Crystal Structures of Tcl1 Family Oncoproteins and Their Conserved Surface Features

John M. Petock¹, Ivan Y. Torshin¹, Yuan-Fang Wang¹, Garrett C. Du Bois³, Carlo M. Croce³, Robert W. Harrison² and Irene T. Weber^{1,*}

¹Departments of Biology and Chemistry, Georgia State University, Atlanta, GA;

²Department of Computer Science, Georgia State University, Atlanta, GA; ³Department of Microbiology and Immunology, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA

E-mail: biojmp@langate.gsu.edu; biotiy@asterix.cs.gsu.edu; bioyfw@langate.gsu.edu; garrett.dubois@mail.tju.edu; carlo.croce@mail.tju.edu; rharrison@cs.gsu.edu; * iweber@gsu.edu

Received February 12, 2001; Revised May 9, 2002; Accepted May 13, 2002; Published July 4, 2002

Members of the TCL1 family of oncogenes are abnormally expressed in mature T-cell leukemias and B-cell lymphomas. The proteins are involved in the coactivation of protein kinase B (Akt/PKB), a key intracellular kinase. The sequences and crystal structures of three Tcl1 proteins were analyzed in order to understand their interactions with Akt/PKB and the implications for lymphocyte malignancies. Tcl1 proteins are ~15 kD and share 25–80% amino acid sequence identity. The tertiary structures of mouse Tcl1, human Tcl1, and Mtcp1 are very similar. Analysis of the structures revealed conserved semi-planar surfaces that have characteristics of surfaces involved in protein-protein interactions. The Tcl1 proteins show differences in surface charge distribution and oligomeric state suggesting that they do not interact in the same way with Akt/PKB and other cellular protein(s).

KEY WORDS: leukemia, oncoprotein, Tcl1, Akt/protein kinase B, X-ray crystallography

DOMAINS: bioinformatics, oncology, enzymology and protein-protein interaction, structural biology

ROLE OF TCL1 IN LYMPHOCYTE MALIGNANCY

The TCL1 family of oncogenes are abnormally expressed in mature T-cell leukemias and B-cell lymphomas[1,2]. This gene family includes human TCL1 (T-Cell Leukemia/lymphoma 1), TCL1b, and MTCPl (Mature T-Cell Proliferation 1). Both TCL1 and TCL1b genes are found at

FIGURE 1. Sequence alignment of Tc1 and Mtcp1 proteins. Sequences are shown for human Tc1 (hTc1), mouse Tc1 (mTc1), and human Mtcp1 (hMtcp1). The elements of secondary structure are shown for human Tc1 and Mtcp1 with “a” indicating the short helix and “b” for beta strand. The conserved serine (Ser89 in human Tc1) is shown in bold.

the human TCL1 locus. TCL1 genes are expressed in embryonic tissues and immature B- and T-cells. Mature T-cells do not normally express TCL1 genes. Abnormal expression in mature lymphocytes is induced by chromosomal rearrangements that position the regulatory elements of T-cell receptor genes next to the TCL1 locus[2]. The TCL1 locus is activated in the majority of cases of T-cell prolymphocytic leukemia and T-cell chronic lymphocytic leukemia. Rearrangements involving MTCP1 are less commonly associated with mature T-cell leukemia. The oncogenic nature of TCL1 and MTCP1 has been confirmed by analysis of transgenic mouse models[3,4].

Members of the TCL1 family encode for ~15-kD proteins that share 25–80% amino acid sequence identity. The sequences of human Tc1, mouse Tc1, and Mtcp1 proteins are shown in Fig. 1. The normal physiological role of Tc1 proteins is not well defined. Functional analysis revealed that Tc1 proteins coactivate protein kinase B (Akt/PKB)[5,6]. No other protein is known to interact with Tc1 proteins. Akt/PKB has a key role in diverse cellular processes including glucose metabolism, transcription, cell growth, survival, and migration[7]. Therefore, interactions between Tc1 and Akt/PKB are likely to be important for the functioning of the whole cell. Akt/PKB is a serine/threonine kinase that comprises three functional domains: an N-terminal pleckstrin homology (PH) domain, a catalytic (kinase) domain, and a C-terminal regulatory domain. A Tc1 dimer is proposed to bind to the PH domain forming an oligomeric complex with Akt/PKB, followed by Akt/PKB activation by other kinases. The activated Akt/PKB can phosphorylate many proteins involved in cell proliferation and survival. Therefore, abnormal coactivation of Akt/PKB by Tc1 in mature lymphocytes can lead to cancer.

ANALYSIS OF TCL1 AND MTCP1 PROTEIN STRUCTURES

The crystal structures were determined for the recombinant proteins human Tc1 (PDB identifier 1JSG)[8], mouse Tc1 (1JNP)[9], and human Mtcp1 (1A1X)[10]. These structures were determined at 2.0–2.5 Å resolution. The refinement parameters and statistics are summarized in Table 1. Whereas human Tc1 and Mtcp1 were solved as monomers in the *I*222 and *P*6₂2 space groups, respectively, the mouse Tc1 crystal structure was solved as a dimer in the *C*2 space

TABLE 1
Crystallographic Statistics for Human Tc11, Mouse Tc11, and Human Mtcp1 Structures

	Human Tc11	Mouse Tc11	Human Mtcp1
Space group	I_{222}	C_12_1	$P6_{222}$
Unit cell	38.9, 82.8, 117.7 90.0°, 90.0°, 90.0°	89.3, 115.9, 37.9 90.0°, 115.2°, 90.0°	62.7, 62.7, 86.0 90.0°, 90.0°, 120°
R merge	0.09	0.06	0.05
Resolution	2.5 Å	2.5 Å	2.0 Å
R factor	19%	23%	21%
R free	26%	24%	25%
Bond length error	0.006	0.02	0.007
Angle error	1.3	2.1	1.4

TABLE 2
Structural Similarity for Mouse Tc11, Human Tc11, and Human Mtcp1

	Mouse Tc11A*	Mouse Tc11B	Human Tc11	Human Mtcp1	Internal Symmetry
Mouse Tc11A	-	0.9 (100%)	0.6 (50%)	1.6 (36%)	1.3 (12%)
Mouse Tc11B	0.9 (100%)	-	0.6 (50%)	1.5 (36%)	1.1 (12%)
Human Tc11	0.6 (50%)	0.6 (50%)	-	1.5 (41%)	1.3 (13%)
Human Mtcp1	1.6 (36%)	1.5 (36%)	1.5 (41%)	-	1.7 (13%)

Note: The crystal structure of mouse Tc11 comprises the two subunits Tc11A and Tc11B.

* Root mean square (RMS) differences are given in Ångstroms with the percentage amino acid sequence identity in parentheses.

group. The three Tc11 proteins show different possible subunit–subunit interfaces in the crystals. In solution, Mtcp1 is likely to be a monomer, while human Tc11 can form dimers[11]. Moreover, mouse Tc11 may form trimers in solution[6]. Therefore, the oligomeric state and subunit interface may differ among these proteins.

The crystal structures of mouse Tc11, human Tc11, and Mtcp1 have very similar tertiary structures as shown in Fig. 2A. However, no other similar structures were found in the Protein Data Bank[12]. The sequences and structures of Tc11 proteins are compared in Table 2. Human and mouse Tc11 structures have a root mean square (RMS) difference of 0.6 Å for 100 superimposed Cα atoms and share 50% sequence identity, while human Tc11 and Mtcp1 show 1.5 Å RMS difference for 100 Cα atoms and 41% sequence identity[10]. The structures of mouse Tc11 and human Mtcp1 have 1.6 Å RMS difference for 100 aligned Cα atoms. The proteins share an 8-stranded beta barrel structure of unique topology. The beta barrel structure has a long surface loop with a short helical region that separates two 4-stranded pseudo-symmetric “half-barrel” structures (Fig. 2B). The three protein structures have high internal symmetry for the “half-barrel” structure with RMS differences ranging from 1.1–1.7 Å, despite the lack of significant sequence identity between the halves (12–13%).

FIGURE 2a. **FIGURE 2b.**

FIGURE 2. Superposition of alpha carbon backbone atoms of the Tcl1 family members: mouse Tcl1 (red for residues 8-57, blue for 67-108), human Tcl1 (white), and human Mtcp1 (gray). The red/blue color scheme is shown to emphasize the half-barrel structure shown in (B). Two tandem halves of mouse Tcl1 structure superimposed to show the internal symmetry (B). Residues 8-57 (red) and 67-108 (blue) are included.

FIGURE 3. The largest conserved semi-planar surfaces of the Tc11 protein members is shown with the surface charge distribution for: (A) human Tc11, (B) mouse Tc11, and (C) human Mtcp1. Blue indicates positive charge distribution and red indicates negative. The human Tc11 residues Pro36, Leu37, and Thr38 found to be important for dimer formation are shown and equivalent residues are indicated in the other proteins. The Tc11 surfaces proposed to interact with Akt/PKB are shown for: (D) human Tc11, (E) mouse Tc11, and (F) human Mtcp1. This surface is located opposite to the dimer surface shown in views A-C. The conserved serine is indicated. Human Tc11 Asp16 and Ile74 found to be important for interactions with Akt are shown in D, and the equivalent residues in mouse Tc11 and Mtcp1 are indicated in E and F. The surface pictures were generated with the program WebLab ViewerLite[16] using a probe radius of 2.5 Å.

ANALYSIS OF TCL1 PROTEIN SURFACES

Human Tc11 residues involved in homodimer formation and association with Akt/PKB have been identified recently[13]. Mutational analysis of human Tc11 suggested that amino acids 35–37 are involved in dimer formation, while residues Asp16 and Ile74 are important for Tc11-Akt/PKB interactions. It is not known whether the equivalent residues in mouse Tc11 and human Mtcp1 have the same function. Presumably, additional Tc11 residues are involved in these protein–protein interactions. Therefore, the molecular surfaces of Tc11 and Mtcp1 structures were analyzed in relation to the human Tc11 mutations. The Tc11 proteins show three conserved nearly planar surfaces[10]. These large surfaces have characteristic features with many “knobs” and “clefts” similar to the interfaces observed in homodimers and other protein–protein complexes[14,15]. The Tc11 mutations that interfere with dimer formation and interactions with Akt/PKB lie on two of these large surfaces.

The human Tc11 residues 36–38 that were shown to be involved in dimer formation[13] lie on the largest of the conserved semi-planar surfaces of Tc11 proteins. The proposed Tc11 dimer-forming surface is roughly 500 Å² in size and is shown in Fig. 3A–C. However, the surface distribution of negative and positive charges is different in each of the Tc11 proteins. We identified the surface accessible residues comprising this dimer interface in all three Tc11 crystal structures (Table 3). These residues are *Glu22*, *Leu35*, *Leu37*, Thr38, Ile39, Glu40, Ile41, Lys42, Leu50, Arg52, Glu54, **Val56**, Val57, Arg60, Thr63, Gln66, Pro69, Ser70, Leu71, Ile100, Asp101, and **Val103** in human Tc11 (identical residues in bold, similar residues in italics). Only 2 out of 22 surface residues are identical and 3 are similar in all three proteins (23% [5/22] conserved residues). Thus, the majority of residues forming this surface differ among the Tc11 proteins.

TABLE 3
Comparison of Surface Residues for Human Tcl1, Mouse Tcl1, and Human Mtcp1 Proteins

Akt-Interacting Surface			Dimer Forming Surface		
Human Tcl1	Mouse Tcl1	Human Mtcp1	Human Tcl1	Mouse Tcl1	Human Mtcp1
<i>Asp16</i>	Asn16	<i>Asp12</i>	<i>Glu22</i>	<i>Glu22</i>	<i>Gln18</i>
<i>Arg17</i>	<i>Arg17</i>	<i>His13</i>	<i>Leu35</i>	Leu35	<i>Val31</i>
Trp19	Trp19	Trp15	<i>Leu37</i>	<i>Val37</i>	<i>Val33</i>
Trp21	Trp21	His17	Thr38	Val38	Val34
Glu29	Glu29	Glu25	Ile39	Ile39	Glu35
Lys30	Phe30	Tyr26	Glu40	Lys40	Glu36
Gln31	Arg31	Gln27	Ile41	Ser41	Glu37
Arg60	Glu58	Asp54	Lys42	Asn42	Thr38
Pro61	Ala59	Ala55	Leu50	Ile48	Arg44
Thr63	Ser61	Arg57	Arg52	Arg50	Gln46
Pro64	Pro62	Pro58	Glu54	Glu52	Ile48
<i>Ile74</i>	<i>Leu72</i>	<i>Leu68</i>	Val56	Val54	Val50
Met75	Met73	Met69	Val57	Thr55	Pro51
Gln77	Gln75	Gln71	Arg60	Glu58	Asp54
Tyr79	Tyr77	Tyr73	Thr63	Ser61	Arg57
Pro80	Pro78	Pro74	Gln66	Gln64	His60
Asp81	Lys79	Glu75	Pro69	Pro67	Thr63
Arg83	Arg81	Arg77	<i>Ser70</i>	Tyr68	Ser64
Arg85	Arg83	Met79	Leu71	Glu69	Gln65
Ser87	Ala85	Asn81	Ile100	Phe98	Val94
Asp88	<i>Asp86</i>	<i>Asn82</i>	Asp101	Arg99	Arg95
Ser89	Ser87	Ser83	Val103	Val101	Val97
Ser90	Met88	Arg84			

The molecular surface of human Tcl1 that interacts with Akt/PKB can be identified from the two residues Asp16 and Ile74 that were shown to be important for Tcl1-Akt/PKB interactions[13]. The tentative Akt/PKB binding surface of Tcl1 corresponds to another conserved semi-planar region in the structures of human Tcl1, mouse Tcl1, and human Mtcp1, as shown in Fig. 3D–F. The surface accessible residues on the proposed Akt/PKB binding surface of human Tcl1 are *Asp16*, *Arg17*, **Trp19**, Trp21, **Glu29**, Lys30, Gln31, Arg60, Pro61, Thr63, **Pro64**, *Ile74*, **Met75**, **Gln77**, **Tyr79**, **Pro80**, Asp81, **Arg83**, Arg85, Ser87, *Asp88*, **Ser89**, and Ser90 (identical residues in bold, similar residues in italics). These 23 residues are likely to be important for interacting with Akt/PKB in the three Tcl1 proteins. Out of 23 residues forming the surface, 9 are identical and 4 are similar residues, suggesting a higher degree of conservation than in the putative dimer interface described above (52% [13/23] compared to 23%). Interestingly, the residues Asp16 and Ile74 shown to be important for interactions with Akt/PKB are not identical in all three proteins. Like the largest semi-planar surface of Tcl1 proteins, the charge distributions of the interacting surfaces differ among the three proteins. This suggests that different Tcl1 proteins do not bind in an identical way to Akt/PKB. Indeed, a difference in affinity for Akt/PKB was observed in studies with Tcl1, Tcl1b, and Mtcp1[5,6]. The activation of

Akt/PKB by interaction with Tc11 was tenfold higher than that of Mtcp1. In addition, the three isoforms of Akt/PKB differ in their specificity for Tc11 oncoproteins; isozyme Akt3/PKB- γ is most specific for Tc11[18].

The potential phosphorylation sites differ for Tc11 proteins[7]. Mouse Tc11 shows a potential CK2 phosphorylation site at residues 55–58 on the dimer interface and a potential site for tyrosine kinase phosphorylation at residues 83–89 on the putative Akt/PKB interacting surface. No known phosphorylation sites were found in the Mtcp1 sequence. These differences in the location and the types of potential phosphorylation sites in relation to the molecular surfaces suggest that the three Tc11 proteins interact with different cellular kinases.

IMPLICATIONS FOR TCL1 INTERACTIONS WITH AKT/PKB

The overall coactivation of Akt/PKB by Tc11 appears to be a complex process[5,6,13,19,20,21]. Initially, a growth factor signal activates cell surface receptors and causes phosphoinositide 3-kinase (PI3K) to produce phosphoinositides. These products bind to the PH domain of Akt/PKB for its recruitment to the plasma membrane. Next, a Tc11 dimer binds to the PH domain of Akt/PKB forming large Tc11-Akt/PKB complexes of unknown stoichiometry. Then, Akt/PKB is phosphorylated by PDK (3-phosphoinositide-dependent protein kinase 1) at Thr308 and at Ser473 by an unknown kinase. Once activated, Akt/PKB phosphorylates its downstream targets in the cytoplasm and possibly in the nucleus.

Our analysis of Tc11 proteins has suggested another possible type of interaction with Akt/PKB. The consensus sequence for Akt/PKB phosphorylation is reported to be RxR-x(2)-[ST][22]. Human Tc11, Mtcp1, and mouse Tc11 show only one conserved and solvent accessible serine (Ser89 in human Tc11) in the turn between beta strands 6 and 7 (Fig. 1 and 3). This conserved serine is also present in human Tc11b. The sequence around the conserved serine has the pattern of RxR-x(3)-S in human and mouse Tc11 and RxM-x(3)-S in Mtcp1 (Fig. 1). The sequence in Tc11 resembles the consensus pattern for Akt/PKB phosphorylation, although there is an extra residue between the conserved RxR and S. However, the sequence consensus of a phosphorylation site can be degenerate. For example, a tyrosine kinase can phosphorylate sequences of different consensus patterns such as [RK]-x(2)-[DE]-x(3)-Y or [RK]-x(3)-[DE]-x(2)-Y (23;24). Therefore, it is possible that Akt/PKB can phosphorylate the conserved serine in the Tc11 proteins. Alternately, the Rx[RM]-x(3)-S region may act as a substrate analog of Akt/PKB. The importance of the conserved Ser89 in human Tc11 is consistent with its location being on the Akt/PKB interacting surface about 16 and 11Å from the residues Asp16 and Ile74, respectively (Fig. 3D).

Because Akt/PKB is important for proliferation and survival of lymphocytes, abnormal coactivation by Tc11 in mature lymphocytes can lead to malignancies. Differences in the oligomeric form, subunit interface, surface accessible residues, and potential phosphorylation sites between Tc11 and Mtcp1 proteins are likely to contribute to the tenfold differences[5,6] in their interactions with Akt/PKB. Hence, despite the highly conserved tertiary structures of the Tc11 proteins, each Tc11 family member may interact with different cellular proteins. These interacting proteins may be different isoforms of Akt/PKB or other unidentified proteins. Presently, only a few of the Tc11 residues important for interactions with Akt/PKB have been experimentally defined. Further analysis is needed to fully define the interacting residues in the Tc11-Akt/PKB complexes as well as the stoichiometry of such complexes. This review provides a rationale for more detailed mutational analysis of the Tc11 proteins.

ACKNOWLEDGEMENTS

This work was supported by the National Cancer Institute grant CA76259. J.M.P. was supported in part by the Georgia State University Research Program Enhancement grant.

REFERENCES

1. Stern, M.H., Soulier, J., Rosenzweig, M., Nakahara, K., Canki-Klain, N., Aurias, A., Sigaux, F., and Kirsch, I.R. (1993) MTCP-1: a novel gene on the human chromosome Xq28 translocated to the T cell receptor alpha/delta locus in mature T cell proliferations. *Oncogene* **8**, 2475–2483.
2. Virgilio, L., Isobe, M., Narducci, M.G., Carotenuto, P., Camerini, B., Kurosawa, N., Abbas-ar-Rushdi, Croce, C.M., and Russo, G. (1993) Chromosome walking on the TCL1 locus involved in T-cell neoplasia. *Proc. Natl. Acad. Sci. U. S. A.* **90**, 9275–9279.
3. Gritti, C., Dastot, H., Soulier, J., Janin, A., Daniel, M.T., Madani, A., Grimber, G., Briand, P., Sigaux, F., and Stern, M.H. (1998) Transgenic mice for MTCP1 develop T-cell prolymphocytic leukemia. *Blood* **92**(2), 368–373.
4. Virgilio, L., Lazzeri, C., Bichi, R., Nibu, K.I., Narducci, M.G., Russo, G., Rothstein, J., and Croce, C.M. (1998) Deregulated expression of TCL1 causes T cell leukemia in mice. *Proc. Natl. Acad. Sci. U. S. A.* **95**, 3885–3889.
5. Pekarsky, Y., Koval, A., Hallas, C., Bichi, R., Tresini, M., Malstrom, S., Russo, G., Tsichlis, P., and Croce, C.M. (2000) Tcl1 enhances Akt kinase activity and mediates its nuclear translocation. *Proc. Natl. Acad. Sci. U. S. A.* **97**, 3028–3033.
6. Laine, J., Künstle, G., Obata, T., Sha, M., and Noguchi, M. (2000) The protooncogene TCL1 is an Akt kinase coactivator. *Mol. Cell.* **6**, 395–407.
7. Brazil, D.P. and Hemmings, B.A. (2001) Ten years of protein kinase B signaling: a hard Akt to follow. *TRENDS Biochem. Sci.* **26**(11), 657–664.
8. Hoh, F., Yang, Y.S., Guignard, L., Padilla, A., Stern, M.H., Lhoste, J.M., and van Tilbeurgh, H. (1998) Crystal structure of p14TCL1, an oncogene product involved in T-cell prolymphocytic leukemia, reveals a novel beta-barrel topology. *Structure* **6**, 147–155.
9. Fu, Z.Q., Du Bois, G.C., Song, S.P., Kulikovskaya, I., Virgilio, L., Croce, C.M., Weber, I.T., and Harrison, R.W. (1998) Crystal structure of MTCP-1: implications for role of TCL-1 and MTCP-1 in T cell malignancies. *Proc. Natl. Acad. Sci. U. S. A.* **95**, 3413–3418.
10. Petock, J.M., Torshin, I.Y., Wang, Y.F., Dubois, G.C., Croce, C.M., Harrison, R.W., and Weber, I.T. (2001) Structure of mouse Tcl1 at 2.5 Å resolution and implications for the TCL oncogene family. *Acta Crystallogr., Sect. D* **57**, 1545–1551.
11. Du Bois, G.C., Song, S.P., Kulikovskaya, I., Virgilio, L., Varnum, J., Germann, M.W., and Croce, C.M. (1998) Purification and characterization of recombinant forms of TCL-1 and MTCP-1 proteins. *Protein Expr. Purif.* **12**, 215–225.
12. Berman, H.M., Westbrook, J., Feng, Z., Gilliland, G., Bhat, T.N., Weissig, H., Shindyalov, I.N., and Bourne, P.E. (2000) The Protein Data Bank. *Nucleic Acids Res.* **28**, 235–242. <http://www.rcsb.org/>.
13. Künstle, G., Laine, J., Pierron, G., Kagami, S.S., Nakajima, H., Hoh, F., Roumestand, C., Stern, M.H., and Noguchi, M. (2002) Identification of Akt association and oligomerization domains of the Akt kinase coactivator TCL1. *Mol. Cell. Biol.* **22**(5), 1513–1525.
14. Laskowski, R.A., Luscombe, N.M., Swindells, M.B., and Thornton, J.M. (1996) Protein clefts in molecular recognition and function. *Protein Sci.* **12**, 2438–2452.
15. Norel, R., Lin, S.L., Wolfson, H.J., and Nussinov, R. (1994) Shape complementarity at protein-protein interfaces. *Biopolymers* **7**, 933–940.
16. Molecular Simulations Inc. MSI WebLab Viewer Lite. 9685 Scranton Road, San Diego, CA 92121, (858) 458-9990, Fax: (858) 458-0136.
17. Torshin, I. (1999) Molecular surface sequence analysis of several E. coli enzymes and implications for existence of casein kinase-2 bacterial predecessor. *Front. Biosci.* **4**, D394–407.
18. Laine, J., Künstle, G., Obata, T., and Noguchi, M.J. (2002) Differential regulation of Akt kinase isoforms by the members of the TCL1 oncogene family. *J. Biol. Chem.* **277**, 3743–3751.
19. Bellacosa, A., Chan, T.O., Ahmed, N.N., Datta, K., Malstrom, S., Stokoe, D., McCormick, F., Feng, J., and Tsichlis, P. (1998) Akt activation by growth factors is a multiple-step process: the role of the PH domain. *Oncogene* **17**(3), 313–325.
20. Stephens, L., Anderson, K., Stokoe, D., Erdjument-Bromage, H., Painter, G.F., Holmes, A.B., Gaffney, P.R., Reese, C.B., McCormick, F., Tempst, P., Coadwell, J., and Hawkins, P.T. (1998) Protein kinase B kinases that mediate phosphatidylinositol 3,4,5-trisphosphate-dependent activation of protein kinase B. *Science* **279**(5351), 710–714.

21. Pekarsky, Y., Hallas, C., and Croce, C.M. (2001) Molecular basis of mature T-cell leukemia. *JAMA* **286(18)**, 2308–2314.
22. Obata, T., Yaffe, M.B., Leparo, G.G., Piro, E.T., Maegawa, H., Kashiwagi, A., Kikkawa, R., and Cantley, L.C. (2000) Peptide and protein library screening defines optimal substrate motifs for AKT/PKB. *J. Biol. Chem.* **275(46)**, 36108–36115.
23. Falquet, L., Pagni, M., Bucher, P., Hulo, N., Sigrist, C.J., Hofmann, K., Bairoch, A. (2002) The PROSITE database, its status in 2002. *Nucleic Acids Res.* **30**, 235–238.
24. Hofmann, K., Bucher, P., Falquet, L., and Bairoch, A. (1999) PROSITE data base UI - 99063695, and (1999) The PROSITE database, its status in 1999. *Nucleic Acids Res.* **27(1)**, 215–219.

This article should be referenced as follows:

Petock, J.M., Torshin, I.Y., Wang, Y-F., Du Bois G.C., Croce, C.M., Harrison, R.W., and Weber, I.T. (2002) Crystal structures of Tcl1 family oncoproteins and their conserved surface features. *TheScientificWorldJOURNAL* **2**, 1876–1884.

Handling Editor:

Pierre Kremers, Associate Editor for *Enzymology and Protein–Protein Interaction* — a domain of *TheScientificWorldJOURNAL*.