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Commentary

Inhibiting Phosphoinositide 3-Kinases

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Commentary to:
PWT-458, A Novel Pegylated-17-Hydroxywortmannin, Inhibits Phosphatidylinositol 3-Kinase Signaling and Suppresses Growth of Solid Tumors


Phosphoinositide kinases (PIKs) are lipid kinases that function as signal transducers downstream of cell surface receptors and mediate pathways important for cell growth, proliferation, adhesion, survival and motility. As indicated by their names, PIKs are enzymes that phosphorylate the inositol ring of phosphoinositides. Depending on the particular position of the phosphorylated carbohydrate, PIKs are categorized into three families: phosphoinositide 3-kinases (PI3Ks), phosphoinositide 4-kinases (PI4Ks), and phosphoinositide 5-kinases (PI5Ks). PI3Ks are further grouped as class I, II or III, depending on their subunit structure, their regulation, and substrate selectivity. To make things even more complicated, different subgroups contain various isoforms—amounting to eight isoforms in total.1

Class I PI3Ks which are made up of a catalytic and a regulatory subunit, phosphorylate phosphatidylinositol4,5 bisphosphate (PIP2) at the 3-position of the inositol ring, forming the secondary messenger phosphatidylinositol3-5 triphosphate (PIP3). PIP3 serves as an anchor for PH (Pleckstrin Homology) domain-containing proteins which recruit AKT serine/threonine kinase (also known as protein kinase B; PKB) and 3-phosphoinositide-dependent protein kinase-1 (PDK1) to the cell membrane. AKT then gets phosphorylated and activated by PDK1, allowing it to regulate numerous important cellular pathways.2,3

It is therefore no surprise that several PI3K isoforms have been implicated in human diseases. PI3Kγ is known to relay inflammatory signals in mouse mast cells as PI3Kγ-null bone marrow derived mast cells are less sensitive to antigen-IgE stimulation compared to wild type cells.4 Similar results were obtained for PI3Kδ knockout mast cells.5 Scientists hope that pharmaceutical targeting of PI3Kγ and PI3Kδ will ease allergic response inflammation. PI3Kδ is mutated in a significant fraction of colorectal, breast, brain and other tumor types,6–9 and several of these mutations have been shown to have oncogenic potential.6,10 PTEN which antagonizes PI3K activity, is frequently deleted in many cancer types supporting a significant role of this pathway in cancer development.11,12

Two PI3K inhibitors, Wortmannin and LY294002, have been widely used as research tools to supply evidence for the participation of the PI3K pathway in various systems. However, these agents inhibit several PI3K isoforms as well as other non-PI3K enzymes.13 Both agents also suffer from low stability or poor pharmacokinetics, and their development as potential drugs has therefore been given low priority. However, the inhibition of cancer cell growth in vitro as well as tumor growth in vivo by both compounds14–16 has encouraged some companies and academic groups to develop derivatives of these compounds. For example, Thrombogenix developed a series of analogs closely related to LY29400217,18 and Wyeth set out to develop Wortmannin derivatives.19

In this issue of Cancer Biology & Therapy, Yu et al. describe their successful attempt to improve the pharmacokinetics of Wortmannin.19 The authors pegylated the Wortmannin derivative 17-hydroxywortmannin (17-HWT) to get PWT-458. Pegylation is the process of attaching a polyethylene-glycol chain to the drug of choice. This strategy has been extensively employed to improve drug efficacy and stability as evidenced by several drugs on the market, like Macugen (Pfizer), Peg-Intron (Enzon Pharmaceuticals) and Doxil (ALZA Corporation), and agents clinical trials, like CDP870 (phase III; Pfizer) and PEG-Alfacen (phase I; Nektar Therapeutics, InterMune).20,21 In Wyeth’s case, PWT-458 is more water soluble than 17-HWT most likely due to the associated two or three water molecules on each ethylene glycol subunit. It is also more stable because the PEG polymer, along with the associated water molecules, protects the drug from a possible nucleophilic attack on the furan ring and the opening of the lactone ring. Furthermore, the electron-withdrawing alkylthio moiety at the position of the acid portion aids in the hydrolysis of the ester bond and thus allows the continuous release of the active drug 17-HWT.

A single intravenous injection of PWT-458 rapidly inhibited PI3K signaling, as measured by a complete loss of AKT (ser-473) phosphorylation in xenograft tumors grown in nude mice. Following a daily X5 dosing regimen, PWT-458 demonstrated single-agent antitumor
activity in three nude mouse xenograft models. Efficacious doses ranged from 0.5 mg/kg to 10 mg/kg, achieving a superior therapeutic index over 17-HWT. Yu et al. also show that the combination therapy of PWT-458 and Intron-A (Biogen Idec) produced synergistic antitumor activity leading to an impressive regression in tumor size, which was not achieved by either agent alone.19 Most interestingly, minimal doses of PWT-458 and Pegylated-Rapamycin in combination could achieve superior antitumor activity against PTEN-negative nude mouse xenograft models of U87MG glioma. These data provide proof-of-principle for targeting the PI3K pathway as novel cancer therapy for major solid tumors.

Looking to the future, development of compounds that inhibit specific PI3K isoforms can be expected to further decrease drug-induced toxicity. In cancer, an additional benefit might be achieved if agents could be developed that target only mutant forms of PI3Kα rather than also affecting proteins in wild-type form. Eventually, such initiatives will allow disease-specific therapy where individualized agents are offered based on the presence of tumor-specific genetic alterations within the PI3K pathway. Since this pathway is commonly defective in many cancers, such therapeutic strategies will impact and benefit a large patient population. Fortunately, numerous academic investigators and companies are striving towards this goal.17-19,22

References