

Preclinical testing of novel treatments in pancreas cancer xenograft models

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Science, Sept 4, 2008

Scienceexpress

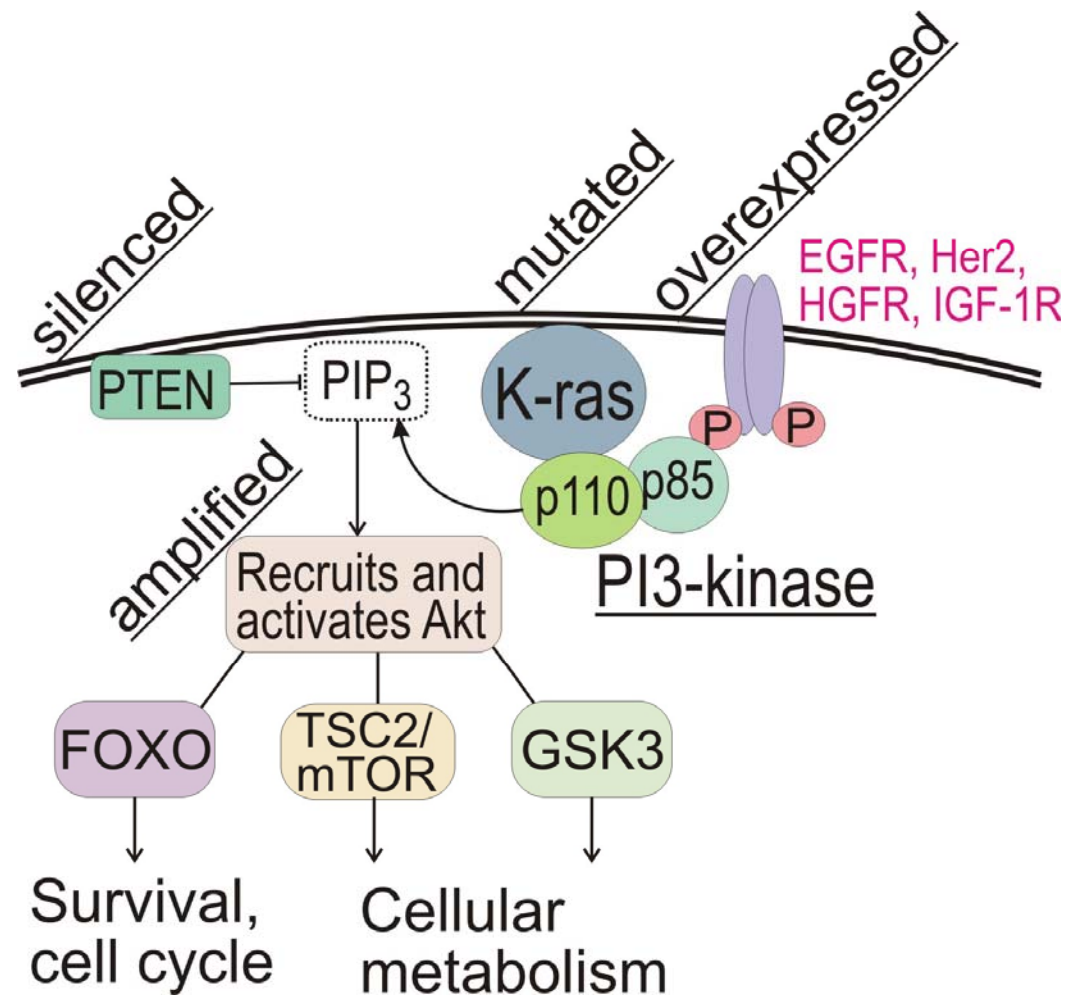
Research Article

Core Signaling Pathways in Human Pancreatic Cancers Revealed by Global Genomic Analyses

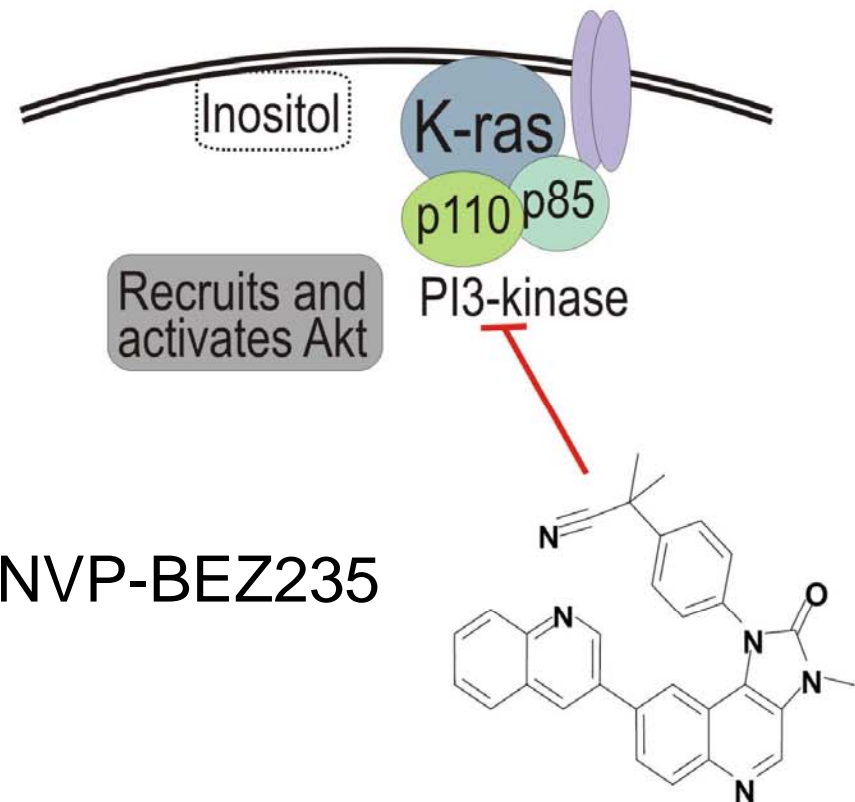
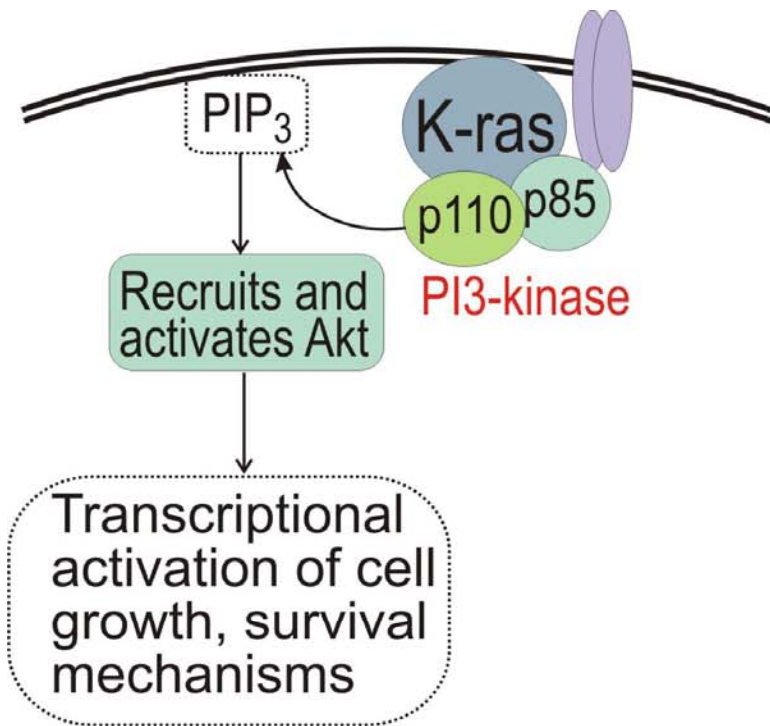
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At the genomic level, all pancreatic cancers are different. But they become similar if you think in terms of signaling pathways rather than individual genes

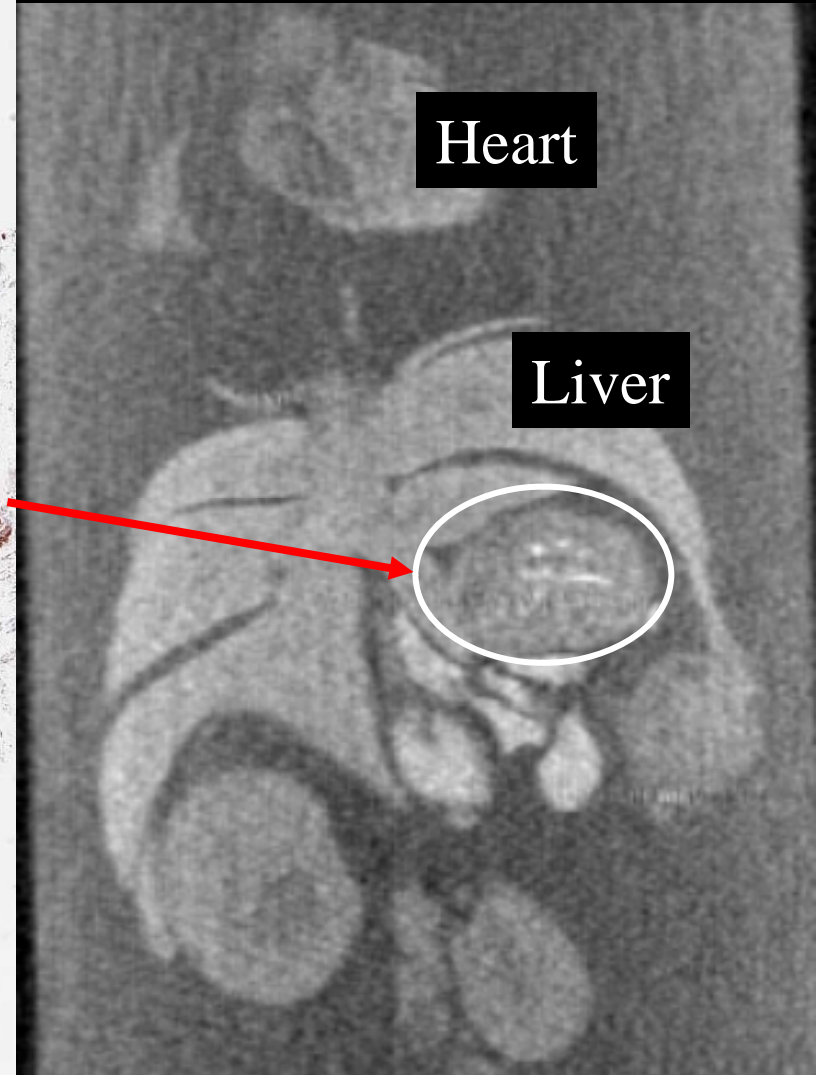
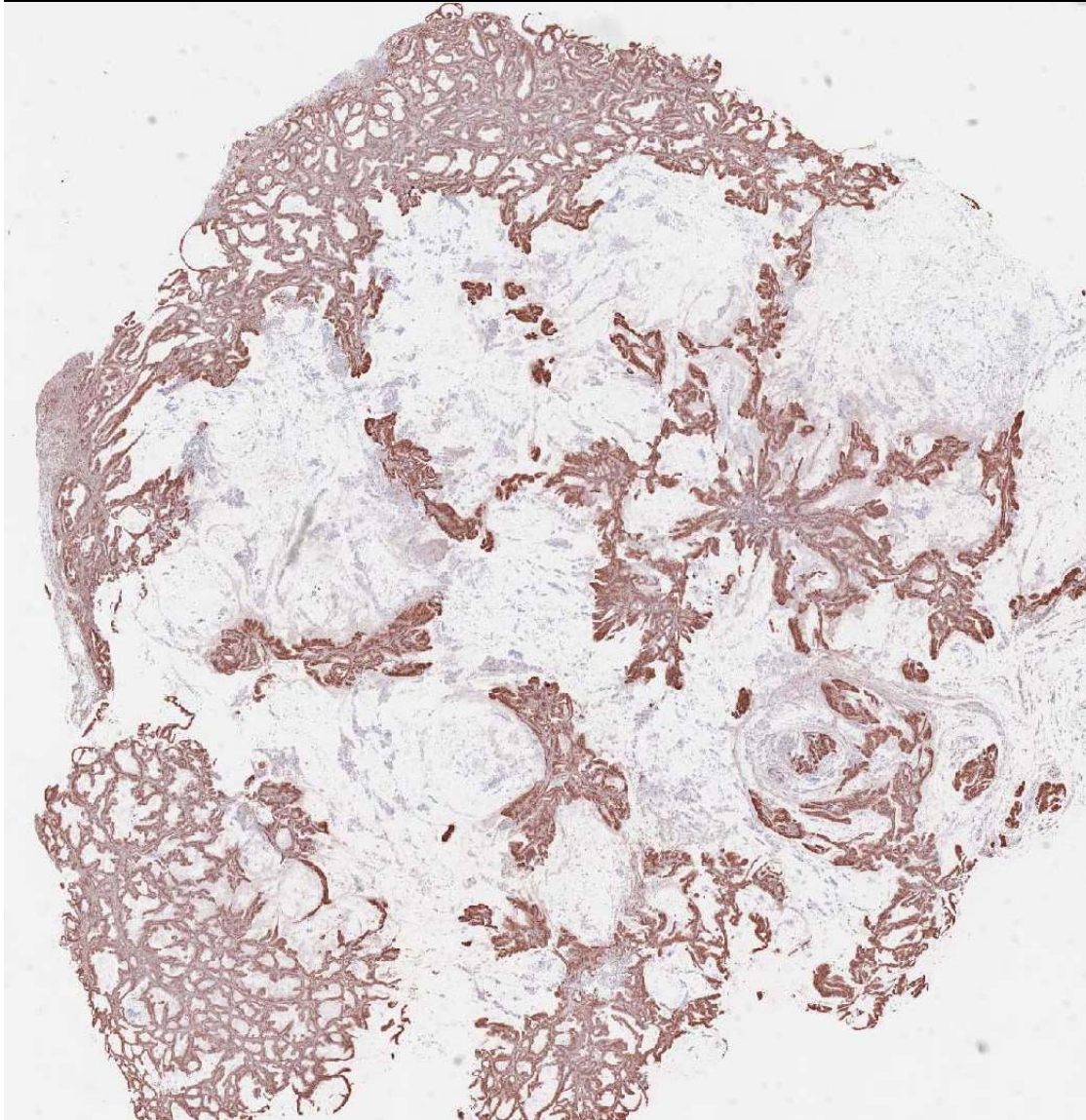
Several genetic changes can activate the PI3-kinase pathway in pancreatic cancer - only one is sensitive to EGFR inhibitors!



We now have drugs to block signaling pathways where the upstream effectors converge - but how safe are they?

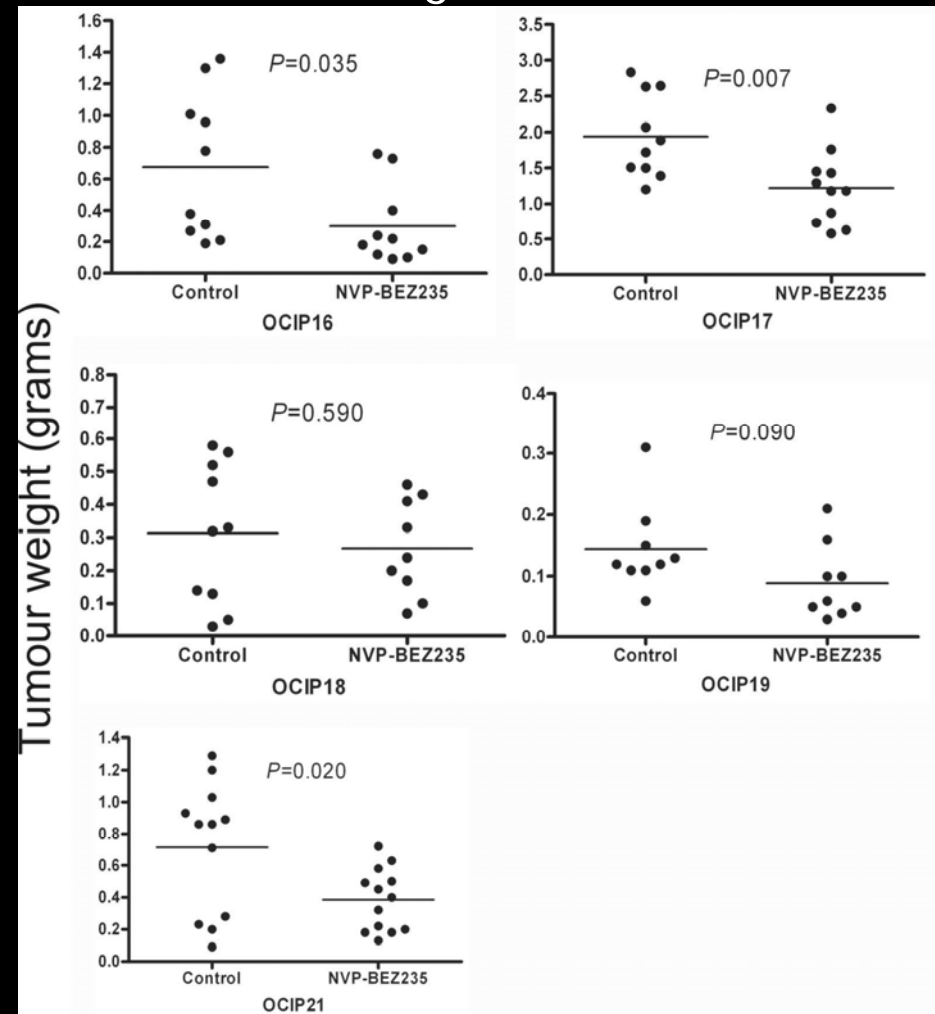
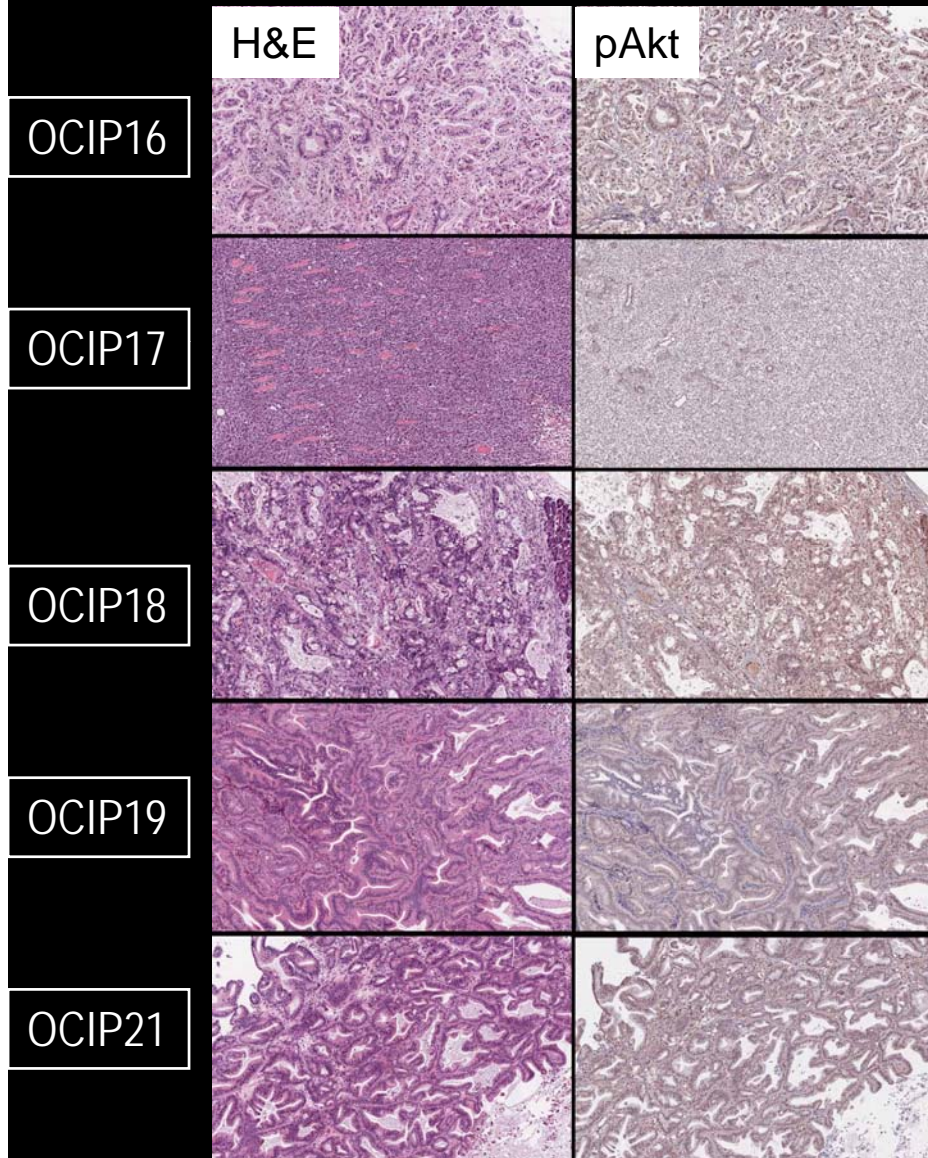


Simulating clinical trials using primary pancreas cancer xenografts, grown orthotopically



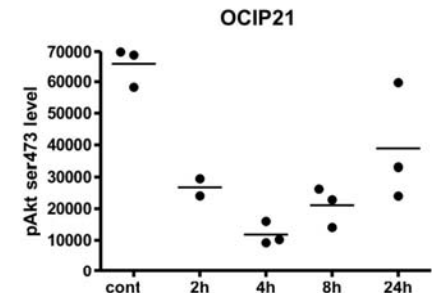
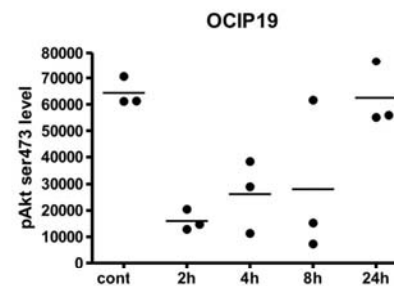
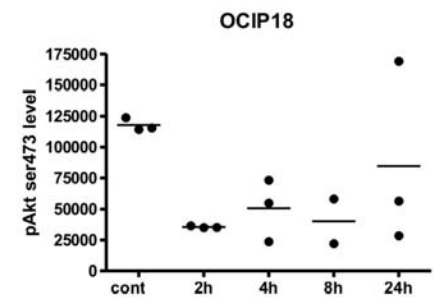
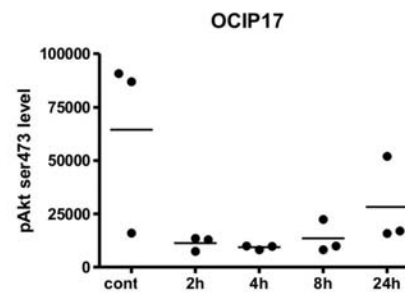
"Clinical trial" testing BEZ235 in 5 pancreas cancer patients as orthotopic implants in mice

Effects of daily dosing with BEZ235 on tumour weights



How far can you push chronic dosing with a PI3-kinase inhibitor?

- Following acute single dose, pAkt goes down, but recovers at 24 hr
- In chronic dosing, we still find pAkt at the end of treatment
- Mice lose weight at higher dose levels
- You cannot have 100% inhibition of a major signaling pathway 100% of the time!



Future Directions

- Drugs that block major downstream pathways are different from drugs that block surface receptors
- Alternative dose schedules
 - is intermittent high dose better?
 - are some cancers “addicted” to PI3-kinase?
 - if so, how do we identify them?
- How to combine with chemotherapy
- How do we develop combinations of molecular-targeted agents?
- Linking oncology with pancreatic cancer genomics