

NSCLC Evolution Studies Refine Biomarkers

Latest insights from TRACERx could lead to new prognostic tests and cellular immunotherapies

New biomarkers derived from an ongoing analysis of patients with non-small cell lung cancer (NSCLC) could help clinicians better predict the likelihood of recurrence, according to the latest data from TRACERx, a major British effort to understand the genetic landscape of this disease.

These findings from the \$18 million project—now more than halfway through its 9-year timeline—are described in two concurrently published articles. A third report sheds light on the spatial nature of antitumor immune responses, and pinpoints T-cell receptors (TCR) that could potentially be co-opted to combat NSCLC.

Collectively, the results of the three new studies are “highly promising,” says Aadel Chaudhuri, MD, PhD, of Washington University School of Medicine in St. Louis, MO, who was not involved in the research. “TRACERx is giving us a better understanding of tumor heterogeneity and genomics through multiregion sequencing, and now we have new biomarkers to test that could be practice-changing clinically.”

In the first study, a team co-led by TRACERx head Charles Swanton, PhD, of the Francis Crick Institute and University College London (UCL) in the UK, uncovered a 23-gene prognostic signature that accounts for heterogeneity within tumors, a problem that results in sampling bias and has long confounded other molecular biomarker tests (Nat Med 2019;25:1540–8).

Dubbed ORACLE, this new signature builds on the team’s 2017 finding that lung cancer genomes are prone to widespread DNA copy-number variation within tumors (Cancer Discov 2017;7:546). Here, the team looked at transcriptomic differences, analyzing 156 tumor regions from 48 patients and showing that RNA-expression profiles, too, varied widely from one cancer subclone to the next.

The researchers then focused on genes whose RNA expression was stable intratumorally, but highly variable between patients. A machine-learning algorithm winnowed the candidate list down to 23 genes, and ORACLE was born. Using this signature, Swanton and colleagues stratified a cohort of 60 patients with stage I NSCLC into high- and low-risk subgroups with significantly different survival times.

“What they did is really clever,” says Samuel Bakhom, MD, PhD, of Memorial Sloan Kettering Cancer Center in New York, NY, of this effort to address RNA-level intratumoral heterogeneity. “It’s a paradigm shift of how we should be thinking about transcriptional biomarkers.”

Meanwhile, another team from the TRACERx consortium, led by Caroline Dive, PhD, and Ged Brady, PhD, of the Cancer Research UK Manchester Institute, reported on a biomarker—one based on blood and not tissue—that could be indicative of patient outcomes after surgery (Nat Med 2019;25:1534–9).

Some of Swanton’s earlier work had shown the prognostic value of using circulating tumor DNA to help identify patients likely to experience recurrence (Nature 2017;545:446–51). However, such a test would rely on blood samples collected postoperatively, after the regrowing cancer had released measurable quantities of cell-free DNA. Instead, for an earlier readout of relapse risk, Dive’s group searched for circulating tumor cells (CTC) in pulmonary vein (PV) rather than peripheral blood samples, obtained from 100 patients during surgery.

PV-CTCs were found in nearly half of those evaluated, and patients with larger numbers of these disseminated cells were more likely to experience disease recurrence within the next 4 years. This suggests that PV-CTC profiling could help identify patients who stand to benefit from increased monitoring or who may be good candidates to receive chemotherapy after surgery, notes Dive. However, she cautions that “we need to do a prospective larger study to really qualify that as a biomarker of lung-specific recurrence.” Her team additionally plans to implement alternative CTC-capture technologies to overcome the limited sensitivity of their test—just 32% to 45%, depending on the cutoff selected.

Zeroing in on one patient whose disease spread to his right pleural cavity 10 months after surgery, the researchers used single-cell DNA sequencing to reveal a higher degree of mutational overlap between the patient’s PV-CTCs and his metastatic lesion, compared with the primary tumor: 91% versus 79%.

“It’s one case study,” says Brady, “but there are implications that PV-CTCs obtained at resection can provide unique insights into what’s important for the spread of the disease.” For example, the patient’s PV-CTCs and metastatic lesion, but not his primary tumor, had an inactivating driver mutation in *LZTS1*, a tumor suppressor. “This may be linked to the biological process of those cells escaping the primary tumor,” Brady says. Although there are no drugs directed at *LZTS1*, it “could be a potential therapeutic target eventually.”

UCL’s Benny Chain, PhD, spearheaded the third study, which examined the spatial distribution of TCRs found in the tumor microenvironment of 72 TRACERx participants (Nat Med 2019;25:1549–59). His group showed that some TCRs were found throughout the tumor and others only in particular locations corresponding to regional mutations. As Chain points out, “the immune system, via the T cells, is actually mirroring the genetic diversity” of the tumor.

Notably, many of these TCRs also exist and persist in the bloodstream. “So we could in theory access them” to be harnessed for adoptive T-cell immunotherapy, says Chain. However, tumors have multiple ways of evading immune detection, as evidenced by previous TRACERx findings, so it’s possible that expanded TCRs in the circulatory system may no longer yield antigen-specific immune responses (Nature 2019;567:479–85). “We can’t be sure that the T cells that we see are not the ones the tumor has already escaped from,” says Chain, “and that’s a bit of a problem.”

Future TRACERx studies involving larger sample sizes, longer follow-up periods, and post-treatment outcomes should continue to provide clinically relevant insights into the evolution of NSCLC, notes Bakhom. “I foresee a very critical juncture coming up,” he says. —*Elie Dolgin* ■