Meeting Report

Departing is such sweet sorrow

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'Commitment and death', the theme of such literary epics as *Romeo and Juliet*, was debated by an authorship of the scientific kind at a recent conference on cell death. The chosen venue in New Hampshire provided the perfect environment for this early July meeting, organised by Martin Tenniswood (W. Alton Jones Cell Science Center, Lake Placid, NY) and Douglas Green (La Jolla Institute for Allergy and Immunology, La Jolla, CA). By way of summary, the major aspects included in the program are illustrated in Figure 1. Each is then discussed with reference to the data presented at the meeting and its impact on our current knowledge in the field of cell death.

In addition to the well recognized phenomenon of natural selection between individuals, is the realization that there exists a similar population control of cells within the same genome. Jean Claude Ameisen (Pasteur Institute, Lille, France) discussed the possible evolutionary origins of programmed cell death (tightly associated with cell cycle control), citing examples of *E. coli* population behavior in nutrient-limited environments, and the observation of programmed cell death in several ancient unicellular organisms (Ameisen *et al.*, 1995; Ameisen, 1996).

Implicit in the deliberate nature of such an evolutionarily conserved program of cell death is a point of commitment. When does this point occur, and would all cells demonstrate a similar point of convergence? John Hickman (University of Manchester, UK) discussed the temporal aspects of this issue, suggesting that the apparent enhancement of cellular survival may merely indicate a delay in the inevitable expression of an apoptotic phenotype should manipulation occur downstream from the point of commitment. He questioned not only the critical events which may irreversibly commit a cell to its fate, but perhaps more importantly, the parameters used to determine whether factors such as cytokines or Bcl-2, are truly able to promote and sustain cellular survival. Comparison of data showing short-term survival *versus* clonogenicity illustrated the points made.

Craig Thompson (University of Chicago, IL) discussed the anti-apoptotic effects of Bcl-X_L with regards to its potential role as a channel forming protein in the outer mitochondrial membrane. Interaction between Bcl-X_L and Bak is mediated by a 55 amino acid (35–78) loop within Bcl-X_L. However, when deleted, it produced only a partial suppression of cellular survival, suggesting that Bcl-X_L-

mediated protection is not entirely effected by the neutralisation of Bak activity. Instead, the protective function of Bcl-X_L was suggested to be attributed to its ability to regulate transmembrane ion flux, as illustrated by the Bcl-X_L mediated extrusion of Cl[−] ions from lipid vesicles. Bcl-X_L effectively blocked oligomycin-induced cell death by the dissipation of excess H⁺ produced in response to the uncoupling of the Fo/F1 ATPase proton pump. This conservation of the transmembrane H⁺ ion gradient prevented hyperpolarization and associated loss in mitochondrial membrane potential. Interestingly, John Reed (The Burnham Institute, La Jolla, CA) commented that yeast mutants resistant to Bax-induced death were all characterized by a mutation in the mitochondrial Fo/F1 ATPase proton pump, suggesting that Bcl-2-like proteins may share a common ability to regulate transmembrane ion fluxes.

In another series of experiments described by John Reed, in which the putative channel-forming domains of pro (Bax/Bak) and anti (Bcl-2/Bcl-X_L) apoptotic proteins were exchanged, they were unable to substantiate that differing modulation of ion movement and/or ion type could account for opposing protein function. John Reed also discussed the cloning of a novel ER-associated Bcl-2 homolog, BI-1, which partially protected against both drug and growth factor withdrawal-induced apoptosis, although to a lesser extent than Bcl-2 itself. Suppression of Bax-mediated death was limited to the neutralization of membrane-associated Bax but did not inhibit the effect of that within the cytosol.

The role of the mitochondria in the apoptotic process and whether signals arising from these organelles constitute the central regulatory mechanism for cellular commitment to apoptosis represented the theme of a number of presentations. Guido Kroemer (Centre National de la Recherche Scientifique, Villejuif, France) suggested that a loss in mitochondrial permeability transition represents the universal and final commitment of a cell to undergo apoptosis (Kroemer, 1997). This was in contrast to data presented by Mark Wilson (University of Wollongong, NSW, Australia), which clearly showed that DNA fragmentation could proceed either in the absence of a detectable change in, or despite a direct inhibition of, a loss in mitochondrial membrane permeability. Furthermore, Donald Newmeyer (La Jolla Institute for Allergy and Immunology, La Jolla, CA) showed that cytochrome c release could

occur independently of a detectable depolarization of the mitochondrial membrane. It was suggested by Guido Kroemer that such discrepancies may be reconciled by the concept of a discontinuous, or 'flickering' mitochondrial permeability transition (Ichas *et al*, 1997). Whether the collapse of mitochondrial membrane polarity does indeed represent the point of irreversible commitment remains a point for much discussion. Data shown by Kroemer however, did suggest that events beyond this point determined the type of cell death activated. Caspase activation appeared to be specifically associated with an

apoptotic cell death, whilst the inhibition of caspase activation, beyond the putative point of commitment, resulted in necrosis.

The critical involvement of mitochondrial events in the mediation of apoptosis was discussed further by Donald Newmeyer. Using the *Xenopus* cell free extract system, cytochrome c-mediated caspase activation was shown to be directly inhibitable by Bcl-2 at the point of mitochondrial release (Kluck *et al*, 1997). Reaper, the pro-apoptotic drosophila protein, was demonstrated to function upstream of cytochrome c to promote its release from mitochondria.

Figure 1 Commitment to cell death. Summary of signals promoting irreversible commitment to cell death and how major components of the apoptotic pathway, including the caspases and Bcl-2 proteins may modulate these events to regulate cellular survival

The physiological relevance of this observation and whether or not there exists a similar mechanism in the mammalian system remain to be identified. The exogenous addition of caspase-8 (FLICE) appeared to promote caspase cleavage, either directly, or by the induction of cytochrome c release from mitochondria. Yuri Lazebnik (Cold Spring Harbor Laboratories, Cold Spring Harbor, NY) also described a cytochrome c-independent pathway for the activation of caspases (particularly caspases -3 and -6), which was inducible by the expression of the adenovirus, E1A. It was suggested that the exclusive expression of this oncogenic generated activity (OGA) could represent a target for the selective induction of cell death in tumourigenic cells (Fearnhead *et al*, 1997).

Grace Wong (Millenium Pharmaceuticals, Cambridge, MA) also highlighted the differing chemo and radio sensitivities of transformed cells *versus* their normal counterparts in terms of the relative expression and inducibility of manganese superoxide dismutase (MnSOD). Lymphotoxin (LT) induced expression of MnSOD conferred protection to normal cells but rendered tumor cells more sensitive to death induced by several chemotherapeutic agents and to irradiation. *In vivo* studies demonstrated LT-induced sensitization of colon carcinomas and the suppression of tumor formation in nude mice. The protective effects of MnSOD appeared to be dependent upon its localization to the mitochondria and was inversely correlated with the expression of caspases.

In contrast to much of the meeting, which focused on the mechanistic aspects of the cell death process itself, Scott Lowe (Cold Spring Harbor Laboratories, Cold Spring Harbor, NY) presented data highlighting the importance of oncogene expression in the regulation of apoptosis and how this may impact on tumor resistance. Overexpression of E1A was shown to confer chemosensitivity in primary fibroblasts via the p53-dependent induction of apoptosis. These effects of p53 appeared to be partially mediated by Bax, although elevated levels of Bax could not overcome resistance promoted by a non-functional p53. Using a series of E1A mutants, two conserved regions (CR1 and CR2), which are essential for the binding of Rb and related proteins, p130 and p300, were identified as essential for both the induction of chemosensitivity and the transforming activities of E1A. Specific mutation of the N terminal CR1 region was shown to only partially affect E1A mediated chemosensitivity, whilst mutation in the CR2 region completely eliminated E1A induced apoptosis. Interestingly, the expression of a non-functional CR2 in the complete absence of Rb, fully restored cellular chemosensitivity.

Barbara Osborne (University of Massachusetts, MA) focused on the role of the nuclear hormone receptor, Nur77 in the regulation of apoptosis. Based on the characterized ability of hormone receptors to interact with related proteins, the yeast two hybrid system was used to isolate potential protein partners for Nur77. Using this approach, Notch-1 was identified, which exhibits extra-cellular homology to EGF. Expression of TAN1, the human homolog of Notch-1 protected cells from Nur77-induced apoptosis, but was without effect on Nur77-independent

death. Barbara Osborne speculated that intracellular proteolysis of Notch-1 to release a steroid hormone-like domain may permit the direct transcriptional regulation of genes essential for the suppression of apoptosis. Given the homology of Nur77 with the invertebrate ecdysone receptor, the effect of overexpression of Notch-1 was assessed in drosophila. Data showing Notch-1-mediated rescue of ecdysone treated drosophila S2 cells suggested that this pathway may represent an evolutionarily conserved mechanism for the promotion of cellular survival.

The caspase family, first identified via CED3 homology, has seen a rapid expansion over the last year. These aspartate-specific cysteine proteases are often viewed as the grim reaper's scythes, terminally degrading cellular integrity. However, recent studies have suggested that members of the caspase family may function in a hierarchical cascade where upstream caspases act as early transducers of diverse apoptotic stimuli to activate downstream caspases which in turn effect the proteolytic degradation of target substrates. For example, caspase-8 (FLICE) is thought to be an upstream caspase, functioning as part of both the TNF receptor and Fas signaling complexes. However, although it appears physically proximal, there is only limited evidence to suggest that caspase-8 or other caspases function prior to commitment and that their effects or activation are reversible (Longthorne and Williams, 1997). It will be important to determine the functional order of caspase-mediated events if intervention in the caspase cascade is to be correctly interpreted as an inhibition, or merely as a delay of apoptotic events and associated phenotype.

Emad Alnemri (Kimmel Institute, Thomas Jefferson University, PA) described the cloning and characterization of a negative regulator of caspases, designated FLAME-1 (FADD-like antiapoptotic molecule). FLAME-1 was identified through its homology with the large prodomain regions of caspases-8 and -10 and contains two amino-terminal FADD/Mort1 death effector domain homology regions (Srinivasula *et al*, 1997). David Wallach (Weizman Institute of Science, Rehovot, Israel) independently identified this protein, which he called CASH. FLAME-1/CASH abrogates Fas and TNF-induced apoptosis by interfering with the recruitment of caspases-8 and -10 to the intracellular death complex by direct association following death receptor engagement. The high expression of these caspase inhibitors in testes and placenta may be an important mechanism by which these immune privileged tissues overcome Fas-induced apoptosis.

Lois Miller (University of Georgia, Athens, GA) described the suppression of apoptosis via interactions between baculovirus inhibitors of apoptosis (IAPs) with two Drosophila pro-apoptotic proteins Doom and Reaper, via the BIR (baculovirus IAP repeat) motif. This led to the suggestion that IAPs may act as cellular sensors of life or death signals, buffering against proapoptotic factors which, when released from their normal binding partners, are able to activate apoptosis. John Reed illustrated the conservation of this protective mechanism by the demonstration that IAPs directly complex with mammalian caspases to inhibit their cleavage and activation. The inhibitory effects of XIAP

were especially pronounced for caspases-3 and -7, although showed only a partial suppression of caspase-8-mediated processing of caspase-3 (CPP32) (Deveraux *et al*, 1997). David Vaux (Walter and Eliza Hall Institute, Victoria, Australia) discussed the involvement of the mammalian IAPs, MIHB and MIHC in the binding of the TNF-receptor associated factors (TRAFs) 1 and 2 through the BIR domains. However, he showed no correlation between TRAF binding and inhibition of cell death suggesting that the inhibitory effects of these mammalian IAPs are not due to sequestration of TRAFs.

Putative upstream activators of caspases were discussed by Xiaodong Wang (South Western Medical Center, Dallas, TX). He described the purification of two factors Apoptotic Protease Activating Factors (Apaf) 1 and 2 which are necessary to reconstitute the dATP-dependent activation of caspase-3 in a cell-free system (Liu *et al*, 1996). APAF-2 was identified as human cytochrome c. Importantly, Apaf-1 bears homology to both CED-4 and CED-3 (and the ICH-1 adapter RAIDD) in the amino terminus region. The central region of Apaf-1, which resembles CED-4, contains an ATPase domain, whilst the carboxyl terminus contains 12 WD40 motifs, suggesting a role in protein binding. Wang showed evidence for the direct association of Apaf-1 with cytochrome c suggesting that it may function as a cytochrome c binding protein (Zou *et al*, 1997; Vaux, 1997). The isolation and characterization of OGA, as described by Yuri Lazebnik, showed it to be clearly distinguishable from both Apaf-1 and 2. From an evolutionary perspective, it is notable that Miller suggested that CED-4 may stimulate the rate of apoptosis by increasing the processing of CED-3, an event which is blocked by CED-9. This appears to require the prodomain of CED-3 and a conserved lysine within the putative GTP binding site of CED-4.

Michael Hengartner (Cold Spring Harbor Laboratories, Cold Spring Harbor, NY) discussed the role of CED-3 and CED-4 in the homeostatic control of the hermaphrodite gonad. Mutation of CED-4 was able to prevent the massive amount of cell death which occurs during oogenesis in *C. elegans*. Ras expression may also play a regulatory role to control the selection process at a stage when the developing oocyte requires either a survival factor to continue development or CED3/CED-4 expression for the induction of death.

Arnold Greenberg (University of Manitoba, Winnipeg, Manitoba, Canada) introduced the subject of granzyme B-mediated apoptosis with discussion of the characterisation of Nip3 (19K interacting protein 3), a substrate for granzyme B (GraB). The GraB mediated degradation of Nip3 is characterized by cleavage at an IXXD site within Nip3. This pro-apoptotic dimeric protein is localized to mitochondria and induces apoptosis when overexpressed, in addition to increasing the rate of Gra B-mediated cell death. Both these death pathways are inhibited by the caspase inhibitor zVAD-fmk, indicating that caspase activation is required. Chris Bleakley (University of Alberta, AB, Canada) suggested that nuclear localisation of GraB, and associated chromatin condensation occurred only in the presence of perforin. Seamus Martin (Maynooth University College, Ireland)

discussed GraB-mediated cleavage of caspase-3, suggesting by inhibitor studies, that GraB may mediate generation of the small p12 subunit of caspase-3 but that the prodomain is removed by autocatalysis.

Roy Walker (National Research Council of Canada, Ottawa, Ontario, Canada) discussed the cell-type specific degrees of chromatin degradation. He showed that serine protease inhibitors are able to block the secondary stage of fragmentation from large to small fragments, although initial cleavage was unaffected. Two pH and calcium-dependent nuclear endonucleases appear to be involved in the DNA fragmentation process, one of which is loosely associated with the nucleus and the other which is chromatin bound.

An organismal requirement for the induction of apoptosis is that of tissue modeling which was discussed by Zahra Zakeri (City University of New York, Flushing, New York). Amelioration of the limb deformity in Hammertoe mutant mice can be observed following treatment with retinoic acid, although this is thought to be via an indirect mechanism (Ahuja *et al*, 1997). Other events currently being investigated in this model and others, are the expression and activity of Cdk5 and its regulatory subunit p35 in association with cell death. In contrast to that observed in Hammertoe, a direct effect of retinoids in the interdigital mesenchyme (amongst other areas) was demonstrated by Laszlo Nagy (Gene Expression Laboratory, The Salk Institute, La Jolla, CA) by the regulation of tissue transglutaminase gene transcription. It has also been shown that retinoids can afford additional control over apoptosis by the suppression of Bcl-2 expression in HL-60 cells (Nagy *et al*, 1996).

Progress is being made in understanding the recognition and phagocytosis of apoptotic lymphocytes, which involves phosphatidylserine (PS) exposure on the lymphocyte, and expression of the CD14 receptor on the macrophage as discussed by Robert Schlegel (Penn State University, Pennsylvania, PA), although this is not the only recognition system used (Pradhan *et al*, 1997). During cell death in lymphocytes, a putative scramblase is activated via a calcium-dependent mechanism, causing PS externalization. It appears that neither the translocase (an ATPase) (Tang *et al*, 1996) which normally maintains PS in the inner plasma membrane, nor scramblase are caspase targets. Phagocytosis of dying neurons was discussed by Steffany Bennett (W. Alton Jones Cell Science Center, Lake Placid, NY). Specific alterations of platelet activating factor receptor (PAFR) expression were observed in both neurons and glia. Dying neurons expressed PAFR allowing phagocytosis by neighbouring healthy neurons which did not express PAFR. Additionally, PAF caused activation in a subset of PAFR positive astrocytes and microglia, which then also phagocytosed apoptotic neurons.

In addition to the fact that apoptosis is required during the normal development of the eye, various ocular pathologies appear to be closely associated with failure of apoptotic control, as discussed by David Papermaster (University of Connecticut Health Center, Farmington, CT). Transgenic mice expressing the SV40 TAG directed by the interstitial retinol binding protein (IRBP) promoter, developed retinal tumors similar to human retinoblastoma

and pinealoma, or cataracts as a result of lens fiber cell apoptosis. Expression of HPV16 E7 in similar locations resulted in apoptosis of the retina and lens. However, in the absence of p53, multifocal tumors are formed (Howes *et al*, 1994). In contrast, similarly directed expression of Bcl family members or p35 resulted in no immediate detectable pathologies. However, it will be interesting to determine whether apoptosis-regulating genes play a role in inherited retinal degenerative diseases.

Recently the phenomenon of immune privilege has been shown to be an active process, employing the expression of FasL in the anterior chamber of the eye to mediate cell death of infiltrating Fas positive inflammatory cells (Griffith *et al*, 1995; Ferguson and Griffith, 1997). Another important function of the expression of FasL in the eye is the control of choroidal neovascularization. As shown by Thomas Ferguson (Washington University School of Medicine, St. Louis, MO), age related macular degeneration, one of the world's leading causes of blindness, may be associated with loss of functional FasL on the retinal pigment epithelium (RPE). Epithelial cells of choroidal neovascular membranes were shown to be Fas positive, normally providing vascular regulatory control by the RPE via the Fas:FasL interaction.

David Vaux cast some doubt on the sufficiency of Fas ligand expression for protection of allografts from rejection. Using a model of over-expressed FasL directed to murine pancreatic islet beta cells, it was shown that these cells were not protected from subsequent rejection following allogeneic transplant (Allison *et al*, 1997). In contrast, the FasL overexpressing cells induced granulocytic infiltration and cytokine release. In fact the islet cells themselves then died, perhaps ironically, as a direct result of the upregulation of Fas. Our knowledge of immune privilege at this point is not sufficiently complete to allow extrapolation and exploitation in transplantation.

It could be argued that the inhibition of a signaling molecule within the cell death pathway, as opposed to an effector downstream of commitment, constitutes protection. To that effect Richard Kolesnick (Memorial Sloan-Kettering Cancer Center, New York, NY) discussed the suggested, but controversial role of ceramide signaling in mediating apoptosis. bFGF appeared to significantly increase endothelial cell survival following radiation via a reduction in acid sphingomyelinase (ASMase) activity and a consequent decrease in ceramide levels. He proposed that ionising radiation can utilize two pathways in the mediation of cellular damage; a p53-dependent mechanism as seen in the thymus for example and a ceramide-mediated pathway as observed in endothelial cells. The observation that ceramide generation is reduced following ionising radiation in the ASMase knockout mouse supports the hypothesis, although it should be noted that apoptosis is not entirely inhibited (Santana *et al*, 1996).

Richard Kolesnick also presented data showing the inhibition of endothelial cell apoptosis following LPS-induced endotoxic shock. This was achieved by treatment with the TNF-binding protein (extracellular portion of TNFR1) which binds to and inhibits the action of TNF α , in this case the primary extracellular trigger for cell death. The

TNF-induced increase in ceramide levels is therefore prevented. bFGF can protect endothelial cells from apoptosis induced by LPS, and LPS fails to cause significant endothelial cell death in the ASMase knockout mouse, despite raised levels of TNF α in both instances. Continuing with the ceramide theme, Yusuf Hannun (Duke University, Durham, NC) presented data showing that the protective effects of Bcl-2 occurred independently of any alterations in endogenous ceramide levels but that crmA inhibited both ceramide production and TNF-induced apoptosis, but was without effect on ceramide-induced death. Yusuf Hannun also suggested, that since the enzymes of ceramide metabolism appear to act as stress-sensitive switches to determine the ultimate fate of a cell, that they may provide us with potentially novel drug targets.

Rescue differs from protection in that it results in the survival of cells following activation of apoptotic effectors causing detrimental physical changes in the cell. That this could even be a physiologically realistic scenario has not been convincingly proven at the single cell level. Rescue of cellular populations is quite different and usually refers to the resurgence of a subpopulation less sensitive in some way to the apoptotic stimulus. However, interesting evidence of the ability of individual cells to be rescued was presented by Monanish Deshmukh (Washington University School of Medicine, St. Louis, MO). NGF withdrawal-induced apoptosis of embryonic sympathetic neurons can be inhibited by the general caspase inhibitor Boc-aspartyl-fluoromethylketone (BAF) (Deshmukh *et al*, 1996). Early events in the apoptotic cascade, including the phosphorylation of *c-jun* and increased expression of *c-jun* and *c-fos*, are able to proceed even in the presence of BAF. As a consequence, cells exhibit smaller somas, reduced protein synthesis, decreased rates of repolarization and diminished responses to nicotine. Clearly, the apoptotic pathway has been engaged, but interrupted. Most interesting is the observation that NGF can restore the growth and metabolism of the rescued neurons when re-added to the culture, suggesting that additional trophic support may be required to reverse or repair initial pro-apoptotic changes. In an *in vivo* neonatal model of ischemic injury, BAF significantly reduced apoptotic damage when administered prior to, or 3 h following the ischemic insult. This and other data (Lodick *et al*, 1996) clearly implicate caspases in the pathway of hypoxic ischemic neuronal death. However, whether caspase inhibitors are sufficient *in vivo* must be questioned in light of the *in vitro* data, since the rescued neurons may not be functional without supplemental factors.

The phenomenon of rescue may be limited to neuronal cells owing to their terminally differentiated state and their inability to proliferate. It could therefore be argued that the persistence of even semifunctional surviving neurons following an infarct would be preferable to loss of those cells entirely. However, the importance of the functional clarification of what remains following rescue after an apoptotic insult is most acutely illustrated by the possibility of saving oocytes from chemotherapy or radiotherapy-induced damage. This is obviously a case in which protection is preferable to rescue, but furthermore even

protection should be questioned in the aftermath of DNA damaging ionising radiation. This interesting issue was addressed by Jonathan Tilly (Harvard Medical School, Boston, MA). Apoptosis is a key component in the physiological development, growth and function of the ovary, including the germ cells. A great deal of work has described the details of granulosa cyclicity (Martimbeau and Tilly, 1997). Germ cells are also able to undergo apoptosis—either in the formation of the available cohort during reproductive life, during reproductive senescence and also as an unfortunate consequence of chemo- or radiotherapy (Tilly *et al*, 1997). With regard to the latter, it has been determined that chemotherapy-induced oocyte cell death involves Bax, caspase-2, and probably ceramide. The greater the understanding of the molecular triggers of cell death in the oocyte, the closer the possibility of its inhibition. Obviously the most important experiments associated with these studies must be the ability of the oocytes to be fertilized and develop into normal offspring. A more readily achievable goal might be the inhibition of germ cell death in primordial follicles by the inhibition of granulosa cell death, such that the oocyte is affected only indirectly.

The more we understand of the intracellular mechanisms controlling the apoptotic pathway, the greater the possibility of manipulation of these events to therapeutic advantage. This of course may be by the promotion of cell death, such as in chemotherapy, or by the prevention of inappropriate cell death such as that seen in neurodegenerative disease. To date we have been largely unsuccessful in the manipulation of cellular life and death at a physiological level. However, as this meeting highlighted, perhaps we must first address at what point intervention must occur. With respect to prevention of cell death, the terms 'rescue' and 'protection' must be aligned with the phenomenon of 'commitment' as a definable event. Similarly, to engage effective promotion of cell death, it must be determined if intervention prior to commitment is sufficient to complete the process, or whether a post commitment event must be guaranteed in order to be confident of completion.

Consider Romeo. Upon the death of Juliet (his trophic support), he feels that he can no longer live and chooses to commit suicide. However, the timely receipt of a message from Friar Lawrence would have prevented Romeo's decision to initiate his own suicide and ensured his protection and continued survival. Alternatively, prior knowledge of the imminent suicide may have enabled Friar Lawrence to administer an antidote to the poison in time, thereby permitting the rescue of Romeo. In this scenario however, the point at which the poison touched his lips, Romeo was committed to die. Throughout this review we have considered what the cellular equivalent of this act may be. Is it a change in mitochondrial membrane potential or perhaps the engagement of the apoptotic cascade? and once past this point, does a cellular 'antidote to death' exist? Can cells really be halted in the midst of a caspase cascade and the damage effectively repaired to ensure continued cellular survival? Furthermore, even if possible, would it be ultimately beneficial to engage

a program of 'cellular resuscitation' or would we be simply paving the way for adventitious oncogenic changes? We do not have the answers to these questions, but as this meeting indicated, they are within sight for the first time.

The authors would like to point out that it was simply not possible to mention each of the oral and poster presentations, but have instead selected illustrative examples of the most current and recent findings in the field of cell death. We apologise to those that we have not included.

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