

## EDITORIAL

## Apoptosis - the Biochemistry of Rotting, or the Richest Drug Vein in the History of Biotech?

The term apoptosis arose as a result of a collaboration between Alastair Currie, Andrew Wylie and John Kerr. The collaboration began after Currie visited Brisbane and invited Kerr to spend a sabbatical in Aberdeen working with him and his student, Wylie. Although a cell death program had been observed by embryologists in the 19th century and Kerr had first published on cell death as 'shrinkage necrosis' in 1965, it was the landmark paper from Kerr, Wylie and Currie in 1972 that coined the term 'apoptosis'.

It was also Australians, Hewish and Burgoyne, who in 1973 were the first to link cell death with activation of endonucleases and inter-nucleosomal cleavage of the DNA, generating the famous 'ladder' (1), subsequently popularised by Wylie.

However, there was little interest in apoptosis, or cell death in general, until the late 1980s. It is not surprising that one of the seminal observations in the field, also made in Australia, which showed that the protein Bcl-2 was able to prevent cell death resulting from withdrawal of the cytokine IL3 from a IL3-dependent cell line, did not mention the term apoptosis (2,3). Nevertheless, this discovery sparked an explosion of interest in the field, because it suggested that inhibition of cell death caused cancer in humans, and it provided the first molecular handle to understand the mechanism for apoptosis. It set the scene for a fascinating, and still undecided, race to find out how Bcl-2 proteins inhibit cell death.

Given the early discoveries, it is no surprise that Australian researchers are in the vanguard of this particular race, and at international meetings, new findings in this area are often discussed in terms of the 'Australian' and 'Californian' models in honour of the main protagonists. Grant Dewson's article captures the excitement of this particular debate very well.

The discovery that Bcl-2 inhibits cell death following cytokine deprivation was the result of a strong background of cytokine research within Australia that continues today. Paul Ekert's article extends this particular strand of the Bcl-2 story and describes how research in these two areas continues to

overlap and mutually benefit each other. This wasn't always the case and it was an eminent Australian cytokine biologist who first dismissed apoptosis as the 'biochemistry of rotting'.

It is a tradition to claim successful New Zealanders as honorary Australians, and Catherine Day fits this category well. Catherine's lab has made important contributions to a detailed structural understanding of proteins that regulate and initiate apoptosis, describing the first structure for a domain from the inhibitor of apoptosis proteins (IAPs) (4) and continuing with elegant work on Bcl-2 family proteins. Her article discusses recent findings on the role of the IAP ubiquitin ligase activity in regulating apoptosis.

The study of viruses has contributed greatly to our understanding of apoptosis because cells use apoptosis as a defense mechanism to limit viral replication. Viruses are therefore obliged to carry inhibitors of the apoptotic program, and the founding member of the IAP family was discovered in a caterpillar virus. Ian Gentle and Ueli Nachbur's article investigates apoptosis in the context of viral infection. They discuss recent findings on the array of newly discovered molecules that cells use to sense unwanted guests, which have thrown new light on the virus's ability to manipulate the cell's apoptotic program for its own nefarious needs.

Apoptosis researchers are now eagerly awaiting the results of clinical trials of antagonists of Bcl-2 and the IAPs to treat cancers. This will finally show whether the 260,000 publications on cell death are just good for dunny paper, or, as *Fortune Magazine* put it in 1995, "apoptosis looks to be the richest drug vein struck in the two-decade history of biotech."

1. Hewish, D.R., and Burgoyne, L.A. (1973) *Biochem. Biophys. Res. Commun.* **52**, 504-510
2. Vaux, D.L., Cory, S., and Adams, J.M. (1988) *Nature* **335**, 440-442
3. Vaux, D.L. (2004) *Cell Death Differ.* **11**, S28-S32
4. Hinds, M.G., Norton, R.S., Vaux, D.L., and Day, C.L. (1999) *Nat. Struct. Biol.* **6**, 648-651

**John Silke**

Department of Biochemistry, La Trobe University, VIC 3086 j.silke@latrobe.edu.au

### Cover Illustration

Scanning electron micrograph of the thymus of an animal injected with anti-CD3, showing thymocytes with apoptotic morphology.

Image courtesy of Professor Douglas Green, St Jude Children's Research Hospital, Memphis, USA.

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Australian Biochemist – Editor Rebecca Lew, Editorial Officer Liana Friedman

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