tumours in mice, and how the presence of additional genetic alterations — frequently found in close association with *KRAS* mutations in humans — may influence therapeutic response. Specifically, the authors used three genetically engineered mouse models of NSCLC to examine the role of mutations in the tumour-suppressor genes *p53* and *Lkb1*. In these mice, the expression of *Kras*, of *Kras* and *p53*, or of *Kras* and *Lkb1* could be precisely manipulated so that the animals developed multifocal disease that closely emulated human NSCLC, with each lesion progressing at an independent rate, as previous studies have shown[6–8].

Using magnetic resonance imaging and microscopy to assess tumour-cell proliferation and death, Chen and colleagues[1] found that mutation of either *p53* or *Lkb1* in *Kras*-mutant tumours in mice significantly diminished the initial effect of docetaxel on the tumours. The addition of selumetinib enhanced docetaxel's effect on *Kras*- and *Kras/p53*-mutant tumours, and improved progression-free survival — the time elapsed between treatment initiation and tumour progression or death from any cause — in both mouse models. By contrast, *Kras/Lkb1*-mutant tumours were inherently resistant to this combination therapy. Therefore, the docetaxel–selumetinib combination may be less effective in patients with tumours carrying mutations in both *KRAS* and *LKB1*.

To measure metabolic changes in tumours as a possible surrogate for defining early response to the therapy, the authors[1] injected a radiolabelled glucose analogue (^{18}F-fluoro-2-deoxyglucose, FDG) into the mice and traced its concentration in the tumours with positron emission tomography (PET), a powerful imaging technique. They found that *Kras/p53*- and *Kras/Lkb1*-mutant tumours have an overall higher FDG uptake than *Kras*-only mutant tumours. Chen *et al.*[1] note that one partial explanation for this may be increased expression of GLUT1 — a protein that controls glucose uptake into cells — in the *Kras/Lkb1* mutant tumours. Alternatively, the differences in FDG uptake may also reflect disease subtype, stage or both. Importantly, the authors translated these observations to humans by finding a significant correlation between LKB1 expression and FDG avidity in human NSCLC.

The researchers then explored the usefulness of FDG–PET to determine tumour metabolic changes following short-term therapeutic intervention in mice, and found that the combination of docetaxel and selumetinib reduced tumour metabolic activity only in the *Kras*- and *Kras/p53*-mutant mice. These results agree with the authors' microscopic study of tumour-cell proliferation and death rates, and suggest that serial FDG–PET imaging may be useful clinically in predicting antitumour efficacy and patient outcome in *KRAS*-mutant NSCLC treated with this combination therapy.

Of note is that most, if not all, of the lesions examined by Chen *et al.*[1] in the *Kras*- and *Kras/p53*-mutant mice represent an earlier stage of the disease than that typically evaluated in initial, exploratory NSCLC clinical trials for therapeutics. Earlier-stage disease is also generally more responsive to therapy, with better long-term outcomes. So, serial FDG–PET in this context could be more useful if future studies could directly correlate FDG uptake with microscopic analyses detailing tumour stage, subtype, genotype and therapeutic response for each lesion.

Previous reports[9,10] have suggested that elevated FDG uptake in human lung tumours predicts poor outcome in response to conventional anticancer drugs. The results of Chen and colleagues' study[1] suggest that this may also extend to targeted therapies, specifically to the treatment of *KRAS/LKB1*-mutant NSCLC with a combination of selumetinib and docetaxel. The authors propose that FDG–PET imaging may be used to identify patients who are more likely to respond and, therefore, to have a better long-term outcome. However, such an approach should be used in combination with other strategies to facilitate patient stratification, as FDG avidity was insufficient at predicting response in all *Kras/Lkb1*-mutant mice in the authors' report.

Overall, Chen and colleagues' work highlights the vital need to develop improved preclinical and clinical tools to follow and characterize individual tumours throughout the course of treatment. Several tumour attributes should be simultaneously correlated with therapeutic response over time to better understand resistance mechanisms. To this end, we need to develop more sophisticated reporter molecules and *in vivo* imaging modalities than FDG–PET to interrogate key cellular pathways in a dynamic way, and in real time.

The high failure rate of clinical trials for the treatment of late-stage diseases — particularly cancer[11] — underscores the need for improved preclinical models, as well as their translation into clinical-trial design, analysis and predictions. Chen and colleagues[1] present a compelling case for conducting co-clinical trials in genetically engineered mice or in other well-validated, relevant model systems such as patient-derived xenografts (in which a piece of the patient's tumour, or cells derived from it, are transplanted into a laboratory mouse). If done properly, co-clinical trials may help to identify predictive genetic markers that can be validated in real time using samples from patients enrolled in a concurrent clinical trial. These integrated data sets may ultimately be better at predicting the results of the concurrent clinical studies, as well as providing, on the basis of the cancer's genetic profile, a rationale

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50 Years Ago

Applications are invited for a scholarship sponsored by the Worshipful Company of Gardeners, and open to young gardeners who are undergoing or have completed training at the Royal Horticultural Society's Gardens, Wisley, or elsewhere, and who will have had at least four years' practical experience in horticulture ... The scholarship is restricted to male candidates who are unmarried and undertake to remain so during the tenure of the scholarship. The scholarship will be tenable for two years, beginning October 1, and is valued at £300 per annum.
From *Nature* 31 March 1962

100 Years Ago

The metals occurring most frequently are gold and copper. The former is much more widely distributed than the latter, and must have been the first metal to be known in many regions. It is, however, one of the most worthless metals for practical purposes, so that until the rise of Greek and Roman civilisation but little use was made of it. Copper, too, we only find in use to a very limited extent, as it was not well suited for the construction of weapons or useful implements. On the other hand, its alloy with tin afforded a metal which in many physical properties could only be surpassed by iron or steel. According to the views of several ancient writers, Lucretius and Poseidonius, so momentous a discovery as that of metals contained in ores must needs have been brought about by no uncommon cause. According to them, a conflagration consumed forests which covered the outcrop of metalliferous veins, reducing the metals and bringing them to the notice of man, but there are no grounds for such inference.
From *Nature* 28 March 1912