ImmunoTools *special* Award 2021

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Immunophenotyping pancreatic cystic lesions for cancer risk stratification

Background:

Pancreatic cancer (PC) is one of the most lethal malignant diseases worldwide and is estimated as the 7th leading cause of cancer-related death globally. Pancreatic adenocarcinoma is the predominant subtype of PC, representing ~90% of all PC cases. The 5-year survival rate for all pancreatic cancer stages combined is a dismal 5%, making it the only cancer with a 5-year survival rate in the single digits. PC is notoriously difficult to detect and diagnose at early stages, as it frequently manifests without early symptoms. Most patients will have incurable metastatic disease at initial presentation, with the vast majority of patients (~75%) dying within a year of diagnosis.

Generally, PC has a poor response to standard-of-care chemotherapy, with patients achieving only a minimal increase in overall survival. At present, fewer than 20% of newly diagnosed patients are eligible for surgery with curative intent. However, most surgical patients ultimately relapse and succumb to PC within two years. In the case of newer therapeutic approaches, there is currently only one FDA-approved immunotherapy for use in PC patients, which is the immune checkpoint inhibitor Pembrolizumab, highlighting the urgent requirement for additional immunotherapy targets for the vast majority of PC patients.

Pancreatic cystic lesions (PCLs) are typically fluid-filled structures that can be found within or on the surface of the pancreas. Most PCLs are detected incidentally during routine investigations, and ultimately account for ~13.5% of all PC diagnosed. While many PCLs are benign, others such as intraductal papillary mucinous neoplasms (IPMNs, 38% of PCLs) or mucinous cystic neoplasms (MCNs, 23% of PCLs), possess the ability to undergo malignant transformation and can therefore be regarded as precursor lesions of PC. IPMNs can be classified as low- or high-risk reflecting their

propensity to progress to malignancy, but risk stratification is imperfect and remains highly contentious in the field. The ability to identify which patients are at a higher risk of PC would enable earlier treatment interventions and improve patient outcomes, while avoiding unnecessary surgery and surveillance frequency for those at lower risk.

Surprisingly, when considering most cancers, including PC, arise in a background of inflammation, the immune cellular component of the cyst fluid is largely unknown, and its role in malignant progression remains uncharacterised.

Hypothesis:

This study hypothesises that low- and high-risk IPMN cyst fluid has differential effects on anti-tumour immunity and could be used for diagnostic and therapeutic purposes

Overall Objective:

To determine if low- and high-risk IPMN cyst fluid differentially promotes immunosuppression and subsequent risk of malignant progression.

Methodology:

The work carried out within this project will utilise specific innate and adaptive cell population markers to identify immune cell populations within low- and high- risk IPMN cyst fluid and matched patient serum via flow cytometry analysis. In order to characterise the immune cell infiltrate, the following markers (supplied by ImmunoTools) will be used to determine the presence of:

- *T cells:*	CD3, CD4 and CD8
- *NKT cells:*	CD3 and CD56
- *NK cells:*	CD56
- *Macrophages:*	CD68, CD14, CD16 and CD163
- *Monocytes:*	CD11b and CD14
- *B cells:*	CD19 and CD78
- *Dendritic cells:*	CD11c

The impact of cyst fluid on T cell activation and anti-tumour function will also be assessed via flow cytometry by examining the expression of activation and exhaustion markers (supplied by ImmunoTools) in T cells that have been cultured in the presence of IPMN cyst fluid.

Additionally, the differentiation and functional status of the immune cells will be examined via flow cytometry analysis through the use of functional markers including CD95, CD40 and CD66adecb (supplied by ImmunoTools).

The use of ImmunoTools reagents will invaluably aid in this research due to the vast array of immunological work demanded by this project, particularly immunophenotyping of IPMN cyst fluid via flow cytometry analysis. The support from the ImmunoTools Award 2021 would greatly assist me in my project and enable me to elucidate the immune component within PCLs and the subsequent identification of the role of the immune profile in malignant transformation to PC. The knowledge generated from this research project has high potential for translational use in the diagnostic and therapeutic setting of PC.

ImmunoTools *special* AWARD for **Rebecca Lyons** includes 10 reagents

FITC - conjugated anti-human CD14, CD56

PE - conjugated anti-human CD11b, CD11c, CD66adecb, CD95

APC - conjugated anti-human CD16, CD19, CD40

recombinant human rh IFNgamma

DETAILS more AWARDS