Nature Reviews Clinical Oncology **9**, 188 (2012); published online 28 February 2012; doi:10.1038/nrclinonc.2012.26

GENETICS

Gene fusion power

The receptor tyrosine kinases ALK and ROS are expressed as oncogenic fusion proteins in a small proportion of non-small-cell lung carcinomas (NSCLC) and other tumor types. For patients who harbor these genetic rearrangements, targeting fusion proteins has proved to be a very successful treatment. So successful, in fact, that the tyrosine kinase inhibitor crizotinib was approved by the FDA shortly after it was developed. "Since then, the hunt has been on to find other fusion genes that can be tested for in advance and used as specific drug targets," explains Ross Camidge, an expert in the field at the University of Colorado. This hunt has now provided us with three articles published recently in *Nature Medicine*, which describe new 5' fusion partners and variants of fusions for both *ALK* and *ROS1*.

In the first of these articles, Takeuchi *et al*. integrated a molecular and histopathology-based screening system to analyze more than 1,500 samples of lung cancer to identify *ALK* and *ROS1* fusions as well as a new class of fusions involving kinesin family member 5B (*KIF5B*), coiled-coil domain containing 6 (*CCDC6*) and *RET* kinase, which may represent new therapeutic targets in adenocarcinoma. "Gene fusions are attractive as they are relatively easy to test for and RET was already a validated target with established drugs in the clinic based on its previous exploration in medullary carcinoma of the thyroid," explains Camidge. Indeed, these results were further confirmed by another of the three studies in which Kohno *et al.* reported *KIF5B–RET* fusions in 1–2% of patients with lung cancer, independent from *ALK* and *ROS1* fusions, and that can potentially be targeted using RET kinase inhibitors. Last but not least, Lipson *et al*. used next-generation sequencing to describe a series of genetic rearrangement in colorectal cancer and NSCLC, identifying previously unknown alterations in NSCLC, such as mutations in *JAK2*, as well as *KIF5B–RET* fusions, both of which may represent druggable targets.

What are the implications of these studies? According to Camidge, "with these papers we now have a stronger idea of the frequency of these abnormalities and the different methodologies that can be used to detect them, including next-generation sequencing, FISH and whole transcriptome sequencing. Although, each abnormality may be present in only a few percentage of cases of lung cancer, the development of cheaper multiplexed assays to assess multiple different abnormalities in each patient offers the potential to routinely parse lung cancer into multiple different clinically relevant molecular disease types in the near future."

Getty

M. Teresa Villanueva

Original articles Kohno, T. *et al*. KIF5B-RET fusions in lung adenocarcinoma. *Nat. Med*. doi:10.1038/nm.2644 | Lipson, D. *et al*. Identification of new ALK and RET gene fusions from colorectal and lung cancer biopsies. *Nat. Med*. doi:10.1038/nm.2673 | Takeuchi, K. *et al*. RET, ROS1 and ALK fusions in lung cancer *Nat. Med*. doi:10.1038/nm.2658