ScientistSpotlight

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New C class tumors hold potential for improved cancer therapy

Introduction

Significant progress has been made over the last several years in the understanding of the molecular biology behind cancers, thanks to many research projects and funding sources. Gordon Mills, MD, PhD, of the University of Texas MD Anderson Cancer Center, is at the forefront of cutting-edge cancer research, and he has found Affymetrix® technology to be instrumental in making key discoveries. Dr. Mills was also a "Dream Team" co-leader in the Stand Up To Cancer® program. In this interview, Dr. Mills discusses the importance of genomic profiling in the discovery of novel predictive markers to improve the effectiveness of cancer treatment.

Affymetrix: What is the Stand Up To Cancer Initiative and what are its goals?

Mills: Stand Up To Cancer (SU2C) is an initiative created about four years ago to accelerate cancer research in order to quickly deliver new targeted therapies to patients and save more lives. The original initiative was organized around interdisciplinary Dream Teams of scientists and clinicians who worked together collaboratively on cancer research projects. This was followed by the funding of a number of highly innovative young investigators to support their career development and research. More recently, SU2C has funded more directed projects with partners such as the Melanoma Research Foundation and the Farrah Fawcett Foundation. The SU2C Dream Team on women's cancers, led by scientists in New York and Texas, did much of the pioneering work on the PI3K (a family of enzymes involved in cellular functions) pathway and included scientists from leading institutions in the US and Spain, along with patient advocates. While that program has now concluded, its work continues on in a number of other projects. Key findings from this initiative were highlighted at the 2014 meeting of the American Association for Cancer Research (AACR).

One of the original goals of the SU2C Dream Team was to determine whether the PI3K pathway plays an important role in cancer. First discovered in the mid-2000s, the PI3K pathway plays a normal role in cell biology and physiology and a key role in signaling. This pathway has been identified to be consistently abnormal in diabetes patients and is now known to be the most commonly activated pathway in cancer. The PI3K pathway is essentially hijacked in many forms of cancer, and it is amplified in breast and ovarian cancer. The challenge now is to target this pathway. Findings like these have steered new research on comprehensive tumor profiling, particularly on mechanisms of resistance.

Affymetrix: How will knowledge about the PI3K pathway be used?

Mills: Team members are working on therapies designed to block abnormal signaling in the PI3K pathway, and they are conducting clinical trials to determine which cancers will respond

Gordon Mills, MD, PhD, is chair of the Department of Systems Biology at MD Anderson Cancer Center at the University of Texas in Houston. He is also Professor of Medicine and the chair for cancer research at the university. A native of Edmonton, Alberta, Mills holds a BS in Medicine, an MD, and a PhD in Biochemistry. He has published over 575 research articles.

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positively to the therapies. The team is also working to identify biomarkers that will indicate how likely a patient is to respond to the therapy.

Affymetrix: What are some of the more recent findings?

Mills: Drugs targeting the PI3K pathway have been somewhat effective, but it is believed that other genetic aberrations are involved with this pathway that cause therapy resistance in patients and limit the effectiveness of the drugs. Therefore the most effective treatment may be one that targets multiple aberrations impacting this pathway. A whole-genome approach is required to reveal what parts of the pathway are affected. Ideally we wanted to identify all the genetic aberrations that we can target at once, so that we can see if there are other targets. There is clearly a population that responds to PI3K inhibitors, but not as many as we would like. Therefore we are looking for related targets and combination therapies.

Affymetrix: Where does the Affymetrix technology fit in?

Mills: A recent publication in *Nature Genetics*[1] analyzed TCGA genomic data from 12 different tumors and classified solid tumors into two mutually exclusive classes: "C" class tumors, which are largely driven by copy number alterations; and "M" class tumors, which are largely driven by somatic mutations. Women's cancers, such as breast and ovarian, which are the research focus of the PI3Kinase Dream Team and our team at MD Anderson, have been classified as C class tumors.

"A recent publication in *Nature Genetics*[1] analyzed TCGA genomic data from 12 different tumors and classified solid tumors into two mutually exclusive classes: "C" class tumors, which are largely driven by copy number alterations; and "M" class tumors, which are largely driven by somatic mutations."

We have worked closely with Affymetrix to apply the company's Molecular Inversion Probe (MIP) technology to the identification of clinically relevant copy number aberrations. This is because OncoScan® FFPE Assay Kit, based on the MIP technology, is particularly effective in detecting copy number from formalin-fixed, paraffin-embedded (FFPE) samples, which are the standard clinical sample type for cancer research and are often highly degraded. This assay is extremely attractive in the clinical research setting because it is robust and fast—you can generate results from extracted DNA in just 48 hours.

Affymetrix: What other technologies are available for copy number detection?

Mills: Next-generation sequencing is another widely used technology, but it has drawbacks when it comes to copy number. When using next-generation sequencing technologies, it is difficult to detect modest but clinically relevant copy number changes from FFPE samples. However, with the help of MIP technology, it is possible to generate robust copy number data from this sample type. The OncoScan FFPE assay is the most robust and reproducible assay available today for the detection of copy number changes in FFPE samples, and this data is useful in stratifying patients for clinical trials.

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Our work has demonstrated the utility of whole-genome copy number analysis, and this has encouraged other researchers to look at this approach.

Affymetrix: What research is currently going on at MD Anderson?

Mills: MD Anderson has a number of ongoing studies using several approaches. These include studies showing the responses of specific tumors to different drugs. There has been remarkable progress in improving responsiveness to therapies in breast cancer, lung cancer, and melanoma by linking molecular changes to drugs. The biggest impact of this work has been in the study of breast cancer. Trastuzumab therapy for HER2 amplified patients has delivered a dramatic impact on some patients' survival rate. However, targeted treatments are still not available for most cancers, and they have not had an impact on survival rate in many patients eligible for targeted therapy. We are continuing to learn more

about why this happens. For example, we now know that a high-level amplification of the mutant allele of PIK3CA causes resistance to selective phosphoinositide 3-kinase inhibitors in HER2 positive breast cancer and keeps the tumor cells alive. Therefore, both the HER2 and PI3Kinase pathways must be targeted with combination therapies for the treatment to be effective. This is where the exciting work is now.

This therapy resistance mechanism was discovered by conducting a whole-genome copy number scan using the OncoScan® assay, and the results have been published in *Oncogenesis,*[2] a Nature journal.

At AACR 2014, researchers presented outcomes of early trials showing work targeting PI3K with impressive outcomes. Combination therapies are also showing more promise, and we will be hearing more about this soon. The whole concept of companion therapeutics is changing as we gain a better understanding of tumors. Five years ago the focus was on testing the effectiveness of available drugs. Now we are focused on druggable targets. MD Anderson is collaborating with many pharmaceutical companies on this research.

Affymetrix: What is the view of the future of personalized medicine?

Mills: While the OncoScan assay represents a big advance in copy number research, more work needs to be done to reduce the cost of clinical trials incorporating targeted therapies. More work is also needed in demonstrating that the results of these tests actually help the patient long-term. Ultimately we can realize real cost savings by reducing wasted therapies that will be demonstrated to be ineffective while advancing more personalized therapies.

Cancer takes one person every minute. Every day in America, 1,500 people die despite the fact that the means to save them are within our reach. For the first time in history, we can envision the possibility of stopping cancer in its tracks.

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1. Ciriello G., *et al*. Emerging landscape of oncogenic signatures across human cancers. *Nature Genetics* **45**(10):1127–1133 (2013). doi: 10.1038/ng.2762.

2. Huw L., *et al.* Acquired PIK3CA amplification causes resistance to selective phosphoinositide 3-kinase inhibitors in breast cancer. *Oncogenesis* **2**:e83 (2013). doi:10.1038/oncsis.2013.46.

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