Glossary

Abl: Abelson tyrosine kinase. The viral analogue (v-Abl) was first identified in the Abelson murine leukemia virus as a fusion protein. The cellular (c-Abl) counterpart was subsequently reported. c-Abl is a nonreceptor tyrosine kinase whose cellular role has yet to be fully clarified. However, it is evident that c-Abl is a key player in the regulation of the cell cycle (as a mediator of DNA damage recognition), has been implicated as a participant in cytoskeletal dynamics, and plays an important role during embryonic development.

Van Etten, R. A. Cycling, stressed-out and nervous: cellular functions of c-Abl. *Trends Cell Biol.* **1999**, *9*, 179−86.

Actin: A self-assembling protein that is present in both monomeric (globular or G-actin) and polymeric (filamentous or F-actin) forms in the cell. This structurally dynamic protein polymer provides the structural framework for cell shape, motility, and organization.

Schoenenberger, C.-A.; Bischler, N.; Fahrenkrog, B.; Aebi, U. Actin's propensity for dynamic filament patterning. *FEBS Lett.* **2002**, *529*, 27−33.

APC Protein: Adenomatous polyposis coli protein. APC is a participant in a wide variety of cellular processes, including the Wnt signaling pathway. Mutations that inactivate APC lead to cellular proliferation. In particular, the APC gene is mutated in about 30% of all patients with familial adenomatous polyposis, a colon cancer predisposition syndrome.

Dikovskaya, D.; Zumbrunn, J.; Penman, G. A.; Nathke, I. S. The adenomatous polyposis coli protein: in the limelight out at the edge. *Trends Cell Biol.* **2001**, *11*, 378−84.

AFAP-110: Actin filament-associated protein of 110 kDa. An adaptor protein that links Src kinase family members to actin filaments. AFAP-110 serves as a molecular platform for the assembly of large multicomponent signaling complexes. Changes in AFAP-110 structure lead to changes in actin filament integrity as well as alterations in Src kinase activity.

Baisden, J. M.; Qian, Y.; Zot, H. M.; Flynn, D. C. The actin filament-associated protein AFAP-110 is an adaptor protein that modulates changes in actin filament integrity. *Oncogene* **2001**, *20*, 6435−47.

AKAP: A-kinase anchoring protein. A family of functionally related proteins that bind to the regulatory subunit of PKA and thereby confine the protein kinase to specific subcellular compartments. AKAPs also coordinate to other signaling proteins, thereby assembling members of a signaling pathway onto a common molecular platform.

Michel, J. J.; Scott, J. D. AKAP mediated signal transduction. *Annu. Rev. Pharmacol. Toxicol.* **2002**, *42*, 235−57.

ASAP1: Arf Gap containing SH3, ANK repeat and PH domains. This protein interacts with members of the Src tyrosine kinase and ADP-ribosylation factor (Arf) families. ASAP1 likely plays a role in the membrane remodeling events that transpire during cell growth.

Brown, M. T.; Andrade, J.; Radhakrishna, H.; Donaldson, J. G.; Cooper, J. A.; Randazzo, P. A. ASAP1, a phospholipid-dependent Arf GTPase-activating protein that associates with and is phosphorylated by Src. *Mol. Cell. Biol.* **1998**, *18*, 7038−51.

Bcr-Abl: The aberrant Philadelphia chromosome is frequently found in acute lymphoblastic leukemia. This chromosome contains two translocated genes that are fused together [Bcr (breakpoint cluster region) and Abl], and the amalgamated gene codes

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for the corresponding Bcr-Abl fusion protein. Abl tyrosine kinase activity is unregulated when present in Bcr-Abl. The recently introduced drug Gleevec, which is used to treat chronic myelogeneous leukemia, inhibits Abl.

Capdeville, R.; Buchdunger, E.; Zimmermann, J.; Matter, A. Glivec (STI571, imatinib), a rationally developed, targeted anticancer drug. *Nat. Rev. Drug Discov.* **2002**, *1*, 493−502.

Brk: Breast tumor kinase. Brk is a nonreceptor tyrosine kinase that contains an SH2 and an SH3 domain. This enzyme is a member of the cytoplasmic Frk kinase family. Brk is overexpressed in approximately two-thirds of breast tumors.

Qui, H.; Miller, W. T. Regulation of the nonreceptor tyrosine kinase Brk by autophosphorylation and by autoinhibition *J. Biol. Chem.* **2002**, *277*, 34634−41.

Btk: Bruton's tyrosine kinase. A member of the Tec family of protein kinases (often referred to as the Btk family). Mutations in the gene coding for Btk have been linked to X-linked agammaglobulinemia (XLA). Btk participates in the development of and signaling pathways in B cells.

Khan, W. N. Regulation of B lymphocyte development and activation by Bruton's tyrosine kinase. *Immunol. Res.* **2001**, *23*, 147−56.

Bvp: Baculovirus phosphatase. Along with Mce 1, a member of the RNA triphosphatase subfamily of cysteine phosphatases. However, unlike Mce 1 (which only exhibits triphosphatase activity), Bvp catalyzes the conversion of triphosphates to diphosphates and diphosphates to monophosphates (triphosphate-terminated RNA, ATP, and GTP).

Martins, A.; Shuman, S. Mutational analysis of baculovirus phosphatase identified structural residues important for triphosphatase activity in vitro and in vivo. *Biochemistry* **2002**, *41*, 13403−9.

Cas: Crk-associated substrate. There are several Cas proteins, including Cas-130, HEF1/Cas-L, and Efs/Sin. Cas-130 was first identified as a protein that is hyperphosphorylated in v-Src- and v-Crk-transformed cells. The Cas proteins are adaptors that link signaling networks to the actin-cytoskeleton and thereby play a key role in transmitting signals that control cell shape, motility, and possibly apoptosis and transformation.

O'Neill, G. M.; Fashena, S. J.; Golemis, E. A. Integrin signaling: a new Cas(t) of characters enters the stage. *Trends Cell Biol.* **2000**, *10*, 111−9.

Cbl: First identified as the oncogene in Casitas B-lineage lymphoma. Cbl proteins (c-Cbl, Cbl-b, and Cbl-3) are ubiquitin ligases, proteins that simultaneously bind activated receptor tyrosine kinases and ubiquitin-conjugating enzymes. The activated receptor tyrosine kinases then suffer multi-ubiquination and are down-regulated. Cbl also recognizes nonreceptor tyrosine kinases.

Thien, C. B.; Langdon, W. Y. Cbl: many adaptations to regulate protein tyrosine kinases. *Nat. Rev. Mol. Cell. Biol.* **2001**, *2*, 294−307.

Cdc14: A member of the family of proteins required for the cell division cycle. A protein phosphatase required for mitotic exit. Cdc14 dephosphorylates several substrates, an action that ultimately leads to the degradation of specific cyclins and the accumulation of a cyclin-dependent kinase inhibitor.

Jensen, S.; Geymonat, M.; Johnston, L. H. Mitotic exit: delaying the end without FEAR. *Curr. Biol.* **2002**, *12*, R221−3.

Cdc25: A member of the family of proteins required for the cell division cycle. A dual specific protein phosphatase family that regulates the cell division cycle via the dephosphorylation (and therefore activation) of cyclin-dependent protein kinases.

Nilsson, I.; Hoffmann, I. Cell cycle regulation by the Cdc25 phosphatase family. *Prog. Cell. Cycle Res.* **2000**, *4*, 107−14.

CED-12 (ELMO1): The family of *C. elegans* proteins required for the 131 normal cell deaths that occur; identified via mutational analysis and therefore referred to as cell death abnormal (the mammalian counterpart engulfment and cell motility). CED12 plays an essential role in cell migration and the effective engulfment of apoptotic cells. There are two ELMO proteins in mammalian cells. ELMO1 is a participant in the pathway that controls phagocytosis. Computer analysis suggests that neither CED-12 nor the ELMO proteins possess a catalytic region. However, a potential binding SH3 site was identified, as was a putative PH domain in the mammalian homologues.

Gumienny, T. L.; Brugnera, E.; Tosello-Trampont, A. C.; Kinchen, J. M.; Haney, L. B.; Nishiwaki, K.; Walk, S. F.; Nemergut, M. E.; Macara, I. G.; Francis, R.; Schedl, T.; Qin, Y.; Van Aelst, L.; Hengartner, M. O.; Ravichandran, K. S. CED-12/ELMO, a novel member of the CrkII/Dock180/Rac pathway, is required for phagocytosis and cell migration. *Cell* **2001**, *107*, 27−41.

Chimaerins: A chimaera between BCR and the C1 regulatory region of PKC isozymes. The chimaerin family (4 isoforms identified to date) is a guanine nucleotide exchange factor for Rac. The chimaerins, along with RasGRP and Munc-13, contain a C1 domain, which binds the tumor promoting phorbol esters (and the corresponding endogenous phorbol ester counterpart diacylglycerol).

Kazanietz, M. G. Eyes wide shut: protein kinase C isozymes are not the only receptors for the phorbol ester tumor promoters. *Mol. Carcinog.* **2000**, *28*, 5−11.

CMS/CD2-associated Protein: Cas ligand with multiple SH3 domains. This protein contains three SH3 domains. CMS and its structurally related homologue, CIN85, are adaptor proteins that drive the assembly of signaling complexes that control a variety of functions, including neuronal cell death and T cell activation. These proteins play an important role in the down-regulation of activated receptor tyrosine kinases.

Dikic, I. CIN85/CMS family of adaptor molecules. *FEBS Lett.* **2002**, *529*, 110−5.

Cofilin (ADF): Also known as actin depolymerization factor, members of the ADF/cofilin family of proteins are characterized by their ability to bind actin and to depolymerize and sever F-actin. These proteins play an important role in the remodeling of the actin cytoskeleton during such processes as cell motility and division.

Maciver, S. K.; Hussey, P. J. The ADF/cofilin family: actin-remodeling proteins. *Genome Biol.* **2002**, *3*, reviews3007.

Crk: Chicken tumor virus No. 10 [CT10] regulator of kinase. The viral analogue (v-Crk) was first identified from a chicken fibrosarcoma sample as a fusion protein. The cellular (c-Crk) counterpart was subsequently reported. This family of SH2/SH3-containing adaptor proteins mediate the transduction of an array of extracellular signals and are known to interact with a number of different proteins, including members of the Cas, Cbl, and Abl families. Crk-driven signaling pathways are responsible for changes in cellular migration and adhesion.

Feller, S. M. Crk family adaptors-signaling complex formation and biological roles. *Oncogene* **2001**, *20*, 6348−71.

Csk: C-terminal Src kinase. A negative regulator of the Src kinase family of protein kinases. Csk down-regulates Src kinase activity via phosphorylation of a tyrosine residue positioned on the C-terminal tail of Src.

Latour, S.; Veillette, A. Proximal protein tyrosine kinases in immunoreceptor signaling. *Curr. Opin. Immunol.* **2001**, *13*, 299−306.

CDK: Cyclin-dependent kinase. As the name implies, these protein kinases are regulated by cyclins, a family of proteins (cyclins A, B, D, E) whose cellular levels rise and fall at different times during the cell cycle.

Obayaa, A. J.; Sedivy, J. M. Regulation of cyclin-Cdk activity in mammalian cells. *Cell. Mol. Life Sci.* **2002**, *59*, 126−142.

EGFR (erbB-1, Her-1): Epidermal growth factor receptor. A member of the erbB family of membrane-bound receptor tyrosine kinases. Members of this receptor/tyrosine kinase family have received intense scrutiny as molecular targets for the treatment of various solid tumors (especially breast cancer). As the name implies, the EGF receptor is activated by epidermal growth factor (as well as other extracellular ligands, such as TGF-α).

Baselga, J. Why the epidermal growth factor receptor? The rationale for cancer therapy. *Oncologist* **2002**, *7* (Suppl. 4), 2−8.

Endosome: A membrane-associated organelle that transports endocytosed materials (e.g., proteins) to lysosomes (an organelle containing digestive enzymes)

Etk (Bmx): Endothelial/epithelial tyrosine kinase. Etk/Bmx is a member of the nonreceptor Tec family of tyrosine kinases (often referred to as the Btk family). Etk/Bmx contains PH, Tec homology, SH2, and SH3 domains and is predominantly expressed in B cells, where it is essential for B cell development.

Qui, Y.; Kung, H. J. Signaling network of the Btk family kinases. *Oncogene* **2000**, *19*, 5651−61.

FAK: Focal adhesion kinase. A cytoplasmic tyrosine kinase that mediates integrin-dependent signals responsible for a variety of cellular processes, including motility and survival. FAK contains several proline-rich sequences as well as sites of tyrosine phosphorylation that are recognized by SH3 and SH2 domains, respectively.

Schaller, M. D. Biochemical signals and biological responses elicited by the focal adhesion kinase. *Biochim. Biophys. Acta* **2001**, *1540*, 1−21.

Farnesyltransferase (farnesyl protein transferase): Farnesyl protein transferase catalyzes the addition of the farnesyl group to conserved residues near the C-terminus of proteins, a post-translational modification that promotes membrane association and subsequent biological activity. Proteins such as Ras and Rho undergo farnesylation and inhibitors of farnesyltransferase are considered to be potential therapeutic agents for the treatment of cancer.

Haluska, P.; Dy, G. K.; Adjei, A. A. Farnesyl transferase inhibitors as anticancer agents. *Eur. J. Cancer* **2002**, *38*, 1685−700.

Fas (Apo-1/CD-95): Fas is also known as apoptosis antigen-1 (Apo-1). A member of the tumor necrosis factor receptor protein family. The interaction of the Fas ligand with Fas stimulates the formation of the death inducing signaling complex, which ultimately results in apoptosis. Fas-antibodies have been developed that serve as agonists for the Fas pathway. The latter has promising therapeutic implications since many tumors express the Fas receptor.

Wajant, H. The Fas signaling pathway: more than a paradigm. *Science* **2002**, *296*, 1635−6.

Fpr3: FKBP (FK 506-binding protein) proline rotomase 3. A member of a family of four nucleolar immunophilins (i.e., a peptidyl prolyl isomerase) in yeast.

Davey, M.; Hannam, C.; Wong, C.; Brandl, C. J. The yeast peptidyl proline isomerases FPR3 and FPR4, in high copy numbers, suppress defects resulting from the absence of the E3 ubiquitin ligase TOM1. *Mol. Gen. Genet.* **2000**, *263*, 520−6.

Grb2: Growth factor receptor bound protein 2. An adaptor protein that contains two SH3 domains and a single SH2 domain. The interaction of Grb2 with Sos and activated receptors initiates the subsequent activation of the MAP kinase cascade.

Tari, A. M.; Lopez-Berestein, G. GRB2: a pivotal protein in signal transduction. *Semin. Oncol.* **2001**, *28* (5 Suppl. 16), 142−7.

GTPase: The activity displayed by a large family of proteins (heterotrimeric and small G proteins) that serve as key transducers of signaling pathways. These proteins are activated upon binding GTP, but their intrinsic GTPase activity ensures that their signaling activity is transient. G proteins play a key role in stimulating a wide variety of cellular activities, including growth, proliferation, and apoptosis. There are five major groups of the monomeric family of GTPases: Arf, Rab, Ran, Ras, and Rho.

Ehrhardt, A.; Ehrhardt, G. R. A.; Guo, X.; Schrader, J. W. Ras and relatives−job sharing and networking keep an old family together. *Exp. Hematol.* **2002**, *30*, 1089−1106.

Her-2/neu/erbB-2: Human epidermal growth factor receptor, the human analogue of the rat gene *neu* associated with neuroblastoma. A member of the erbB family of membrane-bound receptor tyrosine kinases (Her-2 is also known as erbB-2). Members of this receptor/tyrosine kinase family have received intense scrutiny as molecular targets for the treatment of various solid tumors (especially breast cancer).

Normanno, N.; Maiello, M. R.; De Luca, A. Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs): simple drugs with a complex mechanism of action? *J. Cell. Physiol.* **2003**, *194*, 13−9.

Hck: Hematopoietic cell kinase. A member of the Src kinase family. Hck is primarily expressed in hematopoietic cells, particularly granulocytes. Like Src, Hck contains, in addition to the catalytic domain (SH1), an SH2 and SH3 domain.

Sicheri, F.; Kuriyan, J. Structures of Src-family tyrosine kinases. *Cur. Opin. Struct. Biol.* **1997**, *7*, 777−785.

Histone: A family of Arg/Lys-rich small proteins present in nucleosomes, small beadlike structures present in eukaryotic chromosomes. Histones H2A, H2B, H3, and H4 form an octameric core about which a 146-nucleotide pair of DNA double helix is wrapped.

Alberts, B.; Johnson, A.; Lewis, J.; Raff, M.; Roberts, K.; Walter P. *Molecular Biology of the Cell*, 4th ed.; Garland Science: New York; pp 211−216.

hnRNP: Heterogeneous nuclear ribonucleoproteins. These pre-mRNA- and mRNA-binding proteins play a key role in various aspects of the lifecycle of messenger RNA, including transport, processing, and function.

Dreyfuss, G.; Kim, V. N.; Kataoka, N. Messenger-RNA-binding proteins and the messages they carry. *Nat. Mol. Cell. Biol.* **2002**, *3*, 195−205.

IGF-1: Insulin-like growth factor 1. The IGF-1 ligand associates with its cell surface-associated receptor, a tyrosine protein kinase. Complexation between ligand and receptor results in autophosphorylation of the cytoplasmic face of the receptor, which initiates a signaling cascade that promotes cell growth. IGF-1, insulin growth factor, and their corresponding receptors are responsible for distinct, yet overlapping, physiological functions.

Kim, J. J.; Accili, D. Signaling through IGF-1 and insulin receptors: where is the specificity? *Growth Horm. IGF Res.* **2002**, *12*, 81−3.

IL-2: Interleukin-2. A member of a class of cytokines (a peptide or protein that acts in a localized fashion) produced by leukocytes. IL-2 stimulates B, T, and Natural Killer cell growth. IL-2 has shown promise as a therapeutic agent.

Atkins, M. B. Interleukin-2: clinical applications. *Semin. Oncol.* **2002**, *29*, 12−7.

IL-6: Interleukin-6. A member of a class of cytokines (extracellular peptides/proteins that acts in a localized fashion) produced by leukocytes. IL-6 stimulates a wide range of activities in response to infection, including fever, the acute-phase response, and the activation of B and T cells.

Gruol, D. L.; Nelson, T. E. Physiological and pathological roles of interleukin-6 in the central nervous system. *Mol. Neurobiol.* **1997**, *15*, 307−39.

IL-12: Interleukin-12. A member of a class of cytokines (extracellular peptides/proteins that acts in a localized fashion) produced by leukocytes. IL-12 stimulates the activation of natural killer cells, the differentiation of CD4 T cells to TH1 cells, and the production of interferon γ.

Trinchieri, G. Interleukin-12 and the regulation of innate resistance and adaptive immunity. *Nat. Rev. Immunol.* **2003**, *3*, 133−46.

IRK: Insulin receptor tyrosine kinase. Upon complexation of the insulin growth factor ligand with IRK, the latter suffers autophosphorylation on its cytoplasmic face, which initiates a signaling cascade that promotes cell growth. IGF-1, insulin growth factor, and their corresponding receptors are responsible for distinct, yet overlapping, physiological functions.

Kim, J. J.; Accili, D. Signalling through IGF-1 and insulin receptors: where is the specificity? *Growth Horm. IGF Res.* **2002**, *12*, 81−3.

IRS-1: Insulin receptor substrate-1. IRS-1 belongs to a small family of IRS proteins that link the activated insulin and insulin-like receptors to appropriate signaling cascades. IRS proteins contain PH and PTB domains and sites of tyrosine phosphorylation that can bind to other signaling proteins.

White, M. F. IRS proteins and the common path to diabetes. *Am. J. Physiol. Endocrinol. Metab.* **2002**, *283*, E4 13−22.

ITAM: Immunoreceptor tyrosine-based activation motif. The signaling properties of multisubunit immune recognition receptors (e.g., antigen receptors on T cells) is dependent upon the presence of ITAMs located on the cytoplasmic portion of the receptor. ITAMs consist of two repeats of the sequence YXXL/I, which are separated by 6−8 amino acid residues.

Gergely, J.; Pecht, I.; Sarmay, G. Immunoreceptor tyrosine-based inhibition motif-bearing receptors regulate the immunoreceptor tyrosine-based activation motif-induced activation of immune competent cells. *Immunol. Lett.* **1999**, *68*, 3−15.

JAK-2: One of four members (Jak-1, Jak-2, Jak-3, and Tyk2) of the Janus kinase family of proteins; the name JAK was initially derived from just another kinase. This small group of cytoplasmic tyrosine kinases contains two kinase domains (only one of which is a functional catalyst) and is therefore structurally distinct from other protein tyrosine kinases. Their family name is derived from the two-faced Roman god Janus. Jaks are participants of the Jak-STAT (signal transducer and activator of transcription) pathway, which activates gene expression in response to the cell surface binding event between cytokines (extracellular peptides/proteins that acts in a localized fashion) and their receptors.

Aaronson, D. S.; Horvath, C. M. A road map for those who do not know JAK-STAT. *Science* **2002**, *296*, 1653−5.

c-Kit: The cellular homologue of the *kit* oncogene. A tyrosine kinase that serves as a receptor for the Kit ligand (KL), which is also known as mast cell growth factor (MCGF), steel factor (SLF), and stem cell factor (SCF). The c-Kit signaling pathway mediates

signals that promote cell proliferation, adhesion, migration, and survival. Tumorigenic Kit mutants have been reported in a variety of human cancers.

Longley, B. J.; Reguera, M. J.; Ma, Y. Classes of c-KIT activating mutations: proposed mechanisms of action and implications for disease classification and therapy. *Leuk. Res.* **2001**, *25*, 571−6.

KSR: Kinase suppressor of Raf. Mutations that inactivate KSR block the effects of activated Ras, which originally lead to the supposition that KSR is a protein kinase. However, this is incorrect, and it now appears likely that KSR serves as a scaffolding protein that assembles several of the members of the MAP kinase cascade into a supramolecular membrane-localized complex.

Morrison, D. K. KSR: a MAPK scaffold of the Ras pathway? *J. Cell Sci.* **2001**, *114*, 1609−12.

Lck: Lympohid cell kinase. A member of the Src kinase family. Lck is primarily expressed in T lymphocytes and Natural Killer cells. Like Src, Lck contains, in addition to the catalytic domain (SH1), an SH2 and SH3 domain.

Sicheri, F.; Kuriyan, J. Structures of Src-family tyrosine kinases. *Curr. Opin. Struct. Biol.* **1997**, *7*, 777−785.

LIM-Kinase: A small family of two protein kinases that contain LIM (acronym of Lin1 1, Isl-1, and Mec-3, the three proteins in which LIM was first identified) and PDZ protein interaction domains. LIM-kinase-1 phosphorylates and thereby inactivates the actin depolymerization factor cofilin. Patients with William's syndrome display defects in LIM-kinase-1 expression.

Stanyon, C. A.; Brenard, O. LIM-kinase1. *Int. J. Biochem. Cell Biol.* **1999**, *31*, 389−94.

MAPK (ERK, p38, JNK): Mitogen-activated protein kinase. MAPKs are part of a three-membered protein kinase module that consists of a MAP kinase kinase kinase, which phosphorylates and activates a MAP kinase kinase that, in turn, phosphorylates and activates a MAPK. Examples of MAPKs include the extracellular regulated protein kinase 1 and 2 (ERK1 and ERK2), members of the p38 subfamily (p38α, p38β, p38γ, and p38δ), and the c-Jun NH_2-terminal kinase subfamily (JNK 1, JNK 2, and JNK 3). Each of these kinases is activated by specific stimuli leading to well-defined cellular responses.

Johnson, G. L.; Lapadat, R. Mitogen-activated protein kinase pathways mediated by ERK, JNK, and p38 protein kinases. *Science* **2002**, *298*, 1911−2.

MAPKK (MEK): Mitogen-activated protein kinase kinase, also known as the extracellular regulated protein kinase kinase (MAPK/ERK kinase or MEK). MAPKKs/MEKs are part of a three-membered protein kinase cascade system that consists of a MAP kinase kinase kinase, which phosphorylates and activates a MAPKK/MEK that, in turn, phosphorylates and activates a MAP kinase. MAPKKs/MEKs are dual specificity protein kinases that phosphorylate specific MAPK substrates on both a tyrosine residue and a serine or threonine residue. Members of the MAPKK subfamily include MEK1 − MEK7, all of which are referred to by other names as well.

English, J. M.; Cobb, M. H. Pharmacological inhibitors of MAPK pathways. *Trends Pharmacol. Sci.* **2002**, *23*, 40−45.

MAPKKK (MEKK): Mitogen-activated protein kinase kinase kinase (or MEK kinase). MAPKKKs/MEKKs are part of a three-membered protein kinase cascade system that consists of the MAPKKK that phosphorylates and activates a MAP kinase kinase that, in turn, phosphorylates and activates a MAP kinase. Members of the MAPKKK family include the Raf subfamily, the TGF-β-activated kinase, the mixed lineage kinases 1−3, and many others.

Schlesinger, T. K.; Fanger, G. R.; Yujiri, T.; Johnson, G. L. The Tao of MEKK. *Front. Biosci.* **1988**, *3*, 1181−6.

Mce 1: Mammalian capping enzyme 1. Along with BVP, a member of the RNA triphosphatase subfamily of cysteine phosphatases. However, unlike BVP (which is both a triphosphatase and a diphosphatase), Mce 1 only catalyzes the conversion of triphosphates to diphosphates (triphosphatte-terminated RNA, ATP, and GTP).

Martins, A.; Shuman, S. Mutational analysis of baculovirus phosphatase identified structural residues important for triphosphatases activity in vitro and in vivo. *Biochemistry* **2002**, *41*, 13403−9.

MP1: MEK partner 1. A scaffolding protein that binds MEK1 (a MAP kinase kinase) and ERK1 (a MAP kinase). MP1 enhances activation of Erk1 by MEK1 and MEK1 by B−Raf. MP1 binds MEK1 via a proline rich domain.

Garrington, T. P.; Johnson, G. L. Organization and regulation of mitogen-activated protein kinase signaling pathways. *Curr. Opin. Cell Biol.* **1999**, *11*, 211−8.

MTOR/FRAP/RAFT/RAPT: Mammlian homologue of the target of rampamicin, also known as FKBP-rapamycin-associated protein, rapamycin and FKBP12 target, and rapamycin protein target. A member of the family of phosphatidylinositol kinase related protein kinases. These enzymes are serine/threonine protein kinases that contain a C-terminal region with strong homology to phosphatidylinositol 3-kinase (PI3K) and phosphatidylinositol 4-kinase. However, none of the protein kinases display lipid kinase activity. This enzyme family has been implicated in the signaling pathways that drive a diverse array of cellular behaviors.

Schmelzle, T.; Hall, M. N. TOR, a central controller of cell growth. *Cell* **2000**, *103*, 253−62.

Munc: Mammalian homologue of the uncoordinated mutant-13 (Unc-13) identified in *C. elegans*. The Munc-13 protein family, along with chimaerins and RasGRP, contain a C1 domain, which binds the tumor promoting phorbol esters (and the corresponding endogenous phorbol ester counterpart diacylglycerol). The Munc-13s serve as scaffold proteins for exocytotic proteins.

Kazanietz, M. G. Eyes wide shut: protein kinase C isozymes are not the only receptors for the phorbol ester tumor promoters. *Mol. Carcinog.* **2000**, *28*, 5−11.

Myc: Myelocytomatosis viral oncogene homolog. A transcription factors whose inappropriate expression has been observed in a wide range of human cancers. Myc activates a diverse array of genes by forming a heterodimer with a second transcription factor, Max.

Pelengaris, S.; Khan, M.; Evan, G. C-Myc: more than just a matter of life and death. *Nat. Rev. Cancer* **2002**, *2*, 764−6.

Myotubularin: Protein product of the myotubular myopathy gene, MTM1. There are at least seven genes that encode structurally homologous proteins. Myotubularin is a lipid phosphatase that catalyzes the dephosphorylation of the second messenger phosphatidylinositol 3-phosphate.

Maehama, T.; Taylor, G. S.; Dixon, J. E. PTEN and myotubularin: novel phosphoinositide phosphatases. *Annu. Rev. Biochem.* **2001**; *70*, 247−79.

Nef: Negative factor. A viral protein that is required for HIV and SIV infectivity and replication. Nef is recruited (via myristoylation) to the membrane of the infected cell, where it performs a host of functions, including downregulation of receptors and alterations in T cell signaling.

Facler, O. T.; Baur, A. S. Live and let die: Nef functions beyond HIV replication.

Immunity **2002**, *16*, 493−7.

NGF: Nerve growth factor**.** NGF controls neuron cell survival and regulates the outgrowth of axons and dendrites. NGF binds to the NGF receptor, one of seven subfamilies of receptor tyrosine kinases.

Kirstein, M.; Farinas, I. Sensing life: regulation of sensory neuron survival by neurotrophins. *Cell Mol. Life Sci.* **2002**, *59*, 1787−802.

NPM-ALK: Nucleophosmin-anaplastic lymphoma kinase. A fusion protein that arises via a translocation that merges the individual genes coding for NPM and ALK. Nearly half of all patients with anaplastic large cell lymphoma display the fusion gene product.

Duyster, J.; Bai, R. Y.; Morris, S. W. Translocations incolving anaplastic lymphoma kinase (ALK). *Oncogene* **2001**, *10*, 5623−37.

$p16^{INK4A}$: p16 Inhibitor of Cdk4. A stress-induced cyclin-dependent protein kinase inhibitor family of four proteins. INK4 arrests cells in G1 when overexpressed, but only if Rb is present. INK4 reduces the affinity of cyclin D and ATP for the Cdk4/cyclin D/ATP and Cdk6/cyclin D/ATP complexes.

Ortega, S.; Malumbres, M.; Barbacid, M. Cyclin D-dependent kinases, INK4 inhibitors and cancer. *Biochim. Biophys. Acta* **2002**, *1602*, 73−87.

$p62^{dok}$: Downstream of tyrosine kinase. Isolated as a hyperphosphorylated protein from human chronic myelogenous leukemia cells, fibroblasts transformed by various oncogenes, EGF-stimulated cells, as well as from other activated cell lines. Dok-1 associates with p21RasGap and contains a PH domain as well as several potential SH2 and SH3 domain-binding sites. The biological role of Dok-1 remains to be elucidated, but recent studies have implicated this protein in T lymphocyte activation.

Harriague, J.; Debre, P.; Bismuth, G.; Hubert, P. Priming of CD2-induced p62Dok tyrosine phosphorylation by CD3 in Jurkat T cells. *Eur. J. Immunol.* **2000**, *30*, 3319−28.

Paxillin: Paxillin is an adaptor protein that recruits a wide variety of additional proteins to focal adhesions, a small region on the cell that serves as an anchor to the extracellular matrix. Paxillin contains an array of protein−protein-mediating structural motifs: SH2 and SH3 binding site sequences as well as multiple LIM domains and LD motifs [a leucine rich sequence that begins with leucine (L) and aspartic acid (D)]. Paxillin plays an important role in embryonic development and cell motility.

Schaller, M. D. Paxillin: a focal adhesion-associated adaptor protein. *Oncogene* **2001**, *20*: 6459−72.

PDGF and **PDGFR:** Platelet-derived growth factor and platelet-derived growth factor receptor. A mitogen, PDGF stimulates the survival, growth, and proliferation of a broad array of different cell types. PDGF binds to the PDGF receptor, one of seven subfamilies of receptor tyrosine kinases. The tyrosine kinase activity of the PDGF receptor has been identified as a target for therapeutic intervention for the treatment of cancer.

George, D. Platelet-derived growth factor receptors: a therapeutic target in solid tumors. *Semin. Oncol.* **2001**, *28*, 27−33.

PDK1: 3′-phosphoinositide-dependent kinase 1. A serine/threonine protein kinase whose catalytic domain is closely related to those of the ACG family of protein kinases (i.e., PKA, PKC, and PKG). PDK1 contains a PH domain and the enzyme phosphorylates PKB/Akt in a PIP_3-dependent fashion. By contrast, PDK1 catalyzes the phosphorylation of other proteins (e.g., p70 S6 kinase) in a PIP_3-independent manner.

Vanhaesebroeck, B.; Alessi, D. R. The PI3K−PDK1 connection: more than just a road to PKB. *Biochem. J.* **2000**, *346*, 561−76.

PDZ Domain: Acronym of the first three proteins found to possess this domain: the postsynaptic protein PSD95, the *Drosophila* protein Discs Large, and the tight junction protein ZO-1. A protein interaction domain that preferentially binds to specific amino acid sequences positioned on the C-terminus of targeted proteins. The interaction between a PDZ domain and the appropriate amino acid sequence often results in protein translocation to specific membraneous structures.

Hung, A. Y.; Sheng, M. PDZ domains: structural modules for protein complex assembly. *J. Biol. Chem*. **2002**, *277*, 5699−702.

PH Domain: Pleckstrin homology domain. PH domains preferentially bind phosphoinositides, which often promotes recruitment of the PH domain-containing protein to the plasma membrane. PH domains are commonly found in proteins that regulate cytoskeletal events (e.g., actin assembly). A number of other phosphoinositide-binding domains have been described as well, including PX and ENTH domains.

Itoh, T.; Takenawa, T. Phosphoinositide-binding domains: functional units for temporal and spatial regulation of intracellular signaling. *Cell Signalling* **2002**, *14*, 733−43.

PKA: cAMP-dependent protein kinase, also known as protein kinase A. PKA was one of the first protein kinases to be identified, is a member of the first signal transduction pathway to be described (activation of glycogenolysis), and is the first protein kinase to have its' crystal structure solved. In its inactive form, PKA exists as a tetrameric holoenzyme complex containing two regulatory (R) and two catalytic (C) subunits. Upon exposure to the second messenger cAMP, the affinity of R for C decreases by 5 orders of magnitude. The released C subunit (the active form of PKA) then phosphorylates the appropriate endogenous protein substrates.

Meinkoth, J. L.; Alberts, A. S.; Went, W.; Fantozzi, D.; Taylor, S. S.; Hagiwara, M.; Montminy, M.; Feramisco, J. R. Signal transduction through the cAMP-dependent protein kinase. *Mol. Cell. Biochem*. **1993**, *127−128*, 179−86.

PKB/Akt: Protein kinase B/the oncogene derived from the Akt8 murine leukemia virus. The PH domain-containing PKB is involved in the signaling pathways that drive such diverse processes as glucose metabolism, gene transcription, cell proliferation, death, and migration.

Brazil, D. P.; Hemmings, B. A. Ten years of protein kinase B signalling: a hard Akt to follow. *Trends Biochem. Sci.* **2001**, *26*, 657−64.

PKC: Protein kinase C. A protein kinase family composed of conventional (α, βI, βII, and γ), atypical (ι and ζ), novel (ϵ, η, δ, and θ), and other (PKN and PKD) isoform families. Members of the conventional isoform subfamily were identified first (1977) and are activated by phosphatidylserine and diacylglycerol in a Ca^{2+}-dependent fashion. In 1982, Nishizuka reported that the tumor promoting phorbol esters target the conventional PKCs for activation. The atypical (Ca^{2+}-independent, phorbol ester/diacylglycerol-independent) and novel (Ca^{2+}-independent) isoforms are regulated differently from those of their conventional counterparts. PKCs have attracted widespread interest due to their apparent role in a wide variety of disease states.

Dempsey, E. C.; Newton, A. C.; Mochly-Rosen, D.; Fields, A. P.; Reyland, M. E.; Insel, P. A.; Messing, R. O. Protein kinase C isozymes and the regulation of diverse cell responses. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **2000**, *279*, L429−38.

PKD: Protein kinase D. A family of serine/threonine protein kinases that includes PKD1/PKCμ, PKCν, and PKD2. These enzymes contain a PH domain as well as a C1 domain that binds phorbol esters and diacylglycerol. The PKD family members have been implicated as players in a number of biological events, including immune system regulation, as a link between the PDGF and EGF pathways, a down-regulator of differentiation, and as a scaffold to recruit phosphatidylinositol 4-kinase and a phosphatidylinositol-4-phosphate 5-kinase to the Golgi apparatus.

Lint, J. V.; Rykx, A.; Vantus, T.; Vandenheede, J. R. Getting to know protein kinase D. *Int. J. Biochem. Cell Biol.* **2002**, *34*, 577−81.

PKG: cGMP-dependent protein kinase, also known as protein kinase G. A mediator of the NO-induced second messenger cGMP, the PKG family is composed of three-members. These enzymes participate in the signaling pathways that control smooth muscle relaxation and proliferation, inhibit platelet aggregation, and activate the memory and learning pathways known as long-term potentiation and depression.

Hofmann, F.; Ammendola, A.; Schlossmann, J. Rising behind NO: cGMP-dependent protein kinases. *J. Cell Sci.* **2000**, *113*, 1671−6.

PTB Domain: Phosphotyrosine binding domain. A protein interaction domain that recognizes sequences encompassing phosphotyrosine. However, unlike SH2 domains, PTB domains can also bind sequences that lack phosphorylated tyrosine residues as well as phospholipids. PTP domains display a close 3-dimensional structural homology to PH domains.

Yan, K. S.; Zhou, M. M. PTP or not PTB − that is the question. *FEBS Lett.* **2002**, *513*, 67−70.

PI-3 kinase: Phosphoinositide 3-kinase. Catalyzes the conversion of phosphatidyl-inositol-4,5-bisphosphate to phosphatidylinositol-3,4,5-triphosphate. Proteins that contain PH domains assemble at sites of PI3 kinase activity. PI3 kinase plays an important role in several signaling pathways, including those responsible for cell survival, metabolism, and cytoskeletal structure. Aberrant signaling through these pathways has been implicated in cancer and diabetes.

Cantley, L. C. The phosphoinositide 3-kinase pathway. *Science* **2002**, *296*, 1655−7.

PTEN: Phosphatase and tensin homolog. A phosphoinositide phosphatase that participates in the signaling pathways regulating cell growth and apoptosis. Mutations in the *PTEN* gene are associated with a variety of disorders, including cancer. PTEN is an example of a tumor suppressor protein.

Maehama, T.; Taylor, G. S.; Dixon, J. E. PTEN and myotubularin: novel phospho-inositide phosphatases. *Annu. Rev. Biochem.* **2001**, *70*, 247−79.

PTP1B: Protein tyrosine phosphatase 1B. PTP1B catalyzes the dephosphorylation of the insulin receptor, which turns off the insulin signaling pathway. Consequently, inhibitors of PTP1B are likely to prove useful as therapeutic agents for the treatment of diabetes.

Zhang, Z. Y. Protein tyrosine phosphatases: structure and function, substrate specificity, and inhibitor development. *Annu. Rev Pharmacol. Toxicol.* **2002**, *42*, 209−34.

Rac: Ras-related C3 botulinum toxin substrate. A GTPase that is structurally homologous to Ras. Rac is a participant in the signaling pathways that regulate cytoskeletal reorganization and gene expression.

Price, L. S.; Collard, J. G. Regulation of the cytoskeleton by Rho-family GTPases: implications for tumor cell invasion. *Semin. Cancer Biol.* **2001**, *11*, 167−73.

Raf: Rafs are members of the MAP kinase kinase kinase family of protein kinases and serve as a switch from tyrosine kinase phosphorylation to serine/threonine kinase signaling. Three closely related Raf proteins have been identified to date: A-Raf, B−Raf, and c-Raf (also known as Raf-1). These protein kinases are participants of the signaling pathways that regulate cell death, growth, and differentiation.

Dhillon, A. S.; Kolch, W. Untying the regulation of the Raf-1 kinase. *Arch. Biochem. Biophys.* **2002**, *404*, 3−9.

Rap1: Ras-related protein 1. A GTPase that is structurally homologous to Ras. Rap1 has been implicated as a modulator of ERK activity and it thought to play a role in cell migration and morphogenesis.

Bos, R. L.; de Rooij, J.; Reedquist, K. A. Rap1 signaling: adhering to new models. *Nat. Rev. Mol. Cell. Biol.* **2001**, *2*, 369−77.

Ras: The *ras* gene was first described in viruses that induce rat sarcomas. Ras is a GTPase that transduces signals from the cell surface to the nucleus via the MAP kinase pathway. Ras is one of the most commonly mutated genes in human cancers.

Downard, J. Targeting Ras signaling pathways in cancer therapy. *Nat. Rev. Cancer* **2003**, *3*, 11−22.

RasGRP: Ras guanyl releasing protein. RasGRP is a guanine nucleotide exchange factor for Ras. RasGRP, along with chimaerins and Munc-13, contain a C1 domain, which binds the tumor promoting phorbol esters (and the corresponding endogenous phorbol ester counterpart diacylglycerol).

Kazanietz, M. G. Eyes wide shut: protein kinase C isozymes are not the only receptors for the phorbol ester tumor promoters. *Mol. Carcinog.* **2000**, *28*, 5−11.

Rb: Originally identified as the protein mutated in retinoblastoma, an inherited form of eye cancer in children, Rb was subsequently found to be mutated in a variety of cancers. Rb is a tumor suppressor protein that serves as a universal regulator of the cell cycle by blocking the transcription of S-phase genes via binding to the E2F transcription factor. As the cell enters S phase, CDK-mediated phosphorylation of Rb releases E2F.

Classon, M.; Harlow, E. The retinoblastoma tumor suppressor in development and cancer. *Nat. Rev. Cancer* **2002**, *2*, 910−7.

RET: Rearranged during transfection. A tyrosine kinase receptor that binds neurotrophic ligands. Mutations and rearrangements in *ret* are responsible for a wide variety of different human tumors. c-RET is mainly expressed in neural crest-derived cells and the protein likely plays an important role in cell differentiation, proliferation, and motility.

Porter, A. C.; Vaillancourt, R. R. Tyrosine kinase receptor-activated signal transduction pathways which lead to oncogenesis. *Oncogene* **1998**, *17*, 1343−52.

Rho: Ras homologous protein. A family of GTPases that participate in the signaling pathways that regulate the actin cytoskeleton. Signaling pathways that control cell polarity, gene transcription, and a host of other cellular activities are also Rho-regulated. The best-characterized members of the Rho family are Cdc42, Rac1, and RhoA.

Etienne-Manneville, S.; Hall, A. Rho GTPases in cell biology. *Nature* **2002**, *420*, 629−35.

RIN1: Protein product of the Ras interaction/interference gene. Overexpression of RIN1 interferes with Ras signaling. RIN1 binds directly to Ras, competing with Raf for the same binding site on Ras. RIN1 may serve as a switch that diverts signals from the Ras/MAPK pathway to alternate pathways.

Wang, Y.; Waldron, R. T.; Dhaka, A.; Patel, A.; Riley, M. M.; Rozengurt, E.; Colicelli, J. The Ras effector RIN1 directly competes with RAF and is regulatyed by 14−3−3 proteins. *Mol. Cell. Biol.* **2002**, *22*, 916−26.

RSK: A cell cycle regulated s6 (a ribosomal protein) protein kinase. The three RSK family members are phosphorylated by and therefore positioned downstream of ERK. RSKs contain two functional serine/threonine kinase domains. The N-terminal kinase

domain catalyzes the phosphorylation of RSK substrates, which include ribosomal proteins, the cAMP response element binding protein, Sos, c-Fos, and others. The C-terminal kinase domain is phosphorylated and thereby activated by ERK. Subsequent C-terminal kinase domain-mediated autophosphorylation is required for the full activation of RSK.

Frodin, M.; Gammeltoft, S. Role and regulation of 90 kDa ribosomal S6 kinase (RSK) in signal transduction. *Mol. Cell. Endocrinol.* **1999**, *151*, 65−77.

Sam68: Src-associated during mitosis of 68 kDa. Sam68 was originally reported as a protein that binds strongly to and is phosphorylated by Src during mitosis. Srp, Sam68, and Gld-1 are members of the GSG protein family that likely play a role in linking signalling pathways to mRNA nuclear export. Sam68 interacts with proteins that contain SH2 and SH3 domains and, consequently, may play a role as an adaptor protein.

Feuillet, V.; Semichon, M.; Restouin, A.; Harriague, J.; Janzen, J.; Magee, A.; Collette, Y.; Bismuth, G. The distinct capacity of Fyn and Lck to phosphorylate Sam68 in T cells is essentially governed by SH3/SH2 domain linker interactions. *Oncogene* **2002**, *21*, 7205−13.

SH2 Domain: Src homology 2 domain. A protein interaction domain that recognizes sequences encompassing phosphotyrosine. SH2 domains not only play an important role in the self-regulation of tyrosine kinases (e.g., the Src kinase family), but also act as receptors by coupling SH2-containing proteins with specific phosphotyrosine-bearing sequences on appropriate protein ligands.

Yaffe, M. B. Phosphotyrosine-binding domains in signal transduction. *Nat. Rev. Mol. Cell. Biol.* **2002**, *3*, 177−86.

SH3 Domain: Src homology 3 domain. A protein interaction domain that recognizes sequences encompassing proline residues. SH3 domains not only play an important role in the self-regulation of tyrosine kinases (e.g., the Src kinase family), but also act as receptors by coupling SH3-containing proteins with specific proline-bearing sequences on appropriate protein ligands.

Mayer, B. J. SH3 domains: complexity in moderation. *J. Cell Sci.* **2001**, *114*, 1253−63.

Shc: Src homology and collagen like protein. A family of PTP- and SH2-containing adaptor proteins that bind to activated receptors. Shc family members participate in signaling pathways that regulate a diverse array of behaviors, including cell growth and death.

Luzi, L.; Confalonieri, S.; Di Fiore, P. P.; Pelicci, P. G. Evolution of Shc functions from nematode to human. *Curr. Opin. Genet. Dev.* **2000**, *10*, 668−74.

SHP: SH2-containing protein tyrosine phosphatase. The family members SHP-1 and SHP-2 catalyze the dephosphorylation of an array of substrates. Both SHP-1 and −2 contain two adjacent SH2 domains. SHP-1 is a negative regulator of B cell function, whereas SHP-2 serves as a positive regulator.

Tamir, I.; Porto, J. M. D.; Cambier, J. C. Cytoplasmic protein tyrosine phosphatases SHP-1 and SHP-2: regulators of B cell signal transduction. *Curr. Opin. Immunol.* **2000**, *12*, 307−15.

Sin (EFS): Src-interacting protein, also known as the embryonal-Fyn associated substrate. Sin/EFS is a member of the Cas family of proteins that simultaneously binds to the SH3 and SH2 domains of Src.

O'Neill, G. M.; Fashena, S. J.; Golemis, E. A. Integrin signaling: a new Cas(t) of characters enters the stage. *Trends Cell Biol.* **2000**, *10*, 111−9.

SLP-76: SH2 domain containing leukocyte protein of 76 kDa. A Grb2-related adaptor protein that contains an SH2 domain as well as consensus sequences for binding to other SH2 and SH3 domains. SLP-76 overexpression results in T cell receptor-stimulated IL-2 production.

Jordan, M. S.; Singer, A. L.; Koretzky, G. A. Adaptors as central mediators of signal transduction in immune cells. *Nat. Immunol.* **2003**, *4*, 110−6.

SOS: Son of sevenless. A guanine nucleotide exchange factor (GEF) that stimulates Ras and Rac activity. Identified in Drosophila as a downstream signaling pathway participant initiated by the Sevenless receptor tyrosine kinase.

Wittinghofer, F. Ras signaling: caught in the act of the switch-on. *Nature* **1998**, *394*, 317−20.

Src (p60^{c-src}): Identified as the oncogene present in the Rous *sarc*oma virus. Src is a member of the Src kinase family of nonreceptor tyrosine protein kinases (other members include Blk, Fgr, Fyn, Hck, Lck, Lyn, and Yes). All family members contain SH3, SH2, and kinase (SH1) domains. These enzymes bind to activated transmembrane receptors and thereby link, both physically and biochemically, the activated receptors to downstream signaling pathways. Src family members are differentially expressed in a wide variety of tissues.

Erikson, R. L.; Purchio, A. F.; Erikson, E.; Collett, M. S.; Brugge, J. S. Molecular events in cells transformed by Rous Sarcoma virus. *J. Cell Biol.* **1980**, *87*, 319−25.

Tec: Tyrosine kinase expressed in hepatocellular carcinoma. A family of nonreceptor tyrosine kinases, of which five are expressed in mammals (Atk/Btk, Emt/Itk/Tsk, Etk/Bmx, Rlk/Txk, and Tec). Nearly all Tec kinases contain a PH domain, and most Tec members possess a TH domain. In addition, Tec kinases contain a SH3, SH2, and a SH1 (catalytic core) domain. The Tec kinases are differentially expressed in various tissues.

Smith, C. I.; Islam, T. C.; Mattsson, P. T.; Mohamed, A. J.; Nore, B. F.; Vihinen, M. The Tec family of cytoplasmic tyrosine kinases: mammalian Btk, Bmx, Itk, Tec, Txk and homologs in other species. *Bioessays* **2001**, *23*, 436−46.

TGF-β: Transforming growth factor β. A large family of structurally related secreted proteins that regulate a wide variety of biological functions, including proliferation, differentiation, and cell death. TGF-βs bind to transmembrane receptors that contain a serine/threonine kinase domain on the cytoplasmic face.

Attisano, L.; Wrana, J. L. Signal transduction by the TGF-beta superfamily. *Science* **2002**, *296*, 1646−7.

TH Domain: Tec homology domain. TH domains contain one or two proline rich regions that are preceded by a Btk homology motif. The latter binds Zn^{2+} and is essential for Tec family PH domain function.

Smith, C. I.; Islam, T. C.; Mattsson, P. T.; Mohamed, A. J.; Nore, B. F.; Vihinen, M. The Tec family of cytoplasmic tyrosine kinases: mammalian Btk, Bmx, Itk, Tec, Txk and homologs in other species. *Bioessays* **2001**, *23*, 436−46.

VEGFR/Flt/KDR: Vascular endothelial growth factor receptor, also known as fms-like tyrosine kinase and kinase-insert-domain-containing receptor. The VEGF family of proteins is comprised of angiogenic cytokines that promote the formation of new blood vessels from existing ones. The VEGFR-1 (Flt-1) gene codes for both a membrane bound and a cytoplasmic form of the VEGF receptor, which displays tyrosine kinase activity. In addition to VEGFR-1, there are two other members of the VEGFR family: VEGFR-2 (KDR/Flk-1) and VEGFR-3 (Flt-4).

Shibuya, M. Structure and dual function of vascular endothelial growth factor receptor-1 (Flt-1). *Int. J. Biochem. Cell. Biol.* **2001**, *33*, 409−20.

VH1: Vaccinia virus H1 gene product. The first protein to be identified as a dual specificity phosphatase. The H1 core of the vaccinia viral genome is highly conserved

among pox viruses and VH1 appears to be essential for viral viability. VH1 acts by blocking gamma interferon signaling.

Najarro, P.; Traktman, P.; Lewis, J. A. Vaccinia virus blocks gamma interferon signal transduction: viral VH1 phosphatase reverses Stat1 activation. *J. Virol.* **2001**, *75*, 3185−96.

WASP: Wiskott-Aldrich syndrome protein**.** This protein is defective in patients with Wiskott-Aldrich syndrome. WASP serves as a regulator of the cytoskeleton by activating Arp2/3 (actin related protein), which nucleates the formation of actin filaments.

Caron, E. Regulation of the Wiskott-Aldrich syndrome protein and related molecules. *Curr. Opin. Cell Biol.* **2002**, *14*, 82−7.

WW Domain: A protein interaction domain that contains two conserved tryptophans. WW domains recognize sequences encompassing proline residues as well as phosphoserine-proline and phosphothreonine-proline motifs. By contrast, phosphorylation of tyrosine in the motif Pro-Xaa-Tyr disrupts WW/ligand interactions.

Ilsley, J. L.; Sudol, M.; Winder, S. J. The WW domain: linking cell signaling to the membrane cytoskeleton. *Cell Signalling* **2002**, *14*, 183−9.

ZAP-70: ζ-associated polypeptide of 71 kDa. ZAP-70 is member of the Syk family of cytoplasmic tyrosine kinases. This 70 kDa protein plays a key role in T cell receptor (TCR)-initiated signaling by binding to ITAMs on the ζ-chain of the TCR. ZAP-70 contains two SH2 domains as well as sites of tyrosine phosphorylation that serve as ligands for other SH2-containing proteins.

Qian, D.; Weiss, A. T cell antigen receptor signal transduction. *Curr. Opin. Cell Biol.* **1997**, *9*, 205−12.

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