The B cell lymphoma-2 (Bcl-2) homologs myeloid cell leukemia-1 (Mcl-1) and A1 are prosurvival factors that selectively bind a subset of proapoptotic Bcl homology (BH) 3-only proteins. To investigate the molecular basis of the selectivity, we determined the solution structure of the C-terminal Bcl-2-like domain of Mcl-1. This domain shares features expected of a prosurvival Bcl-2 protein, having a helical fold centered on a core hydrophobic helix and a surface-exposed hydrophobic groove for binding its cognate partners. A number of residues in the binding groove differentiate Mcl-1 from its homologs, and in contrast to other Bcl-2 homologs, Mcl-1 has a binding groove in a conformation intermediate between the open structures characterized by peptide complexes and the closed state observed in unliganded structures. Mutagenesis of potential binding site residues was used to probe the contributions of groove residues to the binding properties of Mcl-1. Although mutations in Mcl-1 had little impact on binding, a single mutation in the BH3-only ligand Bad enabled it to bind both Mcl-1 and A1 while retaining its binding to Bcl-2, Bcl-xL, and Bcl-w. Elucidating the selective action of certain BH3-only ligands is required for delineating their mode of action and will aid the search for effective BH3-mimetic drugs.

Programmed cell death (apoptosis) is a highly conserved and regulated process used by metazoa to eliminate damaged and surplus cells, such as those generated during development (1). Important arbiters of this process are the B cell lymphoma-2 (Bcl-2) family of proteins that comprise prosurvival (Bcl-2, Bcl-xL, Bcl-w, Mcl-1, A1) and proapoptotic members (2). The proapoptotic proteins are subdivided into the Bax-like (Bax, Bak, Bok) and the BH3-only proteins (Bad, Bim, Bmf, Bik, Hrk, Bid, Puma, Noxa) (3). Affiliates of the subgroups are defined by their sequence similarities and biological function. Prosurvival members contain up to four regions of sequence homology known as “Bcl-2 homology” domains (BH1–4), whereas Bax, Bak, and Bok bear only BH1–3. The minimalist BH3-only molecules have only the short BH3 domain (3). Cell survival is thought to be critically dependent on the interactions between the opposing factions of this family.

Myeloid cell leukemia-1 (Mcl-1) was cloned as an early response gene up-regulated in myeloid cells following addition of cytokines (4), although its expression is now appreciated to be widespread. Consistent with this, Mcl-1 appears to play an important role during development as germ line disruption of the mouse mcl-1 gene resulted in failure of blastocyst implantation (5). Tissue-selective deletion of Mcl-1 in the T- or B-lymphoid compartment resulted in lymphopenia (6); interestingly, Mcl-1, but not Bcl-2 or Bcl-xL, expression may be critical for survival of myeloma cells (7).

Given its key biological roles, it is not surprising that Mcl-1 is regulated at multiple levels. In many hematopoietic cells, growth factors promote cell survival by triggering mcl-1 transcription and stabilizing Mcl-1 protein (8, 9). Conversely, cytokine withdrawal and other stress signals such as UV irradiation initiate cell death by promoting Mcl-1 degradation (10). Although its C-terminal region shares sequence identity with Bcl-2 (4), the N-terminal region is unique among this class of proteins, containing regions of low sequence complexity and PEST (proline, glutamic acid, serine, threonine) sequences known to target proteins for rapid turnover through proteasomal degradation (11).

Precisely how the stability of Mcl-1 is controlled is unclear, although it is likely that its protein partners may affect this. Mcl-1, like other prosurvival Bcl-2 proteins, is neutralized by binding proapoptotic BH3-only proteins (1, 2). During lymphoid development Mcl-1 is probably controlled, at least in part, by Bim because loss of this BH3-only protein led to excess lymphocytes (12), the opposite effect to Mcl-1 loss. In contrast, loss of Bad, which is also expressed in this tissue and activated by cytokine deprivation, did not impact on lymphocytes (13). A plausible explanation for this difference is that Bim, but not Bad, binds Mcl-1 (6). In the lymphoid compartment, the similarities observed between the loss of Mcl-1 (6), Bcl-2 (14), and Bcl-xL (15) suggest that Mcl-1 has an essential, non-redundant function. The idea that Mcl-1 has a distinct role during cell death is also supported by observations that genotoxic stress kills HeLa cells through the inactivation of Mcl-1, which appears to selectively trigger Bak activation (16). Collectively,
these and other studies point to the critical and distinct role(s) of Mcl-1 in maintaining cell survival.

A growing body of data suggests that the prosurvival Bcl-2 proteins have distinct biological and biochemical properties (1, 17, 18). Although the determinants of these differences remain poorly defined, the recently described ability of Bcl-2 to selectively bind specific BH3-only proteins may be important (6, 17). Interactions between BH3 domains and Bcl-2 proteins varied over 10,000-fold in affinity, and particular protein pairings were highly preferred. To examine the molecular basis of this specificity, which may explain some of the distinctive functional properties of Mcl-1, we have solved the solution structure of the Bcl-2 domain of Mcl-1. Like Bcl-2, Bcl-xL, and Bcl-w, it shares a conserved α-helical fold. An analysis of the binding groove revealed differences that contribute to the distinct binding profile of this protein. Defining the molecular basis of specific binding may allow small molecules that target specific prosurvival members to be developed.

EXPERIMENTAL PROCEDURES

Expression and Purification of Proteins—Mouse Mcl-1 (NCBI accession number AAC31790), A1 (AAC38747), Bad (NP_031548), Noxa (NP_067426), and Bim (AAC40030) were expressed as glutathione S-transferase (GST) fusion proteins in Escherichia coli BL21(DE3) and purified as described (19). Human Bcl-w (Q92843), Bcl-2 (P10415), and Bcl-xL (NP_612815) were expressed in a BL21(DE3) and purified as described (19). Human Bcl-w richia coli structure determinations are positions as colored bars on the sequence of the Bcl-2 domain of Mcl-1. Like Bcl-2, Bcl-xL, and Bcl-w, it shares a conserved /H9251 -helical fold. An analysis of the binding groove revealed differences that contribute to the distinct binding profile of this protein. Defining the molecular basis of specific binding may allow small molecules that target specific prosurvival members to be developed.

Solution and Binding Properties of Mcl-1—The structure of Mcl-1 shares sequence identity with Bcl-2, whereas its region of Mcl-1 shares sequence identity with Bcl-2, whereas its

Structure of Mcl-1

Transient Transfection, Immunoprecipitation, and Immunoblotting—Maintenance, transfection, metabolic labeling of human embryonic kidney 293T cells with [35S]methionine/cysteine and co-immunoprecipitation have been described (20). Equivalent trichloroacetic acid-precipitable lysates were immunoprecipitated using mouse monoclonal antibodies to HA (HA.11; CRP, Covance Research Products), FLAG (M2, Sigma), or control Glu-Glu (CRP) tags. Proteins were resolved by SDS-PAGE, transferred to nitrocellulose membranes, and detected by fluorography. Immunoblotting was performed using rat monoclonal anti-Bim (3C5), anti-FLAG (9H1) (18), or rabbit polyclonal anti-Bad (Cell Signaling) detected by horseradish peroxidase-conjugated goat anti-rat (SouthernBiotech) or anti-rabbit antibodies (Bio-Rad).

NMR Spectroscopy and Spectral Assignments—Spectra were recorded at 25 °C on a Bruker DRX-600 spectrometer equipped with triple resonance probes and pulsed field gradients or AV-500 with a cryogenically cooled probe, operating at 600 and 500 MHz, respectively. A series of 1D, 2D, and 3D NMR experiments were recorded using either 15N or 13C. 15N double labeled Mcl-1ANC23 (24). Spectra were processed using XWINNMR (Bruker AG) and analyzed using XEASY (25).

Distance and Dihedral Angle Restraints—Distance restraints were measured from the 120-ns mixing time three-dimensional 15N-edited NOEY, 13C-edited NOEY, and two-dimensional NOEY spectra. Hydrogen-deuterium exchange was monitored using XWINNMR (Bruker AG) and analyzed using XEASY (25).

Structure Calculation and Analysis—Initial structures were calculated using DYANA 1.5 (28), optimized to obtain low target functions, and refined with XPLOR-NIH 2.9.3 (29) in the PROLSQ force field (30). PROCHECK_NMR (31) and MOLMOL (32) were used for the analysis of structure quality. The final structures had no experimental distance violations greater than 0.3 Å or dihedral angle violations greater than 5°. Structural figures were generated in MOLMOL.

RESULTS

Solution and Binding Properties of Mcl-1—The C-terminal region of Mcl-1 shares sequence identity with Bcl-2, whereas its N-terminal region contains low complexity and proline, glutamic acid, serine, and threonine (PEST) sequences (4) (Fig. 1). Binding studies in 293T cells revealed that Mcl-1 with either N- or C-terminal truncations retained its avidity for Bim (Fig. 2A and data not shown), indicating that the Bcl-2 domain had not been disrupted by a 151-residue truncation at the N terminus or 11- and 23-residue C-terminal truncations. To obtain soluble recombinant proteins from E. coli, it was necessary to

L. Chen, S. N. Willis, A. Wei, B. J. Smith, J. I. Fletcher, M. G. Hinds, P. M. Colman, C. L. Day, J. M. Adams, and D. C. S. Huang, unpublished results.
Figure 2. The BH3 binding activity is located in the Bcl-2 homology domain, and the C-terminal residues of this domain mediate ligand binding. A, immunoprecipitation of Mcl-1 variants from 293FT cells. Equivalent 18S-labeled cell lysates from cells expressing FLAG-Mcl-1 variants and EE-BimNH2 were immunoprecipitated using anti-FLAG M2 (α-F), anti-EE (α-E), or control anti-HA (α-H) monoclonal antibodies and fractionated on SDS-PAGE gels (left column). Western blots (middle and right columns) were performed with anti-Bim and anti-FLAG 9H1 antibodies. Mcl-1 degradation product is indicated by *. B, kinetic data for binding of BimBH3 peptide to Mcl-1NC23 and Mcl-1NC11. BimBH3 peptide was immobilized. C, Mcl-1NC23 and Mcl-1NC11 bind to the same proapoptotic proteins. The ability of the Mcl-1 proteins to bind to proapoptotic proteins was tested using GST pull-down experiments. Equivalent amounts of the GST fusion proteins were used in each experiment. Bound Mcl-1 was detected by Coomassie staining.

The three-dimensional structure of Mcl-1NC23 (Fig. 3) has a well-defined helical core, with the less ordered regions of the structure located at the N terminus (residues 152–154, in addition to the 5 N-terminal cloning artifacts), C terminus (residues 300–308), and a 12-residue loop (residues 173–184) connecting helices α1 (residues 155–172) and α2 (residues 185–205). Like the other Bcl-2 homologs, Mcl-1 has a central hydrophobic helix, α5 (residues 242–261), surrounded by a set of amphipathic helices that pack against this helix. The hydrophobic BH3 binding groove is formed from α2, α3 (residues 206–214), and α4 (residues 224–233), with α5 and α8 (residues 293–299) forming the base of the groove. A sharp turn connects α5 with the nearly parallel helix, α6 (residues 265–282). Two short helices, α7 (residues 284–289), which is an extension of α6 after a kink at Lys-283, and α8, which is perpendicular to α5, terminate the helical fold.

Structural Comparison with Other Bcl-2 Family Members—The topology of the Bcl-2 domain in Mcl-1 is very similar to that of other Bcl-2 homologs. The backbone (Cα, N, C') r.m.s.d. to Bcl-2, Bcl-xL, and Bcl-w are 1.74, 1.88, and 1.96 Å, respectively, over the common secondary structural elements as defined in Fig. 1, showing the structures are in close agreement. There is low sequence identity among the Bcl-2 family. Excluding the N-terminal 151 residues, Mcl-1 shares ~24% sequence identity and 35–46% similarity with Bcl-2, Bcl-xL, Bcl-w, and A1 and is most similar to A1. Mcl-1 and A1 lack the N-terminal BH4 domain, and neither protein shares any significant sequence identity with Bcl-2, Bcl-xL, or Bcl-w over this region. Despite lacking this domain, Mcl-1 retains a helix (α1) that has a similar disposition with respect to the helical bundle as seen in the other Bcl-2 molecules. Also, although the sequences differ, Mcl-1 has a short α1-α2 loop with a restricted conformational space, reminiscent of Bcl-w. Equivalent residues in other structures lack any order (33–35).

As with other protein families sharing a low level of sequence identity, the Bcl-2 proteins have a conserved three-dimensional scaffold, but the surface features differ. Notably, mouse Mcl-1 contains 14 lysines, 10 of which are found in the Bcl-2 homology domain (Fig. 1), and with the exception of Lys-283 all are solvent-accessible. These residues are not only potential candidates for ubiquitinylation but also contribute to the electrostatic properties of Mcl-1, the surface of which is more electropositive than that of other Bcl-2 proteins. In particular, a number of positively charged residues are present on α3, the α3-α4 loop, and α4 in Mcl-1 (Fig. 1), and the groove to which ligands bind is flanked by positive electrostatic potential (supplemental Fig. 6). In addition, two histidines, His-258 and His-301, are on the periphery and two others, His-233 and His-205, lie in the groove. In comparison, Bcl-xL has an essentially uncharged groove.

Small differences in the position of some surface-exposed helices are also apparent. In Mcl-1, α3, which forms part of the binding groove, is extended. In contrast to Bcl-xL, the conformation of α3 is more like that of CED-9 (36, 37), the Caenorhabditis elegans Bcl-2 homolog, where there is a sharp change in direction of α2. Consequently, in contrast to the published residues had partial side chain assignment. Structures were calculated based on a total of 3507 NMR-derived distance constraints and 335 angle restraints. The ensemble of 20 low energy structures refined in XPLOR-NIH (29) is shown in Fig. 3A, and a ribbon representation of the structure closest to the geometric mean in Fig. 3B. Table I enumerates the structural statistics for Mcl-1NC23, showing they are an energetically reasonable NMR ensemble displaying acceptable covalent geometry with all residues lying in allowed areas of the Ramachandran plot.
structures of ligand-free molecules, the binding groove on Mcl-1 is in a more open "ready-to-bind" conformation (Fig. 4A). Ligand-free Bcl-2, Bcl-xL, and CED-9 have α3 and α4 more tightly packed and aligned in parallel relative to Mcl-1 (Fig. 4 and data not shown). Two residues, Gln-111 on α3 and Glu-129 on α4, in Bcl-xL form a hydrogen bond across the helices that may help stabilize their close packing (Fig. 4A, left panel). The equivalent hydrogen bond in Mcl-1 would be disrupted, as the corresponding residues are Lys-215 and His-233, respectively, and this may contribute to the open conformation found in Mcl-1-NC23. Like Mcl-1, Bcl-w also has α3 and α4 in an open conformation, but here the C-terminal residues occupy the binding groove and may influence the conformation (23, 38). These differences in the binding groove likely contribute to the specific binding properties of Mcl-1.

BH3-only Binding Site of Mcl-1—The heterodimerization surface of prosurvival Bcl-xL is provided by residues located on helices α2-α5 and α8 (33, 34, 39) (Fig. 4A). Although the sequences of the bound BH3 peptides differ (Fig. 4B), essentially the same residues form the intermolecular contacts in all three complex structures, and residues conserved across the prosurvival proteins on Bcl-xL interact with the few conserved residues on the BH3-only ligand. For example, the conserved Leu of the BH3-only molecule lies in a hydrophobic pocket formed by Phe-97, Phe-105, Leu-130, Ala-142, and Phe-146 (Fig. 4A, middle panel) (Bcl-xL numbering), and the key Asp residue forms a salt bridge to Arg-139 and hydrogen bonds to Asn-136, 2 residues that are conserved in both Bcl-2- and Bax-like proteins.

The putative binding groove of Mcl-1 is depicted in Fig. 4A and illustrates that many structurally equivalent binding residues are identical or conservatively substituted in Mcl-1 (Figs. 1 and 4A), although differences exist. For example, Phe-97 (Bcl-xL), which packs against 3 of the buried hydrophobic residues in ligand-bound Bcl-xL, is replaced by Val-201 in Mcl-1. To evaluate the importance of individual residues in determining selectivity, site-specific mutants of Mcl-1 were made. Residues to mutate were selected based on comparison of predicted contact residues in Mcl-1 and A1 that differed from those conserved in Bcl-xL, Bcl-w, and Bcl-2 (Figs. 1, 5A, and supplemental Fig. 7). Their ability to bind BH3-only proteins was evaluated (Fig. 5A). The mutants, like wild-type Mcl-1, retained Bim binding, indicating they were correctly folded. However, these mutations to the equivalent residue in Bcl-xL were insufficient to confer Bad binding ability on Mcl-1. The pliable nature of the binding groove, where a productive interaction probably depends on a number of favorable contacts, is highlighted by the ability of Mcl-1 point mutations to retain binding selectivity.

Conferring Mcl-1 Binding on Bad—The ability of Bad to tightly bind Bcl-xL, but not Mcl-1 or its mutants, suggests the
FIG. 4. **Comparison of Mcl-1 and Bcl-xL binding grooves.** A, Bcl-xL, and Mcl-1 binding sites. Left and middle, unliganded Bcl-xL (PDB 1PJ0) (39) and Bcl-xL-Bim complex with the Bim ligand removed (PDB 1PQ1) (39) (respectively, ribbon residues: 90–139 and 191–196). Right, the equivalent residues (194–264 and 296–301) on Mcl-1. The orientation is the same as Fig. 3. Side chains displayed on Bcl-xL-Bim (middle) are those of residues that have atoms within 4 Å of Ile-97 and Phe-101 of Bim. B, sequences of BH3 domains of mouse BH3-only proteins. The color scheme indicates key interactions consistent with those in panel A. Residues underlined in Bim and Bad are those that are helical in their Bcl-xL complexes (34, 39). The heptads are indicated.

**FIG. 5. Mutation analysis of the binding interface.** A, the effect of site-specific mutations on the binding properties of Mcl-1 was evaluated using GST pulldown experiments. Wild-type or the indicated point mutant GST-Mcl-1NC23 proteins were used to pull down the indicated soluble BH3-only molecules. Bound proteins were detected using antibodies after fractionation by SDS-PAGE, B, the ability of mutant Bad proteins to bind to prosurvival proteins using GST pulldown experiments. As in panel A, the indicated immobilized GST prosurvival proteins were used to pull down purified soluble Bad, and bound proteins were detected using anti-Bad antibodies.

The sequence of the BH3 domain in Bad is a critical determinant for binding Mcl-1. Based on sequence comparison with other BH3-only proteins (Fig. 4B) and the likelihood that they made unfavorable contacts with Mcl-1, 3 residues in Bad (Tyr-105, Gly-106, and Ser-113) were changed to the equivalent residues in Bim. A point mutation in Bad, Y105I, yielded a protein that bound all prosurvival proteins (Fig. 5B), whereas S113G only improved affinity for A1. The ability of proteins containing the Y105I mutation to bind Mcl-1 suggests that, although restricted binding may arise from the collective effects of a number of sequence differences, heptad position 2d and its contact residues have a dominant role. In BH3-only proteins, this residue (Fig. 4B) is the least conserved of the 4 hydrophobic contact residues. The binding pocket for heptad 2d is formed by a combination of conserved and non-conserved residues on α3 and φ4 (Ala-104, Leu-108, Glu-111, Leu-112, and Val-126 in Bcl-xL) in all Bcl-2 proteins, and the ability of favorable contacts to form appears to have a critical role in restricting binding. The hydrophobic contact residues of the central heptads 3a and 3d are highly conserved compared with the two peripheral heptads, 2d and 4a, and although they contribute to complex stability their role in determining binding selectivity is less clear.

**DISCUSSION**

It is apparent from recent work (1, 6, 10, 16) that prosurvival Bcl-2 proteins are more functionally divergent than initially anticipated. The profoundly dissimilar phenotypes observed in mice lacking each prosurvival protein were initially attributed to differences in their tissue expression. However, the similar consequence of losing Mcl-1, Bcl-2, or Bcl-xL, in a single tissue compartment implies overlapping functions in addition to their distinct activities (40). At a molecular level, the distinctive function of Mcl-1 may reflect its unique regulation (10), protein partners, and its tissue distribution (41). To gain an understanding for the molecular basis of the unique properties of Mcl-1, we have solved its solution structure.

Mcl-1 shares a common helical scaffold with other Bcl-2 proteins (Fig. 3), yet it has unique sequence and interaction profiles (6). Notably, although the N-terminal BH4 region is missing from Mcl-1 the equivalent N-terminal α helix is retained, indicating that specific residues forming BH4 domains are not necessary for prosurvival activity and, like proapoptotic Bax (42), not required for structural homology. In contrast to the conserved fold, the groove of Mcl-1 is distinguished from that of other prosurvival proteins by being flanked by regions of positive electrostatic potential and by having a conformation intermediate between that of ligand-bound and ligand-free Bcl-xL (39).
Biochemical data show Mcl-1 does not bind all BH3-only proteins equally. Bim, Puma, and Noxa bind tightly, whereas Bmf, Bik, and Hrk have weaker affinity and Bad has no detectable binding. How is the binding specificity of Mcl-1 achieved? Structures of Bcl-xL in complex with Bak (33), Bad (34), Bim (39), and the CED-9-EGL-1 complex (37) provide clues. Bak, Bad, and Bim BH3 domains share the same contact residues on Bcl-xL, although their sequences are different. By analogy with these complexes, the predicted binding surface of Mcl-1 would form from a combination of conserved and unique residues, some of which have a distinct conformation in ligand-free Mcl-1, because helices α3 and α4 are not closely packed. The flexibility of residues on α3 and α4 may also influence binding. When Bcl-xL binds Bim (Fig. 4), Bak or Bad residues in α3 become less well ordered, whereas in the case of the CED-9-EGL-1 complex (EGL-1 is a Caenorhabditis elegans BH3-only protein) α4 undergoes a rearrangement on binding (37). Compared with residues in α3 and α4, the conformation of binding residues on helices α2, α5, and α8 is more similar in the bound and free forms. Thus, productive binding appears to be dependent on both the conformational adaptability and dynamic properties of residues in the binding groove. This supports an induced fit mechanism of binding, with the unique binding profile of Mcl-1 determined by differences in sequence and structure of the residues forming the groove.

BH3 ligands undergo a significant conformational transition upon binding, switching from an unstructured or partially structured state to a well ordered helix (34). Although they share little sequence identity, even over the BH3 domain (Fig. 4B), each of 4 buried hydrophobic residues on the BH3-only ligand interacts with complementary residues on Bcl-xL (Fig. 4A). The 2 conserved residues, Leu and Asp (Fig. 4A), interact with conserved residues on the prosurvival partner. The distinct selectivity of the BH3-only proteins must therefore be largely determined by other contacts. However, mutation of predicted contact residues in the binding groove of Mcl-1, based on known Bcl-xL complexes (Fig. 5A), did not generate a protein that could bind Bad. In contrast, Bad containing the mutation Y105I has an increased affinity for Mcl-1, and both S113G and Y105I Bad mutants (Fig. 5B) have an increased affinity for A1 and retain the ability to bind Bcl-w, Bcl-xL, and Bcl-2. A similar result was found with Noxa, where two mutations changed the binding profile of this protein. Together, these results suggest that a small number of residues underpin the restricted binding profile of BH3-only proteins.

The binding groove appears to have 2 functions, to bind BH3 domains and to sequester the hydrophobic C-terminal residues. Mcl-1, like its congeners, Bcl-2, Bcl-xL, and Bcl-w, is closely associated with intracellular membranes (10, 18, 41, 43). In the case of Bcl-w, tight membrane association occurs subsequent to BH3-only protein binding, a process known to displace the C-terminal residues from the groove (18, 23). Given that the C-terminal residues in Mcl-1, Bcl-xL and Bcl-w are important for membrane association and that their presence restricts ligand binding (Fig. 2), it is tempting to propose a common function for these residues that is coordinately regulated with ligand binding (18, 23). These parallels also suggest that like other prosurvival Bcl-2 proteins, the C-terminal residues in Mcl-1 are not only required for correct organelle localization but are also necessary for prosurvival activity.

The critical role of prosurvival Bcl-2 molecules in human diseases has made them the focus of intense efforts at small molecule targeting and drug design (2). The discovery of small molecules as potent selective antagonists to protein-protein interactions between p53 and MDM2 (44) suggests a similar approach targeting the binding groove of the Bcl-2-related proteins is possible. The selective binding of prosurvival Bcl-2 proteins by their proapoptotic BH3-only ligands gives rise to the expectation that their specific targeting is possible. To this end, a conformationally constrained BidBH3 mimetic peptide specifically activated apoptosis in leukemia cells and demonstrated the ability of targeting the binding groove of Bcl-2 proteins (45). Structures such as that of Mcl-1 reported here present opportunities and challenges for discovering small chemical entities that target particular prosurvival molecules for the treatment of certain cancers.

Acknowledgments—We thank R. Fredericks-Short and J. Risk for excellent technical assistance, P. Colman for critically reading the manuscript, J. Adams and S. Cory for discussions, and K. Morishita for reagents.

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Solution Structure of Prosurvival Mcl-1 and Characterization of Its Binding by Proapoptotic BH3-only Ligands
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J. Biol. Chem. 2005, 280:4738-4744.
doi: 10.1074/jbc.M411434200 originally published online November 18, 2004

Access the most updated version of this article at doi: 10.1074/jbc.M411434200

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