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Opinion Article

Oligonucleotide-Based Therapies in Hematologic Malignancies

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DESCRIPTION

The therapeutic landscape for hematologic malignancies has been significantly expanded by the development of oligonucleotide-based therapies capable of targeting previously "undruggable" disease drivers. While conventional small molecule and antibody approaches have traditionally focused on cell surface receptors and enzymes with accessible binding pockets, oligonucleotide-based strategies enable direct modulation of gene expression through complementary sequence recognition. These approaches, including Antisense Oligonucleotides (ASOs), Small Interfering RNAs (siRNAs), microRNA modulators, and aptamers, offer unprecedented specificity and the potential to address fundamental oncogenic mechanisms beyond the reach of conventional therapeutics.

Antisense oligonucleotides represent the most clinically advanced oligonucleotide platform in hematologic malignancies. These synthetic single-stranded DNA analogues bind complementary mRNA sequences through Watson-Crick base pairing, inducing target degradation via RNase H recruitment or sterically blocking translation. Chemical modifications including phosphorothioate linkages, 2'-O-methoxyethyl substitutions, and locked nucleic acids have dramatically improved pharmacokinetic properties and nuclease resistance, enabling clinically feasible dosing regimens. The development of conjugation strategies with cell-penetrating peptides, lipid nanoparticles, and antibodies has further enhanced cellular delivery and target tissue specificity.

The clinical utility of ASO approaches in hematologic malignancies has been demonstrated by inotersen targeting transthyretin in amyloidosis, though applications in leukemia and lymphoma have lagged behind. Current investigational ASOs in advanced clinical development include AZD4785 targeting KRAS, danvatirsen targeting STAT3, and IONIS-STAT3-2.5Rx also targeting STAT3. These agents address fundamental oncogenic drivers previously considered undruggable by conventional approaches. Early clinical results demonstrate promising pharmacodynamic evidence of target modulation, though translation to robust clinical responses has proved challenging, likely reflecting the redundancy of oncogenic signaling pathways and need for rational combinations.

RNA Interference (RNAi) approaches utilizing small interfering RNAs (siRNAs) offer an alternative oligonucleotide strategy with distinct advantages. These double-stranded RNA molecules harness the endogenous RNA-Induced Silencing Complex (RISC) machinery to degrade target mRNAs with remarkable efficiency and potency. Chemical stabilization through 2'-O-methyl modifications and conjugation with N-acetylgalactosamine (GalNAc) for asialoglycoprotein receptor-mediated delivery have enabled clinical translation. The encouraging results with patisiran in transthyretin amyloidosis demonstrate the potential of this modality, though applications in hematologic malignancies remain predominately preclinical. Current investigations focus on siRNAs targeting BCL-2 family members, transcription factors including MYC, and fusion oncoproteins unique to specific leukemia subtypes such as PML-RARA and AML1-ETO.

MicroRNA modulation represents a particularly intriguing approach given the dysregulation of these small non-coding RNAs in hematologic malignancies and their capacity to regulate multiple genes simultaneously through imperfect base pairing. MicroRNA mimics aim to replace downregulated tumor suppressor microRNAs, while antagomirs inhibit oncogenic microRNAs (oncomiRs) overexpressed in malignant cells. MRX34, a miR-34a mimic encapsulated in lipid nanoparticles, demonstrated preliminary activity in a phase I study including patients with multiple myeloma, though development was halted due to immune-related adverse events. Improved delivery systems and modified chemical structures are being investigated to enhance the therapeutic window of microRNA-based approaches.

Aptamers, synthetic oligonucleotides that fold into three-dimensional structures capable of binding specific targets with antibody-like affinity, represent another versatile oligonucleotide platform. These molecules can function as direct inhibitors of protein-protein interactions or as targeting moieties for delivery of therapeutic payloads. AS1411, a guanine-rich aptamer targeting nucleolin overexpressed on malignant cells, has

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demonstrated modest activity in AML in early clinical trials. Novel aptamer-drug conjugates and bi-specific aptamers targeting CD30, CD22, and other hematologic malignancy-associated antigens are under preclinical investigation.