Monitor Editor: Matthew Thorne
m.thorne@elsevier.com

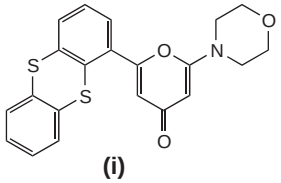
monitor

MOLECULES

Sensitization to radio- and chemo-therapy by a novel inhibitor of ATM kinase

Ataxia-telangiectasia mutated (ATM) kinase is a serine/threonine kinase known to have an important role in the maintenance of genomic integrity via signalling to cell cycle and DNA repair pathways, involving phosphorylation of targets such as p53, CHK2, NBS1 and BRCA1 [1]. The hypothesis that ATM inhibition would sensitize cancer cells to radio- and chemo-therapy has previously been tested using the relatively non-specific phosphatidylinositol 3′-kinase (PI3K)-related kinase family inhibitors wortmannin and caffeine, which are known to have spectra of kinase inhibitory effects that include ATM [2].

The screening of a combinatorial compound library based on the non-specific PI3K and DNA-dependent protein kinase inhibitor LY294002 led to the identification of KU55933 (**i**), a novel, specific and potent small molecule inhibitor of ATM [3]. In addition to inhibiting ATM with an IC_{50} of 13 nM and a K_i of 2.2 nM, KU55933 also showed specificity for inhibition of ATM with respect to a panel of related kinases. KU55933 also sensitized HeLa cells to a range of radiation doses with a sensitizer enhancement ratio of 2.6 at 2.0 Gy (KU55933 concentration of 10 μM). Cellular chemosensitization to DNA double-strand break-inducing agents, such as etoposide, doxorubicin and camptothecin, by KU55933 was also demonstrated. The identification of KU55933 provides a relatively specific molecular tool to study the cellular biochemistry of ATM, and a starting point for the development of more potent and pharmaceutically acceptable ATM inhibitors with future potential for clinical evaluation.



(i)

1 Shiloh, Y. *et al.* (2003) ATM and related protein kinases: safeguarding genome integrity. *Nat. Rev. Cancer* 3, 155–168
2 Sarkaria, J.N. *et al.* (1998) Inhibition of phosphoinositide 3-kinase related kinases by the radiosensitizing agent wortmannin. *Cancer Res.* 58, 4375–4382
3 Hickson, I. *et al.* (2004) Identification and characterization of a novel and specific inhibitor of the ataxia-telangiectasia mutated kinase ATM. *Cancer Res.* 64, 9152–9159

Andrew D. Westwell
Andrew.Westwell@nottingham.ac.uk

SIGNALLING

Forever young

Ageing diminishes the regenerative capacity of tissues. Previous studies have shown that the activation of the Notch signalling pathway is essential for the activation, proliferation and myogenic lineage progression of satellite cells necessary for muscle regeneration. In old muscles, the activation of this particular pathway fails. However, aged muscles successfully regenerate when grafted in young recipient, but young muscles display impaired regeneration when grafted in old recipient. These observations led to the hypothesis that there are systemic factors that support the regeneration of tissues in young animals and/or inhibit regeneration in old animals.

1359-6446/04/$ – see front matter PII: S1359-6446(04)03377-5