# IN BRIEF

## THERAPY

### Novel mutant-selective EGFR kinase inhibitors against EGFR T790M

Zhou, W. *et al. Nature* **462**, 1070–1074 (2009)

Strategies to inhibit mutant epidermal growth factor receptor (EGFR) in non-small-cell lung cancer have been limited by the development of drug-resistant mutations, including the T790M mutation, and toxicity caused by inhibition of wild-type EGFR. By screening an irreversible kinase inhibitor library against EGFR T790M, the authors identified new EGFR inhibitors that are 30–100-fold more potent against EGFR T790M and 100-fold less potent against wild-type EGFR than conventional quinazoline-based EGFR inhibitors. This study illustrates the power of functional pharmacological screens to identify new mutant-selective kinase inhibitors.

## GENOMIC INSTABILITY

### FANCM connects the genome instability disorders Bloom's syndrome and Fanconi anemia

Deans, A. J. & West, S. C. *Mol. Cell* **36**, 943–953 (2009)

The genetic disorders Fanconi anaemia (FA) and Bloom's syndrome (BS) have overlapping phenotypes, which include aberrant DNA repair and a predisposition to cancer. The authors show that FANCM links these two diseases by mediating the association of FA and BS complex proteins with interstrand crosslinks. They identified two distinct conserved protein–protein interaction motifs in FANCM that independently activate the FA and BS pathways.

## LYMPHOMA

### Chronic active B-cell-receptor signalling in diffuse large B-cell lymphoma

Davis, R. E. *et al. Nature* **463**, 88–92 (2010)

Although B cell receptor (BCR) signalling has been implicated in B cell lymphomas, functional genetic evidence has been lacking. Staudt and colleagues now demonstrate that chronic active BCR signalling is required for the survival of the activated B cell (ABC) subtype of diffuse large B cell lymphoma (DLBCL). They also identified somatic mutations in the proximal BCR subunits CD79A and CD79B that contribute to BCR activation in ABC DLBCLs. The results indicate that targeting this oncogenic BCR signalling pathway could be of therapeutic value.

## TUMORIGENESIS

### Deubiquitinase USP9X stabilizes MCL1 and promotes tumour cell survival

Schwickart, M. *et al. Nature* 20 Dec 2009 (doi:10.1038/nature08646)

The pro-survival BCL2 family member MCL1 is overexpressed and contributes to chemoresistance and disease relapse in multiple myeloma and chronic myeloid leukaemia. Dixit and colleagues show that MCL1 levels are regulated through the deubiquitinase USP9X, which binds and removes the ubiquitin chains that normally target MCL1 for degradation. They found that USP9X expression correlates with MCL1 expression and is also a prognostic indicator. Knock down of USP9X increased MCL1 degradation and improved the cytotoxicity induced by the BH3 mimetic ABT-737, suggesting that therapeutic targeting of USP9X might be beneficial.