Pancreatic cancer heterogeneity and response to anti-MEK therapy

K. Pedersen[1], MT. Salcedo[2, 3], T. Macarulla[2], D. Massó[1], M. Carreras[2], X. Serres[2], M. Abu-Suboh[2], J. Balsells[2], H. Allende[2], L. Soucek[1], J. Tabernero[2, 4] and J. Arribas[1, 5, 6]

[1] Preclinical Research Program, Vall d'Hebron Institute of Oncology (VHIO), 08035 Barcelona, Spain. kp@kim-pedersen.com; jarribas@vhio.net

[2] Vall d'Hebron University Hospital, 08035 Barcelona, Spain.

[3] Department of Anatomy, Universitat Autonoma de Barcelona, Campus de la UAB, 08193 Bellaterra, Spain.

[4] Clinical Research Program, Vall d'Hebron Institute of Oncology (VHIO), 08035 Barcelona, Spain.

[5] Department of Biochemistry and Molecular Biology, Universitat Autonoma de Barcelona, Campus de la UAB, 08193 Bellaterra, Spain.

[6] Institució Catalana de Recerca i Estudis Avançats (ICREA), 08010 Barcelona, Spain.

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Abstract

Infiltrating ductal adenocarcinoma, the most common malignancy of pancreas, remains an almost uniformly fatal disease. New strategies are desperately needed to combat this singularly chemo and radiation therapy resistant cancer.

In collaboration with pharmaceutical companies we are currently using our collection of patient derived mouse xenografts to test the possibility of enhancing the efficacy of gemcitabine plus nab-paclitaxel (standard clinical care) by adding a third compound to the treatment. These include inhibitors of MEK, SMO and DNA methyltransferase. The MEK inhibitor is promising since around 90% of pancreatic ductal adenocarcinomas contain tumor cells with activating mutations in KRAS, making them at least partially dependent on MEK signaling. The SMO inhibitor leads to inhibition of Hedgehog pathway signaling, which in certain models have been shown to reduce the development of a compact stroma. Finally, transcription of tumor suppressors is often suppressed by epigenomic reprogramming, at least partially through DNA methylation. Therefore, by inhibiting DNA methyltransferase it is possible that a concomitant increase in tumor suppressor expression will sensitize the cells to subsequent chemotherapeutic agents.