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Director's Update

NCI-Frederick's Unique Combination of Resources and Flexibility

NCI-Frederick is much more than a satellite campus of NCI. It is a unique biomedical research resource and one of only 36 Federally Funded Research and Development Centers (FFRDCs) in the country. These facilities are not part of the government, but are operated by universities and nonprofit corporations under federal contracts. They fulfill some of our country's pressing research needs by bridging public and private sectors. FFRDCs study a variety of defense and national security issues, but only one FFRDC—NCI-Frederick—is devoted solely to biomedical research.

This special issue of the *NCI Cancer Bulletin* pays tribute to NCI-Frederick, which has, for more than 30 years, provided core scientific expertise and advanced technology development to NCI's intramural and extramural researchers, as well as to other NIH institutes and federal agencies.

Through its many advanced technologies, NCI-Frederick strives to speed the translation of laboratory discoveries into therapies for patients. Its capabilities include the capacity to rapidly deliver prototype drugs that meet the FDA's stringent Good

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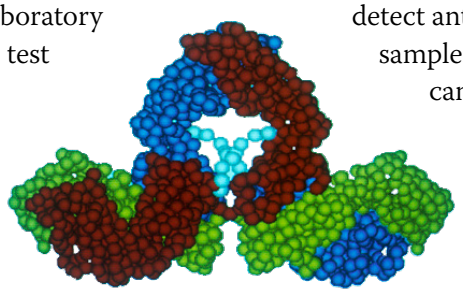
NCI-Frederick to Help Build Proteomics Pipeline

In the coming months, NCI will establish an Antibody Characterization Laboratory at NCI-Frederick to test antibodies that are produced as part of a new proteomics pipeline created by the Clinical Proteomic Technologies for Cancer Initiative (CPTI).



Computer model of an antibody

Antibodies are proteins produced by the immune system in response to other proteins, which are called antigens. In the clinical context, antigens are usually associated with unwanted invaders. Researchers can use these antibodies in a similar fashion to detect antigens in biological samples that may be tied to cancer.

Though antibodies are essential in research and diagnostic laboratories around the world and thousands are available commercially, "the majority of these antibodies are poorly characterized and their quality is unreliable," notes Dr. Henry Rodriguez, who directs NCI's

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Manufacturing Practice (GMP) regulations for use in clinical trials—expertise that can help win regulatory approval for new drugs, vaccines, and other therapies. NCI-Frederick has been involved in more than 300 clinical trials, including a vaccine for lymphoma, a vaccine that can prevent cervical cancer, and the test that protects the nation's blood supply from contamination by the AIDS virus.

NCI-Frederick also supports research that is conducted outside its walls. In 2005 and 2006, for example, it acquired more than 1.5 million tissue samples from clinical trials and provided more than 1 million novel research animals to more than 1,100 investigators at more than 200 institutions.

NCI-Frederick's technologies—from advanced imaging to nanotechnology research to large-scale supercomputing—are at the center of an emerging Advanced Technology Partnership Initiative (ATPI). This public-private partnership has the potential to make NCI-Frederick a test-bed for new technologies and novel research concepts. Researchers hope in the next few years to expand the ATPI through a state-of-the-art research park in the Frederick area.

NCI-Frederick owes a debt of gratitude to a group of dedicated cancer advocates and legislators, including philanthropist Mary Lasker, Senator Charles Mathias (R-MD), and Benno Schmidt, chairman of the Panel of Consultants on the Conquest of Cancer. During deliberations over the National Cancer Act of 1971, they pushed for a cancer research campus in Maryland at Fort Detrick. Their foresight made possible the FFRDC designation in 1975. Without that special distinction, we clearly wouldn't have made the kind of progress against cancer—at the speed we have made those lifesaving discoveries—over the last three decades. ◆

Dr. John E. Niederhuber
Director, National Cancer Institute

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Clinical Proteomic Technologies for Cancer (CPTC) program.

Two years ago, NCI sponsored a workshop to determine what reagent resources were needed by the cancer research community to facilitate the identification of proteins and peptides of interest. The unanimous message was that one of the biggest bottlenecks is a lack of well-characterized antibodies.

"As industry and academia invest significant resources in the promise of proteomics and ultimately molecular-based tools, well-characterized antibodies will be vital to advancing these disciplines," says Dr. Rodriguez. "This is especially true of proteomics, where an antibody can be used to recognize a unique protein in the midst of millions of other proteins that the human proteome comprises."

The Antibody Characterization Laboratory will be part of NCI-Frederick's Advanced Technology Program (ATP), which includes teams working on protein analysis, structure, and molecular imaging. "We have quite a broad program with a variety of different protein characterization technologies," says Dr. Tim Harris, who directs ATP. When the antibodies start to arrive in Frederick in the coming months, Dr. Gordon Whiteley will lead the characterization team.

The CPTI pipeline starts with the Argonne National Laboratory, where cancer-related proteins are being produced. Later this year, private laboratories will be contracted to manufacture three monoclonal antibodies for each of these proteins and send these to NCI-Frederick for standard operating procedures-driven characterization. Promising antibodies will then travel to the Human Protein Atlas project in Stockholm, Sweden, and to the Harvard Institute of Proteomics for further analysis. All characterization data will be accessible to the scientific community through a Web site, with antibodies and hybridoma cells distributed by the Developmental Studies Hybridoma Bank at the University of Iowa.

"This program will spur the development of resources that accelerate biomarker discovery and validation, translational research, molecular diagnostics, and therapeutic monitoring," says Dr. Rodriguez. "I'm convinced that when this happens, we will have a solid foundation on which to create a real impact with proteomics in cancer."

Plans for the pipeline were announced last month at the first CPTI annual meeting, where NCI Director Dr. John Niederhuber said that progress in clinical proteomics will require technological advances similar to those that have enabled recent progress in genomics. He added that the efforts of the CPTC will contribute fundamentally to the early detection and treatment of cancer, and affect all diseases. ◆

Highlights in the History of NCI-Frederick

2007 Clinical Proteomic Technologies Initiative begins

2006 Vaccine Pilot Plant opens

2005 Nanotechnology Characterization Laboratory opens

1998 Rapid Access to Intervention Development begins to speed up the transfer of investigational drugs into clinical trials

1993 Biopharmaceutical Development Program begins to support prototype drugs, vaccines, and other therapies

Large-scale production of geldanamycin (more than 3 kilograms) begins in the NCI-Frederick fermentation plant's 10,000L fermentor, which permits the introduction of 17-allylaminogeldanamycin (17-AAG) as the first signal-transduction molecule in human clinical trials

Taxol is approved for use by the FDA

1992 Two anti-HIV plant-derived agents are identified by NCI scientists from collections in Cameroon (Michellamine B) and in Sarawak (Calanolide A); large-scale collection and horticultural programs established in these countries

1991 The Natural Products Repository begins distribution to permit intra- and extramural investigators of all types to study samples collected and processed at NCI-Frederick

1990 The first NCI letter of collection is signed with the Republic of Madagascar, 3 years before the Convention on Biodiversity

1986 The Natural Products Repository is established
The first supercomputer dedicated to biomedical research is established at NCI-Frederick

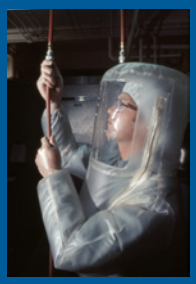
1985 HIV antibody testing begins at NCI-Frederick, leading to a test used to safeguard the nation's blood supply against contamination

1982 Central Repository is established to assist investigators in storing research specimens

1981 Biological Response Modifiers Program is established to bring new therapeutic agents to clinical trials

1977 Taxol is developed from samples of the Pacific yew tree's bark, which came from the Natural Products Branch's previous collection program with the USDA

1975 NCI-Frederick is designated as an FFRDC dedicated to biomedical research



NCI-Frederick is established at Fort Detrick in Frederick, Maryland

1972

A Conversation With... Dr. Craig Reynolds

Dr. Reynolds has been a member of the NCI-Frederick research community for more than 25 years. He currently serves as NCI associate director and director of the Office of Scientific Operations at NCI-Frederick. Here, he discusses the Advanced Technology Program (ATP) at NCI-Frederick, which supports the facilities and research discussed throughout the rest of this special issue.

What makes the ATP at NCI-Frederick special?

NCI-Frederick's Advanced Technology Program is not only special; it's unique. Among our national laboratories, indeed among all national resources, the ATP offers highly specialized support in a complex and fast-paced biomedical research environment. Among the ATP's participating laboratories, we count such initiatives as genomics, proteomics, metabolomics, nanotechnology characterization, protein expression, histopathology, confocal and electron microscopy image analysis, and GMP manufacturing. NCI-Frederick's ATP is also home to the Advanced Biomedical Computing Center (ABCC) and the only high-performance, high-capacity computer dedicated solely to medical research. The ABCC provides solutions for data-intensive computational biological problems and offers a broad spectrum of computer architectures, software packages, and consulting expertise. The ABCC also engages in collaborative research and training in computational biology and biomedical research.

Can researchers outside of NCI use ATP resources?

That's the best part. We provide these ATP services not only to NCI and NIH scientists, but, on a space-available basis, to other federal agencies and extramural biomedical researchers, as well. To see the full range of research support services, I encourage you to visit http://www.ncifcrf.gov/atp.

Why is it important for NCI-Frederick, a federal entity, to maintain the resources and programs available under ATP?

When others work with our scientists, it enables them to extend their inquiries to depths and in directions perhaps otherwise inaccessible. Our biomedical research scientists' work touches all aspects of scientific exploration, from routine laboratory processes to complex experimental design and interpretation of results. Providing these ATP services to others is not entirely altruistic on our part. Through the synergy we build with public-private collaborations and partnerships, we're able to bring the intellectual and empirical capital of the entire scientific community—academia, industry, philanthropy, government—to bear on two of the most critical health care issues of our times, cancer and AIDS.

In the most recent survey by the *The Scientist* magazine, which showed that NCI-Frederick is ranked second among the best places to work in research, respondents listed core facilities, such as those of the ATP, as a high-level factor in their job satisfaction. What are other reasons why people might enjoy working at NCI-Frederick?

In addition to our employees valuing their proximity to the ATP, they also gave top scores to our scientific library, its consistently forward-looking management and its holdings. I find it significant that an overwhelming number of the respondents cited their peers as excellent scientists, and 98 percent affirmed a high level of cooperation and collegiality among their peers. Those ringing endorsements of personal and professional satisfaction, coupled with almost universal agreement that core facilities and infrastructure are excellent, can't help but make for an ideal place to work. We're proud to be a part of this important and essential effort to improve the health of all people. ◆

A National Treasury of Biological Specimens

In addition to housing some of the most advanced cancer research programs and tools in the country, NCI-Frederick houses one of the largest biobanks, comprising five distinct repositories.

The largest of these is the Central Repository. It holds more than 10 million biological samples for researchers who work at NCI-Frederick, as well as intramural researchers from the main NIH campus in Bethesda and from other federal agencies. The repository is operated by Fisher BioServices, which subcontracts with SAIC-Frederick. The largest proportion of the repository comes from population science research studies in support of the Division of Cancer Epidemiology and Genetics.

"We're not just a repository," explains Dr. Kathleen Groover, who oversees this repository for Fisher. "We investigate things that other biobanks may not have the financial resources, ability, or desire to do," she says. "Whatever we learn, we share with the larger community." Dr. Groover, for example, has an article in press on how compressor cycles in mechanical freezers can indicate potential equipment failure.

The Natural Products Repository contains more than 75,000 plant and marine specimens collected from around the globe through contracts with nonprofit groups and agreements with countries from which the samples are procured. These samples are available to government, academic, and industry researchers through materials transfer agreements that protect the rights of the source country, should the work lead to a commercial application.

An offshoot of early Division of Cancer Treatment and Diagnosis (DCTD) drug screening programs, the Tumor Bank Repository includes more than 50 thousand vials of rodent tumor fragments, human tumor cell lines, tumor tissue in liquid suspension, ascites, and yeast, as well as four types of tissue microarray slides. These are shared with researchers in the government, academic institutions, and private companies worldwide.

The Biological Resources Branch Repository is also open primarily to nonprofit and academic researchers. It includes cytokines, antibodies, and other biological response modifiers, as well as imaging reagents and reference standards, most of which have been donated by companies or researchers that retired their programs but did not want the materials to go to waste. "All of these are available to researchers at no cost through our automated online ordering system," says Dr. Rosemarie Aurigemma, who oversees the repository and is a program director in the Biological Resources Branch in NCI's DCTD. "All we ask is that they pay for shipping."

The last repository was developed with advice from NCI's Mouse Models of Human Cancer Consortium. The NCI Mouse Repository maintains more than 100 strains of genetically engineered mice and strains used to derive cancer models. These mice are available to researchers at academic, nonprofit, and commercial institutions around the world for only the cost of shipping. The repository also accepts new models as they are developed, so they can be archived and shared. The NCI Mouse Repository is a member of an international network of repositories that develops best practices for strain maintenance and cryo-preservation, and minimizes duplication of mouse stocks.

Repositories at NCI-Frederick use state-of-the-art equipment and information technology. But even so, there are some limits on what they can hold. "Everything that comes

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Drug Discovery and Development at NCI-Frederick

NCI-Frederick provides services for several drug discovery and development programs that are sponsored by NCI's Division of Cancer Treatment and Diagnosis. These programs are the backbone of NCI's drug development pipeline. The repositories mentioned in this article help to support these programs, but there are many more discovery and development resources and services that can be provided to researchers around the world. More information about these programs and services can be found at http://dctd.cancer.gov/ProgramPages/DTP-resources.htm. ◆

(Specimens continued from page 5)

to the repositories here fits in with the FFRDC mission," notes Dr. Mark Cosentino, who oversees the Central Repository for SAIC-Frederick. "It's not our objective to compete with private industry. Rather, we accept and archive samples that private biobanks are not well suited to handle." ◆

From the Ends of the Earth, the Search for a Cure

"Drugs to fight cancer don't just drop out of the sky," says Dr. David Newman, who directs NCI-Frederick's Natural Products Branch (NPB), "but they can come out of the ground." A good example of this is the bark of the Pacific yew tree (*Taxus brevifolia*), which is the source of paclitaxel (Taxol), a successful anticancer agent.

In fact, as of 2006, more than two-thirds of the 178 anticancer agents approved by the FDA and regulation agencies in other countries owe their existence to structures from the Earth's flora and fauna. And this isn't only with cancer: The cholesterol-lowering drug atorvastatin (Lipitor), for example, which is the top drug sold worldwide, is a synthetically modified version of a fungal metabolite.

NPB manages a global effort to find, collect, and process species of life that may be a source of raw material for new therapies. Either contract field collectors or collaborating organizations in the source countries provide NPB with a network to mine potential specimens in more than

25 countries. This collection is heaviest between the tropics, where the majority of the Earth's 250,000 plant species thrive and marine invertebrates live in waters conducive to diving.

NPB is using its collection to provide researchers with promising leads for new drug development and the material with which to pursue it. NPB shares its samples with researchers from around the world who are working on any disease or medical issue of interest to the NIH.

Before researchers can receive NPB samples, however, they must sign a letter of collection, which, says Dr. Newman, "includes one fiercely nonnegotiable tenet: The source country must be involved in any subsequent drug commercialization." This stipulation came from wording in NCI's letter of collection, first signed with the Republic of Madagascar, 3 years before the Convention on Biological Diversity (CBD), an international treaty that protects global biodiversity and the rights of countries.

Since its inception in 1986, NPB's terrestrial collection has amassed more than 60,000 plant samples. Marine products form a distinct category, contributing more than 14,000 animal samples (most of them invertebrates) plus 3,000 species of algae.

A fast growing collection is microorganisms, especially fungi and bacteria developed and maintained in conjunction with the USDA at Fort Detrick, with some 30,000 of these microbes characterized. Researchers are finding an increasing number of the significant bioactive components in animal and plant species are probably produced by microbes associated with the plant or marine samples.

Chemists working with NPB process and refine all of the material into extracts and keep them in a freezer with bar codes that capture detailed information about their origin. Then they conduct initial screens using the NCI-60 cell lines and other relevant assays for biological activity against cancer. ◆

A Unique Animal Imaging Program

When the Small Animal Imaging Program (SAIP) opened at the NCI-Frederick campus in October 2006, "it was a huge thing for Frederick researchers," says Dr. Peter Choyke of the Center for Cancer Research (CCR) and NCI project officer overseeing the facility. Now the most comprehensive animal-imaging program at NCI, the SAIP offers state-of-the-art facilities including CT, ultrasound, fluorescence optical imaging, PET-SPECT CT, and a human 3 Tesla MRI machine specially configured to scan up to 6 mice

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at once, allowing high-throughput analysis for large experiments.

Unusual among small-animal imaging facilities, animals entering the SAIP from the main animal holding facility at Frederick can be returned afterwards for further study or follow-up. Most animal imaging facilities, which scan animals brought in from outside laboratories, harbor pathogens that could present a risk if introduced back into the laboratory environment; therefore, the animals must be euthanized after the imaging procedures. However, the SAIP maintains the same pathogen-free environment as the adjacent animal facilities.

"An animal in an adjacent facility could come through our pass-through door and be in the same environment that they would have been in their own holding area. So this allows us to do repeated scans on that animal," says Dr. Choyke. This is especially important for studies monitoring the spontaneous development of cancer in transgenic animal models, he explains. "Much like [carcinogenesis] in humans, we don't know when a tumor is going to occur or where it's going to occur, so we need to take serial images."

Many NCI researchers based in Bethesda also make use of the SAIP though collaborative relationships with scientists at NCI-Frederick, or by establishing their own animal colonies at the main animal facility in Frederick, which is part of the Laboratory Animal Sciences Program.

Although extramural investigators do not have direct access to the SAIP, the laboratory provides inclusive educational opportunities including training programs, visiting fellowships, workshops, and shared imaging protocols. Members of the SAIP are also working with small-animal imaging facilities across the country to develop a common informatics system to store and access imaging data. ◆

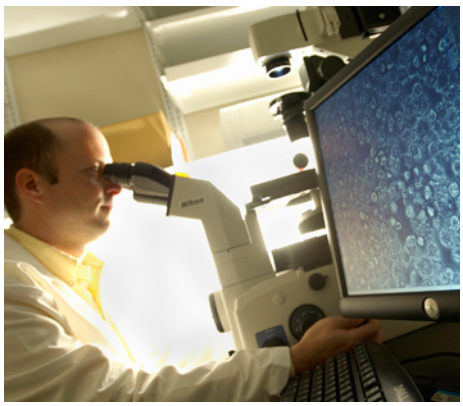
A Closer Look at Nanotechnology

One challenge faced by cancer researchers who work with nanotechnology constructs—structures smaller than one-billionth of a meter in size—is how to effectively characterize these novel particles to obtain FDA permission to advance to human clinical trials. The Nanotechnology Characterization Laboratory (NCL), located at NCI-Frederick, was created to respond to this challenge. NCL is a part of a large initiative, the NCI Alliance for Nanotechnology in Cancer, which funds extramural research and training programs to improve prevention, diagnosis, and treatment of cancer using nanotechnology.

Funded by NCI under the Alliance program with collaboration from FDA and the National Institute of Standards and Technology, the NCL provides free preclinical testing and characterization of nanomaterials to partners in academia and small business. Since its inception, the laboratory has characterized more than 100 nanotechnology strategies with a rigorous assay cascade that includes physicochemical analysis, toxicology, pharmacology, and efficacy testing.

Results from this assay provide the information needed by the investigators to apply for an Investigational New Drug or Investigational Device Exemption application and, importantly, provides the NCL with data and experience to compile best practice guidelines to aid the process of characterizing nanomaterials for future clinical applications. "We find that the typical users of our protocols are small businesses attempting to do preclinical characterization," says Dr. Scott McNeil, director of the NCL.

The NCL assay cascade has already confronted challenges related to the



inherent properties of nanomaterials. NCL investigators quickly learned that nanoparticles, many of which have catalytic or fluorescent properties, can interfere with traditional assays.

"Early on, we put some nanoparticles into an endotoxin assay, which is based on the cleavage of a protein to indicate bacterial contamination," explains Dr. McNeil. "The nanoparticles caused a robust response that was even more pronounced than if there had been bacteria present, because they were actually cleaving that protein."

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Developing new controls to test for enhancement and inhibition of such standard assays has become an important part of NCL research. Location at the NCI-Frederick campus offers important advantages in this process, says Dr. McNeil. "For example, the Advanced Technology Program has half-a-dozen mass spectrometers, plus capillary electrophoresis, genomics and proteomics technology, and electron microscopy. So rather than NCL hiring those types of expertise as additional staff, we can simply walk downstairs and have access to those resources." ◆

A Good Neighbor to Nearby Communities

NCI-Frederick takes very seriously its role as a major "corporate citizen" in its small, semi-rural hometown of Frederick, Maryland, located about 50 miles north of Washington, DC. In addition to traditional graduate and postdoctoral positions, the NCI-Frederick campus offers an array of top-quality science education and outreach programs that are tailored for students and residents who live in neighboring communities of Maryland, Virginia, and West Virginia.

The longest-running program is the Werner H. Kirsten Student Intern Program (SIP), which is designed to expose local high school seniors to research and administrative management in a health care environment. SIP was launched in 1989 by Dr. Werner Kirsten, who was associate director of NCI-Frederick from 1989–1992. "There weren't a lot of opportunities here for the local school children in the public school system," recalls Barbara Birnman, who administers SIP as part of NCI-Frederick's Office of Scientific Operations.

SIP began with only a handful of students during the first year of its summer program, but has expanded and evolved to teach and inspire 545 high schoolers since then, including the 52 pupils currently enrolled in the program. The SIP scientific interns arrive at NCI-Frederick early in the summer before their senior year of high school. They work 9 weeks during the summer for a stipend of about $3,400. The program is mentor-driven, with more than 40 volunteer mentors among the NCI lab scientists.

"Summer is a training period and the students work not only with the mentor but with other people in the labs, as well, to learn how to use the equipment and about procedures, lab safety, and other important research techniques or research issues," Ms. Birnman explains. "When the school year starts, each intern is given a project that is usually a subset of what the mentor's lab is working on." The SIP students commit to at least 3 hours a day in the lab during the school week, time that's unpaid but earns them academic credit from their high schools.

In addition to the SIP program, NCI-Frederick also hosts a Summer Student Seminar Series that allows summer interns and other students to meet one another and hear scientists talk about the broad range of research being carried out on the Frederick campus. At the end of the summer, they're invited to participate in a Summer Student Poster Day.

NCI-Frederick's Elementary Outreach Program grew out of the efforts of an NCI scientist in the early 1990s who had children in a local elementary school and was giving science lessons to his children's classes. "It was so popular that other teachers in the school wanted him to teach science lessons in their classes," notes Julie Hartman, who works in the Office of Scientific Operations. "We now have teams for each grade level who go to four or five Frederick County elementary schools throughout the school year," providing 60-minute, hands-on science lessons and demonstrations.

Plans for new educational programs are well underway at NCI-Frederick. These include establishing an undergraduate intern program, offering teaching opportunities for NCI graduate and postdoctoral fellows at nearby Hood College, and partnering with several local universities to offer extensive course offerings at higher education facilities. ◆