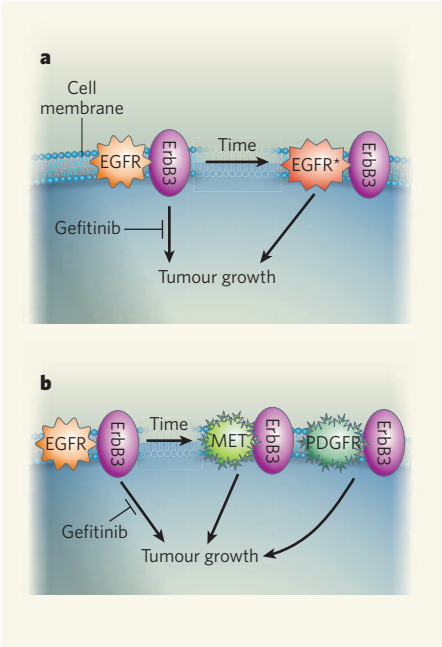

Figure 1 | The battle of tumours and drugs. Receptor tyrosine kinases (RTKs) have essential functions in mediating communication between a cell and its environment, and consequently activate downstream signalling cascades. One such RTK is EGFR, which following a primary, or driver, mutation couples with another RTK, ErbB3, promoting tumour-cell growth. EGFR-inhibitor drugs, such as gefitinib, block the oncogenic activity of EGFR, leading to tumour shrinkage. However, with time, tumour cells become resistant to RTK inhibitors by one of two mechanisms. **a**, It is well established that drug resistance can be caused by a secondary mutation in EGFR (EGFR*), which prevents drug binding and restores tumour growth. One way to tackle this might be to develop second-generation EGFR inhibitors. **b**, Two new studies[2,3] reveal an alternative mechanism of drug resistance. They show that, although gefitinib inhibits EGFR, other RTKs, such as MET or PDGFR, which are unaffected by this drug, might instead couple with ErbB3 and take over the task of tumour regrowth. In this case, a cocktail of drugs to simultaneously inhibit EGFR, MET and PDGFR is required.

mutation is in a kinase known as EGFR. This belongs to a group of kinases known as receptor tyrosine kinases (RTKs). The authors found that these cells, which initially responded to an EGFR-inhibitor drug, gefitinib, subsequently became resistant, but the resistance was not due to a secondary mutation in EGFR. Instead, in these cells, the levels of another RTK, MET, were unusually high owing to amplification of the gene that encodes it. The researchers then inhibited MET activity and found that, in the presence of EGFR inhibitors, this treatment restored the cancerous cells' drug sensitivity — an observation that makes a case for combination therapy in the treatment of drug-resistant forms of lung cancer.

Before this work, the only known cause of resistance to EGFR inhibitors in lung cancer was a secondary mutation — from threonine to methionine — at position 790 in the amino-acid sequence of EGFR, abbreviated to T790M (ref. 4). The T790 residue is evolutionarily conserved among kinases and is implicated in drug resistance with other kinase–inhibitor pairings in other cancers. The T790M mutation occurs in more than half of patients with non-small-cell lung cancer who relapse after treatment with gefitinib or another EGFR-inhibitor drug, erlotinib. Engelman *et al.*[2] suggest that amplification of MET activity may account for 20% of the remaining cases of resistance.

The work of Engelman *et al.* highlights the principle that, in cancer, signal-transduction pathways are remarkably flexible and amenable to rewiring. In this case, MET doesn't overcome EGFR inhibition by simply driving the canonical MET-mediated signalling pathways. Instead, it undergoes a form of molecular morphing, whereby it becomes an illicit partner of the EGFR co-receptor ErbB3 and acquires the signalling properties of EGFR (Fig. 1).

If resistance options are viewed from the perspective of a cancer cell, this RTK switch mechanism seems an easy strategy by which to escape drug inhibition, compared with the evolutionary work involved in selecting a rare second-site mutation that would impair drug activity without crippling the oncogenicity of the original RTK. Yet, so far, second-site mutations are much more commonly documented. This presumably reflects the fact that very few tumour cell types have the molecular circuitry to allow RTK switching. Mathematically, the probability of generating secondary mutations is low[5], but the probability of acquiring the still-unknown genetic makeup required to rewire a signal-transduction pathway must be lower.

In another study, Stommel and colleagues[3] describe a conceptually related RTK switch in glioblastoma. As in the lung study[2], the authors show that MET can substitute for EGFR function, but with a new twist. They find that the tumour cells are resistant to EGFR inhibitors upfront (rather than acquiring resistance after prolonged drug exposure), but become sensitive when MET and EGFR are inhibited in parallel. So it is as if these tumours have already been through the cycle of drug response and relapse described by Engelman *et al.*, when in reality they have never been exposed to these drugs. Furthermore, inhibition of a third RTK — PDGFR — is required for maximal drug efficacy. It therefore seems as though these cancers have conspired to implement several back-up systems against single-agent kinase-inhibitor treatment.

Cancer cells are admittedly wily, but the more likely interpretation of this behaviour is that the orchestra of RTKs collectively contributes to disease progression. Each player presumably makes an individual contribution, but can pick up the slack if one partner is crippled. Indeed, further analysis of acquired resistance in lung

50 YEARS AGO

In his presidential address to the Library Association ... Dr. J. Bronowski said that a civilized society must preserve what its best minds discover, but preservation alone does not make it an educated or even a cultured society. Moreover, an educated society could exist only when knowledge is not merely stored but is also shared, and it was the invention of printing that made the book an instrument of education ... but in science the public libraries have scarcely played that part at all: if they are to do so, they must have the books to enable them to make the language of science familiar to those who are not professional scientists ... He did not think that the printed book was the last instrument of education we would discover, but he was sure that the printed book and the public library would remain the most powerful means of self-education.

From *Nature* 26 October 1957.

100 YEARS AGO

In India at the present moment the ravages of plague, though not so great as those of the Black Death or of the Great Plague in London, are nevertheless dreadful. During the first six months of this year no less than 1,060,000 deaths from plague occurred in India, and out of these 632,000 occurred in the Punjaub, which has a population of only twenty-five millions, that is to say, one in every forty inhabitants in this district has died of plague between January and June ... The great difficulties in the way of preventative measures are ignorance and apathy, to which superstition is often superadded. In some parts of India there is great prejudice against taking life of any kind ... Cases of plague from time to time arrive at the port of London ... We are pursuing a foolish policy in allowing rat- and flea-infected districts to exist in the East End of London and other similar places.

From *Nature* 24 October 1907.

50 & 100 YEARS AGO