

# Translational science in ACOSOG trials

by David M. Ota, MD, FACS; Heidi Nelson, MD, FACS; and Elaine Mardis, PhD

Laboratory research must be translated into practical applications in order to improve cancer treatment. A unique feature of a surgeon-based clinical trials group is the ability to collect annotated tissue specimens from prospective therapeutic trials for laboratory research. Surgeons are referred patients who have potentially resectable disease, and thus are well-positioned in the health care delivery stream to explain treatment option, explain the purpose of research tissue acquisition, and, above all, obtain patient informed consent. New laboratory research technologies often require fresh tissue specimens that are either frozen or placed in a preservative and shipped to a central specimen bank. This process follows all regulatory laws that protect patient identity and, at the same time, provides specimen access to the scientific community.

Laboratory scientists' need for cancer specimens has changed in the past decade. Genome sequencing, RNA expression, and proteomics require well-preserved specimens in order to extract DNA, RNA, and proteins

with minimal degradation. While much can be accomplished with formalin-fixed paraffin embedded tissues, emerging laboratory technologies are often hindered by the degradation of important molecules in tissue fixatives.

Surgeons are referred patients with resectable disease, at which point they perform routine clinical staging, and discuss treatment options with their patients. Because surgeons stand at this pivotal position of cancer care, their discussion with patients regarding clinical trial participation is becoming crucial to neoadjuvant and adjuvant therapeutic trials and specimen collection.

Neoadjuvant trial designs for locally advanced primary disease offer surgeons an opportunity to obtain a research biopsy of the primary tumor, which is in a relatively accessible site. An important focus of cancer research is to identify a subset of patients whose tumors express a specific biomarker for drug sensitivity. A great example is the breast surgeon who frequently orders hormonal and HER2/neu sensitivity tests in resected primary breast cancer. In the future, surgeons may be ordering tests for specific epidermal growth factor receptor EGFR mutations in non-small cell lung cancer NSCLC to assess sensi-

tivity to EGFR tyrosine kinase inhibitors.\*

The collection of blood samples before surgical resection of primary tumors offers scientists a great opportunity to study biomarkers for early detection of disease; ACOSOG is currently involved with such endeavors. ACOSOG Z4031 is an outstanding example of thoracic surgeons looking to solve the problem of developing a blood test for early detection of NSCLC in a high-risk population. Proteomics are currently being studied by a group led by Steven Dubinett, MD, at the University of California, Los Angeles, CA, using samples from Z4031.

Another remarkable technology application is whole-genome sequencing. A decade ago, the cost of sequencing the first human genome was \$3 billion, and it took 10 years to complete. Today's "next-generation sequencing" instruments can sequence a human genome for \$50,000 in seven days, with further dramatic decreases in cost and throughput. Dr. Mardis (one of the coauthors of this article) is Chair of the ACOSOG Basic and Translational Science Committee and is codirector of The Genome Center at Washington University, St. Louis, MO, where the

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\*Govindan R. INTERESTing biomarker to select IDEAL patients for epidermal growth factor receptor tyrosine kinase inhibitors: Yes, for EGFR mutation analysis, others, I PASS. *J Clin Oncol.* 2009;25:1637.

application of whole genome sequencing to cancer cases is being pursued aggressively.

This genomic technology—along with the analytical software needed to identify key mutations and structural changes in the genome—may provide clues to understanding genetic mechanisms of tumor response or no response in neoadjuvant trial designs, and to identify new targets for systemic treatment. The approach already has identified highly recurrent mutations with prognostic value in acute myeloid leukemia specimens.<sup>†</sup> This approach is also now being applied to ACOSOG Z1031 pretreatment specimens, in order to identify the gene signature profiles of the tumor response/no response to aromatase inhibitor phenotypes. The hypothesis is that tumor response to therapy is genetically determined. If this hypothesis is proven with Z1031, then it may be applied to other ACOSOG neoadjuvant trials, as well.

This research is the culmination of computing technology, DNA sequencing technology, and

massive digital data storage and processing capabilities. The key to unlocking this research capability is appropriately preserved DNA from patients who have given informed consent. Surgeon participation is crucial to obtain such DNA with clinical data.

ACOSOG, with its surgeon network, is well positioned to support cancer DNA, RNA, and protein research. Future clinical trials are needed and may allow surgeons, medical oncologists, and radiation oncologists to tailor therapies to subsets of patients who will likely benefit from specific resection/ablation and systemic therapies.

ACOSOG leaders are excited about the future of a surgeon-oriented national cooperative group and the pivotal role of practicing surgeons in cancer research. Your participation will likely improve cancer treatment outcomes. To learn more about ACOSOG go to <http://www.acosog.org>.

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