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In this issue:

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Publication Break

The *NCI Cancer Bulletin* will not be published on September 2. We will resume publication on our usual schedule with the September 9 issue. ◆

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Director's Update

The Dawn of Personalized Oncology

Wherever I go, someone invariably asks, "Have we really made any progress against cancer?" My answer is, We definitely have—we have made tremendous progress.

I go on to explain how much more we know today than we did just a decade or two ago. We know that the tumor has a very significant and critical microenvironment in which it grows; that the normal-appearing cells of this microenvironment are genetically reprogrammed to support the growing tumor in the critical steps of invasion and metastasis. We know much more about mutations, changes in gene copy number, translocations, the re-expression of genes involved in embryogenesis, and the epigenetic suppression of other genes—and how these changes lead to the growth and spread of cancer.

This new knowledge is being determined and catalogued at a stunning rate, led by our research efforts in functional biology and by our work in genomics and transcriptional regulation. In addition, whole-genome scans that define regions associated with cancer risk are being identified, fine mapped, and sequenced. The Cancer Genome Atlas (TCGA) project is actively sequencing actual patient tumors and finding new gene alterations associated with a specific cancer's development.

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Mobilizing National Drug Discovery

NCI's proposed Chemical Biology Consortium (CBC) will establish an integrated network of chemical biologists, molecular oncologists, and compound screening centers from government, academia, and eventually from industry. The program is being developed by NCI's Division of Cancer Treatment and Diagnosis (DCTD), in conjunction with NCI's Center for Cancer Research (CCR) and the NCI Director's office, to facilitate the discovery and development of new agents to treat cancer.

The NIH Chemical Genomics Center screens for potential new targeted therapies.

"The long-term vision of the CBC is to bridge the gap between basic scientific findings—for example, The Cancer Genome Atlas and genome-wide association studies—and NCI-supported clinical research," noted DCTD Director Dr. James Doroshow.

Dr. Barbara Mroczkowski, special assistant to the DCTD director, is a project lead for CBC. She came to

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Our newly acquired understanding of cancer is leading to specific, targeted therapeutic solutions and the dawn of an age of highly personalized cancer medicine. The future is upon us, and we are now designing precise therapies to home in on specific targets that result from genomic and functional changes, not only in the tumor cell but also in the tumor microenvironment. We are learning that the complexity of altered cellular communications will require the development of multi-agent treatment solutions, in contrast with single drugs. As a result, the future will require innovative strategies and partnerships—between academia, the public sector, and industry—to change the process of determining efficacy and safety, thereby speeding the progress from laboratory to patients. This is not an insurmountable challenge, but clearly is one that will require NCI's involvement and leadership at every step of the new paradigms.

As you will read in this special issue of the *NCI Cancer Bulletin*, the National Cancer Institute and its partners are taking steps to enhance the process of drug development, from target identification to high-throughput screening; to chemical characterization and structural design optimization at the molecular target interaction; to testing in genetically engineered mice; to the design of mechanisms for monitoring *in vivo* activity. At the end of the process is translation into man.

The challenge now is to make sound prioritization decisions about which targets to pursue, and then to move them into a synchronized, efficient platform for development.

To support the critical first steps, a high-throughput screening resource to identify small molecules will complement NCI's Chemical Biology Consortium, a network of institutions that have formally agreed to collaborate in the early phases of the drug discovery process. This will be an integrated research consortium at the interface of chemical biology and molecular oncology—an iterative program in cancer drug discovery.

As potential drugs—small molecules, large molecules, and biologics— emerge, researchers will need to develop new ways to assess their efficacy and establish the proper dosages, given that targeted, selec-

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NCI after 15 years in industry.

"NCI has all this intellectual capital, all the investigators, and everything you need for the late-stage development of clinical compounds," Dr. Mroczkowski said. However, she found that "support for early phase 'discovery' of novel compounds that work against newly discovered molecular and genetic targets for cancer needed to be upgraded." NCI's leadership, in establishing the CBC, saw that there was a need to fill that gap.

NCI received an enthusiastic response to this idea from top-tier, nonprofit chemical biology compound screening centers in the United States, including many centers already participating in the NIH Molecular Libraries Small Molecule Repository program. "These centers have state-of-the-art, high-throughput screening capacity and have the capability and collections of thousands of compounds" that can be useful to CBC, said Dr. Mroczkowski.

The screening centers and other investigators are attracted by NCI's proposal to give CBC participants open access to the institute's late-stage drug development toxicology, pharmacology, and formulation resources, as well as the expertise of NCI's Developmental Therapeutics Program (DTP). CBC members will also benefit from access to NCI's Center for Advanced Preclinical Research, which grew out of NCI's Mouse Models of Human Cancers Consortium efforts and uses genetically engineered mouse models.

In addition, the two NCI research divisions involved with CBC are hiring additional staff with expertise in the discovery field, including a new chemical biology branch chief in CCR and several medicinal chemists in DCTD. The program will benefit from active project management by NCI and its external advisory boards. CBC participants will be managed via a contract mechanism and the data and materials generated by individual members will be added to a centralized data and warehousing system and shared among all CBC members.

Management of intellectual property rights will be a critical factor in the success of CBC. "That issue has been

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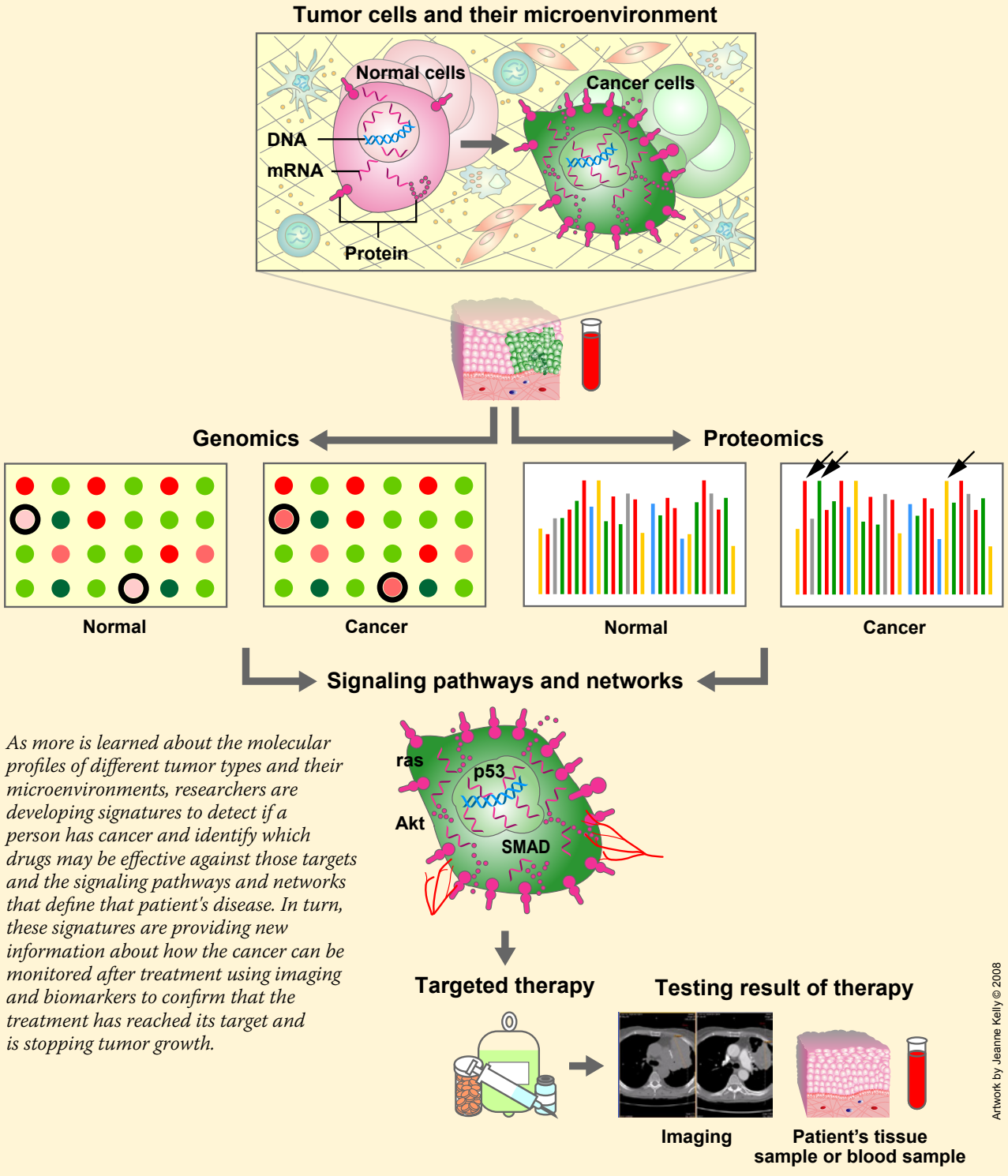
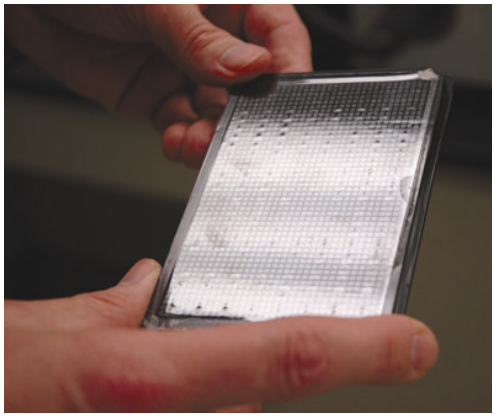
Personalized Drug Development



As more is learned about the molecular profiles of different tumor types and their microenvironments, researchers are developing signatures to detect if a person has cancer and identify which drugs may be effective against those targets and the signaling pathways and networks that define that patient's disease. In turn, these signatures are providing new information about how the cancer can be monitored after treatment using imaging and biomarkers to confirm that the treatment has reached its target and is stopping tumor growth.

A New Paradigm for Drug Discovery

Until recently, cancer drug development has focused on cytotoxic compounds. These drugs kill cancer cells, but they can also kill normal cells, leading to the toxic side-effects of traditional chemotherapy. But recent leaps in understanding of the molecular events that drive a cell to become cancerous have led researchers to agents that specifically target molecular traits of cancer cells. Most targeted agents do not kill cancer cells. Instead, they stop them from growing.



This screening plate holds more than 1,500 compounds that will be tested as possible disease-targeting agents.

Such targeted agents now make up the majority of anticancer drugs under development. "If you look at the current pipeline right now, not counting clinical development, it's probably two-thirds targeted agents and one-third traditional cytotoxic agents. Five years ago that ratio was reversed," says Dr. James Doroshow, director of NCI's Division of Cancer Treatment and Diagnosis (DCTD).

Targeted drug development presents a whole new set of challenges to researchers working on drug discovery. "If you're looking for a cytotoxic drug, then a compound that kills a tumor cell would be a candidate. With a targeted agent, you actually have to know what molecular pathway you're interested in in the first place," explains Dr. Joseph Tomaszewski, deputy director of DCTD. "You need a clear understanding of how disregulation or mutation of a target—for example, a protein or gene—has an impact on the formation, growth, and metastasis of various types of tumors."

DCTD and other divisions in NCI are responding to the need for newer screening techniques designed specifically for targeted agents. One project is extending the capabilities of the NCI-60 cell screen, which has been used for more than 15 years to screen

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Treatment Arsenal Expands with Small Chemicals

The proprietary, one-at-a-time approach to developing safe agents for specific diseases has produced hundreds of drugs in the last 50 years. But those numbers are meager compared to what the future holds.

The laboratory of Dr. Stuart Schreiber, the Harvard-trained organic chemist and founding professor at the Broad Institute of Harvard and MIT, has created a powerful, revolutionary method of synthetic chemistry to actually reach the goal of targeting cancer dependencies—diversity oriented synthesis. "It's likely that many of the proteome's 100,000 proteins have multifunctional roles in cancer, and it follows that molecules that control them will yield a therapeutic benefit," he says.

In 2002, the NCI Office of Cancer Genomics selected Dr. Schreiber's lab as a center in the Initiative for Chemical Genetics (ICG). As the number of useful small molecules they could develop became apparent, a more comprehensive strategy began to coalesce into a new field altogether, known as chemical biology. The ICG essentially provides a national laboratory for high-throughput, small-molecule screening, and has generated and analyzed data for more than 100 different research groups.

Another open-source, data-sharing model Dr. Schreiber has developed is ChemBank, a public, Web-based informatics environment to facilitate chemical genetics.

Chembank provides life scientists access to tools that are associated with private sector industry, and to data from hundreds of biomedically relevant assays that link the states of healthy and diseased cells to more than 700,000 small molecules. This kind of community resource, Dr. Schreiber believes, "enables the drug-hunting community to become more than the sum of its parts." ◆

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for cytotoxic compounds. "We're trying to understand how new [targeted] drugs affect the expression of a large number of genes in those cells—say, 30,000 genes across 50 or 60 different cell types; that is, we're trying to understand whether we can use the NCI-60 as a functional genomic screen" to understand how new drugs affect cancer cells on a molecular level, explains Dr. Doroshow.

Through NCI's Mouse Models of Human Cancers Consortium (NCI-MMHCC), NCI is building relationships and developing private partnerships to further the use of mouse models in preclinical testing of agents from pharmaceutical and biotechnology companies.

"A number of companies are providing their lead compounds to Consortium laboratories to test them in a variety of cancer models," says Dr. Cheryl Marks, associate director for NCI's Division of Cancer Biology and the NCI-MMHCC program director. "This is one way to familiarize the private sector with use of genetically engineered mice in their preclinical research. The goal is to enable the companies to identify tumor sites that would be the most promising choices for phase II and III clinical trials."

Another major need in targeted drug development is for reliable, reproducible pharmacodynamic measurements—measurements of how drugs are affecting the molecular workings of cells in the body. "A lot of the pharmacodynamic assays that scientists have been using for years work to a certain extent but have not been rigorously developed and standardized. As a result, you do not have absolute confidence in the data," says Dr. Tomaszewski. "We've embarked on creating more standardized assays that will allow us to make earlier decisions about whether or not we're having an impact on a target; and in that way, you can establish at an earlier stage whether you will continue down the development pathway or not continue with a particular agent. Once you move beyond the preclinical efforts, you're spending a tremendous amount of money. If your drug fails late in phase III studies, it wastes a tremendous amount of resources." ◆

CMap Extends Drug Use

Drs. Todd Golub, Justin Lamb, and colleagues at the Broad Institute have created a public database of gene-expression profiles and Web-based data-mining tools they call the Connectivity Map (CMap), which allows researchers to uncover functional connections between diseases, gene function, and drug actions.

Using 7,056 genome-wide expression microarrays, CMap provides data for how 1,309 small molecules—including virtually all of the off-patent drugs approved by the Food and Drug Administration (FDA)—have modified mRNA expression in a collection of different cultured human cell lines.

This means that users can query the database with a gene-expression signature of a newly developed small molecule; disease tissue; or a genetic variant, such as a knockout; and immediately identify functionally related chemicals. The result might point to a pathway or specific compounds that could modulate that biological state, possibly even FDA-approved drugs that could be tested as a therapy.

Dr. Lamb and his colleagues have demonstrated some discoveries with CMap, but he is much prouder of the small but growing number of completely independent users who have made crucial connections. Even pharmaceutical companies that traditionally operate with strict confidentiality are enthusiastic about platforms like CMap for sharing basic cell biology data, says Dr. Lamb. ◆

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very much at the forefront of our discussions," noted Dr. Doroshow, who explained that a Request for Information solicited feedback on this from potential partners. "We've created an intellectual property and data-sharing plan for CBC that the various investigators have to review and agree to as the basis for participating in the program," he added.

According to Dr. Joseph Tomaszewski, deputy director of DCTD and the NCI lead for this project, "NCI will issue a Request for Proposals through SAIC-Frederick to solicit contractors to participate in CBC later this year." ◆

Clinical Trials and Personalized Drugs

NCI supports a large number of clinical trials through its divisions, from first-in-man studies to phase III trials. The DCTD Cancer Therapy Evaluation Program (CTEP), for example, currently oversees more than 800 clinical trials evaluating new treatments for patients with all forms of cancer, and "is the institute's primary vehicle for conducting definitive, practice-changing clinical trials," says DCTD Director Dr. James Doroshow.

The Division of Cancer Prevention (DCP), which supports clinical trials of agents that may help prevent cancer from developing, also manages the extramural Community Clinical Oncology Program (CCOP)—a network that enables patients and physicians to participate in prevention, treatment, and supportive care clinical trials in their local communities. NCI even sponsors clinical trials in foreign countries, such as a phase III HPV vaccine trial in Costa Rica that is testing the ability of virus-like particle vaccines, originally developed by CCR investigators, as a means of preventing cervical cancer.

NCI conducts many of its clinical trials intramurally in Bethesda, MD, with "cutting edge clinical research that really isn't feasible at other centers," says Dr. William Figg, head of the Molecular Pharmacology Section in NCI's Center for Cancer Research. "All of our patients come here understanding that they are going to be enrolled on clinical trials, so they are willing to participate in more extensive testing and allow us to capture more data."

Indeed, the intramural program is a testing ground for strategies that can improve clinical testing overall. One of the latest is phase 0 trials. Conducted mostly at the NIH Clinical Center and a few select cancer centers, "Phase 0 allows you to answer very important questions rather than relying on the answers that you've received from animals, which don't always predict what happens in humans," says Dr. Doroshow. These trials, therefore, give a good estimate of whether a drug is worth advancing into phase I and phase II trials, which require a much greater supply of investigational agent, more patients, and more clinical resources.

A common measure of action for conventional chemotherapy has been whether or not a drug kills cancer cells and, therefore, shrinks tumors. Using these criteria, however, many of today's targeted agents would appear not to work. And yet the clinical trials show that they do. For this reason, some researchers are beginning to think about progression-free survival as a worthy endpoint for targeted agents. The monoclonal antibody bevacizumab was recently approved for use in breast cancer based on this endpoint.

Scientists are also exploring how new advances in cancer imaging can be used to measure whether a targeted drug is doing what it should. "In the future we will have targeted therapeutic molecules that, with minor modification, can be imaged to show where they go in the tumor, or if they actually reach the tumor," says Dr. Doroshow. This will open new possibilities for accurate and noninvasive assessment and make the clinical trial experience more patient-friendly and effective. ◆

The PPWG

A new Trans-NCI Pharmacogenomics and Pharmacoepidemiology Working Group (PPWG) is developing recommendations to create a comprehensive, transdisciplinary research agenda for consideration by NCI leadership. This agenda will integrate basic, clinical, and population sciences to identify factors or genomic profiles that can successfully predict those who most likely will respond to a specific preventive drug or cancer therapy, as well as those who may develop adverse events. More information is available at: http://riskfactor.cancer.gov/areas/pharmaco/.

In addition, the NIH Roadmap Initiative is launching a new Transformative R01 Program to fund paradigm disruptive/creating research. Pharmacogenomics will be one of six topics highlighted as a possible transformative research area in a funding opportunity announcement, anticipated to be released in the fall of 2008. ◆

Collaborating with Industry to Drive Drug Development

The last two decades have included a number of successful partnerships between NCI and industry, leading to the development of highly effective cancer therapeutics like paclitaxel (Taxol) and bortezomib (Velcade). Such collaboration is by no means rare. A number of existing NCI programs, including the RAID program and the NCI-60 Screening Project, already facilitate collaboration between NCI and industry.

But, as the institute becomes more of an enabling platform for the translation of new therapeutics from the lab to the clinic, innovative efforts have been launched that both directly and indirectly allow NCI and the private sector to cooperate.

One area of particular emphasis, explains Dr. James Doroshow, director of DCTD, is NCI's greater role as "a broker" in arranging for the conduct of clinical trials to test new cancer drugs. This is especially true for trials in which researchers at academic medical centers hope to test combinations of agents owned by different companies. Dealing with intellectual property concerns and hashing out the minute details of these arrangements can often lead to long delays, if not entire derailment. But with NCI's enhanced involvement, that's beginning to change.

"We now have 100 trials like this going forward, being performed in academic medical centers," Dr. Doroshow said during a recent seminar for medical reporters. "There are very few examples of a single academic site bringing together [companies with] two investigational agents… Anything we can do to speed up [the negotiation] process will speed up the overall development process."

High-throughput screening facilities like this one help academic researchers test their potential drugs and work with industry for development.

Another new initiative is a funding mechanism for small businesses developing promising new anticancer therapies and cancer imaging technologies. With funding from venture capital companies and so-called "angel investors" becoming more difficult for small businesses to secure, NCI's Small Business Innovation Research (SBIR) Program has developed Phase II Bridge Awards to help small businesses fund the work needed to traverse the so-called "valley of death": the period between the completion of early basic and preclinical research and later stage human studies, including phase I and II clinical trials.

The Bridge Award, explains NCI SBIR Director Michael Weingarten, encourages partnerships between NIH's SBIR Phase II awardees and third-party investors and/or strategic partners that have significant prior experience in the commercialization of emerging technologies. To encourage partnerships with third-party investors, the SBIR Program expects the Bridge Award amount to be matched by non-federal funds. Modeled after a highly successful program developed by the National Science Foundation, the Bridge Awards, Mr. Weingarten says, are an ideal way for NCI to "incentivize early collaboration." Applicants must have previously received a SBIR Phase II award from the NIH.

The institute's leaders also believe NCI's Experimental Therapeutics program will expand NCI's ability to collaborate with industry partners in improving drug development. The program's aim is to use very small phase 0 human trials to shorten the time needed to move the most promising investigational agents into larger phase I human clinical trials. The first such trial, a partnership with Abbot Laboratories, was highly successful, demonstrating that the drug was hitting its molecular target, and identifying a biomarker to measure target inhibition without having to do repeated tumor biopsies.

That single trial, says Dr. Jerry Collins, associate director of NCI's Developmental Therapeutics Program, "has turned around opinions on the outside dramatically. It's one thing to deal with the abstract concept of a phase 0 trial. It's another to have a specific example that demonstrates it." ◆

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tive agents may have an optimal dose much lower than the maximum dose a patient can tolerate. Likewise, we need to develop an improved clinical trials system, to better accommodate targeted therapies and accurately assess genomic changes in patients. The challenge in translation is optimally matching the tumor and therapeutic recipe. Proving the importance of these issues, they were front and center at a recent meeting sponsored by the National Cancer Policy Forum of the Institute of Medicine. Solving them is among NCI's top priorities.

So, have we really made any progress against cancer? Consider, if you will, that at several major cancer centers, researchers are currently developing the next phase of personalized care for lung cancer. After a diagnosis, in this new protocol, patients will have a tumor sample extensively analyzed for alterations in six or seven genes known to be critical in the disease. Patients will then be matched with targeted agents, based on the genetic defining of their tumor. As we move forward, this will be the pattern of treatment for all malignancies. Furthermore, the genetic characterization of patients, in a process termed pharmacogenomics, will greatly assist in determining correct dosages and avoiding unsuspected toxicity due to faulty metabolic pathways.

Indeed, we must take steps now to ensure that in the years ahead, targeted therapies are available for all types of cancer. NCI has the opportunity—the obligation, in fact—to connect and coordinate all components of America's cancer enterprise, to make sure this is an opportunity firmly grasped. ◆

Dr. John E. Niederhuber
Director, National Cancer Institute

Helping Technology Collaborations Flourish

The Advanced Technology Partnerships Initiative (ATPI) will use NCI-Frederick's unique authorities to expand collaborations with industry in developing technologies to translate cutting-edge discoveries into new diagnostic tests and treatments. The first collaborative agreement under this program has just been reached with GE Global Research, using nanoparticles as diagnostic imaging agents.

Another NCI program helping to promote technology collaborations is the Center for Cancer Research's (CCR) Office of Science & Technology Partnerships (OSTP), which began in 2002. The OSTP negotiates agreements with companies that allow many CCR researchers to use new technologies for tasks like assessing protein-protein interactions or conducting gene-expression studies—vital research that represents the earliest phases of drug development.

These are often win-win relationships, stresses Dr. David Goldstein, who directs OSTP. CCR researchers get access to cutting-edge technologies and can leverage economies of scale, and the companies often get valuable input that helps in commercialization of their products.

Similarly, novel models developed through NCI's Division of Cancer Biology Mouse Models of Human Cancers Consortium (NCI-MMHCC) are being used more in NCI-supported academic laboratories for preclinical testing that parallels early clinical trials. NCI is exploring public-private partnerships for these studies, and to leverage the preclinical bioinformatics infrastructure that the NCI-MMHCC developed in collaboration with the NCI Center for Bioinformatics. ◆

Other Resources

Patient information on drug development
http://www.cancer.gov/cancertopics/treatment/druginformation

NCI's Developmental Therapeutics Program
http://dtp.nci.nih.gov/index.html

NIH Chemical Genomics Center
http://www.ncgc.nih.gov/

NIH funding for drug development
http://grants.nih.gov/grants/oer.htm

The NIH Drug Discovery Interest Group
http://cmm.cit.nih.gov/DDIG/ddig_links.html