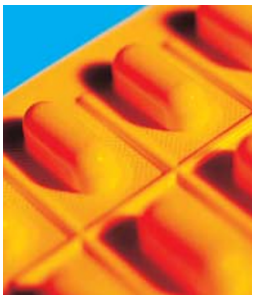


Mutations predict gefitinib response

The identification of 'responder' mutations in *EGFR* is another step forward in cancer pharmacogenetics.

Simon Frantz

Two studies have identified mutations in tumours that could be predictive of which patients benefit from the epidermal growth factor receptor (EGFR) inhibitor gefitinib (Iressa; AstraZeneca) for lung cancer.

Gefitinib was approved by the FDA a year ago for the treatment of advanced non-small-cell lung cancer (NSCLC) without any survival data. But trials showed that it could shrink tumours dramatically — between 50–90% — in around 13% of patients.

This could be explained by the presence of point or deletion mutations in the *EGFR* gene, according to studies published in the *New England Journal of Medicine* and *Science*. In the *NEJM* study, led by Daniel Haber at the Massachusetts General Hospital, tumour biopsies from eight out of nine patients with gefitinib-responsive lung cancer carried these mutations, compared with none from seven non-responders. Similar mutations were detected in tumours from 2 out of 25 patients with primary NSCLC who had not been treated with gefitinib (Lynch, T. J. *et al. N. Engl. J. Med.* published online 29 Apr 2004 doi: 10.1056/NEJMoa040938).

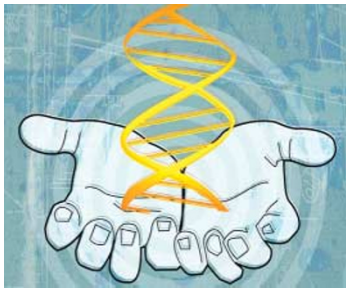
Another Harvard-based group, led by Matthew Meyerson, William Sellers and Bruce Johnson at the Dana-Farber Cancer Institute, showed in their *Science* paper how *EGFR* mutations were found in 15 of 58 unselected tumours from Japan and 1 of 61 from the United States. All five samples selected that had *EGFR* mutations were from treatment responders (Paez, J. G. *et al. Science* published online 29 April 2004 doi: 10.1126/science.1099314).

The mutations affect the tyrosine kinase domain of EGFR, and seem to influence the protein's sensitivity. Haber's group showed that *in vitro*, EGFR mutants had enhanced tyrosine kinase activity in response to epidermal growth factor and increased sensitivity to gefitinib-mediated inhibition. Meyerson's group pointed out that greater responses were more frequent in women, non-smokers and patients with adenocarcinomas.

"The findings show two things," says Meyerson. "First, mutations in *EGFR* are the key factor driving EGFR-dependent tumour growth and determining sensitivity to Iressa. Second, our results and the Herceptin connection to HER2 amplification show that the success of Gleevec [imatinib; Novartis] in treating cancers with mutant kinases is really the start of a new paradigm."

The mutations are unlikely to account for the 30% of patients in which gefitinib causes disease stabilization, but these findings are being hailed a success for cancer pharmacogenetics, as they go some way to fulfilling the ideal that targeted therapy can work for major common tumours, and not just rare ones.

Although these results are exciting, there's still a long way to go before they reach the clinic as diagnostic tests, says Howard McLeod from Washington University School of Medicine, St Louis. "We need to know exactly how predictive these markers are with larger studies. We also need to characterize these EGFR-driven tumours, for example, by looking at the effect of smoking status, and why there seem to be higher responses in Japan, with adenocarcinomas, and in women."



Targeted therapy: *EGFR* mutations can predict response to gefitinib.

Klaus Lindpaintner from Roche adds that the situation is rarely clear-cut in complex diseases. "It is unlikely that there will be 'responders' and 'non-responders'. It's more likely to be individuals who are more or less likely to respond, as other molecular mechanisms can contribute to the response."

There is anecdotal evidence that such factors exist, says Don Stribling at AstraZeneca. David Carbone at the Vanderbilt University Medical Center, Nashville, USA, had also discovered an *EGFR* mutation in a gefitinib-responsive patient. "This patient had responded incredibly within a month, but 18 months later the tumour began to grow again," says Stribling. "The mutation had been discovered post-mortem, and was therefore presumed to be associated with gefitinib resistance. Now we know this mutation could have explained the patient's response, and that other mechanisms could influence its outcome."