transporter expression correlated with resistance to the drug. As well as transporters known to be associated with drug resistance, several transporters that were not previously implicated in drug resistance were identified; again, follow-up experiments confirmed some of these predictions.

So, overall, the database created by the authors provides a resource for identifying transporters whose expression confers drug resistance, and compounds whose effects are antagonized, unaffected or even potentiated by transporter expression, which will be useful in developing strategies to address the problem of multidrug resistance. The database will also be valuable for future data mining to aid in studies of the function of the many ABC transporters that are not well characterized.

Peter Kirkpatrick

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APOPTOSIS

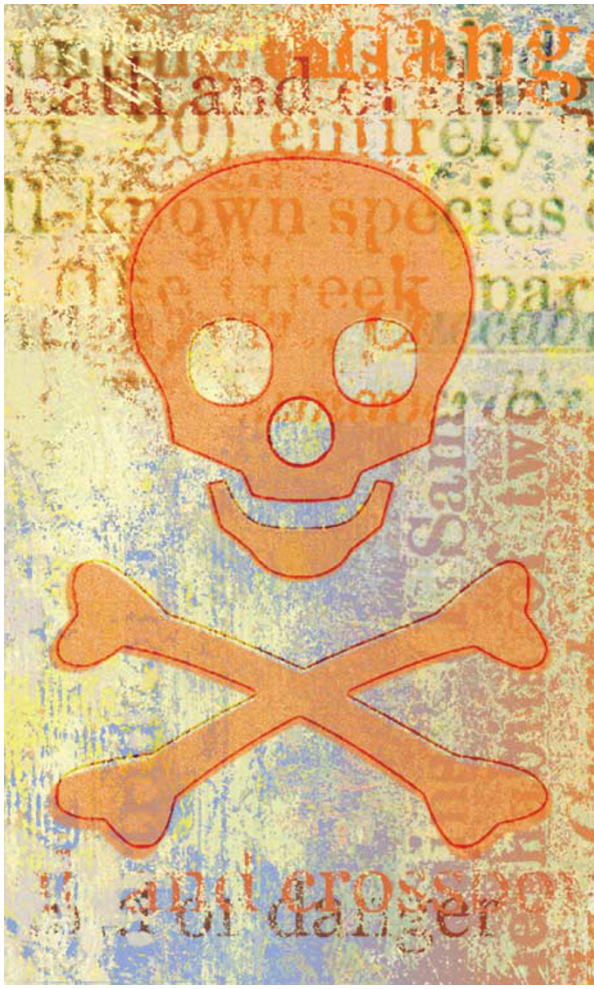
Bid for death

Death and taxes — two things that are famously certain in life. However, as we learn more, it seems that although death might be more complicated than taxes, it is perhaps not as inevitable! Programmed cell death, known as apoptosis, is a crucial process for tissue homeostasis, but uncontrolled cell death is associated with several human pathologies, such as neurodegenerative diseases and ischaemic injuries. In the August issue of *Chemistry & Biology*, Pellecchia and colleagues demonstrate the power of a multidisciplinary NMR-based approach in the rational design of a series of small-molecule antagonists that bind to the pro-apoptotic molecule Bid.

A number of protein families regulate apoptosis, some of which promote death, whereas others maintain life. Although several small-molecule inhibitors of anti-apoptotic proteins have been reported so far, none have been discovered for pro-apoptotic members, including Bid, a key member of the BCL2 protein family. Mice deficient in Bid show resistance to cell death in models of liver injury and stroke, and the molecule is also implicated in mouse models of amyotrophic lateral sclerosis. As the molecular basis for its function is unknown, Bid represents a challenging target for the development of therapeutic agents.

Even though the crystal structure of Bid is unsolved, NMR spectroscopy has revealed the presence of a deep hydrophobic crevice on the surface of the protein, in a region that is conserved between mouse and human Bid. The authors screened a fragment library that is made up of low-molecular-mass compounds that represent a selection of the substructures often found in drugs, and which are amenable to subsequent chemistry. Because of the simplicity of the structures, a few hundred derivatives are sufficient to represent great diversity; however, due to their limited size, and the consequent limited number of possible interactions with a given protein, many of the fragments will show low affinity for the target.

To overcome this problem, solution NMR was used as a screening method, because it allows the detection of very weak binders. The authors named this method structure–activity relationships by interligand nuclear Overhauser effect (SAR by ILOEs); by combining this with molecular modelling and synthetic chemistry they were able to rationally design a series of 4-phenylsulphanyl-phenylamine derivatives capable of occupying the hydrophobic crevice of Bid.



In cell-based assays, one of the newly synthesized compounds, BI-6C9, was able to bind to Bid and dramatically reduce production of mitochondrial SMAC, a downstream Bid-dependent event. Certainly, this compound will be useful in deciphering the mechanism of action of Bid within the complex process of apoptosis; with further optimization, BI-6C9 might also provide a starting point for the development of drug candidates for diseases associated with uncontrolled cell death. In addition, the authors have demonstrated the utility of multidisciplinary SAR by ILOE in tackling challenging drug targets, and possible future applications could include developing inhibitors of protein–protein, or protein–nucleic acid, interactions.

Melanie Brazil

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