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A chronology of cell death

G. Häcker and D. L. Vaux

The Walter and Eliza Hall Institute of Medical Research, Post Office Royal Melbourne Hospital 3050, Victoria, Australia

Cell death is one of the most prolific fields of biological research, with ten new publications appearing every day. Our knowledge of the molecular events during a cell's demise are still fragmentary, and it is too early to write a comprehensive history of cell death research. We have reached a point, however, where many lines of originally independent research have merged to yield a picture of an evolutionary ancient cell death apparatus which has been put to a wide range of uses in many situations during a multicellular organism's lifetime. This chronology of research in physiological cell death attempts to provide a selection of key publications in the field, emphasizing discovery of the molecular mechanisms.

This chronology attempts to illustrate how physiological cell death has been observed in many fields independently, but in each case this cell death turned out to occur by the same molecular mechanism. As in many other areas of research, acquisition of knowledge has frequently flowed in several directions. Thus 'mainstream' cell death research has highlighted or suggested the importance of cell death for other fields, such as immunology, and discoveries made in a separate field, such as virology, have been shown to impact on the cell death mechanism in general. Earlier work on cell death not extensively covered here is described in excellent reviews by Glucksmann (see entry for 1951) and Clarke and Clarke (see entry for 1842).

The selection of papers is an inherently flawed exercise, because of lack of space and the biases of the authors. We apologize for any omissions that may be unjust. We tried to include both the publications which were regarded as breakthroughs at the time as well as work whose implications and significance were only recognized later. Some of the most recent publications whose impact on the field cannot be reliably assessed at present were not included in this selection. We have not included many areas that have been proposed to be part of the cell death mechanism, but where definitive proof is lacking at the present time. For example, we have not included papers on ceramide, clusterin, poly ADP-ribose polymerase, free radicals, transglutamase, c-*jun*, c-*myc*, or p34cdc2. Our anchor points for discrimination were the observations of cell death pathways in *C. elegans*, because it was first shown in this organism that there were genes essential for normal cell death, namely *ced*-3, *ced*-4 and *ced*-9, that appeared to have no other biological role. We have not included references to the cloning all of the members of a gene family, only the first one or two.

We hope that this chronology gives an interesting review of the field from both an historian's and a biologist's point of view, and welcome correspondence suggesting important contributions that we have inadvertently omitted. We will include these in a revised chronology at some later date.

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Correspondence to D. L. Vaux, The Walter and Eliza Hall Institute of Medical Research, Post Office Royal Melbourne Hospital 3050, Victoria, Australia. Fax: (+61) 3 9347 0852; vaux@wehi.edu.au.

Date	Reference	Apoptosis & mechanisms	Cell death in lower organisms	Cell deaths not initially linked to conserved apoptosis mechanism	Observations not initially linked to cell death research
1842	Vogt C. Untersuchungen uber die Entwicklungsgeschichte der Geburtshelferkröte (Alytes obstertricians). *Jent und Gassman, Solothurn* 1842; 130.	First recognition of physiological cell death.			
	Clarke P, Clarke S. Nineteenth century research on naturally occurring cell death and related phenomena. *Anatomy & Embryology* 1996; **193**: 81–99.	Review of early cell death. Observations, including six additional independent discoveries of naturally occurring cell death prior to 1900.			
1951	Glucksmann A. Cell deaths in normal vertebrate ontogeny. *Biol Rev Camb Philos Soc* 1951; **26**: 59–86.	Review and rediscovery of developmental cell death in embryological tissues.			
1964	Lockshin RA, Williams CM. Programmed cell death. II. Endocrine potentiation of the breakdown of the intersegmantal muscles of silkworms. *J Insect Physiol* 1965; **11**: 803–809.		Use of the term 'Programmed Cell Death'		
1966	Tata JR. Requirement for RNA and protein synthesis for induced regression of the tadpole tail in organ culture. *Dev Biol* 1966; **13**: 77–94.	Linking of developmental and hormonally regulated cell death			
1968					
July	Granger GA, Kolb WP. Lymphocyte *in vitro* cytotoxicity: mechanisms of immune and non-immune small lymphocyte mediated target L cell destruction. *J Immunol* 1968; **101**: 111–120.			First descriptions of cytokines that induce cell death	
Dec	Ruddle NH, Waksman BH. Cytotoxicity mediated by soluble antigen and lymphocytes in delayed hypersensitivity. 3. Analysis of mechanism. *J Exp Med* 1968; **128**: 1267–1279.				
1972	Kerr JF, Wyllie AH, Currie AR. Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. *Br J Cancer* 1972; **26**: 239–257.	Proposal of term 'apoptosis' for morphology of physiological cell deaths; apoptosis concept unifies certain pathological cell deaths (shrinkage necrosis) and developmental cell deaths			
1973	Danilevicius Z. Apoptosis: a factor in neoplastic growth? *JAMA* 1973; **223**: 434–435.			Suggestion apoptosis may have role in cancer	

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1976	Sulston JE. Post-embryonic development in the ventral cord of Caenorhabditis elegans. *Philosoph Transact Royal Soc London Series B: Biological Sciences* 1976; **275**: 287–297.		First description of programmed cell death in nematode; first *C. elegans* cell death mutant (*nuc-1*); evidence endonuclease not required for death		
1979	Matyasova J, Skalka M, Cejkova M. Regular character of chromatin degradation in lymphoid tissues after treatment with biological alkylating agents *in vivo*. *Folia Biologica* 1979; **25**: 380–388.			Radiation and alkylating agents cause DNA degradation (DNA ladders)	
1980 Mar	Russell JH, Masakovski VR, Dobos CB. Mechanisms of immune lysis. I. Physiological distinction between target cell death mediated by cytotoxic T lymphocytes and antibody plus complement. *J Immunol* 1980; **124**: 1100–1105.			Observation that CTL cause apoptosis in target cells.	
April	Wyllie AH. Glucocorticoid-induced thymocyte apoptosis is associated with endogenous endonuclease activation. *Nature* 1980; **284**: 555–556.	Endonuclease activation associated with apoptosis (DNA ladders)			
1982	Horvitz HR, Ellis HM, Sternberg PW. Programmed cell death in nematode development. *Neuroscience Commentaries* 1982; **1**: 56–65.		Description of *ced-3* mutant *C. elegans*; first demonstration of genetic pathway for programmed cell death.		
1983	Hedgecock EM, Sulston JE, Thomson JN. Mutations affecting programmed cell deaths in the nematode Caenorhabditis elegans. *Science* 1983; **220**: 1277–1279.		*C. elegans* corpse engulfment mutants (*ced-1*, *ced-2*)		
1985 Oct	Duvall E, Wyllie AH, Morris RG. Macrophage recognition of cells undergoing programmed cell death (apoptosis). *Immunology* 1985; **56**: 351–358.			Demonstration that sugar binding molecules are involved in engulfment of apoptotic cells	
Dec	Clouston WM, Kerr JF. Apoptosis, lymphocytotoxicity and the containment of viral infections. *Med Hypoth* 1985; **18**: 399–404.			Hypothesis that apoptosis is used to counter viruses	
1986 Mar	Ellis HM, Horvitz HR. Genetic control of programmed cell death in the nematode C. elegans. *Cell* 1986; **44**: 817–829.		*Ced-3*, *ced-4* mutant worms described in *C. elegans*, demonstration that specific genes function to kill cells		

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July	Tsujimoto Y, Croce CM. Analysis of the structure, transcripts, and protein products of *bcl-2*, the gene involved in human follicular lymphoma. *Proc Natl Acad Sci USA* 1986; **83**: 5214–5218.				
Oct	Cleary ML, Smith SD, Sklar J. Cloning and structural analysis of cDNAs for *bcl-2* and a hybrid bcl-2 /immunoglobulin transcript resulting from the t(14;18) translocation. *Cell* 1986; **47**: 19–28.				Cloning of *bcl-2*
Sept	Duke RC, Cohen JJ. IL-2 addiction: withdrawal of growth factor activates a suicide program in dependent T cells. *Lymphokine Res* 1986; **5**: 289–299.	Demonstration that death of a cell line from growth factor withdrawal is by apoptosis.		Suggestion that cell death plays a role in immunological processes.	
Oct	Pickup DJ, Ink BS, Hu W, Ray CA, Joklik WK. Hemorrhage in lesions caused by cowpox virus is induced by a viral protein that is related to plasma protein inhibitors of serine proteases. *Proc Natl Acad Sci USA* 1986; **83**: 7698–7702.				Cloning of crmA
1987 July	Friesen PD, Miller LK. Divergent transcription of early 35- and 94-kilodalton protein genes encoded by the HindIII K genome fragment of the baculovirus *Autographa californica* nuclear polyhedrosis virus. *J Virol* 1987; **61**: 2264–2272.				Identification of baculovirus p35
Sept	Pearson GR, Luka J, Petti L, Sample J, Birkenbach M, Braun D, Kieff E. Identification of an Epstein-Barr virus early gene encoding a second component of the restricted early antigen complex. Virology 1987; **160**: 151–161.				BHRF1, a gene from EBV, is found that resembles *bcl-2*, first *bcl-2* homolog identified
1988 Sept	Vaux DL, Cory S, Adams JM. Bcl-2 gene promotes haemopoietic cell survival and cooperates with c-myc to immortalize pre-B cells. *Nature* 1988; **335**: 440–442.	Identification of *bcl-2* as cell death gene; first identification of a cell death gene where sequence known; experimental proof cell death inhibition can cause cancer			
Oct	Laster SM, Wood JG, Gooding LR. Tumor necrosis factor can induce both apoptotic and necrotic forms of cell lysis. *J Immunol* 1988; **141**: 2629–2634.			First description of apoptosis induced by TNF	

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1989 May	Yonehara S, Ishii A, Yonehara M. A cell-killing monoclonal antibody (anti-Fas) to a cell surface antigen co-downregulated with the receptor of tumor necrosis factor. *J Exp Med* 1989; **169**: 1747–1756.			Anti-Fas antibody described	
July	Trauth BC, Klas C, Peters AM, Matzku S, Moller P, Falk W, Debatin KM, Krammer PH. Monoclonal antibody-mediated tumor regression by induction of apoptosis. *Science* 1989; **245**: 301–305.			APO-1 antibody described	
Nov	Tsujimoto Y. Stress-resistance conferred by high level of bcl-2 alpha protein in human B lymphoblastoid cell. *Oncogene* 1989; **4**: 1331–1336.	Bcl-2 provides resistance to stress & chemotherapeutics			
1990 Jan	Savill J, Dransfield I, Hogg N, Haslett C. Vitronectin receptor-mediated phagocytosis of cells undergoing apoptosis. *Nature* 1990; **343**: 170–173.	Identification of molecules used in engulfment of apoptotic cells			
Aug	Engelmann H, Holtmann H, Brakebusch C, Avni YS, Sarov I, Nophar Y, Hadas E, Leitner O, Wallach D. Antibodies to a soluble form of a tumor necrosis factor (TNF) receptor have TNF-like activity. *J Biol Chem* 1990; **265**: 14497–14504.			Evidence that TNF is not intrinsically toxic, rather cell death requires the action of the cell's receptors	
1991 Jan	Poe M, Blake JT, Boulton DA, Gammon M, Sigal NH, Wu JK, Zweerink HJ. Human cytotoxic lymphocyte granzyme B. Its purification from granules and the characterization of substrate and inhibitor specificity. *J Biol Chem* 1991; **266**: 98–103.				Granzyme B is a serine protease that cleaves after aspartate residues
July	Yonish-Rouach E, Resnitzky D, Lotem J, Sachs L, Kimchi A, Oren M. Wild-type p53 induces apoptosis of myeloid leukaemic cells that is inhibited by interleukin-6. *Nature* 1991; **353**: 345–347.			p53 can cause apoptosis	
July	Itoh N, Yonehara S, Ishii A, Yonehara M, Mizushima S, Sameshima M, Hase A, Seto Y, Nagata S. The polypeptide encoded by the cDNA for human cell surface antigen Fas can mediate apoptosis. *Cell* 1991; **66**: 233–243.			Cloning CD95 (Fas/APO-1)	

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Oct	Strasser A, Whittingham S, Vaux DL, Bath ML, Adams JM, Cory S, Harris AW. Enforced BCL2 expression in B-lymphoid cells prolongs antibody responses and elicits autoimmune disease. *Proc Natl Acad Sci USA* 1991; **88**: 8661–8665.	First experimental proof inhibition of cell death can lead to autoimmune disease			
Nov	Clem RJ, Fechheimer M, Miller LK. Prevention of apoptosis by a baculovirus gene during infection of insect cells. *Science* 1991; **254**: 1388–1390.		Identification of p35 as an anti-cell death protein, the first cell death regulator that functions in insects		
1992 Mar	Watanabe FR, Brannan CI, Copeland NG, Jenkins NA, Nagata S. Lymphoproliferation disorder in mice explained by defects in Fas antigen that mediates apoptosis. *Nature* 1992; **356**: 314–317.			Identification of CD95(Fas/APO-1) as gene responsible for *lpr* phenotype	
April	Fadok VA, Voelker DR, Campbell PA, Cohen JJ, Bratton DL, Henson PM. Exposure of phosphatidylserine on the surface of apoptotic lymphocytes triggers specific recognition and removal by macrophages. *J Immunol* 1992; **148**: 2207–2216.			Phosphatidylserine is exposed on apoptotic cells and marks them for engulfment	
April	Hengartner MO, Ellis RE, Horvitz HR. *Caenorhabditis elegans* gene *ced-9* protects cells from programmed cell death. *Nature* 1992; **356**: 494–499.		*ced-9* mutant worms identified; *ced-9* suppresses activity of *ced-3* and *ced-4*		
April	Thornberry NA, Bull HG, Calaycay JR, *et al*. A novel heterodimeric cysteine protease is required for interleukin-1 beta processing in monocytes. *Nature* 1992; **356**: 768–774.				Cloning of ICE
May	Cerretti DP, Kozlosky CJ, Mosley B, *et al*. Molecular cloning of the interleukin-1 beta converting enzyme. *Science* 1992; **256**: 97–100.				Cloning of ICE
May	Ray CA, Black RA, Kronheim SR, Greenstreet TA, Sleath PR, Salvesen GS, Pickup DJ. Viral inhibition of inflammation: cowpox virus encodes an inhibitor of the interleukin-1 beta converting enzyme. *Cell* 1992; **69**: 597–604.				CrmA shown to directly inhibit ICE
Oct	Yuan J, Horvitz HR. The *Caenorhabditis elegans* cell death gene ced-4 encodes a novel protein and is expressed during the period of extensive programmed cell death. *Development* 1992; **116**: 309–320.		Cloning *ced-4*; first sequence of a *C. elegans* cell death gene.		

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Dec	Vaux DL, Weissman IL, Kim SK. Prevention of programmed cell death in *Caenorhabditis elegans* by human *bcl-2*. *Science* 1992; **258**: 1955–1957.	Function of *bcl-2* in *C. elegans*; demonstration that mechanism of cell death in *C. elegans* is similar to apoptosis in mammals.			
1993 April	Kozopas KM, Yang T, Buchan HL, Zhou P, Craig RW. *Mcl*1, a gene expressed in programmed myeloid cell differentiation, has sequence similarity to bcl2. *Proc Natl Acad Sci USA* 1993; **90**: 3516–3520.	Cloning of *mcl*-1, the first mammalian *bcl-2* homolog to be identified			
April	Crook NE, Clem RJ, Miller LK. An apoptosis inhibiting baculovirus gene with a zinc finger like motif. *J Virol* 1993; **67**: 2168–2174.		Identification of IAP from baculovirus		
Aug	Oltvai ZN, Milliman CL, Korsmeyer SJ. Bcl-2 heterodimerizes *in vivo* with a conserved homolog, Bax, that accelerates programmed cell death. *Cell* 1993; **74**: 609–619.	Cloning of *bcl-2* homolog and antagonist, *bax*			
Aug	Boise LH Gonzales-Garcia, M., Postema CE, Ding L, Lindsten T, Turka LA, Mao X, Nunez G, Thompson CB. *bcl*-x, a *bcl-2* related gene that functions as a dominant regulator of apoptotic cell death. *Cell* 1993; **74**: 597–608.	Cloning of *bcl-2* homolog *bcl*-x.			
Nov	Yuan JY, Shaham S, Ledoux S, Ellis HM, Horvitz HR. The *C. elegans cell* death gene *ced 3* encodes a protein similar to mammalian interleukin 1 beta converting enzyme. *Cell* 1993; **75**: 641–652.	Cloning of *ced-3*, similarity to ICE.			
Nov	Miura M, Zhu H, Rotello R, Hartweig EA, Yuan J. Induction of apoptosis in fibroblasts by IL-1β-converting enzyme, a mammalian homolog of the *C. elegans* cell death gene *ced-3. Cell* 1993; **75**: 653–660.	Induction of apoptosis by ICE; blocking of apoptosis by crmA; direct evidence of mechanistic correspondence between programmed cell death in *C. elegans* and apoptosis in mammals.			
Dec	Rabizadeh S, Lacount DJ, Friesen PD, Bredesen DE. Expression of the baculovirus p35 gene inhibits mammalian neural cell death. *J Neurochem* 1993; **61**: 2318–2321.			Demonstration of p35 function in mammalian cells	
1994 Feb	Hengartner MO, Horvitz HR. *C. elegans* cell survival gene *ced-9* encodes a functional homolog of the mammalian proto-oncogene *bcl-2. Cell* 1994; **76**: 665–676.	Cloning of *ced-9*, sequence similarity to *bcl-2*			

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Mar	Vaux DL, Haecker G, Strasser A. An evolutionary perspective on apoptosis. *Cell* 1994; **76**: 777–779.	Model unifying cell autonomous apoptosis and CTL mediated killing; prediction granzyme B would act like cysteine proteases			
April	White K, Grether ME, Abrams JM, Young L, Farrell K, Steller H. Genetic control of programmed cell death in Drosophila. *Science* 1994; **264**: 677–683.		*Reaper* (*rpr*), the first cell death gene identified in *Drosophila*		
April	Chiou SK, Rao L, White E. bcl 2 blocks p53 dependent apoptosis. *Mol Cell Biol* 1994; **14**: 2556–2563.	p53 induced apoptosis is bcl-2 blockable			
May	Sugimoto A, Friesen PD, Rothman JH. Baculovirus p35 prevents developmentally programmed cell death and rescues a *ced 9* mutant in the nematode *Caenorhabditis elegans. Embo J* 1994; **13**: 2023–2028.	Function of p35 in *C. elegans*; connection of p35 to conserved apoptosis pathway			
July	Kumar S, Kinoshita M, Noda M, Copeland NG, Jenkins NA. Induction of apoptosis by the mouse *nedd2* gene, which encodes a protein similar to the product of the *Caenorhabditis elegans* cell death gene *ced 3* and the mammalian IL-1 beta converting enzyme. *Genes Dev* 1994; **8**: 1613–1626.	Cloning and function of mammalian ICE-like protease nedd2 (caspase-2)			
Dec	Fernandes-Alnemri T, Litwack G, Alnemri ES. CPP32, a novel human apoptotic protein with homology to *Caenorhabditis elegans* cell death protein *Ced-3* and mammalian interleukin-1 beta-converting enzyme. *J Biol Chem* 1994; **269**: 30761–30764.	Cloning of the cysteine protease CPP32 (caspase-3)			
1995 Jan	Roy N, Mahadevan MS, Mclean M, *et al.* The gene for neuronal apoptosis inhibitory protein is partially deleted in individuals with spinal muscular atrophy. *Cell* 1995; **80**: 167–178.	SMA candidate gene NAIP is an IAP homolog, first direct evidence alteration of cell death gene may contribute to neurodegenerative disease			
Jan	Alderson MR, Tough TW, Davis ST, Braddy S, Falk B, Schooley KA, Goodwin RG, Smith CA, Ramsdell F, Lynch DH. Fas ligand mediates activation-induced cell death in human T lymphocytes. *J Exp Med* 1995; **181**: 71–77.	Activation induced cell death of lymphocytes is mediated by CD95 / CD95L			

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April	Boldin MP, Varfolomeev EE, Pancer Z, Mett IL, Camonis JH, Wallach D. A novel protein that interacts with the death domain of Fas/APO1 contains a sequence motif related to the death domain. *J Biol Chem* 1995; **270**: 7795–7798.	Cloning of mort-1/FADD			
May	Chinnaiyan AM, O'Rourke K, Tewari M, Dixit VM. FADD, a novel death domain-containing protein, interacts with the death domain of fas and initiates apoptosis. *Cell* 1995; **81**: 505–512.	Cloning of mort-1/FADD			
July	Grether ME, Abrams JM, Agapite J, White K, Steller H. The head involution defective gene of *Drosophila melanogaster* functions in programmed cell death. *Genes Dev* 1995; **9**: 1694–1708.		Cloning *Drosophila* cell death gene *hid*		
Sept	Tewari M, Dixit VM. Fas- and tumor necrosis factor-induced apoptosis is inhibited by the poxvirus crmA gene product. *J Biol Chem* 1995; **270**: 3255–3260.	CrmA blocks TNF and CD95 killing			
Oct	Darmon AJ, Nicholson DW, Bleackley RC. Activation of the apoptotic protease CPP32 by cytotoxic T-cell-derived granzyme B. *Nature* 1995; **377**: 446–448.	Granzyme B activates CPP32 (caspase-3)			
Sept	Bump NJ, Hackett M, Hugunin M, *et al.* Inhibition of ICE family proteases by baculovirus antiapoptotic protein p35. *Science* 1995; **269**: 1885–1888.	p35 is direct cysteine protease inhibitor			
Sept	Xue D, Horvitz HR. Inhibition of the *Caenorhabditis elegans* cell-death protease ced-3 by a ced-3 cleavage site in baculovirus p35 protein. *Nature* 1995; **377**: 248–251.				
1995 Dec	Rothe M, Pan MG, Henzel WJ, Ayres TM, Goeddel DV. The TNFR2-TRAF signaling complex contains two novel proteins related to baculoviral-inhibitor of apoptosis proteins. *Cell* 1995; **83**: 1243–1252.	Cloning and anti-apoptotic function of cellular IAP genes, some IAPs interact with TRAFs			
Dec	Hay BA, Wassarman DA, Rubin GM. *Drosophila* homologs of baculovirus inhibitor of apoptosis proteins function to block cell death. *Cell* 1995; **83**: 1253–1262.				

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1996 Jan	Liston P, Roy N, Tamai K, Lefebvre C, Baird S, Chertonhorvat G, Farahani R, Mclean M, Ikeda JE, Mackenzie A, Korneluk RG. Suppression of apoptosis in mammalian cells by NAIP and a related family of IAP genes. *Nature* 1996; **379**: 349–353.				
May	Uren AG, Pakusch M, Hawkins CJ, Puls KL, Vaux DL. Cloning and expression of apoptosis inhibitory protein homologs that function to inhibit apoptosis and/or bind tumor necrosis factor receptor-associated factors. *Proc Natl Acad Sci USA* 1996; **93**: 4974–4978.				
June	Duckett CS, Nava VE, Gedrich RW, Clem RJ, Vandongen JL, Gilfillan MC, Shiels H, Hardwick JM, Thompson CB. A conserved family of cellular genes related to the baculovirus IAP gene and encoding apoptosis inhibitors. *Embo J* 1996; **15**: 2685–2694.				
1996 Jan	Luciani MF, Chimini G. The ATP binding cassette transporter ABC1, is required for the engulfment of corpses generated by apoptotic cell death. *Embo J* 1996; **15**: 226–235.	Identification of a protein on a phagocytic cell that is involved in engulfment of corpses; similarity to *C. elegans* ced-7			
June	Boldin MP, Goncharov TM, Goltsev YV, Wallach D. Involvement of mach, a novel mort1/FADD-interacting protease, in Fas/APO-1- and TNF receptor-induced cell death. *Cell* 1996; **85**: 803–815.	Cloning mach-1 / FLICE, connection of pathway from cell membrane to cysteine proteases			
June	Muzio M, Chinnaiyan AM, Kischkel FC, *et al*. FLICE, a novel FADD-homologous ICE/ced-3-like protease, is recruited to the cd95 (Fas/APO-1) death-inducing signaling complex. *Cell* 1996; **85**: 817–827.				
July	Chen P, Nordstrom W, Gish B, Abrams JM. Grim, a novel cell death gene in drosophila. *Genes Dev* 1996; **10**: 1773–1782.	Cloning of *Drosophila* cell death gene *grim*			