The Center for Translational Cancer Research

A Collaborative Effort between the Helen F. Graham Cancer Center at Christiana Care, the University of Delaware, and Nemours Biomedical Research

trâns-lāt´-tion-al rē´-sûrch

Medical research that is concerned with facilitating the practical application of scientific discoveries to the development and implementation of new ways to prevent, diagnose, and treat disease—called also *translational medicine.*

—Merriam Webster Online

Translational cancer research transforms the latest discoveries in the laboratory into innovative new treatments for cancer patients. Delaware's Center for Translational Cancer Research (CTCR) represents one model by which community-based cancer centers can expand their impact on the communities they serve. February 1, 2006, marked the beginning of the CTCR—a "center without walls" created to support clinical and basic scientific efforts in translational cancer research within the state of Delaware. Today, the CTCR operates under the direction of Robert Sikes, PhD, of the Department of Biological Sciences at the University of Delaware in Newark, Delaware.

The CTCR is a formal alliance between the University of Delaware, the Helen F. Graham Cancer Center (HFGCC) at Christiana Care Health System, the Nemours Research Foundation/A.I. DuPont Hospital for Children (AIDHC), and the Delaware Biotechnology Institute (DBI) at the University of Delaware. Prior to the CTCR, no coordinated network existed in the state of Delaware to unite local cancer researchers with clinicians who shared a common focus on developing new cancer treatments or identifying new cancer biomarkers for population screening, cancer prevention, and risk management.

Collaborative Efforts

Interdisciplinary research teams in the CTCR include clinicians, scientists, genetic counselors, engineers, and support staff. These teams are involved in translational cancer research projects being conducted at CTCR partner institutions. Examples of translational cancer research projects underway include:

- Function of extracellular matrix proteins and mucins in cancer growth in uterine, prostate, pancreatic, and breast cancer and their metastases.
- The role of cell adhesion and cytoskeleton in prostate and breast cancer metastases to bone and other tissues.
- The role of ion channels in aberrant proliferation and cancer cell death.
- Development of a chick embryo model to study how brain cancer cells invade locally and how metastatic breast cancer cells invade and colonize the brain.
- Tissue engineering replacement for head and neck cancers, such as growing salivary glands, to replace glands damaged by radiation therapy.
- Use of small DNA molecules to induce cell cycle arrest and cell death in targeted cancer cells.
- Development of novel antibacterial biomaterials for stemming bleeding during surgical procedures to remove cancerous tissues.
- The discovery of a stem cell marker that makes it possible to track stem cell overpopulation during colon cancer development and the role of microRNAs in colon cancer development.
- Interaction of bone marrow stromal cells and the bone microenvironment with cancer cells that metastasize to bone.
- Development of novel peptides, having shear-induced flow properties, as tissue glues or scaffolds for tissue regeneration.
- Discovery of novel targets for drug development in childhood leukemia.
- Development of biomarkers for childhood cancers, such as leukemia, medulloblastoma, osteosarcoma, and neuroblastoma.
- Nanotechnology-based drug delivery for childhood cancers.
- Development of targeted drugs for renal clear cell carcinoma.
- High-throughput screening and drug discovery for childhood cancers.

The CTCR's Cancer Biomarkers and Genetics Program

In June 2009, the laboratory and offices of the CTCR's *Cancer Biomarkers and Genetics Program* moved into the new Pavilion on the fourth floor of the Helen F. Graham Cancer Center. The expansion contains 6,000 square feet of laboratory space.

The cancer biomarkers component of this program involves proteomic profiling of patients' fluids (primarily blood or urine) with emerging techniques to identify new biomarkers indicative of disease severity, tissue invasion, and progression. Additional projects study tissue from biopsy specimens for protein biomarkers indicative of disease severity and progression.

Biomarkers. The protein biomarkers program builds on strengths found in each of the CTCR member institutions. Basic science strengths at the University of Delaware/Delaware Biotechnology Institute and at the Nemours Research Foundation/A.I. DuPont Hospital for Children are critical for discovering new biomarker(s) useful for the differential diagnosis of cancer from benign disease. In turn, the col-

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The laboratories of the CTCR at the Helen F. Graham Cancer Center are the first research-oriented wet lab space at the Christiana Care Health System and are the crossroads for translation research efforts.

laboration with physicians at the Helen F. Graham Cancer Center is necessary to translate these discoveries into new applied diagnostics.

One example of how this partnership benefits cancer patients in the community is a program that has been developed for patients at high risk for primary liver cancer (hepatomas). A collaborative effort of the Hepatobiliary Multidisciplinary Team at the Helen F. Graham Cancer Center, interventional radiologists, and community-based private practice gastroenterologists, the Hepatoma Center, located at the HFGCC, screens individuals at high risk for developing primary liver cancer.

Other biomarker projects under development at the CTCR seek to create new assays for following patients with metastatic breast or prostate cancer, with a primary goal of developing sensitive assays to determine if cancer cells have returned to bone or other common sites of metastasis such as liver or lung. A third biomarkers project seeks to identify cancer stem cells present in patient tissues, with an emphasis on colorectal cancers. This project is investigating the role of microRNAs in colon cancer development. This latter research project indicates that these small regulatory molecules cause upregulation of stem cell division that leads to stem cell overproduction in colon cancer

Genetics. The genetics component of CTCR's program uses information from the High-Risk Family Cancer Registry at the HFGCC, which presently includes more than 2,000 families and 100,000 individuals from across the state. This registry includes families whose generations have presented with cancers of the breast, ovary, prostate and/or colon and rectum. Today, individuals in these families can be tested for certain genetic mutations that predispose them towards the development of certain cancers. These "high-risk" individuals can be identified through screening and offered chemopreventive agents, increased surveillance, or prophylactic surgery. Additionally, there are often individuals in families with a strong history of cancer in each generation who are negative for known gene mutations. These individuals provide a means of discovering new cancer genes.

One exciting new class of cancer genes are microRNAs that inactivate tumor suppressors and allow cancer to develop. Part of the CTCR's genetics research program is able to tap into the scientific expertise at the University of Delaware/Delaware Biotechnology Institute and at the Nemours Research Foundation/A.I. DuPont Hospital for Children for the discovery of these new genes and their mutations that can serve in population screening at the Helen F. Graham Cancer Center.

Equipment and Technology

The CRTC's *Cancer Biomarkers and Genetics Program* requires specific technology to accelerate the pace of discovery as it is applied directly to Delaware families and patients being treated at the Helen F. Graham Cancer Center. This technology includes:

- Proteomic profiling with a state-of-the-art molecular modeling visualization facility
- Genetic mutation screening technology
- A tissue culture facility for lymphocyte immortalization, as well as establishing and growing new and existing cancer cell lines
- Confocal and fluorescent microscopes
- An automated tissue stainer for increased sample capacity
- High throughput flow cytometry and cell sorting.

The resources to acquire the technology and instruments needed to support these projects were obtained by grant funding whenever possible, but also through philanthropic efforts.

With the move of the CTCR's *Cancer Biomarkers and Genetics Program* to the new space within the Helen F. Graham Cancer Center, a strategic research partnership continues to develop with the Tissue Procurement Facility

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Director of Cancer Genetics and Stem Cell Biology, Bruce Boman, MD, PhD, with students in the new 6,000-square-foot lab at the Helen F. Graham Cancer Center.

in the Department of Pathology at Christiana Care. This partnership has greatly enhanced the CTCR's capability for assessment of protein biomarkers and for direct analysis of genetic signatures associated with cancer prognosis and risk. Furthermore, the partnership will speed the application of research discovery to the treatment of individual patients, such as, for example, being able to identify individuals who are likely to respond to a particular targeted drug therapy (personalized medicine).

Biospecimen Banking Description and Current Program

The Tissue Procurement Facility at the Helen F. Graham Cancer Center was developed in 2003, under the direction of Nicholas Petrelli, MD, in collaboration with physicians, staff, and the Department of Pathology at Christiana Care. In May 2003, selected individuals from the Cancer Center and the Department of Pathology and Laboratory Medicine received training at the Tissue Procurement Training Workshop hosted by the University of Alabama and the Cooperative Human Tissue Network, Southern Division. Key components of this training included the goals and methods of collection, quality control, safety and biohazards, Institutional Review Board (IRB) approval, and legal and ethical considerations.

The Tissue Procurement Facility was constructed with the goal of banking tissue appropriate for DNA and RNA extraction, tissue arrays, laser-capture microdissection, and immunohistochemistry. Information technology (IT) specialists at Christiana Care designed a dedicated Microsoft Access database for the Tissue Procurement Facility in order to provide documentation of tumor characteristics (e.g., grade and stage) and non-identifying personal information (e.g., age or gender) while protecting patient confidentiality. This system allows for the retrieval of a significant amount of pre-diagnostic and post-surgical information.

The Christiana Care Health System data collection system was subsequently converted to the National Cancer Institute (NCI) Cancer Bioinformatics Grid (caBIG®) tissue program (caTissue) in January 2009. To date more than 3,000 tissue specimens have been collected. In addition to the pathological samples, blood collection on patients also is performed. This program has enabled the Helen F. Graham Cancer Center to participate in the Cancer Genome Atlas Project through its membership in the NCI Community Cancer Centers Programs (NCCCP).

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Recruitment

Staffing the *Cancer Biomarkers and Genetics Program* has required recruitment in both the scientific and clinical arenas. Bruce Boman, MD, PhD, the new Director of Cancer Genetics and Stem Cell Biology at the Helen F. Graham Cancer Center, was jointly recruited by the Cancer Center and the Department of Biological Sciences at the University of Delaware. Using this model, the CTCR plans to recruit additional research-minded physicians and scientists who will divide their time between laboratory research and clinical responsibilities, as well as undergraduate and graduate student education. New investigators will be recruited with either their own grant funding secured or with start-up financial support supplied by the partner institutions for two years and the expectation that, after the start-up phase, outside funding will be obtained by the investigator.

Another mechanism is joint recruitment between the Helen F. Graham Cancer Center and private practice medical, surgical, or radiation oncologists.

The University of Delaware also plans to add additional faculty members with a primary research interest in translational cancer research. State funds have been secured to recruit these positions, and the search committees include both clinicians and basic scientists from the CTCR.

The long-term plan is to continue to recruit faculty and staff into the CTCR who will then serve as principal investigators on applications for federal grant funding. These individuals will serve as research mentors for clinical resi-

dents, postdoctoral fellows, and students at various levels, who will work in the CTCR laboratory at the new Helen F. Graham Cancer Center Pavilion. This co-mingling of researchers and clinicians, on the Christiana Care campus, will foster an environment for translation of discoveries from bench to the bedside, speeding patient recovery.

The Power of Collaboration

Through collaborative efforts such as the CTCR, community cancer centers and basic science centers can join forces to participate in gratifying, stimulating, and collegial exchange that strengthens the institutions and all of the involved investigators and clinicians. The benefits are many:

- The science that emerges is more attuned to patient care issues that include diagnosis, prognosis, and therapy.
- Basic science benefits from a better understanding of the state of the art in disease management, presentation, and outcomes.
- Better research design is fostered with clearly established or desired outcomes that are agreed upon by all parties.
- Graduate and undergraduate students benefit from clinical exposure that would be impossible without the formalized interactions established in the CTCR, while residents are beginning to benefit from research years that immerse them in the university environment and bench science.

Translational research brings advances from bench to bedside, helping to save lives through more rapid development and implementation of ideas that are the result of clinician and scientist interactions.

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