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Review Article

Transforming Oncology: Cutting-Edge Developments In Radionuclide Therapies

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A B S T R A C T

Main objective of this study was to list out the recent advancement in radionuclide therapy.Cancer rates are increasing globally at a rapid pace. This trend is influenced by a combination of factors, including the aging and expansionof the population, as well as shifts in the prevalence and distribution of key cancer risk factors.Current cancer treatments, such as surgery and external beam radiotherapy, become less effective once a tumor has spread. Targeted radionuclide therapy (TRT) uses radio-labeled biologics or other carriers to precisely deliver a cytotoxic dose of radiation to inoperable or metastatic cancer, emitting Auger electrons, β-particles, or α-particles.β-particle-emitting RPT agents have highly promising clinical and preclinical preliminary results with RPT agents using other α-particle-emitting radionuclides has reignited interest in RPT.Recent advancements in radionuclide therapies have shown promising results in various cancers. Astatine-211 (211At) has demonstrated potential in treating paraganglioma, acute leukemia, and thyroid cancer. 225Ac-DOTATATE has shown promise for gastroenteropancreatic neuroendocrine tumors. Bismuth-213 (213Bi) and Lead-212 have also shown positive results in treating different cancers, including small lung cancer. Boron neutron capture therapy (BNCT), recently FDA-approved, has improved outcomes in head and neck cancer. Additionally, nanomaterials are being used to deliver radionuclides more effectively, enhancing treatment precision and patient outcomes.

In conclusion there is a wide advancement in radionuclide therapy in today's world and preparing for the future therapies. Radionuclide therapy is a door for the multitude of cancers and thus is a potential treatment option for those with advanced cancers and failed established therapeutics.

Keywords: Cancer, Radiopharmaceuticals Therapy, Radionuclide, Radioisotope, Clinical Trials,

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INTRODUCTION

Cancer has been the primary cause of death worldwide in recent decades. In 2018, there were in approximately 18.1 million new cancer cases, and 9.6 million deaths occurred due to disease [1]. Currently, surgery, chemotherapy, and radiation (RT) are the mainstays of traditional cancer treatment procedures. Incomplete figures indicate that 50–70% of cancer patients, particularly those in advanced stages, receive radiation therapy (RT) to prevent the cancer from getting worse. By employing a high radiation dosage, radiation therapy, or RT, can destroy tumor cells or impede their growth by causing damage to their DNA, so halting the advancement and reappearance of cancer [2]. In contemporary cancer treatment, radiotherapy, which encompasses radioisotope therapy (RIT) and external beam radiation therapy, is a crucial and widely utilized method. It is vital to minimize radiation exposure to healthy tissues while accurately delivering radioisotopes to tumor sites to enhance the effectiveness of RIT. Over the past decade, researchers have developed versatile nanomaterials that leverage the enhanced permeability and retention (EPR) effect—resulting from the leaky blood vessels in tumors—to deliver radionuclides directly to tumors. To mitigate side effects, these nanomaterials are often designed to be biodegradable and responsive to specific conditions within the tumor microenvironment, such as pH and enzyme activity. Among the various radioisotopes used in radiotherapy, beta particles tend to cause more significant damage to cancer cells compared to gamma rays, due to their higher linear energy transfer (LET). Common radioisotopes like 131I, 177Lu, 186Re, and 188Re, which emit both beta

and gamma radiation, have been widely used in clinical RIT. Notably, 32-phosphorus (32P) stands out as a suitable option since it is a pure beta-emitting radioisotope that can bind to the DNA of cancer cells, allowing it to accumulate in tumors and effectively induce cell death. Therefore, creating biocompatible and biodegradable nanomaterials for the targeted delivery of 32P presents a promising strategy for cancer RIT [3].

In the last five years, the FDA has approved three radiopharmaceuticals for targeted radionuclide therapy (TRT): Radium-223 (Xofigo®) for treating metastatic castration-resistant prostate cancer (mCRPC) with symptomatic bone metastases; Lutetium-177 (LUTATHERA®) for somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (NETs); and Iodine-131 (AZEDRA®) for metastatic pheochromocytoma or paraganglioma. While many patients can achieve effective control of local or locoregional tumours, significant rates of distant relapse remain in some patient groups, creating opportunities for further research in TRT development [4].

Radiation in nanomedicine not only enhances the biological activity of engineered nano systems but also serves as a promising technique for synthesizing various nanoparticles. This eliminates the need for additional initiators, catalysts, or harmful chemicals that would require complete removal from the final product after synthesis. Consequently, this approach results in more cost-effective and safer end products [5].

Recent advancements in radionuclide chemistry, the physical properties of radionuclides, and biological insights into specific molecular targets have enabled the integration of disease imaging with radionuclide therapy in recent years.[6]

Using radioisotopes in cancer therapy offers several advantages over traditional methods. α-particles can specifically target and destroy tumor cells while sparing nearby healthy tissue, as their range in human tissue is very limited, typically less than 0.1 mm[7]. α emitters induce highly effective cell damage by causing DNA double-strand breaks and cluster damage, owing to their high energy and significant linear energy transfer (LET) . Notably, these effects are mostly unaffected by the cell cycle phase or oxygen levels. [8,9,10]. Thus, α radioisotopes can provide a therapeutic option for patients who are resistant to therapy with β− or gamma radiation or chemotherapeutic medications [11,12,13].Research shows that while tens of thousands of β− particles are needed to kill 99.99% of cells, only a few α particles can achieve the same effect. This is due to the higher energy and localized damage caused by α particles, making them more effective in cell destruction [14].

Table 1: List of the FDA Approved Radionuclide Therapies [15]

FDA Approved Radionucliods	Therapeutic Emmision	Approximate Emmision Range In Tissue	Radionuclioide Half Life
Samarium-153	β−	0.4	46.5 hrs
Yttrium-90	β−	5.30	64.1 hours
Iodine-131	β−	0.8	8.0 days
Lutetium-177	β−	0.62	6.6 days
Astatine-211	α	0.05	7.2 hrs
Lead-212	β−	<0.1	10.6hrs
Bismuth-212	α	0.05	1.0 hrs
Radium-223	α	0.05-0.08	11.4 days
Actinium-225	α	0.05-0.08	10.0 days
Thorium-227	α	0.05-0.08	18.7 days

Radionuclide Emission Properties

When choosing a radionuclide for therapeutic use, it's important to consider its physical characteristics, including half-life, radiation energy, type of emissions, daughter products, production method, and radionuclide purity. Ideally, the physical half-life should range from 6 hours to 7 days. Radionuclides with longer half-lives will expose the target tumor and surrounding tissues to radiation for extended periods. Conversely, those with very short half-lives face challenges related to delivery timing; adequate retention time is necessary to ensure that the emissions reach the tumor target effectively [15].

Radionuclides used in radionuclide therapy (RPT) mainly include beta-particle emitters (0.2 keV/m), alpha-particle emitters (50–230 keV/m), and Auger electron emitters (4–26 keV/m). A summary of various radionuclides and their characteristics can be found in Table 1. Each type of radiation causes ionization along its path and is completely absorbed by the cell. This radiation can damage cells both directly and indirectly. To achieve optimal destruction of targeted cells while minimizing ionization effects on healthy cells, it's important to consider the distance particles travel and the energy they deposit in the cells [16,17].

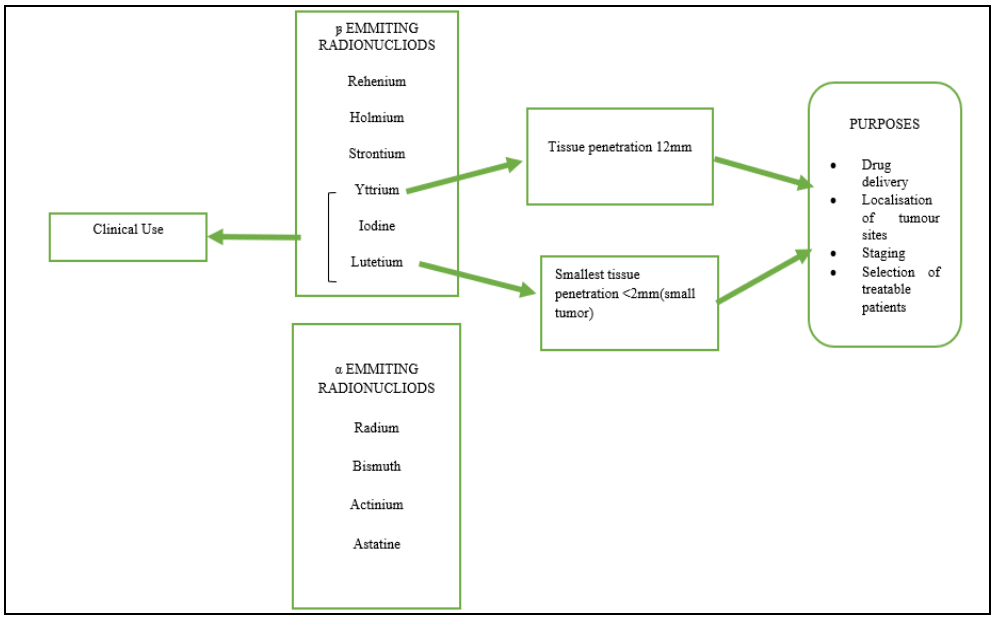

Figure 1: Types of Radionuclides and their Characteristics.[16-18]

1. Advancement and Applications of Astatine-211(^{211}at) Radionuclide Therapy: Ongoing Clinical Trials:

Astatine was first synthesized at the University of California, Berkeley, in 1940, and the initial report of its use in human treatment appeared as early as 1954. Astatine gets its name from the ancient Greek word "astatos," which means "unstable," because it has no stable or long-lived isotopes. It is commonly known as "the rarest element on Earth". Astatine is found naturally in the Earth's crust only in isotopes 214–219, which exist in equilibrium with uranium. It is estimated that there are only about 0.07 grams of astatine present at any given moment, posing a challenge for availability. However, significant quantities of astatine-211 (211At) can be generated using cyclotrons [19].

Ongoing clinical trial on astatine-211(^{211}AT)

Fred hutchinson cancer center in seattle: The anti-CD45 murine IgG1 monoclonal construct 211At-BC8-B10 has progressed to three early-phase clinical trials (NCT03128034, NCT03670966, NCT04083183) following encouraging preclinical results, including successful outcomes in canine models.

The NCT03128034 trial is evaluating escalating doses of 211At-BC8-B10 in conjunction with allogeneic hematopoietic cell transplantation (HCT) for patients with high-risk acute leukaemia or myelodysplastic syndrome, enrolling 40 participants. Preliminary findings indicate a 1-year overall survival rate of 43% and a recurrence-free survival rate of 35%.

The NCT04083183 trial aims to determine the optimal dose of total body irradiation combined with 211At-BC8-B10 for patients with non-malignant conditions, with graft rejection as the primary endpoint. As of July 2021, a total of 43 patients have been treated in these trials, while results from NCT04083183 are still pending [20-21].

Osaka, japan, [^{211}AT] naat in thyroid cancer: At Osaka University, research has shown that astatine-211 ([211At] NaAt) is effectively absorbed by thyroid cells due to its similarity to iodine, which is used in treating differentiated thyroid cancer. Adding 1% ascorbic acid to the [211At] solution improved radiochemical purity and increased uptake in thyroid cancer cells. Preclinical toxicity studies have supported the launch of a clinical trial.

The investigator-initiated phase I trial (NCT05275946) of TAH-1005 ([211At] NaAt) for targeted alpha therapy began this year, with three of the planned eleven participants already enrolled. The study, which involves a single intravenous dose for patients with papillary or follicular thyroid cancer unresponsive to standard treatments, will escalate doses from 1.25 MBq/kg to a maximum of 10 MBq/kg. The trial aims to evaluate safety, pharmacokinetics, absorbed dose, and efficacy, to determine the recommended dose for a phase II trial [22-23].

Fukushima, japan, ^{211}AT-MABG: Fukushima Medical University Hospital has launched a phase I dose escalation trial of [211At] astatine-benzylguanidine ([211At] MABG) for patients with malignant pheochromocytoma or paraganglioma. Based on promising preclinical results, the trial begins with a dose of 0.65 MBq/kg, with potential escalation to 1.3 MBq/kg and 2.6 MBq/kg. Included 18 participantsin study. The primary goals are to assess safety and determine the maximum tolerated dose (MTD), while secondary objectives include pharmacokinetics, urinary radioactivity excretion, and efficacy measures like urinary catecholamine response rate and progression-free survival (PFS) [24].

Table 2: Current Clinical Trial In Astatine-211(^{211}at) Going On In Following Institutes [19-24]

Organization reference	Clinical scenario	Objectives of study	TAT-agent/ Carrier	Target area	Primary outcome
Fred Hutchinson Cancer Center, Seattle, USA	Multiple Myeloma	Feasibility and safety	^{211}At-OKT10-B10	CD38	MTD
Fred Hutchinson Cancer Center, Seattle, USA	Multiple Myeloma	Dose escalation	^{211}At-OKT10-B10	CD38	MTD
Fred Hutchinson Cancer Center, Seattle, USA	HCT for non-malignant disease	Dose escalation	^{211}At- BC8-B10	CD45	Graft rejection
Fred Hutchinson Cancer Center, Seattle, USA	High-risk acute leukemia or MDS	Dose-escalation	^{211}At- BC8-B10	CD45	Toxicity
Fred Hutchinson Cancer Center, Seattle, USA	High-risk ALL, AML, MDS or Mixed-phenotype acute leukemia	Dose-escalation	^{211}At- BC8-B10	CD45	Toxicity, MTD
Fukushima Medical University, Japan	Malignant pheochromocytoma	Dose escalation	^{211}At-MABG	Norepinephrine transporter	Toxicity, MTD
Osaka University Hospital, Suita, Japan	Thyroid cancer	To establish recommended dose for Phase II trial	[^{211}At] NaAt	NIS	Treatment-related adverse events

2. Dotatate Targated Alpha Therapy (Tat) Has Shown Promising Results In Trials

In targeted alpha therapy (TAT), there are only a limited number of suitable α-particle emitters, with 225Ac and its short-lived daughter nuclide 213Bi being the most prominent in current clinical research. Furthermore, the gamma decays resulting from the radioactive decay of 225Ac can be leveraged for SPECT imaging, which enhances the potential for theranostic applications in nuclear medicine[25].

While interest in 225Ac as an α-emitting radiolabel has been growing, significant clinical investigations into many radiopharmaceutical candidates are hindered by the limited global availability of 225Ac. This review aims to enhance the understanding of 225Ac by detailing its fundamental physical properties and outlining its current and potential production methods [25].

a) Actinium-225 targeted alpha particle therapy in prostate cancer:

Prostate cancer (PCa) is the most common non-skin cancer in men and poses a major public health risk. In 2024, about 299,010 men in the U.S. are expected to be diagnosed, making up roughly 29% of all cancers. Its lethality is largely due to its ability to metastasize, resulting in serious health complications and fatalities.Particles are highly charged particles with a short travel range of 40-100 µm, making them ideal for accurately and locally targeting cancer cells[26].

Background: Actinium-225 (225Ac) prostate-specific membrane antigen (PSMA) radioligand therapy (RLT) is emerging as a promising treatment for metastatic castration-resistant prostate cancer (mCRPC). This study aims to evaluate the safety and anti-tumour efficacy of 225Ac-PSMA RLT across a large, diverse cohort from multiple international centres.

Methods:This retrospective study pooled data from seven institutes across India, Australia, South Africa, and Germany, analyzing patients of all ages and performance statuses diagnosed with prostate adenocarcinoma who received 8 MBq of 225Ac-PSMA RLT for mCRPC. Prior treatments included taxane chemotherapy, androgen-receptor inhibitors, 177Lu PSMA RLT, and radium-223. The primary outcomes were total survival (TS) and progression-free interval (PFI).

Findings: Between January 1, 2016, and May 31, 2023, 488 men with metastatic castration-resistant prostate cancer (mCRPC) underwent a total of 1,174 cycles of 225Ac-PSMA radioligand therapy (RLT), with an average of two cycles per patient. The average age of participants was 68.1years,Prior treatments included cabazitaxel, enzalutamide, docetaxel, abiraterone,radium-223 and 177Lu-PSMA RLT (32%). 225Ac-PSMA RLT demonstrated significant antitumor effects and shows promise for patients who have already received other treatments. While xerostomia was a frequent side effect, severe bone marrow and kidney toxicities were less common [27].

b) Phase 11 clinical trial on 225ac dotatate showed emergent results in advanced stage gastroenteropancreatic neuroendocrine tumor patients:

The clinical evidence for targeted alpha therapy (TAT) in gastroenteropancreatic neuroendocrine tumours (GEP-NETs) is limited, and there is currently no long-term efficacy data available. In a pilot study of 32 patients, we previously reported promising results for 225Ac-DOTATATE TAT in GEP-NET patients.From April 2018 to June 2021, we enrolled 83 consecutive patients (34 women, 49 men; mean age 54 years, range 25–74). The first treatment with 225Ac-DOTATATE was administered in April 2018, and the last patient was recruited in June 2021. Patients received systemic 225Ac-DOTATATE (100-120 kBq/kg body weight) along with a renal protection protocol intravenously every eight weeks.

This study assessed the effectiveness and safety of 225Ac-DOTATATE TAT in 83 adults, including those previously treated with 177Lu-DOTATATE. Key findings include:

- Response Rates: 2.7% achieved a complete response, 43.2% had a partial response, and 20% experienced disease progression.
- Survival: The overall survival rate at 12 months was 85.3%, and at 24 months it was 67.6%, with a median overall survival below 50% at 27 months.
- Safety: Most patients reported mild side effects, with only one case of grade 3 thrombocytopenia. Disease-related complications accounted for 11 deaths.
- Overall, 225Ac-DOTATATE TAT shows promise, particularly for patients resistant to prior treatments, justifying further Phase III trials to compare its efficacy with 177Lu-DOTATATE [28].

3. Bismuth-213 (213bi) Is A Radioisotope Used In Targeted Alpha Therapy (Tat) For Treating Various Cancers

a. Therapeutic potential of 213Bi-conjugated single-domain antibodies in a preclinical ovarian cancer model

Targeted alpha-particle therapy (TAT) offers a potential solution for HER2-positive metastatic cancer, overcoming resistance to standard treatments. This study combines the alpha-emitter bismuth-213 ([213Bi]) with HER2-targeting single-domain antibodies (sdAbs), evaluating their targeting, binding, and cytotoxicity on HER2-positive cells. In vivo, biodistribution was tracked using serial dissections and Cherenkov/micro-SPECT/CT imaging. The therapeutic potential and toxicity of [213Bi]Bi-DTPA-2Rs15d were tested in a HER2-positive peritoneal metastasis model.

In vitro, [213Bi]Bi-DTPA-2Rs15d selectively targeted HER2-positive cells, and in mice, it showed high tumour uptake within 15 minutes and low normal tissue accumulation. Treatment with [213Bi]Bi-DTPA-2Rs15d, alone or with trastuzumab, significantly improved median survival. This study is the first to successfully label an HER2-sdAb with [213Bi], demonstrating its stability, specific tissue accumulation, and potential as a novel radio-conjugate for TAT, either alone or combined with trastuzumab, for treating HER2-positive metastatic cancer [29].

b. Use of 213bi-labeled pyridyl benzofuran for targeted α-therapy of amyloid-β aggregates in alzheimer's disease:

Alzheimer's disease is a neurodegenerative disorder with few treatment options, marked by biomarkers like amyloid-β aggregates that cause oxidative stress and neuronal damage. Targeted alpha-therapy (TAT), effective in metastatic cancer, uses localized alpha-particle emission to disrupt disease-related covalent bonds while limiting radiation exposure to healthy tissues. We hypothesized that TAT could similarly break covalent bonds in amyloid-β aggregates, aiding natural plaque clearance mechanisms.as shown in FIG2[30].

Methods: We synthesized a 213Bi-chelate–linked benzofuran pyridyl derivative (BiBPy) and successfully produced [213Bi]BiBPy, attaining a specific activity of 120.6 GBq/μg, a dissociation constant of 11 ± 1.5 nM, and a logP value of 0.14 ± 0.03.

Results: In experiments with brain homogenates from APP/PS1 double-transgenic male mice (6–9 months old), [213Bi]BiBPy significantly reduced amyloid-β plaques, confirmed by enzyme-linked immunosorbent and Western blot assays, with a half-maximal effective concentration of 3.72 kBq/pg.

Conclusion: These findings indicate that [213Bi]BiBPy can effectively reduce amyloid plaque concentration in vitro, supporting its potential for targeted alpha therapy and future in vivo studies[30]

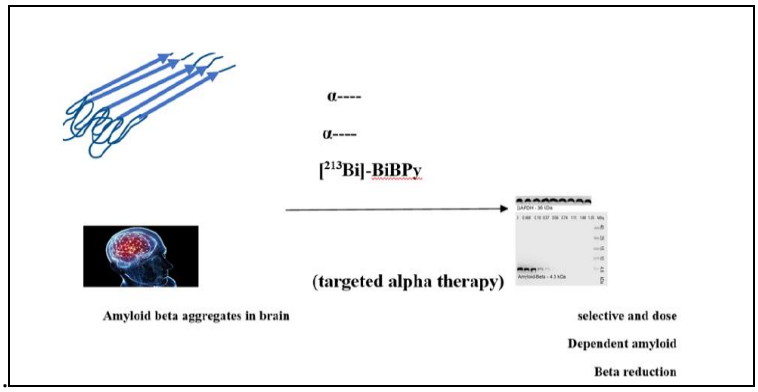

Figure 2: 213bi-Labeled Pyridyl Benzofuran Acting on Amyloid-B Aggregates In Alzheimer's Disease

LEAD 212(212PB) PROMISING RADIONUCLIDE FOR TARGETED THERAPY:

Lead-212, has a half-life of 10.64 hours, it is a short-lived alpha-emitting daughter, offer advantages in the synthesis and purification of complex radiopharmaceuticals by

minimizing radioactivity loss during preparation. Additionally, the findings from preclinical studies, which evaluate therapeutic and tolerance doses, as well as insights from recent clinical trials involving targeted radiopharmaceuticals, are also highlighted [31].

Lead-212 Radio-darpinTherapeutic (RDT) targeting delta-like ligand 3 (DLL3) demonstrates encouraging preclinical anti-tumor efficacy and tolerability in small cell lung cancer:

DARPins (Designed Ankyrin Repeat Proteins) are a versatile class of small binding proteins effective against various tumor targets.Lead-212 ([212Pb]) is an alpha-particle-emitting isotope with a 10.6-hour half-life, So it is ideal for targeted alpha therapy.

Methods: We created single-cysteine DARPin variants for site-specific conjugation using maleimide chemistry. Picomolar affinity binders against DLL3 were selected via ribosome display, conjugated to DOTAM chelator, and radiolabelled with 212Pb for in vivo studies. To reduce kidney retention, we engineered surface-optimized variants, which were further refined using affinity maturation and half-life extension (HLE) strategies.

Results: In vivo studies showed improved biodistribution with reduced kidney accumulation and unchanged tumour uptake compared to parental binders. HLE strategies enhanced tumour retention, improving the tumour-to-kidney ratio significantly. Substantial tumor regression was observed in mouse models, with no significant adverse effects at doses of up to 40 µCi of 212Pb-DLL3.

Conclusions: These preclinical results support 212Pb-Radio-DARPin therapeutics targeting DLL3 as a promising option for small cell lung cancer (SCLC), demonstrating significant anti-tumour activity and a good safety profile, while showcasing the RDT platform's versatility for future therapies[32].

1. BORON NEUTRON CAPTURE THERAPY (BNCT)

Radiation therapy is a well-established treatment for cancer, needed by at least 50% of patients. While traditionally viewed as a local treatment, it can lead to serious complications, particularly in cases of recurrent cancer, complicating symptoms and treatment. Advances in biological and physical technologies have led to new solutions, one of which is boron neutron capture therapy (BNCT), based on boron nuclear reactions [33].

In BNCT, when neutrons irradiate boron-10 (10B), it becomes unstable boron-11 (11B), which then decays, emitting alpha particles (4He) and lithium-7 (7Li) recoil particles, along with a small amount of gamma rays, releasing significant energy.This approach involves the preferential uptake of non-radioactive boron agents by tumor cells, followed by neutron exposure to irradiate the targeted area. This process releases high-energy particles that specifically destroy tumour cells within a limited range, as shown in FIG 3[33].

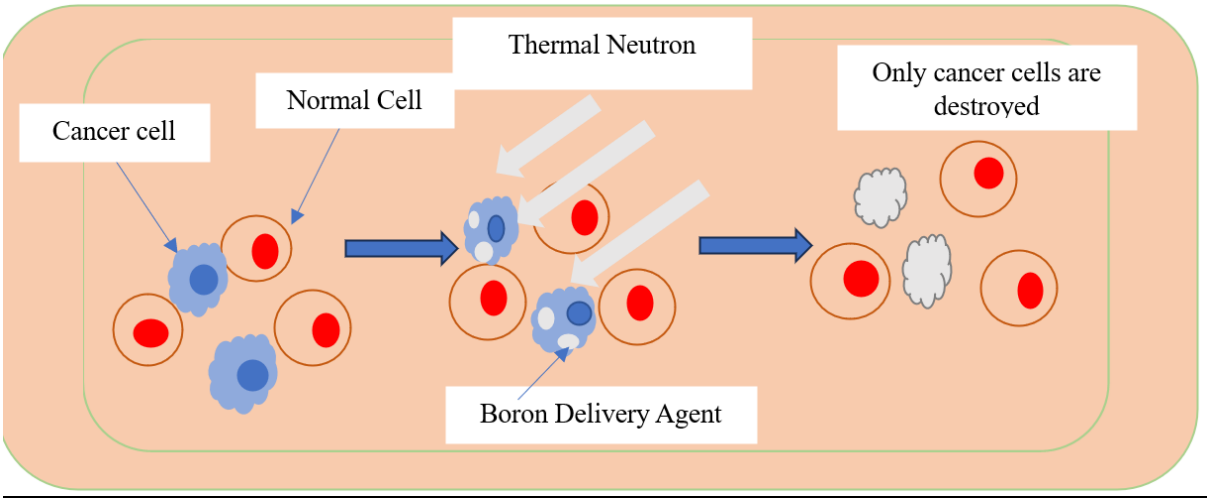

Figure 3: Schematic Diagram of Boron Neutron Capture Therapy (Bnct) Selective Killer Tumor Cells.

a) Clinical trials for treating recurrent head and neck cancer with boron neutron capture therapy:

Head and neck (HN) cancer is endemic in Taiwan, with locally recurrent cases after full-dose irradiation posing significant challenges. Boron neutron capture therapy (BNCT) may offer durable local control with acceptable toxicity. The Tsing-Hua Open Pool Reactor (THOR) at National Tsing-Hua University supports research on Boron Neutron Capture Therapy (BNCT).

From 2010 to 2013, we conducted a phase I/II trial of BNCT for recurrent HN cancer, enrolling 17 patients with 23 tumours previously treated with high-dose photon irradiation. Using a fructose complex of L-boronophenylalanine, patients received two BNCT fractions at 28-day intervals. While the

response rate was high (12/17), re-recurrence was common [34].

In 2014, we began a second trial combining BNCT with image-guided intensity-modulated radiotherapy (IG-IMRT) for improved local control. As of May 2017, seven patients have been treated, showing similar toxicity to prior BNCT applications, with three achieving complete responses. However, locoregional recurrence remained a challenge. Future research at THOR will explore the potential of combining BNCT with other therapies for recurrent head and neck cancer.[34].

b) Investigating the upper energy threshold of effective epithermal neutrons for boron neutron capture therapy in various tissues:

Boron Neutron Capture Therapy (BNCT) is increasingly recognized as a promising radiotherapy, particularly with advancements in accelerator-based systems. These developments have spurred global efforts to integrate BNCT into clinical practice. Key to this is the design of neutron beams, which must adhere to specific quality constraints, particularly the definition of epithermal neutrons up to 10 keV and the control of fast neutron contributions [35].

The dose distribution resulting from neutron interactions in different tissues was evaluated using Monte Carlo simulations with the MCNP6.2 code. The analysis focused on areas such as the head, brain, and neck, and liver, utilizing the Snyder model for the skull and brain, and the MIRD-ORNL male model for the abdomen and neck. Dose calculations utilized F4 tallies, weighted by corresponding kerma factors. The total dose (D) was determined as follows:

D=wtDt+wfDf+wBDB+wγDγD = w_tD_t + w_fD_f + w_B D_B + w_\gamma D_\gammaD=wtDt+wfDf+wBDB+wγDγ

Simulations were conducted with monoenergetic, parallel neutron beams of diameters 10 cm and 25 cm, along with variations in beam divergence, set at 0.7 using a uniform cosine distribution. Two realistic case examples were provided: one featured a dose map from a slice of the Snyder brain model with a beam exceeding the 10 keV threshold, and the second used a realistic spectrum inspired by CBENS, with a 25 cm aperture and a divergence of 0.7, highlighting the impact of neutrons slightly above 10 keV on beam quality.

Tissue discretization along the beam axis was implemented, with voxel sizes of 0.4 cm for the Snyder model and 0.5 cm for the abdomen and neck in the MIRD-ORNL model. Thermal neutron scattering was modelled using light water at 300 K. Various Figures of Merit (FoM) were evaluated, including:

1. Advantage Depth (AD): Maximum depth where tumour dose exceeds healthy tissue dose.
2. Double Dose Depth (DDD): Maximum depth where tumour dose is at least double that of normal tissue.
3. Triple Dose Depth (TDD): Maximum depth where tumour dose is at least triple that of normal tissue.
4. Maximum Therapeutic Ratio (MTR): Maximum ratio of tumour to normal tissue dose.

The relationship of these FoMs to neutron energy was examined within the 1 keV to 50 keV range.

This study confirms that neutrons above the traditional 10 keV epithermal limit can still be effective for BNCT, with a useful range extending from 10 to 40 keV in various tissues. These findings suggest a need to revise the fixed 10 keV upper limit set by IAEA recommendations to at least 20 keV, as criteria can vary based on tissue types and beam characteristics. Emphasizing in-phantom evaluations will aid in more effective neutron beam design for BNCT, highlighting the potential utility of slightly higher energy neutrons in treatment[36].

2. Radionuclide Nanopartcals As Targated Therapy Developer:

Radiolabeled tracers are essential for imaging and therapy in both preclinical and clinical settings. Techniques like Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) enable the visualization of in vivo processes, aiding in the study of diseases and pharmacokinetics. However, these methods have low spatial resolution. To address this, optical imaging techniques like Cerenkov Luminescence Imaging (CLI) have been developed. CLI utilizes Cerenkov radiation emitted by certain radionuclides, including many used in PET, to enhance imaging capabilities. This is particularly beneficial for beta emitters, which cannot be visualized with traditional nuclear medicine techniques [37-38].

The use of radionuclides in conjunction with nanomaterials has been applied in many biological contexts, including disease diagnosis and treatment, As shown in FIG 4. This strategy typically entails attaching the radionuclide, functioning as a diagnostic or therapeutic agent, to a nanoparticle that guides it to the intended tissue. Because radioactive decay cannot be externally managed, radiolabeled components remain detectable irrespective of their biological interactions [39].

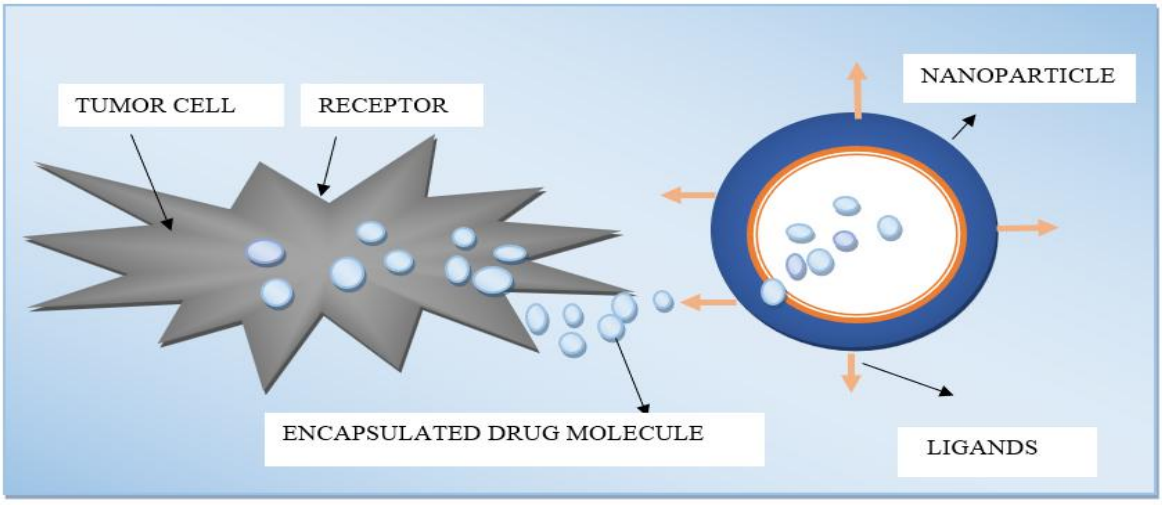

Figure 4: Radionulcide Nanoparticles Acting On Cancer Cells

Cerenkov Luminescence Imaging (CLI) from radionuclide:

Cerenkov Luminescence (CL) occurs when charged particles polarize a medium, emitting Cerenkov radiation (CR) as they return to equilibrium. The intensity of this radiation is inversely related to the square of the wavelength, leading to emission primarily in the ultraviolet or blue spectrum. Although discovered decades ago, its application in biomedical research was first reported in 2009, sparking interest in its use for optical visualization of radioactive materials [40].

CLI offers several advantages: it enables simultaneous imaging of multiple animals, has shorter acquisition times, is less expensive than traditional nuclear imaging, eliminates the need for external excitation sources, and allows for the imaging of therapeutic radionuclides that are typically hard to detect. Most clinically used isotopes exceed the energy threshold needed to generate CR in tissue, facilitating optical imaging.

However, CLI faces challenges, including the dominance of the ultraviolet spectrum, which limits detection in deeper tissues, and the low intensity of CL, which can hinder clinical applications. To address these issues, combining CR with nanomaterials is a potential strategy. Further discussions on the principles of Cerenkov luminescence and suitable radioisotopes have been covered in other literature [40].

Different types of nanoparticles:

a) Quantum dots:

Quantum dots (QDs) are inorganic nanoparticles known for their exceptional optical properties due to quantum confinement. Made from elements like Cd, Te, Se, and Zn, QDs exhibit size-dependent optical and electronic characteristics that make them useful in bioimaging, biosensing, drug delivery, diagnostics, and cancer therapy[41].

Compared to traditional dyes and fluorescent proteins,Quantum dots(QDs) offer advantages such as enhanced brightness, reduced photobleaching, and the ability to produce multiple fluorescence colors. Consequently, QDs are widely used in optical imaging.Quantum dots (QDs), when excited by blue light, can interact with CR emitters to produce remarkable effects, including the significant conversion of chemiluminescence (CL) signals to red-weighted wavelengths. This interaction facilitates enhanced in vivo imaging with improved tissue penetration[42].

b) Gold nanoparticles:

Metallic nanoparticles, particularly gold nanoparticles (AuNPs), have significant applications in medicine due to their unique properties. AuNPs are easy to synthesize, possess tunable optical and electronic characteristics, have high X-ray absorption, excellent biocompatibility, and photostability, allowing for precise control over their properties. As a result, they are increasingly used as luminescence probes and energy converters for fluorescence imaging [43].

Volotskova and her team demonstrated that gold nanoclusters (AuNCs) attached to bovine serum albumin (BSA) could efficiently act as CRET agents by interacting with 18F-FDG and 90Y.There in vitro studies indicated a linear relationship between luminescence intensity, activity, and nanoparticle concentration. In vivo imaging in breast tumour-bearing mice further suggested that AuNCs are efficient energy transfer mediators when paired with clinical radionuclides [44].

The β emitter 198Au, which has an energy exceeding the threshold needed to generate Cerenkov radiation in biological tissue, offers potential for radiochemical doping methods.

first demonstrated the CL phenomenon using 198Au incorporated into Au nanostructures for Cerenkov luminescence imaging (CLI). In their study, 198Au-doped AuNCs were administered to mice with EMT-6 tumours, resulting in high bioluminescence intensity in the tumour that increased over time, highlighting significant nanoparticle uptake by the reticuloendothelial system. This proof-of-concept study highlighted the potential of radiolabeled nanoparticles for in vivo optical imaging.[45].

c) Fluoride a rare earth nanoparticle:

Lanthanide elements, along with yttrium and scandium, are classified as rare-earth elements known for their strong and long-lasting fluorescent emissions via intra-4f or 4f–5d transitions. Their photobleaching resistance, monochromaticity, and large Stokes shift make them highly appealing for bio probe applications, including Cerenkov radiation (CR) conversion.Rare-earth nanoparticles (RENPs) can be excited by ultraviolet/blue or near-infrared (NIR) light and have shown enhanced luminescence when used alongside CR sources like 18F-FDG. For instance, NaYF4:Er3+, Yb3+ hollow microtubes nearly doubled luminescence intensity in vivo and improved tissue penetration significantly.

Additionally, RENPs are being used for combined X-ray and optical imaging, such as X-ray luminescence computed tomography (XLCT), allowing deep tissue visualization. Studies on Ba0.55Y0.3F2:Eu3+ nanophosphors showed a correlation between luminescence and radioactivity, with higher nanoparticle concentrations yielding increased luminescence due to absorption and energy transfer effects [46].

d) Oxide another rare earth nanoparticle:

Metal oxide nanoparticles (NPs) offer appealing features such as unique redox and catalytic properties, enhanced mechanical stability, and biocompatibility, making them widely used in bioimaging, biosensing, and other biomedical applications. Recent research has investigated the interactions between ionizing radiation and rare-earth metal oxide nanoparticles, particularly those of gadolinium, europium andtitanium.

Examined the scintillation-excitation mechanisms of europium oxide (EO) NPs by comparing luminescence from irradiation with 18F-FDG, which emits γ-radiation and β+ particles, and 99mTc-MDP, which emits only γ-radiation. The in vitro results indicated that the emission strength of EO was affected by the radionuclides' activity levels and their decay pathways. While both isotopes could excite the nanoparticles, excitation was predominantly influenced by γ radiation.

The researchers also compared radiopharmaceutical-excited fluorescence imaging (REFI), Cerenkov Luminescence Imaging (CLI), and fluorescence molecular imaging (FMI) in mice with various tumors. REFI demonstrated excellent imaging capability with europium oxide NPs combined with 18F-FDG, allowing for tumor visualization where PET and CLI failed. Notably, REFI showed higher sensitivity than PET for detecting small tumours[47].

Conclusion and Future Prospective:

Therapeutic nuclear medicine is rapidly emerging as an alternative treatment option in oncology. therapeutic radionuclides are now gaining recognition for their ability to target tumors through various routes and mechanisms. The field of radionuclide therapy is currently experiencing a dynamic phase and is anticipated to undergo substantial growth and advancements in the coming years. For example, the high incidence of thyroid and liver diseases in Asia has spurred a number of innovative developments and clinical trials aimed at targeted radionuclide therapy.

This is a pivotal moment in molecular imaging and therapy, marking a shift towards personalized and precise medicine, where patients who previously had limited treatment options or were ineligible for other therapies now have more choices, supported by concrete data demonstrating improved outcomes.Nanomedicine is another vibrant area of research within radiation oncology. The term "theranostics" was initially created to describe a treatment approach that combines diagnostic testing with targeted therapy based on the results. Recent studies are enabling the integration of nanotechnology into a theranostic framework, allowing for both diagnosis and the delivery of targeted therapies.

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