IMMUNOWATCH

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RADIOPHARMACEUTICALS

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THE BIOTHERAPY EXPERT

INTRODUCTION

MabDesign's ImmunoWatch is a specialized intelligence newsletter focused on the evolving field of biologics. It has been designed to deliver to actors and stakeholders in the field, timely and high-value insights curated through the combined expertise of MabDesign and its network of contributors in scientific research, business intelligence, market analysis, and intellectual property.

Each edition is dedicated to a specific therapeutic area or trending class of biologics, providing a comprehensive overview of current trends and strategic developments. The content typically includes market research, financial and economic data, expert perspectives from academic and industrial teams, and an in-depth intellectual property analysis. The editorial direction is ensured by a chief-editor board of at least two field experts, with theme selection and content development overseen by MabDesign's permanent editorial team.

Finally, we would like to acknowledge the continued support and strategic oversight provided by MabDesign's Comité d'Orientation Stratégique et Scientifique de Filière (COSSF) for their significant contribution to the quality and relevance of each edition of ImmunoWatch.

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EDITORIAL

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Co-founder & CEO, Aken Medical

Beyond Chelation: How Nanoparticle Encapsulation Is Redefining Targeted Radionuclide Therapy

Targeted Radionuclide Therapy (TRT) has entered a new era. The landmark approvals of Lutathera® and Pluvicto® have demonstrated that selectively delivering ionizing radiation to tumor cells — while sparing healthy tissue — is not only scientifically sound but clinically transformative. Today, the field is evolving rapidly: alpha emitters are gaining momentum over beta emitters for their superior cytotoxic potency at the single-cell level, theranostics is redefining what a radiopharmaceutical can do, and personalized dosimetry is emerging as the next frontier. Yet beneath this momentum lies a set of unresolved challenges that constrain the field's broader ambition.

The conventional approach couples a radionuclide to a biological vector through a chelating agent. For established beta-emitters like ^{177}Lu, this strategy has proven robust. The picture is more complex for alpha-emitting radionuclides such as ^{225}Ac, whose successive decay daughters carry recoil energy sufficient to rupture the chelator bond — freeing daughter nuclides to migrate and irradiate healthy tissue, precisely the outcome TRT aims to prevent.

"For long-chain alpha generators, recoil energy is not a marginal inconvenience — it is a fundamental physical constraint that demands a fundamentally different containment strategy."

Nanoparticle-based platforms are emerging as a scientifically compelling response. Their physicochemical properties — size, surface charge, and composition — shape pharmacokinetics and influence tumor accumulation through both passive mechanisms such as the Enhanced Permeability and Retention (EPR) effect, and active targeting when conjugated to tumor-specific ligands such as antibodies or peptides. In the context of TRT, nanoparticles offer an additional and critical advantage: the ability to physically confine a radionuclide and its radioactive progeny throughout the decay chain, independently of chelation chemistry.

This approach also opens the door to theranostics — the simultaneous delivery of a therapeutic radionuclide and a diagnostic imaging agent within a single platform. Rather than administering separate agents sequentially, a theranostic nanoparticle enables real-time monitoring of biodistribution and tumor uptake, providing the quantitative dosimetric data that is standard in external beam radiotherapy but largely absent from current TRT practice. This is a prerequisite for truly personalized treatment: tailoring the administered activity (MBq/kg) and treatment cycles to each patient's actual pharmacokinetics rather than population-level estimates.

Looking further ahead, the rich dataset generated by theranostic platforms — spatial distribution, kinetics, absorbed dose per organ — is precisely the structured input on which AI-assisted models can be trained, pioneering data-driven methods to predict optimal administered activity and anticipate tumor response. This convergence of nanomedicine, theranostics, and artificial intelligence may define the next chapter of precision oncology.

At Aken Medical, we are pioneering this approach — simultaneously encapsulating Actinium-225 and a PET-compatible imaging agent (Zirconium-89) within targeted nanoparticles, and developing AI-assisted dosimetry models to further individualize treatment planning. Our platform is currently in preclinical evaluation for pancreatic cancer, in collaboration with INSERM, CNRS, and leading cancer research institutes.

Nanomedicine and radiopharmaceuticals are converging. The constraints that once defined the boundaries of the field are becoming the engineering challenges that will shape its future.

EDITORIAL

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The Evolution of Nuclear Medecine and the Rise of Targeted Radionuclide Therapy

TRT, short for Targeted Radionuclide Therapy, is an acronym that has recently entered medical terminology. It has been used since the introduction of lutetium-177-labeled vectors in oncology over the past two decades, but its history actually dates to the 1950s.

At that time, therapeutic nuclear medicine was primarily limited to the treatment of thyroid cancer through the oral administration of iodine-131. Although this approach marked a significant advance, its scope of application remained limited.

In the following decades, a few radionuclide-labeled vectors were explored for therapeutic use, though on a limited scale. The choice of available radionuclides was then practically limited to iodine-131. 131I-MIBG (Meta-Iodo-Benzy-Guanidine) was thus used starting in 1983 to treat malignant pheochromocytoma. This molecule demonstrated clinical efficacy by partially reducing malignant tumors and catecholamine hypersecretion [1,2]. Three years later, initial clinical results were also reported with 131I-MIBG in neuroblastoma, validating its use in refractory or relapsed patients, with variable objective responses. Then, in 1997, Quadramet® (samarium-153 lexidronam) received FDA approval for the relief of pain associated with bone metastases, following clinical trials initiated in the late 1980s.

A pivotal step in the development of TRT was the availability of monoclonal antibodies as radionuclide carriers, thanks to the work of Kohler and Milstein in the 1970s, for which they were awarded the Nobel Prize in 1984. Thus, the survival of patients with metastatic medullary thyroid cancer was improved through the administration of ^{131}I coupled to a bivalent hapten, following pre-targeting of the tumor with a bispecific monoclonal antibody [3]. This two-step method made it possible to limit radiation exposure to healthy cells and administer higher therapeutic doses [4]. Despite these advances, the industrial development of this treatment was hampered by the rarity of the disease.

TRT subsequently emerged with the approval, in Europe and the U.S., of vectors labeled with lutetium-177, a beta-emitting radionuclide. In 2017, Lutathera® was approved for the treatment of neuroendocrine tumors, followed in 2022 by Pluvicto® for metastatic prostate cancer. These innovations illustrate the evolution of nuclear medicine, moving from limited treatments to increasingly precise and effective approaches in oncology. Today, the arrival of new alpha-emitting radionuclides (actinium-225, lead-212, astatine-211) and carriers opens promising prospects, particularly for the treatment of refractory cancers.

References

1- Chatal JF, Charbonnel B. Comparison of iodobenzylguanidine imaging with computed tomography locating pheochromocytoma. J Clin Endocrinol Metab 1985 ;61 : 769-772.

2- Charbonnel B, Chatal JF, Brendel AJ et al. Treatment of malignant pheochromocytoma by 131-I-metaiodobenzylguanidine. Ann Endocrinol 1988 ;49 :344-347.

3- Chatal JF, Campion L, Kraeber-Bodéré F et al. Survival improvement in patients with medullary thyroid carcinoma who undergo pretargeted anti-carcinoembryonic-antigen radioimmunotherapy : a collaborative study with the French Endocrine Tumor Group. J Clin Oncol 2006 ;24 :1705-1711.

4- Goldenberg DM, Sharkey RM, Paganelli G, Barbet J, Chatal JF. Antibody pretargeting advances cancer radioimmunodetection and radioimmunotherapy. J Clin Oncol 2006 ;24 :823-834.

EDITORIAL

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Radiopharmaceuticals: From Scientific Promise to Clinical Transformation

The radiopharmaceutical field is experiencing a remarkable acceleration, driven by the convergence of molecular biology, nuclear medicine, radiochemistry, and pharmaceutical development. What was once considered a niche therapeutic modality is rapidly becoming a cornerstone of precision medicine, offering new opportunities to diagnose and treat diseases with unprecedented specificity.

The success of recent targeted radiopharmaceuticals has demonstrated the clinical value of delivering radiation directly to diseased tissues while sparing healthy organs. Beyond oncology, radiopharmaceuticals are opening perspectives in neurology, cardiology, and inflammatory diseases, expanding the horizons of molecular imaging and targeted treatment. This momentum is reflected by growing investments from pharmaceutical companies, increased regulatory engagement, and a surge in innovation across academia and industry.

Yet, the field remains at a pivotal stage. The promise of radiopharmaceuticals will only be fully realized if several scientific and industrial challenges are addressed. The development of novel targeting vectors and novel biological targets, optimization of radionuclide selection, improvement of dosimetry approaches, and better understanding of biological responses to radiation all require sustained research efforts. At the same time, manufacturing scalability, isotope availability, supply chain resilience, and regulatory harmonization must evolve to support broader patient access.

As a biophysicist working in radiopharmaceutical research and development, I witness daily how multidisciplinary collaboration has become the engine of progress. The complexity of these medicines demands expertise spanning target biology, molecular biology, radiochemistry, pharmacokinetics, imaging sciences, drug development, quality control and clinical implementation. Success increasingly depends on the ability of diverse teams to integrate these perspectives into coherent development strategies.

A clear transition is underway in radiopharmaceuticals, from a highly specialized therapeutic modality toward a consolidated and industrialized oncology platform. The coming decade is likely to mark the maturation of the field into a firmly established component of oncologic therapeutic strategies, driven by advances in alpha-emitting radionuclides, combinatorial approaches, personalized dosimetry, and artificial intelligence-driven patient selection, enhancing both efficacy and safety. The radiopharmaceutical revolution is no longer a future prospect, it is underway. Our collective responsibility is now to transform scientific breakthroughs into accessible healthcare solutions that can benefit patients worldwide. Continued innovation, clinical trials, and global collaboration will be essential to fully realize its transformative potential.

SCIENTIFIC ARTICLES

Read the different inputs from the scientific community on Radiopharmaceuticals

RETHINKING DELIVERY: THE RISE OF NON-VIRAL VECTORS

By MabDesign Market Research

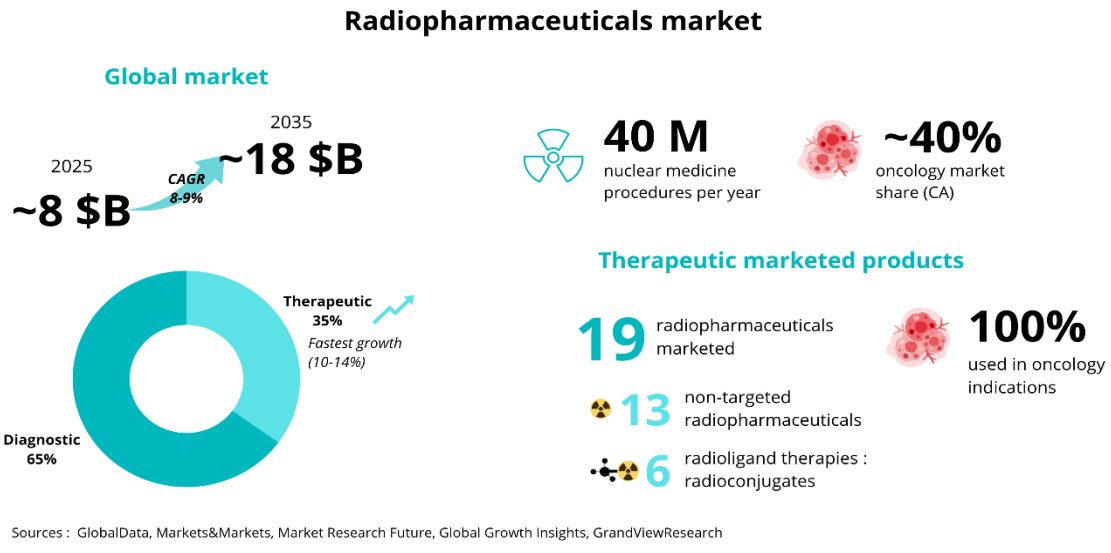
Radiopharmaceuticals: between therapeutic promise and industrial constraints

Historically dominated by diagnostic applications, radiopharmaceuticals are increasingly moving toward targeted therapeutic uses, particularly in oncology. Momentum is building across pipelines and investment activity, but turning this promise into broad clinical adoption will require overcoming significant industrial and operational challenges.

Radiopharmaceuticals are medicinal products that contain a radioactive isotope (radionuclide) and are used in nuclear medicine for diagnostic imaging or targeted therapy. These agents may rely on physiological distribution mechanisms or incorporate targeting moieties such as small molecules, peptides or antibodies to selectively localize in specific tissues or disease sites. When a radionuclide is linked to a targeting molecule, these agents are commonly referred to as radioconjugates.

They have historically been used in nuclear medicine primarily for imaging purposes, notably through PET and SPECT techniques, where radiotracers allow the visualization of physiological and metabolic processes in vivo. This diagnostic use remains the foundation of the field today, with the majority of clinical applications relying on well-established imaging agents. However, advances in targeting strategies and radiochemistry have progressively expanded the scope of radiopharmaceuticals beyond imaging, opening the way for therapeutic applications, which are becoming a growing part of the market.

The radiopharmaceutical market : rise of therapies... and commercial failures



Sources : GlobalData, Markets&Markets, Market Research Future, Global Growth Insights, GrandViewResearch

The radiopharmaceutical sector is currently at a critical crossroads, transitioning from a specialized diagnostic tool to an **emerging modality of precision oncology**. The global market is projected to grow from **$8 billion in 2025 to $18 billion by 2035** and while diagnostic use remains the key application, therapeutic approaches now account for roughly **35% of the market value** and constitute **the fastest-growing segment**. medicine procedures performed annually worldwide, the vast majority being diagnostic, with **oncology representing a major area of application**, accounting for roughly 40% of the market in value terms.

The current market trajectory is defined by a strategic transition from "historical" metabolic systemic treatments toward engineered radioconjugates. Traditional therapeutic radiopharmaceuticals, such as Iodine-131 for thyroid pathologies or Radium-223 dichloride (Xofigo) for osteoblastic metastases, exploit the inherent pharmacokinetic properties and elemental tropism of the radionuclides themselves. In these cases, the isotope serves as both the effector and the targeting agent.

In contrast, contemporary radioligand therapies (RLT) use a radioactive payload conjugated to a targeting vector—typically a synthetic peptide or a small-molecule ligand—designed to recognize specific cell-surface biomarkers. This vector-based approach, validated by the clinical successes of Lutathera and Pluvicto, enables a significant increase in the absorbed dose to the tumor volume while concurrently optimizing the safety profile by limiting off-target ionizing radiation to healthy parenchymal tissues

Therapeutic : Key products & actors

Non-exhaustive

Non-targeted radiopharmaceuticals

Xofigo® radium Ra 223 dichloride
- metastatic prostate cancer
- radium-223
- no ligand, accumualtion in bones

Iodine therapies
- thyroid cancer, hyperthyroidism
- Iodine-131
- no ligand, accumualtion in thyroid tissue

Radioligand therapies (RLT)

Commercial successes - widely used

PLUVICTO® lutetium Lu 177 vipivotide tetraxetan INJECTION FOR INTRAVENOUS USE
- mCR prostate cancer
- lutetium-177
- small molecule (peptidomimetic)

LUTATHERA® (lutetium Lu 177 dotatate) injection, for intravenous use
- GEP-NETs
- lutetium-177
- synthetic peptide

Limited use / recently discontinued

ZEVALIN® (ibritumomab tiuxetan) INJECTION FOR INTRAVENOUS USE
- NH lymphoma
- Yttrium-90
- monoclonal antibody

EU authorization invalid as of 2024

Licartin
marketed in China only
- HCC
- Iodine-131
- monoclonal antibody

iobenguane I-131
- NETs
- Iodine-131
- small molecule

limited commercialization in US hospital use only in EU

Sources : GlobalData, EMA

Nevertheless, despite their therapeutic potential, radioconjugates remain a minority of the treatments administered in clinical practice, as the market is still dominated by non-targeted metabolic agents. Beyond the success of **Lutathera** and **Pluvicto**—which successfully leveraged the **high expression density** of biomarkers like **SSTR** and **PSMA**—the commercial landscape for targeted radiopharmaceuticals is characterized by significant volatility.

Indeed, the commercial landscape of targeted radiopharmaceuticals has been marked by several cases in which **clinically effective agents failed to achieve sustained market availability. Ibritumomab tiuxetan (Zevalin),** despite demonstrated clinical efficacy, remained underused in routine practice and ultimately saw its European marketing authorization lapse in 2024 after several years without commercialization. Similarly, **I-131 iobenguane (Azedra)**, despite having FDA approval on the basis of clinical benefit, had its production discontinued in 2023–2024, because of fixed manufacturing costs and insufficient commercial demand. Together, these cases illustrate a disconnect between clinical efficacy, regulatory approval and sustainable commercial viability for some radioconjugates.

Pipeline & investments : a strong momentum despite risks

M&A Dynamics: From asset access to platform integration

While commercial outcomes for first-generation radiopharmaceuticals remain heterogeneous, the sector is now experiencing a marked acceleration in strategic consolidation. Recent deals suggest that Big Pharma is increasingly seeking broader control over integrated radiopharmaceutical platforms, including pipelines, radiochemistry capabilities, manufacturing infrastructure and supply-chain expertise.

Radiopharmaceuticals : key recent deals

Non-exhaustive

2025	2024	2024	2024
framatome	Bristol Myers Squibb	AstraZeneca	NOVARTIS
Partnership with	**Acquisition of**	**Acquisition of**	**Acquisition of**
iba	RayzeBio	Fusion	mariana ONCOLOGY
The collaboration aims to build a network of alpha-emitting cyclotrons, ensuring the production of Astatine-211 in Europe and USA. A production site is set to be installed in Saint-Herblain in 2027-2028.	Actinium-225 (alpha-emitter) platform and lead candidates for GEP-NETs and lung cancer	Targeted Alpha Therapy (actinium-225 based) capabilities and a proprietary radiogenomics platform	Portfolio of RLT programs spanning lead optimization including an actinium-based RLT in small cell lung cancer
	$4.1 billion	**$2.4 billion**	**$1.75 billion**

BMS's acquisition of RayzeBio and AstraZeneca's takeover of Fusion Pharmaceuticals illustrate a shift toward next-generation radiopharmaceutical platforms, with a particular emphasis on high-potency **alpha-emitting isotopes** such as actinium-225. These transactions reflect growing interest in high linear energy transfer particles and in radioconjugate approaches that could complement existing targeted oncology modalities, including antibody-drug conjugates. Similarly, the collaboration between Framatome and IBA reflects the will to secure a sustainable and robust production of alpha-emitting isotopes, with a first site set to be built in France in 2027-2028.

Recent deals also highlight three strategic drivers for Big Pharma in the radiopharmaceuticals field :

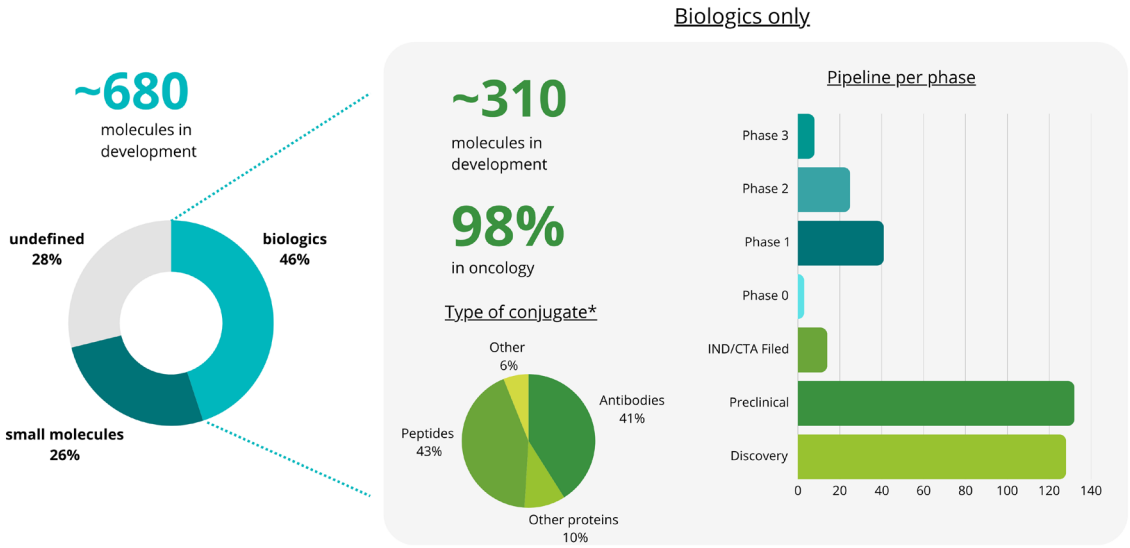
- **Logistical sovereignty**: securing greater end-to-end control over radiopharmaceutical infrastructure — from radiochemistry and manufacturing to supply-chain execution — to manage the complexity of short-lived isotopes.
- **Indication expansion:** moving beyond NET and PSMA into broader solid tumor opportunities, including SCLC, HCC and other high-unmet-need settings.
- **Portfolio synergy**: leveraging established ADC portfolios to develop "plug-and-play" radioligands where the chemical payload could be swapped for a radioisotope.

Following the 2023–2024 wave of platform acquisitions, the sector appears to be entering a second phase focused on consolidating the operational capabilities required to scale radiopharmaceuticals. Novartis provides the clearest example, with continued efforts to secure actinium-225 supply through its agreement with Niowave (2025) and to expand dedicated radioligand therapy manufacturing capacity. Other moves, such as **Regeneron's radiopharma collaboration with Telix (2026),** suggest that access to manufacturing, isotope supply and specialized infrastructure is becoming a central strategic priority for companies that have committed to the radiopharmaceuticals field.

Developing pipeline : A surge in early-stage innovation

The analysis of the **developing pipeline** confirms that radiopharmaceuticals have moved from a niche therapeutic class to a promising strategy in oncology R&D, with more than **680 molecules currently in development.** Biologics represent 46% of this pool, with the vast majority of candidates concentrated in oncology (98%). This shows that industry is betting on radioligands as an **emerging therapeutic modality** within precision oncology

Radiopharmaceuticals pipeline



Sources : GlobalData, MabDesign

*Category "peptides" likely contains synthetic peptides, as precise categorization of early projects is not robust

The domination of biologics in the pipeline is in contrast with their scarcity on the market, illustrating a **transition towards high-affinity precision vectors** : the radiopharmaceutical market is still young, and it is moving from first-generation small molecule-based products **towards radioconjugates,** and notably radio-antibody conjugates (RACs), which now represent 41% of biologics in development. This reflects a growing trend toward using antibody-based targeting strategies **as scaffolds for radioactive payloads**, including the adaptation of clinically validated monoclonal antibodies. This also partially explains the strong oncology focus of the biologics pipeline, as these approaches aim to combine est**ablished tumor-targeting mechanisms** with the cytotoxic effect of localized radiation.

The phase distribution confirms that the biologics pipeline remains **early-stage**, with discovery and preclinical candidates still outnumbering clinical-stage assets. Although this is expected for an emerging modality, it puts the current enthusiasm around biologic radiopharmaceuticals into perspective: despite strong pipeline momentum and recent platform-focused deals, the **field has not yet translated this activity into broad late-stage clinical validation or sustained commercial availability.**

Key limitations: from scientific promise to operational scalability

- Complex raw material sourcing: production depends on specialized nuclear materials and infrastructure, which are available from a limited number of qualified suppliers.
- Limited isotope production capacity: production of radionuclides, especially emerging alpha emitters such as actinium-225, remains constrained relative to expected pipeline demand.
- Fragile and time-sensitive supply chains: short isotope half-lives impose tight coordination between production, radiolabelling, quality control, shipment and patient administration.
- Stringent regulatory & radiation-safety compliance: manufacturing requires GMP compliance as well as radiation protection, handling, transport and site-qualification procedures.

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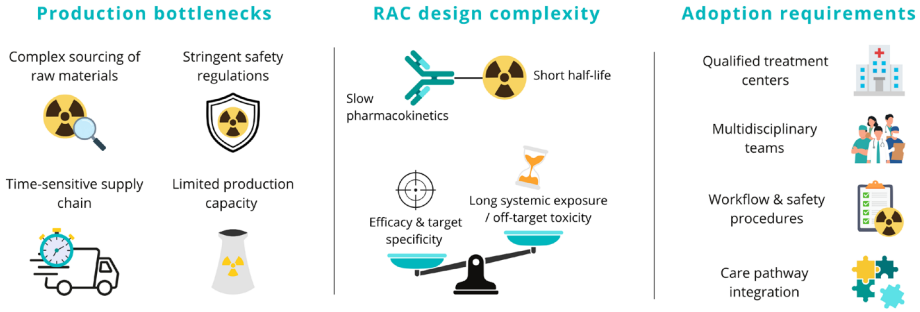

This challenge is even sharper for next-generation radioconjugates. For antibody-based formats, high target specificity must be balanced against slow pharmacokinetics and prolonged systemic exposure, which can increase off-target irradiation and complicate the match between vector kinetics and radionuclide half-life. As a result, biologic radioconjugates cannot simply replicate the ADC model: they require dedicated optimization of vector format, linker chemistry, isotope choice, and dose optimization.

Ultimately, and as illustrated by past commercial discontinuations, clinical efficacy alone will not be sufficient. Successful radiopharmaceuticals will need to be manufacturable, logistically deliverable and economically viable within real-world oncology care.

Beyond these industrial constraints, broader adoption will also depend on healthcare system readiness. Radiopharmaceuticals require qualified nuclear medicine centers, trained multidisciplinary teams, radiation-safety procedures, waste management and coordination between oncology and nuclear medicine departments. Their uptake will therefore depend not only on product performance, but also on reimbursement models, hospital workflows and the ability to integrate these therapies into routine oncology pathways.

Outlook: the path toward broader adoption

Radiopharmaceuticals have strong potential to gain a larger role in precision oncology, driven by their ability to **combine targeted delivery with localized radiation-induced cytotoxicity. In this context, the theranostic approach** is particularly relevant because it helps secure patient stratification: diagnostic imaging can confirm target expression and support patient selection before administration of a matched therapeutic radiopharmaceutical**. This strengthens the fit between radiopharmaceuticals and precision oncology**, where treatment benefit depends on identifying the right patients upfront.

Recent platform-focused deals also show that major industry players now see radiopharmaceuticals as **a strategic oncology modality,** rather than niche products. However, broader adoption will depend on the field's ability to overcome its **important constraints linked to the use of radionuclides:** isotope access, scalable manufacturing, radiolabelling capacity, qualified treatment centers, radiation-safety procedures and reimbursement models will all be critical to real-world deployment.

In practice, the success of radiopharmaceuticals will depend less on scientific promise alone than on **reliable industrial infrastructure and feasible clinical delivery pathways.** This will likely require long-term isotope supply agreements, redundant manufacturing networks, standardized radiolabelling and quality-control processes, and broader access to qualified nuclear medicine sites.

In this sense, the most successful players may not be those with the largest number of pipeline assets, but those **able to convert radiopharmaceutical innovation into reproducible, scalable and economically sustainable treatment pathways.**

Abbreviations

ADC: Antibody-Drug Conjugate

GMP: Good Manufacturing Practice

HCC: Hepatocellular Carcinoma

LET: Linear Energy Transfer

M&A: Mergers and Acquisitions

NET: Neuroendocrine Tumor

PET: Positron Emission Tomography

PSMA: Prostate-Specific Membrane Antigen

RAC: Radio-Antibody Conjugate

RLT: Radioligand Therapy

SCLC: Small Cell Lung Cancer

SPECT: Single-Photon Emission Computed Tomography

SSTR: Somatostatin Receptor

Sources

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GlobalData

Precedence Research- https://www.precedenceresearch.com/radiopharmaceuticals-market

MarketResearchFuture- https://www.marketresearchfuture.com/reports/radio-pharmaceutical-market-1650

Roots Analysis https://www.rootsanalysis.com/reports/radiopharmaceuticals-market.html

EMA- https://www.ema.europa.eu/en/documents/public-statement/public-statement-zevalin-cessation-validity-marketing-authorisation-european-union_en.pdf

SNMMI- https://snmmi.org/Web/News/Articles/Lantheus-to-Discontinue-Production-of-Azedra.aspx

Fierce Pharma - https://www.fiercepharma.com/pharma/2025-forecast-companies-rush-radiopharmaceuticals-oncology-whats-next

https://www.investopedia.com/eli-lilly-buys-point-biopharma-to-boost-its-cancer-fighting-therapies-8346951

https://www.ajmc.com/view/will-the-coming-radiopharmaceutical-wave-reach-more-patients-with-cancer-

Novartis- https://www.novartis.com/news/media-releases/novartis-add-radioligand-therapy-manufacturing-facility-winter-park-florida-fourth-us-serve-patients-and-advance-23-billion-investment

Telix - https://telixpharma.com/news-views/telix-and-regeneron-announce-strategic-radiopharma-collaboration/

Niowaveinc- https://niowaveinc.com/index.php/2026/02/11/niowave-and-novartis-enter-global-actinium-225-supply-agreement-to-advance-next-generation-cancer-therapies/

BIOCONJUGATION STRATEGIES FOR RADIOIMMUNOCONJUGATES IN NUCLEAR IMAGING AND THERAPY

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1) Introduction

Radiopharmaceuticals enable the targeted delivery of radionuclides to specific tissues. Depending on the radionuclide employed, these agents can perform either diagnosis – such as positron emission tomography (PET), single-photon emission computed tomography (SPECT) – or treatment – targeted radionuclide therapy (TRT) – of a broad range of conditions. In some cases, the same construct can be used for both imaging and therapy by simply changing the radionuclide. Such compounds are referred to as radiotheranostics.

Radiopharmaceuticals are composed of several key components (Figure 1):

1. A vector directed against a specific target overexpressed in the disease of interest
2. A radionuclide selected according to the intended application

This review will focus specifically on radiometal-based radiopharmaceuticals, which require two additional components:

3. A chelator, designed to stably coordinate the radiometal
4. A linker used to attach the chelator-radionuclide complex to the targeting vector.

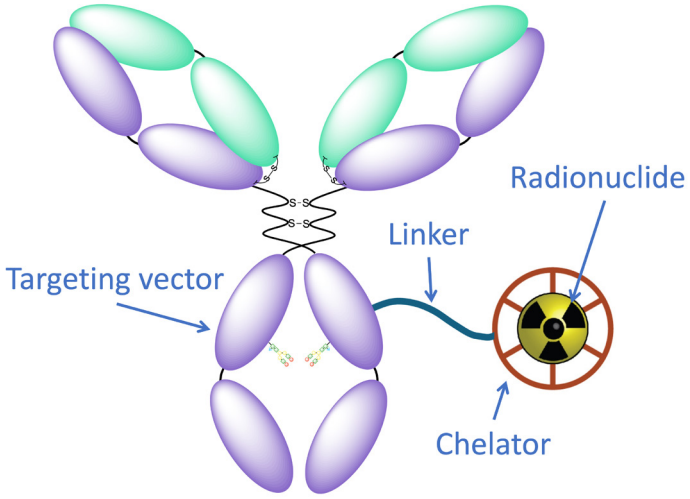

Figure 1: General structure of a radioimmunoconjugate

Vectors vary in size, ranging from small molecules with rapid pharmacokinetics to full-length antibodies with half-lives of several days (Figure 2). The latter exhibit unmatched affinity and selectivity but also result in prolonged exposure of healthy tissues. In contrast, smaller vectors are distributed and cleared much more rapidly, although often with lower targeting efficiency. Beyond the circulation time, the clearance pathway is also different. Constructs with a molecular weight below 60 kDa are mostly eliminated through renal excretion, whereas larger molecules are mainly cleared *via* the hepatic pathway.

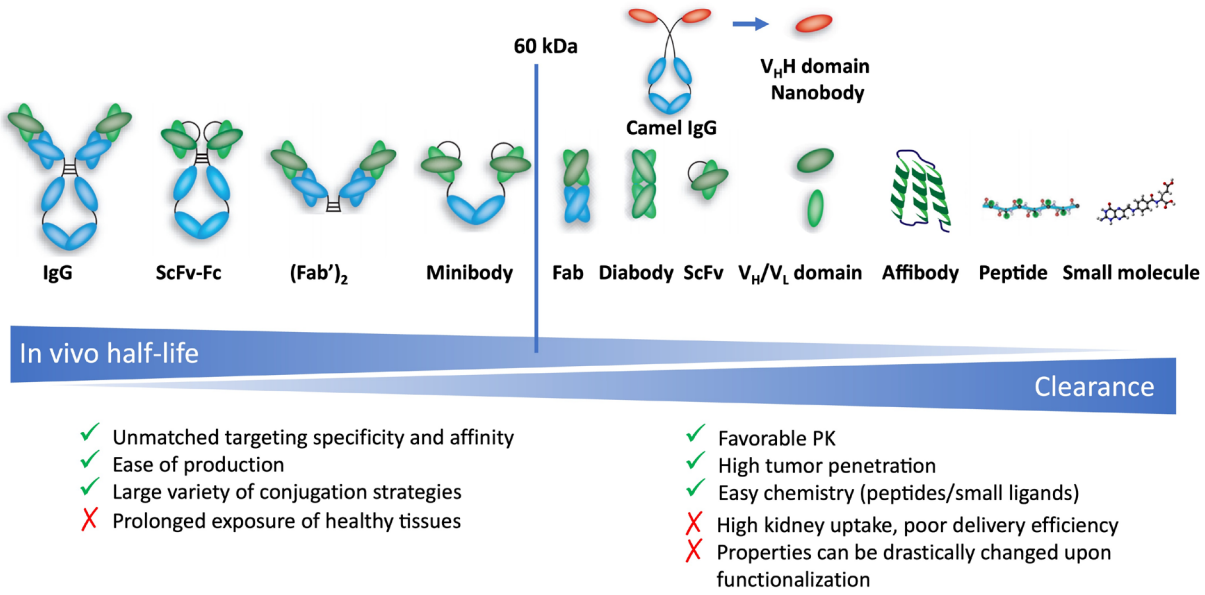

Figure 2: Different targeting vectors in radiopharmaceuticals. Adapted from Holliger et al.[1]

The application of a radionuclide depends primarily on its decay properties. Positron-emitting radionuclides are used for PET imaging whereas gamma emitters are suitable for SPECT imaging. Therapeutic radionuclides, on the other hand, are mostly α or ß- emitters. However, the intended application is not the only factor to consider when selecting a radionuclide. The size and pharmacokinetics of the targeting vector are also critical parameters as the radionuclide half-life must match the biological circulation time of the construct. For example, both ^{68}Ga and ^{89}Zr are positron emitters used for PET imaging. Yet, the short half-life of ^{68}Ga (68 min) makes it more suitable for small molecules or peptides whereas the longer half-life of ^{89}Zr (3.3 days) is better adapted to antibodies.

Chelators are designed to stably coordinate radiometals, and therefore exist in a wide variety of structures adapted to the coordination chemistry of different metals (Figure 3). The selection of an appropriate chelator is essential to ensure radiolabeling efficiency, complex stability, and optimal *in vivo* behavior.

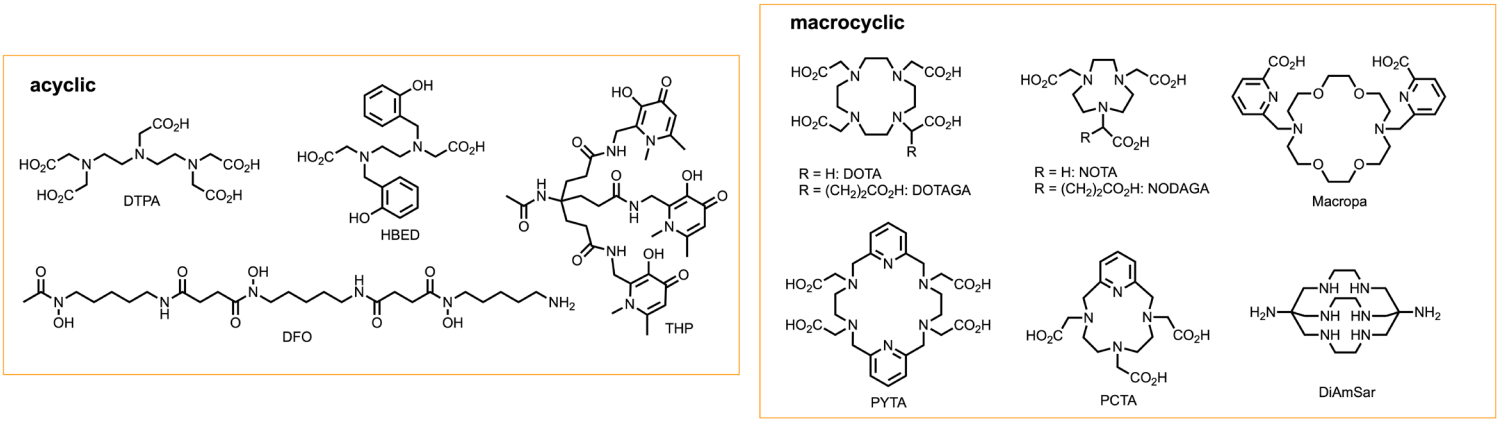

Figure 3: Examples of chelators used for radiometal coordination

A final key aspect is the linker, whose purpose is to attach – or bioconjugate – the chelator-radiometal complex to the vector while preserving its biological and pharmacokinetic properties.

In this review, we will briefly discuss the different antibody conjugation strategies employed in nuclear imaging and therapy. Then, we will provide a non-exhaustive overview of multimodal radioimmunoconjugates, an emerging field developed to meet evolving clinical needs. Lastly, we will address pretargeting strategies.

2) Random versus site-specific bioconjugation strategies

a) Random conjugation

The most widely used conjugation strategy is a stochastic method relying on antibody lysine residues.[1] Briefly, the chelator is functionalized with an amine-reactive group such as an N-hydroxysuccinimide (NHS) ester or an isothiocyanate (NCS) moiety, which reacts with the primary amine of lysine side chains. As lysine residue are highly abundant (approximately 70 to 90 per antibody, of which 30 to 40 accessible), this strategy is rapid and straightforward to implement. However, this method presents several drawbacks. First, neither the location nor the number of binding sites can be controlled, leading to a two-level heterogeneity. Then, this lack of control may cause a possible loss of immunoreactivity, if lysine located within or near the paratope are modified. Finally, in addition to the limitations commonly encountered with others antibody conjugates, radioimmunoconjugates face another important challenge: radiolysis, i.e. the degradation of the conjugation bond induced by ionizing radiation. Depending on the radiometal employed, radiolysis may occur to varying extents, and not all linkers exhibit sufficient radiochemical stability. For example, a study from our laboratory has demonstrated that NCS-based linkers are particularly susceptible to radiolysis whereas squaramide linker displays improved resistance.[2]

b) Site-specific approaches

In contrast, site-specific approaches produce defined and homogeneous conjugates through the modification of specific residues. These strategies are generally classified into four main categories: i) thiol-based conjugation, ii) glycan engineering, iii) peptide-tag-based approaches, and iv) incorporation of unnatural amino-acids (Figure 4). As several comprehensive reviews on site-specific conjugation have already been published, we will only provide a brief overview of the different techniques.[3–7]

The first class relies on thiol groups present either on the native protein – cysteines involved in disulfide bonds that become accessible upon reduction – or on engineered cysteine residues. In the first case, which is the most commonly used strategy in the development of antibody-drug conjugates, the approach is more accurately described as site-selective rather than truly site-specific, as up to eight conjugation sites may be modified on an IgG1 antibody.

The second category involves chemoenzymatic modification of the glycans, highly conserved sugar chains located in the Fc region.[8,9] First, an enzyme is used to remove (PNGaseF) or trim (EndoS or ß-1,4-galactosidase) the sugars. Subsequently, a mutant galactosyltransferase (GalT(Y289L)) enables the introduction of modified sugars bearing azide moieties. Finally, the payload can be conjugated to the antibody through click chemistry.

The third class encompasses conjugation strategies based either on the recognition of peptide tags genetically inserted into the antibody sequence or, by extension, on the recognition of native structural motifs within antibodies. These approaches include enzymatic methods such as sortase,[9,10] lysine acylation conjugation enzyme (LACE),[10] or MTGase-mediated transamidation of glutamine 295 following antibody deglycosylation[11–15], and affinity-guided conjugation using AJICAP reagents.[16]

The incorporation of unnatural amino acids into the antibody sequence is a very elegant strategy for the generation of homogeneous constructs.[17] However, it has been scarcely used in nuclear medicine, likely because of the method complexity.

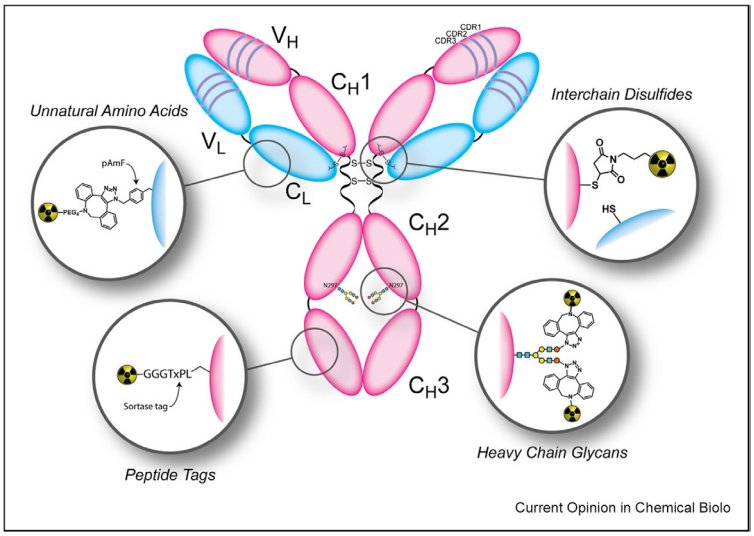

Figure 4: Site-specific conjugation strategies. Reproduced from Ref. [8] under the terms of the Creative Commons Attribution–NonCommercial–NoDerivatives 4.0 International License.

c) Impact on radiopharmaceutical in vivo behavior

An increasing number of preclinical studies have investigated site-specific or site-selective conjugation methods. Depending on the antibody and conjugation strategy employed, these studies generally report improved *in vitro* properties compared with randomly conjugated counterparts, particularly in terms of affinity, while maintaining at least comparable *in vivo* performance. [18–21]
A side-by-side comparison conducted in our laboratory between bimodal probes obtained either through random conjugation or site-specific glycan modification of trastuzumab demonstrated a clear advantage of the site-specific approach in terms of affinity, specificity, and biodistribution.[20] Unlike most of the precedent studies involving relatively hydrophilic chelators, this bimodal probe (concept discussed further in the next paragraph) incorporated a DOTAGA and an Aza-BODIPY fluorophore, which may explain the marked improvement observed upon site-specific conjugation.
In 2024, the first-in-human study comparing random and site-specific conjugation (glycans modification) was conducted at the Memorial Sloan Kettering Cancer Center.[22] The results demonstrated the safety, favorable dosimetry, and potential clinical applications of 89Zr-ss-pertuzumab PET/CT, which appeared to detect more lesions than randomly conjugated 89Zr-DFO-pertuzumab.

3) Multimodality

a) Rationale for multimodal bioconjugates

With the growing interest in personalized medicine, a new class of bioconjugates has emerged in preclinical research: multifunctional constructs integrating two or more complementary modalities within a single molecular entity. Various modality combinations have been explored, including: nuclear and optical imaging (e.g. PET or SPECT for lesion detection combined with fluorescence guided-surgery),[23–26] nuclear imaging and ADC to either select the patients and/or monitor the biodistribution of the therapeutic conjugate,[29–32] and combinations of nuclear imaging and radionuclide therapy.[33–36]

b) Strategies for bimodal functionalization

The different modalities can be introduced sequentially or simultaneously with the use of multifunctional platform. In the first approach, at least one of the modalities is generally attached *via* random conjugation, resulting in limited control over both the conjugation sites and the ratio between the two modalities. [23–25,27–29,37] In the second approach – the Multifunctional, Single-Attachment Point (MSAP) method – the stoichiometry is dictated by the platform itself. When combined with a site-specific conjugation strategy, this approach can provide fully homogeneous multifunctional constructs.

c) Multifunctional platforms

The MSAP concept was introduced by Garanger *et al.* in 2008 to simplify the synthesis of complex multimodal nanomaterials.[38] They developed a Lys-Cys dipeptide scaffold that was later adapted by Hernot and co-workers for the preparation of a SPECT/OI bimodal nanobody. In our laboratory, several trivalent platforms have also been developed. Lysine was used as a scaffold to obtain bimodal PET/NIRF imaging probes targeting HER2-positive tumors through glycan-based conjugation.[39,40] 3,6-dichlorotetrazine was also derivatized with two different nucleophiles to generate either bimodal SPECT/OI[41] or PET/NIRF probes.[42,43] In both cases, click chemistry was used to attach the bimodal probe to the vector. Finally, we also developed bimodal probes based on the aza-BODIPY fluorophore: i) a SPECT/OI probe and ii) a fluorescent antibody-drug conjugate.[44–46]

4) Pretargeting

a) Concept and rationale

Antibodies present exquisite affinity and specificity. However, their slow pharmacokinetics result in prolonged exposure of healthy tissues to radiation. To circumvent this limitation, Goodwin and co-workers proposed in 1988 to administer the antibody and the radiolabel separately, a strategy known as pretargeting.[47] Briefly, an unlabeled antibody recognizing both the target antigen and a low-molecular-weight radiolabeled compound (hapten) is injected first and allowed sufficient time to accumulate in the tumor while clearing from the bloodstream. Then, the radiolabel hapten is administered and, owing to its rapid circulation time, is efficiently cleared from non-target tissues while selectively accumulating at the tumor site through interaction with the tumor-bound antibody. By decoupling vector targeting from radionuclide delivery, pretargeting enables the use of short-lived radionuclides that would otherwise be incompatible with the biological half-life of antibodies (Figure 5A). In addition to bispecific antibody-hapten system, several pretargeting approaches have been developed, including: i) the high-affinity interaction between biotin and streptavidin, ii) complementary oligonucleotides, iii) biorthogonal click chemistry and iv) host-guest interactions. (Figure 5B).

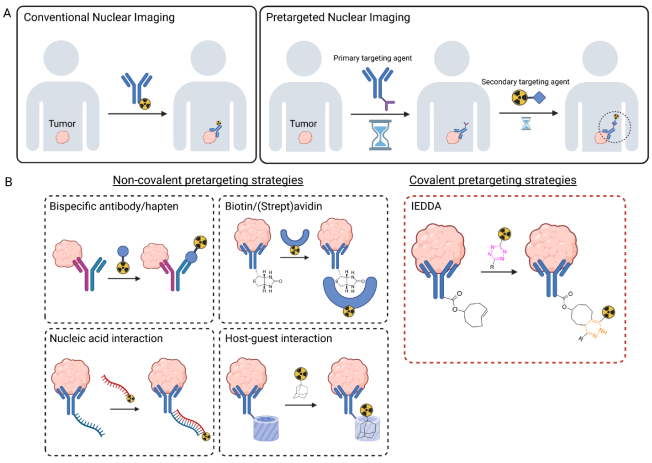

Figure 5: Pretargeting concept and strategies. Reproduced from Ref. [49] under the Creative Commons Attribution 4.0 International License (CC BY 4.0).

b) Applications in imaging and therapy

As this topic has already been extensively covered,[49–55] we will just provide a few original examples of pretargeting strategies involving radiometals, focusing on biorthogonal chemistry and host-guest interactions.

The improvement of *in vivo* behavior through more homogeneous and controlled site-specific conjugation is also an active area of research in pretargeting. Pratt *et al.* compared site-specific conjugation of TCO onto an antibody carrying two engineered cysteines with random lysine conjugation [56]. They also evaluated two different radiolabeling strategies based on using ^{18}F-Al-NOTA chemistry and longer-lived Copper-64 sarcophagine chelates. Their results demonstrated that tumor uptake depended on both the TCO conjugation strategy and the radiotracer used. Site-specific conjugation improved tumor uptake with the [^{18}F]F-Al-NOTA-PEG$_7$-Tz whereas random conjugation resulted in higher tumor uptake with ^{64}Cu. In another study, Zabrocki *et al.* compared random, site-selective (using an azide-bearing pentafluorophenyl (PFP) reagent to modify a single lysine residue on each light chain [57]) and site-specific (glycan modifications with a dendrimer scaffold to obtain higher DOL) TCO conjugation on CC49 antibody [58]. Although random conjugation produced the highest tumoral uptake – potentially due to higher TCO loading – both site-selective and site-specific conjugations improved tumor-to-blood ratios.

Theranostic concepts are also attracting growing interest in pretargeting radioimmunotherapy. Keinänen *et al.* developed a pretargeting strategy based on a true theranostic radionuclide pair, in which a ^{64}Cu-tetrazine was injected for imaging and a ^{67}Cu-tetrazine for therapy.[34]

Pretargeting is most often associated with large vectors to compensate their slow pharmacokinetics. However, it may also benefit smaller vectors, like nanobodies, by improving their therapeutic index. Poty *et al.* demonstrated that pretargeting strategy could successfully reduce kidney retention [59]. Finally, pretargeting approaches have also been explored to reduce off-target toxicity associated with targeted alpha therapy [60].

At the end of the 2010s, another pretargeting strategy emerged: host-guest interactions. Unlike previous approaches, this strategy does not rely on covalent bonding but rather on the high affinity between two complementary species. Initial proof-of-concept studies investigated the cucurbit[7]uril–adamantane pair using radiolabeled adamantane derivatives carrying either carbon-11 or fluorine-18 to evaluate the impact of host–guest complexation on *in vivo* biodistribution [61]. More recently, the Houghton group extended this concept to *in vivo* radiometal-based pretargeting applications by bioconjugating the host molecule to targeting vectors and investigating alternative host–guest systems such as the cucurbit[7]uril–ferrocene pair [62–64]. We have recently shown that this approach can be used successfully the other way around, with the small guest molecule being conjugated to the antibody and various radiometals introduced onto a DOTA-CB[7] [65].

5) Challenges and futur directions

Radiopharmaceuticals are becoming increasingly sophisticated. In this short review, we have discussed different bioconjugation strategies employed to generate radioimmunoconjugates with optimized *in vivo* behavior and to address evolving clinical needs. Significant preclinical efforts are currently dedicated to the development of homogeneous and reproducible constructs through site-specific conjugation. In parallel, multimodality and pretargeting strategies provide additional flexibility by enabling patient stratification, image-guided interventions, and improved therapeutic indices. However, the increasing complexity of these systems may also represent a barrier to clinical translation. The implementation of site-specific and enzymatic conjugation strategies raises challenges related to manufacturing, scalability, cost, and compatibility with good manufacturing practice (GMP) requirements. Therefore, beyond demonstrating improved biological performance, future developments will also need to address robustness, accessibility, and industrial feasibility to facilitate routine clinical implementation.

6) About

The RITM team (ICMUB) develops and evaluates novel radiopharmaceuticals, mainly based on radiometals. These compounds are designed within the framework of a theranostic approach and aim to improve patients' early diagnosis and therapy.

To this end, the RITM team is developing new molecular tools and methodologies for optimizing the various components of a radiopharmaceutical (vector, chelator, spacer, bioconjugation linker, etc.) and evaluating them in vitro and in vivo. RITM members' skills range from coordination chemistry to peptide chemistry, from bioconjugation to radiochemistry, from radiopharmaceuticals to preclinical nuclear imaging.

7) Acknowledgments

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1. Dewulf J, Adhikari K, Vangestel C, Wyngaert TVD, Elvas F. Development of Antibody Immuno-PET/SPECT Radiopharmaceuticals for Imaging of Oncological Disorders—An Update. Cancers. 2020; 12: 1868.

2. Vizier R, Adumeau P, Moreau M, Goncalves V, Denat F. Moving Beyond Isothiocyanates: A Look at the Stability of Conjugation Links Toward Radiolysis in 89Zr-Labeled Immunoconjugates. Bioconjug Chem. 2024; 35: 633–7.

3. Adumeau P, Sharma SK, Brent C, Zeglis BM. Site-Specifically Labeled Immunoconjugates for Molecular Imaging--Part 1: Cysteine Residues and Glycans. Mol Imaging Biol. 2016; 18: 1–17.

4. Adumeau P, Sharma SK, Brent C, Zeglis BM. Site-Specifically Labeled Immunoconjugates for Molecular Imaging--Part 2: Peptide Tags and Unnatural Amino Acids. Mol Imaging Biol. 2016; 18: 153–65.

5. Morais M, Ma MT. Site-specific chelator-antibody conjugation for PET and SPECT imaging with radiometals. Drug Discov Today Technol. 2018; 30: 91–104.

6. Rodriguez C, Delaney S, Sarrett SM, Keinänen OM, Zeglis BM. Antibody Engineering for Nuclear Imaging and Radioimmunotherapy. J Nucl Med. 2022; 63: 1316–22.

7. Sebastiano J, Samuels ZV, Kao W-S, Zeglis BM. Site-specific bioconjugation and nuclear imaging. Curr Opin Chem Biol. 2024; 81: 102471.

8. Zeglis BM, Davis CB, Aggeler R, et al. Enzyme-mediated methodology for the site-specific radiolabeling of antibodies based on catalyst-free click chemistry. Bioconjug Chem. 2013; 24: 1057–67.

9. Vivier D, Sharma SK, Adumeau P, Rodriguez C, Fung K, Zeglis BM. The Impact of FcγRI Binding on Immuno-PET. J Nucl Med. 2019; 60: 1174–82.

10. Wang J, Tolmachova KA, Bode JW. Chemoenzymatic Site-Specific Lysine Modification of Nanobodies and Subsequent Bioconjugation via Potassium Acyltrifluoroborate (KAT) Ligations. J Am Chem Soc. 2025; 147: 15389–96.

11. Mindt TL, Jungi V, Wyss S, et al. Modification of Different IgG1 Antibodies via Glutamine and Lysine using Bacterial and Human Tissue Transglutaminase. Bioconjug Chem. 2008; 19: 271–8.

12. Jeger S, Zimmermann K, Blanc A, et al. Site-Specific and Stoichiometric Modification of Antibodies by Bacterial Transglutaminase. Angew Chem Int Ed. 2010; 49: 9995–7.

13. Dennler P, Schibli R, Fischer E. Enzymatic antibody modification by bacterial transglutaminase. Methods Mol Biol Clifton NJ. 2013; 1045: 205–15.

14. Dennler P, Chiotellis A, Fischer E, et al. Transglutaminase-based chemo-enzymatic conjugation approach yields homogeneous antibody-drug conjugates. Bioconjug Chem. 2014; 25: 569–78.

15. Wehrmüller JE, Frei JC, Hechler T, et al. Site-Specific Modification of Native IgGs with Flexible Drug-Load. ChemBioChem. 2025; 26: 202400511.

16. Grimaldi C, Sebastiano J, Kao W-SM, et al. Harnessing Fc-Directed Bioconjugation for the Synthesis of Site-Specifically Modified Radioimmunoconjugates. Bioconjug Chem. 2025; 36: 1588–94.

17. Hallam TJ, Wold E, Wahl A, Smider VV. Antibody Conjugates with Unnatural Amino Acids. Mol Pharm. 2015; 12: 1848–62.

18. Sarrett SM, Rodriguez C, Rymarczyk G, et al. Lysine-Directed Site-Selective Bioconjugation for the Creation of Radioimmunoconjugates. Bioconjug Chem. 2022; 33: 1750–60.

19. Fayn S, King AP, Gutsche NT, et al. Site-Specifically Conjugated Single-Domain Antibody Successfully Identifies Glypican-3–Expressing Liver Cancer by Immuno-PET. J Nucl Med. 2023; 64: 1017–23.

20. Privat M, Bellaye P-S, Chazeau E, et al. First Comparison Study of the In Vitro and In Vivo Properties of a Randomly and Site-Specifically Conjugated SPECT/NIRF Monomolecular Multimodal Imaging Probe (MOMIP) Based on an aza-BODIPY Fluorophore. Bioconjug Chem. 2023; 34: 621–8.

21. Allen KJH, Frank C, Jiao R, et al. In Vitro and In Vivo Comparison of Random versus Site-Specific Conjugation of Bifunctional Chelating Agents to the CD33-Binding Antibody for Use in Alpha- and Beta-Radioimmunotherapy. ACS Omega. 2024; 9: 50000–11.

22. Yeh R, O'Donoghue JA, Jayaprakasam VS, et al. First-in-Human Evaluation of Site-Specifically Labeled 89Zr-Pertuzumab in Patients with HER2-Positive Breast Cancer. J Nucl Med. 2024; 65: 386–93.

23. Lee HJ, Ehlerding EB, Jiang D, et al. Dual-labeled pertuzumab for multimodality image-guided ovarian tumor resection. Am J Cancer Res. 2019; 9: 1454–68.

24. Cohen R, Vugts DJ, Stigter-van Walsum M, Visser GWM, van Dongen GAMS. Inert coupling of IRDye800CW and zirconium-89 to monoclonal antibodies for single- or dual-mode fluorescence and PET imaging. Nat Protoc. 2013; 8: 1010–8.

25. Deken MM, Bos DL, Tummers WSFJ, et al. Multimodal image-guided surgery of HER2-positive breast cancer using [111In]In-DTPA-trastuzumab-IRDye800CW in an orthotopic breast tumor model. EJNMMI Res. 2019; 9: 98.

26. Ariztia J, Solmont K, Moïse NP, et al. PET/Fluorescence Imaging: An Overview of the Chemical Strategies to Build Dual Imaging Tools. Bioconjug Chem. 2022; 33: 24–52.

27. Huang W, Li L, Zhou Y, et al. Preclinical evaluation of zirconium-89 labeled anti-Trop2 antibody–drug conjugate (Trodelvy) for imaging in gastric cancer and triple-negative breast cancer. Eur J Nucl Med Mol Imaging. 2025; 52: 2369–83.

28. Huang W, Wang T, Liang Y, et al. A zirconium-89-labeled antibody-drug conjugate PET probe for noninvasive monitoring of Nectin4 expression in breast cancer and lung cancer. Cell Rep Phys Sci. 2025; 6.

29. Jacobson O, Li Q, Chen H, et al. PET-Guided Evaluation and Optimization of Internalized Antibody–Drug Conjugates Targeting Erythropoietin-Producing Hepatoma A2 Receptor. J Nucl Med. 2017; 58: 1838–44.

30. Adumeau P, Vivier D, Sharma SK, et al. A Site-Specifically Labeled Antibody-Drug Conjugate for Simultaneous Therapy and ImmunoPET. Mol Pharm. 2018; 15: 892–8.

31. Ketchemen JP, Babeker H, Tikum AF, et al. Biparatopic anti-HER2 drug radioconjugates as breast cancer theranostics. Br J Cancer. 2023; 129: 153–62.

32. Wichmann CW, Burvenich IJG, Guo N, et al. Preclinical radiolabeling, in vivo biodistribution and positron emission tomography of a novel pyrrolobenzodiazepine (PBD)-based antibody drug conjugate targeting ASCT2. Nucl Med Biol. 2023; 122–123: 108366.

33. Song IH, Lee TS, Park YS, et al. Immuno-PET Imaging and Radioimmunotherapy of 64Cu-/177Lu-Labeled Anti-EGFR Antibody in Esophageal Squamous Cell Carcinoma Model. J Nucl Med. 2016; 57: 1105–11.

34. Keinänen O, Fung K, Brennan JM, et al. Harnessing 64Cu/67Cu for a theranostic approach to pretargeted radioimmunotherapy. Proc Natl Acad Sci. 2020; 117: 28316–27.

35. Lyashchenko SK, Esposito TV, Tran T, et al. Radiolabeling of CHX-A□-DTPA-Antibody Conjugates with [89Zr]ZrCl4. J Nucl Med. 2026; 67: 132–8.

36. Wood JL, Ghosh S, Houston ZH, et al. A first-in-class dual-chelator theranostic agent designed for use with imaging-therapy radiometal pairs of different elements. Chem Sci. 2024; 15: 11748–60.

37. Ketchemen JP, Babeker H, Tikum AF, et al. Biparatopic anti-HER2 drug radioconjugates as breast cancer theranostics. Br J Cancer. 2023; 129: 153–62.

38. Garanger E, Aikawa E, Reynolds F, Weissleder R, Josephson L. Simplified syntheses of complex multifunctional nanomaterials. Chem Commun. 2008; 0: 4792–4.

39. Adumeau P, Raavé R, Boswinkel M, et al. Site-Specific, Platform-Based Conjugation Strategy for the Synthesis of Dual-Labeled Immunoconjugates for Bimodal PET/NIRF Imaging of HER2-Positive Tumors. Bioconjug Chem. 2022; 33: 530–40.

40. Debie P, Declerck NB, van Willigen D, et al. The Design and Preclinical Evaluation of a Single-Label Bimodal Nanobody Tracer for Image-Guided Surgery. Biomolecules. 2021; 11: 360.

41. Canovas C, Moreau M, Vrigneaud J-M, et al. Modular Assembly of Multimodal Imaging Agents through an Inverse Electron Demand Diels–Alder Reaction. Bioconjug Chem. 2019; 30: 888–97.

42. Vivier D, Hautière M, Pineau D, et al. Synthesis and preclinical fuorescence imaging of dually functionalized antibody conjugates targeting endothelin receptor-Positive Tumors. Bioconjug Chem. 2023; 34: 2144–53.

43. Hautiere M, Vivier D, Dorval P, et al. Preoperative PET imaging and fluorescence-guided surgery of human glioblastoma using dual-labeled antibody targeting ETA receptors in a preclinical mouse model: A theranostic approach. Theranostics. 2024; 14: 6268–80.

44. Privat M, Bellaye P-S, Lescure R, et al. Development of an Easily Bioconjugatable Water-Soluble Single-Photon Emission-Computed Tomography/Optical Imaging Bimodal Imaging Probe Based on the aza-BODIPY Fluorophore. J Med Chem. 2021; 64: 11063–73.

45. Privat M, Massot A, Hermetet F, et al. Development of an Immuno-SPECT/Fluorescent Bimodal Tracer Targeting Human or Murine PD-L1 on Preclinical Models. J Med Chem. 2024; 67: 2188–201.

46. Chazeau E, Pipier A, Wegner KD, et al. NIR-II aza-BODIPY Platform for the Development of a Fluorescent Antibody Drug Conjugate. J Med Chem. 2025; 68: 7232–42.

47. Goodwin DA, Meares CF, McCall MJ, McTigue M, Chaovapong W. Pre-targeted immunoscintigraphy of murine tumors with indium-111-labeled bifunctional haptens. J Nucl Med Off Publ Soc Nucl Med. 1988; 29: 226–34.

48. Bohrmann L, Poulie CBM, Rodríguez-Rodríguez C, et al. Development of a 99mTc-labeled tetrazine for pretargeted SPECT imaging using an alendronic acid-based bone targeting model. PLOS ONE. 2024; 19: e0300466.

49. Altai M, Membreno R, Cook B, Tolmachev V, Zeglis BM. Pretargeted Imaging and Therapy. J Nucl Med. 2017; 58: 1553–9.

50. Verhoeven M, Seimbille Y, Dalm SU. Therapeutic Applications of Pretargeting. Pharmaceutics. 2019; 11: 434.

51. Hapuarachchige S, Artemov D. Theranostic Pretargeting Drug Delivery and Imaging Platforms in Cancer Precision Medicine. Front Oncol. 2020; 10: 1131.

52. Huang Z, Hu Y, Yang Y, Huang W, Wang Y, Ye D. Recent Advances in Pretargeted Imaging of Tumors in Vivo. Anal Sens. 2022; 2: e202200013.

53. Tian Y, Huang Z, Luo J, Ye D. Recent Advances in Pretargeted Strategy for Cancer Theranostics. ChemMedChem. 2024; 19: e202400462.

54. Gan J, Yu Y, Li Y, Wu D, Yu G. Host–guest Architectures: Advancing pretargeting strategies for precision theranostics. Precis Med Eng. 2025; 2: 100035.

55. Meng Y, Pang H, Zhou W, et al. The Critical Dosing Interval in Oncology Pretargeted Radionuclide Imaging and Therapy: Mechanisms, Optimization, and Dosimetric Impact. Bioconjug Chem. 2026; 37(6): 1073-1088.

56. Pratt EC, Mandleywala K, Bauer D, et al. ImmunoPET for mesothelin positive tissues using bio-orthogonal in-vivo click chemistry. Nucl Med Biol. 2025; 148–149: 109051.

57. Sarrett SM, Rodriguez C, Rymarczyk G, et al. Lysine-Directed Site-Selective Bioconjugation for the Creation of Radioimmunoconjugates. Bioconjug Chem. 2022; 33: 1750–60.

58. Zabrocki M, Delaney S, Hvass L, Battisti UM, Kjær A, Herth MM. In Vivo Comparison of Site-Specific and Site-Selective Methods for Pretargeted Imaging in a Murine Model of Colorectal Cancer. Mol Pharm. 2026; 23: 2089–96.

59. Poty S, Ordas L, Dekempeneer Y, et al. Optimizing the Therapeutic Index of sdAb-Based Radiopharmaceuticals Using Pretargeting. J Nucl Med. 2024; 65: 1564–70.

60. Mack KN, Bauer D, Carter LM, et al. Pretargeted alpha therapy in MUC16-positive high-grade serous ovarian cancer. Nucl Med Biol. 2025; 140–141: 108976.

61. Strebl MG, Yang J, Isaacs L, Hooker JM. Adamantane/Cucurbituril: A Potential Pretargeted Imaging Strategy in Immuno-PET. Mol Imaging. 2018; 17: 1536012118799838.

62. Jallinoja VIJ, Carney BD, Zhu M, Bhatt K, Yazaki PJ, Houghton JL. Cucurbituril–Ferrocene: Host–Guest Based Pretargeted Positron Emission Tomography in a Xenograft Model. Bioconjug Chem. 2021; 32: 1554–8.

63. Jallinoja VIJ, Carney BD, Bhatt K, et al. Investigation of Copper-64-Based Host–Guest Chemistry Pretargeted Positron Emission Tomography. Mol Pharm. 2022; 19: 2268–78.

64. Jallinoja VIJ, Abbriano CH, Bhatt K, et al. Pretargeting with Cucurbituril–Adamantane Host–Guest Pair in Xenograft Models. J Nucl Med. 2023; 64: 1203–9.

65. Vizier R, Boswinkel M, Moreau M, et al. Supramolecular Chemistry Enables Radiolabeling of Proteins under Mild Conditions. Mol Pharm. 2025; 22 (11): 7142-7149.

ASTATINE FOR BLADDER CANCER

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Bladder cancer

Bladder cancer most often presents with urinary symptoms, the most common of which is blood in the urine, sometimes without any associated pain. The cancer originates in the bladder lining; it remains superficial for a long time (non-muscle-invasive bladder cancer or NMIBC). If left untreated, it can invade the bladder muscle and then spread outside the bladder to the lymph nodes and eventually to distant sites, resulting in a poor prognosis.

Treatment for NMIBC involves transurethral resection of the tumor (TURT), followed - depending on the risk of recurrence - by intravesical instillations of chemotherapy and/or BCG, with close cystoscopy monitoring. The choice of treatment (mitomycin C, epirubicin, BCG) and the intensity of therapy depend on risk stratification (low, intermediate, and high) based on tumor size, multifocality, and grade.

The 5-year recurrence risk ranges from 46% to 78% for intermediate-grade NMIBC and increases for high-grade tumors with risk factors such as multiple tumors, prior recurrences, and a tumor size greater than 3 cm [1, 2].

When a patient does not respond or no longer responds to BCG therapy, management relies on a combination of multidisciplinary decision-making and referral for radical cystectomy or, if the patient is inoperable or refuses surgery, for conservative treatment options.

Total cystectomy with urinary reconstruction remains the standard of care for patients at high risk of disease progression (T1 Grade 2/3, carcinoma in situ, multiple recurrences) who no longer respond to BCG, as it provides the best local control and reduces the risk of progression to muscle-invasive cancer. Total cystectomy is particularly recommended for surgically eligible patients, following prior discussion of morbidity (ureterocutaneous fistula, diversions, complications) and quality of life.

In the absence of immediate cystectomy, several options are considered, depending on risk factors and local availability:

- Intravesical immunotherapies
- Alternating BCG or BCG combined with immunomodulatory agents (in clinical trials or off label) aim to restore a bladder immune response.
- Intravesical chemotherapy
- Instillations of monotherapies (mitomycin, gemcitabine, docetaxel, etc.) in short or sequential regimens, especially for high-grade papillary tumors.
- Innovative intravesical therapies
- Gene or viral therapies (e.g., instillations of viral vectors expressing cytokines or genes that restore the immune response, currently in development/clinical trials).

The most recently approved commercial product is Anktiva (nogapendekin alfa-inbakicept) in combination with BCG. Alongside it, pembrolizumab and nadofaragene firadenovec are the main FDA-approved bladder-preserving options with intravesical gemcitabine/docetaxel as emerging alternatives in selected centers.

The recommended overall strategy systematically includes discussing radical cystectomy as a first-line option for high-risk BCG-unresponsive NMIBC. In cases of refusal or surgical contraindications a sequential approach (intravesical chemotherapy, followed by innovative intravesical immunotherapy or systemic immunotherapy) and/or enrollment in clinical trials (intravesical or systemic) when possible, can be proposed. In any case it is proposed to maintain close monitoring (cystoscopies, biopsies, imaging) to rapidly detect any progression to a muscle-invasive stage, in which case cystectomy should be promptly reconsidered.

A New Therapeutic Approach: Alpha Immunotherapy

In this context, it seems advisable to develop alternative treatments tailored to the anatomical and histological characteristics of the residual tumor tissue in this type of cancer.

Over the past 10 years, targeted radionuclide therapy has demonstrated its efficacy in two clinical indications—neuroendocrine tumors and metastatic prostate cancer—using vectors labeled with the electron-emitting radionuclide lutetium-177. Approvals have been obtained in the US and Europe for these two clinical indications, leading to a large number of clinical developments involving this radionuclide across multiple indications.

During the same period, preclinical and clinical studies using the new class of alpha-emitting radionuclides have proliferated. Alpha particles consist of two protons and two neutrons, like the helium nucleus. They are characterized by a very short range from their point of emission - less than 0.1 mm - and very high energy, capable of causing virtually irreparable breaks in both strands of the DNA of the tumor cells. Given these two characteristics, the clinical indication of a bladder tumor that has not infiltrated the muscle is a particularly appropriate clinical target.

Indeed, following surgical resection, tumor residues are located on the bladder lumen surface and thus in direct contact with a vector labeled with an alpha-particle emitter instilled into the bladder. This situation is therefore well suited to the very short range of alpha particles.

Three radionuclides are currently being developed for alpha-immunotherapy: actinium-225 with a half-life of 10 days, lead-212 with a half-life of 10.6 hours, and astatine-211 with a half-life of 7.2 hours. The latter has the advantage of being produced in a cyclotron with an energy of 28 MeV. The number of such cyclotrons is still limited in Europe but is expected to increase with the growing number of clinical studies using astatine-211. In Nantes, the GIP Arronax cyclotron has sufficient energy to produce astatine-211.

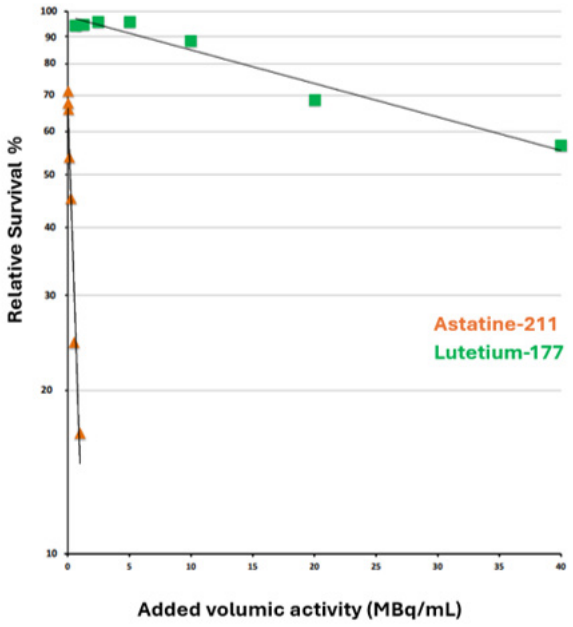
In this context, the biotech company Atonco has developed an alpha-immunotherapy project for bladder cancer that does not infiltrate the muscle and does not respond, or no longer responds, to conventional BCG treatment. It acquired a license to commercialize an anti-CA-IX antibody that recognizes more than 80% of non-Carcinoma in Situ (CIS) bladder cancer cells, as well as a method for radiolabeling the antibody with astatine-211, provided by the Australian radiopharmaceutical company Telix Pharmaceuticals. It subsequently developed a preclinical study program to demonstrate the feasibility of alpha-immunotherapy with astatine-211 for this indication [3].

Preliminary studies of alpha-immunotherapy for bladder cancer

The first step was to select a model to target tumor cells in residual tumor tissues following surgical resection. The choice fell on the CA-IX, which is expressed in 80% of tumor cells in stages Ta and T1 [4] and girentuximab, an anti-CA-IX antibody.

Girentuximab, was labeled with astatine-211 ([^{211}At]At-girentuximab, ATO-101™) and tested on the RT-112 cell line of human urinary bladder transitional cell carcinoma by exposing the cells to increasing activities of astatine-211 and, in another experiment, to increasing activities of lutetium-177 to compare the cytotoxic effects of these two radionuclides. Exposure of RT112 cells to 1 MBq/mL of [^{211}At]At-girnetuximab (ATO-101™) resulted in 85% cell death, whereas exposure to a 40-fold higher concentration, i.e., 40 MBq/mL of [^{177}Lu]Lu-girentuximab, resulted in a very modest cytotoxic effect estimated at only about 45% cell death. This result confirms that the cytotoxic effect of astatine-211 alpha particles is much higher than that of electrons emitted by lutetium-177 when irradiation is performed on low cell concentrations. This in vitro situation of tumor cells in a test tube can be roughly compared to the in vivo situation of superficial tumor cells in a bladder into which the radiopharmaceutical is instilled. This cytotoxicity result is encouraging for the prospect of clinical efficacy in Phase 1.

Figure 1. Cytotoxicity study of ATO-101™. Survival of RT112 cell line of human urinary bladder transitional cell carcinoma at D5 after exposure to [^{211}At]At-girentuximab (ATO-101™) and [^{177}Lu]Lu-girentuximab



In a second step, a biodistribution study was conducted in healthy mice to ensure that the radiopharmaceutical [^{211}At]At-girentuximab (ATO-101™), when instilled directly into the bladder, does not spread beyond the bladder into the rest of the body. As expected, the biodistribution study in healthy mice showed low radioactive uptake in systemic organs and tissues (<1% injected dose/gram) at 1 h, except in the bladder, which is the consequence of intravesical instillation. Hence, radioactive accumulation remained elevated despite the bladders being rinsed and emptied according to protocol. Four hours after emptying, a slight increase in activity was observed in some tissues such as the blood, lungs, spleen, and, mainly, stomach. Activity in the stomach is postulated to be due to ingestion related to animal self-grooming after instillation rather than a biodistribution effect.

The potential toxicity of intravesical instillation of [^{211}At]At-girentuximab was evaluated in healthy mice by histological examination of the bladder mucosa which showed no microscopic abnormal observations which could be attributed to the experimental procedure. The extrapolation of these data in healthy mice (0.7MBq in 30 µl volume of [^{211}At]At-girentuximab antibody dosed intravesically) corresponds to an activity of 933 MBq in 40 mL of [^{211}At]At-girnetuximab antibody intravesically instilled in human bladder. This level of activity is significantly higher than that planned for Phase 1.

Secondly, a clinical feasibility study (Pertinence, NCT04897763) was performed by Telix Pharmaceuticals and the Institut de Cancérologie de l'Ouest involving PET/CT imaging in six patients using [^{89}Zr]Zr-girentuximab to demonstrate tumor uptake and the absence of radioactivity diffusion beyond the bladder following intravesical instillation. This study confirmed the absence of extravesical leakage, except in one patient whose urethra had been injured during the insertion of the urinary catheter. It also visualized macroscopic tumor residue in one patient, while in the other patients the tumor residues were absent or too small to be visualized.

Following these studies, a Phase 1 First-in-Human (FIH) protocol was submitted to the French National Agency for Medicines and Health Products Safety (ANSM), which issued a favorable opinion in November 2025 (NCT07260162). This study (PERSEVERANCE EU) will evaluate Safety, Tolerability and Response of ATO-101™ in 24 Patients With Non-Muscle-Invasive Bladder Cancer.

About ATONCO

Atonco is a French biotechnology company specializing in the development of innovative radiopharmaceutical therapies based on alpha emitters, particularly astatine-211.

In collaboration with research centers and hospital partners, Atonco designs and develops targeted treatments for cancers resistant to conventional approaches. Its mission is to offer new safe, effective and personalized therapeutic options for cancer patients.

For more information, please visit www.atonco-pharma.com

ClinicalTrials.gov – NCT07260162

References

1- Sharma V, Chamie K, Schoenberg M et al. Natural history of multiple recurrences in intermediate-risk non-muscle invasive bladder cancer : lessons from a prospective cohort. Urology 2023 ;173 :134-141.

2- Grabe-Heyne K, Henne C, Mariappan P et al. Intermediate and high-risk non-muscle-invasive bladder cancer : an overview of epidemiology, burden, and unmet needs. Front Oncol 2023 ;13.1170124.

3- Rousseau C, Baumgartner P, Heymann MF et al. Preclinical and clinical feasibility studies as the first step before forthcoming intravesical instillation of (211At) At-anti-CA-IX antibody (ATO-101TM) study in patients with non-muscle-invasive bladder cancer unresponsive to standard of care. Cancers 2025 ;31 :1190.

4- Klatte T, Seligson DB, Rao JY et al. Carbonic anhydrase IX in bladder cancer. Cancer 2009 ;115 :1448-1458.

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PROMETHE ASSOCIATION – OVERVIEW

Alexia Daoust, Présidente déléguée

PROMETHE
PRecision Oncology MEdicine THEranostics

Since the early 2000s, cancer treatment options have significantly improved with the emergence of targeted therapies. However, cancer remains the leading cause of death in France, highlighting the continued need for innovative treatments. Radiotheranostics is increasingly recognized as a transformative approach in oncology.

Although radiotheranostics is emerging, its large-scale implementation still faces significant challenges. The defining challenge now is not whether the modality works, but whether the ecosystem can scale quickly enough to support its continued growth. The development of radiotheranostics requires close coordination between research institutions, hospitals, pharmaceutical and biotechnology companies, nuclear medicine specialists, and radioactive isotope production and distribution networks. In addition, the growing number of compounds entering clinical development is increasing the need for collaboration, expertise sharing, specialized training, and industrial infrastructure.

To address these challenges and support the rapid expansion of the field, PROMETHE (Precision Oncology Medicine Theranostics) was created and established under French non-profit association law in 2023.
The association was founded by Oncodesign Precision Medicine (OPM) and the Georges-François Leclerc Cancer Center (CGFL). Philippe Genne, President of OPM and founder of Oncodesign, serves as President of the association. Charles Coutant, Director General of CGFL and a renowned cancer surgeon and researcher, serves as Secretary.

PROMETHE brings together expertise from academia, hospitals, biotechnology and pharmaceutical companies and nuclear medicine stakeholders. Its founders have extensive experience in oncology research, drug development, innovation ecosystems and healthcare management.

PROMETHE pursues five main objectives:

1. Build regional, national and European network capable of accelerating and improving the discovery, development, and distribution of radiotheranostic medicines.
2. Develop a community of leading experts to enhance research and development productivity and facilitate faster patient access to innovative therapies.
3. Deploy a collaborative digital platform enabling knowledge sharing, networking, training and collaboration among hospitals, research laboratories, companies, and production facilities involved in nuclear medicine.
4. Promote the adoption of radiotheranostics in oncology by engaging pharmaceutical companies, academic institutions, hospitals, biotechnology firms, startups, CROs, students, public health organizations, and healthcare authorities.
5. Support industrial solutions for the distribution of medical radioactive materials, addressing one of the key challenges for the large-scale deployment of radiotheranostic treatments.

Through these initiatives, PROMETHE aims to strengthen the radiotheranostics ecosystem, foster innovation, and accelerate the availability of next-generation nuclear medicine therapies for cancer patients.

contact@promethe.eu

UNLOCKING THE FUTURE OF RADIOTHERANOSTICS THROUGH AI-POWERED DRUG DEVELOPMENT

Alexia Daoust [1], Kenji Shoji [1], Stéphane Gerart [1], Leila Outemzabet [1], Maria Eugenia Riveiro [1], Jan Hoflack [1], Philippe Genne [1]

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Introduction to radiotheranostics

Over the last two decades, radiotheranostics has progressively established its clinical value in oncology, particularly in advanced and treatment-resistant disease settings[1]. Initially regarded as a niche therapeutic modality, radiotheranostics has demonstrated meaningful clinical benefit in heavily pretreated patients while maintaining a favourable therapeutic index, establishing targeted radionuclide delivery as a durable component of modern cancer care. Nowadays, for example, PSMA-radiopharmaceutical (Pluvicto®, ^{177}Lu-vipivotide tetraxetan) is being tested in earlier lines of prostate cancer treatment, as demonstrated by the VISION trial and then the PSMAfore trial, which moved treatment to patients who had progressed after one androgen receptor pathway inhibitor but had not yet received taxane chemotherapy. The study demonstrated a significant improvement in radiographic progression-free survival, supporting earlier intervention[2]. This evidence led the FDA in 2025 to expand the indication of Pluvicto to patients eligible to delay chemotherapy, marking one of the first regulatory validations of radiotheranostics in an earlier treatment setting3. Likewise, in neuroendocrine tumors, the pivotal NETTER-1 trial established ^{177}Lu-DOTATATE (Lutathera®) as a practice-changing therapy, demonstrating a marked improvement in progression-free survival and a 79% reduction in the risk of progression or death compared with high-dose octreotide in patients with advanced midgut NETs[4].

Although only a limited number of indications have obtained regulatory approval, these successes have been transformative for the field.

The flow of capital into the sector has mirrored its commercial progress. In recent years, major pharmaceutical companies have completed several multi-billion-dollar acquisitions aimed at securing access to radiopharmaceutical technologies, development pipelines, and manufacturing networks, underscoring growing confidence in the long-term value of the field.
A fundamental shift is underway in oncology. As earlier diagnosis, precision imaging, targeted therapies, immunotherapies, and combinatorial schemes continue to improve outcomes, an increasing number of patients are living longer, and it is expected to treat 10 times more patients by radiotheranostics in the next 10 years[5].
For many tumor types, cancer is increasingly becoming a condition that can be monitored and managed over extended periods, with long-term disease control and quality of life emerging as central therapeutic goals. Yet, despite significant advances in surgery, chemotherapy, radiotherapy, and immunotherapy, disease progression remains inevitable for many patients, often driven by treatment resistance and tumor heterogeneity. These challenges have accelerated the shift toward precision medicine, which seeks to identify and exploit actionable molecular targets throughout the course of disease. In this setting, radiopharmaceuticals uniquely combine molecular imaging and targeted therapy, enabling both disease characterization and treatment within a single platform and positioning theranostic as a key component of modern oncology.

At OPM, we believe radiotheranostics is not a transient trend but rather a diagnostic and therapeutic platform that is becoming firmly embedded within the oncology arsenal. While the scientific rationale for radiotheranostics is compelling, the number of clinically actionable targets currently exploited remains extremely small relative to the biological complexity of advanced cancers. The next wave of radiotheranostics innovation, however, will require a significant expansion of validated molecular targets to address broader patient populations and new tumor types.

From Target Prioritization to Validation: Choosing Novel Radiotheranostic Targets

The human genome encodes a vast number of potential therapeutic targets, yet only a small fraction has reached clinical success. In radiotheranostic, identifying novel targets remains especially challenging because biological evidence is fragmented, validation cycles are long, attrition is high, and the development paradigm differs from conventional drug discovery. Both antibody drug conjugates (ADCs) and radiotheranostic share one logic, a targeting vector delivers a cytotoxic agent (a small-molecule payload for ADCs, a radioisotope for radiotheranostics) selectively to tumor cells. However, the number of targets that achieve sufficient efficacy without unacceptable toxicity remains very limited, and as a result, there is still little empirical guidance on what constitutes an optimal target.

We know that an ideal target for radiotheranostic should be highly expressed in tumor tissue, minimally expressed in healthy organs, addressable, and sufficiently stable throughout disease progression, including in metastatic sites. No framework is foolproof. A target may satisfy most selection criteria yet fail due to factors not apparent during prioritization. For example, GPA33, expressed in over 95% of colorectal cancers and exhibiting favourable biological characteristics, repeatedly failed probably due to the fast renewal of colon cells or due to the epithelial cell polarity[6-8]

MUC1 provides a complementary example. Although highly expressed across multiple tumor types and aberrantly glycosylated in cancer, its extensive shedding creates a soluble-antigen sink, while epitope accessibility is restricted by dense glycocalyx. Consequently, numerous therapeutic programs have delivered limited clinical benefit[9-10].

The shared lessons shape how we prioritize: specificity and abundance are necessary but not sufficient. The variables that most often prove decisive: homogeneity across the cells that survive treatment, the size of the shed-antigen sink, and the accessibility of the chosen epitope must be interrogated early and cheaply (single-cell or RNAscope analysis, and explicit characterization of shedding and epitope masking) before committing the resource that validation demands. A prioritization framework earns its value not only by identifying promising targets, but also by rapidly de-prioritizing those unlikely to succeed.

Conventional target discovery approaches are often slow, costly, and constrained by the complexity of cancer biology, particularly tumor heterogeneity and the vast amounts of genomic, transcriptomic, proteomic, and imaging data that must be integrated simultaneously. As a result, many potentially relevant targets are overlooked or cannot be efficiently validated using traditional experimental methods. In this context, we consider augmented intelligence, particularly deep learning approaches, to represent a promising solution to this bottleneck. Here, augmented intelligence refers to a human-in-the-loop decision-support framework in which computational models help scientists and clinicians integrate complex evidence, identify relevant biological patterns and prioritize hypotheses, while expert judgment remains central to interpretation and validation. By enabling the integration of multi-omics datasets, biological network information and patient-level clinical data, augmented intelligence can help identify novel therapeutic targets with greater accuracy, efficiency and translational relevance. Knowledge graph-based approaches can first provide a structured framework to integrate heterogeneous data sources, including genomic, transcriptomic, proteomic, spatial transcriptomic, protein localization and patient-level clinical data such as treatment history, prior therapeutic exposure and response patterns. Deep neural networks and graph neural networks (GNNs) can then be applied to this integrated representation to identify candidate molecules that are not only biologically relevant, but also clinically actionable and more likely to exhibit the characteristics required for successful radiotheranostic targeting.

Furthermore, we argue that target identification alone is insufficient for radiotheranostic development. Once a candidate target has been identified, its druggability, targeted epitope and its ability to bind radiolabeled ligands with high affinity must be evaluated. Here, augmented intelligence provides additional value through protein structure prediction and drug–target interaction modeling.

Technologies such as AlphaFold can support protein structure prediction and provide structural hypotheses for binding-site identification and rational ligand design[11]. In parallel, graph-based and deep learning models can help prioritize ligand–target pairs before experimental validation. For example, GraphDTA, a GNN-based drug–target affinity (DTA) model, can estimate drug–target binding affinity[12], while DTI-HETA, a drug–target interaction (DTI) model based on heterogeneous graphs with attention mechanisms, can predict potential drug–target interactions[13]. Knowledge graph-based approaches can first provide a structured framework to integrate heterogeneous data sources, including genomic, transcriptomic, proteomic, spatial transcriptomic, protein localization and patient-level clinical data such as treatment history, prior therapeutic exposure and response patterns. Deep neural networks and GNNs can then be applied to this integrated representation to identify candidate molecules that are not only biologically relevant, but also clinically actionable and more likely to exhibit the characteristics required for successful radiotheranostic targeting.

These approaches should be considered as prioritization tools rather than substitutes for biochemical, cellular, imaging and dosimetry validation, but they may help reduce the experimental search space and accelerate early-stage de-risking.

Importantly, we propose that future augmented intelligence applications in radiotheranostics should extend beyond conventional drug discovery frameworks and incorporate radiopharmaceutical-specific considerations. Unlike traditional therapeutics, radiopharmaceuticals are influenced by radionuclide decay, radiation-induced molecular damage, chelator stability, and unique pharmacokinetic properties. Therefore, next-generation augmented intelligence models should integrate biological target information with radionuclide characteristics, radiochemistry parameters, and molecular imaging data in order to optimize both target selection and radioligand design. Overall, we propose an augmented intelligence -driven development pipeline in which multi-omics integration, target discovery, target validation, ligand optimization, and molecular imaging are connected within a continuous workflow. Such an approach could substantially accelerate the identification of novel targets and facilitate the expansion of personalized radiotheranostic to a broader range of cancers

A framework for de-risking drug development of novel targets with augmented intelligence

The OncoSNIPE program run by OPM is a multicentric, interventional study with the primary objective to identify early and / or late markers of resistance to non-interventional treatment, in 600 adult patients with locally advanced or metastatic triple negative or Luminal B breast cancer, non-small-cell lung cancer or pancreatic ductal adenocarcinoma. The primary aim of OncoSNIPE is to elucidate the resistance mechanisms that emerge in patients by monitoring their treatment response over time. OPM has collected multiple data including high-throughput sequencing (Exome-seq and RNAseq), clinical data, medical images, patient derived organoids and immunological profile by ELISA. OncoSNIPE provides a relevant framework for applying augmented intelligence to the de-risking of novel radiotheranostic targets. Its value lies not only in the size of the cohort, but also in the prospective, multimodal and longitudinal nature of the data collected. OncoSNIPE integrates clinical annotations, tumor molecular profiling, blood-based longitudinal analyses, medical imaging and, in selected settings, patient-derived biological models such as organoids[14] (see figure 1). This heterogeneity enables a dynamic understanding of treatment response, resistance and disease evolution. Because the program reflects current clinical practice, it provides access to patient trajectories that are more closely aligned with today's standards of care than those captured in many older public datasets. This is important because target relevance may change with evolving treatment strategies.

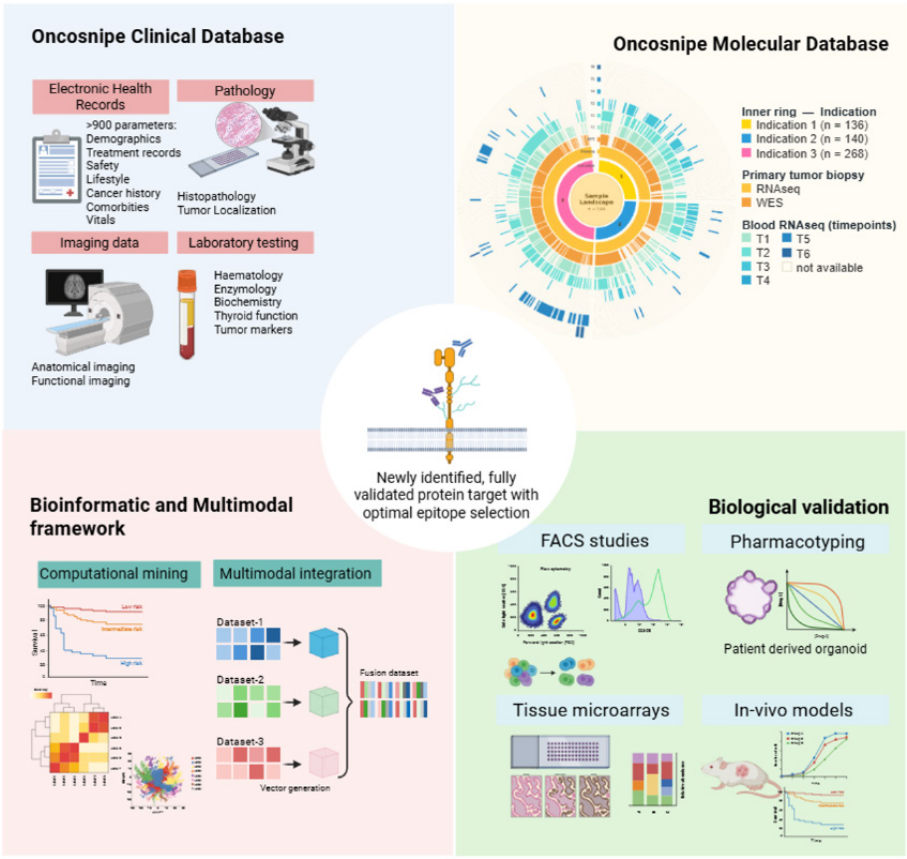

Figure 1: Integrated multi-omics and clinical platform accelerating target discovery and precision medicine development

For radiotheranostics, this type of resource can help answer a more translational question: not only “which genes are expressed?”, but “which targets remain biologically relevant, detectable, safe and actionable in patients exposed to modern therapeutic pressure?”. In this context, augmented intelligence can help identify weak but coherent biological signals across heterogeneous data layers, prioritize hypotheses for experimental validation and eliminate non-viable targets earlier in development. Several complementary analytical layers can be derived from a resource such as OncoSNIPE. Clinical data can define robust phenotypes, including durable responders, rapid progressors, primary resistant patients and patients developing acquired resistance. Tumor RNA-seq and exome data can be used to characterize differential expression, pathway activity, molecular subtypes, mutational landscapes, copy-number alterations and fusion events. Longitudinal blood transcriptomics can capture systemic immune and inflammatory dynamics over time. Imaging and radiomic features can describe tumor burden, lesion heterogeneity and progression patterns. Finally, patient-derived organoids provide a functional validation layer by enabling computational predictions to be tested in experimental models established from the same patient tumors, thereby linking molecular insights to observed drug responses[15-17].

These analyses can then be integrated into a radiotheranostic-specific target assessment workflow. Candidate targets can first be detected through molecular and pathway analyses, then filtered according to target-specific criteria such as expression level, tumor selectivity, reproducibility across patients and lesions, and biological relevance to disease progression or treatment resistance. A second filter can then evaluate radiotheranostic-specific feasibility, including cell-surface or extracellular accessibility, ligand/vector tractability, imageability, internalization, residence time, dosimetry compatibility, normal-tissue exposure and patient stratification potential[18-20].(see figure 1 and 2)

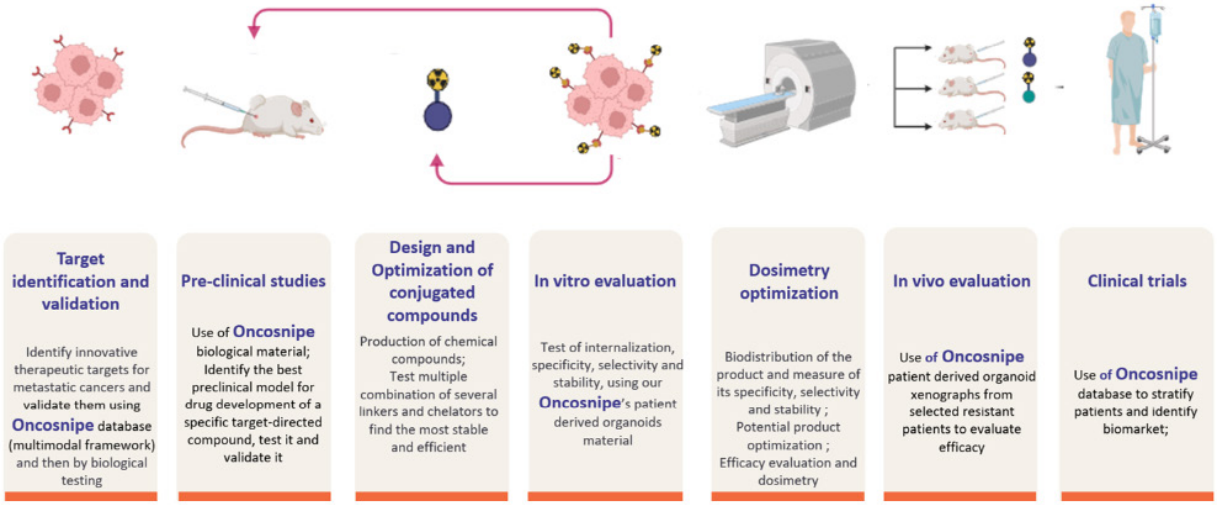

*Figure 2: From target to clinic: developing targeted (radio)therapeutic compounds with the Oncosnipe® database. Schematic overview of the sequential pipeline used to identify, design, and validate target-directed conjugated compounds for the treatment of metastatic cancers. The workflow comprises seven stages: (1) **Target identification and validation** — innovative therapeutic targets are identified using the Oncosnipe multimodal framework and confirmed by biological testing; (2) **Pre-clinical studies** — Oncosnipe-derived biological material is used to select and validate the most appropriate preclinical model for a given target-directed compound; (3) **Design and optimization of conjugated compounds** — chemical compounds are produced and iteratively refined by screening combinations of linkers and chelators to maximize stability and efficiency (iterative loop indicated by the arrows); (4) **In vitro evaluation** — internalization, specificity, selectivity, and stability are assessed using Oncosnipe patient-derived organoids; (5) **Dosimetry optimization** — biodistribution, specificity, selectivity, and stability are measured, followed by efficacy evaluation, dosimetry, and further product optimization; (6) **In vivo evaluation** — efficacy is tested in patient-derived organoid xenografts established from selected treatment-resistant patients; and (7) **Clinical trials** — the Oncosnipe database is used to stratify patients and identify predictive biomarkers. Illustrations above each stage depict the corresponding experimental steps, from tumor cell models and murine studies through radiolabeled compound design, imaging-based evaluation, and eventual clinical translation.*

Human-in-the-loop: augmented intelligence, not automation

This process must remain human-in-the-loop, where augmented intelligence serves as a decision-support layer rather than an autonomous decision-maker. Its role is to synthesize complex multimodal evidence and surface prioritized hypotheses, while leaving final target selection and translational decisions to the expert judgment. In radiotheranostic, this approach is intended to support, not replace, expert decision-making by improving the transparency, consistency, and speed of target prioritization and go/no-go decisions.

At OPM, we believe that augmented intelligence will be transformative for the future of radiotheranostic. AI-driven discovery frameworks have the potential to accelerate target identification, uncover previously underexplored biological associations, and generate actionable hypotheses for preclinical validation. In addition, they can support de-risking across radiopharmaceutical-specific aspects of drug development, including epitope selection and radioligand design, as well as later-stage activities such as biomarker identification and patient stratification.

Conclusion

Currently, the challenge is no longer to demonstrate that radiotheranostic has established its place in oncology, but rather to define how to best harness its full potential. The future of radiotheranostics will depend on more than radionuclide chemistry or vector engineering alone. It will depend on the ability to select the right targets for the right patients, using the right combination of biological evidence, chemistry, clinical context, imaging feasibility and translational judgment. Multimodal programs such as OncoSNIPE can help make this possible by transforming patient-derived data into an evidence-based framework to support drug development de-risking for target de-risking. Augmented intelligence is an enabling layer for the next generation of radiotheranostic innovation. The central challenge is no longer to discover more targets, but to navigate biological complexity in a more informed and systematic way in order to identify and prioritize those most likely to shape the next generation of molecular radiotherapy. The central challenge now lies in navigating biological complexity in a more informed and systematic way, to identify and prioritize the targets that will shape the next generation of radiotheranostics.

About OPM: Oncodesign Precision Medicine (OPM) is a French biopharmaceutical company focused on precision medicine, developing targeted therapies for patients with resistant and metastatic cancers. The company places the patient at the center of its technology platforms, aiming to deliver more personalized and effective cancer treatments.

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REFERENCES

1. Jadvar H, Quinn DI. Targeted Alpha-Particle and Beta-Particle Therapy in Prostate Cancer. PET Clinics. 2017.
2. Morris MJ, et al. Phase III PSMAfore Trial of Lutetium-177–PSMA-617 in Taxane-Naïve Patients with Metastatic Castration-Resistant Prostate Cancer. Journal of Clinical Oncology. 2024.
3. U.S. Food and Drug Administration (FDA). FDA expands indication for Pluvicto® (lutetium Lu 177 vipivotide tetraxetan) for PSMA-positive metastatic castration-resistant prostate cancer. 2025.
Available at: https://www.fda.gov
4. Strosberg J et al. NETTER-1 Trial Investigators. Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors. N Engl J Med. 2017.
5. Khalifé, Accélérer le développement de la médecine nucléaire thérapeutique en oncologie. Sénat 2026.
Available at : https://www.senat.fr/leg/exposes-des-motifs/ppl25-527-expose.html
6. Welt S, et al. Phase I/II Studies of GPA33-Targeted Radioimmunotherapy in Colorectal Cancer. Clinical Cancer Research. 2003.
7. Infante JR, et al. Safety and Pharmacokinetics of Humanized Anti-GPA33 Antibody in Advanced Colorectal Cancer. 2013.
8. Börding T, et al. Advances in GPA33-Targeted Radiopharmaceutical Development. 2024.
9. Schimanski CC, et al. MUC1-Targeted Immunotherapy in Colorectal Cancer Liver Metastases. 2020.
10. ABCSG-34 Trial Investigators. MUC1-Based Immunotherapy in Early Breast Cancer. 2024.
11. Jumper et al. Highly Accurate Protein Structure Prediction with AlphaFold. Nature. 2021.
12. Nguyen et al. GraphDTA: Predicting Drug–Target Binding Affinity with Graph Neural Networks. Bioinformatics. 2021.

13. Shao et al. DTI-HETA: Prediction of Drug–Target Interactions Based on GCN and GAT on Heterogeneous Graph. Briefings in Bioinformatics. 2022.
14. Vachenc et al. OncoSNIPE® Study Protocol, a Study of Molecular Profiles Associated with Development of Resistance in Solid Cancer Patients. BMC Cancer. 2022.
15. Nikolaou et al. A Machine Learning Approach for Multimodal Data Fusion for Survival Prediction in Cancer Patients. Npj Precision Oncology. 2025.
16. Kang et al. Application of Radiomics-Based Multiomics Combinations in the Tumor Microenvironment and Cancer Prognosis. J Transl Med. 2023.
17. Thorel et al. Patient-Derived Tumor Organoids: A New Avenue for Preclinical Research and Precision Medicine in Oncology. Experimental and Molecular Medicine. 2024.
18. Primac et al. The Molecular Blueprint of Targeted Radionuclide Therapy. 2025.
19. Berton et al. New Tactics in the Design of Theranostic Radiotracers. Nat Rev Clin Oncol. 2024.
20. Pandit-Taskar et al. Dosimetry in Clinical Radiopharmaceutical Therapy of Cancer: Practicality Versus Perfection in Current Practice. J Nucl Med. 2021.

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🗓️Tuesday, September 15

📍 Morning : PSCC, The Hive, Villejuif | Afternoon : CEA, Service Hospitalier Frédéric Joliot, Orsay

🕛 9 :00 – 17 :00 *(Welcome coffee from 8:45)*

The programme will feature:

- An **opening keynote** by **Dr. Désirée Déandréis**, Head of the Nuclear Medicine Department at Gustave Roussy.
- An overview of **current market dynamics** presented by **MabDesign**.
- **Expert panel discussions on theranostics, radioligand therapy, and ecosystem strategy,** bringing together start-ups, clinicians, industry leaders, and institutional stakeholders.
- An afternoon **learning expedition to the CEA**, offering participants a unique opportunity to discover its facilities and expertise

Register now: Next-Generation Radiopharmaceuticals Symposium - Driving Innovation in Cancer Care - Home

UPCOMING MABDESIGN EVENTS

Join us at our next scientific and networking events in 2026

EVENTS 2026

11TH BIOPRODUCTION CONGRESS

22-23 September 2026 - Lyon - France

by mabdesign THE BIOTHERAPY EXPERT & c3p build tomorrow

TRACKS

Biologics developability · Analytical methods · Process modelling & Digital twins · Sustainable manufacturing · Quality & Regulatory · Breakthrough innovations in bioproduction

KEY FIGURES OF THE 2025 EDITION

550+ Attendees

75+ Expert Speakers

53 Sponsors & Exhibitors

600+ B2B meetings

5 Workshops

www.biopcongress.com

Immunotherapies & Innovations for Infectious Diseases

10th Edition - November 2026 - Lyon France

TRACKS

Alternatives to current Antibiotics · Immunotherapies & new biotherapeutics · Latest developments in Vaccines · Diagnostic Prognostic and theragnostic Biomarkers

KEY FIGURES OF 2025 EDITION

280+ Attendees

29 High-profile speakers

20 Sponsors & Exhibitors

250+ B2B meetings

MABDESIGN ONLINE RESOURCE CENTER

BIO-HUB

MABDESIGN'S RESOURCE CENTER

Launched in 2024, MabDesign's Bio-hub houses a collection of pillar articles, insights from our in-house analysts, experts & KOL interviews and monthly biopharmaceutical pipeline analysis together with a dedicated section for our famous Immunowatch and BioprocessWatch editions. Check out our extensive content in the field of biopharmaceuticals and bioprocessing here: **https://mabdesign.fr/en/bio-hub-mabdesign/**

Next on Watch

- **2026 : Immunowatch Radiopharmaceuticals, Immunowatch Genetic Disorders**

- **2027: Calendar to be announced in December**

We are currently looking for scientific contributions and sponsors for these various editions. Reach out to Gavin Vuddamalay, our Head of Scientific Affairs **gavin.vuddamalay@mabdesign.fr**, to learn about the available opportunities and deadlines.

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Disclaimer: *While MabDesign cannot guarantee that this Immunowatch edition is error-free due to the non-exhaustiveness of our various databases and sources, we will do our best to correct any omission or errors brought to our attention. Every amended version will be archived on our website.*

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