

NTRK1: A new oncogene and target in lung cancer

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To the list of oncogenic drivers of lung cancer that includes ALK, EGFR, ROS1 and RET, results of a University of Colorado Cancer Center study presented at ASCO 2013 show that mutations in the gene NTRK1 cause a subset of lung cancers.

"We're reconceptualizing lung cancer as many, related diseases. And we need to learn to identify and treat each individually. We can treat the forms of the disease that depend on ALK and EGFR mutations. We're getting very close to treating lung cancers that depend on ROS1 and RET. And now we show another oncogenic driver of the disease that begs its own targeted treatment," says Robert C. Doebele, MD, PhD, investigator at the CU Cancer Center and assistant professor of [medical oncology](#) at the CU School of Medicine.

The group, in collaboration with Pasi A. Jänne, MD, PhD from the Dana-Farber Cancer Institute, started with lung cancer tumor samples from 36 "pan-negative" patients, meaning that no other driver [oncogene](#) had been identified. So if not EGFR, ALK and the like, what was driving the cancer? Doebele and colleagues took the question to Foundation Medicine (Cambridge, MA), which used targeted, next-gen sequencing to analyze the samples for possible mutations in a couple hundred potential oncogenes identified as drivers of other cancers. NTRK1 had been identified as a driver of [thyroid cancer](#) and so was included in the panel (though drug development had stalled due in part to the relative rarity of the [thyroid disease](#)). Sure enough, next-gen sequencing identified NTRK1 gene fusions as the potential driver in two of these

samples.

Doebele and colleagues took the lead back to the CU labs, where Marileila Varella Garcia, PhD, developed a specific test for NTRK1 fusions based on fluorescence in situ hybridization (FISH), similar to what is used for ALK, ROS1 and RET fusions. This allowed the group to validate the finding of NTRK1 as a novel oncogene in these patient samples.

But the study went a step beyond identifying the oncogene. Doebele describes the relative ease with which genes that are improperly activated can be silenced – "whether a drug is already in clinical trials, or already approved for another cancer, or just sitting on the pharma shelf somewhere, many drugs exist that turn off these candidate genes," Doebele says.

In this case, Doebele describes "walking up the street to Array BioPharma (Boulder, CO), who happened to have several compounds specific for this gene."

The group showed that mutated NTRK1 genes in cells treated with drug candidates ARRY-772, -523, and -470 and others was effectively turned off.

"This is still preclinical work," Doebele says, "but it's the first – and maybe even second and third! – important steps toward picking off another subset of [lung cancer](#) with a treatment targeted to the disease's specific genetic weaknesses."

Provided by University of Colorado Denver

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