Biomarker BI-010, a novel protein for diagnosing cholangiocarcinoma and monitoring response to treatment.

We have recently identified the novel marker BI-010 for use in the diagnosis of pancreatic tumours and cholangiocarcinoma. BI-010 has never been studied in any cancer ever before and nothing is known about its function in cells. We have used antibodies that recognise BI-010 to stain pancreatic tumour, chronic pancreatitis and normal pancreas tissue to determine how much BI-010 is expressed in these different tissues (Figure 1). These results demonstrated that there is very little expression of BI-010 in normal and chronic pancreatitis but very high levels in pancreatic cancer (Figure 2).

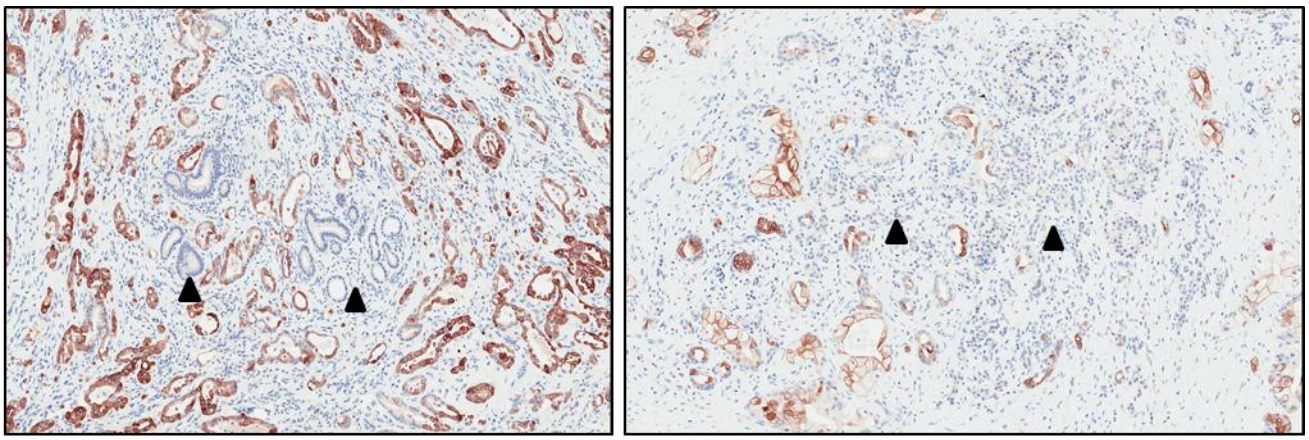

Figure 1: BI-010 detects pancreatic cancer (brown) but not normal pancreas (left panel) or chronic pancreatitis (right panel) (black arrowheads).

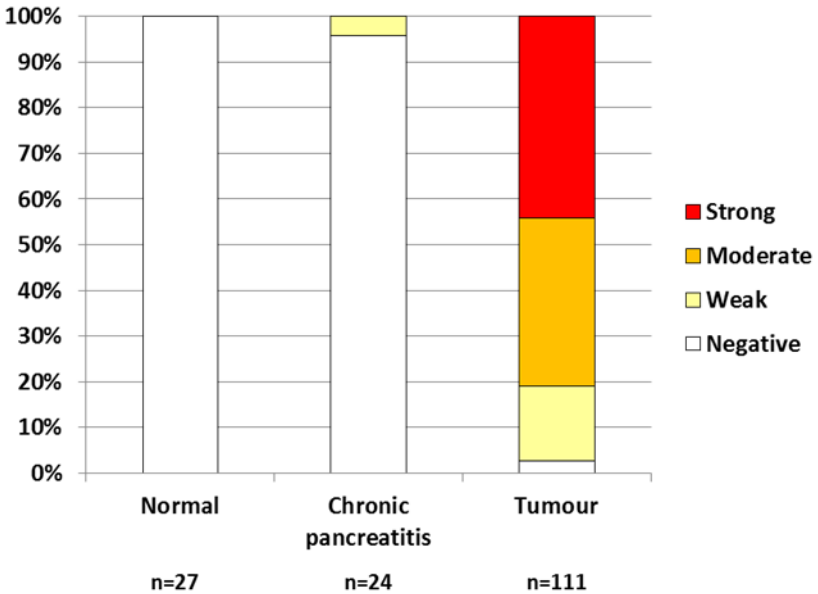

Figure 2: BI-010 is expressed in pancreatic cancer but not normal pancreas or chronic pancreatitis.

Although the pancreatic cancer data are very exciting, cholangiocarcinoma provides the biggest challenge for early and accurate diagnosis with current biomarkers only able to offer a diagnosis in ~30% of patients. The currently favoured marker for diagnosing cholangiocarcinoma, in tissue or biliary brushings, is IMP3 and so we have compared BI-010 to IMP3 in a number of cholangiocarcinoma cases. One of the key characteristics of a marker of cholangiocarcinoma is that it is not expressed in inflammatory reactive tissue often seen in patients with stents. In our cohort we evaluated the expression of IMP3 and BI-010 in the reactive, cancerous and dysplastic tissue of each slide where possible. An example of BI-010 expression in cholangiocarcimona is shown in Figure 3. The results from 9 patients are shown in Table 1 and suggest that BI-010 is much more sensitive at detecting dysplasia and cholangiocarcinoma than IMP3 although it may lack some of the specificity of IMP3 as it is weakly expressed in ~20% of reactive

tissue. We are currently evaluating a larger number of patients as well as the utility of BI-010 in cytology from biliary brushings.

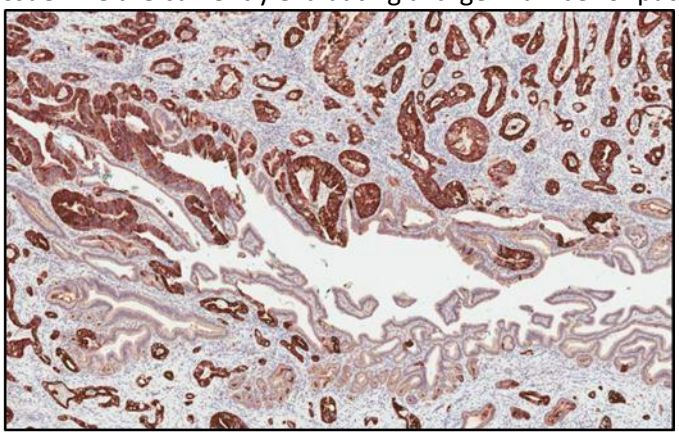

Figure 3: BI-010 detects cholangiocarcinoma (black arrowheads) but not reactive tissue.

	Reactive/inflammatory	Dysplastic	Cancer
IMP3	0% +ve 100% -ve	62% +ve 38% -ve	56% +ve 44% -ve
BI-010	21% weakly +ve 78% –ve 11% +ve pseudopyloric metaplasia	100% +ve 0% -ve	89% +ve 11% -ve

Table 1: A comparison of IMP3 and BI-010 in tissue from patients with cholangiocarcinoma. Tissue was assessed over 20 slides from 9 different patients.

Future plans

Our group, based at the Cancer Research UK Cambridge Research Institute has a well developed biomarker pipeline which promotes the rapid progression from tissue markers to a fluid based ELISA test. This pipeline is already funded by Cancer Research UK and is completed in collaboration with the Clinical Biochemistry Department, Addenbrookes Hospital where it is funded by NIHR. This close collaboration allows us to develop tests within an NHS environment providing a rapid means of translation into clinical practise. As BI-010 is a membrane protein we believe it will be secreted, sloughed off or shed into cyst fluid and possibly the blood making it ideal for an ELISA, fluid test. This would be cheaper and less painful than repeated biopsies for diagnosis and offers the chance to monitor response to treatment with a simple blood test. To develop a test we require recombinant protein which is not commercially available for BI-010 as it is a novel protein with very few reagents available. We have sourced a company who will produce sufficient protein for us to develop and test an ELISA in a robust way for £3.5K. We seek funding for this and the cost of antibodies to allow us to develop this test. In total we would require £5K to take this work forward rapidly in the short term. This pump priming would allow us to generate robust early data which is the first step towards larger, more widely tested study.