The story of gefitinib, an EGFR kinase that works in lung cancer

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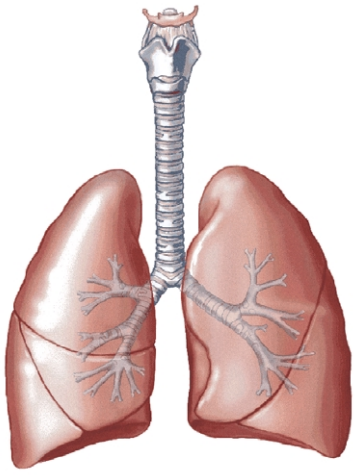

The reports that gefitinib (also known as Iressa/ZD1839) can treat human lung cancers is unfolding as one of the big stories in drug discovery. Two papers, one in *Science* and one in *The New England Journal of Medicine*, suggest that gefitinib is effective only in lung cancer patients with tumours that are driven by activated forms of extracellular growth factor receptor (EGFR) kinase [1, 2]. These results are having a major impact in the industrial and research communities.

Daniel Louvard , Director of Research at the Institute Curie (http://www.curie.fr) and CNRS (http://www.cnrs.fr), Paris, France, says that gefitinib is an example of how 20 years of research on the signalling pathways in cell biology can be used to give a genuine benefit to patients suffering from solid tumours.

Failure in Phase III

The path taken by gefitinib from drug discovery to identifying the molecular basis for responders has not been straightforward. As recently as March 2004, at the 95th annual meeting of the American Association of Cancer Research (AACR; http://www.aacr.org) in Orlando, Florida, the failure of gefitinib to show benefit in two large Phase III trials was still being discussed in several keynote symposia. The recent papers now offer a sound explanation as to how gefitinib works and in which clinical situations it should be prescribed. By using different sequencing strategies, the two independent groups reported that, in 13/14 cases (the sum of both studies), patients that have responded to gefitinib treatments harbour activating mutations within the catalytic domain of the EGFR kinase. By contrast, mutations were not found within sequences collected from 11 patients who did not respond to treatment. In tests *in vitro*, cells that express one of these naturally occurring mutations of EGFR kinase are more sensitive to gefitinib than cells that express the wild-type EGFR kinase.

Mutations

The number of lung cancers that harbour activating EGFR kinase mutations is believed to be small, in the order of 10% in lung cancer patients from an American population but as high as 26% from a Japanese population, which correlates with the response rates of gefitinib in American and Japanese clinical trials. These small percentages hide large patient populations because the number of deaths caused by lung cancer is similar to that caused by prostate, breast and colon cancers combined. Therefore, many patients are likely to benefit from gefitinib and possibly other small molecules that also target EGFR kinase.

Lessons learned

Like any good story, there is more than one lesson to be learned from gefitinib. It is the first time that a targeted molecular approach is shown to be effective in treating a solid tumour. The story of Glivec, an inhibitor of the fusion protein kinase Bcr/Abl that drives chronic myeloid leukaemia, has been retold many times, but there was always the feeling that leukaemia is easier to treat than solid tumours (such as lung cancer) and therefore we should not expect to use a Glivec approach for solid tumours. Gefitinib has put this misconception to rest.

The final chapter has yet to be written on gefitinib. Louvard suggests that gefitinib shows us that lung cancer is not one disease but many diseases, and we still need to refine our approaches to identify the pedigree of each cancer. He feels that today, serendipity is still important but with a multidisciplinary approach – using information from cell biology, genomics, and even biophysics – we will continue to improve the targeted approach to find and successfully treat patients afflicted with life threatening tumours.

References

1 Paez, J.G. *et al.* (2004) EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science*. DOI: 10.1126/science.1099314 (E-Pub ahead of print; http://www.sciencemag.org)

2 Lynch, T.J. *et al.* (2004) Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *New Eng. J. Med.* 350, 1–11

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