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Review Article

Beyond Inhibition: Emerging Small-Molecule Modalities in Oncology (Molecular Glues, Covalents, and Radiotheranostics)

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Abstract:

Background: Small-molecule drugs have transformed oncology, but conventional inhibitors are limited by resistance, restricted target scope, and declining durability. **Methods:** We reviewed emerging small-molecule modalities—molecular glues, covalent inhibitors, and radiotheranostics—focusing on their mechanisms, clinical applications, and translational challenges. Key clinical trials and representative examples were identified from recent oncology literature.

Results: Molecular glues enable targeted degradation of previously undruggable proteins, with clinical success in multiple myeloma (IMiDs). Covalent inhibitors achieve durable suppression of oncogenic drivers such as KRAS^G12C and BTK, as shown in CodeBreaK100 (sotorasib; N=126; ORR 37%). Radiotheranostics combine imaging and therapy, exemplified by VISION (PSMA-617; N=831; OS HR 0.62) and NETTER-1 (Lutathera; N=229; PFS HR 0.21). Collectively, these modalities expand the druggable proteome, improve durability, and advance precision oncology.

Conclusion: Emerging small-molecule approaches mark a paradigm shift from inhibition alone to targeted degradation, durable covalent engagement, and diagnostic–therapeutic hybrids. Future priorities include improving selectivity, biomarker integration, scalable manufacturing, and equitable global access.

Keywords: Molecular Glues; Covalent Inhibitors; Radiotheranostics; Oncology Drug Discovery; Targeted Protein Degradation; Precision Oncology

Introduction

For the last forty years, tiny molecules have been very important to making progress in cancer treatment. From the early use of hormone therapies for breast and prostate cancer to the introduction of kinase inhibitors that changed the way chronic myeloid leukaemia and non-small cell lung cancer are treated, these drugs have shown that chemical precision can lead to big improvements in health (1). The path of traditional small-molecule drug discovery has, however, reached a crucial turning point. Resistance to inhibitors arises almost invariably, whether via secondary mutations in the drug target, adaptive bypass routes, or modifications in drug transport and metabolism. Also, the fact that humans rely on well-defined catalytic niches has made many parts of the cancer proteome, especially transcription factors, scaffolding proteins, and disordered domains, "undruggable"(2). These facts show both the strengths and weaknesses of the classic inhibition model.

Recent advancements have expanded the chemical conceptualisation in oncology beyond the mere inhibition of enzyme activity. A new generation of small-molecule methods is pushing the limits of what is possible by using alternative ways to regulate proteins and deliver drugs. Molecular glues, for example, do not stop new protein-protein connections; instead, they encourage them. This changes the way cells break down proteins, making it easier for oncogenic drivers to get to them. Covalent small compounds were originally looked at with trepidation because of safety concerns, but today they are known to be able to permanently silence hard-to-reach targets like KRAS^G12C and BTK. Simultaneously, radiotheranostics are changing the role of tiny molecules into precise tools that can diagnose and cure cancer at the same time through isotope conjugation (3).

This study analyses these three new modalities, focusing on their molecular underpinnings, clinical uses, and translational challenges. We want to show both their potential and the important questions that will influence their future by putting them in the context of the larger history of small-molecule oncology.

Despite decades of progress, the field now faces a critical challenge: conventional small-molecule inhibitors are increasingly limited by resistance, restricted target scope, and diminishing clinical returns. Addressing these limitations is significant because most oncogenic drivers remain “undruggable,” and patients with resistant disease urgently need more durable therapeutic options. This study examines three emerging small-molecule modalities—molecular glues, covalent inhibitors, and radiotheranostics—as innovative strategies to overcome these barriers and redefine the future of precision oncology.

Limitations of Conventional Small-Molecule Inhibitors

The literature used in this review was selected from peer-reviewed articles published between 2015 and 2020 from databases such as PubMed, Scopus and Google Scholar using search terms such as ‘drug discovery’, ‘pharmacological innovations’, ‘AI in drug development’, ‘challenges of drug discovery’. Papers were selected based on relevance to the theme, content quality and recency. No protocol of systematic review was used. Generative AI tools were not used in the preparation of this manuscript. Minor language editing tools were used to improve clarity and grammar.

Even while they have the potential to change things, traditional small-molecule inhibitors have well-known problems that restrict their usefulness in the long term. One of the most important of these is the fact that resistance is almost certain to happen. Tumour cells are very good at changing the way they send signals to avoid drug pressure. For tyrosine kinase inhibitors, subsequent mutations in the target often make it harder for the medicine to bind. For example, the EGFR T790M mutation in lung cancer or the G1202R mutation in ALK-driven tumours (4).

Even when the main binding site is still there, malignancies often use adaptive bypass signalling to turn on parallel pathways that bring back signals for growth and survival. Efflux pumps and changes in metabolic pathways make it even harder for drugs to build up inside cells. This makes it possible for tumours that were sensitive at first to come back. The range of targets available for classical inhibition is equally limited. Successful inhibitors usually depend on clearly defined, deep binding pockets that can hold a lot of affinity (5). This condition leaves out a lot of the proteome, including transcription factors, scaffolding proteins, and intrinsically disordered regions, which don't have such voids. These types of proteins are very important in the development of cancer, but they can't be targeted by typical drug design. This supports the idea of the "undruggable" proteome.

Selectivity is another problem that keeps coming up. Even when inhibitors have a high target affinity, it's hard to avoid off-target interactions, especially in protein families with conserved structural features, like kinases. This can lead to unforeseen physiological consequences, varying from mild side

effects to dose-limiting toxicities. At the same time, great on-target potency may not necessarily be a good thing. For example, some kinase inhibitors might be cardiotoxic because they completely block signalling, which stops normal tissue activities (6).

All of these things together make up what could be called a clinical plateau. Inhibitors often produce remarkable initial responses, especially in genetically characterised malignancies; nevertheless, these advantages are typically ephemeral. Resistance develops, tumour heterogeneity manifests, and lasting cures continue to be unattainable for the majority of advanced malignancies. Consequently, the field faces a biological limitation intrinsic to the paradigm of inhibition. To go over this plateau, we need treatment techniques that can extend the druggable proteome, get around adaptive resistance, and keep tumours under control for a long time without causing too much harm. These unmet needs have spurred the quest for novel small-molecule modalities that transcend mere inhibition to embrace fundamentally distinct mechanisms of action (7).

These unmet needs have spurred the quest for novel small-molecule modalities that transcend inhibition. The next section explores molecular glues, a pioneering approach that expands the druggable proteome through targeted degradation.

Molecular Glues: Inducing Protein-Protein Interactions

Mechanistic Basis

Molecular glues signify a transformative advancement in drug development, operating not as inhibitors but as enhancers of novel protein–protein interactions. Molecular glues don't stop an enzyme from working by blocking its active site. Instead, they stabilise weak or temporary connections between a target protein and an E3 ubiquitin ligase, which eventually leads to the target protein being broken down by the proteasomal pathway. This technique makes it possible to selectively get rid of proteins that have long been thought to be "undruggable," such as several transcription factors and scaffolding proteins that are important for cancer growth (8). Figure 1 shows how molecular glues work at their most basic level. It depicts how the glue molecule brings the E3 ligase and the target protein closer together, which helps the ubiquitination process. This leads to the target being broken down by proteasomes, which stops it from being able to cause cancer. This change from stopping proteins from working to breaking them down is a new way to treat cancer. It opens up new proteins that were previously inaccessible to classic small-molecule therapies (3). Table 1 gives a summary of the differences across small-molecule modalities, including their mechanisms, clinical uses, and examples. This table makes it easy to see how Molecular Glues, Covalent Inhibitors, and Radiotheranostics all work differently to fight cancer.

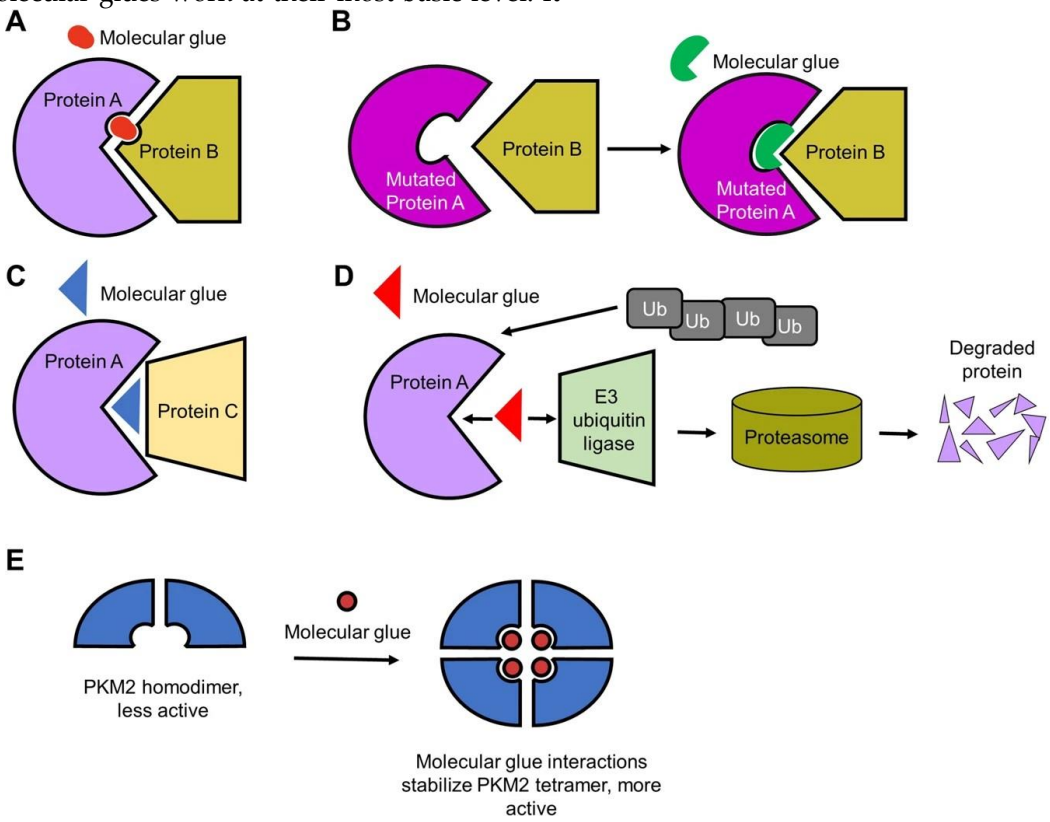

Figure 1 (Molecular Glue Mechanism).

"Mechanism of Molecular Glue-Mediated Targeted Protein Degradation. The schematic shows how molecular glues bridge an E3 ligase and a protein of interest (POI), leading to polyubiquitination and proteasomal degradation. Unlike inhibitors that block function, glues catalytically eliminate the protein, expanding druggable targets." Weagel EG, Foulks JM, Siddiqui A, Warner SL. Molecular glues: enhanced protein-protein interactions and cell proteome editing.

Table 1 (Comparison of Modalities): Comparison of Small-Molecule Modalities. The table outlines the mechanisms, representative clinical applications, and examples of molecular glues, covalent inhibitors, and radiotheranostics.

Modality	**Mechanism**	**Clinical Applications**	**Examples**
Molecular Glues(8)	Facilitate protein-protein interactions, leading to protein degradation	Targeting transcription factors and scaffolding proteins in cancer	Thalidomide, Lenalidomide
Covalent Inhibitors(9)	Irreversible bond formation with target proteins	Inhibition of oncogenic drivers like KRAS, BTK	Sotorasib (KRAS G12C), Ibrutinib (BTK)
Radiotheranostics(10)	Conjugation of small molecules to radioisotopes for imaging and therapy	Diagnosis and treatment of cancer, e.g., prostate cancer	PSMA-617 (prostate cancer), Lutetium-177-DOTATATE (neuroendocrine tumors)

Historical Perspective

The field's origins are closely linked to thalidomide, which was first sold as a sedative in the 1950s. Its retraction due to disastrous teratogenic consequences serves as a cautionary example in pharmacology. But decades later, the discovery that thalidomide and its derivatives work as molecular glues for the CRBN E3 ligase complex changed its legacy. Thalidomide drugs, lenalidomide and pomalidomide, became powerful immunomodulatory medicines (IMiDs) by encouraging the breakdown of important transcription factors in multiple myeloma. This dual legacy shows both the risks of unexpected off-target interactions and the chances that come with rethinking molecular mechanisms. This sets the foundation for the systematic creation of glue-based degraders (11).

Key Case Studies

The IMiD class exemplifies molecular glues. Lenalidomide and pomalidomide have become pivotal in the treatment of multiple myeloma by enlisting the E3 ligase cereblon to facilitate the degradation of transcription factors like IKAROS Family Zinc Finger 1 (IKZF1) and IKAROS Family Zinc Finger 3 (IKZF3). Their success confirmed that degradation, rather than only inhibition, could ensure lasting disease management. Significantly, these drugs demonstrated the potential immunomodulatory effects of targeted degradation, as their anticancer activity is partially derived from modified cytokine signalling and T cell activation (12).

Indisulam has recently shown that molecular glue action is not limited to cereblon. Indisulam facilitates the recruitment of the DCAF15 substrate receptor, resulting in the degradation of RBM39, an RNA splicing factor. Despite its inconsistent clinical trajectory, indisulam demonstrated that novel ligase–substrate combinations may be utilised by relatively tiny compounds. This facilitated the expansion of glue-mediated degradation.

In addition to Cereblon (CRBN) and DCAF15, current research has uncovered new degraders that function via different ligases or unique substrate profiles. This includes chemicals that function independently of CRBN, expanding the resources for addressing resistant tumours and diversifying the degradable proteome (13). Collectively, these case studies highlight that molecular glues can reveal therapeutic vulnerabilities that orthodox drug discovery methods have overlooked.

Oncologic Applications

Molecular glues hold a lot of promise as medicines, notably in cancer treatment, where transcription factors and scaffolding proteins are very important yet have always been hard to work with in traditional pharmacology. IKZF1 and IKZF3 degradation in multiple myeloma highlights this accomplishment, indicating that transcriptional regulators can be successfully removed in a therapeutic environment (14). Emerging glue degraders that target splicing factors and scaffolding proteins also point to a way to break down cancer-causing networks that rely

on protein–protein interactions instead of enzymes. These applications highlight the distinctive capacity of molecular glues to convert hitherto unattainable proteins into viable therapeutic targets in haematologic and potentially solid cancers (8).

Challenges

Molecular glues are quite difficult to work with, even though they hold a lot of promise. It is still not easy to predict degradable substrates because interactions caused by glue depend on small structural compatibilities. Resistance can develop due to mutations in E3 ligase components, as evidenced in clinical contexts. These problems show how important it is to have better discovery platforms and a better understanding of how glue-mediated relationships work (15).

Future Outlook

Rational and computationally guided discovery is the way forward for molecular glues. Artificial intelligence and machine learning are starting to be able to forecast how well ligases and substrates will work together. This opens up new methods to create things instead of just finding them by chance. To fully realise their therapeutic potential, it will be necessary to extend beyond CRBN and VHL to a more extensive ligase repertoire. Table 2 shows that each new modality has its own pros and cons. This table shows the pros and cons of each modality for use in oncology, including target range, durability, and safety. It also lists the problems that still need to be fixed (16).

While molecular glues open new doors for targeting undruggable proteins, another emerging class—covalent inhibitors—demonstrates how chemical precision can be leveraged to achieve durable target engagement.

Table 2. Advantages and Challenges of Emerging Modalities:

Modality	Advantages	Challenges
Molecular Glues(16)	Target previously 'undruggable' proteins, with potential for durable response	Predicting degradable substrates, resistance through ligase mutations
Covalent Inhibitors(9)	Sustained target inhibition, overcoming resistance, high potency	Off-target reactivity, potential immunogenicity, and irreversible binding risks
Radiotheranostics(10)	Dual function: imaging and therapy, precise tumor targeting	Challenges in isotope production, off-target accumulation, and limited tumor accessibility

Covalent Small Molecules: Locking Targets with Chemical Precision

Mechanistic Rationale

Covalent inhibitors are a conscious revival of one of chemistry's oldest techniques: utilising bonds that can't be broken to stop biological action. Covalent drugs, on the other hand, create a persistent chemical bond—usually to a nucleophilic residue like cysteine, lysine, or serine—within the active site or a nearby regulatory domain. This is different from typical reversible inhibitors, which depend on equilibrium occupancy. This link guarantees extended target inactivation, surpassing the plasma clearance of the medication and thereby separating pharmacokinetics from pharmacodynamics. This method works especially well for kinases and other proteins that have cysteine residues that are easy to get to near functional regions (17).

By covalently attaching the inhibitor, it is possible to get a high level of activity even when the systemic concentrations are low. Additionally, these connections can avoid competition with plentiful cellular substrates like ATP. This mechanical rationale is what has brought back interest in covalent small molecules in oncology. What was formerly seen as risky is now a key part of therapeutic discovery (18). Figure 1 shows how covalent inhibitors make permanent connections with their target proteins, which keeps them from working.

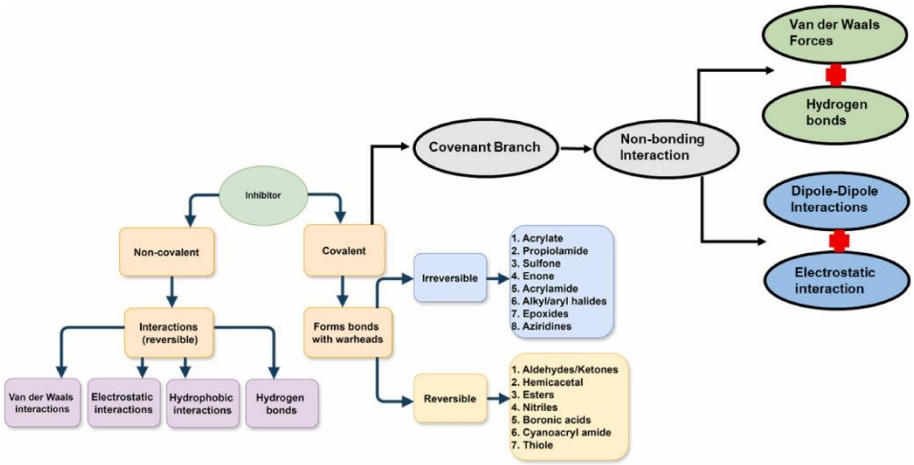

Figure [1]: Mechanism of Small-Molecule Inhibition via Covalent Bond Formation.

This figure illustrates the interaction between a covalent inhibitor and its target protein, highlighting the formation of a covalent bond between the inhibitor and a nucleophilic residue in the protein's active site. The diagram emphasizes the irreversible nature of this binding, which leads to prolonged target inhibition and can overcome certain resistance mechanisms associated with reversible inhibitors. This mechanism is exemplified by covalent inhibitors targeting proteins like KRAS^G12C and Bruton's tyrosine kinase (BTK), showcasing their potential in oncology therapeutics.

Case Studies in Oncology

The most obvious triumph of covalent chemistry in cancer treatment is the creation of KRAS^G12C inhibitors. For many years, KRAS was a symbol of the "undruggable" oncogene. The identification of a reactive cysteine at codon 12 facilitated the development of drugs such as sotorasib (AMG 510) and adagrasib. These medications permanently change KRAS^G12C, keeping it in an inactive GDP-bound state and stopping MAPK signalling from happening. Clinical trials have shown significant responses in non-small cell lung cancer, representing a significant achievement in addressing a long-sought driver (19).

By targeting Bruton's tyrosine kinase (BTK), covalent inhibitors have also changed the way haematologic cancers are treated. Ibrutinib, the first drug in its class, makes a covalent link with Cys481, which stops B-cell receptor signalling. Later drugs like acalabrutinib and zanubrutinib improved this method by making it more selective, which lowered off-target toxicities while keeping BTK inhibition strong (20).

Covalent inhibition has improved the treatment of EGFR-mutant lung cancer in solid tumours. Osimertinib, an irreversible EGFR inhibitor, was especially engineered to counteract the T790M resistance mutation that compromised previous generations of reversible inhibitors. Osimertinib exerts strong suppression by covalently binding to Cys797 at the ATP-binding region. This leads to clinically significant increases in progression-free survival (21). These case studies collectively demonstrate the adaptability of covalent methodologies across various oncogenic drivers.

Advantages

The pharmacological stability of covalent inhibitors is what makes them appealing. Because binding is permanent, target inhibition can last long after the medication has been cleared from the body. This means that smaller doses can be given more often, which may help keep drug levels more stable. This extended interaction is especially advantageous when contending with elevated amounts of natural substrates, such as ATP in kinase active sites. Covalent inhibitors can also get around some resistance mechanisms. For example, changes that make it harder for reversible ligands to bind may nevertheless leave reactive residues open for covalent capture. The result is a therapeutic profile that can include strength, selectivity, and clinical resilience (17).

Concerns

Even though covalent inhibitors have these benefits, they also have their own hazards. Off-target reactivity is still a big worry since random covalent binding could cause immunological responses or cell death. The interaction is permanent, which means that accidental changes to proteins could have long-lasting negative repercussions. Additionally, covalent binding can generate neoantigens that provoke immunogenicity, hence complicating safety evaluations. In oncology, where patients frequently undergo prolonged pharmacotherapy, these risks are significant. Resistance can also develop by mutations that remove or protect the reactive residue, as seen with specific BTK mutations. These risks make it even more important to plan carefully and keep a close eye on patients (22).

Emerging Innovations

The next generation of covalent medicines intends to develop this method with greater precision. Reversible covalent inhibitors, which generate bonds that can break down in the body, try to find a compromise between safety and durability. Improvements in covalent fragment-based drug discovery are broadening the range of chemicals that may be studied, making it possible to systematically look for reactive warheads and binding motifs. Covalent techniques are no longer limited to enzymes and kinases; they are now being applied to non-enzymatic proteins, such as transcription factors and scaffolding proteins that were previously considered unattainable. These new ideas show that covalent chemistry will continue to be an important part of modern oncology, always changing to deal with problems of safety and resistance (23). Beyond covalent strategies, radiotheranostics illustrate how small molecules can serve as dual-purpose agents, bridging diagnosis and therapy in real time."

Radiotheranostics: Small Molecules as Diagnostic–Therapeutic Hybrids

Conceptual Framework

Radiotheranostics is a very promising new area of precision oncology. It combines the separate tasks of diagnosis and therapy into one chemical entity. The basic idea is simple: tiny compounds are made to only bind to tumor-associated antigens or molecular markers, and these ligands are linked to radioisotopes. The conjugate can either send diagnostic signals (usually by positron emission tomography) or send lethal radiation directly to cancerous cells, depending on the isotope chosen. This duality enables the utilisation of the same molecular scaffold for staging, therapy selection, and therapeutic intervention, establishing an unparalleled continuity of care(24).

Radiotheranostics are important because they combine real-time functional imaging with targeted therapy, which lets doctors measure how much of a tumour is taken up before treatment and adjust the dose accordingly. Radiotheranostics represent a paradigm change, converting tiny compounds into multifunctional diagnostic-therapeutic hybrids capable of directing precision treatment regimens with remarkable accuracy(10). Figure 1 shows how the radiotheranostic workflow works. It shows how tiny compounds attached to radioisotopes can help with both diagnostic imaging and targeted radiation therapy for tumour cells at the same time.

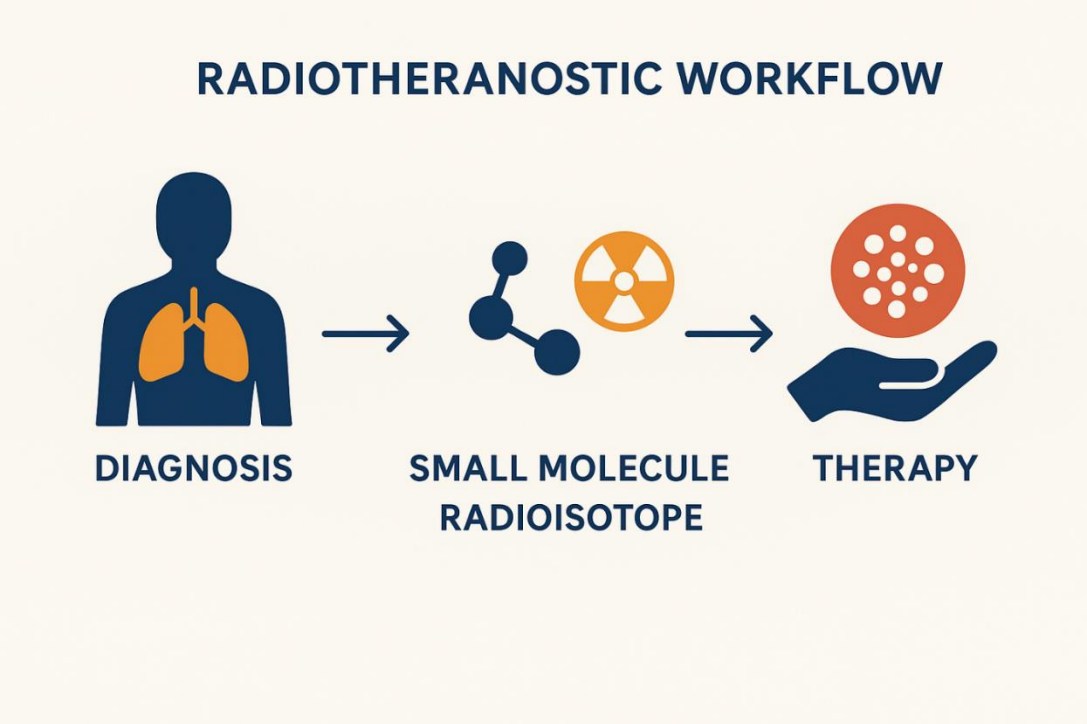

Fig 3: Mechanism of Radiotheranostic Workflow. This diagram illustrates the process by which small molecules, conjugated to radioisotopes, target tumor-associated antigens for both diagnostic imaging and therapeutic radiation delivery. The integration of these dual functions exemplifies the precision and potential of radiotheranostics in personalized oncology treatments.

Clinical Success Stories

The most convincing proof of radiotheranostics may come from prostate cancer. Prostate-specific membrane antigen (PSMA) is present in large amounts on cancerous prostate cells, making it a great target. In phase III trials, lutetium-177-PSMA-617 showed great effectiveness in males with metastatic castration-resistant prostate cancer, leading to both tumour shrinkage and a significant survival advantage. The integration of diagnostic imaging utilising PSMA PET tracers with the therapeutic administration of ^177Lu has set a novel standard of care in advanced illness (25).

The use of somatostatin receptor-targeted analogues in neuroendocrine tumours is another important example. Lutetium-177-DOTATATE is a radiolabeled peptide that only binds to somatostatin receptor subtype 2, which is seen in large amounts in these tumours. Clinical investigations have demonstrated significant enhancements in progression-free survival and symptomatic management, accompanied by sustained responses in previously refractory cases.

In addition to these well-known uses, fibroblast activation protein (FAP)-targeted ligands are becoming useful radiotheranostic treatments for solid tumours. FAP is expressed in cancer-associated fibroblasts across many malignancies, establishing it as a universally relevant stromal target. Preliminary investigations utilising FAP-targeted radioligands indicate significant diagnostic sensitivity and therapeutic potential. These clinical achievements demonstrate the versatility of radiotheranostic methods in various oncological settings (26). Table 3 shows that a number of radiotheranostic medicines have been very successful in treating certain types of cancer. This table shows the main drugs, the tumours they target, and their clinical outcomes. It gives real-life instances of how radiotheranostics are changing oncology.

Table 3. Clinical Success Stories in Radiotheranostics:

Agent	Cancer Type	Clinical Outcome
PSMA-617(27)	Prostate Cancer	Tumor regression and improved survival in metastatic castration-resistant prostate cancer
Lutetium-177-DOTATATE(28)	Neuroendocrine Tumors	Significant improvement in progression-free survival and symptomatic control

Advantages

Radiotheranostics have a number of benefits over standard treatments. Using them as companion diagnostics lets doctors choose the right patients: only those who show tracer uptake are treated, which cuts down on unnecessary exposure. Real-time imaging of radiotracer distribution gives us information about pharmacokinetics and tissue biodistribution, which helps with personalised dosing and lessens off-target effects. Moreover, the capacity to visualise tumour uptake before and throughout therapy facilitates adaptive treatment techniques, enabling doctors to customise regimens based on observed tumour biology. This integration of diagnosis, treatment planning, and therapy on a single platform demonstrates the fundamental promise of precision medicine in oncology (29).

Limitations

Radiotheranostics provide certain benefits, but they also have some practical and biological problems. To make and send out therapeutic radioisotopes like Lutetium-177, you need particular infrastructure and a dependable supply chain, which aren't always available around the world. Another issue is off-target accumulation, which is when tracer uptake happens in places where it shouldn't, such as the salivary glands and kidneys. This might cause xerostomia or renal toxicity. Furthermore, not all tumours exhibit adequate quantities of the targeted antigen to attain treatment success, hence constraining universal application. These issues underscore the necessity for continuous enhancement in ligand design, isotope chemistry, and supportive care measures to broaden safe and equitable access to radiotheranostic therapy (24).

Next-Generation Radiotheranostics

The next generation of radiotheranostics is already starting to take shape. Alpha-emitting isotopes like Actinium-225 and Thorium-227 are more powerful because they emit high-energy, short-range particles that disrupt DNA in a way that can't be fixed while leaving nearby tissues unharmed. Scientists are working on bispecific ligands that can bind to two different targets at the same time. This will make tumours more specific and help them deal with antigen heterogeneity. Finally, improvements in computational chemistry and artificial intelligence are speeding up the process of making ligand scaffolds better, which helps both tumour uptake and pharmacokinetics. These new

ideas point to a future where radiotheranostics becomes a very flexible, patient-specific platform that works well with other precision oncology methods (30).

Integrative Perspectives: Synergizing Modalities

The advent of molecular glues, covalent inhibitors, and radiotheranostics signifies a significant augmentation of the treatment arsenal in oncology. These modalities are not mutually exclusive; instead, they are highly complementary, presenting new options for logical combinations and synergistic methods. For instance, molecular glues that break down oncogenic transcription factors could be used with immune checkpoint inhibitors to change the tumour microenvironment and boost antitumor immunity (31). Covalent inhibitors and targeted degraders can also be used together against kinases to stop adaptive resistance by using different ways to stop it. Radiotheranostics, by inflicting specific DNA damage, could be integrated with inhibitors of DNA damage response pathways (e.g., PARP or ATR inhibitors), enhancing therapeutic efficacy through synthetic lethality (30).

It will be important to use systems biology and network-based methods to map these relationships that function together. Researchers can find weaknesses that certain types of treatments or combinations of treatments may be best able to exploit by combining multi-omics datasets with computational models. This framework facilitates a more predictive methodology for therapeutic design, advancing from empirical combinations to mechanism-driven solutions.

These new methods work together to make the druggable proteome bigger, which means that it can now target things that were previously "undruggable," like transcription factors, scaffolding proteins, and stromal components. Furthermore, their convergence indicates the potential for modular therapeutic platforms, wherein the selection of chemical modality is customised to the tumor's biology, the vulnerabilities identified through systems-level research, and the clinical setting. This view redefines oncology not as a binary opposition of inhibitors and biologics, but as a spectrum of small-molecule methods, each adaptable to distinct molecular architectures and therapeutic goals. This integrative approach has the potential to reshape the future of precision oncology (32).

Challenges and Future Directions

Safety and Selectivity

Even while they show promise, new small-molecule modalities create serious safety issues. Molecular glues can cause unexpected degradation of substrates, as demonstrated by the teratogenic effects of thalidomide, highlighting the challenges in forecasting degradome scope. Covalent inhibitors, while meticulously engineered, may interact with unexpected nucleophilic residues, resulting in permanent toxicity and possible immunogenicity. Radiotheranostics come with their own set of dangers, such as radiation damage to the salivary glands, kidneys, or bone marrow. To make sure that the advantages of treatment are greater than the risks for different groups of patients, careful engineering of selectivity and long-term pharmacovigilance will be necessary (33).

While these risks are significant, they also highlight avenues for improvement. Engineering greater substrate specificity, designing reversible covalent chemistries, and developing protective co-therapies could mitigate these limitations and enable safer clinical translation.

Manufacturing and Global Access

Another problem is that production is complicated. For example, radiotheranostics need isotopes with short half-lives, which means they need to be close to nuclear reactors or cyclotrons. These are not evenly spread out over the world. This weak supply chain makes it harder to get things, especially in low- and middle-income countries (LMICs). To keep molecular glues and covalent inhibitors reproducible and cheap, we also need to make progress in chemical synthesis. To fix these unfair situations, the world will need to invest in radiopharmaceutical infrastructure, make regulations easier to follow, and encourage public-private partnerships that put equal access first. This will make sure that advances in chemical oncology are not limited to health systems with a lot of resources (34).

Predictive Biomarkers

As these medicines progress, reliable biomarkers are essential for patient selection and monitoring. For molecular glues, the degrees of ligase expression and the state of mutations will affect how well they break down and how well they work as drugs. For covalent inhibitors, molecular diagnostics like KRAS mutation testing or BTK resistance profiling help doctors decide how to utilise them. Radiotheranostics uniquely benefit from companion imaging modalities such as PSMA PET, which simultaneously predicts therapeutic uptake and efficacy (35). The advancement of biomarkers in the future will necessitate the

amalgamation of multi-omics platforms and longitudinal monitoring, hence enabling a more accurate correlation between patient biology and therapeutic modalities (36).

Future Direction

Integration with cutting-edge technologies may speed up progress in the future. Artificial intelligence and proteomics can help find targets faster, guess which substrates will be degraded, and improve ligand design. Hybrid modalities are coming soon. For example, covalent degraders combine irreversible binding with induced degradation, while radioglucosides combine metabolic targeting with radionuclide payloads. Ultimately, these discoveries will come together in precision oncology ecosystems that combine small medicines with immunotherapy, gene editing, and cell-based approaches. This forward-thinking model sees a modular and flexible therapeutic environment that will change oncology through chemical creativity and personalised treatment at the systems level (37).

Conclusion

The evolution of small-molecule therapies in oncology signifies a significant conceptual transformation: transitioning from the conventional model of direct enzyme inhibition to more adaptable approaches that regulate, degrade, or accurately distribute therapeutic agents. Molecular glues show how chemical scaffolds can change the way cells work to get rid of proteins that were thought to be "undruggable" before. Covalent inhibitors, on the other hand, stop oncogenic drivers for a long time by being very precise with chemicals. Radiotheranostics, on the other hand, combine diagnostic and treatment into one system, allowing for real-time surveillance of how well treatment is working and where it is going (8,38).

However, the final test for these technologies is still whether they can be used to help people in real life. The real effect of these changes will depend on how long they last, how well they can get beyond resistance, and how well they can be used in places other than well-funded centres. This necessitates a dual emphasis: scientific innovation to expand the druggable proteome, and health-system foresight to guarantee equitable implementation.

In practical terms, these modalities could expand therapeutic options for resistant and hard-to-treat cancers, offering clinicians tools that go beyond the limits of inhibition. Future research should prioritise biomarker-guided patient selection, global manufacturing solutions, and integration with immuno-oncology. Together, these steps will determine whether the promise of molecular glues, covalent inhibitors, and radiotheranostics translates into durable and equitable improvements in cancer care (39).

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