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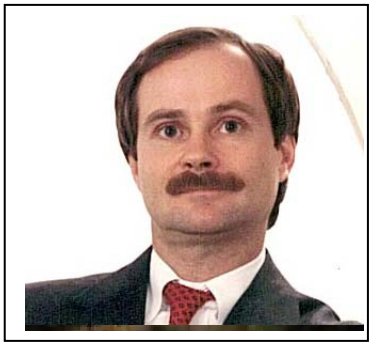

Research in our laboratory focuses on basic and translational studies related to pathobiology and therapy of pancreatic cancer. Our current studies are focused alone two lines of investigation. (1) We were first to report that interactions among STAT3, Ron kinase and TGFβ signaling contributes to progression of pancreatic cancer. Hyperactivity of STAT3 occurs as an early event in the development of pancreatic cancer and that there is reciprocal negative regulation of STAT3 and Smad activities. Ron kinase expression is induced as a late event in pancreatic cancer progression and cooperates with TGFβ signaling promotes tumor growth and invasion during a critical stage of cancer progression. Our goals are to further define the molecular networks activated by the TGFβ/Ron/STAT3 signaling axis and to do pre-clinical testing fro determining whether targeting these networks improves therapy. (2) Pancreatic cancer stem cells express high levels of CD44 that interacts with hyaluronan expressed by stromal cells. This interaction of CD44 and hyaluronan activates tumor promoting pathways, promotes resistance to therapy and activates pancreatic stellate cells that facilitates desmoplasia. Our research is directed at disrupting CD44-hyaluronan interaction with an overall aim of improving therapy by diminishing stromal/epithelial signaling, by inhibiting desmoplasia and by effectively targeting the cancer stem-cell population.

Recent Publications:

1. Zhao, S., Ammanamanchi, S., Lazor, J, Sperry, J and **Freeman JW**. Smad4-dependent TGF-β signaling suppresses RON receptor tyrosine kinase-dependent motility and invasion of pancreatic cancer cells. J. Biol. Chem. 283:11293-11301, 2008.
2. Zhao S, Kolaparthi VS, Lazor JW, Sperry J, Jin C, Cao L, and **Freeman JW**. Inhibition of STAT3Tyr705 phosphorylation by Smad4 suppresses TGFβ-mediated invasion and metastasis in pancreatic cancer cells. Cancer Res. 68:4221-4228, 2008
3. Gazitt Y, Venkatasubbarao K, Moncada K, Thomas C, **Freeman, JW**. Targeted therapy of human osteosarcoma with 17AAG or rapamycin: Characterization of induced apoptosis and inhibition of mTOR and Akt/MAPK/Wnt pathways. Int J Oncol 34, 551-562 2009
4. **Freeman, JW**, Wang, Y and Giles, F. Epigenetic modulation and attacking the hedgehog pathway. Cancer Biol. & Ther. 8:14, 1-3, 2009
5. Zhao, S., Cao, L, Wang, Y and **Freeman, JW**. Expression of oncogenic K-ras and loss of Smad4 synergize to induce the expression of EGFR and to promote invasion of immortalized human pancreas ductal cells. (In Press).

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