

 ANTICANCER DRUGS

# Activating the executioner

**DOI:**

10.1038/nrd2164

**URLs**

Caspase 3  
[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full\\_report&list\\_uids=836](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=836)

All cells can undergo apoptosis, and so it has been difficult to find a target that can be exploited to induce death in cancerous, but not normal, cells. Paul Hergenrother and colleagues have now identified a small molecule that can induce apoptosis in various cancer cell lines and mouse tumours, but that seems to be relatively non-toxic to normal cells.

Many therapies being developed to trigger apoptosis are designed to activate early or intermediate steps in the apoptotic cascade, and therefore cancers with mutations that are downstream of these steps might be resistant. The authors reasoned that it would be ideal to activate a protein that is far downstream in the cascade, so they focused on the conversion of procaspase 3 to **cas**pase 3. Caspase 3 is an 'executioner' caspase that catalyses the hydrolysis of many proteins. It is kept in its inactive procaspase 3 form in cells until needed, and, paradoxically, many tumour cells have high procaspase 3 expression whereas normal cells do not.

The authors screened a library of 20,500 small molecules for their capacity to convert procaspase 3 to caspase 3 *in vitro*, and found one compound, procaspase-activating compound 1 (PAC1), that has a high specific dose-dependent activity. PAC1 induced apoptosis in various cancer cell lines, and there was a correlation between the levels of procaspase 3 expressed in the cells and

PAC1-induced apoptosis. *In vitro*, PAC1 also effectively killed cancerous cells in resected colon tumours, but adjacent normal cells were resistant. To further examine the effect of PAC1 on normal cells, the authors also looked at several non-cancerous cell lines, and found that these cells had low procaspase 3 levels and were not affected by PAC1 treatment.

Will PAC1 be effective against tumours *in vivo*? The authors tested PAC1 in mouse xenograft models of renal and lung cancer. In the renal model they implanted a slow-release pellet of PAC1, and in the lung model they gave PAC1 orally. Both methods of delivering PAC1 slowed tumour growth in a dose-dependent manner, and PAC1 seemed to be well tolerated by the animals. Although the tumours did not regress, the authors propose that this might be because the doses of PAC1 used led to relatively low serum concentrations of the drug. Finally, they injected lung cancer cells into the tail vein of mice and gave PAC1 orally on days 1–4 and 7–11. After 28 days, the mice treated with PAC1 had a lower tumour burden than the control mice.

Hergenrother and colleagues have shown that PAC1 has the potential to treat cancers that have increased levels of procaspase 3, but a systematic analysis of procaspase 3 concentrations in different human cancer types is needed to determine which cancers

will be most amenable to treatment with PAC1. Also, PAC1 might need to be modified to increase its oral availability and potency in humans. So, PAC1 might not be the magic bullet that cancer researchers are searching for, but it could be one step closer to it.

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**ORIGINAL RESEARCH PAPER** Putt, K. S. *et al.*  
 Small-molecule activation of procaspase-3 to caspase-3 as a personalized anticancer strategy. *Nature Chem. Biol.* 27 August 2006 (doi:10.1038/nchembio814)

