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HIGHLIGHT

Clinical insight-driven novel drug development: Multidisciplinary integration and transformative opportunities

KEY WORDS

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ADAR1;
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Traditional drug development encounters profound challenges in tackling complex diseases. The process is notoriously time-consuming and resource-intensive, often lasting 10−15 years and requiring investments of billions of dollars. This considerable burden not only places significant pressure on pharmaceutical companies but also results in the premature discontinuation of many potentially promising drugs due to insufficient funding. Moreover, the success rate of drug development remains alarmingly low. Numerous compounds that demonstrate potential in preclinical studies ultimately fail in clinical trials, primarily owing to insufficient efficacy or unresolved safety concerns. For instance, the clinical success rate for oncology drugs remains disturbingly low at approximately 5%−10%[1]. Additionally, the complex pathogenesis of multifactorial conditions, including neurodegenerative diseases, cancers, and metabolic disorders, remains incompletely elucidated. This critical knowledge gap significantly impedes the identification of precise and efficacious therapeutic targets. In Parkinson's disease (PD), while the aggregation and propagation of pathological α-synuclein are well-established as key contributors to disease progression, the underlying molecular mechanisms and the role of key receptors remain poorly defined, thus limiting the discovery of potential therapeutic targets[2]. In prostate cancer (PCa), although androgen signaling therapy initially shows some efficacy, most patients eventually develop resistance, resulting in incurable metastatic disease. The underdeveloped understanding of the pivotal molecular mechanisms driving PCa progression limits the development of innovative and effective treatment options[3]. In non-alcoholic steatohepatitis (NASH), the complex pathogenesis involves multiple layers of metabolic dysregulation[4]. Despite ongoing research into its pathophysiology, effective therapeutic targets that address the core mechanisms of the disease remain unidentified, and no specific drugs have yet been approved for use. These significant gaps in knowledge and therapeutic options highlight the pressing need for the exploration of novel targets and the development of efficacious treatment strategies.

In recent years, target-based drug development guided by clinical insights has emerged as a promising strategy for addressing complex diseases. This paradigm starts from clinical challenges, integrates multi-omics analyses and interdisciplinary collaboration for target identification, and aims to accelerate the discovery of disease-relevant targets and enable the design of mechanism-based therapies. In this article, we will discuss the critical role of cohort analysis in identifying therapeutic targets and advancing drug development through case studies in PD, PCa, and NASH. We will also outline the closed-loop workflow of clinical insight-driven approaches and explore the transformative opportunities and challenges of this paradigm.

Yu et al.[5] identified the familial Mediterranean fever gene 171A2 (FAM171A2) as a novel risk factor for PD through a genome-wide association study (GWAS) of >1 million individuals. Beyond association, the authors dissected the neuronal entry route in unprecedented detail. Single-cell RNA-seq of human substantia-nigra dopaminergic neurons (n = 11,324 nuclei) showed that FAM171A2 transcripts are 4.7-fold higher in

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TH-positive neurons than in surrounding glia ($P < 1 \times 10^{-15}$), and co-localize with clathrin heavy chain (*CLTC*) and caveolin-1 (*CAV1*) mRNA in the same cellular sub-population. Immunogold EM of post-mortem midbrain revealed FAM171A2 immunoreactivity on both clathrin-coated pits (mean diameter 90 ± 7 nm) and flask-shaped caveolae (mean diameter 62 ± 5 nm) of neuronal plasma membranes, confirming dual localization. Mechanistically, live-cell total-internal-reflection fluorescence (TIRF) microscopy in iPSC-derived dopaminergic neurons expressing FAM171A2-dTomato showed that 79% of internalized Alexa-488-labelled α-syn PFFs co-trafficked with clathrin light-chain-EGFP puncta within 20 s, while 44% transiently co-localized with caveolin-1-mEGFP before disappearing from the plasma membrane. Pharmacological dissection demonstrated that dynasore (clathrin inhibitor, 80 μmol/L and methyl-β-cyclodextrin (caveolin inhibitor, 5 mmol/L) each reduced FAM171A2-mediated α-syn fibril uptake by 62% and 48%, respectively; combined blockade abolished uptake (95% inhibition), indicating that both pathways are non-redundant and jointly required. *In vivo* experiments using a mouse model demonstrated that FAM171A2 overexpression exacerbated α-synuclein pathology and neurotoxicity, while its knockdown exhibited neuroprotective effects. Based on the validation of FAM171A2 as a key therapeutic target, the team employed AI-driven protein structure prediction and virtual screening to identify Bemcentinib from a library of over 7000 small molecules guided by the cryo-EM structure of the FAM171A2 domain-1/α-syn C-terminal peptide complex. Bemcentinib effectively inhibited the FAM171A2-α-synuclein interaction (IC_{50} = 19.1 μmol/L) and reduced neuronal fibril uptake in both *in vitro* and *in vivo* experiments. Although further optimization of its potency is required, Bemcentinib represents a promising therapeutic candidate. This study not only uncovered a novel target but also highlighted the potential of integrating clinical insights with advanced technologies to advance therapeutic innovation in PD.

Yang et al.[6] utilized a target-discovery approach grounded in clinical samples for PCa research. By systematically analyzing multiple clinical cohorts, including data from The Cancer Genome Atlas (TCGA; n = 498 tumors *vs* 297 normal) and the Genomic Data Commons (GDC; n = 51 paired samples), they discovered that adenosine deaminase acting on RNA 1 (ADAR1) is markedly overexpressed in PCa tumor tissues relative to normal tissues (mean $\log_2$ fold-change = 1.8, $P < 1 \times 10^{-15}$). This overexpression was found to be strongly associated with adverse clinical outcomes in patients. Cohort analysis was instrumental in this study. Through the comprehensive evaluation of large-scale gene expression and clinical prognosis data derived from PCa patients, the research team validated ADAR1 as a promising therapeutic target and elucidated its mechanisms underlying tumor cell proliferation and invasion. At the cellular level, the knockdown or knockout of ADAR1 significantly inhibited PCa cell proliferation, migration, and invasion, induced cell cycle arrest, and promoted apoptosis. *In vivo* experiments demonstrated that the implantation of ADAR1-knockdown cells into mice markedly inhibited tumor growth. Furthermore, this study revealed that ADAR1 modulates PCa cell proliferation and invasion by editing three specific adenosines (A→I) within the 3′ UTR of MTDH mRNA (editing frequency 37% in tumors *vs* 8% in normal), which enhances ribosome occupancy (RPL22-IP enrichment reduced from 1.8- to 0.6-fold upon ADAR1 loss) and MTDH protein levels (Western blot intensity normalized to GAPDH: 1.0 *vs* 0.25, P = 0.0006) without altering mRNA stability ($t_{1/2}$ = 6.1 *vs* 6.3 h, P = 0.52). ADAR1 depletion also activates the IFN signaling pathway (IFNβ secretion increased from 12 to 142 pg/mL), thereby influencing the tumor microenvironment. In the pursuit of developing ADAR1 inhibitors, the team conducted structure-based virtual screening to identify a lead compound. Guided by molecular docking results, they optimized the compound's structure, ultimately yielding compound **ZYS-1**. Experimental data revealed that **ZYS-1** exhibits significant inhibitory activity against ADAR1 deaminase (IC_{50} = 0.946 μmol/L) and directly binds to the ADAR1 protein. In addition, **ZYS-1** has shown potent antiproliferative activity against a variety of prostate cancer cells (IC_{50} = 0.11−0.31 μmol/L) while sparing normal prostate epithelial cells ($IC_{50} > 1.4$ μmol/L). *In vivo* studies indicated that **ZYS-1** effectively suppresses tumor growth, activates the IFN signaling pathway within tumors, and exhibits favorable safety profiles. Notably, **ZYS-1** enhanced antitumor efficacy when combined with immunotherapy and showed significant inhibitory activity against various cancer cell lines and primary acute myeloid leukemia cells. This study highlights the potential of integrating clinical insights with advanced drug discovery technologies for identifying novel therapeutic targets and developing promising therapeutic agents for PCa.

Xie et al.[7] applied clinical cohort analysis to uncover therapeutic targets for NASH, sphingomyelin phosphodiesterase 3 (SMPD3) in hepatocytes as a critical factor in NASH pathogenesis. Large-scale cohort analysis demonstrated a strong correlation between SMPD3 expression and the severity of hepatic steatosis and inflammation. In a validation cohort of 168 biopsy-confirmed NASH patients, serum IFN-γ levels were significantly elevated in the high-SMPD3-expression subgroup (mean 142.6 pg/mL) compared to the low-expression subgroup (mean 68.3 pg/mL, $P < 0.01$), indicating that SMPD3 upregulation is associated with IFN-γ-mediated inflammatory signaling activation. To clarify the causal link between SMPD3-mediated ceramide/sphingomyelin (Cer/SM) ratio dysregulation and NASH pathology, targeted lipidomics was performed on liver biopsies from 71 NASH patients and GAN-diet mouse models. SMPD3-high NASH livers exhibited a 2.7-fold increase in C16:0 ceramide, a 2.1-fold increase in C18:0 ceramide, and a 1.9-fold increase in C24:1 ceramide compared to healthy controls, while total sphingomyelin levels decreased by 34%, leading to a 3.1-fold elevation in the Cer/SM ratio ($P < 0.001$). These ceramide subtypes have been implicated in mitochondrial dysfunction and NLRP3 inflammasome activation in NASH[8]. Mechanistically, SMPD3 knockout in mouse models reversed C16:0 ceramide accumulation by 61%, reduced NLRP3 protein levels by 42%, and decreased caspase-1 activity by 36%, confirming the subtype-specific role of ceramides in SMPD3-driven pathology. Cohort analysis was pivotal in providing key evidence for target discovery. By comprehensively analyzing liver tissue samples and clinical data from NASH patients, the research team validated SMPD3's critical role in disease pathogenesis and elucidated its regulatory mechanisms in lipid metabolism. In target validation studies, SMPD3 knockout in mouse models resulted in a significant reduction of hepatic steatosis and inflammation. Mechanistic investigations revealed that SMPD3 influences lipid transport and storage by regulating sphingolipid metabolism in cell membranes, thereby playing a central role in NASH development. Building on these findings, the team employed virtual screening and structural optimization to discover a series of small-molecule inhibitors targeting SMPD3. Specifically, **DC-17** showed an IC_{50} value of 3.7 μmol/L for SMPD3 inhibition. In animal models, it reduced the Cer/SM ratio

and EV release, and improved NASH pathology by lowering NAS scores by 42%, serum ALT by 36%, and hepatic triglycerides by 48%. These results highlight the therapeutic potential of **DC-17** in targeting the SIRT1−SMPD3 axis for NASH treatment. This study not only provides a novel target for NASH therapy but also serves as another successful example of drug discovery based on clinical cohort analysis, further underscoring the therapeutic potential of targeting SMPD3 in NASH.

Original target-based drug development guided by clinical insights has emerged as a powerful strategy for advancing therapeutic innovation across multiple disease areas (Fig. 1). This approach not only facilitates the precise targeting of disease mechanisms but also holds significant promise for the advancement of precision medicine. By analyzing extensive clinical samples, researchers can identify targets directly linked to diseases, enabling drugs to act more effectively on core disease pathways. For instance, FAM171A2, ADAR1, and SMPD3 have been accurately identified as key targets in PD, PCa, and NASH, respectively. These discoveries exemplify a closed-loop translational paradigm that begins with large-scale clinical cohorts to pinpoint aberrant gene or metabolite expression, integrates multi-omics profiling to delineate underlying mechanisms and build working models, and then employs genetic or pharmacological interventions to validate causal relationships between target function and disease phenotypes. Subsequent target-drugability assessments culminate in the rational design of small-molecule agents whose efficacy and safety are rigorously evaluated in animal models before clinical translation. This workflow—demonstrated for PD, PCa, and NASH—offers a versatile template for other disorders, underscoring the imperative to start from patient samples, traverse mechanistic discovery *via* multi-omics, and ultimately return to the bedside to realize precision, low-toxicity therapies.

For example, in cardiovascular research, analyzing genetic and clinical phenotypic data from large patient cohorts can help identify key disease-related genes and proteins for therapeutic targeting. Similarly, in the field of antiviral drug development, it can also be applied. Drug development can be guided by discovering the host's protein expression patterns following microbial infection. The journey from target discovery to effective drug development requires the integration of knowledge and technologies from multiple disciplines. As demonstrated in the three case studies, close cooperation among medicine, biology, chemistry, bioinformatics, and computer science is essential. Medicine provides clinical samples and disease information, biology investigates disease mechanisms and validates target functions, chemistry handles drug molecule design and synthesis, bioinformatics manages data analysis and target screening, and computer science supports AI-driven drug development. This

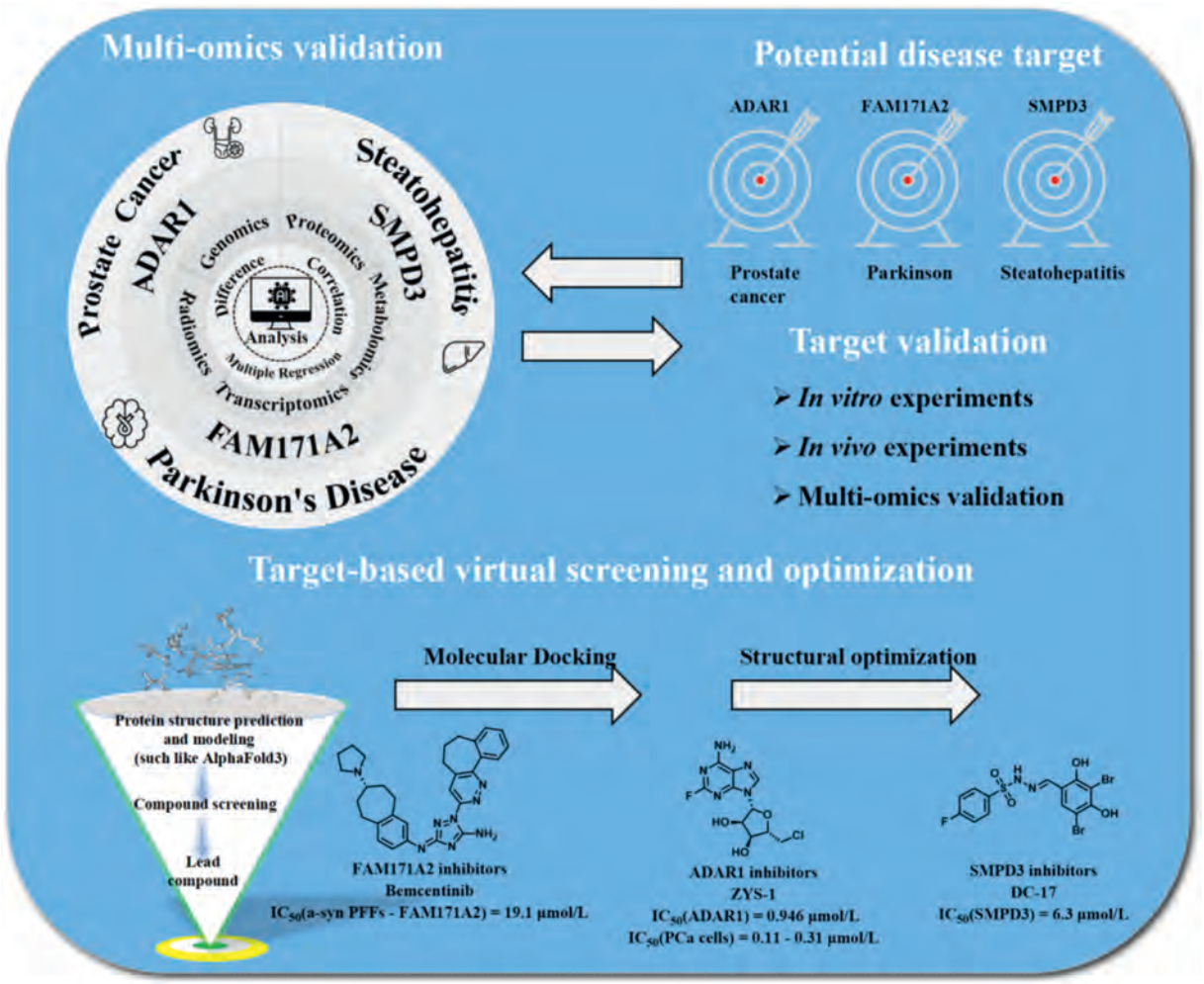

Figure 1 Drug development model based on clinically discovered novel targets.

multidisciplinary integration leverages diverse strengths, accelerates the drug development process, and provides a platform for training interdisciplinary talent.

While original target-based drug development holds great promise, it faces several key challenges. First, species-specific differences obscure translational relevance: In FAM171A2-overexpressing mice, intrastriatal injection of α-synuclein preformed fibrils (PFFs) leads to progressive p-α-syn pathology over 3−6 months in the substantia nigra[9]. By contrast, non-human primates (macaques) exhibit accelerated pathology after intrastriatal α-syn PFF injection, with dopaminergic neurodegeneration and Lewy pathology detectable within weeks[10]. Second, off-target risks persist despite optimization-ADAR1 inhibitor **ZYS-1** exhibits >100-fold selectivity over ADAR2 (IC_{50} 0.946 *vs* > 100 μmol/L) and does not alter ADAR2-dependent GLI1 editing in PCa cells[6]. Notably, small α-syn aggregates trigger neurodegeneration in primates but not in mice, highlighting fundamental interspecies differences in aggregate toxicity and microglial activation patterns. Third, pharmacokinetic hurdles remain critical: Bemcentinib's brain/plasma concentration ratio in mice is only 0.12, necessitating structure-activity relationship (SAR) studies to enhance CNS penetration[7]. These examples underscore the need for iterative validation across species, rigorous selectivity profiling, and quantitative PK/PD modeling to de-risk clinical translation. Addressing these challenges requires careful consideration of the multifaceted nature of disease mechanisms, the limitations of current drug discovery technologies, and the critical factors influencing clinical trial success. Nevertheless, advancements in artificial intelligence (AI) are offering new solutions to these long-standing issues. Exmplified by the iterative generative-AI protocol reported by Blinov et al.[11] *de novo* nanobodies targeting the 4-1BB co-stimulatory receptor can be designed within weeks using diffusion models and subsequently validated for binding activity and serum stability through both *in vitro* and *in vivo* assays. Such algorithm-driven platforms furnish precise, end-to-end tools for drug discovery, spanning target validation to preclinical optimization. Drug development anchored by clinically identified original targets offers a transformative solution to address persistent bottlenecks in the pharmaceutical industry. By integrating clinical cohort analysis, multi-omics profiling, and AI-driven computational modeling, this paradigm accelerates the discovery of disease-relevant targets and enables the design of mechanism-based therapies. Despite challenges in target validation, drug optimization, and clinical translation, advancements in AI-powered drug design and multidisciplinary collaboration-spanning pharmacology, structural biology, and bioinformatics-are expanding its applicability across complex diseases, from neurodegeneration to metabolic disorders.

To sustain this momentum, the field must prioritize two interdependent objectives.

(1) Advancing original scientific research: continuous innovation in target discovery requires deepening the integration of basic science with clinical practice. For example, leveraging patient-derived organoids and spatial transcriptomics can enhance the physiological relevance of target validation, while AI algorithms like AlphaFold3 enable real-time prediction of drug−target interaction dynamics. Such approaches not only accelerate the identification of novel therapeutic nodes but also foster a mechanistic understanding of disease heterogeneity, critical for developing personalized treatment strategies.

(2) Cultivating interdisciplinary talent: the convergence of AI and pharmacy demands a new generation of researchers proficient in both pharmacological principles and computational methodologies. Training programs should emphasize cross-disciplinary competencies, including clinical data mining, machine learning for SAR analysis, and ethical considerations in AI-driven research. Industry−academia−research collaborations-such as joint training initiatives with pharmaceutical companies and AI laboratories-will bridge the gap between academic discovery and industrial application, ensuring graduates are equipped to lead "AI + Pharmacy" innovation.

Establishing integrated platforms that span drug R&D, clinical translation, and basic research is essential to institutionalize these advancements. These hubs should facilitate seamless data sharing across disciplines, host collaborative projects addressing unmet clinical needs (*e.g.*, drug resistance in oncology), and promote public engagement through science communication initiatives. By fostering a culture of transdisciplinarity, such platforms will not only redefine the drug innovation lifecycle-from target identification to post-marketing surveillance—but also drive medical education toward a "predictive-preventive-personalized" paradigm, where AI enables proactive health management and precision therapies.

Collectively, this dual focus on scientific rigor and talent cultivation, supported by robust interdisciplinary infrastructure, will propel the field toward delivering globally impactful breakthroughs in original drug development. As a leader in "Medicine + Pharmacy" AI integration, the discipline is poised to redefine therapeutic landscapes for complex diseases and contribute meaningfully to global health equity.

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Author contributions

Peng Zhan conceived the idea. Baohu Li, Hui Xu and Xiaoyu Shi wrote the draft manuscript. Peng Zhan, JinFei Yang and Chunhua Ma revised the manuscript. All authors have read and approved submission of the final manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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