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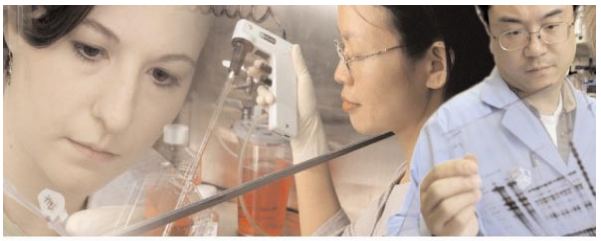
Panel Calls for Increased Emphasis on Translational Research

The President's Cancer Panel (PCP) released a new report last week calling for some far-reaching changes aimed at improving the translation of cancer research findings into new interventions and the delivery of those interventions to health care providers and patients.

The report includes 20 recommendations and identifies groups and organizations that should be involved in their development and implementation. The recommendations call for new ways to address patent and intellectual property issues that often prevent research on promising compounds or combinations of licensed drugs, increased support for the dissemination of information about and adoption of new interventions, and increased funding for team science and systemic changes that promote careers in translational research.



The latter issue was raised "over and over again" during the four hearings the PCP held on translational research, said the Panel's chairman, Dr. LaSalle

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Director's Update

A New Generation of Researchers for a New Kind of Research

Last week, while attending some events on the National Institutes of Health (NIH) campus, I saw the past, present, and future of cancer research. At the General Motors Cancer Research Annual Scientific Conference, I had the opportunity to hear talks by Nobel laureates and other icons of science about our remarkable progress against breast cancer and where research on prevention, diagnosis, and treatment of breast cancer is headed.

A short while later, I met with 250 National Cancer Institute (NCI) summer interns—some of the best, brightest, and most enthusiastic high school, college, and medical school students in the country. They can be the leaders, I told them, who will take us to an unbelievable destination.

And finally, I spoke at a meeting of leaders from academic medical centers, comprehensive cancer centers, and others who have established exciting programs aimed at turning out a new generation of translational cancer researchers—researchers who have a knowledge and expertise that spans from the bench to the bedside, and even to computational sciences, engineering, and mathematics.

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Leffall, Jr. These aren't empty sentiments, Dr. Leffall told attendees last week at a conference on translational research training programs jointly sponsored by NCI and the Howard Hughes Medical Institute. "The team science concept is permeating many institutions," he added.

Changes such as revamping the reward systems at academic medical centers, allowances by funding agencies for co-principal investigators, and allocating more resources to translational research all could make the research climate more amenable to team science, Dr. Leffall said.

NCI Director Dr. Andrew C. von Eschenbach noted that NCI has been working with NIH leadership to establish a co-principal investigator mechanism. "It's a work in progress," he said.

More than 80 people—clinical investigators, advocates, health insurance representatives, and many other stakeholders—testified during the PCP hearings. The testimony was the basis for the PCP's report, *Translating Research into Care: Delivering on the Promise*. Other recommendations from the report include:

- The formation of a task force to examine modifying the existing rewards system for academic researchers to encourage collaborative research
- Increased funding by NCI for activities aimed at dissemination and adoption of cancer research advances, especially through NCI-designated Comprehensive Cancer Centers
- Research sponsors requiring early community participation in designing clinical trial protocols and implementing research findings
- Designating all new biologics and cancer chemoprevention and chemotherapy drugs as "orphan drugs"

The latter recommendation is aimed at kick-starting what has been a significant lag in the development and approval of new cancer drugs. Under the Orphan Drug Act, drugs for diseases that have fewer than 200,000 cases—which would include many cancer drugs—can be given an "orphan" designation, which provides additional benefits to the drugs' manufacturers, such as an extended period of exclusive marketing rights, tax credits, and grants to defray clinical trial costs.

The PCP called for an evaluation in 5 years of how effective programs and initiatives have been at accelerating "the translation of basic science discoveries into improved cancer prevention and care."

The report is available at http://pcp.cancer.gov. ◆

(Director's Update continued from page 1)

This particular meeting, sponsored by NCI and the Howard Hughes Medical Institute (HHMI), sparked important discussions about the need for and how best to develop a robust cadre of translational researchers. Dr. Philip Pizzo, dean of the Stanford University School of Medicine, talked about the intriguing approach his institution is taking. Stanford, in fact, has retooled its program, embracing the importance of translational medicine by intertwining clinical medicine and basic science. HHMI's Dr. William Galey told attendees about a new training program called the Interfaces Initiative, a partnership between HHMI and the National Institute of Biomedical Imaging and Bioengineering that marries biomedical sciences with the physical sciences, as well as the computational, engineering, and mathematical disciplines.

NCI has a firm commitment to translational research. Thanks to the work of the NCI-FDA Task Force, for example, earlier this year the NCI-FDA Research and Regulatory Review Fellowship program was established. This program will train researchers to master the drug development process—from scientific discovery to regulatory review—and shepherd new interventions to market. Other programs, such as the NCI Paul Calabresi Award for Clinical Oncology, are supporting institutions' efforts to build vital new bridges between clinical and basic researchers.

At the recent National Cancer Advisory Board meeting, I announced the formation of the Translational Research Working Group (TRWG). Following the excellent example set by the Clinical Trials Working Group, the TRWG will review NCI's translational research portfolio and provide a blueprint for how best to harness our resources and advance translational research as quickly and efficiently as possible.

Dr. Ernie Hawk, who will chair the TRWG, reminded attendees at the NCI/HHMI meeting of a quote from Louis Pasteur: "There are not two sciences. There is science and the application of science, and these two are linked as the fruit is to the tree."

The way we conduct research is changing rapidly. Delivery, which is the ultimate translation of discoveries made in the lab, is fast becoming an important discovery platform. With that in mind, Pasteur's quote reinforces for all of us that our research is incomplete if we fail to apply what we learn and that, in applying what we learn, we inform discovery anew.◆

Dr. Andrew C. von Eschenbach
Director, National Cancer Institute

Spotlight

Moving Health Records into the Electronic Age

Some oncologists at Dana-Farber Cancer Institute have a hypothesis: Patients will more accurately report the ill effects of treatment if they can do it in real time. To test this hypothesis, beginning this September, some patients will use their home Internet connections to record instances of nausea, fatigue, and other treatment-related symptoms into their individual Dana-Farber electronic medical record (EMR).

"We need to know the true toxicity of the treatments we're delivering if we want to do a better job of controlling it," says Dr. Lawrence Shulman, the cancer center's chief medical officer.

Dana-Farber is just one of many large health care systems that have developed their own EMR systems and are finding innovative uses for them. Now the U.S. Department of Health and Human Services (HHS) is trying to make sure that all Americans have their own electronic health records by 2015.

HHS Secretary Michael Leavitt announced the effort earlier this month. Much like an ATM card can be used at nearly any ATM machine across the country, the EMRs would be accessible, with the appropriate security measures, at any medical facility. Their development will be driven by a national public-private sector collaboration that establishes essential items such as data standards, IT structure, and privacy and security policies, Sec. Leavitt said.

While the data on the potential impact of EMRs are limited, many health care experts believe their widespread use can improve care and save money. The latter is no trivial matter. Current estimates put the annual U.S. health care costs at approximately $1.8 trillion, more than 15 percent of the nation's gross domestic product.

caBIG and EMRs

NCI has taken several steps to ensure that the cancer Biomedical Informatics Grid (caBIG) will be compatible with an eventual national electronic health record. caBIG has been an "early adopter" of standards identified by HHS as essential for interoperability, and NCI works closely with the HHS Office of the National Coordinator for Health Information Technology to be sure caBIG remains aligned with emerging efforts.

The EMR used at the University of Texas M.D. Anderson Cancer Center, dubbed ClinicStation, was launched in 2001, primarily to provide the cancer center's clinicians with easy access to the millions of clinical images produced during the standard course of care and research. Over time, though, it has morphed into an internally developed EMR to address the complexity of research-driven patient care.

"All clinical data are now reviewed through ClinicStation," explains Dr. Kevin W. McEnery, associate division head for Informatics at M.D. Anderson. "There is no paper chart. If somebody wants to review a patient's clinical data or clinical notes, they review it through ClinicStation."

The system is available on more than 7,000 desktops at the institution, and about 6,500 caregivers use ClinicStation. In May, there were almost 60 million transactions on the system. More than 1 million imaging studies and 100 million individual images dating back to November 2000 can be instantly accessed through the system.

Although no formal study has been done, officials at M.D. Anderson estimate ClinicStation will save the institution anywhere from $8 million to $30 million by the end of the decade. They also believe the system has improved the quality of care.

"Patients at M.D. Anderson all receive multidisciplinary care, where routinely several physicians are involved in the management of a patient's care plan at the same time," Dr. McEnery says. "With ClinicStation, these physicians can efficiently collaborate in a patient's care because they have simultaneous access to the same information."

Dana-Farber shares its EMR with its seven sister institutions, including Brigham and Women's Hospital and Partners HealthCare system. In addition to information including patients' laboratory data, pathology and radiology results, medications used, and office notes, the EMR also includes oncology-specific modules, such as infusion flow sheets for chemotherapy and blood products.

"Every bit of data on a patient in any of our institutions is collated in reverse chronological order," Dr. Shulman says. "For us, it's very important, because many patients often go back and forth between the different institutions."

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Cancer Research Highlights

Assembling the Puzzle Pieces of Breast Cancer at GM Conference

At the General Motors Cancer Research Foundation 2005 Annual Scientific Conference at NIH last week, keynote speaker Dr. Larry Norton of Memorial Sloan-Kettering Cancer Center framed breast cancer as a puzzle and told participants that "we're beginning to assemble the pieces of that puzzle in molecular terms into a picture that can guide clinicians." Conference sessions illustrated his metaphor.

One puzzle piece has to do with the different ways in which cancer cells operate. Sessions on how *BRCA2* suppresses cell growth and how *CHK2* mutations impede DNA repair illustrated the contributions of genetics and cell biology.

A second puzzle piece looks at how mammary epithelial cells interact in a particular biological microenvironment. The extracellular matrix can destabilize the genome, cause local tissue changes, and alter gene expression, cell growth and death, and drug resistance.

The third puzzle piece involves tumor behavior. Oncogenes provide only part of the answer, with a number of other regulatory molecules now under study. Tissue-specific cancer stem cells, for example, may drive a central aspect of tumor growth.

Puzzle piece four is cancer at the patient and population levels. While crucial, the genomic mechanisms of breast cancer do not capture the profound influences of the environment, nor do they reflect the experience over the life spans of women facing cancer.

Effective treatments provide the final piece of the puzzle model of clinical oncology. Herceptin (trastuzumab) shows how years of work at the molecular and genetic levels built a successful targeted therapy for a specific population. Gene expression profiling and similar approaches also allow phased treatment strategies to track progress and improve prognosis.

Gefitinib Use Restricted by New Label

The Food and Drug Administration (FDA) has approved new labeling for gefitinib (Iressa) that will restrict use to lung cancer patients who are currently taking the tablets or who have previously benefited from the treatment in the judgments of their doctors.

New patients with non-small-cell lung cancer (NSCLC) will not receive the drug unless they are participants in clinical trials that were approved by an Institutional Review Board prior to June 17, 2005, the day the FDA and the drug's manufacturer, AstraZeneca PLC, announced the label change.

The FDA's decision was based on a review of data from two trials in which gefitinib did not help lung cancer patients live longer. The agency noted that patients with NSCLC have other treatment options. Even before the announcement, many doctors were prescribing erlotinib (Tarceva) for patients with NSCLC.

Gefitinib was approved for use in NSCLC in May 2003 through the agency's early approval mechanism. The approval was based on the drug's ability to shrink tumors in about 10 percent of patients and was contingent on follow-up studies.

One of the follow-up trials, which included nearly 1,700 patients who had failed one or two previous treatment regimens, found no significant survival benefit in the overall study population. Nor did patients with high levels of epidermal growth factor receptor (EGFR), the protein targeted by gefitinib, benefit significantly.

As of September 15, 2005, patients will receive gefitinib through a single mail-order pharmacy. Approximately 4,000 patients are currently taking gefitinib in the United States. The FDA is not considering withdrawing gefitinib from the market at this time.

Colorectal Cancer Risk Increased by Red and Processed Meat Diet

High levels of consumption of red and processed meat are associated with an increased risk of colorectal cancer, while high levels of fish consumption are associated with a decreased risk of the disease, according to a new European study published in the June 15 *Journal of the National Cancer Institute*.

Drs. Elio Riboli and Teresa Norat of the International Agency for Research on Cancer in Lyon, France, and their colleagues used data from the European Prospective Investigation into Cancer and Nutrition (EPIC), a cohort of 478,000 Western Europeans enrolled between 1992 and 1998.

At a mean follow-up of 4.8 years, 1,329 cases of colorectal cancer were diagnosed. Within the EPIC population, the risk of developing colorectal cancer over a 10-year period was 1.71 percent for subjects in the highest category of red and processed meat consumption (more than 160 grams daily) compared with 1.28 percent for those in the lowest category (less than 20 grams daily).

Among subjects in the highest category of fish consumption (more than 80 grams daily), the risk of developing colorectal cancer over a 10-year period was 1.28 percent compared with 1.86 percent among those in the lowest category (less than 20 grams daily). The researchers found no association between poultry consumption and colorectal cancer risk.

Although the findings confirm previous studies, "the results reported here are from one of the largest cohorts of men and women that has been developed specifically to examine the relationship between diet and cancer," the researchers note.

Thyroid Cancer Risk Related to Radiotherapy for Childhood Cancer

Radiotherapy used to treat childhood cancers may contribute to survivors developing subsequent thyroid cancer, say researchers from NCI's Division of Cancer Epidemiology and Genetics (DCEG) in the June 11 *Lancet*. Chemotherapy given for the original cancer had no impact on later thyroid cancer risk, nor did it modify the risk found from radiotherapy.

The Childhood Cancer Survivor Study is a cohort of more than 14,000 individuals who were diagnosed with cancer between 1970 and 1986 and survived at least 5 years following diagnosis.

By correlating the dose of cumulative radiation received with the occurrence of secondary thyroid cancer, the researchers found evidence for decline in risk at high doses that earlier studies could not. The risk varies with the radiation that the researchers calculated was absorbed by the patient's thyroid gland at the time of original treatment. From 1 Gy up to 20 Gy, the risk increases, peaking between 20 and 29 Gy. Above 30 Gy and up to 50 Gy the risk decreases, "consistent with a cell-killing effect at high doses," said the authors. The study results do not have implications for clinical treatment decisions with regard to childhood cancers because other serious late effects of radiotherapy and chemotherapy do show increasing risk with increasing doses.

"Childhood cancer survivors with a history of radiation exposure to the chest, neck, or head should be considered at risk for thyroid cancer and these patients should have yearly thyroid and neck examinations," the authors said.

This nested case-control study, led by Dr. Alice J. Sigurdson from the Radiation Epidemiology Branch of DCEG, identified 72 children who were under 21 years of age when they were diagnosed with a childhood cancer, had survived more than 5 years, and later developed thyroid cancer. For each patient, a set of four controls with healthy, intact thyroid glands were matched by gender, approximate age of first cancer diagnosis, and follow-up interval.

In an editorial, Dr. Judith Kingston of the Royal London Hospital said the study clearly showed "that the thyroid gland in younger children is more susceptible to the oncogenic effects of radiation than in older children."

Erlotinib Effective Against Some Brain Tumors

A report in the June 15 *Journal of the National Cancer Institute* provides the first hints of how to identify brain tumor patients who will respond to the drug erlotinib (Tarceva), originally developed for lung cancer.

In lung cancer, researchers are finding that patients who respond to the drug have a specific molecular signature. The current study examined similar signatures in glioblastomas.

Drs. Daphne A. Haas-Kogan and David Stokoe of the University of California, San Francisco, and colleagues studied tissue samples from 41 participants in a phase I trial of erlotinib for glioblastoma. They wanted to know if levels of the protein biomarker, epidermal growth factor receptor (EGFR), could predict which patients would respond. Erlotinib is a small molecule that targets that specific protein.

Eight of the 41 glioma patients responded to erlotinib treatment. The researchers report that response was predicted by high levels of EGFR and low levels of a related enzyme, PKB/Akt. None of the 22 patients whose tumors had high levels of phosphorylated PKB/Akt responded to erlotinib, whereas 8 of the 18 patients with low levels of phosphorylated PKB/Akt did respond. The researchers plan to use these results in the design of a phase II trial.

"Future trials of EGFR inhibitors should build on our current findings and, with prospective molecular profiling, should establish the most appropriate agent(s) for each individual patient. Clearly, in clinical trials testing signaling inhibitors, selection of patients with appropriate molecular characteristics will not only help to assess the true efficacy of specific novel agents but will also maximize benefits to individual patients," the authors wrote.◆

(Spotlight continued from page 3)

As the Dana-Farber toxicity study illustrates, EMRs have potentially broad research applications. The NCI-funded Cancer Research Network (CRN), a coalition of 11 managed care systems that collectively has more than 10 million enrollees, is already using EMRs to perform several studies.

CRN investigators recently used EMRs to examine the relationship between screening practices and late-stage diagnoses of breast and cervical cancers in CRN systems. More than half of late-stage cervical cancer diagnoses, they found, were attributable to failure to undergo screening in the 3 years before diagnosis. Women in specific subgroups had a greater likelihood of falling into this category. The participating managed care systems are now designing interventions to increase screening among plan members from those subgroups, explained Dr. Edward Wagner of the Center for Health Studies at the Group Health Cooperative in Seattle during a recent presentation on the CRN to NCI's National Cancer Advisory Board. In another CRN study, EMRs are being used to provide individualized feedback to primary care physicians on their provision of smoking cessation services.

If the goal of a secure but easily accessible EMR for every American can be achieved, that will mean big things for cancer research and care, according to Dr. McEnery.

Among other things, when patients travel to a tertiary care center, it would eliminate the hours spent reviewing outside paper records for information. In addition, he adds, because everything about patients' treatment at the cancer center would be captured in their records, "patients will experience more efficient care in their own hometown from their own provider." ◆

Featured Clinical Trial

Vaccine to Prevent Cervical Cancer

Name of the Trial

Phase II Randomized Study of SGN-00101 Vaccine in Human Papillomavirus-16-Positive Patients with Atypical Squamous Cells of Undetermined Significance or Low-Grade Squamous Intraepithelial Lesions of the Cervix (UCIRVINE-02-55). See the protocol summary at http://cancer.gov/clinicaltrials/UCIRVINE-02-55.

Dr. Bradley J. Monk and Dr. Dorothy J. Wiley.

Principal Investigators

Dr. Bradley J. Monk, University of California, Irvine, and Dr. Dorothy J. Wiley, University of California, Los Angeles

Why Is This Trial Important?

Human papillomavirus (HPV) infection is common among women throughout the world. It is responsible for nearly all cervical cancers and most cell changes associated with low- and high-grade Pap test abnormalities.

Some types of HPV are associated with cervical cancer more often than others; for example, HPV-Type 16 (HPV-16) is found in half of cervical cancers worldwide. However, the vast majority of women infected with HPV-16 will never develop cervical cancer and will clear their infections spontaneously because of immune responses to the virus. Nonetheless, developing therapeutic interventions for viral infections associated with low-grade cellular changes may allow us to block the effects of HPV long before a precancerous change or a malignancy develops.

In this study, researchers are testing a vaccine in women infected with HPV-16 who have LSIL or ASCUS Pap test results. The goal is to determine whether women who receive the study vaccine clear their infections and resolve their low-grade Pap test abnormalities more often than women who receive placebo (sterile water).

"Some women with HPV infections develop cancer because they don't seem to develop an appropriate immune response to the cancer-causing components of HPV," said Dr. Wiley. "We hope that this vaccine will help women develop that immune response."

Who Can Join This Trial?

Researchers seek to enroll approximately 140 patients aged 18 to 50 who have Pap tests showing ASCUS or LSIL. See the list of eligibility criteria at http://cancer.gov/clinicaltrials/UCIRVINE-02-55.

Where Is This Trial Taking Place?

The study is being conducted at the Chao Family Comprehensive Cancer Center at UC-Irvine and at UCLA's Jonsson Comprehensive Cancer Center.

Contact Information

See the list of study contacts at http://cancer.gov/UCIRVINE-02-55 or contact the NCI Cancer Information Service at 1-800-4-CANCER (1-800-422-6237). The toll-free call is confidential. ◆

An archive of "Featured Clinical Trial" columns is available at http://cancer.gov/clinicaltrials/ft-all-featured-trials.

Notes

RAPID Program Welcomes Inquiries

NCI encourages applications to the ongoing Rapid Access to Preventive Intervention Development (RAPID) initiative. RAPID makes the contract resources from NCI's Division of Cancer Prevention available to academic and academically affiliated investigators for preclinical and early clinical drug development.

RAPID's goal is to promote the swift movement of novel molecules and compounds from the laboratory to the clinic for phase I and II clinical trials of efficacy. RAPID will assist investigators who submit successful requests by providing some or all of the preclinical and phase I clinical developmental requirements for phase II clinical efficacy trials. These include, for example, preclinical pharmacology, toxicology, and animal model efficacy studies. Suitable types of agents for RAPID may range from single chemical or biological entities to defined complex mixtures with the potential to prevent, reverse, or delay carcinogenesis. For more detailed information, go to http://cancer.gov/prevention/RAPID.

Instructions for requesting RAPID resources are described on the Web site. Written requests will be evaluated by a specially constituted RAPID panel, consisting of outside experts from academia and industry. Requests must be received on or before Nov. 1, 2005. Pre-application inquiries to clarify issues are encouraged. Please contact RAPID Program Official Izet Kapetanovic, 301-435-5011; e-mail: kapetani@mail.nih.gov or 301-594-0459; e-mail: jc94h@nih.gov.

Clauser Named Outcomes Research Chief

Dr. Steven Clauser has accepted the position of chief of NCI's Outcomes Research Branch (ORB) in the Applied Research Program of NCI's Division of Cancer Control and Population Sciences. ORB coordinates and sponsors research to measure, evaluate, and improve the outcomes of cancer care. Dr. Clauser joined NCI in 2002 to develop research related to cancer care outcomes measurement and quality of care. His primary research interests are quality-of-care performance measurement and improvement, assessment of patient-reported outcomes, and factors that influence the use of evidence-based medicine in health delivery. Previously, Dr. Clauser held several senior policy research positions within the Centers for Medicare & Medicaid Services. He serves on several national advisory committees on performance measurement, and has published more than 20 peer-reviewed papers and book chapters.

Nanoparticles Transport Drug to Tumor Cells in Mice

Research suggesting that attaching anticancer drugs to dendrimers for targeted delivery to tumor cells could increase the therapeutic response has now been confirmed in an animal model of cancer by researchers at the University of Michigan. "This is the first study to demonstrate a nanoparticle-targeted drug actually leaving the bloodstream, being concentrated in cancer cells, and having a biological effect on the animal's tumor," said Dr. James Baker, Jr., who directed the study, which was published in the June 15 *Cancer Research*. Additional information about this NCI-supported study can be found at http://nano.cancer.gov/.

Immunology Conference Set for September

NCI's Center for Cancer Research (CCR) will sponsor a national meeting Sept. 22–23, in the Masur Auditorium in the NIH Clinical Center on "Translational Immunology Related to Cancer." This meeting will host the leaders in the field of cancer immunotherapy, and will also serve to highlight CCR's Center of Excellence in Immunology. This conference will focus on novel immunotherapy strategies for the prevention and/or treatment of a range of human cancers. Topics will include the innovative uses of monoclonal antibodies, cytokines, cell-based therapies, vaccines, and transplantation in the prevention and therapy of human cancers. There is no registration fee and all investigators working in this field are encouraged to register at http://web.ncifcrf.gov/events/tirc/ and submit abstracts by July 30 for poster presentations. The Web site also contains the list of sessions and speakers. NCI Director Dr. Andrew C. von Eschenbach and CCR Director Dr. Robert Wiltrout will present introductory remarks highlighting the importance of this meeting. Please contact Carlei O'Neal at carleioneal@adelphia.net or 301-846-6333 for additional information. ◆

A Conversation with Dr. Larry Norton

Dr. Larry Norton is deputy physician-in-chief for Breast Cancer Programs at Memorial Hospital and medical director of the Evelyn H. Lauder Breast Center at Memorial Sloan-Kettering Cancer Center. He delivered the keynote address at the General Motors Cancer Research Foundation 2005 Annual Scientific Conference at NIH June 13–14. Co-author of the Norton-Simon Model, Dr. Norton's ideas have helped to shape the field of medical oncology.

Where did the Norton-Simon model come from?

The intellectual germ was Dr. Howard Skipper's idea of summarizing how cancers behaved when treated with drugs with a model, rather than using the voluminous dataset itself. I came to NIH at a pivotal time in cancer research, working alongside a legendary Medical Branch team and people such as Dr. Vince deVita, Dr. Paul Carbone, and Dr. Richard Simon, a brilliant biostatistician, who is now chief of the Biometric Research Branch in the Divison of Cancer Treatment and Diagnosis.

In a nutshell, we recognized the importance of what others had already noted: that cancers follow Gompertzian growth curves, meaning that "small things change in size relatively faster." About 1976 we saw this relationship applied not only to unimpeded tumor growth, but also to regression in response to treatment. To my knowledge no clinical exception has been found in the almost 30 years since.

How has this idea influenced cancer research and treatment?

There has been a steady evolution of these ideas as a consequence of clinical and laboratory experiments. We learned that the sequential use of different drugs worked better than alternating therapies, and that "dose density," using effective dose levels over a shorter period of time, both improved results and minimized toxicity, cutting the relapse rate from primary estrogen receptor-negative, node-positive breast cancer by more than half compared with where we were in the mid-1980s. With NCI support, Dr. Joan Massagué and I are now exploring the biochemical reasons for the phenomenon, based on his seminal observations concerning the molecular genetics of metastases. We are hypothesizing that cancers, in fact, seed themselves as well as distant sites, so that a malignant mass is, in effect, a collection of small Gompertzian tumors.

Where does fractal geometry come in?

Fractal geometry quantifies complex shapes that have fractional dimensions, unlike simple forms such as sheets and solids. According to this, small cellular masses are more dense than larger ones; hence, they have a higher fraction of dividing cells and grow relatively faster. The small tumors that make up the conglomerate each have their own growth curve—so the more self-seeding, the greater density, the faster growth rate, and the larger the eventual whole-mass size.

We have traditionally thought that cancers metastasize because they grow large and thereby generate distant-seeding mutants. But perhaps cancers are large because they self-seed, and self-seeding is a step toward distant seeding. By identifying the genes responsible for this process we hope to improve prognostication and therapy. ◆

Featured Meetings and Events

A comprehensive calendar of cancer-related scientific meetings and events sponsored by NCI and other scientific organizations is available at http://calendar.cancer.gov/ ◆

The *NCI Cancer Bulletin* is produced by the National Cancer Institute (NCI). NCI, which was established in 1937, leads the national effort to eliminate the suffering and death due to cancer. Through basic, clinical, and population-based biomedical research and training, NCI conducts and supports research that will lead to a future in which we can identify the environmental and genetic causes of cancer, prevent cancer before it starts, identify cancers that do develop at the earliest stage, eliminate cancers through innovative treatment interventions, and biologically control those cancers that we cannot eliminate so they become manageable, chronic diseases.

For more information on cancer, call 1-800-4-CANCER or visit http://www.cancer.gov.

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