

## **Insight into Viral Inhibition of Apoptosis: Structure of the M11L:Bak BH3 Complex**

**M. Kvensakul<sup>1</sup>, M. F. Van Delft<sup>2</sup>, E. F. Lee<sup>1</sup>, J. M. Gulbis<sup>1</sup>, W. D. Fairlie<sup>1</sup>, D. C.S. Huang<sup>2</sup>, P. M. Colman<sup>1</sup>**

<sup>1</sup>*Division of Structural Biology, The Walter and Eliza Hall Institute, Parkville, VIC, Australia*

<sup>2</sup>*Division of Molecular Genetics of Cancer, The Walter and Eliza Hall Institute, Parkville, VIC, Australia*

To circumvent host defences, many viruses express anti-apoptotic proteins to promote viral propagation. Some  $\gamma$ -herpesviruses express homologs of pro-survival Bcl-2 that act to counter the host's cell death machinery. Myxoma virus, a double-stranded DNA virus of the pox family, harbors anti-apoptotic M11L, first discovered as the virulence factor for this poxvirus of the Leporipoxvirus genus that is the causative agent of myxomatosis in European rabbits. Intriguingly, M11L has been reported to associate with Bax and Bak, two pro-death members of the Bcl-2 family. As part of a further investigation into the molecular basis of M11L's anti-apoptotic action, we determined the crystal structures of M11L in the presence and absence of the human Bak BH3 domain. Unexpectedly, M11L adopts a Bcl-2 protein fold despite lacking any primary sequence similarity and, like mammalian Bcl-2 proteins, acts primarily by restraining Bax and Bak, the essential cell death mediators, thereby blocking their pro-apoptotic action. Furthermore, M11L is not subject to control via BH3-only proteins with the exception of Bim, thus enabling myxoma virus to wrest control of the apoptotic machinery from its host. Consequently, our findings lend support to the concept that pro-death BH3-only proteins of the Bcl-2 family act indirectly by disabling anti-apoptotic Bcl-2 members, instead of directly activating other pro-death Bcl-2 members such as Bax and Bak.