IN BRIEF

THERAPEUTICS

Ubiquitylation block

The F-box protein SKP2 is an E3 ubiquitin ligase that is involved in substrate recognition as part of SKP1–CUL1–F-box protein (SCF) ubiquitin ligase complexes. SKP2 is overexpressed in many cancers, and can promote tumorigenesis and tumour progression, so it has been put forwards as a possible therapeutic target. Using structure-based, high-throughput *in silico* screening, Chan *et al.* identified a compound that can bind to SKP2 and can inhibit its E3 ligase activity by blocking its interaction with SKP1; importantly, the compound did not affect the activity of SCF complexes containing other F-box proteins. The inhibitor also mimics the effects of genetic knockout of *Skp2*. *In vitro*, the SKP2 inhibitor reduced the survival of several cancer cell lines and increased their sensitivity to chemotherapy. In mice with established prostate or lung xenograft tumours, the inhibitor significantly reduced tumour volume, supporting its therapeutic potential. Furthermore, inhibition of SKP2 reduced both sphere formation and the number of cells with cancer stem cell markers in prostate cancer cell lines, indicating that SKP2 may have a role in promoting cancer stem cell properties.

ORIGINAL RESEARCH PAPER Chan, C. H. *et al.* Pharmacological inactivation of Skp2 SCF ubiquitin ligase restricts cancer stem cell traits and cancer progression. *Cell* **154**, 556–568 (2013)

BREAST CANCER

Giving tamoxifen a boost

Oestrogen receptor (ER)-positive breast tumours, commonly treated with tamoxifen, often express high levels of the pro-survival protein BCL-2. Vaillant *et al.* found that treatment of ER^+ patient-derived breast tumour xenografts with the BH3 mimetic ABT-737 or a BCL-2-selective inhibitor (ABT-199) improved the response to tamoxifen. Additional benefit was obtained by adding inhibitors of PI3K or mTOR, as the PI3K–mTOR pathway is commonly activated in breast cancer, to tumours that only partially responded to BH3 mimetics and tamoxifen. Interestingly, BH3 mimetics could also reduce endometrial hyperplasia, a common side effect of tamoxifen treatment. These results support the clinical evaluation of BH3 mimetics in ER^+ breast cancer, and BCL-2 expression may provide a useful biomarker to predict efficacy.

ORIGINAL RESEARCH PAPER Vaillant, F. *et al.* Targeting BCL-2 with the BH3 mimetic ABT-199 in estrogen receptor-positive breast cancer. *Cancer Cell* **24**, 120–129 (2013)

PREVENTION

Risk prediction

Although there are several models available to predict a woman's risk of developing breast cancer, there are few models for predicting the risk of ovarian and endometrial cancers, which have similar risk factors to breast cancer. Using several easily obtainable parameters (such as parity, menopausal status and body mass index) from two population-based cohort studies, Pfeiffer *et al.* developed models to predict the absolute risk of breast, ovarian and endometrial cancers in non-Hispanic white women age 50 years or older. Validation of the models with an independent cohort indicated that expected/observed cancer ratios were close to 1 for ovarian and breast cancers, and were overestimated for endometrial cancers. These models may assist in clinical decision making, although it is unclear whether they will be useful for women of other ages or races.

ORIGINAL RESEARCH PAPER Pfeiffer, R. M. *et al.* Risk prediction for breast, endometrial, and ovarian cancer in white women aged 50 y or older: derivation and validation from population-based cohort studies. *PLoS Med.* **10**, e1001492 (2013)