

Pancreatic Cancer

PGCR 2007 (Abstract 206)

WP1066, a Potent Inhibitor of Jak2/STAT3 Pathway, Inhibits Pancreatic Cancer Growth Both in vitro and in vivo

A. Chakraborty,¹ S. Guha,² A. Kunnumakkara,¹ S. Szymanski,¹ I. Fokt,¹ J. Abbruzzese,³ R. Kazerooni,³ B. Aggarwal,¹ T. Madden,¹ W. Priebe¹

¹Department of Experimental Therapeutics

²Department of Gastrointestinal Medicine and Nutrition

³Department Gastrointestinal Medical Oncology, Department of Pharmacy
University of Texas M. D. Anderson Cancer Center
Houston, Texas, USA

Background: Pancreatic cancer (PaCa) is now the fourth leading cause of cancer-related mortality in the United States. Its intransigence to current chemotherapy regimens stimulated our interest in exploring novel targets for therapeutic development.

Constitutive activation of signal transducer and activator of transcription-3 (STAT3) in PaCa cells is associated with vascular endothelial growth factor (VEGF) expression, and when suppressed, leads to inhibition of VEGF expression, angiogenesis, tumor growth, and subsequent metastasis in vivo. In addition to VEGF expression, STAT3 activation also promotes tumor cell proliferation and survival pathways in vivo. Epidermal growth factor (EGF)- and interleukin-6 (IL-6)-mediated mitogenic signaling pathways can also induce Jak2/STAT3 phosphorylation in PaCa. Thus, Jak2/STAT3 proteins are potential novel therapeutic targets in PaCa.

Currently available Jak2/STAT3 pathway inhibitors including AG490 can block STAT3 phosphorylation at concentrations of 50 to 100 μ M but are not active in vivo. The striking similarity of AG490 to the natural products of the caffeic acid family, and our comparison of caffeic acid benzyl ester to AG490, showing no additional benefit for AG490 in vitro, led us to the design of novel potent inhibitors. We have discovered a

new class of compounds that inhibits IL-6–induced Jak2 and STAT3 phosphorylation and suppression of related downstream signaling pathways. Next, we selected compound WP1066 for more detailed evaluation in PaCa.

Aim: Determine the effects of a novel Jak2/STAT3 inhibitor WP1066 on PaCa cells both in vitro and in vivo.

Methods and Results: WP1066 significantly inhibited proliferation and induced apoptosis of PaCa cells including Colo357FG and MIA PaCa-2 with an IC₅₀ of 2.5 μM. WP1066 potently blocked constitutive and IL-6–induced STAT3 phosphorylation in Colo357FG cells in a dose-dependent manner with maximal effects noted at 5 μM. WP1066 (5 μM) also suppressed expression of STAT3–dependent antiapoptotic proteins including Bcl-xL and survivin. However, WP1066 did not block AKT phosphorylation (S473) and NF-κB activity in Colo357FG cells. Next, we evaluated in vivo effects of WP1066 in *nu/nu* murine subcutaneous xenograft model for PaCa. WP1066 was injected intraperitoneally thrice weekly for 4 weeks at 40 mg/kg per mouse. WP1066 was well tolerated and no adverse events were noted. WP1066 significantly inhibited Colo357FG tumor growth by four-fold after 4 weeks of treatment ($P<.005$ with $n=6$ per group). Further, WP1066-treated tumors showed a significant ($P<.05$) decrease in Ki-67⁺ (proliferation index) and CD31⁺ cells (microvessel density).

Conclusion: Our studies show that targeting Jak2/STAT3 pathway with novel drugs including WP1066 significantly blocked PaCa cell proliferation in vitro and tumor growth in vivo. Thus, drugs including WP1066 should potentially be considered as one of the future strategies for treatment of PaCa.

Supported by NCI SPORE in PaCa P20 CA101936 and The Morton and Angela Topfer PaCa Research Fund.