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A new approach for treating pancreatic cancer

Pancreatic ductal adenocarcinoma (PDA) is refractory to treatment with existing chemotherapeutic agents, but the underlying cause of this resistance has been difficult to elucidate using standard animal models. A study carried out by Olive *et al.* [1] used a unique mouse model to probe this question further and provide a method for overcoming drug insensitivity by targeting the Hedgehog signaling pathway. The KPC mouse model differs significantly from standard mouse-xenograft models in that it uses a genetically engineered mouse strain which develops pancreatic tumors resembling those seen in humans. When treated with gemcitabine, the current standard of care therapy, the pancreatic tumors in the KPC mice show a poor response to the drug similar to human PDA. By contrast, pancreatic tumors subcutaneously implanted into mice are sensitive to gemcitabine treatment. The KPC mouse-derived tumors themselves are intrinsically sensitive to gemcitabine, as demonstrated by a xenograft mouse model, but only become resistant when they are orthotopically expressed in the KPC mice. Further investigation of the induced KPC-tumors showed that the tumors were less vascularized than implanted tumors and that the surrounding stroma obstructed their access to blood vessels. Therefore, it appears that drug resistance of the pancreatic tumors is probably because of relatively poor circulation of the KPC-tumors resulting in poor drug exposure.

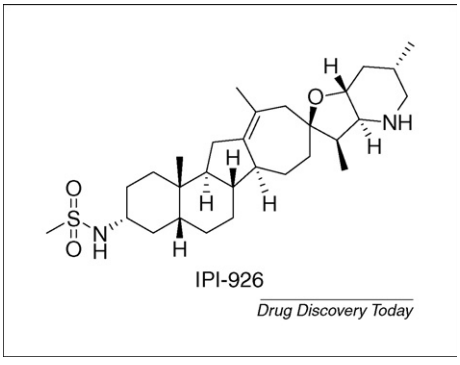

FIGURE 1
Structure of IPI-926.

This is where the Hedgehog signaling pathway comes in because it is believed that tumors can use this pathway to promote desmoplasia in the surrounding stromal tissue, which in the case of PDA would prevent the tumor from accessing adjacent blood vessels. IPI-926 (Fig. 1) is a potent inhibitor of the Hedgehog signaling pathway, acting primarily by blocking the Smoothened (Smo) protein (EC_{50} = 7 nM). When treated with IPI-926 the KPC-tumors exhibited a reduction in tumor-associated stroma and unexpectedly, an increase in mean vessel density (MVD) in the tumors. When IPI-926 was used in conjunction with gemcitabine in the KPC mice there was a measurable increase in the intratumoral concentration of the drug which resulted in an increase in median survival from 11 days to 25 days, improved tumor response and a decrease in metastasis to the liver, compared to treatment with gemcitabine alone. Unfortunately, the increase in tumor-vascularization appears to be transient in that the MVD at the end of the treatment was similar to control. Nonetheless the study was successful in demonstrating that an improved response of PDA to chemotherapy can be achieved using agents that promote tumor-vascularization.

1 Olive, K.P. *et al.* (2009) Inhibition of Hedgehog signaling enhances delivery of chemotherapy in mouse model of pancreatic cancer. *Science* 324, 1457–1461

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1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2009.08.007