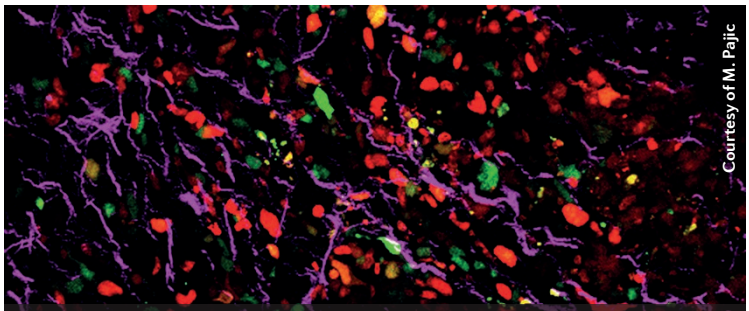
Nature Reviews Gastroenterology & Hepatology | Published online 15 Nov 2017; doi:10.1038/nrgastro.2017.163



PANCREATIC CANCER

Tailored therapy for pancreatic tumour subtype

Molecular subtypes have been identified in pancreatic ductal adenocarcinoma (PDAC), but few studies have examined whether these subtypes can be targeted therapeutically. In a new study published in *Gut*, an FDA-approved cyclin-dependent kinase (CDK) 4/6 inhibitor (palbociclib; PD-0332991) was found to be superior to standard therapy in treating a specific subtype of PDAC at multiple stages.

The molecular heterogeneity of PDAC contributes to the difficulty in developing new therapeutics for this aggressive disease. The CDK4/6 pathway, which includes retinoblastoma-associated protein 1 (RB1) and promotes G1-to-S phase transition, is one of the key signalling pathways that is dysregulated in PDAC. "We hypothesized that targeting pancreatic cancer subtypes that are dependent on CDK4/6 signalling may be a reasonable therapeutic approach," explains author Marina Pajic.

In 19 patient-derived PDAC cell lines, the investigators first found that expression levels of RB1 were the best predictor of *in vitro* sensitivity to palbociclib. Using a range of *in vitro* and *in vivo* subcutaneous, orthotopic and intrasplenic models, including patient-derived xenografts, the investigators then examined the therapeutic efficacy of palbociclib in PDAC, alone and in combination with gemcitabine. 2D and 3D assays were used to characterize the mechanism of action of palbociclib in pancreatic cancers that highly express RB1, and the effects on extracellular matrix (ECM) were also examined. *In vivo*, a fluorescence ubiquitylation cell cycle indicator was used to determine the cell cycle status of cells.

"We observed significant anti-invasive, anti-proliferative, pro-apoptotic and ECM-modulatory effects of palbociclib in 3D *in vitro* models of RB1-high pancreatic cancer … these effects were further confirmed *in vivo* [in mice]," reports Pajic. Palbociclib also facilitated remodelling of the ECM to improve therapeutic efficacy of gemcitabine in a subtype-specific manner and hindered metastatic colonization in the liver. "As robust efficacy was observed in multiple, independent models of RB1-high PDAC, RB1-based stratification could potentially facilitate a more tailored treatment approach for CDK4/6-targeting therapy in pancreatic cancer," says Pajic.

The investigators assessed RB1 protein level status in >500 human pancreatic cancer samples from three different cohorts. High RB1 levels were prevalent in a substantial proportion of patients with pancreatic cancer and were identified as an independent prognostic factor for patient survival. "Moreover, we observed good concordance in RB1 levels in the small set of available matched primary and metastatic tissue also analysed as part of this study, lending hope that metastases might be co-targeted with this type of therapy," concludes Pajic. "Pending further validation, use of a tissue-based assay for RB1 expression could be adapted for clinical application in diagnostics." As CDK4/6 inhibitors are already in non-biomarker-driven trials for pancreatic cancer with unselected patients, the researchers are also planning retrospective analyses of RB1 levels as a predictive biomarker for treatment response.

Iain Dickson

ORIGINAL ARTICLE Chou, A. *et al.* Tailored first-line and second-line CDK4-targeting treatment combinations in mouse models of pancreatic cancer. *Gut* http://dx.doi.org/10.1136/gutjnl-2017-315144 (2017)