Introduction:

Fibroblast activation protein (FAP) can be targeted on PET scan (FAPI-PET/CT) to detect small foci of pancreatic ductal adenocarcinoma (PDAC). Given its potential role in early diagnosis, we aimed to determine if FAP expression could distinguish high-grade dysplasia (HGD) and stage I PDAC from benign pathology.

Methods:

Cases for tissue analysis were contributed by the Australian Pancreatic Cancer Genome Initiative and included patients who had undergone pancreatic resection or biopsy between 1972 and 2007. We performed immunohistochemistry against FAP on tumour microarrays of intraductal papillary mucinous neoplasm (IPMN) with low-grade dysplasia (LGD; n=13), IPMN with HGD (n=11), stage I PDAC (n=25), stage II-IV PDAC (n=50) and chronic pancreatitis (CP; n=48). Stromal and epithelial FAP expression were scored separately using a semi-quantitative analysis, with a score > 3 representing positive expression for that cell type. Total FAP expression was calculated as the sum of stromal and epithelial scores. We compared mean FAP expression, as well as odds of any positive expression, between benign (LGD, CP) and malignant pathology (HGD, Stage I, Stage II-IV PDAC). We also prospectively recruited patients with pancreatic cystic neoplasm (PCN; n=5) to undergo FAPI-PET/CT and monitored progress for 18 months.

Results:

All groups of malignant neoplasia had higher total FAP expression than LGD and CP (median: LGD=4; CP=4; HGD=8, Stage I=7; Stage II-IV=7; $P<0.05$ for all bivariate comparisons). Each malignant group had higher odds of positive FAP expression than LGD (OR[95% CI]: HGD=7.2[1.23-62.0]; Stage I=18.4 [3.44-151]; Stage II-IV=14.4[3.57-67.6]) and CP (HGD=2.34[0.51-16.9]; Stage I=5.98 [1.45-40.9]; Stage II-IV=4.68[1.57-16.0]). Expression was primarily epithelial if present in LGD, stromal in CP, and on both cell types in malignant neoplasia. Focal avidity on FAPI-PET/CT was observed in 3 cases of PCN, and these were the same 3 to later show malignant features on histopathology, cytology, or interval imaging.

Conclusions:

The transition to malignant dysplasia in the pancreas is marked by changes in FAP, both in the amount of expression and cell type involved. This can be detected on FAPI-PET/CT and therefore may facilitate diagnosis of PDAC at a curable stage.

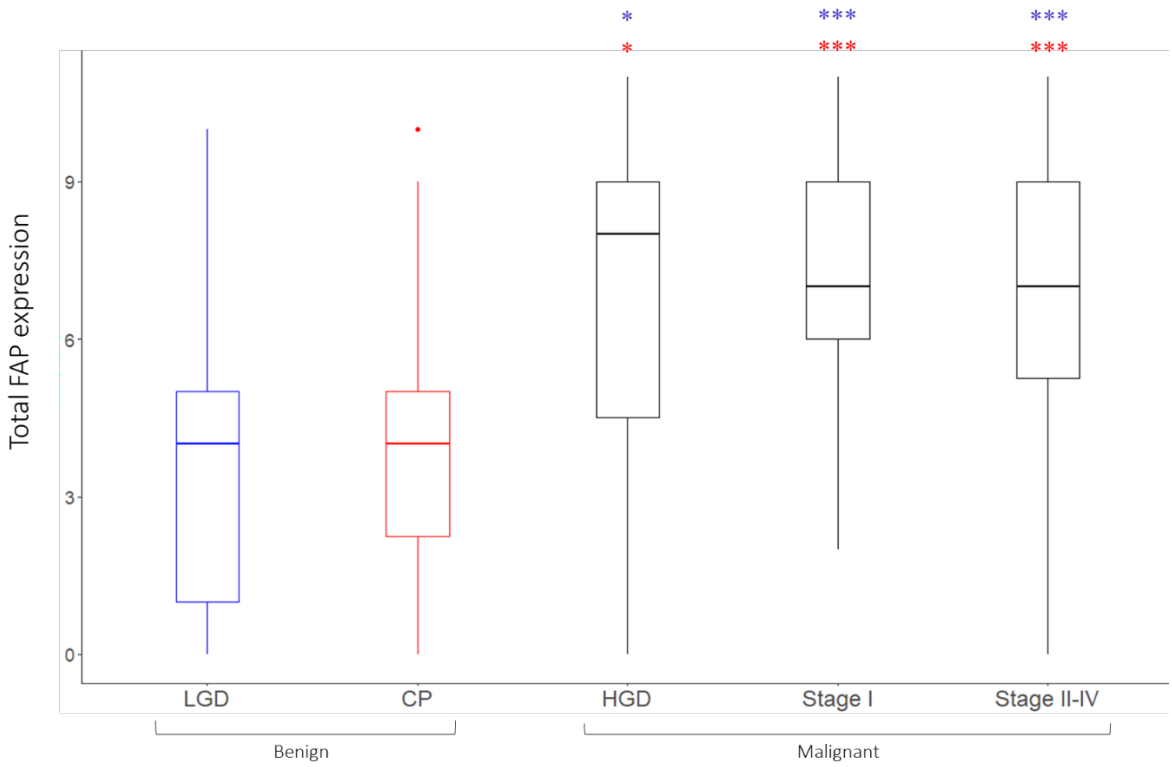

Figure 1. Box and whisker plots for total FAP expression among benign and malignant pathological groups. Degree of statistical significance for each bi-variate comparison is shown above each malignant group. LGD = Low-grade dysplasia; CP = Chronic pancreatitis; HGD = High-grade dysplasia. *=P<0.05, ** = P<0.01; ***= P<0.001. Blue = comparison with LGD; Red = comparison with CP.