Immuno-PET

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“Immuno-PET” merges the high target selectivity and specificity of antibodies and engineered fragments toward a given tumor cell surface marker with the high spatial resolution, sensitivity, and quantitative capabilities of positron emission tomography (PET) imaging techniques. In this review, we detail and provide examples of the clinical limitations of current imaging techniques for diagnosing PDAC.

PDAC pancreatic cancer diagnostic imaging immuno-PET

1. Introduction

Despite multiple diagnostic and therapeutic advances, pancreatic ductal adenocarcinoma (PDAC) presents a high mortality rate, representing the fourth cause of cancer death in developing countries [1][2]. This lethality can be associated with a late diagnosis, caused by the absence of symptoms at an early stage of the disease. Most cases of PDAC are located in the head of the pancreas (70%), followed in frequency by the uncinate process (18.66%), body (10–20%), and tail (5–10%) [3][4]. At present, complete surgical resection is the only potentially curative treatment for these tumors. However, only the initial stages benefit from surgery, representing only 10–15% of patients [5][6][7]. In only 10% of cases, the lesion is limited to the pancreatic gland and surrounded by normal pancreatic tissue [5][8]. At the time of diagnosis, 40–50% of cases present distant metastases, and approximately 40% of patients present signs of locally advanced disease; therefore, surgery in these cases is not indicated.

Several imaging techniques for PDAC diagnosis are available, including computed tomography (CT), magnetic resonance imaging (MRI), or endoscopic ultrasound (EUS) [9][10]. While they are widely used in the clinic and are very useful for the diagnosis of PDAC, they present several limitations.

Unlike other neoplastic processes (breast, colon, prostate…) there are no effective diagnostic screening methods for PDAC. Furthermore, due to the absolute low risk of developing this disease, population screening is not indicated. Only, in those groups [11] considered to be at-risk population, monitoring by pancreatic MRI or Cholangio-MRI, and EUS is indicated to detect small precursor lesions, such as cystic neoplasms. In these cases, CT would provide a suboptimal degree of lesion detection, compared to EUS and MRI, besides being a source of radiation [11]. Additionally, the probability of detecting lesions using these techniques is low, no more than 20% [12][13].

The development of “omics” has identified potentially relevant alterations in PDAC that still need to be integrated into the clinical management of PDAC patients. This is due, in part, to the deficiency of non-invasive imaging biomarkers [14]. “Immunotargeted imaging” represents a novel, innovative, and attractive option that combines the

target specificity and selectivity of antibodies, and their variants, toward a biomarker with given imaging technique capabilities.

2. Novel Non-Invasive Immunotargeted Imaging Methods for PDAC

The revolution in cancer genomics has uncovered clinically relevant alterations that have yet to be integrated into patients' clinical management, in part due to the lack of non-invasive imaging biomarkers [14]. An innovative and attractive option is termed "immunotargeted imaging". This approach combines the target selectivity and specificity of antibodies and engineered fragments toward a given tumor cell surface marker with the capabilities of a given imaging technique.

2.1. Immunotargeted Imaging Features

To develop immunotargeted imaging, three features must be taken into account (Figure 1): I)Selection of a specific molecular target for imaging; II) Selection of the optimally engineered antibodies for imaging applications; III) Selection of a suitable radionuclide modality-specific imaging agent. For immunoPET. it is important to match the physical half-life of the positron-emitting radionuclide with the biological half-life of the antibody or fragment being used.

Figure 1. Representation of the three main components of immuno-PET techniques: target, antibodies, and radionuclides. Abbreviations: Ab-Antibody; Fab-Fragment antigen-binding; $F(ab')_2$-Fab dimer; scFv- single-chain variable fragment; Nb-Nanobody, ^{18}F-fluorine; ^{44}Sc-scandium; ^{52}Mn-manganese; ^{64}Cu-copper; ^{68}Ga-gallium; ^{76}Br-bromine; ^{86}Y-yttrium; ^{89}Zr-zirconium; ^{124}I-iodine [15][16]. Image generated with BioRender.

As shown in Table 1, membrane proteins that are overexpressed on tumor or tumor-associated cells have been potentially suitable for tumor-targeted imaging; other components of the tumor microenvironment, such as extracellular matrix proteins, have also been promising candidates for the development of diagnostic approaches in PDAC.

Table 1. Immuno-PET applications in PDAC.

PET Imaging Probes	Conjugation Strategy	Targets	Hallmark	Models	References
[^{64}Cu]Cu-DOTA-anti-PD-1 [^{64}Cu]Cu-NOTA-anti-PD-1 [^{64}Cu]Cu-NOTA-anti-PD-L1	Lysine-based random	PD-1/PD-L1	Imaging of immune checkpoints	Orthotopic KRAS murine PDAC	[17]
[^{89}Zr]Zr-Df-10D7 (anti-CDCP1 mAb)	Lysine-based random	CUB Domain-Containing Protein 1 (CDCP1)	CDCP1 regulates migration, invasion, and extracellular matrix degradation	Patient-derived subcutaneous and orthotopic xenografts (PDX) mice	[18]
[^{64}Cu]Cu-PCTA-cetuximab	Lysine-based random	Epidermal Growth Factor Receptor (EGFR)	EGFR is overexpressed in a wide variety of cancers	Resectable orthotopic xenograft mouse model with human PC XPA-1 cells	[19]
[^{89}Zr]Zr-Df-MVT-2163 (human HuMab-5B1 Ab)	**Lysine-based random**	**CA19-9 (Sialyl Lewis A)**	**CA19-9 is the most commonly used serum tumor marker for PDAC**	**Patients with primary PDAC and metastases (Phase 1)**	[20][21]
[^{64}Cu]Cu-NOTA-NJB2 (nanobody)	Sortase-Mediated Radiolabeling	Alternatively spliced EIIIB (EDB) domain of fibronectin tumor extracellular matrix and neovasculature	Fibronectin is a glycoprotein that forms a major constituent of tumor extracellular	(K-ras$^{LSL.G12D/+}$; p53$^{R172H/+}$; PdxCre) KPC mouse models of PDAC	[22]

PET Imaging Probes	Conjugation Strategy	Targets	Hallmark	Models	References
			matrix and neovasculature		
[^{89}Zr]Zr-Df-LEM2/15 (anti-MM1-MMP mAb)	Lysine-based random	MT1-MMP	Metalloprotease MT1-MMP is overexpressed in many tumors and associates with tumor growth, invasion, metastasis, and poor prognosis	Subcutaneous xenograft mouse model with Capan-2 cells, and subcutaneous and orthotopic PDX mice.	[23]
[^{89}Zr]Zr-Df-MEHD7945A (duligotuzumab)	Lysine-based random	EGFR and Receptor tyrosine-proteinase kinase erbB-3 (HER3)	EGFR and HER3 are highly expressed in PDAC, marking this aggressive disease with poor survival rates	Subcutaneous xenograft mouse model with AsPC-1 cells	[23]
[^{124}I]-A2cDb (anti-PSCA 2B3 A2 cys-diabody) [^{124}I]-A11 Mb (anti-PSCA minibody)	Direct iodination	Prostate stem cell antigen (PSCA)	PSCA is also overexpressed in pancreatic carcinoma	Subcutaneous PDX mice	[24]
[^{64}Cu]Cu-NOTA-3B4 (single chain Fv)	Lysine-based random	Receptor for advanced glycation end products (RAGE)	RAGE is overexpressed in human pancreatic tumors; it is a critical promoter in the transition of premalignant epithelial precursors (PanIN) to PDAC	Balb c/nude mice bearing Panc02 tumors. No PET study, only ex vivo biodistribution.	[25]
[^{89}Zr]Zr-Df-ALT-836 (anti-human TF mAb)	Lysine-based random	Tissue factor (TF)	Overexpression of TF in pancreatic cancer has been correlated with high tumor grade, the primary disease's extent, and local and	Subcutaneous xenograft mouse model with BxPC-3 or PANC-1 cells	[26]

PET Imaging Probes	Conjugation Strategy	Targets	Hallmark	Models	References
			distant metastatic invasion.		
[^{64}Cu]Cu-NOTA-heterodimer-ZW800 (bispecific immunoconjugate of CD105 and TF Fab′ antibody fragments)	Lysine-based random	Endoglobin (CD105) and TF	CD105 is a cell surface glycoprotein expressed on endothelial cells, and its overexpression in cancer has been linked to angiogenesis, metastasis, and cancer progression	Subcutaneous xenograft mouse model with BxPC-3 or PANC-1 cells	[27]
[^{89}Zr]Zr-Df-5B1 (anti-CA19.9 mAb)	Lysine-based random	CA19-9	CA19-9 is the most commonly used serum tumor marker for PDAC	Orthotopic xenograft mouse model with CAPAN-2 cells	[28]
[^{89}Zr]Zr-Df-1A2G11 (anti-IGF-1R mAb)	Lysine-based random	Insulin-like growth factor-1 receptor (IGF-1R)	IGF-1R is a transmembrane receptor of the tyrosine kinase class involved in cell growth, apoptosis, and tumor invasion in cancer	Subcutaneous xenograft mouse model with MIA PaCa-2 or BxPC-3 cells	[28][29]
[^{64}Cu]Cu-DOTA-MAb159 (anti-GRP78 mAb)	Lysine-based random	Glucose-regulated protein (GRP78)	Cell-surface GRP78 expression, an immuno-globulin heavy-chain binding protein, has been detected in pancreatic cancer.	Subcutaneous xenograft mouse model with BxPC-3 cells	[30]
[^{64}Cu]Cu-DOTA-11-25 (anti-Mesothelin mAb)	Lysine-based random	Mesothelin (MSLN)	MSLN is a cell differentiation-associated glycoprotein, overexpressed in	Subcutaneous xenograft mouse model with CFPAC-1 or BxPC-3 cells	[31]

PET Imaging Probes	Conjugation Strategy	Targets	Hallmark	Models	References
			various cancers, including PDAC		
[^{89}Zr]Zr-Df-TSP-A01 (anti-transferrin receptor mAb)	Lysine-based random	Transferrin receptor (TfR)	TfR is upregulated on the cell surface of many cancer types, including pancreatic cancer	Subcutaneous xenograft mouse model with MIA PaCa-2 cells	[32]
[^{89}Zr]Zr-Df-059-053 (human anti-CD147 mAb)	Lysine-based random	CD147	CD147 (so-called EMMPRIN) is a transmembrane protein of the immunoglobulin superfamily and is expressed in many types of tumors, including PDAC	Subcutaneous xenograft mouse model with MIA PaCa-2 cells	[33]
[^{64}Cu]Cu-NOTA-panitumumab-F(ab′)$_2$	Lysine-based random	EGFR	EGFR is overexpressed in a wide variety of cancers	Subcutaneous xenograft mouse model with PANC-1 cells, and subcutaneous and orthotopic PDX OCIP23 mice	[34]
[^{89}Zr]Zr-Df-5B1 (anti-CA19.9 mAb)	Lysine-based random	CA19-9	CA19-9 is the most commonly used serum tumor marker for PDAC	Subcutaneous xenograft mouse model with BxPC3 cells	[35]
[^{124}I]-A2cDb (anti-CA19.9 diabody)	Direct iodination	CA19-9	CA19-9 is the most commonly used serum tumor marker for PDAC	Subcutaneous xenograft mouse model with BxPC3 or CAPAN-2 cells	[36]
[^{64}Cu]Cu-NOTA-ALT-836 (anti-human TF mAb)	Lysine-based random	Tissue factor (TF)	Overexpression of TF in pancreatic cancer has been correlated with high tumor grade,	Subcutaneous xenograft mouse model with BxPC-3, PANC-1, or ASPC-1 cells	[37]

PET Imaging Probes	Conjugation Strategy	Targets	Hallmark	Models	References
			the primary disease's extent, and local and distant metastatic invasion.		
[^{64}Cu]Cu-DOTA-2A3 (2A3 is an anti-CEACAM6 nanobody) [^{64}Cu]Cu-DOTA-2A3-mFc (2A3 fused with a murine Fc fragment) [^{64}Cu]Cu-DOTA-9A6 (anti-CEACAM6 murine mAb)	Lysine-based random	Carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM-6)	CEACAM-6 is a cell surface glycoprotein known to be highly expressed in most cancers	Subcutaneous xenograft mouse model with BxPC3 cells	[38]
[^{124}I]-H310A (anti-CEA scFv-Fc)	Direct iodination	Carcinoembryonic antigen (CEA)	CEA is a GPI-linked glycoprotein overexpressed in gastrointestinal epithelial tumors, including PDAC	Subcutaneous xenograft mouse model with BxPC-3, CAPAN-1, or HPAF-II cells	[37]

Antibody-based PET imaging probes for PDAC ordered by the most recent publication date. Bioconjugation strategy has been categorized into three methods: lysine-based random, site-specific via sortase-mediated reaction, and direct iodination. Antibody-based PET imaging probes reaching clinical trials are highlighted in bold.

With the rise of immunotherapy in recent years, PET imaging of immune checkpoint inhibitors (ICIs) may serve as a robust biomarker to predict and monitor responses to ICIs, complementing the existing immunohistochemical techniques [39][40]; it has been described that PET imaging using antibodies against the programmed cell death receptor 1 (PD-1)/programmed cell death ligand 1 (PD-L1) pathway can be a useful method for evaluating PD-L1 expression in orthotopic pancreatic cancer models [41]. To date, most of the PET imaging probes have been designed to target PDAC tumors in preclinical models (Figure 2), and only one study has been conducted with an [^{89}Zr]Zr-labeled human monoclonal antibody in patients with pancreatic cancer or other CA19-9 positive malignancies [42].

Figure 2. ImmunoPET–CT of MT1-MMP metalloproteinase in a preclinical model of PDAC. (**A**) Coronal, (**B**) axial, and (**C**) sagittal views of fused Immuno-PET and CT images of an orthotopic pancreatic patient-derived xenograft mouse. White arrows indicate tumor location. The imaging probe used was [^{89}Zr]Zr-DFO-LEM2/15, a mAb developed against the MT1-MMP metalloproteinase [23]. Owing to the central role that this metalloproteinase plays in collagen-induced gemcitabine resistance, this probe could be used for the early prediction of resistance to gemcitabine in metastatic PDAC patients.

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