Chicago Cancer Genome Project studies genetics of 1,000 tumors

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No two tumors are alike, but analyzing the genetics of cancers from different parts of the body may reveal surprising details useful for treatment and prevention.

That process is already gaining traction at the University of Chicago's Institute for Genomics and Systems Biology (IGSB), where researchers are one year into a three-year project to collect and analyze the genetic sequence and variations of every gene expressed by 1,000 tumors.

Over the past year, working closely with physicians, the IGSB team collected complete sequence data for genes expressed by 100 tumors--primarily breast cancer, head and neck cancer, and leukemia. Correlating genetic data with patient outcomes, they have begun to identify genetic patterns within tumors that may help them predict how a cancer will behave. Many experts believe such information will increasingly guide treatment.

"The long-term goal," said IGSB Director Kevin White, James and Karen Frank Family Professor in human genetics and ecology and evolution, "is to translate genomic discoveries into useful diagnostic tools and therapeutic strategies. This should improve patient care."

Not to be confused with the "1,000 Genomes Project"--an international effort to sequence all of the DNA from 1,000 individuals selected from hundreds of distinct populations worldwide--the Chicago 1,000-cancer-genomes project is based entirely at the University of Chicago and

tightly focused on the genetics of this common disease.

"The Chicago Cancer Genome Project is aimed at teaching us how to use the genetic state of the cells as a guidepost for which treatments should be offered to specific patients," White said.

Cancer is a genetic disease. Each tumor's genes provide clues about the severity of the disease. They can sometimes predict whether a cancer will respond to specific treatments, develop resistance to radiation or chemotherapy, relapse after therapy, or spread to a distant site.

Many established cancer treatments grew out of genetic information, beginning at the University of Chicago with Elwood Jensen's discovery of the estrogen receptor in 1958, which led to the development of estrogen blockers such as tamoxifen, and Janet Rowley's descriptions of the first chromosomal translocations in 1972, work that led to the targeted therapy known as Glevec.

But the Chicago Cancer Genome Project is among the first efforts to combine a focus on the genes expressed by multiple cancers with broad scale, systematic implementation. During the pilot phase--sequencing expressed genes from the first 100 tumors--the team established and refined a project framework utilizing the latest in gene-sequencing technology and computational analysis.

"We now know how to do this," said White. "We have the basic structure in place. In the process, we have identified novel genes associated with clinical outcome in selected cancers."

The next steps are to determine how these altered genes act and expand the project to include more tumor types, including cancers of the bladder, lung, pancreas, prostate, as well as several childhood cancers such as rhabdosarcomas and neuroblastomas.

Analyzing a wide variety of tumors may reveal previously unknown genetic similarities in cancers typically classified as different according to tissue of origin, White said.

The genetics of cancer can be extraordinarily complex, said Michelle LeBeau, PhD, director of the University of Chicago Cancer Research Center. "Kevin's team at the IGSB brings all the right tools," she said. "They have the ability to collect and manipulate large amounts of genetic data, the capacity to study not just single genes but entire genetic pathways and their interactions, and a close working relationship with multiple teams of cancer specialists."

The Chicago approach differs from several large-scale cancer-genome efforts in progress. A year ago a team from Washington University published the first cancer genome, from a patient with leukemia. Since then, genomes for breast cancer, melanoma and lung cancer have appeared, and the National Cancer Institute is compiling its Cancer Genome Atlas.

Unlike those projects, the Chicago researchers will study only the genes that are expressed by these tumors—one to two percent of an individual's genome--but will collect genetic data from many more tumors.

"If we eliminate 98 percent of the genome, that makes it 50 times cheaper and easier," said White. "That's still quite a lot of DNA," he emphasized, the equivalent of 20 entire genomes, or about 60 billion base pairs. Collecting genetic information from 1,000 tumors will take about three years, he said, but it will provide information that "can more rapidly be applied to answer clinical questions."

The project also will gather genetic data on how the genes expressed by tumors evolve over time. Whenever possible, the researchers will

compare tumor samples taken from a patient before and after treatments, to learn how cancers accumulate additional genetic changes that enable them to resist radiation or chemotherapy or to spread to distant sites.

All patients must provide prior consent for their tissues to be catalogued and studied. Because the researchers are focused on how genetic clues can predict cancer behavior, the team follows each patient's progress through his or her clinical course.

Most patients have been eager to donate, said cancer specialist Kevin Roggin, MD, assistant professor of surgery, who offers each patient with a pancreatic cancer the opportunity to contribute to a project that could, over time, make a difference in treatment and outcome.

"It is already starting to help," he added. "We are accumulating data that we hope to develop into a molecular fingerprint, a DNA profile that may help us predict which pancreatic cystic tumors are likely to remain benign and which ones will develop into cancers."

Donating tumor tissue requires no extra effort or expense for the patient, said Roggin. "First we make sure we don't compromise the pathologists' ability to make a diagnosis. Second, if there is extra tissue, we flash freeze it to 80 below zero and log it into a database. Then we can store the tissue indefinitely and take what we need to generate DNA and RNA."

The project meshes well with the Medical Center's established program in cancer pharmacogenomics, which studies how certain gene variations influence patient responses to various anti-cancer drugs and develops genetic tests to predict side effects.

"By studying both the tumor and the patient we will, increasingly, be

able to design optimal treatment strategies that offer the best hope for control of the cancer with the least toxicity for the patient," said Richard Schilsky, MD, professor of medicine and chief of hematology/oncology at the Medical Center and past president of the American Society for Clinical Oncology.

"It's a long road from having a piece of genome sequence to improving patient care," White cautioned. "But the path of discovery is clear. In many cases we know enough now to connect the dots."

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