IN BRIEF

CHEMOTHERAPY

Dasatinib crosses the blood–brain barrier and is an efficient therapy for central nervous system Philadelphia chromosome-positive leukemia.

Porkka, K. *et al. Blood* 13 May 2008 (doi: 10.1182/blood-2008-02-140-665)

The treatment of Philadelphia chromosome (Ph)$^+$ leukaemia is complicated by the fact that the gold-standard treatment imatinib, a BCR–ABL tyrosine kinase inhibitor, cannot effectively cross the blood–brain barrier and thus cannot prevent central nervous system (CNS) relapse. Dasatinib, a dual-specificity SRC and BCR–ABL kinase inhibitor, however, demonstrated activity in clinical trials of patients with Ph$^+$ CNS leukaemia. In total, 11 of 14 patients achieved long-lasting remission. The authors conclude that dasatinib is a promising therapeutic option in patients with intercranial leukaemia and those experiencing CNS relapse while on imatinib.

IMMUNOTHERAPY

Effective tumor treatment targeting a melanoma/melanocyte-associated antigen triggers severe ocular autoimmunity

Palmer, D. C. *et al. Proc. Natl Acad. Sci USA* 10 Jun 2008 (doi: 10.73/pnas.0710929105)

The development of autoimmune responses can be a serious problem for the use of immunotherapeutic regimens that target self antigens. Experiments in mice and clinical trials in humans with malignant melanoma indicate that the more aggressive the immune-based therapy (such as lymphodepletion followed by the adoptive transfer of CD8$^+$ T cells that target melanocytes and administration of interleukin 2) the more likely it is that tumours will regress, and side effects such as vitiligo and melanocyte-specific ocular autoimmunity will occur. The authors suggest that the development of immunotherapy regimens targeting cancer–testis or unique tumour-specific antigens, rather than those targeting non-mutated differentiation antigens, might prove to be more prudent strategies in the future.

DNA REPAIR

Mdm2 promotes genetic instability and transformation independently of p53

Bouska, A. *et al. Mol. Cell. Biol.* 9 Jun 2008 (doi:10.1128.MCB.01584-07)

p53-independent functions of MDM2 remain poorly understood. This study implicates MDM2 in DNA repair through association with NBS1, a component of the MRE11–RAD50–NBS1 DNA repair complex. Upon DNA damage, MDM2 overexpression in p53-null cells led to a reduction in the number of γH2AX foci and decreased levels of activated ATM, and ATM and ATR downstream target proteins. These defects resulted in increased chromosome and chromatid breaks, attenuated DNA repair and enhanced transformation. Interestingly, these effects do not require the E3-ligase activity of MDM2, suggesting the involvement of alternative mechanisms that warrant elucidation. The inhibition of MDM2 is an exciting therapeutic strategy that has led to the development of small molecules such as the Nutlins, which interfere with the MDM2–p53 interaction. These data suggest that the efficacy of such treatments may be further improved by modulation of the MDM2–NSB1 complex in patients whose tumours overexpress MDM2.