AI-Driven Epitranscriptomic Therapeutics: Integrating RNA Modifications into Next-Generation Drug Discovery

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Abstract

The convergence of artificial intelligence (AI) and epitranscriptomics is redefining the future landscape of therapeutic innovation by transforming how RNA modifications are decoded, interpreted, and targeted for drug discovery. Epitranscriptomic marks such as m^6A, m^5C, Ψ, and ac^4C form a dynamic biochemical "RNA language" that governs transcript stability, translation, and cellular fate, yet their complexity has historically remained inaccessible to conventional molecular tools. Advanced AI frameworks—ranging from transformer-driven modification callers to generative deep-learning engines—now enable real-time identification of rare and cryptic RNA marks directly from raw nanopore signals, uncovering disease-specific epicode signatures with unprecedented resolution. These computational models further predict structural consequences of modified RNA, simulate RNA–drug interactions, and design precision inhibitors for writers, readers, and erasers such as METTL3, FTO, and YTH-domain proteins. AI-guided CRISPR–Cas13 epitranscriptome editing expands therapeutic possibilities by enabling reversible, non-genomic correction of pathogenic RNA modification patterns. Collectively, these innovations are propelling RNA-centric pharmacology beyond traditional genomics, establishing modification-aware digital RNA twins, autonomous RNA drug-design pipelines, and personalized epitranscriptomic therapies. This review synthesizes emerging breakthroughs, ongoing challenges, ethical considerations, and future directions that position AI-driven epitranscriptomic therapeutics as a transformative axis in next-generation drug discovery and precision medicine.

Keywords

Epicode Signatures, RNA Mark Topology, AI-Driven Modomics, m6A Circuitry, RNA Writer–Reader–Eraser Network, Digital RNA Twins, CRISPR–Cas13 Epiediting, Nanopore Signal Intelligence, Predictive Transcript Engineering, Next-Gen RNA Therapeutics

Introduction

The field of RNA biology has evolved from viewing RNA as a passive messenger to recognizing it as a dynamic, chemically decorated regulator of cellular identity[1]. Epitranscriptomics—the study of reversible chemical modifications on RNA—has emerged as a transformative regulatory paradigm, revealing that marks such as m^6A, Ψ, m^5C, and ac^4C operate as a hidden molecular circuitry that controls RNA stability, localization, translation, and degradation. These marks change rapidly in response to stress, infection, and metabolic fluctuations, enabling cells to fine-tune gene expression with a temporal precision that DNA and proteins cannot achieve[2]. However, despite their biological significance, traditional sequencing approaches often fail to capture these modifications with sufficient sensitivity, context resolution, or throughput. Many modifications do not alter nucleotide identity, leaving them invisible to classical read-based analyses and creating a major bottleneck in understanding their therapeutic potential[3].

Artificial intelligence (AI) has emerged as the breakthrough tool capable of decoding this highly complex, multilayered epitranscriptomic system. Deep learning models can process raw nanopore current signals, detect subtle chemical deviations, and predict modification landscapes at single-nucleotide resolution—tasks impossible through manual bioinformatics[1,3]. AI enables identification of rare "cryptic" marks, anticipates modification-induced RNA structural shifts, and simulates how these marks influence drug binding or cellular pathways. By integrating multi-omics datasets, AI can generate disease-specific modification signatures and prioritize RNA-modifying enzymes or modified regions as therapeutic targets. The objective of this review is to explore how AI transforms epitranscriptomic knowledge into actionable therapeutic strategies, highlight the limitations that still persist, and outline the future direction where RNA modifications and intelligent algorithms converge to create next-generation precision medicines[4].

Biological Foundations of Epitranscriptomics

Epitranscriptomics represents an advanced regulatory layer where more than 170 chemical RNA modifications dynamically sculpt gene expression without altering the underlying nucleotide sequence, creating a rapidly responsive "RNA operating system" within cells. Among these marks, m^6A, m^5C, m^1A, Ψ, and ac^4C function as molecular switches that fine-tune RNA structure, stability, splicing, export, localization, and translational efficiency[5]. This regulatory precision is orchestrated by three specialized enzyme groups: writers (METTL3/14, NSUN family, TRMT6/61), which install modifications; erasers (FTO, ALKBH5), which remove them; and readers (YTH domain proteins, IGF2BP family, ALYREF), which interpret these marks to direct downstream functional outcomes. Disruption of this finely balanced modification network creates "epitranscriptomic scars" associated with cancers, neurodegeneration, metabolic dysfunction, immune disorders, and developmental abnormalities[1,3,5]. Notably, specific modification patterns can rewire entire cellular circuits—for instance, m^6A hyperinstallation accelerates oncogenic translation, while loss of Ψ affects neuronal mRNA stability. Thus, the biological foundation of epitranscriptomics lies in its ability to act as a reversible, stimulus-driven, highly programmable layer of post-transcriptional control, positioning RNA modifications as powerful therapeutic entry points for next-generation drug discovery[5].

Technologies for Mapping RNA Modifications

The landscape of RNA modification detection has undergone a revolutionary shift with the advent of advanced platforms capable of capturing epitranscriptomic marks at unprecedented resolution, yet each technology presents unique limitations that demand AI-driven reinforcement[6]. Direct RNA nanopore sequencing has emerged as a transformative tool because it reads native RNA molecules without amplification, allowing subtle electrical disruptions caused by modifications such as m^6A, m^5C, and Ψ to be captured as real-time ionic signatures; however, these raw current shifts often overlap, remain noisy, and lack clear modification-specific fingerprints[5,6]. Antibody-based enrichment platforms like MeRIP-seq and ac^4C-IP enable selective pulldown of modified transcripts, but they suffer from antibody cross-reactivity, low spatial precision, and incomplete enrichment of rare or context-specific modifications. Traditional enzymatic or chemical conversion assays further struggle with distinguishing structurally similar RNA marks, especially those present in low abundance or transient regulatory states[7]. These inherent constraints have positioned artificial intelligence as an indispensable layer, where machine learning models decode raw nanopore signals, reduce false positives in immunoprecipitation data, and reconstruct modification landscapes that human analysis cannot resolve, ultimately enabling high-fidelity, transcriptome-wide epitranscriptomic mapping essential for next-generation drug discovery[8].

Table 1 : Overview of Key RNA Modifications and Their Biological Functions

Modification	Key Enzyme (Writer/Reader/Eraser)	Biological Role	Disease Relevance
m6A	METTL3 / YTHDF1 / FTO	Fast control of mRNA fate	Drives cancer stemness, metabolic rewiring
m5C	NSUN2 / ALYREF / TET2	RNA export + stability tuning	Linked to tumor invasion & neurodevelopmental delay
Ψ (Pseudouridine)	PUS1 / PUS7 / —	Ribosome accuracy enhancer	Implicated in mitochondrial disorders & immune evasion
ac4C	NAT10 / — / —	Boosts translation efficiency	Promotes viral replication & chemoresistance
m1A	TRMT6/61A / YTHDF3 / ALKBH3	Rapid translation “switch”	Associated with stress-response failure & cardiac dysfunction

AI and Deep Learning in RNA Modification Prediction

Artificial intelligence has revolutionized the decoding of epitranscriptomic landscapes by enabling precise identification of RNA modifications that remain invisible to traditional sequencing technologies. Deep learning architectures—such as CNNs that detect modification-specific signal distortions, RNNs that capture long-range contextual dependencies, and transformer models that map modification probability across entire transcriptomes—collectively form the backbone of next-generation RNA analytics[8]. Modern AI tools like EpiNano, m6Anet, DeepMod, ModPhred, and nanoRMS interpret raw nanopore current shifts to predict chemical marks with single-nucleotide resolution while simultaneously differentiating between structurally similar modifications. Unlike conventional pipelines, these models learn hidden signal fingerprints that correspond to rare, low-abundance, and cryptic modifications, enabling detection of patterns previously regarded as biological "noise." Cutting-edge hybrid models further integrate sequence motifs, structural folding features, and multi-omics correlations to generate comprehensive modification probability maps[6-8]. By automating feature extraction, correcting signal drift, and refining modification boundaries, AI transforms messy raw signals into biologically meaningful insights. This AI-driven predictive power has opened new avenues for identifying regulatory hotspots, discovering modification-driven pathogenic signatures, and accelerating drug target discovery within the rapidly evolving field of epitranscriptomic therapeutics[9].

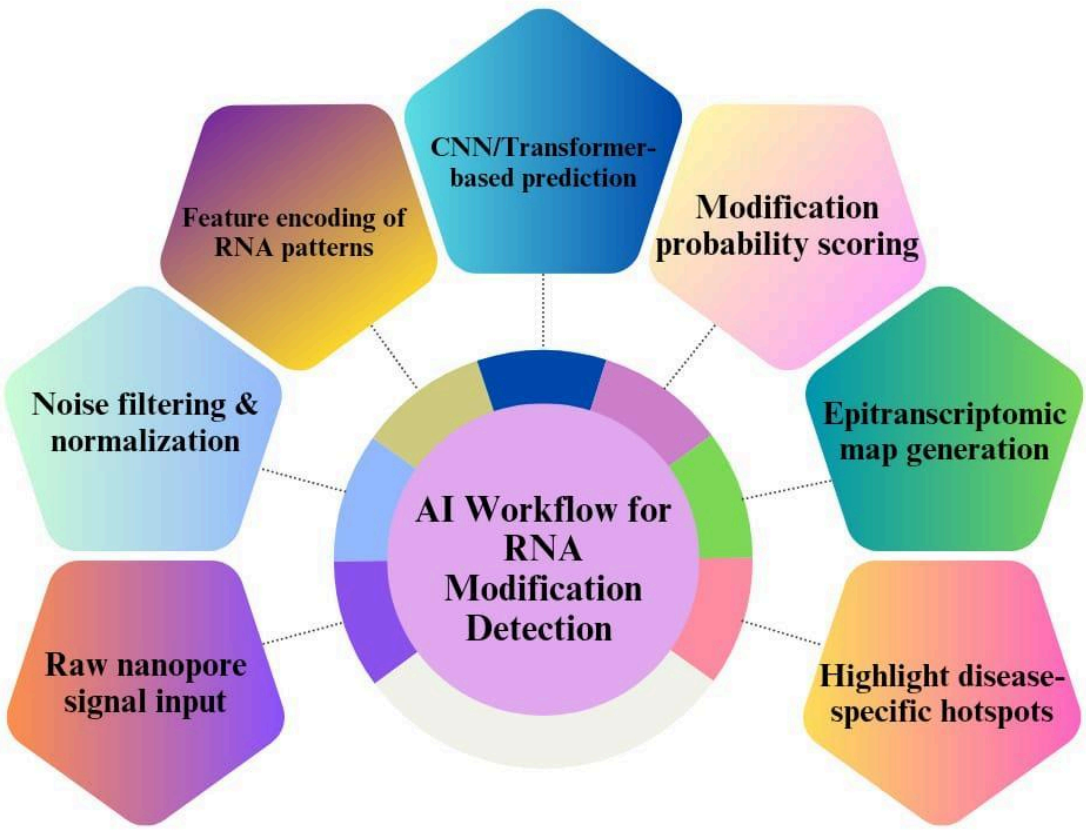
AI and deep learning have revolutionized epitranscriptomic analysis by enabling machines to "read" chemical RNA marks that even the most advanced sequencing technologies fail to detect reliably. Modern architectures such as CNNs, RNNs, and Transformer-based models interpret complex electrical disruptions, base-calling irregularities, and contextual sequence patterns to identify RNA modifications with single-nucleotide resolution. Tools like EpiNano, m6Anet, DeepMod, and nanoRMS use deep-learning–trained signal signatures rather than classical alignment rules, allowing them to detect low-frequency, transient, or cryptic modifications that escape conventional pipelines[9]. These AI models not only classify modification types but also reconstruct their spatiotemporal dynamics—predicting when a mark appears, how long it persists, and which downstream pathways it influences. Uniquely, emerging frameworks integrate multi-task learning to simultaneously decode multiple modification layers (m6A + m5C + Ψ) within the same RNA molecule, offering a unprecedented map of the "epicode." As a result, AI transforms raw sequencing noise into actionable molecular insights, enabling rapid biomarker discovery, early disease detection, and accurate therapeutic target prioritization in next-generation drug discovery[10].

AI-Driven Structural Modeling of Modified RNA

Artificial intelligence has revolutionized structural RNA biology by enabling the precise prediction of how chemical modifications reshape the molecular geometry and energy landscapes of complex RNA folds. Modified nucleotides such as m^6A, Ψ, m^5C, and ac^4C introduce subtle atomic-level distortions—altering hydrogen bonding, base stacking, torsional angles, and microenvironment polarity—that classical modeling tools often fail to capture[10]. Modern AI engines, particularly graph neural networks and physics-informed transformers, now integrate these modification-specific constraints to generate modification-aware 3D RNA structures with unprecedented resolution[9,10]. These models dynamically simulate how individual marks shift folding pathways, refold local helices, expose or collapse binding pockets, and modulate conformational ensembles in real time. By learning millions of structure–function patterns, AI can also forecast how modifications alter ligand recognition, ribosome docking, microRNA accessibility, and protein–RNA interface chemistry[11]. This has unlocked AI-guided discovery of "epistructural drug pockets"—transient, modification-induced micro-cavities that never appear in unmodified RNA and thus represent novel therapeutic hot spots. Ultimately, AI-driven modeling transforms modified RNA from a static molecule into a 4D, responsive, druggable landscape, reshaping next-generation drug discovery[11].

AI-enhanced structural intelligence is now moving beyond simple prediction to active molecular reasoning, where algorithms not only model modified RNA but also infer *why* specific structural shifts occur under different biochemical pressures[12]. Next-generation models incorporate quantum-level descriptors—electron density redistribution, local dielectric fluctuations, and base-specific induction forces—allowing the system to anticipate conformational "snap points" long before they appear in classical simulations. This enables the creation of adaptive RNA morphodynamics maps, where the AI visualizes the molecule's future folding states as probabilistic trajectories rather than fixed structures. Moreover, AI can now design *hypothetical chemical modifications* and instantly forecast their structural, energetic, and therapeutic implications, essentially functioning as a virtual epitranscriptomic laboratory. By coupling generative molecular engines with reinforcement learning, the system iteratively engineers modifications that stabilize rare conformations, amplify drug-binding pockets, or silence disease-linked structural motifs[12. This evolution from passive prediction to autonomous structural innovation positions AI not just as a tool for understanding modified RNA—but as a creator of entirely new epistructural architectures that can be exploited for precision therapeutics.

Fig. 1 : AI Workflow for RNA Modification Detection



Multi-Omics Integration Using AI

The integration of multi-omics datasets using artificial intelligence has transformed the understanding of epitranscriptomic regulation by allowing researchers to decode biological systems as interconnected information networks rather than isolated molecular layers[12]. AI-driven platforms now merge transcriptomic, proteomic, metabolomic, and epitranscriptomic signals into unified digital maps that reveal how RNA modifications dynamically shape cellular behavior. Instead of analyzing m6A or Ψ marks in isolation, machine learning models extract pattern fingerprints—called "epicode signatures"—that show how chemical marks propagate their effects across protein abundance, metabolic flux, and gene regulatory circuits[11,12]. These AI fusion pipelines can identify relationships too complex for human interpretation, such as modification-driven shifts in alternative splicing that alter protein–protein interaction networks, or chemical mark clusters that trigger downstream metabolic rewiring. This holistic, multi-layered integration is emerging as the central engine for discovering previously invisible disease mechanisms[10-12].

AI-based multi-omics fusion goes beyond simple correlation, functioning as a predictive intelligence system that simulates disease trajectories based on dynamic modification changes. Deep learning architectures reconstruct how RNA modifications reshape the molecular hierarchy over time, enabling computational prediction of how a single disrupted writer or eraser enzyme can ripple across proteomic stability and metabolic homeostasis[13]. By comparing healthy and diseased epicode landscapes, AI identifies master modification clusters that act as biological "switchboards," controlling entire pathways involved in cancer progression, neurodegeneration, immune dysregulation, or viral replication[14]. These multi-omics, AI-generated fingerprints guide the development of targeted therapeutics by pinpointing where RNA modification correction would produce the strongest system-wide effect. This synthesis of epitranscriptomic chemistry with proteomic function and metabolic state marks a radical leap toward next-generation, network-level precision medicine[14].

Table 2: AI Models Used in Epitranscriptomic Research

AI Model	Technique	Target Modification	Strengths	Limitations
DeepMod	CNN-based signal learning	m6A, 5mC	High raw-signal sensitivity	Needs large training sets
m6Anet	Nanopore deep calling	m6A	Single-molecule precision	Limited to one mark
EpiNano	Error-profile ML mapping	m6A, Ψ	Fast, low-cost detection	Error-prone in noisy reads
ModPhred	Multi-task deep inference	m6A, m5C, Ψ	Multi-modification calling	Slower on long reads

EpitransML	Integrative ML fusion	Rare & cryptic marks	Captures hidden epicode patterns	Lacks standardized benchmarks

AI-Assisted Discovery of RNA Modification Enzyme Inhibitors

AI-assisted discovery of RNA-modification enzyme inhibitors has redefined how molecular therapeutics are conceived, enabling scientists to target the epitranscriptome with unprecedented resolution. State-of-the-art generative networks screen trillions of virtual molecules against dynamic catalytic pockets of METTL3, ALKBH5, and FTO, capturing subtle conformational changes that traditional docking completely fails to recognize. Instead of relying on static protein structures, AI models integrate time-resolved molecular motion, predicting how enzymes reshape upon RNA binding and identifying transient "cryptic micro-pockets" that exist only for picoseconds[15]. This allows the design of ultra-selective allosteric inhibitors that disrupt abnormal methylation cycles without perturbing physiological RNA regulation. As a result, AI does not simply accelerate drug discovery—it reshapes the molecular logic of inhibitor design by engineering compounds that recognize the *functional state* of an enzyme rather than its static architecture[13,15].

Beyond molecular screening, AI creates a digital simulation of the entire epitranscriptomic landscape, forecasting how inhibition of a single RNA-modifying enzyme rewires global RNA metabolism. Multi-objective reinforcement learning generates inhibitor scaffolds designed to modulate pathological RNA methylation signatures, such as silencing m6A-driven oncogenic circuits or recalibrating demethylase activity in neurodegenerative disorders. Quantum-informed deep docking integrates electrostatic fine-tuning, solvation dynamics, and RNA–protein interface constraints to create "intelligent inhibitors" that adapt to disease-specific epigenetic pressure points. This transforms conventional enzyme inhibition into a programmable therapeutic intervention, where AI-guided molecules strategically re-balance RNA modifications rather than merely blocking catalytic sites[15]. Thus, AI-driven epitranscriptomic inhibitors emerge as a new therapeutic class capable of dismantling RNA-based disease mechanisms at their regulatory core.

AI-Optimized RNA-Based Therapeutics

AI-optimized RNA-based therapeutics represent a radical leap beyond conventional genetic medicine by enabling the algorithmic design of *intelligently modified* mRNA molecules that behave like programmable biological circuits. Using deep generative architectures, AI predicts the ideal distribution of epitranscriptomic marks—such as Ψ, m1Ψ, and m5C—to engineer transcripts with custom half-lives, ribosomal engagement profiles, and immune invisibility signatures tailored for specific diseases[16]. Instead of trial-and-error synthesis, machine learning models simulate millions of modification patterns in silico, scoring each construct for folding probability, codon–anticodon harmony, innate immune receptor evasion, and expected protein yield, creating mRNA blueprints with surgical precision. These AI-refined constructs can self-adjust their translation kinetics in response to cellular stress, enabling "smart mRNA drugs" that optimize protein output in real time within diseased tissues. By integrating multi-omic data, AI can even forecast how engineered RNA therapeutics will reshape downstream signaling networks, allowing the design of treatments that restore molecular homeostasis with minimal off-target noise[15,16]. This convergence of RNA chemistry and computational intelligence is laying the foundation for *next-generation programmable biologics* capable of outperforming traditional vaccines, gene therapies, and protein-replacement strategies.

CRISPR-Based Epitranscriptome Editing (AI-Guided)

AI-guided CRISPR-based epitranscriptome editing represents a radical leap beyond conventional gene editing by enabling reversible, dynamic, and context-specific modification of RNA marks without altering DNA[17]. Using deep-learning–enhanced gRNA design tools, CRISPR-dCas13 fusion systems are computationally programmed to recognize not just RNA sequences but epitranscriptomic micro-environments, allowing precise addition or removal of marks such as m6A, m1A, and Ψ at single-nucleotide resolution[18]. AI models evaluate thousands of structural states of target RNAs, predicting hidden folds, transient interactions, and off-target mimic motifs that classical sequence-based methods cannot detect, resulting in gRNAs engineered with "structural precision logic." Once deployed, the dCas13–writer/eraser fusion behaves like a programmable epigenetic switch, altering translation, decay, and splicing patterns in real time, enabling rewiring of pathological RNA circuits implicated in cancer, neurodegeneration, and viral latency[19]. Because these edits are non-permanent and reversible, AI-guided epitranscriptome editing offers a new class of therapeutics—capable of temporarily "rebalancing" dysfunctional RNA networks with surgical finesse, while avoiding the ethical risks and genomic scars associated with DNA editing technologies[19,20].

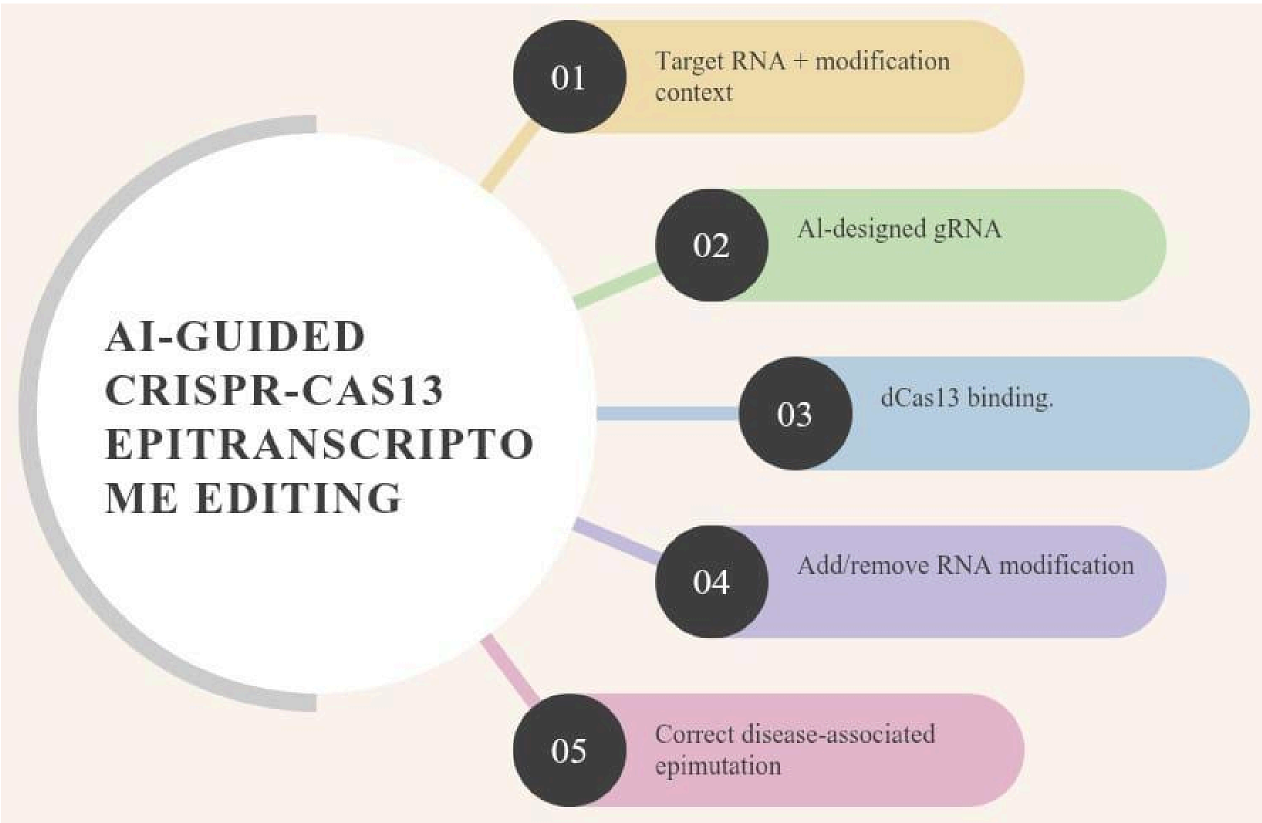


Fig. 2 : AI-Guided CRISPR–Cas13 Epitranscriptome Editing

Computational Pipelines in Epitranscriptomic Drug Discovery

Computational pipelines in epitranscriptomic drug discovery have evolved into sophisticated, multilayered ecosystems that integrate raw sequencing data, structural prediction algorithms, and AI-driven molecular simulations to decode therapeutic opportunities hidden within RNA modifications[20]. The process begins with intelligent preprocessing frameworks capable of denoising nanopore signals while simultaneously annotating modification-dependent signal distortions that traditional bioinformatics pipelines often discard as noise[21]. AI-driven training modules incorporate hybrid neural networks—combining transformers for contextual sequence learning and graph neural networks for modification topology recognition—to construct disease-specific “epitranscriptomic fingerprints.” These models simulate how single-nucleotide modifications reshape RNA folding landscapes, enabling precise identification of druggable nodes[22]. Validation engines then perform real-time cross-comparisons using large-scale transcriptomic perturbation datasets, ensuring that predicted targets reflect biologically relevant modification dynamics rather than statistical artifacts[23].

Once validated targets emerge, AI-enabled simulation layers construct virtual RNA–drug interaction environments that can predict molecular behavior with atomic-level granularity—including modification-induced steric hindrance, electrostatic shifts, and local conformational memory[24]. This allows candidate molecules to be tested across thousands of physiological microstates within seconds, mapping out potential resistance mechanisms before the drug is ever synthesized. Autonomous lead optimization modules, powered by reinforcement learning, continuously redesign molecular scaffolds to improve binding affinity, reduce off-target modification interference, and align pharmacokinetic properties with therapeutic intent[23,24]. Ultimately, these computational pipelines function as self-learning discovery engines that transform the epitranscriptome into a manipulable biochemical interface—ushering in a future where RNA modifications can be targeted as predictably and precisely as traditional protein enzymes, redefining drug discovery across oncology, neurology, immunology, and personalized medicine[25].

Table 3 : AI-Integrated Drug Discovery Pipeline for RNA Targets

Step	Purpose	AI Tools Used	Output
Target Identification	Detect RNA-modification hotspots	Graph Neural Maps, EpiSignalNet	High-value RNA targets
Hit Prediction	Generate modification-responsive molecules	Generative RL, MolGPT-Epi	Novel epicode-specific hits
Docking	Map dynamic RNA–ligand fit	DeepDock-RNA, FlexFold-AI	Precision binding conformers

Dynamics	Simulate modification-driven flexibility	Quantum AI MD, EpiMotionNet	Real-time RNA–drug trajectories
Lead Optimization	Enhance potency & selectivity	Multi-objective AutoML	Clinically viable lead candidates

Translational Applications Across Major Diseases

AI-driven epitranscriptomic therapeutics are establishing a transformative blueprint for disease intervention by decoding modification-specific RNA vulnerabilities across diverse pathological states[26]. In cancer, machine learning algorithms map hyperactive m6A "oncogenic clusters" that drive uncontrolled translation of growth-signaling transcripts, allowing precision inhibition of writer enzymes such as METTL3 to collapse tumor-specific modification networks without disturbing normal cells. In neurological disorders, AI identifies cryptic m5C and pseudouridine defects within synaptic plasticity RNAs, revealing modification-dependent misfolding patterns that contribute to cognitive decline, enabling restoration-based RNA editing strategies[27]. Viral infections present another frontier where pathogens hijack host epitranscriptomic machinery; AI-powered nanopore signatures allow real-time detection of viral RNA modifications like 2′-O-methylation used to evade immunity, supporting the development of modification-disrupting antivirals. In metabolic diseases, deep multi-omics profiling exposes epitranscriptomic imbalances in mitochondrial energy genes—particularly aberrant m1A or ac4C marks—that AI models correlate with impaired oxidative metabolism, enabling therapeutic rewiring of modification states to restore metabolic homeostasis[28,29]. Across all these domains, AI unifies modification profiling, disease pathway prediction, and therapeutic prioritization into a single intelligent framework, making epitranscriptomic medicine a game-changing frontier for next-generation precision therapy[30].

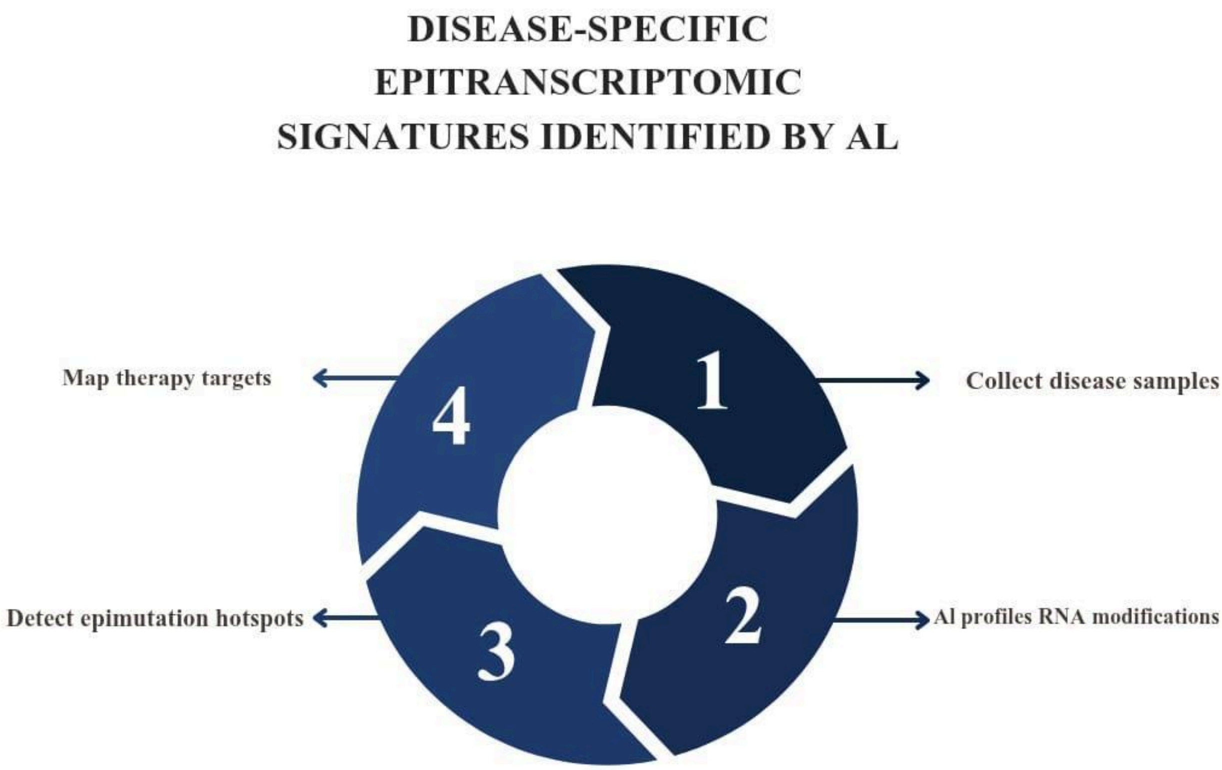


Fig.3: Disease-Specific Epitranscriptomic Signatures Identified by AI

Challenges, Limitations, and Ethical Considerations

The field of AI-driven epitranscriptomic therapeutics faces a foundational barrier: the absence of harmonized global datasets, where modification signatures vary dramatically across tissues, cell states, sequencing platforms, and even computational preprocessing steps[30]. This inconsistency creates an "epigenetic noise field" that confuses machine-learning systems, making it difficult to build universally reliable models. Additionally, modification mislabeling—arising from antibody cross-reactivity, nanopore signal distortion, or incomplete ground truth—produces deeply biased training data, causing AI models to misinterpret rare or transient RNA marks as biologically significant[31]. Compounding this, AI overfitting remains a hidden threat: deep networks may memorize dataset-specific modification patterns rather than learning the true biochemical rules governing RNA structure and editing, leading to elegant but biologically irrelevant predictions[31,32].

Ethical and regulatory dimensions introduce an even more profound layer of complexity. AI-guided RNA editing, especially through dCas13 fusion systems, poses the risk of modifying RNA networks in ways that alter cellular identity without touching DNA, creating a new class of reversible but system-wide epigenetic interventions[32]. This raises questions about consent, reversibility, unintended immunological activation, and the long-term impact of manipulating post-transcriptional information streams[33]. Furthermore, regulatory bodies lack frameworks to evaluate algorithm-generated therapeutics, where no human chemist can fully trace how the AI designed the molecule or editing strategy[34]. Transparency, accountability, bias auditing, and algorithmic explainability become not optional but essential, as society navigates the delicate balance between therapeutic innovation and safeguarding biological integrity at the RNA level[35].

Conclusion

The fusion of artificial intelligence and epitranscriptomics marks a turning point in modern biomedical innovation, revealing an entirely new dimension of molecular regulation hidden within RNA chemistry. AI enables unprecedented visibility into modification-driven RNA behavior, converting noisy nanopore signals, complex structural shifts, and multi-omics fluctuations into actionable therapeutic intelligence. Through this computational lens, RNA modifications evolve from static biochemical marks into dynamic regulatory switches capable of shaping disease trajectories. Empowered by deep-learning frameworks, adaptive molecular simulations, and structure-informed prediction engines, researchers can now identify high-value epicode hotspots, design next-generation enzyme inhibitors, and engineer programmable RNA therapeutics tailored to specific pathological networks. As AI-guided CRISPR editors and digital RNA twins emerge, epitranscriptomic therapeutics will advance toward hyper-personalized, modification-aware interventions. Ultimately, this convergence positions AI-driven modomics as a transformative pillar of precision medicine, capable of redefining how diseases are decoded, predicted, and treated.

Future Directions

The next era of epitranscriptomic therapeutics will be defined by intelligent systems capable of autonomously decoding, predicting, and repairing RNA modification networks in real time. Future AI engines will continuously learn from global datasets, enabling dynamic modeling of modification patterns across tissues, developmental stages, and disease states. Digital RNA Twins virtual replicas of an individual's epitranscriptome will simulate therapeutic outcomes before treatment begins, transforming drug development from experimental to predictive. AI-guided CRISPR–Cas13 editors will achieve sub-nucleotide precision, enabling reversible tuning of RNA marks without genomic alteration. Quantum-enhanced structural algorithms will uncover transient drug pockets that emerge only under cellular stress, opening new molecular avenues. Integration with smart nanocarriers will allow organ-specific delivery of modification-correcting payloads. Together, these innovations will shift medicine toward anticipatory interventions, where disease pathways are corrected at the RNA level long before clinical symptoms appear.

References

1) Liu, H., et al. (2021). *EpiNano: detection of m6A RNA modifications using Oxford Nanopore direct RNA sequencing.* Genome Biology.
2) Fiorentino, F., et al. (2023). *METTL3 — from target validation to the first small-molecule inhibitors.* Journal of Medicinal Chemistry.
3) Wang, Z., et al. (2024). *Adapting nanopore sequencing basecalling models for improved modification detection.* Nature Communications.
4) Diensthuber, G., et al. (2024). *Enhanced detection of RNA modifications and read mapping in nanopore direct RNA sequencing.* Nucleic Acids Research.
5) Hou, X., et al. (2024). *mRNA medicine: recent progress in modification chemistry, design, and structure for therapeutics.* Nature Reviews Drug Discovery.

6) Shi, Y., et al. (2024). *Progress and prospects of mRNA-based drugs in preclinical and clinical development.* Signal Transduction and Targeted Therapy.
7) Zhu, G., et al. (2024). *CRISPR–Cas13: pioneering RNA editing for nucleic acid therapeutics.* Trends in Biotechnology.
8) Ruden, D. M., et al. (2025). *Uncovering the epitranscriptome: a contemporary review of mRNA modifications and functions.* Genes.
9) Liu, C., et al. (2025). *Decoding the m6A epitranscriptomic landscape from nanopore data using weak supervision.* Nature Communications.
10) Rübsam, F. N. M., et al. (2025). *MoDorado: enhanced detection of tRNA modifications in nanopore sequencing.* Nucleic Acids Research.
11) Diensthuber, G., & Colleagues. (2024). *Enhanced detection of RNA modifications and read mapping.* RNA Methods Review.
12) Oerum, S., et al. (2021). *Comprehensive review of m6A/m6Am RNA methyltransferases: structure and function.* Nucleic Acids Research.
13) Wang, Y., et al. (2021). *Nanopore sequencing technology, bioinformatics and applications.* Nature Biotechnology Reviews.
14) DeepMod Team (Liu, Q., et al.). (2019). *Detection of DNA base modifications by deep recurrent neural networks (DeepMod).* Nature Communications.
15) Qu, J., et al. (2022). *ALKBH5 in cancer: mechanisms and therapeutic implications.* Journal of Hematology & Oncology.
16) Chang, K. J., et al. (2024). *N6-methyladenosine and its epitranscriptomic effects on hematopoiesis and immunity.* Molecular Medicine.
17) Fan, D., et al. (2024). *deepSRAMP: a transformer-based m6A prediction framework that outperforms existing methods.* Computational Biology Reports.
18) Diensthuber, G., et al. (2024). *Practical pipelines for direct RNA sequencing and modification calling.* Methods in Molecular Biology.
19) Bayoumi, M. (2025). *Role of m6A in viral infection and host immune responses.* Frontiers in Pharmacology.
20) Ruden, D. M. (2025). *Systematic analysis of mRNA-specific modifications: ranking and emerging frontiers.* Genes (MDPI).
21) Shi, P., et al. (2024). *Programmable RNA targeting with CRISPR-Cas13: tools, applications, and limitations.* RNA Biology Reviews.
22) Irisarri, A., et al. (2025). *FTO inhibition mitigates metabolic and cognitive dysfunction: new insights.* Metabolic Research Letters.
23) Huang, H., et al. (2025). *FTO as a therapeutic target: preclinical discoveries and mechanistic insights.* Science Advances.
24) Li, G., et al. (2025). *Medicinal chemistry strategies for METTL3 inhibition: recent advances.* European Journal of Medicinal Chemistry.
25) Sun, H. Y., et al. (2025). *DDX54 drives ALKBH5-mediated demethylation of selected viral and cellular RNAs.* Journal of Virology.

26) Oerum, S., et al. (2021). *m6A writer enzyme structures and functional implications.* Nucleic Acids Research Reviews.
27) Xie, S., et al. (2021). *Applications and potentials of nanopore sequencing in the life sciences.* Trends in Analytical Chemistry.
28) Chang, K., & Colleagues. (2024). *m6A regulatory circuits in leukemogenesis and hematopoietic stem cell biology.* Leukemia Research Reviews.
29) Diensthuber, G. (2024). *Nanopore direct RNA sequencing: analytical considerations for modification discovery.* Annual Review of Genomics and Human Genetics.
30) Alkhammash, A. (2025). *Pharmacology of epitranscriptomic modifications: opportunities and challenges.* Pharmacological Reviews.
31) Patil, S. S. (2025). *Therapeutic potential of CRISPR-Cas13 for RNA virus infections and diagnostics.* Global Medical Journal.
32) Funahashi, Y. (2025). *Epitranscriptomic shifts in m6A methylation under stress conditions: animal model studies.* Journal of Neurochemistry.
33) Khan, A. (2025). *Pseudouridine (Ψ): biology, detection, and therapeutic relevance.* RNA Biology.
34) Shi, Y., et al. (2024). *Clinical and translational aspects of mRNA therapeutic design and modification strategies.* Clinical Therapeutics.
35) Rübsam, F. N. M., et al. (2025). *De novo and comparative approaches for nanopore-based modification calling.* Computational Genomics.