Deamplifying lung cancer

By Chris Cain, Staff Writer

An international research collaboration has found amplification of *fibroblast growth factor receptor 1* in a substantial fraction of squamous cell lung cancer cases, providing a new therapeutic target for the disease and a new indication for companies developing inhibitors for the receptor for other cancers.¹ Next month, the investigators plan to start a Phase I trial of a small molecule inhibitor for this target.

Squamous cell lung cancer is a form of non-small cell lung cancer (NSCLC) that is commonly associated with a history of smoking. Although oncogenic mutations have been identified and exploited to treat adenocarcinoma, another distinct form of NSCLC, these mutations are rarely found in squamous cell lung cancer.

Previous studies had identified only one gene that is commonly amplified in squamous cell lung cancer: *SOX2*.² The problem is that *SOX2* codes for a transcription factor, which makes it a challenging drug target at best.

To identify new therapeutic targets, a team led by Roman Thomas, principal investigator at the **Max Planck Institute for Neurological Research** and professor of internal medicine and integrated oncology at the **University of Cologne**, examined the genomes of 155 primary squamous cell lung cancer samples using high-resolution SNP arrays. These samples were collected as part of the Clinical Lung Cancer Genome Project, a worldwide collaboration between 14 centers that is headed by Thomas.

Thomas' team initially found *fibroblast growth factor receptor 1* (*FGFR1*; *CD331*) amplification in 9.7% of specimens. *FGFR1* is a member of a family of four tyrosine kinases closely related to VEGF receptor (VEGFR). The team went on to show that in an independent set of 153 samples, 22% had high-level amplification of *FGFR1* as measured by fluorescent *in situ* hybridization. The 22% of samples were all from current or former smokers.

Next, the researchers tested the therapeutic potential of *FGFR1* inhibition. In xenograft mice with squamous lung cancer cells that had amplified *FGFR1*, PD173074, a research-grade *FGFR* inhibitor, decreased tumor size compared with vehicle control. Although *FGFR* inhibitors are nonspecific and can affect more than one type of

FGFR, RNAi and mutational analysis confirmed that *FGFR1* inhibition specifically was responsible for the effect of the drug.

Results were published in *Science Translational Medicine*, and researchers hope these findings are only the first of many to come from this collection of almost 2,000 lung cancer samples with accompanying clinical data.

Thomas told *SciBX*, "Finding *FGFR1* amplification was the first result of this endeavor; we had just begun to analyze the data from the first couple of hundred samples when we saw this strikingly frequent genomic alteration, and we expect additional findings will emerge as we further analyze these large datasets."

Fighting FGFR

Next month, the University of Cologne plans to start a Phase I trial of an undisclosed small molecule *FGFR* inhibitor to treat patients with *FGFR1*-amplified squamous cell lung cancer.

Thomas did say that because there is a strong precedent for resistance to develop against inhibitors of a growth factor receptor in lung cancer, "we expect resistance to be a problem, and we are already working on establishing models of acquired resistance. We know resistance will occur, and we want to understand both upfront resistance and acquired resistance."

Raffaella Sordella, assistant professor at **Cold Spring Harbor Laboratory**, agreed that resistance to *FGFR* inhibitors is almost a given in lung cancer. Her lab is focused on understanding how resistance develops in epidermal growth factor receptor (*EGFR*)-mutant lung adenocarcinoma. "It would be interesting to see if these *FGFR1*-amplified cancer cells become oncogenically addicted through the same signaling pathways as *EGFR* mutant cells because that could suggest a common downstream target to go after. It is known that upregulation of certain FGF receptors can promote resistance

to *EGFR* inhibitors, but the similarities and differences in signaling are unclear at this point."

FGFR1 amplification has previously been detected in breast cancer, and overexpression of *FGFR1* has been detected in many other cancers, suggesting that inhibiting excess signaling of the receptor could help treat forms of cancer outside of the lung.³

At least one company—**Five Prime Therapeutics Inc.**—has been mulling the lung cancer indication for its FP-1039 candidate, a soluble fusion protein that contains the extracellular portion of *FGFR1* attached to a human antibody. The compound acts as a ligand trap and inhibits *FGFR* signaling by neutralizing the effect of most FGF molecules, potentially causing fewer side effects than small molecule kinase inhibitors because it does not block all *FGFR* signaling.

"We have already tested our compound and have promising results in a number of lung cell lines used in xenograft mouse models. Based in part on these results, we advanced FP-1039 into a Phase I trial to

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—Lewis Williams,
Five Prime Therapeutics Inc.

treat solid tumors. We are quite excited about the findings in the paper because they provide further validation of a pathway that we have been working on. The results of this paper have reaffirmed our plans to study the effects of FP-1039 in lung cancer and suggest the patient population in which FP-1039 might be most effective,” said Lewis Williams, executive chairman and founder of Five Prime.

FP-1039 is in a Phase I trial to treat solid tumors and is expected to complete this trial in 1Q11. The company plans to conduct additional clinical trials of FP-1039 but would not disclose a timeline.

Small molecule FGFR inhibitors in the clinic include **AstraZeneca plc**’s AZD4547, which is in Phase IIa testing to treat patients with estrogen receptor–positive breast cancer with high levels of FGFR1, and **Novartis AG**’s BGJ398, which is in Phase I trials to treat solid tumors with FGFR1 or FGFR2 amplification or FGFR3 mutation. Both companies declined to comment on the *Science Translational Medicine* paper.

Thomas has not filed patent applications covering the work described in the paper.

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