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COMBATING CANCER THROUGH AI: DEEP LEARNING FOR RATIONAL DESIGN OF SMALL MOLECULE COMBINATION THERAPIES

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Abstract

The complexity and adaptability of cancer demand innovative therapeutic strategies beyond traditional monotherapies. Artificial intelligence (AI), particularly deep learning, is transforming the landscape of oncology by enabling the rational design of small molecule combination therapies. These models leverage large-scale pharmacogenomic and multi-omics data to predict synergistic drug pairs tailored to individual tumor profiles. Deep learning frameworks, including convolutional and graph neural networks, are uncovering intricate relationships between molecular features and therapeutic response, offering a more precise and personalized approach to treatment. Additionally, explainable AI enhances the interpretability of these predictions, supporting clinical decision-making and accelerating translation. This communication highlights the promise of AI-driven approaches in redefining cancer treatment paradigms and advancing precision oncology.

Keywords

Deep learning, Small molecule combination therapy, Precision oncology, Drug synergy prediction, Artificial intelligence

The advent of artificial intelligence (AI), particularly deep learning, is revolutionizing cancer therapeutics by enabling the rational design of small molecule combination therapies. Traditional drug development and empirical combination screening are time-consuming, expensive, and often fall short in accounting for the dynamic nature of tumor heterogeneity and resistance mechanisms (1). AI-driven models offer the potential to predict synergistic drug interactions, optimize therapeutic windows, and personalize treatments with unprecedented precision (2).

Deep learning frameworks, including convolutional neural networks (CNNs) and graph neural networks (GNNs), have been successfully trained on large-scale pharmacogenomic datasets to uncover patterns between chemical structures, cellular response profiles, and genomic alterations (3). These models are capable of integrating multi-omics data including transcriptomics, proteomics, and epigenomics to forecast cancer cell vulnerabilities and recommend effective compound pairings tailored to specific molecular contexts (4).

Notably, platforms such as DeepSynergy and MatchMaker have demonstrated the ability to predict synergistic drug pairs across multiple cancer types. Furthermore, reinforcement learning algorithms are now being employed to iteratively optimize drug combinations while considering adverse effect profiles and dose constraints (5). This is particularly valuable in targeting adaptive resistance mechanisms in cancers such as triple-negative breast cancer (TNBC), non-small cell lung cancer (NSCLC), and glioblastoma, where single-agent therapies often fail (6) (Table 1).

Beyond prediction, explainable AI (XAI) is emerging as a vital component in validating AI-driven decisions and facilitating their translation to the clinic. By identifying key molecular features responsible for drug synergy, XAI enhances the interpretability and credibility of computational predictions, thus accelerating their adoption in clinical workflows (7).

Conventional cancer therapies often follow a one-size-fits-all approach, resulting in varied patient outcomes such as inefficacy or adverse effects. Recent advances in artificial intelligence offer a paradigm shift by enabling personalized treatment strategies tailored to individual patient profiles. AI-driven models can analyze complex biological data to predict effective small molecule combinations, enhancing therapeutic precision and success (8, 9) (Figure 1).

In conclusion, deep learning holds immense promise for rationally designing small molecule combination therapies that are both effective and personalized. The integration of AI into cancer pharmacology not only expedites the drug development pipeline but also aligns with the principles of precision oncology.

References

1. Wang L, Song Y, Wang H, Zhang X, Wang M, He J, et al. Advances of Artificial Intelligence in Anti-Cancer Drug Design: A Review of the Past Decade. Pharmaceuticals. 2023 Feb 7;16(2):253.

2. Serrano DR, Luciano FC, Anaya BJ, Ongoren B, Kara A, Molina G, et al. Artificial Intelligence (AI) Applications in Drug Discovery and Drug Delivery: Revolutionizing Personalized Medicine. Pharmaceutics. 2024 Oct 14;16(10):1328.

3. Askr H, Elgeldawi E, Aboul Ella H, Elshaier YAMM, Gomaa MM, Hassanien AE. Deep learning in drug discovery: an integrative review and future challenges. Artif Intell Rev. 2023 Jul;56(7):5975–6037.

4. Menyhárt O, Győrffy B. Multi-omics approaches in cancer research with applications in tumor subtyping, prognosis, and diagnosis. Computational and Structural Biotechnology Journal. 2021;19:949–60.

5. Tang YC, Gottlieb A. SynPathy: Predicting Drug Synergy through Drug-Associated Pathways Using Deep Learning. Molecular Cancer Research. 2022 May 4;20(5):762–9.

6. Nakai K, Hung MC, Yamaguchi H. A perspective on anti-EGFR therapies targeting triple-negative breast cancer. Am J Cancer Res. 2016;6(8):1609–23.

7. Saarela M, Podgorelec V. Recent Applications of Explainable AI (XAI): A Systematic Literature Review. Applied Sciences. 2024 Oct 2;14(19):8884.

8. Sudhakaran G. Updated liquid biopsy techniques for non-invasive oral cancer detection and monitoring in 2024. Oral Oncology Reports. 2024 Jun 1;10:100537.

9. Dharani R, Danesh K. Optimized Deep Learning Ensemble for Accurate Oral Cancer Detection Using CNNs and Metaheuristic Tuning. Intelligence-Based Medicine. 2025 May 19:100258.

Figure 1 This image illustrates the contrast between traditional one-size-fits-all cancer treatment by healthcare professionals and AI-assisted personalized therapy. In conventional approaches, identical treatments can lead to varied outcomes ranging from expected effects to no response or adverse reactions due to individual differences.

In contrast, AI leverages patient-specific data to tailor drug combinations, maximizing therapeutic effectiveness and minimizing risks across diverse patient populations.

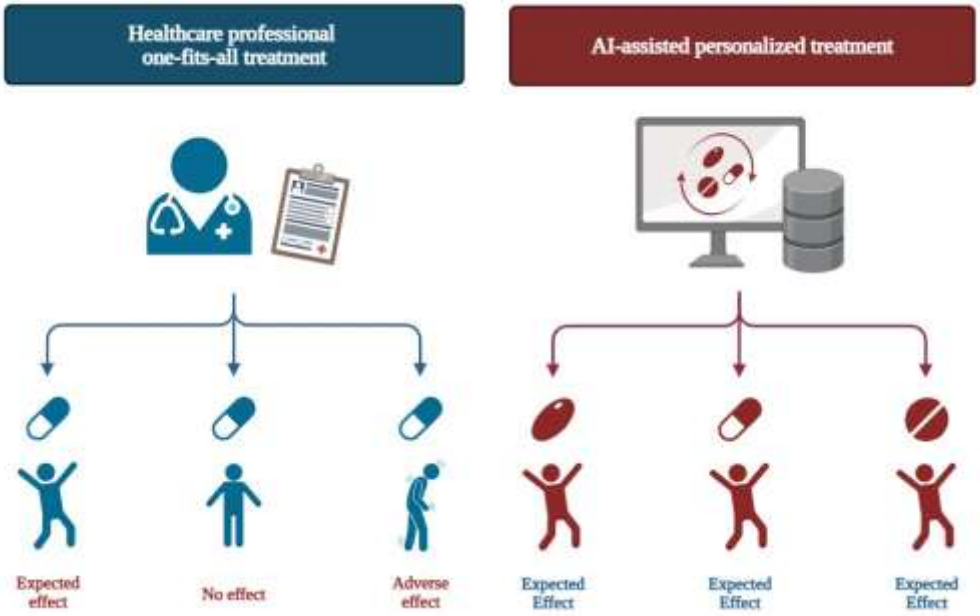

Table 1. Summarizes the application of AI, particularly deep learning, in designing small molecule combination therapies for cancer. It outlines the use of neural network models, multi-omics data integration, and AI platforms in predicting drug synergy. Reinforcement learning and explainable AI further enhance safety, efficacy, and clinical interpretability. These innovations aim to improve outcomes in hard-to-treat cancers through personalized combination strategies.

Component	Description	Clinical/Research Utility	References
Deep Learning Models	Includes CNNs and GNNs trained on pharmacogenomic and omics data	Predict drug synergy and identify optimal combination therapies	(1), (2), (3)
Multi-Omics Integration	Transcriptomics, proteomics, epigenomics integrated into models	Tailors therapies to tumor-specific molecular profiles	(4)
Platforms (e.g., DeepSynergy, MatchMaker)	AI tools that forecast effective drug pairs	Demonstrated success across various cancer types	(5)
Reinforcement Learning	Iteratively refines combinations considering toxicity and dose limits	Enhances safety and efficacy in drug regimens	(5), (6)
Explainable AI (XAI)	Identifies molecular drivers of synergy for transparency and trust	Supports clinical adoption through interpretability	(7)
Targeted Cancers	Includes TNBC, NSCLC, glioblastoma	Addresses resistance where monotherapies often fail	(6)