REVIEW ARTICLE

Smart Drug Design: AI in Transcriptional Modulation and Clinical Innovation

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Abstract

Transcriptional regulation is a critical mechanism controlling DNA segment expression and theatres a main portion in cancer, genetic disorders, and complex diseases. However, developing drugs that precisely target transcriptional processes remnants exciting due to the structural complication of transcription factors and risks of off-target effects. Recent advances in artificial intelligence (AI) have transformed drug discovery by enabling better modelling of genomic and regulatory landscapes. This review highlights AI-driven approaches in transcription modulator discovery, including in silico target identification, multi-omics integration, and structure–activity optimization. It also discusses deep learning and transformer-based genomic models for identifying disease-specific regulators and DNA elements. Furthermore, the review examines progress in developing small-molecule, epigenetic, and RNA-targeting drugs. Finally, it emphasises the importance of explainable AI and personalised therapeutics in advancing precision medicine and next-generation transcription-based drug discovery.

Keywords: Artificial intelligence; Transcriptional regulation; Gene-regulating drugs; Multi-omics integration; Precision medicine; Clinical translation

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Introduction

Transcriptional Regulation's Significance in Health and Illness

A key biological mechanism in the transformation of genetic information contained in DNA into useful RNA molecules is transcriptional control. In the end, this process controls cellular identity, function, and reaction to external stimuli. For healthy growth, equilibrium, and physiological adaptation, transcriptional regulation must be precisely controlled. This process is orchestrated through a complex interplay of transcriptional regulators, co-regulators, enhancers, promoters, chromatin regulators, and epigenetic regulators.[1] Any alteration in transcriptional regulation can cause aberrant transcriptional patterns, contributing to the onset of many diseases.

One of the main characteristics of cancer is aberrant transcriptional regulation. Oncogenes and tumour suppressor genes are expressed uncontrollably, which leads to cancer.[2] Likewise, transcriptional abnormalities play an important role in the pathogenesis of genetic disorders, rare genetic disorders, neurodegenerative disorders, inflammatory disorders, and metabolic syndromes, among others. Transcriptional regulation, therefore, being an important part of disease biology, is an attractive target for therapeutic intervention, given the potential that drugs targeting transcriptional regulation may provide the opportunity for the therapeutic management of disease-causing molecular programs at the origin of the disease, as opposed to the management of disease symptoms.[3,4] The translation of this potential into effective therapeutic agents, however, has provided a significant scientific challenge.

Limitations of Conventional Drug Discovery for Transcription Factors and Gene Regulators

In spite of the importance of transcription factors and gene regulators as therapeutic targets, they have traditionally been considered "undruggable" targets for therapeutic intervention. This is because, unlike enzymes or receptors that possess specific target locations for medication activity, transcription factors lack stable target locations for medication activity. interaction. This activity is often mediated in a protein–protein or protein–DNA manner that is dynamic, transient, and context-dependent, which makes it difficult to target in a classical way.[5]

Transcriptome regulation is highly complex and context-dependent, making traditional screening methods inefficient, costly, and prone to failure due to variable effects and off-target toxicity.[6]

Artificial Intelligence's Rise in Genomics-Based Drug Development

Unprecedented chances to comprehend transcription control at the systems level have been made possible by the enormous increase of genomic, transcriptomic, and epigenomic data. In order to analyse these enormous volumes of data and find intricate non-linear patterns in the data that cannot be found using traditional analytical tools, artificial intelligence (AI), including machine and deep learning techniques, has been highlighted as a crucial tool. AI can accurately discover these relationships by combining and analysing a variety of data sources, such as DNA sequences, chromatin accessibility, transcription factor binding, and gene expression profiles.[7]

In the process of finding new drugs, AI has the ability to accelerate the process of finding new drugs, including target proof, screening, and structure-activity relationship optimization. Genomic transformer models and network-based AI tools have the ability to predict transcription factor binding, enhancer-promoter interaction, and gene expression in response to chemical compounds. By facilitating in-silico prioritization of high confidence targets and compounds, AI can minimize the experimental effort and maximize the efficiency of the translation process.[8] Perhaps most significantly, AI-based approaches can provide continuous feedback loops between prediction and experiment, facilitating the development of adaptive processes that are more efficient and precise.

Scope and Objectives

This assessment goals to provide a complete and critical overview of AI-guided strategies in the discovery and development of transcription-modulating drugs. It will cover the impact of advanced computational models on the discovery and development of targets, the design of gene-regulating therapeutics, and the translation process.[9] This review highlights how AI is transforming genomic modeling and drug development by enabling precise targeting of transcription factors and regulatory DNA. It emphasizes the role of multi-omics integration, novel AI-designed therapeutics, and the pathway from computational discovery to clinical application. It also addresses key challenges like ethics, interpretability, and regulation, showing AI's potential to advance precision medicine..[10]

Molecular Basis of Transcriptional Regulation

Overview of the Transcription Machinery

Transcription is the molecular process that transforms genetic information contained in DNA into messenger RNA. It is the initial stage of the gene expression process. The enzyme RNA polymerase II is responsible for transcription in eukaryotic cells. But the enzyme doesn't function alone.. It requires the coordinated action of several regulatory proteins to execute its role in the process of transcription. Transcript features (TFs) are the key proteins that recognize specific DNA sequences

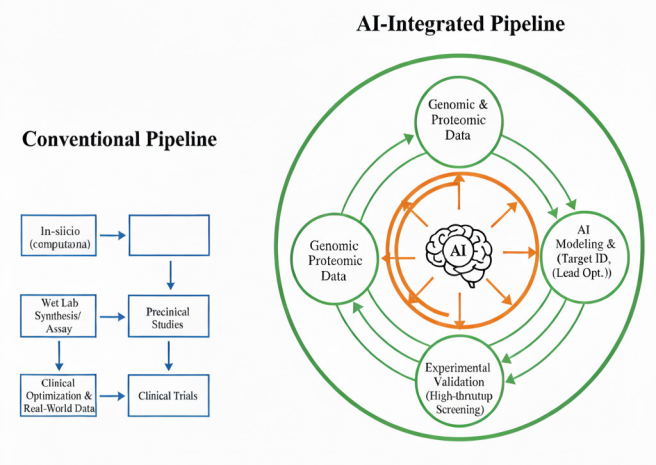


Figure 1: Comparison of conventional and AI- Guided Discovery Pipelines

and recruit the enzyme to the promoter regions of the DNA.[11]

While specific transcription factors are in charge of modulating the process in response to particular cell signals, general transcription factors are in charge of assembling at the promoter regions to start the transcription process.. Co-activators and co-repressors regulate the process in a specific manner. These proteins do not have DNA-binding capabilities but regulate the levels of gene expression through interaction with transcription factors and chromatin-modifying enzymes. This complex interplay of RNA polymerase, transcription factors, and regulatory cofactors is essential to regulate the timing and location of transcription.[12]

Regulatory DNA Elements and Chromatin Remodeling

Gene transcription is regulated through various DNA elements, which are unique to the regulation of gene expression. These DNA elements are known as promoters, enhancers, and silencers. A promoter is usually located near the transcription initiation site and acts as a docking site for the transcriptional machinery. Enhancers are located at a distance from the promoter and have the ability to activate transcription through looping to interact with the promoter, whereas silencers inhibit gene expression through the recruitment of transcriptional repressors.[13]

This process is crucial in controlling the access to these regulatory regions. DNA and histone proteins make up chromatin, which is where DNA is arranged. Whether a gene is transcriptionally active or dormant depends on the degree of chromatin compaction. Chromatin remodelling complexes regulate nucleosome placement to govern transcription factors' access to particular genomic areas..[14]

Epigenetic Control of Transcription

Changes in gene expression patterns that do not modify the underlying DNA sequence are referred to as epigenetic control. Histone protein changes and DNA methylation are the primary mechanisms of epigenetic regulation. Both acetylation and methylation can occur in histone

proteins. Because transcription factors cannot bind to DNA methylation, transcription is often repressed. Histone modifications can either open or compact the chromatin structure. Acetylation of the histones is generally linked to the activation of the transcription process, whereas the effects of the methylation process can either activate or suppress the transcription process.[15]

Disease Relevance of Transcriptional Dysregulation

Dysregulation in the process of transcriptional regulation is a common feature in all human diseases. Abnormal activation of oncogenic transcription factors or inactivation of tumor suppressors in the case of cancer results in the uncontrolled growth and survival of cells. Genetic disorders are often the end results of mutations in the transcription factors or DNA regulatory elements, causing inappropriate patterns of gene expression. Neurological disorders are also the end results of the dysregulation in the process of transcriptional regulation.[16]

As such, due to its importance in the pathogenesis of disease, transcriptional regulation is an attractive target in the development of new therapies, including AI-based drug development to specifically target gene expression and utilize this understanding to treat disease. Thus, the molecular mechanism of transcription is vital in the development of innovative therapies and drugs to treat disease, including the AI's application in medication development.[17]

Tasks in Targeting Transcription with Conventional Drugs

Transcription Factors as "Undruggable" Targets

A vast family of useful proteins known as transcription factors (TFs) are essential for controlling gene expression, but these have been difficult to target as therapeutics in the past. These differ from other targets, such as enzymes or membrane-bound receptors, as these do not have a deep binding pocket to which a drug can be designed to bind to. Their functional domains have been reported to be disordered, relying on

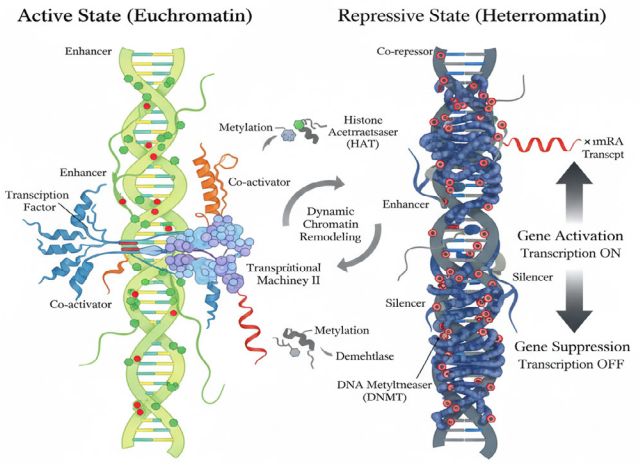


Figure 2: Mechanism of Transcriptional Regulation: transcription factor binding, Chromatin states and gene activation and suppression

transient interactions with other proteins or DNA, which has made the rational drug design of these difficult. This has led to a lack of success in the identification of transcription factors as targets of conventional drug screening, which has hindered the development of transcription-targeting therapeutics.[18]

Limited Structural Information for Drug Design.

In structure-based drug discovery, detailed structural information is often obtained through approaches like X-ray crystallography or cryo-electron microscopy. For transcriptional regulators and their complexes, detailed structural information may be incomplete or lacking altogether. Transcription factors often work in the context of very large dynamic multiprotein complexes that cannot be easily crystallized. The absence of structural information limits the effectiveness of computational docking, modeling, and structure-activity relationship studies.[19]

Context-Dependent and Dynamic Gene Regulation

Transcription factors can behave differently in various contexts, and gene regulation is highly context-dependent, differing between cell types, developmental stages, and disease situations. Conventional drug discovery often fails to capture this complexity, leading to non-specific drugs and inconsistent patient outcomes. Additionally, the dynamic nature of transcriptional networks makes target validation challenging due to constantly changing regulatory interactions.[20]

Off-Target Effects and Toxicity Concerns

Transcriptional regulators have the capacity to influence a variety of biological pathways as they target multiple genes. Non-selective transcriptional regulators can alter normal cellular function, leading to off-target effects as well as toxicity issues. Conventional screening strategies emphasize functional activity over specificity, thus increasing the potential for adverse effects during clinical trials. Drug toxicity is a leading reason for drug failures during clinical trials, especially for transcriptional regulators.[21]

High Attrition Rates in Clinical Translation

Despite showing promise during preclinical studies, transcription-targeting drugs have a high failure rate during clinical trials. These failures stem from issues of efficacy, toxicity, as well as stratification. Conventional strategies have failed to accurately predict transcriptional responses as well as patient stratification. These limitations underscore the need to develop novel and more efficient techniques, such as the application of artificial intelligence.[22]

AI Technologies Used in Transcription Modulation-Targeting Drug Discovery

Artificial intelligence has emerged as a key driver in transcription modulation-targeting drug discovery, especially for targeting transcription factors (TFs) and regulatory DNA elements, which have traditionally been viewed as "undruggable" targets. By integrating machine learning

Table 1: Key Limitations of Conventional Approaches in Transcription-Modulating Drug Discovery

Challenge	*Detailed Description*	*Underlying Cause*	*Clinical Impact*	*Reference*
Undruggable transcription factors (TFs)	TFs lack stable binding sites and rely on dynamic interactions, making them difficult drug targets.	Intrinsically disordered protein regions and dynamic interaction interfaces	Low hit identification rates and limited availability of selective transcription-modulating drugs	23
Context-dependent gene regulation	TF activity varies across tissues and conditions, affecting treatment consistency.	Complex transcriptional networks and environment-specific regulatory cues	Reduced therapeutic efficacy and inconsistent clinical outcomes across patient populations	24
Off-target effects and toxicity	Non-specific TF targeting disrupts multiple genes and normal cellular functions.	Broad regulatory roles of transcription factors and lack of target specificity	Increased adverse effects, dose-limiting toxicity, and frequent clinical trial discontinuation	25
High cost and prolonged development timelines	Drug discovery is slow and expensive due to sequential processes and failures.	Linear discovery workflows and late-stage failure detection	High attrition rates and financial burden	26

(ML) and deep AI systems can find patterns in transcriptional regulation that would be difficult to find using traditional computational methods by using deep learning (DL) techniques with high-dimensional genomic data..[27]

Models for Deep Learning and Machine Learning :

Supervised and unsupervised learning paradigms can be used to broadly categorise machine learning-based methods for transcriptional regulation. The transcriptional regulatory process can be successfully identified using supervised learning-based algorithms.These methods can also be very effective if there is access to well-annotated data. In contrast to this, unsupervised methods use unlabeled data to identify hidden patterns and relationships in the data. They can be very useful in the discovery of novel regulatory elements.[28]

Deep learning methods have also helped in the effective modeling of complex genomic features. Convolutional neural networks (CNNs) can be effectively used to identify patterns in DNA sequences such as sequence motifs and local regulatory elements. Long short-term memory (LSTM) networks and other variations of recurrent neural networks (RNNs) can also be highly successful in identifying and comprehending long-range correlations in genomic data.[30] These relationships can be very important in the understanding and regulation of gene transcription. Graph neural networks (GNNs) can also be very effective in the understanding and modeling of complex gene regulatory networks and chromatin interactions. One of the main uses of such models is the prediction of transcription factor binding sites more accurately. Apart from the binding sites, the foundation models can also be used for the integration of epigenetic data, along with the accessibility data, for modeling the enhancer-promoter relationships, which is an important part of gene regulation. The foundation models can thus be used for the comprehensive understanding of transcriptional regulation, as they can capture both the local features as well as the long-range relationships between the genomic sequences.[31]

AI-Guided Identification of Transcription-Modulating Drug Targets:

Artificial intelligence has increasingly been bridging the gap between the creation of genomic data and the translational discovery of drugs by identifying transcription-modulating therapeutic targets using

AI-guided frameworks. Instead of focusing on a particular gene, AI-guided frameworks use large-scaletranscriptomics and epigenomics data to identify disease-relevant transcriptional networks. Such frameworks allow researchers to identify the key transcriptional programs responsible for the pathologic state triggered through diseases such as tumor, inflammatory diseases, and neuro-degenerative ailments.[35]

The identification and characterisation of regulatory DNA regions, such as enhancers and super-enhancers, which are essential for the regulation of genes related to disease, is one of the main advantages of AI-guided frameworks. Additionally, chromatin accessibility and histone modification patterns are identified by AI-guided frameworks, and 3D genome architecture to identify the regulatory regions that are highly sensitive to pharmacological modulation. In parallel, network-based algorithms focus on transcription factor-cofactor complexes rather than individual TFs, which better represents the cooperative nature of transcriptional regulation and enhances the prospects for draggability.[36]

Crucially, AI facilitates the discovery of disease-specific transcriptional vulnerabilities by comparing the regulatory landscape of diseased and normal tissues. This contextual understanding of prioritization aids in the development of precision medicine interventions that target disease-specific transcriptional regulation with minimal impact on normal cellular function.[37]

AI-Designed Transcription-Modulating Therapeutics

Small-molecule transcription modulators

AI-assisted drug development has significantly increased the range of small molecules that can modulate the transcription

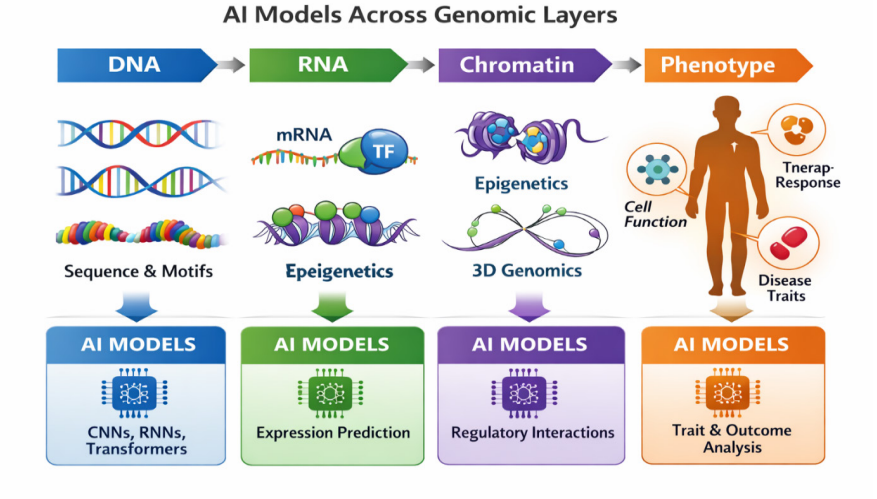


Figure 3: AI Models across genomic layers and machine learning.

Table 2: Transcription-Focused Drug Discovery Using AI Models

AI Model	*Core Principle*	*Key Applications in Transcription Modulation*	*Input Data Types*	*Model Output*	*Relevance to Drug Discovery*	*Reference*
Convolutional Neural Networks (CNNs)	Detect local spatial patterns through convolutional filters	Predicts TF binding sites and identifies regulatory DNA elements	DNA sequences, ChIP-seq, ATAC-seq	Binding scores, motif maps, element classification	Identifies regulatory regions for targeted drug design	32
Transformer-Based Models	Attention mechanisms capture long-range dependencies	Models gene regulation and predicts transcriptional changes	Genomic, epigenomic, RNA-seq data	Gene expression predictions, impact scores	Enables prediction of complex transcriptional responses	33
Graph Neural Networks (GNNs)	Learn from graph-structured biological networks	Analyzes gene regulatory networks to identify key targets	PPI networks, drug-target data, gene networks	Target scores, network metrics	Helps prioritize therapeutic transcriptional targets	34

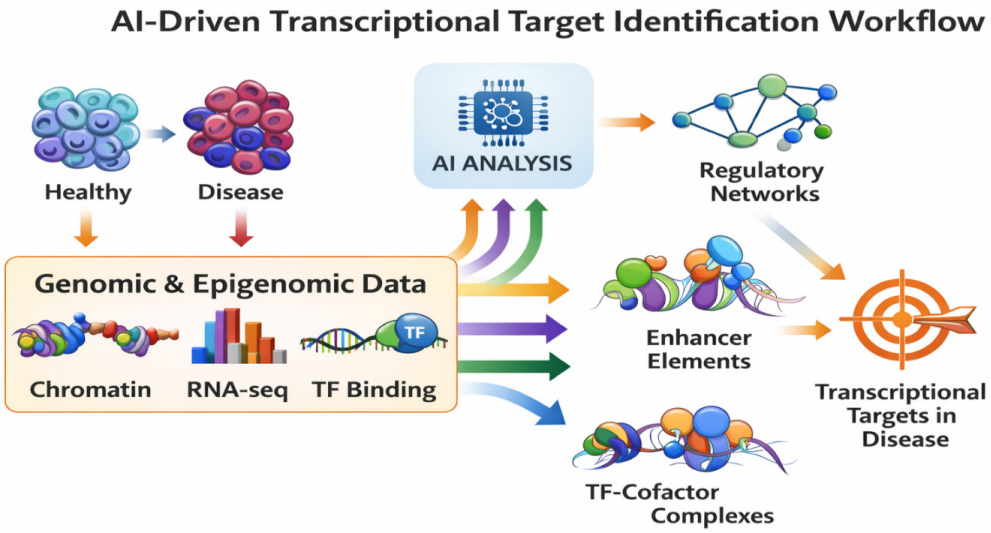


Figure 4: AI- Driven Transcriptional target identification workflow

Table 3: Classes of AI-Designed Transcription-Modulating Drugs

Drug class	*Primary target*	*Role of artificial intelligence*	*Representative disease areas*	*References*
Small-molecule transcription modulators	Transcription factor–DNA interfaces and associated regulatory complexes	AI enables virtual screening and identification of allosteric or transient binding sites for better targeting	Oncology, particularly transcription-driven cancers	42
RNA-targeted therapeutics	Regulatory non-coding RNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs)	AI predicts RNA structure and optimizes oligonucleotide design for targeted gene regulation	Neurological and neurodegenerative disorders	43
Epigenetic drugs	Chromatin-modifying enzymes, histone acetylation, and methylation	AI improves SAR analysis to enhance selectivity and reduce off-target effects	Rare and genetically driven diseases	44

apparatus. Instead of targeting transcription factors through poorly characterized binding sites, AI methods have identified allosteric sites, "interfacial" regions, and protein-protein interaction "hotspots" of the transcription apparatus. Machine learning techniques have also compared vast libraries of chemicals with structural and functional data sets, predicting molecules that can indirectly modulate the activity of transcription factors.[38]

RNA-targeted transcription regulators

Artificial intelligence has also enabled the creation of RNA-focused therapies that modulate transcriptional regulation at the RNA level. Using AI algorithms to predict RNA secondary structure and sequence motifs enables the identification of transcriptional regulators at the RNA level such as enhancer RNAs and lengthy non-coding RNAs. AI-assisted design of antisense oligonucleotides and small interfering RNAs enables the specificity, stability, and delivery of these RNA therapies. Such RNA-targeting therapies enable a reversible and adaptable approach for the modulation of transcriptional regulation.[39]

Epigenetic drugs targeting chromatin regulators

AI is advancing epigenetic drug discovery by analyzing chromatin accessibility, histone modifications, and transcriptional data to identify targets like HDACs and BET proteins. It also helps design selective inhibitors with better safety by reducing off-target effects. Additionally, AI-driven SAR modeling accelerates lead optimization by predicting drug potency, specificity, and toxicity.[41]

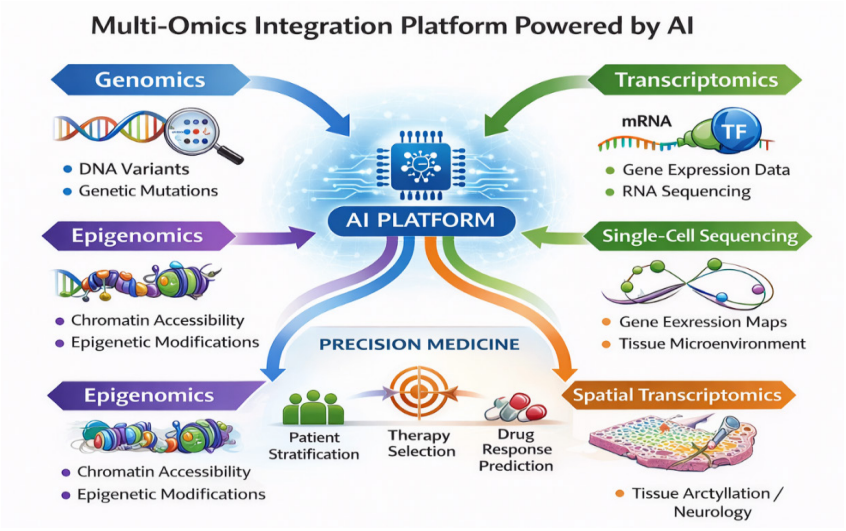
Integration of Multi-Omics Data Using AI

Integration of genomics, transcriptomics, and epigenomics

The integration of many omics data layers that are in charge of controlling gene expression depends heavily on artificial intelligence. Genomic data give us information on genetic or acquired mutations in the DNA sequence, transcriptomic data give us information on the expression patterns of genes, and epigenomic data give us information on the chromatin structure and different modifications that occur during gene expression. AI helps in the integration of these different layers of omics data to understand the gene expression process.[45]

Spatial transcriptomics and single-cell sequencing

Recent advances in spatial transcriptomics and single-cell sequencing have provided us with complicated data that calls for advanced analysis. AI is essential to the examination of this complicated data**.** .[46]



Somatic mutations in cancer

Artificial intelligence helps identify cancer-related mutations and cellular heterogeneity by clustering cell populations and reconstructing lineages. It also enhances spatial transcriptomics through image analysis, linking gene expression with tissue structure to better understand complex transcriptional programs.[47]

AI-driven patient stratification

Within the addition of multi-omics information from patient cohorts, AI can stratify patients into specific groups. This stratification model can identify transcriptional signatures related to disease progression, prognosis, and therapy. This data-driven patient stratification can lead to personalized therapy through the matching of therapy and regulation profiles.[48]

Prediction of transcriptional drug response

With the development of AI models, pharmacological therapy can be predicted to respond to transcriptional networks. This can be achieved through the use of multi-omics drug response data.[49]

Translational Pathway: From In-Silico Models to Clinical Therapeutics

Transition from in-silico predictions to experimental validation

The predictions made in in-silico models regarding transcription-modulating drug targets, drug molecules, and their predicted effects on gene expression are validated experimentally to ensure their biological relevance. For this purpose, in-vitro studies are performed on cells to confirm the target engagement and functional consequences.[51]

In-vivo validation in disease-relevant models:

After in-vitro studies have confirmed the predictions made in in-silico models regarding the in-vitro effects of transcriptional modulators identified using AI tools, in-vivo studies are performed to assess their pharmacokinetics, pharmacodynamics, and safety profiles. These studies help to assess if the predictions made in in-silico models regarding the in-vivo effects of transcriptional modulators identified using AI tools are correct.[52]

Biomarker-driven clinical trial design

The use of AI helps in the identification of transcriptional, epigenetic, or molecular biomarkers related to drug response. By classifying patients who are more likely to benefit from the medication, this aids in the creation of a better clinical study.[53]

AI-assisted dose optimization

This is a predictive modeling approach that incorporates preclinical data, patient characteristics, and early clinical data to predict the optimal dose strategy. This helps in selecting a dose that is both effective and minimizes adverse effects.[54]

Regulatory considerations and compliance

The FDA and EMA require that AI methodologies used in drug discovery and development should be transparent, reproducible, and validated. This ensures that the AI-assisted drug discovery and development processes adhere to regulatory requirements, making them more acceptable for use in the clinic.[55]

Case Studies and Emerging Clinical Evidence

AI-Designed Epigenetic Drugs in Oncology

Recent translational studies have shown the utility of AI in accelerating the discovery of epigenetic inhibitors of chromatin regulators of oncogenic transcriptional programs. Machine learning-based approaches have been applied to integrate epigenomic and transcriptomic information to design and select inhibitors of chromatin regulators. Preclinical studies have shown the efficacy of these inhibitors in suppressing tumor-specific transcriptional dependencies with minimal effects on chromatin. Clinical trials have shown improved selectivity and safety of these inhibitors in comparison to previous epigenetic inhibitors.[57]

Transcription-Targeted Therapies in Rare Genetic Diseases

AI-based methods have been utilised to cure rare genetic illnesses in order to comprehend the function of aberrant

Table 4: Representative Case Studies of AI-Guided Transcription-Modulating Drugs

Therapeutic area	*Target class*	*Role of ai*	*Stage of development*	*Key outcomes and insights*	*References*
Oncology	Epigenetic regulators	AI integrates omics data to identify targets and optimize drug selectivity	Preclinical to early clinical evaluation	Selective suppression of oncogenic transcription	60
Rare genetic diseases	Transcription factors and enhancers	AI identifies compensatory transcriptional targets using network models	Preclinical and compassionate-use studies	Partial restoration of gene expression	61
Inflammatory and immune-related disorders	Transcriptional signaling hubs	AI stratifies patients using transcriptional biomarkers	Early-phase clinical trials	Improved responder identification	62
Precision medicine pipelines	Transcriptional response signatures	AI analyzes transcriptomic data to guide trials and dosing	Ongoing clinical trials	Enhanced trial efficiency and precision	63

transcriptional programs brought on by single-gene mutations. The usefulness of AI in finding aberrant transcriptional programs and choosing transcription factors, enhancers, and RNAs that have been altered in disease states has been demonstrated through a number of case studies. This strategy has been used to repair abnormal gene expression in disease situations by repurposing transcription-modulating medications.[58]

Ongoing clinical trials utilizing AI-generated hypotheses

Several ongoing clinical trials are utilizing AI-generated hypotheses at different stages, such as target identification, biomarker identification, and dose optimization. Although the molecular details remain proprietary, the publicly available information on ongoing clinical trials indicates that AI-generated transcriptional signatures are being increasingly utilized for patient stratification and response assessment. These ongoing clinical trials represent the emerging acceptance of AI-assisted transcription-based drug development.[59]

Ethical, Regulatory, and Interpretability Challenges

Black box in AI models

In addition, some of the sophisticated drug discovery tools in transcription-focused drug discovery utilize black box AI models. This makes it difficult to understand how the prediction was made. This may raise issues of trust and accountability in drug discovery.

Concerns of data bias and reproducibility

AI models rely heavily on the value of the statistics used to train the model. This may lead to issues of reproducibility and bias in the results obtained. This may limit the generalisation of the transcriptional therapy developed using AI.[64]

Explainable artificial intelligence (XAI)

Explainable AI improves transparency in drug discovery by identifying key features behind predictions, aiding interpretation and validation of results.

Regulatory acceptance of AI-designed drugs

Regulatory authorities demand clear evidence of the reliability and validation of the results obtained using AI in drug discovery. This helps to improve trust in the results obtained through the use of AI in drug discovery.[65]

Future Perspectives and Opportunities

- The integration of AI with human expertise will act as a decision-support system, improving efficiency and innovation in transcription-targeted drug discovery.
- Advances in biosensing and high-throughput sequencing will enable real-time monitoring of transcription, supporting better drug response evaluation and adaptive treatments.[66]
- AI-driven personalized transcription-modulating therapies, combined with gene editing and RNA-based approaches, enable precise and reversible control of gene expression, improving treatment efficacy and reducing side effects in precision medicine.[67]

Conclusion

Artificial intelligence has transformed transcriptional medication detection by allowing the examination of complex regulatory networks, identification of novel targets, and integration of multi-omics data for precision-guided therapies. Its ability to capture context-dependent gene regulation offers significant advantages over conventional approaches. However, challenges such as data limitations, interpretability, and validation must be addressed to ensure reliability and clinical success. Despite these hurdles, the integration of AI into transcription-based therapeutics presents a promising pathway for developing next-generation gene-regulating drugs. Ultimately, AI-driven approaches have the potential to revolutionize disease understanding and significantly improve the effectiveness and personalization of clinical treatments.

Declaration

We hereby declare that AI tools are been used to create diagrams and used to support and design data interpretation with final verifications.

Reference

1. Alberts B, Johnson A, Lewis J, Morgan D, Raff M, Roberts K, Walter P. *Molecular Biology of the Cell*. 6th ed. New York: Garland Science; 2015
2. Hanahan D. Hallmarks of cancer: new dimensions. *Cell*. 2022;185(8):1315–37.
3. Nott A, Holtman IR, Coufal NG, Schlachetzki JCM, Yu M, Hu R, Han CZ, et al. Brain cell type–specific enhancer–promoter interactome maps and disease-risk association. *Science*. 2019;366(6469):1134–9.
4. Papavassiliou AG, Musti AM. The multifaceted output of c-Jun biological activity: focus at the junction of transcription, DNA damage response and cancer. *Oncogene*. 2020;39(45):6645–56
5. Darnell JE Jr. Transcription factors as targets for cancer therapy. *Nat Rev Cancer*. 2002;2(10):740–9
6. InglesEspiritu JP, Kothari A, Gray NS. Challenges and opportunities in targeting transcriptional regulation in disease. *Nat Rev Drug Discov*. 2021;20(7):507–26
7. Zhang DD, Li Q, Wang C, et al. *The transformative role of artificial intelligence in genomics: opportunities and challenges*. Gene Rep. 2025;41:102314. doi:10.1016/j.genrep.2025.102314.
8. Ahmed FS, Aly S, Liu X. EPI-Trans: an effective transformer-based deep learning model for enhancer promoter interaction prediction**.** *BMC Bioinformatics*. 2024;25:216
9. Niazi SK**.** *Artificial intelligence in small-molecule drug discovery: a critical review of methods, applications, and real-*

world outcomes. Pharmaceuticals (Basel). 2025;18(9):1271
10. Vamathevan J, Clark D, Czodrowski P, Dunham I, Ferran E, Lee G, et al. *Applications of machine learning in drug discovery and development*. Nat Rev Drug Discov. 2024;23(2):115–33.
11. Cramer P. *Organization and regulation of gene transcription.* Nature. 2019;573(7772):45–54
12. Roeder RG. *The role of general initiation factors in transcription by RNA polymerase II.* Trends Biochem Sci. 2019;44(7):529–42.
13. Kieffer-Kwon KR, Tang Z, Matos MD, et al. *Enhancer–promoter interactions and transcription regulation through chromatin architecture.* Annu Rev Cell Dev Biol. 2022;38:369–94.
14. Clapier CR, Iwasa J, Cairns BR, Peterson CL. *Mechanisms of chromatin remodeling and regulation.* Annu Rev Biochem. 2024;93:55–82
15. Jones PA, Ohtani H, Chakravarthy A, De Carvalho DD. *Epigenetic therapy in immune-oncology.* Nat Rev Cancer. 2024;24(4):221–37
16. Shao Z, Flynn RA, Yu Y, et al. *Mechanisms of transcriptional dysregulation in human disease.* Cell. 2025;186(1):12–30.
17. Schneider P, Walters WP, Plowright AT, Sieroka N, Listgarten J, Goodnow RA Jr, et al. *Rethinking drug design in the artificial intelligence era*. Nat Rev Drug Discov. 2020;19(5):353–64.
18. Bushweller JH. Targeting transcription factors in cancer—from undruggable to reality. *Nat Rev Cancer*. 2019;19(11):611–24.
19. Dang CV, Reddy EP, Shokat KM, Soucek L. Drugging the 'undruggable' cancer targets. *Nat Rev Cancer*. 2017;17(8):502–8.
20. Cramer P. Organization and regulation of gene transcription. *Nature*. 2019;573(7772):45–54.
21. Santos R, Ursu O, Gaulton A, Bento AP, Donadi RS, Bologa CG, et al. A comprehensive map of molecular drug targets. *Nat Rev Drug Discov.* 2017;16(1):19–34.
22. Harrison RK. Phase II and phase III failures: 2013–2015. *Nat Rev Drug Discov.* 2016;15(12):817–8.
23. Lambert M, Jambon S, Depauw S, David-Cordonnier MH. Targeting transcription factors for cancer treatment. *Molecules*. 2018;23(6):1479.
24. Spitz F, Furlong EEM. Transcription factors: from enhancer binding to developmental control. *Nat Rev Genet*. 2012;13(9):613–26.
25. Swinney DC, Anthony J. How were new medicines discovered? *Nat Rev Drug Discov.* 2011;10(7):507–19.
26. Scannell JW, Blanckley A, Boldon H, Warrington B. Diagnosing the decline in pharmaceutical R&D efficiency. *Nat Rev Drug Discov.* 2012;11(3):191–200.
27. Avsec Ž, Agarwal V, Visentin D, Ledsam JR, Grabska-Barwińska A, Taylor KR, et al. Effective gene expression prediction from sequence by integrating long-range interactions. *Nat Methods*. 2021;18(10):1196–203.
28. Ji Y, Zhou Z, Liu H, Davuluri RV. DNABERT: pre-trained bidirectional encoder representations from transformers model for DNA-language in genome. *Bioinformatics*. 2021;37(15):2112–20.
29. Zhou J, Troyanskaya OG. Predicting effects of noncoding variants with deep learning–based sequence model. *Nat Methods*. 2015;12(10):931–4.
30. Zitnik M, Agrawal M, Leskovec J. Modeling polypharmacy side effects with graph convolutional networks. *Bioinformatics*. 2018;34(13):i457–66.
31. Kelley DR. Cross-species regulatory sequence activity prediction. *PLoS Comput Biol*. 2020;16(7):e1008050.
32. Kelley DR, Snoek J, Rinn JL. Basset: learning the regulatory code of the accessible genome with deep convolutional neural networks. *Genome Res*. 2016;26(7):990–9.
33. Avsec Ž, Agarwal V, Visentin D, Ledsam JR, Grabska-Barwińska A, Taylor KR, et al. Effective gene expression prediction from sequence by integrating long-range interactions. *Nat Methods*. 2021;18(10):1196–203.
34. Zitnik M, Agrawal M, Leskovec J. Modeling polypharmacy side effects with graph convolutional networks. *Bioinformatics*. 2018;34(13):i457–66.
35. Karczewski KJ, Francioli LC, Tiao G, Cummings BB, Alföldi J, Wang Q, et al. *The mutational constraint spectrum quantified from variation in 141,456 humans*. Nature. 2020;581(7809):434–43.
36. Avsec Ž, Weilert M, Shrikumar A, Krueger S, Alexandari A, Dalal K, et al. *Base-resolution models of transcription-factor binding reveal soft motif syntax*. Nat Genet. 2021;53(3):354–66.
37. Schreiber J, Durham T, Bilmes J, Noble WS. *Avocado: a multi-scale deep tensor factorization method learns a latent representation of the human epigenome.* Genome Biol. 2020;21(1):81.
38. Zhavoronkov A, Ivanenkov YA, Aliper A, Veselov MS, Aladinskiy VA, Aladinskaya AV, et al. Deep learning enables rapid identification of potent DDR1 kinase inhibitors. *Nat Biotechnol*. 2019;37(9):1038–40.
39. Wesselhoeft RA, Kowalski PS, Parker-Hale FC, Huang Y, Bisaria N, Anderson DG. RNA-targeting therapeutics: molecular mechanisms and delivery strategies. *Nat Rev Drug Discov.* 2022;21(8):583–603.
40. Melesina J, Robaa D, Pierce S, Romier C, Sippl W, Jung M. Epigenetic regulation of transcription: targeting histone deacetylases and bromodomain proteins. *ChemMedChem*. 2021;16(9):1336–57.
41. Vamathevan J, Clark D, Czodrowski P, Dunham I, Ferran E, Lee G, et al. Applications of machine learning in drug discovery and development. *Nat Rev Drug Discov.* 2019;18(6):463–77.
42. Jumper J, Evans R, Pritzel A, Green T, Figurnov M, Ronneberger O, et al. Highly accurate protein structure prediction with AlphaFold. Nature. 2021;596(7873):583-9.
43. Townshend RJL, Eismann S, Watkins AM, Rangan R, Karelina M, Das R, et al. Geometric deep learning of RNA structure. Science. 2021;373(6558):1047-51.

44. Chen H, Engkvist O, Wang Y, Olivecrona M, Blaschke T. The rise of deep learning in drug discovery. Drug Discov Today. 2018;23(6):1241-50.
45. Argelaguet R, Arnol D, Bredikhin D, Deloro Y, Velten B, Marioni JC, et al. MOFA+: a statistical framework for comprehensive integration of multi-modal single-cell data. Genome Biol. 2020;21(1):111.
46. Bergen V, Lange M, Peidli S, Wolf FA, Theis FJ. Generalizing RNA velocity to transient cell states through dynamical modeling. Nat Biotechnol. 2020;38(12):1408-14.
47. Yuan Y, Failmezger H, Rueda OM, Ali HR, Gräf S, Chin SF, et al. Quantitative image analysis of cellular heterogeneity in breast tumors complements genomic profiling. Sci Transl Med. 2012;4(157):157ra143.
48. Chaibub Neto E, Pratap A, Perumal TM, Tummalacherla M, Snyder P, Bot BM, et al. Personalized disease subtyping using multi-omics and machine learning. Nat Commun. 2022;13(1):4514.
49. Costello JC, Heiser LM, Georgii E, Gönen M, Menden MP, Wang NJ, et al. A community effort to assess and improve drug sensitivity prediction algorithms. Nat Biotechnol. 2014;32(12):1202-12.Top of Form
50. Hasin Y, Seldin M, Lusis A. Multi-omics approaches to disease. Genome Biol. 2017;18(1):83
51. Vamathevan J, Clark D, Czodrowski P, Dunham I, Ferran E, Lee G, et al. Applications of machine learning in drug discovery and development. Nat Rev Drug Discov. 2019;18(6):463-77.
52. Ekins S, Puhl AC, Zorn KM, Lane TR, Russo DP, Klein JJ, et al. Exploiting machine learning for end-to-end drug discovery and development. Nat Mater. 2019;18(5):435-41.
53. Simon R. Clinical trial designs for evaluating the medical utility of prognostic and predictive biomarkers in oncology. Clin Cancer Res. 2010;16(10):2728-34.
54. Darwich AS, Ogungbenro K, Vinks AA, Powell JR, Reny JL, Marsousi N, et al. Why has model-informed precision dosing not yet become common clinical reality? Lessons from the past and a roadmap for the future. Clin Pharmacol Ther. 2017;101(5):646-56.
55. US Food and Drug Administration. Artificial intelligence and machine learning in drug development. FDA Discussion Paper. 2023
56. Mak KK, Pichika MR. Artificial intelligence in drug development: present status and future prospects. Drug Discov Today. 2019;24(3):773-80.
57. Chan SY, Loscalzo J. The emerging paradigm of network medicine in the study of human disease. Circ Res. 2012;111(3):359-74.
58. Cummings BB, Marshall JL, Tukiainen T, Lek M, Donkervoort S, Foley AR, et al. Improving genetic diagnosis in Mendelian disease with transcriptome sequencing. Sci Transl Med. 2017;9(386):eaal5209.
59. Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. Nat Med. 2019;25(1):44-56
60. Dawson MA, Kouzarides T. Cancer epigenetics: from mechanism to therapy. Cell. 2012;150(1):12-27.
61. Lee TI, Young RA. Transcriptional regulation and its misregulation in disease. Cell. 2013;152(6):1237-51.
62. Li B, Severson E, Pignon JC, Zhao H, Li T, Novak J, et al. Comprehensive analyses of tumor immunity: implications for cancer immunotherapy. Genome Biol. 2016;17(1):174.
63. Schork NJ. Personalized medicine: time for one-person trials. Nature. 2015;520(7549):609-11
64. Rudin C. Stop explaining black box machine learning models for high stakes decisions and use interpretable models instead. Nat Mach Intell. 2019;1(5):206-15.
65. US Food and Drug Administration. Artificial intelligence and machine learning in drug development. FDA Discussion Paper. 2023.
66. Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. Nat Med. 2019;25(1):44-56.
67. Chen G, Ning B, Shi T. Single-cell RNA-seq technologies and related computational data analysis. Front Genet. 2019;10:317.

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