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The Akt/PKB pathway: molecular target for cancer drug discovery

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The serine/threonine kinase Akt/PKB pathway presents an exciting new target for molecular therapeutics, as it functions as a cardinal nodal point for transducing extracellular (growth factor and insulin) and intracellular (receptor tyrosine kinases, Ras and Src) oncogenic signals. In addition, alterations of the Akt pathway have been detected in a number of human malignancies. Ectopic expression of Akt, especially constitutively activated Akt, is sufficient to induce oncogenic transformation of cells and tumor formation in transgenic mice as well as chemoresistance. Akt has a wide range of downstream targets that regulate tumor-associated cell processes such as cell growth, cell cycle progression, survival, migration, epithelial–mesenchymal transition and angiogenesis. Blockage of Akt signaling results in apoptosis and growth inhibition of tumor cells with elevated Akt. The observed dependence of certain tumors on Akt signaling for survival and growth has wide implications for cancer therapy, offering the potential for preferential tumor cell killing. In the last several years, through combinatorial chemistry, high-throughput and virtual screening, and traditional medicinal chemistry, a number of inhibitors of the Akt pathway have been identified. This review focuses on ongoing translational efforts to therapeutically target the Akt pathway.
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Akt proteins: overview and rationale as antitumor targets

Akt was originally discovered as an oncogene transduced by the acute transforming retrovirus (Akt-8), which was isolated from an AKR thymoma (Staal *et al*., 1977; Staal, 1987), and subsequently found to encode a serine/threonine protein kinase (Bellacosa *et al*., 1991). Akt is also known as protein kinase B (Coffer and Woodgett, 1991) and RAC-PK (Jones *et al*., 1991). Viral akt highly activated and oncogenic due to the fact that v-akt is associated with the cell membrane through a myristylated Gag protein sequence fused to the N-terminus of Akt (Bellacosa *et al*., 1991). The important role of Akt in transformation and cancer was shortly thereafter strengthened by the cloning of the *AKT2* gene (Cheng *et al*., 1992) and the discovery that *AKT2* is frequently amplified and overexpressed in human cancers (Cheng *et al*., 1992, 1996; Bellacosa *et al*., 1995). To date, three Akt family members have been identified in mammals, designated Akt1/PKBα, Akt2/PKBβ and Akt3/PKBγ (Testa and Bellacosa, 2001). The members of Akt family share similar domain structure and are activated by various stimuli in a phosphatidylinositol 3-kinase (PI3K)-dependent manner (Burgering and Coffer, 1995; Franke *et al*., 1995; Liu *et al*., 1998; Shaw *et al*., 1998). Activation of Akt depends on the integrity of the pleckstrin homology (PH) domain, which mediates its membrane translocation, and on the phosphorylation of Thr^{308} in the activation loop and Ser^{473} (Chan *et al*., 1999; Datta *et al*., 1999; Testa and Bellacosa, 2001; Brazil *et al*., 2002). Phosphoinositides, PtdIns-3,4-P2 and PtdIns-3,4,5-P3, produced by PI3 K bind directly to the PH domain of Akt, driving a conformational change in the molecule, which enables the activation loop of Akt to be phosphorylated by PDK1 at Thr^{308} (Alessi *et al*., 1997). Full activation of AKT1 is also associated with phosphorylation of Ser^{473} (Alessi *et al*., 1996) within a C-terminal hydrophobic motif characteristic of kinases in the AGC kinase family. Although the role of PDK1 in Thr^{308} phosphorylation is well established, the mechanism of Ser^{473} phosphorylation is controversial. A number of candidate enzymes responsible for this modification have been put forward, including integrin-linked kinase (Persad *et al*., 2001), PDK1 when in a complex with the kinase PRK2 (Balendran *et al*., 1999), Akt itself, through autophosphorylation (Toker and Newton, 2000), PKCα (Partovian and Simons, 2004), PKCβII (Kawakami *et al*., 2004), DNA-dependent kinase (Feng *et al*., 2004), and the rictor-mTOR complex (Sarbassov *et al*., 2005). The activity of Akt is negatively regulated by tumor suppressor *PTEN*, which is frequently mutated in human malignancy (Li *et al*., 1997; Steck *et al*., 1997; Parsons, 2004). *PTEN* encodes a dual-specificity protein and lipid phosphatase that reduces intracellular levels of PtdIns-3,4,5-P3 by converting them to PtdIns-4,5-P2, thereby inhibiting the PI3K/Akt pathway (Stambolic *et al*., 1998). Akt phosphorylates and/or interacts with a number of molecules to exert its normal cellular functions, which include roles in cell proliferation,

et al., 1999; Testa and Bellacosa, 2001; Brazil *et al*., 2002). Gene knockout studies have defined the biological importance of Akt members in normal cells. In particular, *Akt2*-null mice develop typical type II diabetes (Cho *et al*., 2001a, b), while *Akt1*- and *Akt3*-deficient mice do not display a diabetic phenotype but exhibit a decrease in the sizes of all organs and a selective impairment of brain development, respectively (Chen *et al*., 2001; Cho *et al*., 2001a, b; Easton *et al*., 2005; Tschopp *et al*., 2005). Moreover, although *Akt1*- and *Akt3*-deficient brains are reduced in size to approximately the same degree, the absence of *Akt1* reduces neuronal cell number, whereas the lack of *Akt3* results in smaller and fewer cells in which mTOR signaling is attenuated (Easton *et al*., 2005).

Several lines of evidence suggest that Akt is a critical target for anticancer drug discovery. First, Akt sits at the crossroads of multiple oncogenic and tumor suppressor signaling networks (see related Reviews in this issue). Almost all known oncogenic growth factors, angiogenic factors and cytokines activate Akt by binding to cognate receptors on cell surface. Further, Akt is also activated by steroid hormones, such as estrogen and androgen through a mechanism independent of their nuclear receptors (Sun *et al*., 2001a; Sun *et al*., 2003). In addition, Akt is shown to be activated by constitutively active Ras and Src (Datta *et al*., 1996; Liu *et al*., 1998). Second, frequent deregulations of many components of the Akt signaling pathway have been observed in human cancer (see review by Altomare and Testa in this issue). Of the Akt family, only the *AKT2* gene is frequently amplified in human cancer. Further, overexpression of AKT2 RNA and/or protein is also more commonly observed in human cancer than are AKT1 and AKT3 (Testa and Bellacosa, 2001; Kim *et al*., 2005). However, recurrent activation of the three Akt family members has been detected in a variety of types of human malignancy (Yuan *et al*., 2000; Sun *et al*., 2001a, b, 2003; Altomare *et al*., 2003, 2004, 2005; Balsara *et al*., 2004). Activation of Akt is primarily the result of aberrant upstream molecules of Akt, which include overproduction of growth factors, upregulation and/or mutation of receptor tyrosine kinases, Ras and Src as well as PIK3CA and PTEN. While a point mutation of *AKT2* has been reported in familial diabetes (George *et al*., 2004), a dominant mutation of Akt has not been identified in human tumor. Third, ectopic expression of constitutively active Akt and even wild-type Akt2 results in oncogenic transformation *in vitro* and *in vivo* (Cheng *et al*., 1997; Hutchinson *et al*., 2001; Malstrom *et al*., 2001; Mende *et al*., 2001; Sun *et al*., 2001a, b; Majumder *et al*., 2003). Furthermore, a number of studies have shown that overexpression and/or activation of Akt render tumor cells resistant to chemotherapeutic drugs and signal molecule inhibitors such as Gleevec, Iressa, Herceptin and retinoid acid (Cheng *et al*., 2002; Arlt *et al*., 2003; Knuefermann *et al*., 2003; Yuan *et al*., 2003; Nagata *et al*., 2004). In addition, Akt targets many signal molecules to regulate tumor development-associated cell processes such as apoptosis, cell proliferation, differentiation, migration and angiogenesis. Finally, knockdown of Akt by antisense or siRNA significantly reduces tumor growth and invasiveness and induces apoptosis and cell growth arrest only in tumor cells overexperssing Akt (Cheng *et al*., 1996; Chen *et al*., 2001; Asnaghi *et al*., 2004; Remy *et al*., 2004; Tabellini *et al*., 2005).

These observations make Akt an attractive target for anticancer drug discovery, and it has been postulated that inhibition of Akt alone or in combination with standard cancer chemotherapeutics will reduce the apoptotic threshold and preferentially kill cancer cells. The development of specific and potent inhibitors will allow this hypothesis to be tested in animals. The majority of small molecule inhibitors in this nascent field are classic ATP-competitive inhibitors, which provide little specificity. Phosphatidylinositol (PI) analogs have been reported to inhibit Akt, but these inhibitors may also have specificity problems with respect to other PH domain containing proteins and may have poor bioavailability. Recently, small chemical compounds triciribine/Akt/protein kinase B inhibitor-2 (API-2) and allosteric inhibitors have been reported which are PH domain dependent, and the latter also exhibit Akt isozyme selectivity. In addition, inhibitors toward upstream regulators and downstream targets of Akt have also been tested for their capability of reversing the phenotype of cancer cells expressing altered Akt. This review focuses on the ongoing efforts to therapeutically target individual components of Akt pathway including Akt itself as well as its upstream regulators and downstream effectors (Figure 1). Some of these efforts involve AKT-specific inhibition based on structure-based analyses (see also the Review by Kumar and Madison in this issue).

Therapeutic targeting of upstream regulators of Akt

PDK1 inhibitors

PDK1 is a serine/threonine protein kinase that can phosphorylate and activate a number of kinases in the AGC kinase superfamily (Mora *et al*., 2004). The first identified and best characterized PDK1 substrates are the three members of the Akt family (Mitsiades *et al*., 2004). PDK1 phosphorylates the activation loop of Akt (also called the T-loop) on residue Thr^{308}, which primarily regulates Akt activation (Alessi *et al*., 1997). Therefore, a PDK1 inhibitor should significantly block activation of Akt.

Three potent PDK1 inhibitors, BX-795, BX-912 and BX-320 (Figure 2a), recently identified by screening of compound libraries, have IC_{50} between 11 and 30 nM (Feldman *et al*., 2005). The inhibitors blocked PDK1/Akt signaling in tumor cells resulting in the inhibition of anchorage-independent growth and the induction of apoptosis in a variety of tumor cell lines. A number of cancer cell lines with elevated Akt activity were >30-fold more sensitive to growth inhibition by PDK1 inhibitors in soft agar than on tissue culture plastic, consistent with the cell survival function of the PDK1/

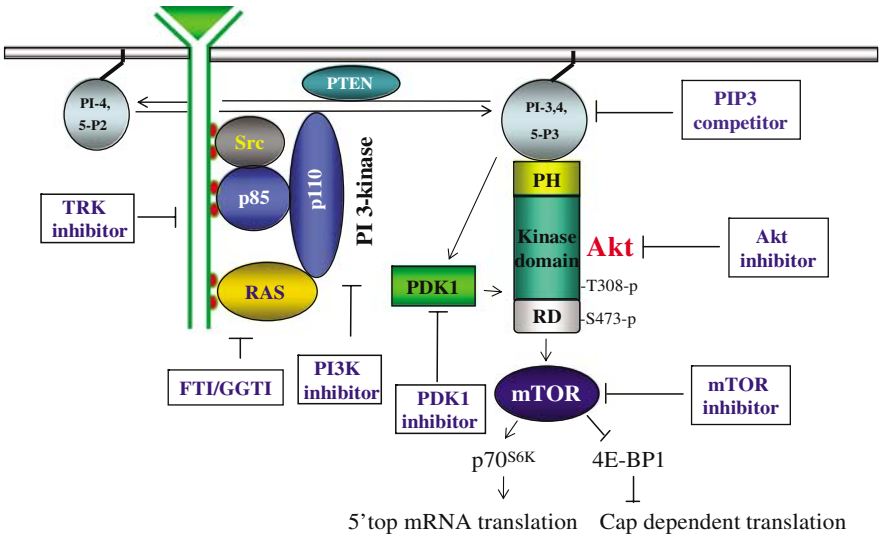

Figure 1 Therapeutic targeting of the Akt pathway including Akt itself as well as its upstream regulators and downstream effectors

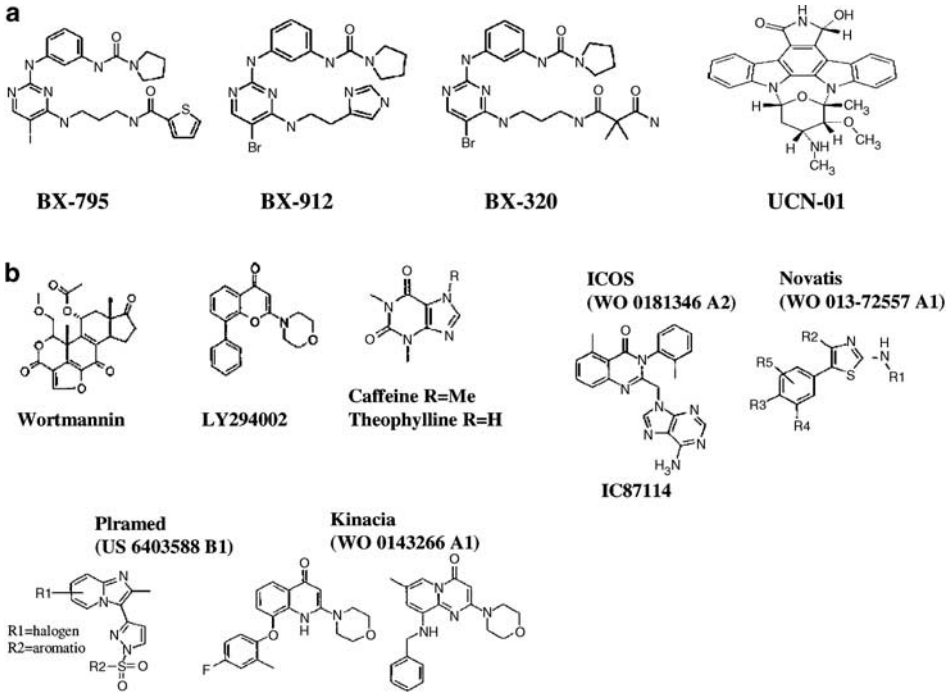

Figure 2 Compound structures for inhibitors of PDK1 (**a**) and PI3K (**b**)

Akt signaling pathway, which is particularly important for unattached cells. BX-320 inhibited the growth of LOX melanoma tumors in the lungs of nude mice after injection of tumor cells into the tail vein. The effect of BX-320 on cancer cell growth *in vitro* and *in vivo* indicates that PDK1 inhibitors may have clinical utility as anticancer agents.

The staurosporine derivative UCN-01 (7-hydroxystaurosporine), a drug now in clinical trials, has been shown to potently inhibit PDK1 ($IC_{50} = 33$ nM) *in vitro*. UCN-01-induced PDK1 inhibition was also observed in human tumor xenografts (Sato *et al*., 2002). Overexpression of constitutively active Akt diminished the cytotoxic effects of UCN-01, suggesting that UCN-01 may in part exert its cytotoxicity by inhibiting PDK1/Akt survival pathway. Crystal structure analyses showed that staurosporine and UCN-01 form a complex with the kinase domain of PDK1 (Komander *et al*., 2003). Although staurosporine and UCN-01 interact with the PDK1 active site in an overall similar manner, the UCN-01 7-hydroxy group (Figure 2a), which is not present in staurosporine, generates direct and water-

mediated hydrogen bonds with active-site residues. This moiety is hydrogen-bonded directly to Thr^{222} and indirectly via an ordered water molecule to Gln^{220} of PDK1 (Zhao *et al*., 2002; Johnson and Pinto, 2002; Komander *et al*., 2003). A different water-mediated hydrogen-bonding network is also observed in other UCN-01 complexes and might serve as a starting point for further structure-based optimization. In addition, recent studies show that UCN-01 inhibits other kinases such as PKC and Chk1 and transcriptionally upregulates the cyclin-dependent kinase inhibitor $p21^{waf1/cip1}$ (Senderowicz, 2003a, b).

PI3K inhibitors

Dissection of PI3K/Akt signaling pathway has been aided greatly by two pharmacological PI3K inhibitors, wortmannin and LY294002 (Figure 2b). Wortmannin is a fungal metabolite and a potent inhibitor of type I PI3K, with an IC_{50} range for inhibition of PI3K from 2 to 4 nM (Arcaro and Wymann, 1993; Vlahos *et al*., 1994). Wortmannin inhibits PI3K activity by binding covalently to a conserved lysine residues in the ATP-binding site of the enzyme (Wymann *et al*., 1996). Wortmannin has antitumor activity *in vitro* and *in vivo*, suggesting that it might offer a valuable approach to treat cancer. However, a major disadvantage of the use of wortmannin is its stability in an aqueous environment. Wortmannin is soluble in organic solvents, which may limit its use in clinical trials. Currently, water-soluble wortmannin conjugates are being developed to circumvent this issue. LY294002 is a flavonoid derivative and a reversible, ATP-competitive inhibitor with IC_{50} for recombinant PI3K in the low micromolar range. A number of *in vitro* studies have shown that LY294002 alone has antiproliferative and proapoptotic activities (Wetzker and Rommel, 2004). Relatively, few *in vivo* studies have been conducted to demonstrate the efficacy of LY294002 on the inhibition of tumor growth, but these studies showed that administration of LY294002 in human cancer xenografts inhibited tumor growth and induced apoptosis (Semba *et al*., 2002; Fan *et al*., 2003). Although inhibition of the PI3K/Akt pathway by wortmannin or LY294002 alone may inhibit cell proliferation, promote apoptosis and/or inhibit tumor growth, the combination of wortmannin or LY294002 with traditional cytotoxic drugs or radiation enhances the effectiveness of these treatments (Wetzker and Rommel, 2004).

It is noteworthy that neither wortmannin nor LY294002 displays selectivity for different members of the class I PI3K (Finan and Thomas, 2004). Wortmannin also inhibits class III PI3K to reduce autophagy, a class II programmed cell death (Shintani and Klionsky, 2004). LY294002 also inhibits casein kinase 2 with similar potency to PI3K. At higher concentrations, wortmannin inhibits PI3K-related enzymes, such as mTOR, ATM and PI4-kinase β (Finan and Thomas, 2004). Moreover, methylxanthines, such as caffeine and theophylline, inhibit p110δ, even though their activity is rather weak (Arcaro and Wymann, 1993; Abraham, 2004).

Recently, several new compounds have been described to have some selectivity for individual members of PI3K (Figure 2b). PIramed have described several imidazopyridine derivatives that exhibit excellent PI3K inhibitory activities, especially against p110α. A series of morpholino-substituted compounds related LY294002 have shown isoform selectivity. Quinolone and pyridopyrimidine (Kinacia) are approximately 100-fold more potent against p110α/β as compared to p110γ (Finan and Thomas, 2004). ICOS Corporation has recently claimed a new PI3K inhibitor, IC87114, which selectively inhibits p110δ with $IC_{50} = 0.5\,\mu$M and >50-fold selectivity over the other class PI3K isoforms (Sadhu *et al*., 2003). In addition, Novartis has described 5-phenylthiazole derivatives as PI3K inhibitors (Finan and Thomas, 2004). However, antitumor activity of these compounds needs further investigation both *in vitro* and *in vivo*. It is noteworthy that use of PI3K inhibitors may be associated with undesirable side effects because of the many important cellular targets of this lipid kinase.

Inhibitors of the prenylation

Protein prenylation, including farnesylation and geranylgeranylation, is a lipid post-translational modification required for the cancer-causing activity of proteins such as the GTPase Ras. Farnesyltransferase and geranylgeranyltransferase I inhibitors (FTIs/GGTIs) represent a new class of anticancer drugs that exhibit a remarkable ability to inhibit malignant transformation without significant toxicity to normal cells, especially FTIs are currently in clinical trials. However, the mechanism of FTI and GGTI antitumor activity remains elusive. It has been shown that FTIs inhibit PI3K/Akt-mediated growth factor- and adhesion-dependent survival pathways and induce apoptosis in human cancer cells that overexpress Akt (Jiang *et al*., 2000; Prendergast, 2000; Sebti and Der, 2003). Furthermore, overexpression of Akt, but not oncogenic H-Ras, sensitizes NIH3T3 cells to FTI-277, and a high serum level prevents FTI-277-induced apoptosis in H-Ras- but not Akt-transformed NIH3T3 cells. A constitutively active form of Akt rescues human cancer cells from FTI-277-induced apoptosis. Integrin-dependent activation of Akt is also blocked by FTI-277. In addition, GGTI-298 and GGTI-2166 have also been shown to inhibit PI3K/Akt pathway, resulting in apoptosis in human cancer cells (Dan *et al*., 2004). Thus, a mechanism for FTIs and GGTIs inhibition of human tumor growth is by inducing apoptosis through inhibition of the PI3K/Akt pathway. However, neither FTIs nor GGTIs directly inhibits PI3K/Akt, suggesting that the unidentified prenylated proteins that activate PI3K/Akt are the targets of FTIs and/or GGTIs. Recent studies suggest that RhoB could be a candidate to mediate this action (Liu and Prendergast, 2000; Adini *et al*., 2003; Jiang *et al*., 2004).

RTK inhibitors

Among RTKs, EGFR and Her2/Neu/ErbB2 are frequently altered in human cancer and primarily activate

the PI3K/Akt pathway. Two major approaches have been used to target the ErbB family, that is, small-molecule tyrosine kinase inhibitors and humanized antibodies against the receptor extracellular domains (Yu and Hung, 2000; Chen *et al*., 2003). In general, antibodies bind to the extracellular domain of the receptors, inhibiting their activation by ligand, and promoting receptor internalization and downregulation, whereas small molecules competitively inhibit ATP binding to the receptor, thereby hindering autophosphorylation and kinase activation. At present, the most advanced of the newer therapies in clinical development are anti-EGFR monoclonal antibody IMC-C225 (cetuximab, Erbitux; Imclone), anti-ErbB2 and the reversible small-molecule inhibitors of EGFR, ZD-1839 (gefitinib, Iressa; AstraZeneca) and OSI-774 (erlotinib, Tarceva; OSI Pharmaceuticals). Both ZD-1839 and OSI-774 have been through phase I and phase II trials. Promising single-agent clinical antitumor activity has been reported in advanced NSCLC, head and neck cancer and prostate carcinoma. Furthermore, humanized monoclonal antibodies, IMC-C225 against EGFR and trastuzumab (Herceptin) targeted ErbB2, are also in phase II and phase III trials. These agents potently inhibit EGFR and ErbB2 resulting in the reduction of Akt kinase activity (Yakes *et al*., 2002; Mitsiades *et al*., 2004). A recent study has shown that patients who become resistance to Herceptin have elevated levels of Akt due to loss of PTEN, suggesting that elevated Akt activation is responsible for Herceptin resistance (Nagata *et al*., 2004).

Akt inhibitors

Akt antibody

Antibodies and antibody-based reagents have been used for the treatment of cancer. As described above, the humanized IgG1 trastuzamab (Herceptin) is an effective treatment for breast cancers that overexpress ErbB2 (Yu and Hung, 2000). Genetic engineering of antibodies can be used to modify and enhance antibody efficacy. For example, mouse monoclonal antibodies can be chimerized by such approaches to prevent the production of human antimurine antibodies when administered to immune-competent patients (Clark, 2000). An alternative strategy is to replace the antibody gene present in mouse B cells with human antibody genes. These modified B cells can then be used to produce hybridoma cell lines that express fully humanized monoclonal antibodies that avoid cross-species immune response (Fishwild *et al*., 1996). Over a decade ago, McCafferty *et al*. (1990) demonstrated that recombinant antibody fragments could be displayed on the tip of M13 bacteriophage. Some of the advantages of phage-displayed recombinant antibodies over the conventional polyclonal or monoclonal antibodies are quick generation time, cheap production cost, and, importantly, accessibility to the antibody DNA for further genetic manipulations. Recently, Shin *et al*. (2005) developed novel recombinant anti-Akt single-chain antibodies by panning a mouse phage-displayed scFv recombinant antibody library using GST-Akt1 fusion protein. To generate a membrane-permeable version of the anti-Akt1-scFv, the *scFv* gene was subcloned into a GST expression vector carrying a membrane-translocating sequence (MTS) from Kaposi fibroblast growth factor. A purified GST-anti-Akt1-MTS fusion protein accumulates intracellularly and inhibits activation of all three Akt family members. Interestingly, *in vitro* kinase assay shows that GST-anti-Akt1-MTS also inhibits constitutively active forms of Myr-Akt1, -Akt2 and -Akt3 as well as phosphomimetic mutant of Akt-DD, where Thr308 and Ser473 are replaced with aspartic acid. Furthermore, GST-anti-Akt1-MTS induces apoptosis in cancer cell lines that express constitutively active Akt. In addition, anti-Akt scFv exhibits antitumor activity in PyVmT-expressing transgenic tumors implanted in mouse dorsal window chambers (Shin *et al*., 2005). These data indicate that GST-anti-Akt1-MTS is a cell-permeable inhibitor of Akt and that this approach can be used to generate compounds that target tumor cells dependent on aberrant Akt for their growth.

PI analog inhibitors

As PtdIns(3,4,5)P_3 directly binds to the PH domain of Akt and PDK1 and is required for activation of Akt, the development of a PtdIns(3,4,5)P_3 analog would be a reasonable approach to develop an Akt inhibitor. This mode of inhibition would prevent Akt translocation to the plasma membrane and activation. The feasibility of this approach was suggested by the demonstration that D-3-deoxy-myo-inositols inhibited the growth of transformed cells (Powis *et al*., 1991). It was subsequently found that the inositol derivative DPI had an IC_{50} of 35 μM against H-29 colon cancer cell growth (Kozikowski *et al*., 1995). A recent study examined 24 modified phosphatidylinositol ether lipid analogues (PIAs) and found that five of them, PIA5, 6, 23, 24, and 25 (Figure 3), with modifications at two sites on the inositol ring, inhibited Akt with $IC_{50} < 5\,\mu$M (Castillo *et al*., 2004a, b). PIAs decreased phosphorylation of many downstream targets of Akt without affecting upstream kinases, such as PI3K or PDK1. Importantly, PIAs selectively induced apoptosis in cancer cell lines with high levels of endogenous Akt activity. These findings identify PIAs as effective Akt inhibitors, and provide proof of principle for targeting the PH domain of Akt. However, whether PIAs are effective *in vivo* and whether PIAs affect other PH-domain containing proteins are currently unknown.

Perifosine is a novel orally bioavailable alkylphospholipid and structurally resembles naturally occurring phospholipids (Figure 3). Perifosine is known to be a CDK inhibitor and has displayed significant antiproliferative activity *in vitro* and *in vivo* in several human tumor model systems (Senderowicz, 2003a, b; Vink *et al*., 2005). It has been shown that perifosine can cause cell cycle arrest with induction of $p21^{WAF1/CIP1}$ in a p53-independent fashion. By searching for the under-

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