

Presented at the American Association for Cancer Research's Pancreatic Cancer: Progress and Challenges conference, Lake Tahoe, NV, June 18-21.

**Metformin targets human pancreatic cancer stem cells in preclinical mouse models.** Enza Lonardo, Michele Cioffi, Yolanda Sanchez, Jorge Dorado, Christopher Heeschen. Spanish National Cancer Research Centre, Madrid, Madrid, Spain.

Pancreatic ductal adenocarcinomas contain a subset of exclusively tumorigenic cancer stem cells (CSCs), which are capable of repopulating the entire heterogeneous populations of cancer cells in the tumor and, even more importantly, are highly resistant to standard chemotherapy. Therefore, the identification of drugs that are capable of selectively targeting CSCs is urgently needed. Here, we demonstrate that low dose metformin, a widely used anti-diabetic drug with an exceptional safety profile, selectively targets freshly isolated human pancreatic CSCs. Specifically, metformin pretreated sphere-derived CSCs showed strong activation of AMPK and loss of expression of pluripotency-associated genes and CSC-associated surface markers. Consecutively, the ability of pretreated CSCs to clonally expand in vitro and in vivo was virtually abrogated, while non-CSCs remained mostly unaffected by metformin treatment. Importantly, induction of energetic crisis resulting in enhanced apoptosis was restricted to p53-deficient CSCs, while p53 wild-type CSCs were resistant to the effects of metformin. Intriguingly, the combination of metformin with gemcitabine, the standard chemotherapeutic agent for pancreatic cancer, efficiently erased both CSCs and non-CSCs. Finally, in primary tissue xenograft mouse models this combination treatment effectively reduced tumor burden and prevented relapse as compared to either drug alone. Therefore, these data provide a strong experimental basis for further evaluating the combination of metformin and chemotherapeutic drugs to eventually improve the poor prognosis of patients with pancreatic cancer.