monitor

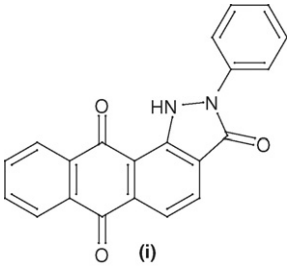
MOLECULES

Selective targeting of *DPC4* (deleted in pancreatic cancer locus 4)-deficient pancreatic cancer cells

In recent years, target-directed cancer drug discovery has been dominated by drugs that are active against gain-of-function alterations in oncoproteins. The small molecule imatinib (Gleevec), which targets BCR-ABL oncoprotein in chronic myelogenous leukaemia (CML) and other related tyrosine kinases, provides perhaps the best-studied example of this approach. Targeting loss-of-function mutations in tumour-suppressor genes to restore normal function has been less well studied, despite the fact that such loss-of-function mutations have important roles in cancer development. A recent example of this approach is the observation that breast cancer cells deficient in the *BRCA1* or *BRCA2* tumour suppressors are sensitive to inhibitors of the DNA damage repair enzyme poly(ADP-ribose)polymerase (PARP) [1].

Pancreatic cancer is the fourth leading cause of cancer death among adults in the USA, with a dismal five-year survival rate of ~4%. One of the most frequently altered genes in this cancer is the loss-of-function mutation in the *DPC4* tumour suppressor (deleted in pancreatic cancer locus 4), where total genetic alterations account for ~55% of tumours taken directly from patients [2]. Loss of *DPC4* expression predicts decreased survival in pancreatic cancer; however, agents that could restore tumour suppressor function to cells lacking DPC4 expression has not been well studied to date.

Wang and co-workers (Translational Genomics Institute, Phoenix, AZ, USA; http://www.tgen.org) have described a novel screening strategy, termed Pharmacological Synthetic Lethal Screening (PSLS), for the identification of compounds that selectively target cancer cells harbouring loss-of-function mutations in tumour suppressor genes such as *DPC4* [3]. The approach involved the generation of *DPC4* isogenic cell lines through restoration of wild-type *DPC4* in a pancreatic cancer cell line BxPC-3. After screening nearly 20K compounds, agent UA62001 **(i)** was identified as having the required selectivity against *DPC4* deficiency in the cell line models (4.6-fold selectivity). Use of further pancreatic cancer cell lines revealed a good correlation between *DPC4* deficiency and sensitivity to (i). Further potential downstream targets, such as cyclin B/CDK2 and minichromosome maintenance complexes, were revealed by gene expression profiling and quantitative real-time reverse transcription-PCR. Further work building on the identification of lead compound UA62001, plus further initiatives in the area of PSLS, is eagerly awaited.



(i)

1 Bryant, H.E. *et al.* (2005) Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose)polymerase. *Nature* 434, 913–917

2 Miyaki, M. *et al.* (2003) Role of Smad4 (DPC4) inactivation in human cancer. *Biochem. Biophys. Res. Commun.* 306, 799–804

3 Wang, H. *et al.* (2006) Identification of an agent selectively targeting DPC4 (deleted in pancreatic cancer locus 4)-deficient pancreatic cancer cells. *Cancer Res.* 66, 9722–9730

Andrew D. Westwell
WestwellA@cf.ac.uk

1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2007.02.007