Journal of Medicinal Chemistry

pubs.acs.org/jmc

Editorial

Future of Medicine: How Small Molecules and Biologics Complement Each Other—A Medicinal Chemist's Perspective

Cite This: J. Med. Chem. 2026, 69, 16130−16134

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1.0. INTRODUCTION

For more than a century, small-molecule therapeutics have served as the foundation of modern drug discovery and development, enabling transformative advances across nearly all major therapeutic areas, including infectious diseases, oncology, cardiology, metabolic disorders, and neurology. Their enduring success can be attributed to their vast chemical diversity, well-characterized pharmacological behavior, ability to access intracellular targets, oral bioavailability, and highly scalable manufacturing processes.[1,2] Collectively, these attributes have positioned small molecules as primary drivers of innovation in both acute and chronic disease management, despite the emergence of newer therapeutic modalities.[2]

In recent decades, the drug discovery landscape has undergone a marked transformation driven by the rapid emergence and maturation of biologics, including monoclonal antibodies, therapeutic peptides, gene and cell therapies, and nucleic acid therapeutics (NATs).[3] The significant clinical impact and strong commercial performance of these approaches—particularly in oncology, immuno-oncology, and rare diseases—have fuelled speculation that small-molecule drug discovery may gradually cede its central role in pharmaceutical innovation. However, a closer evaluation of regulatory approval trends and persistent unmet medical needs present a more balanced reality: rather than representing competing paradigms, small molecules and biologics function as complementary and synergistic components of an increasingly diversified therapeutic toolbox.[4]

Despite the accelerated expansion of biologics, small-molecule therapeutics continue to constitute a substantial fraction of FDA-approved drugs each year, reflecting their sustained importance in modern medicine.[3] Their consistent representation in annual regulatory approvals underscores the enduring versatility, tractability, and clinical value of small molecules across diverse therapeutic areas.[4] From a development perspective, small molecules benefit from well-established discovery paradigms, robust and predictable manufacturing processes, and generally favorable pharmacokinetic and pharmacodynamic profiles, most notably oral bioavailability and broad tissue distribution, which collectively enable efficient modulation of intracellular targets that are often inaccessible or impractical for biologics.[1] Moreover, small molecule therapeutics offer distinct strategic advantages in terms of patient convenience, global accessibility, and cost-effective manufacturing and distribution- attributes that are increasingly critical for addressing chronic diseases and unmet medical needs at a global scale.[5] As our understanding of biology and target identification continues to grow, the range of drug targets available for small molecule discovery is also expanding. Small molecule drug discovery has progressed through several innovative approaches, including structure-based design, rational drug design, data-driven methods, and more recently, AI/ML-enabled drug design. In parallel, new drug discovery strategies such as fragment screening, covalent inhibition, induced proximity approaches (molecular glues, targeted protein degradation) and macrocyclization have further transformed the field of small molecule drug discovery.[6−8] Collectively, these innovations reinforce the view that small-molecule therapeutics will remain a central and indispensable pillar of drug discovery, progressing in parallel with biologics rather than being displaced by them.

Despite more than a century of progress in small-molecule drug discovery, a substantial proportion of disease-relevant targets remain difficult to modulate using conventional approaches, owing not only to physicochemical and pharmacokinetic challenges—such as solubility, metabolic stability, and off-target effects—but also to the structural and functional complexity of many biological targets, including those lacking well-defined ligand-binding pockets. Importantly, these limitations are not intrinsic to small molecules per se but reflect broader challenges in drug design and target biology, many of which are increasingly being addressed through advances in medicinal chemistry and emerging modalities.

2.0. ANALYSIS OF USFDA APPROVED DRUGS FROM 2021−2025

To substantiate the complementary roles of small molecules and biologics, we systematically analyzed all USFDA approved drugs from 2021 to 2025, classifying them by modality, target type, and therapeutic indication. A total of 238 drugs were approved by the USFDA over last five-year period (Table 1).

2.1. Analysis of USFDA Approved Drugs from 2021−2025 Based on Modalities

Analysis of USFDA approved drugs from 2021−2025 indicates that approvals during this period were predominantly driven by small-molecule therapeutics, which accounted for 138

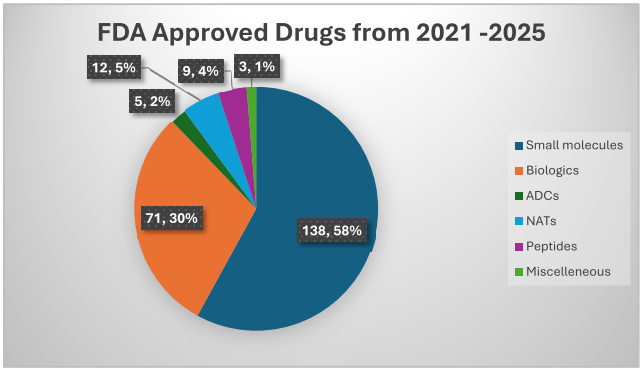
Published: July 23, 2026

Table 1. List of USFDA Novel Drug Approvals Year wise

Sr. No.	Year	FDA Novel Drug Approvals
1	2021	50
2	2022	37
3	2023	55
4	2024	50
5	2025	46

approvals (58%), making them the most prevalent modality. Biologics represented the second-largest category, with 71 approvals (30%), highlighting their continued and growing importance in contemporary drug discovery (Chart 1).

Chart 1. USFDA-Approved Drugs (2021−2025) Categorized by Modalities



Emerging and specialized modalities contributed a comparatively smaller but notable share of approvals, including NATs (12 approvals, 5%), peptides (9 approvals, 4%), and antibody−drug conjugates (ADCs) (5 approvals, 2%). A small fraction (3 approvals, 1%) fell into miscellaneous categories (Chart 1).

Overall, these data reinforce that small molecules and biologics remain the backbone of FDA-approved therapies. At the same time, the steady contribution of newer modalities highlights an evolving therapeutic landscape, reflecting ongoing innovation beyond traditional drug classes.

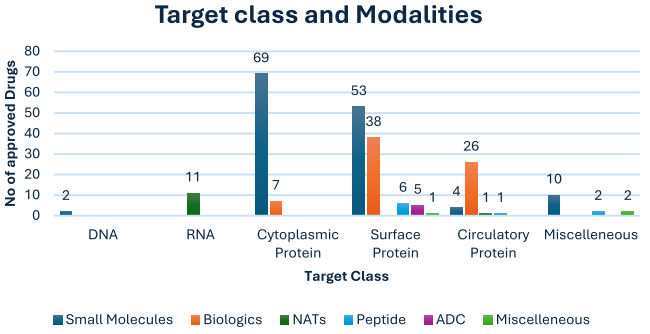
2.2. Analysis of USFDA Approved Drugs from 2021−2025 Based on Target Class

We have further categorized all USFDA approved drugs from 2021 to 2025 by target class and categorized them into cytoplasmic/intracellular protein targets, cell-surface targets, circulatory targets, DNA/RNA targets, and a miscellaneous category.

Overall, proteins—particularly cytoplasmic and surface proteins—dominate as drug targets, with small molecules representing the most prevalent therapeutic modality. Cytoplasmic proteins account for the highest number of approved small-molecule drugs (69), far exceeding biologics (7), underscoring the long-standing success of small molecules in modulating intracellular targets (Chart 2). Among the seven biologics directed at cytoplasmic proteins, five are approved as enzyme replacement therapies for rare or genetic disorders, while the remaining two are botulinum toxin products indicated for conditions such as cervical dystonia or glabellar lines.

Surface proteins also contribute substantially to the approved drug target landscape, led by small molecules (53)

Chart 2. USFDA-Approved Drugs (2021−2025) Categorized by Target Class and Modalities



alongside a significant number of biologics (38). This distribution reflects the intrinsic accessibility of surface targets to antibody-based therapeutics (Chart 2). Additional, smaller contributions from peptides, ADCs, and other modalities are also evident. Importantly, the expansion of biologics in this target class has enabled effective modulation of surface proteins that were previously difficult to address with small molecules, thereby significantly broadening the druggable target space. This progress has also driven the development of hybrid therapeutic strategies such as ADCs, which combine antibody specificity with small-molecule payloads to ultimately engage cytoplasmic targets.

Circulatory proteins are predominantly addressed by biologics (26), with relatively few small-molecule drugs, highlighting the clear suitability of biologics for extracellular targets. Historically, many extracellular targets were not readily amenable to small-molecule intervention, and the emergence of biologics has markedly expanded the scope of drug discovery in this arena (Chart 2).

In contrast, DNA and RNA targets remain minimally represented, reflecting the inherent challenges of directly targeting nucleic acids. The approved DNA-targeting drugs are limited to DNA-alkylating agents, while all approved RNA-targeting therapies fall under NATs, including antisense oligonucleotides, siRNA, and aptamers. Miscellaneous target classes contribute modestly across modalities (Chart 2).

Taken together, these trends reflect a historically aligned—but increasingly convergent—relationship between modality and target class, with small molecules primarily addressing intracellular targets and biologics largely directed toward extracellular and cell-surface proteins. Notably, nucleic acid−targeting strategies remain comparatively underrepresented among approved therapies, consistent with their more recent emergence and ongoing clinical validation.

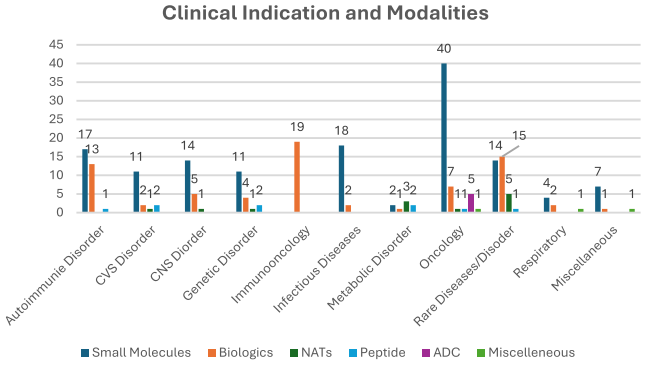
2.3. Analysis of USFDA Approved Drugs from 2021−2025 Based on Clinical Indication

We have further categorized all USFDA approved drugs from 2021 to 2025 by clinical indication and categorized them into oncology, immuno-oncology, autoimmune, cardiovascular (CVS), central nervous system (CNS), genetic, metabolic, respiratory, are diseases/disorders, and miscellaneous category.

In oncology, small molecules (40) account for the largest share among all therapeutic modalities, highlighting their continued central role in cancer drug development. Alongside these, biologics (7), ADCs (5), and NATs (1) show meaningful representation, underscoring the field's growing modality diversity (Chart 3). This distribution reflects the multifaceted biology of cancer, where different therapeutic

https://doi.org/10.1021/acs.jmedchem.6c02013
J. Med. Chem. 2026, 69, 16130−16134

Chart 3. USFDA-Approved Drugs (2021−2025) Categorized by Clinical Indication and Modalities



approaches are required to address distinct disease mechanisms. Small molecules are primarily used to target intracellular kinases and key signaling pathways that drive tumor growth and survival, while biologics are employed to modulate extracellular targets such as immune checkpoints and cell-surface receptors, enabling immune-mediated or receptor-specific interventions. ADCs further expand this toolkit by combining the specificity of antibodies with the potency of cytotoxic agents, allowing targeted delivery of chemotherapy directly to cancer cells and thereby improving efficacy while limiting systemic toxicity. Taken together, these modalities act in a complementary manner, collectively enabling comprehensive targeting and modulation of diverse cancer-related pathways and biological targets, and ultimately supporting more effective and personalized treatment strategies for cancer patients.

Immuno-oncology is dominated almost entirely by biologics (19), reflecting the central role of monoclonal antibodies and immune-modulating agents as the foundation of this therapeutic area from 2021 −2025 (Chart 3). These biologics are specifically designed to engage and regulate the immune system, for example, by targeting immune checkpoints, cytokines, or cell-surface receptors, thereby enhancing antitumor immune responses. The skew toward biologics highlights how immuno-oncology differs from traditional oncology, relying less on direct cytotoxic or intracellular pathway inhibition and more on precise immune system targeting. Consequently, immuno-oncology can be characterized as a predominantly biologics-driven field, closely aligned with therapies that harness, redirect, or amplify immune mechanisms to treat cancer.

Autoimmune disorders show a strong reliance on small molecules (17) and biologics (13), with minimal involvement of peptides or other advanced therapeutic modalities (Chart 3). This distribution reflects the chronic nature of autoimmune diseases, where long-term treatment demands therapies with well-established mechanisms of action, ease of administration, predictable safety profiles, and scalable manufacturing processes. Small molecules offer convenience and suitability for sustained use, while biologics provide targeted modulation of immune pathways. Together, these modalities dominate autoimmune therapy by balancing efficacy, safety, and practicality for lifelong disease management.

Across CNS, CVS, and infectious disease indications, drug development is consistently dominated by small molecules, reflecting modality-specific practicality and biological constraints (Chart 3). In CNS disorders, small molecules have historically predominated, owing to their ability to achieve blood−brain barrier (BBB) penetration, oral bioavailability, and sufficient central exposure. In contrast, biologics have been comparatively limited by delivery challenges associated with restricted BBB permeability, although advances in transport engineering and targeted delivery approaches are increasingly expanding their applicability. Cardiovascular therapies similarly rely on established small-molecule chemistry to modulate metabolic pathways, receptors, and enzymes, supporting long-term safety and chronic use. In infectious diseases, small molecules are favored for their rapid antimicrobial action, oral dosing potential, scalability, and cost efficiency, which are essential for widespread and global use. Collectively, these areas highlight a conservative but rational modality preference driven by clinical feasibility, pharmacokinetics, and real-world treatment demands.

Genetic, metabolic, and rare diseases collectively display a more diverse and evolving modality landscape, reflecting increasing emphasis on precision medicine. Genetic disorders show a balanced mix of small molecules (11), biologics (4), and NATs (1), indicating a gradual shift toward gene-targeted interventions while retaining small molecules for pathway modulation and symptom control (Chart 3). Metabolic disorders demonstrate low overall activity, with modest contributions from small molecules, biologics, and a relatively higher presence of NATs, suggesting early experimentation with gene and RNA-based regulatory strategies. In rare diseases, a near-equal representation of biologics (14) and small molecules (15), alongside notable NATs (5), use highlights a strong push toward tailored, mechanism-driven therapies. Overall, these areas reflect a trend where innovative modalities are gaining traction, while traditional approaches continue to play a complementary role (Chart 3).

Overall, small molecules continue to dominate across most therapeutic areas—including oncology, infectious diseases, and autoimmune disorders—reflecting their versatility, oral bioavailability, and ability to access intracellular targets. Biologics serve as an important complementary modality, with a strong and expanding presence in oncology, immuno-oncology, and rare diseases, driven by their high target specificity and ability to modulate extracellular pathways. Emerging modalities, such as NATs, peptides, and ADCs remain more selectively represented, typically aligned with complex disease biology or areas of high unmet medical need, where conventional approaches have proven insufficient.

3.0. FUTURE DRIVERS FOR SMALL-MOLECULE RESEARCH

3.1. Enduring Appeal of Small Molecules Despite Biologics Success

The success of biologics targeting PCSK9 and the GLP-1 receptor has strongly validated these pathways, while simultaneously driving intense efforts toward small-molecule alternatives. Monoclonal antibodies such as alirocumab and evolocumab produce profound reductions in LDL-cholesterol, establishing PCSK9 inhibition as a highly effective therapeutic strategy, albeit with limitations related to cost, subcutaneous administration, and long-term adherence.[9,10] These drawbacks have fuelled the search for complementary modalities, including RNA interference therapeutics such as inclisiran, which silences hepatic PCSK9 expression and enables infrequent dosing,[10] as well as ongoing medicinal chemistry

https://doi.org/10.1021/acs.jmedchem.6c02013
J. Med. Chem. 2026, 69, 16130−16134

efforts to develop orally bioavailable small-molecule inhibitors that disrupt PCSK9−LDL receptor interactions or intracellular processing.[11,12] In parallel, the GLP-1 receptor axis represents a striking example of peptide success, with agents such as semaglutide and the dual incretin agonist tirzepatide delivering transformative improvements in glycaemic control and weight loss, alongside cardiovascular benefits. Despite this success, the requirement for injectable administration (and the complexity of peptide manufacturing and delivery) has motivated substantial efforts toward nonpeptidic, orally active GLP-1 receptor agonists.[13] Recent advances have led to the emergence of small-molecule agonists such as Orforglipron[14] and Danuglipron,[15] which demonstrate promising efficacy while offering improved convenience and scalability. Collectively, these examples illustrate a broader paradigm in drug discovery: successful biologics not only validate high-value targets but also catalyze innovation in small-molecule modalities aimed at overcoming limitations in delivery, cost, and accessibility. Thus, biologics would complement and sometimes fuel small molecule drug discovery efforts.

3.2. Expanding Demand for ADC Payloads Driving Innovation in Small-Molecule

ADCs represent a class of hybrid therapeutic modality that integrate the targeting specificity of biologics (antibodies) with the potent cytotoxicity of small-molecule drugs. This combination has led to significant improvements in clinical outcomes, particularly in oncology, where ADCs have addressed several unmet medical needs. Notably, most approved and clinical-stage ADCs rely on a limited set of payload classes, primarily DNA damaging agents (e.g., calicheamicins and duocarmycins), topoisomerase I inhibitors (e.g., classical campothecin, deruxtecan and exatecan derivatives) and microtubule inhibitors (e.g., maytansinoids and auristatins). However, the emergence of resistance to these payloads, along with the need to broaden the therapeutic scope of ADCs, underscores the importance of developing new classes of small molecule cytotoxic agents.[16]

Advances in small-molecule modalities such as molecular degraders present a compelling opportunity to expand the therapeutic scope of ADCs. Incorporating these mechanisms into ADCs or degrader−antibody conjugates (DACs) could enable the targeting of previously "undruggable" proteins, particularly those lacking well-defined ligandable pockets for conventional small molecules. In parallel, there is growing interest in diversifying ADC payloads beyond traditional cytotoxic molecules by exploring immune-modulating payloads, RNA-based inhibitors, and other novel mechanisms to enhance efficacy and broaden applicability. Additionally, the strategic repurposing of earlier-generation cytotoxic agents is being actively investigated to accelerate the development of next-generation ADCs.[17,18]

Collectively, these approaches highlight an expanding innovation space aimed at overcoming resistance mechanisms and driving continued growth in ADC therapeutics via novel small molecule research to expand the scope of biologics and thus overall to address unmet medical needs.

3.3. Expanding Small Molecule Frontiers via Molecular Glues, PROTACs, Covalent Chemistry, and AI/ML

Recent advances in small-molecule drug discovery have significantly expanded the therapeutic scope, driven by innovative modalities such as molecular glues, Proteolysis-Targeting Chimeras (PROTACs), covalent inhibitors, and the integration of AI/ML technologies. Molecular glues and PROTACs have enabled targeted protein degradation, offering powerful strategies to modulate previously "undruggable" proteins, particularly those lacking well-defined binding pockets.[19,20] Covalent inhibitors, with their ability to form irreversible or reversible covalent bonds, provide enhanced potency and prolonged target engagement when designed for high selectivity.[21,22]

Complementing these approaches, AI and machine learning are transforming drug discovery by accelerating hit identification, optimizing molecular properties, and improving prediction of efficacy and safety.[23,24] AI has a distinct advantage in small-molecule discovery due to the extensive prior work in the field and relatively more data availability. Small molecules are easier to represent computationally using formats like molecular graphs, and descriptors. This enables effective model training and prediction. Additionally, large historical data sets further enhance AI/ML performance and reliability. Collectively, these advancements are redefining the capabilities of small molecules, enabling access to new target spaces and enhancing the efficiency and success rate of drug discovery efforts.

4.0. HARNESSING THE COMPLEMENTARITY OF SMALL MOLECULES AND BIOLOGICS FOR BETTER OUTCOMES

Advancement in biologics has not only expanded the repertoire of druggable targets but has also created opportunities for synergistic therapeutic strategies. Increasingly, combinations of biologics with small molecules are demonstrating enhanced clinical efficacy compared to either modality alone. Notable examples include the use of immune checkpoint inhibitors with tyrosine kinase inhibitors in oncology, such as pembrolizumab (anti-PD-1) combined with axitinib, avelumab (anti-PD-L1) with axitinib, and nivolumab (anti-PD-1) with cabozantinib for renal cell carcinoma. Similarly, in EGFR mutant nonsmall cell lung cancer, combinations such as erlotinib (EGFR TKI) with bevacizumab (anti-VEGF antibody) or ramucirumab (anti-VEGFR2 antibody) have shown improved outcomes.

5.0. CONCLUSION

Advancements in both small molecules and biologics are collectively expanding the druggable landscape by leveraging their complementary mechanisms of action and improving overall therapeutic efficacy. Ongoing research and development in these modalities are also enabling the emergence of hybrid approaches, such as ADCs. Together, these innovations play a pivotal role in addressing unmet medical needs and delivering better patient outcomes.

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Author Contributions

HM, coconceptualized, conducted the field work, drafted, edited and reviewed the editorial. SKM edited, reviewed and critique the editorial. SNP, coconceptualized, edited, reviewed, and gave overall guidance on the editorial.

https://doi.org/10.1021/acs.jmedchem.6c02013
J. Med. Chem. 2026, 69, 16130−16134

Notes

Views expressed in this editorial are those of the authors and not necessarily the views of the ACS.

■ ACKNOWLEDGMENTS

HM and SNP acknowledge Syngene International Ltd and SKM acknowledge Syngene Scientific Solution Ltd for providing opportunity to publish our views.

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