Recent Pre-Clinical Advancements in Nuclear Medicine: Pioneering the Path to a Limitless Future.

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Abstract

Oncology theranostic practice is an intriguing field of molecular medicine with major implications for individualized treatment. Recent decades have seen significant advancements in this discipline, especially in the use of 177-Lu-radiolabeled to treat neuroendocrine tumors. Somatostatin analogs and, more recently, prostate-specific membrane-antigen targeted radionuclide treatment to treat prostate cancer. The development of this strategy was made possible by the encouraging clinical outcomes seen in these indications. Nuclear medicine is positioned for success due to the ongoing identification of new molecular actors in carcinogenesis, the creation of innovative radiopharmaceuticals, and the possible pairing of immunotherapy and theranostics drugs notable developments. There are three main components to theranostics' approach in oncology: (1) repurposing nuclear medicine drugs for different applications, (2) enhancing currently available radiopharmaceuticals, and (3) creating novel theranostics agents for tumor-specific antigens.

Keywords

Nuclear medicine, Theranostics, Oncology, Immunotherapies.

Introduction

Modern chemotherapy originated with histological staining techniques, but it has since taken on a role in science and real-world application. Therefore, it did not It just so happened that dyes like methylene blue and trypan red were utilized in the first encouraging chemotherapy trials. Early chemotherapy can therefore be thought of as color therapy. [1,2]

In modern oncology, this innovative idea—creating targeted, effective, and harmless chemotherapy drugs to improve patient care—remains extremely relevant even after a century.[3]

In the 1980s, the development of targeted medicines and cytotoxic chemotherapy was hailed as a revolutionary advance in oncology. Both approaches have significantly elevated cancer patients' survival rate and improved their quality of life. [4,5]

The use of tyrosine kinase inhibitors (TKIs), a class of pharmaceutical drugs that block the transduction signal of protein kinases, is one such innovative advancement. The number of TKIs approved by the Food and Drug Administration (FDA) is currently above 50, and their use in cancer treatment is still expanding quickly.[6]

With the remarkable success of TKI therapy in recent years, immunotherapeutic approaches have transformed the field of oncology. Immuno checkpoint inhibitors (ICIs), such as antibodies against cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death-1 (PD-1), have emerged as a crucial turning point in the treatment of cancer. [7,8,9]

Pre-Existing-Based Molecules

The recent approvals of Luthatera for adult patients with advanced neuroendocrine tumors (NETs) and Pluvicto for advanced PCs have established a strong basis for peptide receptor radionuclide therapy (PRRT). These approvals represent important turning points in the PRRT industry. Using a molecule labeled with 68Ga (68Ga-DOTA-TOC and 68Ga-PSMA-11) for the quantitative imaging of tumor antigen expression is an essential initial step in this theranostic method. The same or a similar molecule labeled with a therapeutic molecule is given once the findings of a positron emission tomography (PET) scan indicate that the 68Ga-labeled molecule in the tumor has been positively enriched. [10,11]

Repurposing and Optimization of FDA-Approved Drugs

Somatostatin Receptor 2 (SSTR2) Targeting

Somatostatin receptor expression imaging with Lutathera (177Lu-DOTA-TATE) is a validated method for assessing if PRRT is suitable for NET patients.[12]

Since most NETs have somatostatin receptors (SSTRs) on their cell surface, radiolabelled somatostatin analogues (SSAs) can be used with them. Lutathera is the first FDA-approved PPRT after the NETTER-1 study, which revealed an impressive PFS rate at month 20 of 65.2% compared to 10.8% for octreotide alone. [13,14]

Mechanisms such as the downregulation or alteration of SSTRs, enhanced DNA damage repair mechanisms, or treatment-induced hypoxia could contribute to PRRT resistance. The list of recently developed molecules targeting SSTR2 is presented in **(Table 1)**. [15.16]

Radiotracer	Type of Molecule	Disease Model	Study
153Sm-DOTA-TATE	Agonist	CA20948, pancreatic tumor	Pre-clinical
225Ac-DOTA-TATE	Agonist	H727 and H69cells, Lung neuroendocrine neoplasms	Pre-clinical
212Pb-DOTAMTATE	Agonist	AR42J, pancreatic tumor Neuro-endocrine Tumors	Pre-clinical First in humans
64Cu-SARTATE	Agonist	AR42J, pancreatic Tumors Neuro-endocrine tumours	Pre-clinica First in humans
67Cu-SARTATE	Agonist	AR42J, pancreatic tumour (metastasis) IMR32, neuroblastoma Multifocal Meningioma	Pre-clinical Pre-clinical Clinical
177Lu-DOTA-LM3	Antagonist	AR42J, pancreatic Tumors Neuro-endocrine tumour's	Pre-clinical First in humans
161Tb-DOTA-LM3	Antagonist	AR42J, pancreatic Tumors	Pre-clinical
177Lu-AAZTA5-LM4	Antagonist	HEK293-SST2R transfected cells	Pre-clinical
177Lu-satoreotide tetraxetan	Antagonist	AR42J, pancreatic Tumors	Pre-clinical

Table 1- A Summary of most recent molecules targeting somatostatin Receptors developed for theranostics application.

DOTA-TATE-Based Radiotracer

SARTATE-Based Radiotracer

A part from the intriguing field of clinical research on targeted α-therapy, there exist other potential approaches that are presently in development. Using alternative SSA sarcophagine octreotate (SARTATE) tagged with copper-64 and copper-67 (64Cu/67Cu-SARTATE) is one noteworthy method. The 64Cu/67Cu pair has the distinct benefit of being a "true" theranostic agent, in contrast to 68Ga and 177Lu.

Recent research has further demonstrated this strategy's viability in a neuroblastoma metastatic model. These preclinical findings support its continued clinical development, especially considering 64Cu-DOTATATE's recent licensure as an SSTR imaging alternative.[18]

Radiotracers Based on SSTR2 Antagonists

An innovative and promising strategy to enhance radiation delivery and anticancer effects is to use antagonists instead of agonists. Unlike an agonist, which can only bind the SSTR in an active state, an antagonist can bind the SSTR in an inactive state. Higher tumor uptake and radiation delivery were also shown in preclinical mice models using 177Lu-DOTA-LM3 (antagonist) as opposed to 177Lu-DOTA-TOC (agonist). In comparison to 177Lu-DOTA TATE, Lu-satoreotide tetraxetan therapy improved the median survival of mice with SSTR-positive tumors and had favourable safety. Because 161Tb emits conversion and Auger electrons and has decay qualities comparable to 177Lu, it has become a promising candidate in the field of therapeutic labelling. When compared to 177Lu-DOTA-LM3, 161Tb-DOTA-LM3 showed a survival advantage in mouse models of PDAC Tumors. [19,20]

Prostate-Membrane-Specific Antigen (PSMA) Targeting

A major advancement in the field of prostate cancer that is resistant (mCRPC) was made in 2022 when the FDA approved 177Lu-PSMA 617 (PluvictoTM, Advanced Accelerator Applications USA, Inc. (AAA, a Novartis subsidiary; Millburn, NJ, USA)) for the treatment of patients with PSMA-positive metastatic castration. The FDA's approval was supported by the phase III VISION trial's strong findings, which demonstrated that 177Lu-PSMA 617 improved PFS and OS when compared to the control group. The most recently developed molecules are presented in (**Table 2**). [21,22]

Radiotracer	**Type of Molecule**	**Disease Model**	**Study**
225Ac-PSMA-617	**Peptide**	**mCRPC mCRPC mCRPC mCRPC**	**Clinical study(51patients) Clinical study(26patients) Clinical study(73patients) Clinical study (3cohorts;91,40,18 patients)-Tandem with 177Lu-PSMA-617**

177Lu-L1	**Peptide**	**PC3PIP (PC xenografts)**	**Pre-clinical**
225Ac-L1	**Peptide**	**PC3PIP (PC xenografts)**	**Pre-clinical**
213Bi-L1	**Peptide**	**PC3PIP (PC xenografts)**	**Pre-clinical**
211At-3-Lu	**Peptide**	**PC3PIP (PC xenografts)**	**Pre-clinical**
177Lu-EB-PSMA-617	**Peptide with EB moiety**	**mCRPC, mCRPC HepG2 xenografts, HCC Adenoid cystic carcinoma**	**Clinical study(4patients) Clinical study(28patients) Pre-clinical Clinical(30patients)**
177Lu-LNC1003	**Peptide with EB moiety**	**22Rv (PC xenografts)**	**Pre-clinical**
225Ac-PSMA-TO-1	**Peptide+ albumin binder (naphthyl group)**	**C4-2(PC xenografts)**	**Pre-clinical**
225Ac-PSMA-DA1	**Peptide+ albumin binder (iodophenyl butyric acid derivative)**	**LNCaP (PC xenografts) LNCaP (prostate xenografts)**	**Pre-clinical Pre-clinical**
227Th-BAY2315497	**Antibody**	**PC cell lines and PDXs VCap, ST1273(PC xenografts)**	**Pre-clinical Pre-clinical**

Table 2- Most recent pre-clinical / clinical development using PSMA-targeting agents.

68Ga-PSMA-11/177Lu-PSMA-617 Repurposing

In addition to its role in PC, PSMA overexpression has been identified in various other tumor types, such as glioblastoma or hepatocellular carcinoma (HCC), making them potential candidates for 68Ga-PSMA-11 imaging and 177Lu-PSMA-617 treatment. Seven patients with multiple liver lesions showed high uptake in pilot investigations involving HCC patients. Thirty-six of the thirty-seven lesions had higher uptake of Only 10 lesions were 18F-FDG-avid, compared to 68Ga-PSMA-11. Pre-clinical studies in mice with HCC have shown that a single injection of 177Lu-PSMA-617 can suppress tumor growth and prolong survival, laying the foundation for potential clinical applications in HCC treatment. In this way, 40 HCC patients were examined with 68Ga-PSMA-11, which showed higher specificity than CT for detecting intra- and extra-hepatic lesions, suggesting a potential as a diagnostic agent.

Molecules Expected to Be Translated Soon into Clinical Practice

Fibroblast Activation Protein Inhibitor (FAPI)

Unlike many clinically available tracers that directly target tumour cells, the imaging of the fibroblast activation protein (FAP) allows for the detection of cancer-associated fibroblasts (CAFs). FAP is highly expressed by CAFs, and 90% of epithelial tumours and metastases are positive; meanwhile, it is absent in normal adult tissues.

Gastrin-Releasing Peptide Receptor (GRPR)

Recent evidence indicates that the gastrin-releasing peptide receptor (GRPR), sometimes referred to as bombesin receptor subtype 2 (BB2), shows significant promise as a target for theranostic applications. GRPR is mostly expressed in the pancreas. When GRPR attaches to its ligand, the gastrin-releasing peptide, or GRP, it activates the gastrointestinal hormone and triggers other physiological processes. Prostate, breast, and stomach cancers have been shown to express GRPR. This discovery, along with the low physiological expression of GRPR, makes a compelling case for the use of GRP-derived fragments in theranostics. [23,24]

Major Recent Advances in the Theranostics Field

New medication development and innovative strategy investigation, including the use of immunotherapies in conjunction with other treatments, are now recommended in addition to the medicines that have already improved patient care or show promise moving forward. The most recent compounds created for theranostic use are displayed in **(Figure 1).**

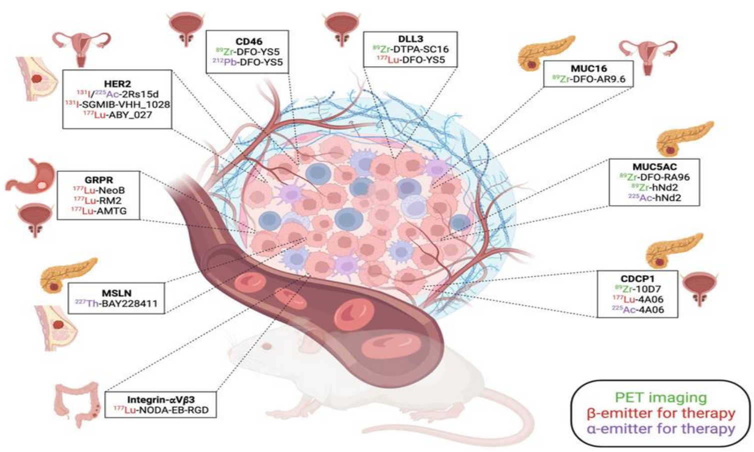

Figure 1 - Summary of the recent pre-clinical development in the theranostic field.

Conclusion

The possible coupling of nuclear therapy with immune checkpoint inhibitors is among the field's most noteworthy recent achievements. Researchers and medical professionals are advancing patient care by utilizing the complimentary mechanisms of immunotherapy and radiation the path for cutting-edge therapeutic approaches that have enormous potential to improve cancer results.

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