

Pancreatic Cancer

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A Novel Small Molecule Inhibitor of Protein Kinase D Blocks Pancreatic Cancer Growth *In Vivo*

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Background: Protein kinase D (PKD) is a novel family (PKD1, PKD2, and PKD3) of serine-threonine kinases with diverse biologic functions including cell proliferation and growth.

Pancreatic cancer (PaCa) is a devastating disease with few therapeutic options. We showed earlier that PKD signaling pathways promote mitogenesis in multiple PaCa cell lines. However, nothing is known about targeting biologic functions of PKD family in PaCa. Our PKD inhibitor discovery program yielded CRT0066101, which specifically blocks activation of PKD family.

Aim: The aim of this study was to determine the effects of CRT0066101 in PaCa, both *in vitro* and *in vivo*.

Methods and Results: Immunohistochemical analysis showed that activated PKD1 (pS916-PKD1) is significantly upregulated in PaCa as compared with normal ducts (91% vs. 22%; $P < .001$). We also showed that PKD1 and PKD2 are over-expressed in multiple PaCa cell lines including Panc-1. Using Panc-1 as a model system, we demonstrated that CRT0066101 blocked proliferation and BrdU incorporation with an IC_{50} of 1 μ M, and also blocked PKD1-dependent NF- κ B activation using luciferase reporter assays. CRT0066101 given orally (80 mg/kg/d) for 4 weeks significantly abrogated growth in a subcutaneous Panc-1 xenograft model ($n=8$; $P < .01$). The expression of activated PKD1 (pS916-PKD1) in the treated tumor explants was significantly inhibited ($P < .05$), with peak plasma CRT0066101 concentration (12 μ M) achieved within 6 hours of oral administration. Further, CRT0066101 given orally (80 mg/kg/d) for 21 days in an

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ABSTRACTS

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orthotopic model potently blocked Panc-1 tumor growth (n=7; $P < .01$). CRT0066101 significantly reduced Ki-67⁺ proliferation index ($P < .01$), increased apoptosis (measured by *in situ* TUNEL assay) of PaCa tumors ($P < .05$), and potently abrogated expression of NF- κ B-regulated multiple proliferative and pro-survival proteins, including cyclin D1, survivin, Bcl-2, Bcl-xL, activated PKD1 (pS916-PKD1), and activated PKD2 (pS876-PKD2).

Conclusion: These results demonstrate *for the first time* that the PKD-specific small molecule inhibitor CRT0066101 blocks PaCa growth both *in vitro* and *in vivo*. Thus, PKD is a novel therapeutic target in PaCa.