values of 0.002 and 0.01 μM, respectively. In mice, ABP309 is well absorbed following an oral dose of 50 mg/kg attaining a C_{max} of 15 μM after 0.5 hours, with 32% bioavailability and elimination half-life of 1.8 hours. Furthermore, ABP309 inhibits VEGF-induced angiogenesis in a murine growth factor inplant angiogenesis model and exerts anti-tumor activity in a range of tumor models. The preclinical pharmacokinetic profile of this 2nd generation VEGFR inhibitor will be presented in more detail, covering the use of different formulations and of salt forms.

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Prostate specific membrane antigen (PSMA) expression in the neo-vasculature of non-prostate cancers: in vitro target validation and in vivo imaging

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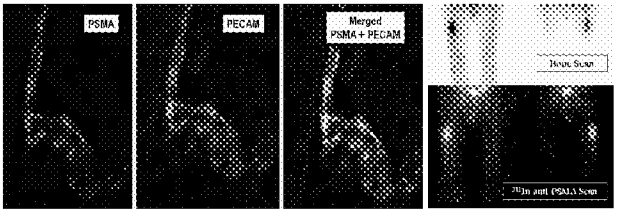
Background: Prostate specific membrane antigen (PSMA), a transmembrane folate hydrolase consisting of 750 amino acids, has been consistently detected in normal and hyperplastic prostate tissues, in pre-cancerous lesions and prostate cancer (PCa) using immunohistochemistry and other techniques. The expression of PSMA in Non-PCa is currently being pursued as a target for diagnostic imaging and anti-cancer antibody therapeutics.
Methods: PSMA expression was measured on a series of fresh frozen and formalin-fixed paraffin embedded non-PCA malignancies by transcriptional profiling (TP) using cDNA microarrays on nylon membranes, RT-PCR (Taqman), in situ hybridization (ISH), western blotting, dual co-localization immunofluorescence (IF) and immunohistochemistry (IHC) both before and after laser capture microdissection (LCM) using both internal domain (7E11) and external domain (MLN591) antibodies. In vivo imaging was performed using ^{111}I-conjugated Anti-PSMA (J591) in patients with primary lung, breast, colorectal and renal carcinomas.
Results: PSMA mRNA expression was localized to the neo-vasculature in 55% of a series of breast, colon, lung and ovarian cancers using an S-35 labeled probe and ISH. PSMA mRNA expression was localized to the endothelium of the tumor vessels after microdissection using Taqman™ RT-PCR. 40% of the same carcinomas were positive for PSMA immunoreactivity of the tumor vasculature by IHC on frozen sections with the MLN591 antibodyDual IF studies using the MLN591 antibody and anti-CD31 (PECAM-1) localized PSMA expression to the endothelium of neo-vasculature in carcinomas of the breast, colon, lung and ovary, in Wilm's tumors and neuroblastomas (Figure). Using the 7E11 antibody on paraffin sections, PSMA staining was observed in 9/10 clear cell renal cell carcinomas, 7/10 infiltrating ductal breast cancers, 6/10 invasive colorectal cancers and 4/10 non-small cell lung cancers. Patients with lung, breast, colorectal and renal cancers (image) were successfully imaged in vivo with the radio-labeled anti-PSMA conjugate.
Conclusion: PSMA expression is regularly associated with the neo-vasculature of many non-PCas and co-localizes with endothelial cell markers. A variety on non-PCas can be detected in vivo by anti-PSMA radiolabeled imaging. Further studies of PSMA in non-PCa as a target for both diagnostic imaging and anti-cancer antibody-based therapies appear warranted.



174 POSTER

Correlation between protein kinase C-beta expression and patient survivals in primary tumors – implications for clinical drug development

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PKC-β is an isoform of protein kinase C, a family of serine-threonine kinases involved in a wide range of signal transduction pathways such as cell proliferation, cell differentiation and apoptosis. Recent evidence implicated the role of PKC-β in signal cascade of vascular endothelial cell growth factor (VEGF), B cell function and B cell receptor signal pathway. PKC-β was also shown to be one of the most prominently overexpressed genes in fatal/refractory DLBCL patients. Therefore, its role in tumor development and angiogenesis makes it a potential therapeutic target in cancer. LY317615 (Enzastaurin HCl) is a potent and selective inhibitor of PKC-β. The compound exhibited antiangiogenic activity in a preclinical animal model and is well tolerated in toxicology studies. In this study, we first analyzed NCI 60 cell line gene expression profiles to identify genes that show correlation with cells' response to LY317615 for growth inhibition. We then analyzed public gene expression profiling data on different types of cancer to investigate if PKC-β gene expression is correlated with patient survival. Our analysis has demonstrated that high PKC-β expression has a strong correlation with poor patient outcome in DLBCL, confirming the observations published in previous publications on these datasets. A similar demonstration of a correlation between PKC-β expression and poor survival was observed in glioblastomas. When we performed similar analyses in other subtypes of lymphoma, such as MCL, CLL as well as other solid tumors, including NSCLC, we did not find a correlation between PKC-β expression and survival. Analysis of microarray data on DLBCL has also indicated that expression of genes in cell survival signaling and proliferation pathway that are closely related with PKC-β expression, consistent with previous findings that PKC-β plays an essential role in these pathways. Taken together, these results suggest that PKC-β in DLBCL and glioblastomas is associated with poor survival suggesting that inhibiting this molecule in patients with such malignancies may provide a clinical benefit.

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Pseudolarix acid B inhibits angiogenesis and reduces hypoxia-inducible factor 1alpha by promoting proteosome-mediated degradation

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Angiogenesis plays a critical role in tumor progression. Vascular endothelial growth factor (VEGF), which can be secreted from neighboring tumor cells, potently stimulates tumor angiogenesis. The inhibition of tumor angiogenesis including inhibition of VEGF signaling pathways has been one of the promising strategies in the development of novel anticancer therapy. Pseudolarix acid B (PAB), the naturally occurring diterpenoid isolated from the root bark of Pseudolarix kaempferi Gordon tree (Pinaceae), possesses potent antifungal and pregnancy-terminating effects that may be tightly associated with angiogenesis. This study was to examine its angiogenic inhibition, impact on VEGF secretion from tumor cells, and the possible molecular mechanism of its action. Results showed that PAB inhibited VEGF-stimulated proliferation and migration, and fetal bovine serum (FBS)-stimulated tube formation of human umbilical vein endothelial cells (HUVECs) in a concentration-dependent manner. The chicken chorioallantoic membrane (CAM) assay further revealed that PAB (10 nmol/egg) significantly suppressed in vivo angiogenesis. ELISA data also showed that PAB could abrogate hypoxia-induced VEGF secretion from human breast cancer MDA-MB-468 cells via reducing the protein level of hypoxia-inducible factor 1α (HIF-1α). Further analysis using LY294002, a phosphatidylinositol 3-kinase (PI3K) inhibitor and U0126, a MEK inhibitor, showed that the increase in HIF-1α protein level was highly dependent on PI3K and p42/p44 mitogen-activated protein kinase (MAPK) activities in hypoxic MDA-MB-468 cells. However, PAB treatment did not affect the active (phosphorylated) forms of Akt and Erk. Interestingly, the selective proteosome inhibitor MG-132 completely reversed the reduction of HIF-1α protein in the PAB-treated MDA-MB-468 cells. Together, the results reveal that PAB displays the dual activities of directly inhibiting endothelial cells and abrogating paracrine stimulation of VEGF from tumor cells. Additionally, PAB accelerates HIF-1α protein degradation probably by stimulating the proteosome pathway in MDA-MB-468 cells. Further studies on the molecular mechanism of its stimulatory effect on the proteosome pathway may well generate new therapeutic opportunities.

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In vitro human metabolism of BAY 57-9352: a novel VEGFR-2/PDGFR kinase inhibitor

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VEGFR-2 and PDGFR are key mediators of tumor angiogenesis. Disruption of signal transduction by these receptors inhibits tumor growth in preclinical