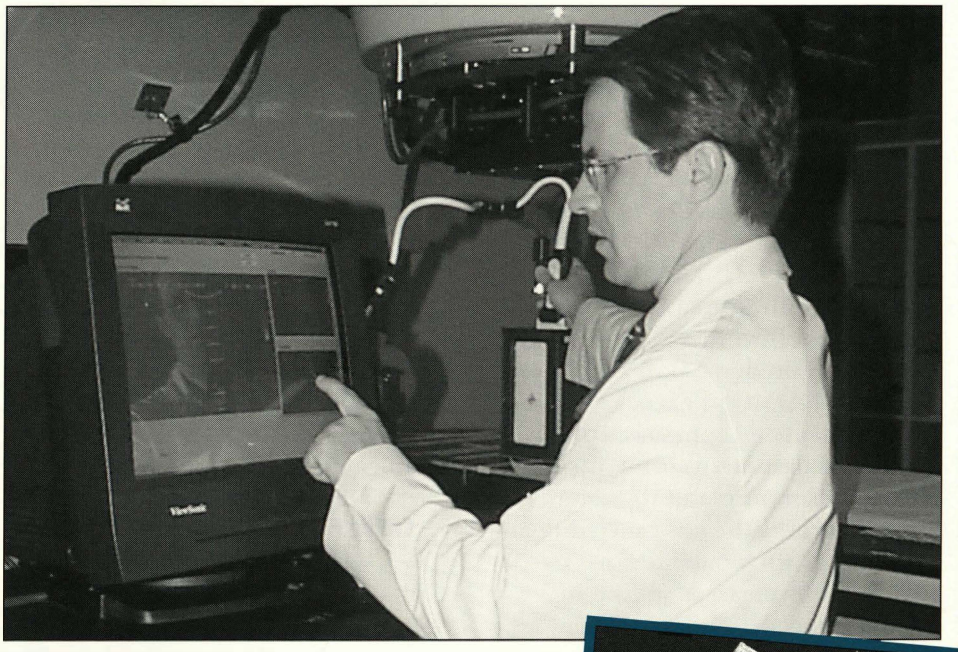
by Dawn Chalaire

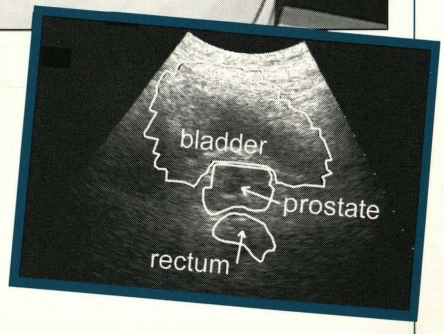
There is a saying among those in the scientific community that if you want a simple answer, don't ask a medical physicist. On the other hand, if there is a tough problem to solve, you will do well to have a physicist on your team.

"The one unique thing about physicists in general is that people who study physics are taught how to solve highly technical problems in innovative and practical ways," said Kenneth R. Hogstrom, Ph.D., chairman of the Department of Radiation Physics, Division of Radiation Oncology, at The University of Texas M. D. Anderson Cancer Center. "Physics teaches you how to reason."

For the most part, modern radiation therapy and diagnostic imaging owe their existence and development to the thoughts of physicists. Basic principles underlying the x-ray tube, computerized tomography, magnetic resonance imaging, gamma-ray imaging, and positron emission tomography were all discovered and developed into diagnostic medical devices by physicists and medical physicists. Similarly, radioactivity, X rays, the cobalt 60 machine, the side-coupled electron linear accelerator, and heavy-particle accelerators used in radiation therapy were all discovered and developed into therapeutic medical devices by physicists and medical physicists.

Today, with the advent of faster, more powerful computers, medical physicists in radiation oncology are focusing their minds on more precise treatment planning and conformal methods of treatment delivery.





John Antolak, Ph.D., *an assistant professor in the Department of Radiation Physics, calibrates the positioning of the NOMOS BAT ultrasound probe to prepare it for use. Ultrasound scans (right) of the prostate and surrounding organs, using the NOMOS BAT, are taken before each treatment to account for any day-to-day changes in position of the prostate during a course of intensity-modulated radiation therapy (IMRT).*

"In my opinion, the field is undergoing a significant transition," Dr. Hogstrom said. "We're changing to conformal therapy—shaping or conforming the radiation dosage to the treatment volume that the radiation oncologist specifies while delivering a smaller dose to nearby normal tissues. Advancements in technology are allowing us to do this in ways that do not require an excessive amount of time for treatment planning or delivery."

Targeting prostate cancer with precise treatment delivery

A significant number of recent advances in radiation oncology at M. D. Anderson have centered around treatment of prostate cancer. According to Dr. Hogstrom, this is due in part to the large population of patients with prostate cancer—the most common cancer among men—and the increasing sophistication of these patients, who are demanding more cutting-edge treatments that have fewer side effects. Among the arsenal of irradiation tools at M. D. Anderson designed to combat prostate cancer is intensity-modulated radiation therapy (IMRT), which uses beams of varying intensity within a collimated field to deliver a prescribed dose to the tumor while providing maximum sparing to the adjoining rectum and bladder, thereby minimizing the side effects of the treatment.

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Medical Physicists Usher in New Technologies

(Continued from **page 5***)*

IMRT is typically delivered daily over a period of about 3 1/2 weeks if used in conjunction with non-intensity modulated conformal therapy or about 8 to 9 weeks if used alone. To ensure that the prostate is targeted accurately each day, variations in its daily position must be taken into account. The NOMOS BAT, an ultrasound localization device, can be used before treatment each day to determine changes in the location of the prostate as small as 1 mm from its reference position.

Professor of Radiation Physics Isaac Rosen, Ph.D., and Assistant Professor John Antolak, Ph.D., led the physics effort that resulted in the clinical implementation of IMRT using the NOMOS Peacock system. Presently, medical physicists plan individual treatments using the NOMOS Corvus planning system and then verify the customized beam delivery for each patient prior to treatment by measuring dose in a water-equivalent phantom that simulates the patient's body. In early 2000, Dr. Hogstrom said, IMRT using dynamic multileaf collimation (DMLC) on a Varian linear accelerator will be available. Medical physicists are currently performing dose measurements and developing procedures for use of the DMLC.

An alternative to IMRT for patients with prostate cancer is ultrasound-guided iodine 125 brachytherapy, in which multiple radioactive iodine 125 seeds are implanted into the prostate, using ultrasound to guide their placement. For this procedure, the medical physicist devises a treatment plan that meets the radiation oncologist's dose prescription, orders the radioactive seeds, ensures seed integrity and proper source strength on receipt, assists the physician in the implant, calculates the dose distribution, and ensures the safety of the procedure.

Professor of Radiation Oncology Alan Pollack, M.D., Ph.D., and Assistant Professor Lewis Smith, M.D., are leading a phase III randomized study that compares IMRT boost to iodine 125 implant boost for patients with intermediate- to high-risk adenocarcinoma of the prostate.

Calibrating treatment equipment to ensure accurate dosing

Before advances in technology can translate into improved patient outcomes, Dr. Hogstrom said, institutions that offer the procedures must have two things: strong medical physics support and physicians who are experienced in utilizing the procedures. With new technologies come more challenges for medical physicists because new equipment and techniques introduce a greater chance for errors. Perhaps the most important thing that medical physicists do to ensure accuracy is to calibrate treatment machines and verify treatment procedures to make sure that the proper dose of radiation is delivered to the patient.

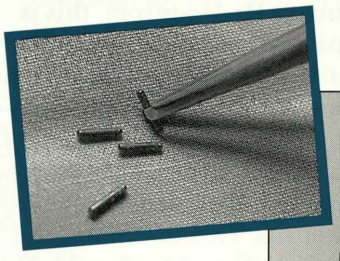
"When delivering radiation treatments, we try to achieve a dose accuracy of 5%," Dr. Hogstrom said, "so the machine delivering the dose should be calibrated to within 2%. That is the most important thing, to make sure the machine is delivering its dose properly."

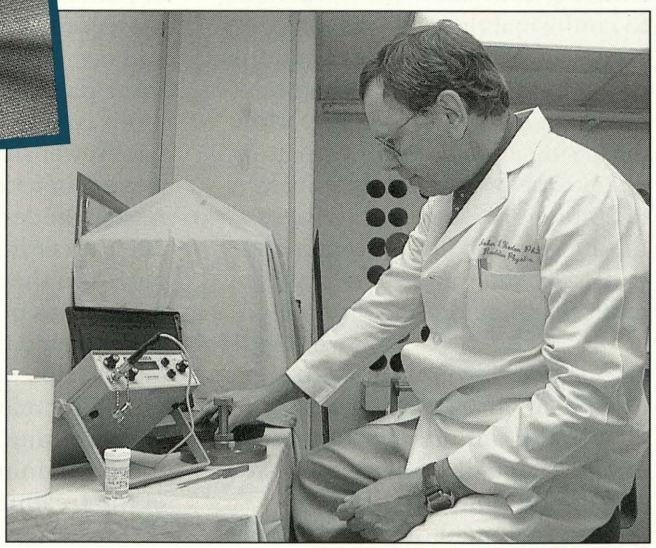
The medical physicists in the Radiological Physics Center (RPC), under the direction of William F. Hanson, Ph.D., chief of the Outreach Physics Section, are responsible for performing quality assurance checks at the participating institutions and reviewing the charts of patients entered into National Cancer Institute (NCI) clinical trials of radiation therapy. Funded by a National Institutes of Health grant for over 30 years, the RPC, which is overseen by the American Association of Physicists in Medicine (AAPM) and whose home base is M. D. Anderson, monitors about 1,300 institutions, including M. D. Anderson, in the United States, Canada, and several other countries.

"Their job is to make sure that the dose delivered by Institution A is the same dose delivered by Institution B for the NCI-sponsored clinical trials," Dr. Hogstrom said.

Ionization chambers, which are used to calibrate treatment machines, must also be calibrated regularly. M. D. Anderson has one of only four AAPM accredited dosimetry calibration laboratories in the United States. Instruments are sent from all over the country to be calibrated against equipment that has, in turn, been calibrated by the National Institute of Standards and Technology.

Under the supervision of Associate Professor of Radiation Physics Marilyn Stovall, Ph.D., the Department of Radiation Physics also offers radiation dosimetry services to institutions that do not have the facilities to measure doses for special circumstances. Dosimeters are sent to the institutions, exposed to radiation,





John Horton, Ph.D., *an associate professor in the Department of Radiation Physics, calibrates iodine 125 seeds before an ultrasound-guided brachytherapy prostate implant. The iodine 125 seeds (above) used for prostate brachytherapy implants are 4.5 mm long.*

Answering the Who, What, and How of Medical Physics

What is medical physics?

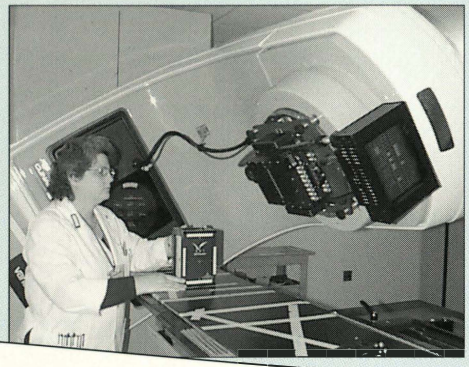
Medical physics is the application of concepts and methods of physics to the diagnosis and treatment of human disease. Medical physics essentially began with the discovery of the X ray and radioactivity by physicists Wilhelm Roentgen in 1895 and Antoine Henri Becquerel in 1896, followed by Marie and Pierre Curie's discovery of the radioactive elements of radium and polonium. Soon after, ionizing radiation began to be used to diagnose and treat disease.

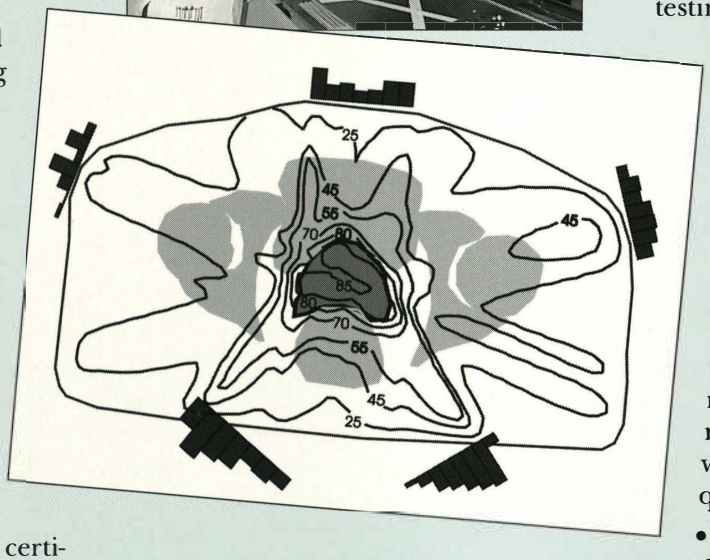
Who are medical physicists?

Most medical physicists have an advanced degree in medical physics, physics, or a related field. All have a sound knowledge of physics and medical physics and clinical training in medical physics.

What credentials do medical physicists have?

Medical physicists must be certified by a national board, typically the American Board of Radiology or the American Board of Medical Physics. Most medical physicists are certified in one of three primary disciplines: **1)** radiation therapy physics, **2)** diagnostic imaging physics, or **3)** nuclear medicine physics. Other specialties include magnetic resonance imaging physics, medical health physics, and hyperthermia physics.





Medical physicist **Laura O'Neill, M.S.**, *(top) verifies beam delivery prior to a course of IMRT treatments by measuring the dose in a treatment delivery verification phantom, which is used to simulate patient anatomy.*

The individualized treatment plan (bottom) shows the dose distribution achieved using IMRT. Note how closely the prescribed dosage (80 Gy) conforms to the prostate volume, which is shown in dark gray.

How do medical physicists practice their profession?

- Medical physicists are responsible for the safe and optimal utilization of radiological equipment and other physical tools used by physicians to diagnose and treat human disease. Medical physicists **1)** develop specifications for equipment; **2)** perform acceptance testing to ensure that the equipment operates properly; **3)** ensure that the installation site is safe for the patient, the workers, and the public; and **4)** determine how the equipment will be used and commission it.
  - Once the equipment is installed and commissioned, the medical physicists are responsible for overseeing maintenance of the equipment and conducting daily, weekly, monthly, and annual quality assurance checks.
  - Medical physicists develop class solutions to treatment problems by developing new equipment or new methods of using existing equipment.
- Medical physicists assist physicians in planning specific treatments or diagnostic tests for individual patients. As part of that process, medical physicists are responsible for daily and weekly checking of radiation oncology patients' charts. ●

and mailed back to M. D. Anderson where the calibration is checked to ensure that the correct dosage is being delivered. This service is also used to check other medical devices such as blood irradiators.

Meeting the demands of new technologies

The role of medical physicists becomes more important as technology changes. In the early stages of technological development, equipment that must be able to work together is often made by different manufacturers and not fully integrated. Medical physicists are responsible for, among other things, configuring the new equipment so that the different parts are able to function together. Because the medical physicists must learn how to use the new technology first, it usually falls to them to teach the radiation therapists, medical dosimetrists, and radiation oncologists about the benefits and limitations of the new technology.

"Within 10 years," Dr. Hogstrom said, "IMRT will become standardized, but for now, its proper use requires considerable effort by the medical physicist. As soon as one technology becomes standardized, then there's usually some other new technology that comes along. For instance, we are presently studying the feasibility of offering proton therapy, which, if implemented, will be the next major challenge for our medical physicists." ●

For more information, *contact Dr. Hogstrom at (713) 792-3216 or Dr. Pollack at (713) 792-0781.*

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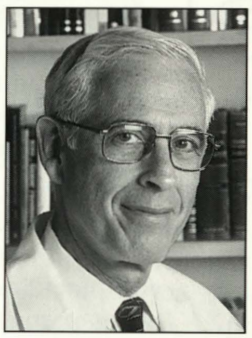
Building Better Patient Care on the Foundation of Scientific Research

John Mendelsohn, M.D.
President, Professor of Clinical Investigation



Today, at the start of a new millennium, we are all reaping the benefits of laboratory investigations that began decades ago in molecular biology, biochemistry, genetics, and immunology. The painstaking research of scientists throughout the world has brought us much closer to understanding what causes cancer and to developing more effective methods for treating this constellation of diseases.

From personal experience, I can help illustrate how laboratory research and medical care are intertwined. In 1983, my colleague Dr. Gordon Sato and I first demonstrated that blocking critical growth-promoting signals with monoclonal antibodies could prevent cancer cell proliferation. This research grew out of understanding that small molecules, called growth factors, trigger cell growth and division by binding to specific receptors on the cell surface and activating signals inside the cell.

Our group produced monoclonal antibodies that could attach tightly to epidermal growth factor (EGF) receptors and prevent activation of the growth-signaling pathway necessary for cancer development. We showed that treatment with anti-EGF receptor monoclonal antibodies could inhibit the growth of human tumor cell xenografts transplanted into athymic (nude) mice. These findings offered a new approach to cancer therapy and helped spur intensive research to discover inhibitors of growth factor receptors.

The receptor blockade concept has also led to development of the antibody Herceptin, which can impede proliferation of human cancer cells expressing the HER2 receptor. Clinical trials have shown that Herceptin is useful when given with chemotherapy for advanced breast cancer.

The anti-EGF receptor monoclonal antibody, now called C225, has demonstrated in ongoing clinical trials that when combined with either radiation or chemotherapy, it is effective against advanced head and neck cancer. Within a few years, I believe that receptor blockage therapy will add a new armamentarium to existing treatments for many cancers.

Research into the basic mechanisms of cancer and new forms of detection and treatment are the building blocks of outstanding patient care. As we move into a new millennium, we are in the midst of an explosion—ignited by basic research—of scientific discoveries that will light the way to even more clinical progress in the years ahead.

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