NATIONAL CANCER INSTITUTE
Office of Cancer Genomics

Published on *Office of Cancer Genomics* (https://ocg.cancer.gov)

Issue 3 : December, 2010

DIRECTOR'S NOTE

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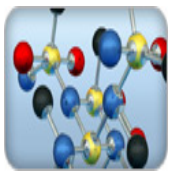
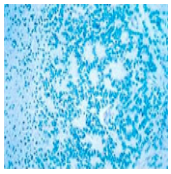
CGCI PROGRAM HIGHLIGHTS



Pediatric Brain Cancer Has Fewer Genetic Changes than Adult Tumors

Pediatric medulloblastoma, the most common malignant brain tumor found in children, contains a fraction of the mutations found in adult cancers, according to a study reported in the Dec. 16 issue of Science. These findings reveal that pediatric tumors are very different from adult tumors of the same cancers.

NCI GENOMIC PROGRAM HIGHLIGHTS



Addition of Immunotherapy Boosts Survival in Neuroblastoma Patients

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CONNECTING THE DATA

New TARGET Data Matrix Designed to Make Data Access User-Friendly

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foster data sharing and team science drawing upon leading research resources across the United States.

FEATURED RESEARCHERS

The Beginning of a Journey: Serving Those Who Have Been Touched by Cancer

The American Association for the Advancement of Science (AAAS) achieves its mission to “advance science, engineering, and innovation throughout the world for the benefit of all people,” through a variety of mechanisms and activities, one of which is the Science & Technology Policy Fellowship program.

DIRECTOR'S NOTE

The Nth Generation Sequencing: How and When will it have an Impact in the Clinic?

Daniela S. Gerhard, Ph.D.

The draft sequence of the human genome was completed in February 2001, and in the decade since publication sequencing technologies have undergone a revolution in throughput and costs. Current methods employ synthesis or ligation for base-call detection, called ‘2nd generation’ sequencing, while recent improvements have introduced the ‘3rd generation.’ The base-call error-rates vary among the technologies. However, these techniques can generate sequence data rapidly such that an entire genome can be obtained to a reasonable coverage in two to four weeks. Moreover, the number of samples sequenced can be easily increased by using more instruments.

The challenge now facing scientists and physicians is how to best apply the data generated to the clinic. Development of analytical pipelines needed to interpret the sequence data will be critical to its success in clinical application. Among the issues to be solved are the volume of raw data generated and the accuracy of the base-calls. Until the analytical challenges are resolved, the existing sequencing methods remain primarily a research tool, rather than a high-throughput, validated method which could be applied routinely in clinical diagnostics and practice.

Once the analytical challenge is overcome, many of the chip-based methods will be replaced with sequencing that will meet a variety of needs including analysis of genome-wide expression profiling, identification of chromosomal aberrations (i.e. amplification, deletion, translocation and/or inversion), epigenetic modifications and disease-associated mutations. Among the advantages of the approach will be the agnostic nature of the test. Since previous knowledge of targets is not required, this approach allows for better precision of the quantitation and improved ability to discover sequence variations as small as one nucleotide and as large as megabase-sized genomic rearrangements.

Sincerely,

Daniela S. Gerhard, Ph.D.
Director, NCI Office of Cancer Genomics

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CGCI PROGRAM HIGHLIGHTS

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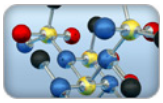

Pediatric medulloblastoma, the most common malignant brain tumor found in children, contains a fraction of the mutations found in adult cancers, according to a study reported in the Dec. 16 issue of *Science*. These findings reveal that pediatric tumors are very different from adult tumors of the same cancers.

Sequencing of expressed exons of almost all genes and miRNAS in nearly two dozen medulloblastoma tumors and analyses of an additional 66 samples revealed a number of genetic changes. This study found the presence of two commonly mutated genes in the epigenetic pathway, *MLL2 and MLL3*, in medulloblastoma tumors. These plus mutations in three additional genes involved in epigenetic imprinting accounted for 20 percent of the mutations in all of the brain cancer samples. In addition, the project found gene mutations in pathways such as Hedgehog and Wnt that control tissue and organ development. Both of these latter two pathways have previously been linked to childhood medulloblastoma.

"With fewer alterations, the hope is that it may be easier to use the information to develop new therapies," said Victor Velculescu, M.D., Ph.D., associate professor of oncology at the Johns Hopkins Kimmel Cancer Center. Johns Hopkins was one of several institutions involved in the study.

"As oncologists, we're working to understand how specific genetic changes found in patients' cancers should guide their treatment," said Will Parsons, M.D., Ph.D., assistant professor at Texas Children's Cancer Center and Baylor College of Medicine. "Any information that allows us to understand a patient's prognosis or provides clues about therapies that may work best in a patient is crucial and will help us provide better care."

The NCI OCG manages the Cancer Genome Characterization Initiative which provided a large portion of the funding for this study at Johns Hopkins University.

Read the full abstract, *The Genetic Landscape of the Childhood Cancer Medulloblastoma.Opens in a New Tab* [2] *Science. 2010 Dec 16.*

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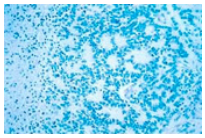
NCI GENOMIC PROGRAM HIGHLIGHTS

Addition of Immunotherapy Boosts Survival in Neuroblastoma Patients



Administering a new form of immunotherapy to children with high-risk neuroblastoma, a nervous system cancer, increased the percentage of those who were alive and free of disease progression after two years, according to a study in the Sept. 30, 2010, *New England Journal of Medicine*. In a randomized phase III clinical trial, 65 percent of children receiving immunotherapy plus standard therapy were free of disease progression compared to 46 percent of children receiving standard therapy alone. Overall survival was also improved in the immunotherapy group with 86 percent of patients alive after two years compared to 75 percent of patients in the standard-therapy group. The clinical trial was coordinated by the Children's Oncology Group (COG), a national consortium of researchers supported by the National Cancer Institute (NCI).

Neuroblastoma is a cancer that arises in immature nerve cells and affects mostly infants and children. The established standard treatment for neuroblastoma employs high-dose chemotherapy, followed by giving back to the patient previously collected blood-forming cells in order to restore immune system function and proper blood cell formation. Patients who respond to this therapy are then given the drug isotretinoin, a vitamin A derivative, to further treat any remaining cancer cells. More than half of high-risk neuroblastoma patients treated with this standard approach succumb to the disease. Researchers are currently searching for a more effective approach to treatment.

A newer approach to cancer treatment is immunotherapy, which in this instance uses an antibody, known as ch14.18, to target a substance on the surface of tumor cells called GD2. Early-phase studies demonstrated the safety and activity of ch14.18 when it was given with other drugs that boost the immune system. Those drugs include a factor which stimulates white blood cell growth and a hormone that increases the number and activity of certain types of immune cells.

"The phase II trial results establish ch14.18 immunotherapy as a new standard treatment for children with high-risk neuroblastoma," said Alice Yu, M.D., Ph.D., University of California, San Diego and study chair of the clinical trial.

A number of side effects did occur in the immunotherapy group; however these were temporary or primarily resolved when treatment was stopped. Future avenues of investigation include developing more effective ways to use ch14.18 that are also less toxic.

Because there was no pharmaceutical company to make ch14.18 when the phase III trial started, NCI manufactured the agent and provided it to COG for the clinical trial. Today, NCI continues to manufacture ch14.18, making it available to children with high-risk neuroblastoma through ongoing Children's Oncology Group clinical trials.

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CONNECTING THE DATA

New TARGET Data Matrix Designed to Make Data Access User-Friendly

Large-scale molecular characterization projects, such as those managed through the NCI Office of Cancer Genomics (OCG), were developed to foster data sharing and team science drawing upon leading research resources across the United States. The ultimate underlying goal of these efforts is to advance the understanding of cancer at the molecular level in order to improve patient care, detect cancer sooner, and treat it more effectively. High quality data generation and sharing are critical to achieving this goal and we have a responsibility to make the data they generate easily accessible and interpretable.

To date, the Therapeutically Applicable Research to Generate Effective Treatments (TARGETOpens in a New Tab [3]) Initiative and Cancer Genome Characterization Initiative (CGCIOpens in a New Tab [4]) have each recently introduced a tabular data matrix approach, with TARGET testing a more detailed format and style that can be incorporated into other OCG projects in the future. The initiative is currently composed of distinct projects examining five childhood cancers, expanding upon a pilot study characterizing patient samples with high-risk acute lymphoblastic leukemia and neuroblastoma. TARGET is making the data generated by its investigators user-friendly and accessible through its tabular TARGET Data MatrixOpens in a New Tab [3], which continues to evolve as data are generated and the community provides feedback.

The TARGET Data Matrix links to as many as four levels of data including names of diseases studied, descriptions of each individual project (pilot and expansion), platforms used to characterize and sequence up to 200 patient samples for each project, and multi-level data ranging from raw to "summarized" for each type of characterization and/or sequencing technique utilized. To facilitate data access, each component of the matrix is hyperlinked to the appropriate data or metadata, which includes descriptive text about the topic, to help the user understand what is available should they choose to explore that particular section. For example, users can quickly learn about a project’s objectives, experimental design and outcome data, allowing researchers to mine the data and foster new scientific discoveries benefiting patients and the scientific and medical communities at large.

OCG projects seek to enhance cancer care through advancing scientific knowledge of the cancer genome that can be linked to treatment outcomes, and by making project data available for mining by the scientific community. This can only be accomplished if the wealth of genomic information generated by OCG initiatives is easily accessible to all users. The data matrices are meant to reflect the needs of researchers accessing the data, and will therefore continually improve through user feedback. Investigators are encouraged to explore the TARGET and CGCI data matrices and provide us with any suggestions to make OCG data access the most user-friendly possible (feedback can be sent to ocg@mail.nih.gov [5]).

OCG Data Portals:

- TARGETOpens in a New Tab [3]
- CGCIOpens in a New Tab [4]
- CGEMSOpens in a New Tab [6]

Select NCI Cancer Genome Data Portals, Integrated Viewers, and Tools

- The Cancer Genome AtlasOpens in a New Tab [7]
- Cancer Genome Workbench (CGWB)Opens in a New Tab [8]

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FEATURED RESEARCHERS

The Beginning of a Journey: Serving Those Who Have Been Touched by Cancer

Robin Shepard Broughton, Ph.D. AAAS Science & Technology Policy Fellow

The American Association for the Advancement of Science (AAAS) achieves its mission to “advance science, engineering, and innovation throughout the world for the benefit of all people,” through a variety of mechanisms and activities, one of which is the Science & Technology Policy Fellowship program. These Fellowships provide scientists with amazing opportunities for professional development and public service by engaging them in policymaking practice and implementation at the federal level. Many of these Fellows continue their career in government service.

My 2010-11 Fellowship year in the Office of Cancer Genomics (OCG) at the National Cancer Institute (NCI) began in September with a AAAS-sponsored fall orientation session. At this orientation, we had the privilege to hear from a diverse group of people, all of whom are working at the intersection of science and policy in various ways, ranging from former congressmen to journalists from the Washington Post. A common theme that echoed throughout many of their messages to us was that of service. We were encouraged to use our unique perspective to discern ways in which we can contribute to the mission of our host agencies.

As a molecular virologist with a focus in HIV biology, serving in OCG signifies a shift for me into a new area of study. For the past few years, I have maintained a strong interest in the concept of personalized medicine, and its potential to transform the way we currently research, diagnose, and treat disease. OCG provides me with the opportunity to better understand the realities underlying this burgeoning field of science. For example, I am currently learning about the utility of genomic and translational technologies in addressing the complex nature of cancer. Moreover, working in this unique capacity affords me the opportunity to appreciate how the NCI, through this and other offices, is actively advancing our knowledge of this burdensome disease.

By linking scientists with expertise in a variety of fields with federally-funded

initiatives focused on understanding cancer etiology through comprehensive approaches, OCG in many ways serves as a conduit for discovery. As a scientist, it is satisfying to see the National Institutes of Health (NIH) function in this manner as it truly exemplifies one of its stated goals, “to foster fundamental creative discoveries, innovative research strategies, and their applications as a basis for ultimately protecting and improving health.”

During my time as a Fellow, my goal is to learn more about how NIH functions and to understand how the various institutes, centers, and offices work together to combat this deadly disease. Within my office, I look forward to gaining a more in-depth understanding of how the information gleaned from genomics studies is translated into novel diagnostics and therapeutics. Over the course of my Fellowship, I hope to contribute my knowledge and skills to aid the Office of Cancer Genomics in their quest to advance scientific discovery in order to better serve those whose lives have been touched by cancer.

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