An inhibitor of the mitotic kinase, MPS1, is selective towards pancreatic cancer cells.

Ruchi Bansal¹, Corrine Blackburn¹, Lyndsey Brown¹, Rachel Gasaway¹, Jose Victorino¹,⁴ Jaesik Jeong², Jesse Gore³, Keith L. March³, Brittney-S. Herbert¹,⁵, Riccardo Colombo⁶, Murray Korc³,⁵, Roger B. Slee¹,⁵# and Brenda R. Grimes¹,⁵#

#joint senior authors

Indiana University School of Medicine (IUSM) ¹Department of Medical and Molecular Genetics, ²Department of Biostatistics, ³Department of Medicine. Additional affiliations: ⁴California State University Dominguez Hills, ⁵Indiana University Melvin and Bren Simon Cancer Center, ⁶Nerviano Medical Sciences, Italy.

The abysmal five year pancreatic cancer survival rate of less than 6% highlights the need for new treatments for this deadly malignancy. Cytotoxic drugs normally target rapidly dividing cancer cells but unfortunately often target stem cells resulting in toxicity. This warrants the development of compounds that selectively target tumor cells. An inhibitor of the mitotic kinase, MPS1, which has been shown to be more selective towards cancer cells than non-tumorigenic cells, shows promise but its effects on stem cells has not been investigated. MPS1 is an essential component of the Spindle Assembly Checkpoint and is proposed to be up-regulated in cancer cells to maintain chromosomal segregation errors within survivable limits. Inhibition of MPS1 kinase causes cancer cell death accompanied by massive aneuploidy. Our studies demonstrate that human adipose stem cells (ASCs) and can tolerate higher levels of a small molecule MPS1 inhibitor than pancreatic cancer cells. In contrast to PANC-1 cancer cells, ASCs and telomerase-immortalized pancreatic ductal epithelial cells did not exhibit elevated chromosome mis-segregation after treatment with the MPS1 inhibitor for 72hrs. In contrast, PANC-1 pancreatic cancer cells exhibited a large increase in chromosomal mis-segregation under similar conditions. Furthermore, growth of ASCs was minimally affected post treatment whereas PANC-1 cells were severely growth impaired suggesting a favorable therapeutic index. Our studies, demonstrate that MPS1 inhibition is selective towards pancreatic cancer cells and that stem cells are less affected in vitro. These data suggest MPS1 inhibition should be further investigated as a new treatment approach in pancreatic cancer.