Cancer-causing mutation discovered in 1982 finally target of clinical trials

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In 1982, the gene TRK was shown to cause a small percentage of colon cancers. In 2013 and 2014, next-generation sequencing of tumor samples found fusions of the TRK family of genes in at least 11 tumor types, including lung, breast, melanoma and more. Now, a recent article in the journal *Cancer Discovery* describes clinical trials at the University of Colorado Cancer Center and elsewhere that match drugs to this long-overlooked oncogene, offering targeted treatment options for cancers that harbor these gene abnormalities (e.g. ClinicalTrials.gov #NCT02122913).

"We didn't initially discover the gene. But now technology lets us find the gene in actual patient samples and drugs are available to target these gene rearrangements, making it possible to treat TRK cancers in clinical trials in ways we only dreamed of thirty-two years ago," says Robert C. Doebele, MD, PhD, investigator at the CU Cancer Center and associate professor of Medical Oncology at the CU School of Medicine.

The TRK family of genes, including NTRK1, NTRK2 and NTRK3 are important in the developing nervous system. In the womb, these genes and the proteins they encode are essential for the growth and survival of new neurons. After birth, these genes are unneeded in many tissues and so are programmed to go dormant. Some cancers wake them up - when improperly fused with other nearby genes, genes in the TRK family can restart their ability to signal cells to grow and become immortal, which in adult tissues can cause cancer.

"What we're finding is that while TRK fusions may not be the major cause in any single, major cancer, it's the cause of small percentages of many cancer types," Doebele says.

For example, the recent article cites studies showing NTRK fusions in 3.3 percent of lung cancers, 1.5 percent of colorectal cancers, 12.3 percent of thyroid cancers, about 2 percent of glioblastomas, and 7.1 percent of pediatric gliomas (brain tumors).

"These numbers add up," Doebele says.

A decade ago, the NTRK fusion and other, related gene rearrangements were un-druggable. Now, an entire class of drugs has been developed to target this type of genetic abnormality, namely "tyrosine kinase inhibitors," which are able to precisely turn off these genes like NTRK that send dangerously misplaced cell-survival signals. For example, the FDA-approved drug crizotinib targets ALK and ROS1 fusion genes in lung cancer.

A host of new drugs in this class of tyrosine kinase inhibitors target TRK fusions, for example investigational anti-cancer agents RXDX-101, TSR-011, LOXO-101, PLX-7486 and more.

"A lot of doctors in academia or community hospitals are ordering next-generation sequencing panels for their patients. If it turns out that patients' tumors have TRK alterations, I want their doctors to know that there are treatment options available via clinical trials," Doebele says.

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