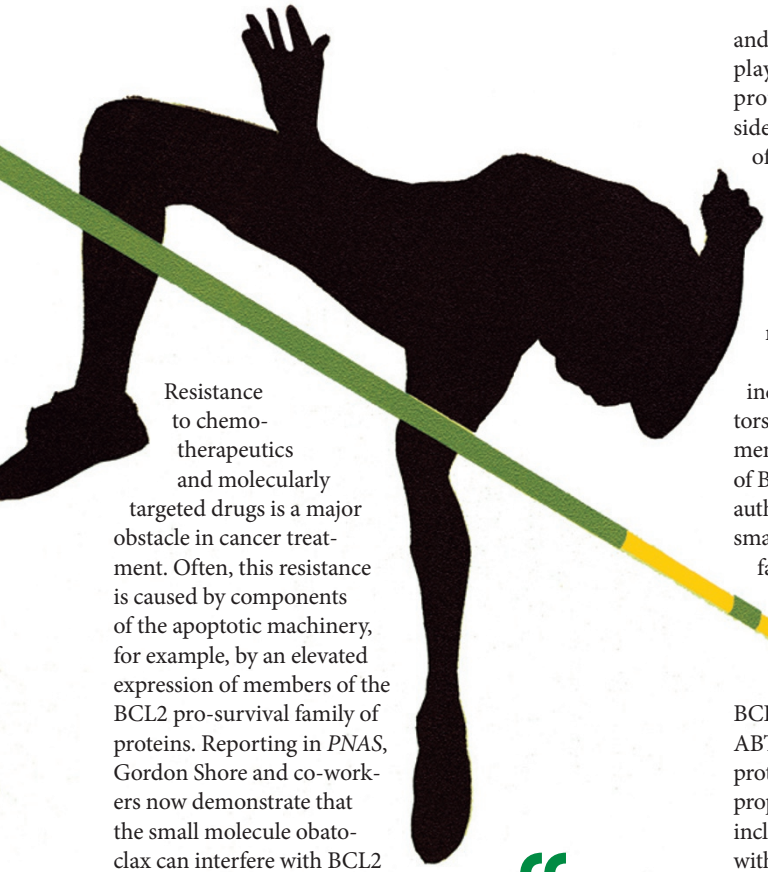
ANTICANCER DRUGS

Reversing resistance



Resistance to chemotherapeutics and molecularly targeted drugs is a major obstacle in cancer treatment. Often, this resistance is caused by components of the apoptotic machinery, for example, by an elevated expression of members of the BCL2 pro-survival family of proteins. Reporting in *PNAS*, Gordon Shore and co-workers now demonstrate that the small molecule obatoclax can interfere with BCL2 family mediated resistance, and restore sensitivity to several new anticancer drugs.

In the transformation of normal cells to cancer cells, the abrogation of apoptosis has a central role. The BCL2 family of proteins, comprising both pro-apoptotic (BAX, BAK) and pro-survival (BCL2, BCL-XL, MCL1 and BCL-W) members, are pivotal players in this process. Protein–protein interactions between the two sides, mediated by the BH3 domain of pro-apoptotic members, which inserts into a groove in the in the surface of the pro-survival members, control the permeability of the mitochondrial outer membrane, and the deadly release of cytochrome *c*.

> “Obatoclax can restore sensitivity to several new anticancer drugs”

Anticancer strategies have included the development of inhibitors of pro-survival BCL2 family members, including the development of BH3 domain mimetics. Now, the authors describe obatoclax, a novel small-molecule inhibitor of BCL2 family pro-survival proteins. Of particular interest is its activity against MCL1, as other recently developed inhibitors of BCL2/BCL-XL, such as the BH3 mimetic ABT-737, are not active against this protein. MCL1 has several unique properties compared with its ‘siblings’, including a constitutive interaction with BAK. It also undergoes a rapid protein turnover, and can therefore accumulate in cells treated with proteasome inhibitors as anticancer agents — leading to drug resistance.

In silico modelling of obatoclax placed its binding site in a hydrophobic pocket of the BH3 binding groove on pro-survival BCL2 family proteins. In *in vitro* experiments with isolated mitochondria, obatoclax strongly inhibited the constitutive interaction of MCL1 with BAK, and in lymphoma cells expressing MCL1, the treatment with obatoclax led to cytochrome release and apoptosis. Together with findings in yeast cells reconstituted with BCL/BAX or BCL/BAK, and in murine cells derived from *Bax*/*Bak* knockout mice, the results indicate that obatoclax antagonizes the BCL2 pro-survival family and induces apoptosis, dependent on BAX and BAK.

Furthermore, *in vitro* experiments with a carcinoma cell line illustrated its potential to sensitize cells that are resistant to ABT-737, or to the proteasome inhibitor bortezomib. *In vivo*, obatoclax displayed single-agent activity in several standard tumour mouse models, including those derived from mouse mammary, human colon, prostate and cervical carcinoma cell lines. Obatoclax has now entered Phase Ib and Phase II clinical trials for various leukaemia, lymphoma and solid tumour malignancies.

Besides its potential as a single-agent drug, obatoclax provides an important clinical development opportunity for cancer indications in which pro-apoptotic BCL2 family members contribute to drug resistance. It is therefore a prime candidate for novel anticancer strategies that include the rational combination of anticancer agents to achieve functional synergies.

Alexandra Flemming

ORIGINAL RESEARCH PAPER Nguyen, M. *et al.* Small molecule obatoclax (GX15-070) antagonizes MCL-1 and overcomes MCL-1-mediated resistance to apoptosis. *Proc. Natl Acad. Sci. USA* **104**, 19512–19517 (2007)