

NEWS IN DEPTH

Q&A: Louis Staudt on Genomics Initiatives

As TCGA wraps up, NCI looks to build a balanced portfolio of 'omics research programs

Louis Staudt, MD, PhD, who has led discoveries on the molecular basis of lymphoid malignancies, runs the National Cancer Institute's (NCI) Center of Cancer Genomics. He talked with *Cancer Discovery's* Eric Bender about progress and plans at the center, now the home for major programs including The Cancer Genome Atlas (TCGA), the Therapeutically Applicable Research to Generate Effective Treatment (TARGET) pediatric study, and the Cancer Target Discovery and Development functional genomics effort.

What was behind the founding of your center?

It was formed a little more than a year ago with the understanding that genomics is with us to stay. We needed some strategic thinking around how best to incorporate genomics into all aspects of work at NCI, from early basic science discovery through clinical trials, and how to partition those efforts.

How will people look back on TCGA?

As we finish up TCGA and tie it up with a bow, we will declare quite a lot of victories. It provided a basic science foundation for understanding the genetics of cancer.

In certain highly diverse cancers such as lung cancer, it's particularly clear that the 500 cases studied in TCGA are a foundation but not the end of the story. We do believe, however, that we have found many of the genetic hallmarks that occur in 5% to 10% of individuals with a particular cancer histology. This has led to an appreciation of cancer pathways that just were not envisioned 4 years ago, such as the pervasive effect of mutations in epigenetic modulators. Of course, in addition to TCGA, there has been much good work done by many other people in systematically studying genetic change in cancer.

What's the strategy behind the suggestion to follow up TCGA by sequencing 10,000 cases for certain heterogeneous cancers?

It's very important to have our current discussion about how we balance the priorities of doing structural genomics versus other NCI priorities.

If we do the math, it is inescapable that gaining a full genetic understanding of the potential driver mutations occurring in 1% or more of individuals with heterogeneous cancers will require us to eventually study 10,000 cases. It would be impossible to do 10,000 cases at the scale of the TCGA studies. But there may be ways to economize in the effort to get to that goal. Technologies are evolving such that we can drive the costs of sequencing way down, and we also may be able to lower expenses by acquiring tumor samples via other clinical activities that will happen as a matter of course.

Can you give an example of piggybacking onto clinical studies to keep costs down?

One is a large lung cancer trial called ALChEMIST (Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial) that combines two agents targeting EGFR and ALK in an adjuvant setting. To ascertain the patients that have those genetic abnormalities for the treatment arm, the trial must look at the tumors of more than 7,000 individuals with lung adenocarcinoma. The trial will prospectively follow those 7,000 patients as a cohort, and if the patient relapses it will collect biopsies at the time of relapse to identify acquired mutations. Giving us the ability to draw on all these biopsies, ALChEMIST is a perfect example of a trial that addresses an important clinical question and lets us learn some needed basic biology and genetics of lung adenocarcinoma in the process.



National Cancer Institute

"Gaining a full genetic understanding of the potential driver mutations occurring in 1% or more of individuals with heterogeneous cancers will require us to eventually study 10,000 cases," says Louis Staudt, MD, PhD.

Are you tightening links to programs outside NCI?

Yes, that's a really important point, and it's one reason we want to foster computational platforms to get more information and more understanding out of the data we've already collected. For example, one big challenge will be to understand the oncogenic functions of mutations in the noncoding portions of the genome, and there the ENCODE (Encyclopedia of DNA Elements) project will be a key starting place.

What new functional genomics programs are under way?

We have some in collaboration with NCI's Division of Cancer Treatment and Diagnosis—for example, the Exceptional Responders initiative, a phenotype-to-genotype study that observes an outlier patient's response to a particular therapeutic agent and looks at the whole genome to try to understand why there was such an unusual response. Another example is the NCI Molecular Analysis for Therapy Choice (MATCH) program, which is a parallel, genotype-to-phenotype study that will attempt to look at particular genomic lesions that may indicate a response to a particular targeted agent.

There are exciting new opportunities having to do with *in vitro* models of cancer as well. Use of ROCK inhibitors and organoid cultures has allowed us to make many new cell lines and complicated cultures derived from epithelial cancers, with the ability to accelerate our understanding of how the genome functions. If we could somehow develop a comprehensive panel of cell lines with the genetics that reflect recurrent abnormalities in tumors, then we could give cancer biologists many new tools. ■

CANCER DISCOVERY

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Cancer Discovery 2013;3:1213. Published OnlineFirst October 24, 2013.

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