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ABSTRACTS SELECTED FOR POSTER PRESENTATIONS

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Pancreatic Cancer

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Protein Kinase D1 Promotes Cell Proliferation and Invasion of Human Pancreatic Cancer Cells

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Background: Protein kinase D1 (PKD1) is the founder member of a novel family of serine-threonine kinases and is a key component in signal transduction pathways initiated by diacylglycerol (DAG) and protein kinase C (PKC) that regulate several biological processes in normal and cancer cells. Pancreatic Cancer (PaCa) is a devastating disease with few therapeutic options. We showed earlier that PKD1 was over-expressed in PaCa and potently promoted DNA synthesis. However, little is known about its biological functions in PaCa. Our PKD-inhibitor discovery program recently yielded CRT0066101 that specifically blocked activation of PKD family both *in vitro* and *in vivo*.

Aim: To investigate whether PKD1 potentiate anchorage-independent growth (soft-agar colony formation) and invasion of PaCa cells *in vitro*.

Methods and Results: To evaluate biological roles of PKD1 in PaCa cells, we generated a stable PKD1 over-expression cell line (Panc1-PKD1) and a stable PKD1 under-expression cell line (Panc-28-shPKD1) by using specific lentiviral vectors for transfections in Panc-1 and Panc-28 PaCa cells. PKD1 expression in these cell lines along with their corresponding control cell lines (Panc-1-mock and Panc-28-mock) were confirmed by western blots. In a soft-agar colony forming assay, we showed that Panc-1-PKD1 significantly increased anchorage-independent growth (50% with $p < 0.01$) as compared to Panc-1-mock and was potently inhibited by CRT0066101 (5 μ M). We observed similar reduction (40% with $p < 0.01$) in soft-agar colony formation by Panc-28-shPKD1 cells as compared to Panc-28-mock. Further, CRT0066101 reduced soft-agar colony formation by 60% in Panc-28-mock cells. This suggests that blockade of other PKD family members potentiate reduction in anchorage-independent growth. Next, we showed that Panc1-PKD1 significantly increased invasion (110% with $p < 0.01$) as compared with Panc-

1-mock cells in MatrigelTM assay and was potently abrogated by CRT0066101 (5 μ M). However, Panc-28-shPKD1 showed only 35% reduction in invasion as compared with Panc-28-mock. In contrast, CRT0066101 attenuated invasion of Panc-28-mock cells by 85%, thus suggesting critical role of other PKD family members in promoting invasion of PaCa cells.

Conclusion: Our results demonstrated *for the first time* that PKD1 potently stimulated soft-agar colony formation and invasion of PaCa cells *in vitro*. These biological effects were significantly attenuated either by a PKD1-specific small-molecule inhibitor CRT0066101 or by using a PKD1-specific shRNA.