Evaluating the specificity of novel monoclonal antibodies for pancreatic ductal adenocarcinoma

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RESEARCH PLAN

A. RATIONALE

Cancer is currently one of the leading causes of death, with roughly 9.6 million deaths annually globally and about 18.1 million newly diagnosed cancer cases every year (4). One of the most lethal types, as well as one of the most common types (8), is pancreatic ductal adenocarcinoma (PDAC). PDAC is an exocrine cancer (35) that is derived from the ducts of the pancreas (11) and makes up roughly 90% of all pancreatic cancers (8), while also being the 12th most common cancer worldwide (16).

Unfortunately, PDAC only has a 9% 5-year survival rate (23), with pancreatic cancer as a whole making up 7% of all cancer deaths (20), making it the 4th deadliest cancer in the United States, (29) and by 2020, it is expected to be the 2nd deadliest (12). However, due to the current lack of reliable therapeutic options for PDAC in-clinic, tumor resection surgery is the best method to treat this cancer (24). Furthermore, since the pancreas is located near many major blood vessels (5), and PDAC is a hyper-aggressive cancer that typically asymptomatic until metastasizing has begun (9), opportunities for tumor resection surgery is rare. Only about 15-20% PDAC patients can undergo tumor resection surgery upon diagnosis (9). At the root of this low survival rate is indubitably the consistent failure to diagnose PDAC at earlier stages, as well as the frequent misdiagnosis of PDAC. Approximately 31.3% of people with PDAC are misdiagnosed with other types of cancers, often resulting in unnecessary surgeries/treatment before the mistake is realized (36). Obviously, the asymptomatic characteristics of PDAC also

play a role in these consistent late diagnosis of PDAC, but unavailability of reliable treatments and efficient techniques to diagnose PDAC also plays a role.

Previous studies attempting to delineate PDAC tumors through the use of antibody-antigen interactions have focused on the interaction between the monoclonal antibody (5B1) and the antigen Carbohydrate Antigen 19.9, or CA19.9 (38). However, CA19.9 is an antigen not exclusive to pancreatic cancers (30), or PDAC. CA19.9 it was first discovered to be expressed by colorectal carcinoma cells (30) and since shown to be expressed in other cancerous and non-cancerous conditions (33). Concerning antibody uptake, numerous studies have shown using PET scans that PDAC tumor can significantly take up the radiolabeled 5B1 (19). However, since CA19.9 is rarely present in asymptomatic populations (30), it is difficult to use this antigen-antibody interaction as suboptimal imaging agent for early diagnosis of PDAC. CA19.9 is also often shed into circulation rather than remaining on surface membranes of cells (15), resulting in relatively high radiation exposure to other parts of the body.

There have also been other relatively successful studies for imaging PDAC tumors that utilize the Carcinoembryonic Antigen (CEA) biomarker, however, similarly to CA19.9, it is typically not expressed by asymptomatic populations (6), and is also shed into circulation (1). In addition, CEA is also expressed by other cancers (17).

Since there is no reliable antigenic markers, it is important to identify new antigenic markers that are exclusive to PDAC and are not shed into circulation as the cancer progresses. This study investigates if two developed antibodies (AB1 and AB2) can successfully reach a PDAC tumor.

B.

RESEARCH QUESTIONs

Can monoclonal antibodies AB1 and AB2 detect PDAC in vitro and in vivo? How specific is the binding of antibodies AB1 and AB2 to PDAC?

Hypothesis

Since antibodies AB1 and AB2 were generated from organoids derived from PDAC, they will show a selective binding to PDAC *in vitro* or *in vivo*.

The ideal antibody would only bind to PDAC tissue and other malignant tissues, but not normal tissue.

C.

PROCEDURE

The handling of radioactively labelled antibodies, tissue and animal studies will performed by mentor. I will ONLY analyze the results from these experiments.

Risk and Safety:

All experiments will be performed by mentor. I will only analyzed the data generated. There will be no more than minimal risk associated.

Analysis of Data:

For data analysis, Microsoft Excel, the BIOSCAN AR 2000, imageJ, the 3D Slicer software (v4.8.1), and the Inveon Research Workspace software (Siemens Medical Solutions, Knoxville, USA) will be used.

The BIOSCAN AR 2000 will be used to construct graphs of radiochemical purity after performing the iTLCs, and then to more accurately determine the exact radiochemical purities.

After the PET scans are performed, individual image volumes will be constructed using the cropping function of the Inveon Research Workspace software. To determine the actual activity concentrations, in % ID/g, of the images, the counting rates will be converted using a system calibration factor, which will be derived from a mouse-sized water-equivalent phantom containing ^{89}Zr. To finish constructing the images, the 3D Slicer software will be used.

The weights of each tissue will be calculated, and the radioactivity bound to each tissue, will be measured in % ID/g, using the 2480 Wizard gamma counter (performed by mentor). Excel will be used to calculate the percentage of tracer uptake, expressed as % ID/g, as the activity bound to the tissue per tissue weight per the actual injected dose, decay-corrected to the time of counting. Relevant graphs and charts composed of the calculated data will then be constructed.

ImageJ will be used on the immunohistochemical stainings to quantify the percentage of stained tissue area versus the percentage of unstained tissue area. The higher the percentage of stained area in the stainings, the higher the presence of an antigen being targeted by the subject antibody in that specific tissue type.

D. **BIBLIOGRAPHY**

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