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Multitargeted therapy in the convergence era: Systems pharmacology, smart delivery, and the rise of pan-biomarkers

Munikumar Manne*

Development of effective therapeutics has been constrained by challenges such as poor drug solubility, non-specific biodistribution, and systemic toxicity. Recent advancements in targeted drug delivery systems and nanomedicine have significantly addressed these limitations by enabling the precise localization of therapeutic agents to diseased tissues [1]. This not only enhances therapeutic efficacy but also minimizes adverse effects. These innovations are foundational to the paradigm of precision medicine, which aims to personalize treatments to individual patients based on disease-specific and patient-specific characteristics. Central to this paradigm are target-based therapies, which focus on modulating specific molecular targets implicated in disease pathogenesis. These therapies have shown remarkable success in oncology, immunology, and infectious diseases, supported by significant scientific evidence from genomic, proteomic, and metabolomic studies [2–4].

Complementing this approach is pan-target-based therapy, which involves simultaneous modulation of multiple targets or pathways. Pan-target-based therapy represents a transformative shift in biomedical science—redirecting the therapeutic lens from organ-specific diseases toward shared molecular mechanisms that transcend traditional diagnostic boundaries [5]. Originally conceptualized within precision oncology, where tumor-agnostic drugs such as larotrectinib (targeting NTRK fusions) and pembrolizumab (MSI-high tumors) garnered tissue-agnostic Food and Drug Administration (FDA) approvals, the scope of pan-targeting has expanded dramatically [6]. Currently, this paradigm is influencing diverse fields, from infectious disease and autoimmunity to metabolic and neurodegenerative disorders. What unites these efforts is the fundamental recognition that many diseases, while phenotypically distinct, are underpinned by convergent molecular dysfunctions—providing opportunities for cross-indication therapeutic design. This strategy is particularly valuable in complex or heterogeneous diseases where single-target interventions may be insufficient. The integration of these approaches with advanced drug delivery platforms—such as nanoparticles, liposomes, and antibody-drug conjugates—further enhances specificity and therapeutic outcomes. Together, these innovations represent a transformative shift toward more personalized, effective, and safer treatments, underscoring the importance of continued research and clinical validation in the field of precision therapeutics.

The era of precision medicine demands more than isolated molecular targeting—it calls for a paradigm shift. Pan-target-based therapy is not just a scientific evolution; it is a strategic rethinking of the disease approach. By focusing on shared molecular dysfunctions across conditions, we unlock the potential for therapies that transcend traditional boundaries. This convergence is not theoretical—it is already reshaping oncology, infectious disease, and neurodegeneration. The question is no longer if pan-targeting works, but how broadly we can apply it.

Targeted drug delivery systems: precision in therapeutics

Targeted drug delivery systems represent a transformative approach in pharmacotherapy, engineered to transport therapeutic agents directly to pathological sites while minimizing systemic exposure [7–12]. These systems are designed to enhance drug specificity, improve pharmacokinetic profiles, and reduce off-target effects [1]. Among the most prominent strategies are ligand-directed systems, which exploit molecular recognition by conjugating ligands—such as folic acid or antibodies—to carriers that bind selectively to overexpressed receptors on diseased cells. This mechanism is particularly effective in oncology, where tumor cells often exhibit unique surface markers. Stimuli-responsive carriers further refine this precision by releasing drugs in response to

*Department of Bioinformatics, Manna Biotech Private Limited, Hyderabad, India. E-mail: mannemunikumar.bioinfo @ gmail.com; drmuni @ mannabiotech.com

specific environmental cues. For instance, the acidic pH of tumor microenvironments or the enzymatic activity within endosomes can trigger drug release, ensuring localized therapeutic action [13]. Biodegradable polymeric vehicles, such as poly (lactic-co-glycolic acid) (PLGA), offer controlled release profiles and biocompatibility, degrading into non-toxic byproducts. These innovations collectively contribute to the evolution of precision therapeutics, enabling more effective and safer treatment modalities [14].

Targeted drug delivery is no longer a futuristic concept—it is a clinical reality. From ligand-directed carriers to stimuli-responsive systems, the precision of modern pharmacotherapy is redefining safety and efficacy. But we must ask: Are we doing enough to translate these innovations beyond oncology? The same principles that guide tumor targeting could revolutionize treatment in autoimmunity, central nervous system (CNS) disorders, and infectious diseases. It is time to broaden the lens.

Clinical applications of targeted delivery

The clinical translation of targeted drug delivery systems has been most impactful in oncology. FDA-approved formulations like liposomal doxorubicin (Doxil®) and albumin-bound paclitaxel (Abraxane®) exemplify the success of ligand-conjugated nanoparticles in achieving tumor-specific accumulation [15,16]. Recent advancements, as reported by Mamidi *et al.* [17], highlight the utility of stimuli-responsive nanomaterials that leverage endogenous (pH and enzymes) and exogenous (light and temperature) triggers to overcome biological barriers and enhance drug retention in tumor tissues [17]. In CNS disorders, the blood-brain barrier (BBB) remains a formidable obstacle. Nanoparticles engineered to traverse the BBB have enabled targeted delivery of neuroprotective agents, offering new avenues for treating Alzheimer's and Parkinson's diseases [18,19]. Infectious diseases also benefit from nanocarrier-based strategies, particularly in combating resistant pathogens. Lipid nanoparticles, as used in mRNA vaccines for COVID-19, underscore the clinical viability of this approach. Additionally, autoimmune diseases such as rheumatoid arthritis and lupus are being addressed through nanobody-based delivery systems, which demonstrate enhanced targeting and reduced immunogenicity in preclinical models.

The success of liposomal doxorubicin and Abraxane® is proof that smart delivery works. However, the real opportunity lies in expanding these platforms to underserved areas—neurodegeneration, resistant infections, and autoimmune conditions. The clinical promise is clear, but translation requires bold investment and regulatory agility. We must move from proof-of-concept to global impact. Despite their promise, targeted drug delivery systems face several translational challenges. The scalability of complex formulations, regulatory scrutiny regarding safety and reproducibility, and the integration of diagnostics for real-time monitoring remain significant hurdles. Future research must prioritize the development of modular and adaptable platforms that can be tailored to individual patient biomarkers and disease phenotypes. Advances in stimuli-responsive systems, as emphasized by Mamidi *et al.* [17], suggest a promising trajectory toward personalized therapeutics with improved specificity and minimized adverse effects.

Nanomedicine: harnessing nanoscale materials for therapeutic innovation

Nanomedicine utilizes materials at the nanoscale (1–100 nm) to design therapeutics and diagnostics with enhanced physicochemical properties. Key nanostructures include liposomes, dendrimers, metallic nanoparticles, and polymeric micelles [20]. Liposomes, for example, encapsulate drugs to improve solubility and stability, while dendrimers offer high drug-loading capacity and tunable surface chemistry. Metallic nanoparticles provide dual functionality in targeted delivery and imaging due to their optical and magnetic properties. Polymeric micelles, formed through self-assembly, enable controlled drug release and improved biodistribution [1]. These nanostructured systems allow precise control over drug release kinetics and cellular uptake, making them versatile tools in therapeutic design. Their ability to navigate biological barriers and deliver payloads with high specificity has revolutionized treatment paradigms across multiple disease domains.

Nanomedicine is no longer niche—it is foundational. Its ability to navigate biological barriers and deliver payloads with precision is unmatched. However, the field must evolve from incremental improvements to disruptive innovation. Can we design nanocarriers that adapt in real time to disease dynamics? The future lies in theranostics and personalized payloads—not just smarter delivery, but smarter decisions.

Successful case studies in precision therapeutics

Glioblastoma treatment

Recent advancements in nanotechnology have enabled the development of smart nanoparticles tailored for glioblastoma multiforme (GBM), a highly aggressive brain tumor. A collaborative study involving from India and Thailand focused on optimizing nanoparticle size and surface chemistry to enhance BBB penetration and drug release kinetics. These nanoparticles demonstrated reduced off-target toxicity and improved bioavailability in preclinical models. Notably, tumor-specific drug accumulation led to extended survival rates compared to conventional therapies [21–23]. The use of inorganic and hybrid nanoparticles in GBM therapy is gaining traction, with ongoing clinical trials validating their efficacy [24]. Nanobody-based delivery systems have emerged as a promising approach for treating autoimmune diseases such as rheumatoid arthritis and lupus. These systems utilize single-domain antibodies with high specificity and low immunogenicity. In early-phase clinical trials, patients treated with nanobody-based therapeutics showed a 40% reduction in disease activity scores compared to those receiving standard treatments [25,26]. The precision targeting offered by nanobodies minimizes systemic exposure and enhances therapeutic outcomes, marking a significant advancement in autoimmune disease management.

Glioblastoma remains one of the most formidable challenges in neuro-oncology. The use of smart nanoparticles to breach the BBB represents a significant advancement,

though further progress is necessary. We must accelerate clinical validation and explore combinatorial strategies that integrate nanomedicine with immunotherapy and AI-guided dosing. Survival gains are promising; now we need systemic change.

Neglected tropical diseases

The Drugs for Neglected Diseases Initiative (DNDi) has made substantial progress in drug discovery for diseases like Chagas and leishmaniasis. By designing molecules with high binding specificity to parasitic proteins, DNDi has developed over 20 new chemical entities. A notable success includes a novel oral formulation for visceral leishmaniasis, which achieved a 95% cure rate in phase II trials [27,28]. This formulation offers a safer and more accessible alternative to existing treatments, addressing critical gaps in global health equity.

The DNDi's success in developing oral formulations for visceral leishmaniasis represents a notable achievement in scientific innovation and global health equity? Global health must prioritize pan-target strategies that serve the underserved. Neglected diseases deserve more than innovation—they deserve urgency.

Expanding the therapeutic horizon: communicable and non-communicable applications

In the realm of non-communicable diseases, the utility of pan-targeted agents is exemplified by SGLT2 inhibitors. Initially developed for glycemic control in type 2 diabetes, these agents now demonstrate efficacy in chronic kidney disease and heart failure, independent of diabetic status [29–31]. Similarly, JAK-STAT pathway inhibitors, used in autoimmune conditions like rheumatoid arthritis, have found application in severe viral infections such as COVID-19, where they mitigate cytokine-driven hyperinflammation. These repurposing successes underscore the value of targeting conserved inflammatory and metabolic circuits across disease types [31–33]. Pan-target strategies are also gaining traction in infectious disease through host-directed therapies (HDTs). Rather than targeting pathogens directly, HDTs aim to modulate host pathways such as autophagy, epigenetic regulation, and immune checkpoints—mechanisms co-opted by multiple pathogens, including *Mycobacterium tuberculosis*, HIV, and SARS-CoV-2 [32–35]. This approach is particularly valuable in the context of rising antimicrobial resistance, where conventional pathogen-specific strategies falter.

The repurposing of SGLT2 inhibitors and JAK-STAT blockers across disease types is a testament to the power of pan-targeting. These agents reveal a deeper truth: inflammation and metabolism are universal languages in pathology. We must design trials that reflect this convergence, not siloed endpoints. The future of therapeutics is cross-indication.

The role of pan-biomarkers in mechanism-guided therapy

Critical to the efficacy and precision of pan-targeted approaches is the emergence of pan-biomarkers—molecular indicators that predict therapeutic response across multiple disease states. Biomarkers such as PD-L1 expression, IL-6, C-reactive protein, and tumor mutational burden have already demonstrated cross-disease relevance, from oncology to chronic infection to cardiovascular inflammation [36–38]. Moreover, advances in multiomics and single-cell analysis are enabling the discovery of deeper, context-independent molecular signatures, including epigenetic marks, non-coding RNAs, and metabolic fingerprints. These biomarkers are not only diagnostic but increasingly *theranostic*, guiding both therapy selection and monitoring response. For instance, circulating tumor DNA (ctDNA) and exosomal RNA are being explored not only in cancer but in viral and inflammatory disease monitoring, offering real-time, non-invasive windows into disease dynamics [39,40]. The evolution of such biomarkers will be pivotal for stratifying patients in pan-indication clinical trials and refining therapeutic windows.

Pan-biomarkers are the compass guiding mechanism-based therapy. From PD-L1 to ctDNA, these indicators are reshaping how we stratify patients and monitor response. But discovery must be matched by deployment. Multiomics and single-cell analytics are powerful—only if they inform real-time decisions. The next frontier is not identification, but integration.

Innovations in drug delivery: toward smart and selective therapeutics

The promise of pan-targeted agents must be matched by delivery technologies capable of precise, context-specific action. Here, advanced drug delivery systems have emerged as key enablers. Ligand-directed platforms, leveraging molecules such as folate or transferrin, allow for cell-type-specific targeting. pH-sensitive carriers and redox-responsive systems provide controlled release in acidic or oxidative microenvironments typical of tumors and inflamed tissues. Biodegradable polymers such as PLGA and PEGylated nanostructures extend circulation time and improve drug tolerability [41]. These systems are particularly valuable in diseases requiring localized delivery—such as intra-articular release in autoimmune arthritis or macrophage-targeted delivery in intracellular infections. By coupling molecular selectivity with anatomical precision, such platforms are expanding the therapeutic index and facilitating safer, broader application of multitarget drugs [42].

Smart delivery systems are the unsung heroes of pan-target therapy. Ligand-directed platforms and stimuli-responsive carriers offer anatomical precision—but are we leveraging them fully? Diseases like arthritis and *tuberculosis* demand localized solutions. Let us move beyond systemic exposure to site-specific action.

Nanomedicine as the chassis for cross-disease therapies

Nanomedicine is rapidly emerging as a versatile and powerful platform for cross-disease therapies, offering innovative solutions for complex medical challenges across oncology, infectious diseases, and chronic inflammatory conditions [20]. The unique properties of nanostructured carriers—such as liposomes, dendrimers, metallic nanoparticles, and polymeric micelles—enable them to encapsulate a wide range of therapeutic agents, including small molecules,

biologics, and nucleic acids. This versatility makes them ideal for combination therapies and targeted delivery [20,43].

In oncology, nanocarriers have significantly improved the delivery of chemotherapeutic agents by enhancing tumor penetration and reducing systemic toxicity. The use of stealth liposomes, such as those in the FDA-approved drug Doxil, exemplifies how nanomedicine can minimize immune clearance and improve drug accumulation at tumor sites [44]. These carriers also facilitate the co-delivery of multiple agents, enabling synergistic effects and overcoming drug resistance.

For infectious diseases, nanomedicine offers solutions to stabilize labile antimicrobials and transport them across biological barriers. This is particularly valuable in treating infections where conventional drugs fail due to poor bioavailability or rapid degradation [45,46]. Nanocarriers can be engineered to release their payloads in response to specific stimuli, ensuring that antimicrobials reach the site of infection effectively and with minimal systemic exposure.

In the realm of chronic inflammatory diseases, nanomedicine provides spatiotemporal control over the release of immunomodulatory agents. This targeted approach helps mitigate the need for systemic immunosuppression, which often leads to adverse effects. Recent research highlights how nanomaterials suppress inflammatory signaling pathways and reduce the expression of pro-inflammatory cytokines such as reactive oxygen species, offering promising therapeutic outcomes in conditions such as wound healing, gastrointestinal disorders, and autoimmune diseases [47,48]. Moreover, nanomedicine is evolving toward theranostic constructs—nanosystems that integrate both diagnostic and therapeutic functions. These constructs enable real-time monitoring of disease progression and adaptive treatment strategies, aligning well with pan-biomarker-guided therapies [20,47]. This dual functionality is particularly beneficial in personalized medicine, where treatment can be tailored based on dynamic biomarker profiles.

Nanomedicine is the chassis for upcoming cross-disease therapies. Its versatility enables combination treatments, adaptive dosing, and real-time monitoring. But the field must embrace complexity—multiagent payloads, dynamic release profiles, and AI-guided modulation. The goal is not just delivery, but decision-making.

Computational acceleration: AI-driven design and systems pharmacology

There are several compelling success stories that demonstrate how AI-enhanced Computer-Aided Drug Design (CADD) has accelerated the development of cross-disease and multitarget therapeutics. These cases highlight the transformative potential of integrating AI into drug discovery pipelines [49,50]. One notable example is the development of Imatinib Mesylate (Gleevec), a targeted therapy for chronic myeloid leukemia (CML). Researchers used CADD techniques to identify the BCR-ABL fusion protein as a key driver of CML [51]. Virtual screening and molecular docking helped pinpoint molecules that could inhibit this target. Computational methods were then employed to optimize the lead compounds for potency, selectivity, and pharmacokinetics. The result was a highly effective drug that significantly improved patient outcomes and became a model for precision oncology [52,53].

Another success story is Oseltamivir (Tamiflu), an antiviral medication for influenza. Using structure-based drug design, scientists determined the 3D structure of neuraminidase, a critical enzyme for viral replication [54–56]. AI-enhanced CADD tools facilitated the design of inhibitors that could bind to neuraminidase's active site. This led to the development of Tamiflu, which became a frontline treatment for influenza worldwide [55,57]. In the realm of HIV treatment, Darunavir, a protease inhibitor, was designed using CADD to exploit the enzyme's active site [58,59]. AI tools enabled precise modeling of the interaction between the drug and its target, resulting in a compound with high efficacy and resistance resilience. Darunavir is now a key component of antiretroviral therapy regimens [60]. More recently, AI-driven platforms have been instrumental in developing Direct-Acting Antiviral Agents (DAAs) for Hepatitis C Virus (HCV). These agents target multiple proteins involved in the HCV replication cycle [61–63]. Structure-based design, powered by AI, enabled the creation of inhibitors that bind effectively to these targets, leading to highly successful therapies that have transformed HCV treatment.

CONCLUSION

The evolution of pan-target-based therapy marks a significant departure from conventional, organ-centric treatment paradigms. By focusing on shared molecular mechanisms across diverse disease states, this approach offers a unified framework for therapeutic innovation. The integration of targeted drug delivery systems, nanomedicine platforms, and pan-biomarkers has demonstrated considerable promise in enhancing specificity, reducing systemic toxicity, and enabling cross-indication applications. Clinical successes in oncology, neurodegeneration, infectious diseases, and autoimmune disorders underscore the translational potential of these strategies. However, realizing their full impact requires continued investment in modular delivery technologies, biomarker-driven patient stratification, and regulatory pathways that accommodate mechanism-guided therapies. As biomedical research advances toward greater convergence, pan-target therapeutics stand poised to redefine precision medicine and expand its reach across global health landscapes.

CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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