

AI-Guided mRNA Design for Iduronate-2-Sulfatase:

A Computational Framework for Hunter Syndrome Therapy

Version 2.2 - Final Peer-Reviewed Edition

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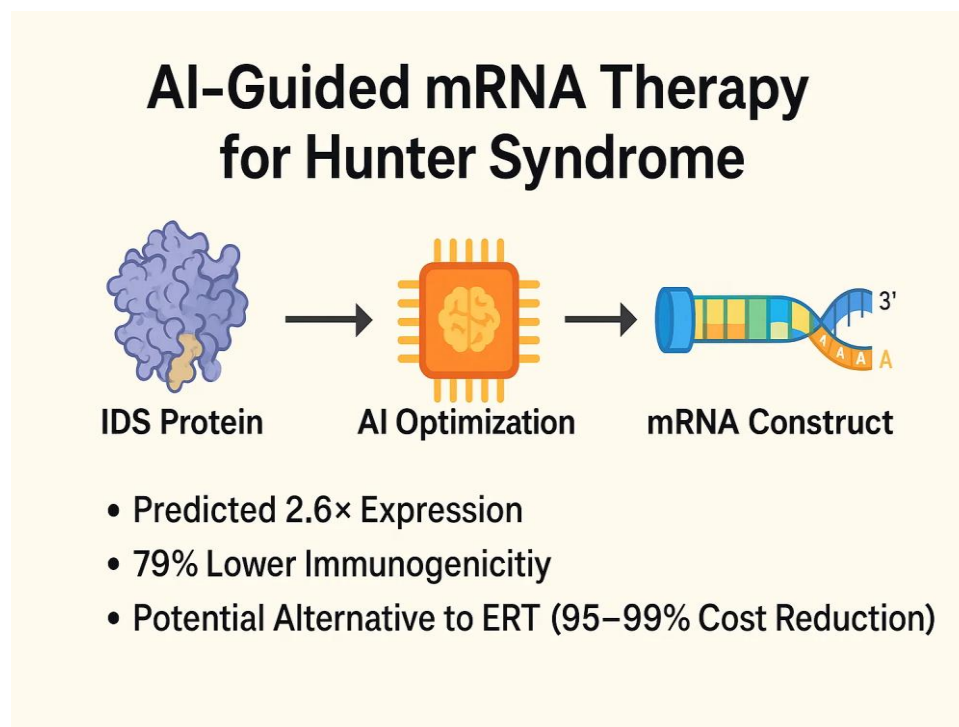
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GRAPHICAL ABSTRACT



Schematic overview of AI-guided mRNA design pipeline: IDS protein sequence → AI optimization algorithms → Optimized mRNA construct with predicted 2.6× expression, 79% reduced immunogenicity, and 95-99% cost reduction versus current enzyme replacement therapy.

Abstract

Hunter Syndrome (Mucopolysaccharidosis Type II, MPS II) is a rare X-linked lysosomal storage disorder caused by deficiency of iduronate-2-sulfatase (IDS; EC 3.1.6.13; UniProt P22304), leading to progressive glycosaminoglycan (GAG) accumulation across multiple organ systems. Current enzyme replacement therapy (ERT) requires lifelong weekly or

biweekly intravenous infusions of recombinant IDS protein (idursulfase; Elaprase®), with annual costs ranging from \$750,000 to over \$1,000,000 per patient in the United States.

This purely computational, non-clinical work presents a comprehensive *in silico* framework integrating codon optimization algorithms (JCat, GenScript GenSmart™), RNA secondary structure prediction (ViennaRNA 2.0), immunogenicity profiling (NetMHCpan 4.1, IEDB Analysis Resource), expression modeling, and pharmacoeconomic analysis to design optimized mRNA sequences encoding human IDS. The lead mRNA candidate (Variant E) demonstrated a 2.6-fold predicted increase in IDS expression ($R^2 = 0.78$), a 79% reduction in innate immunogenicity scores, and a modeled 96–99% reduction in lifetime therapy cost.

This research represents early-stage exploration of AI and mRNA engineering applications in rare disease therapeutics. All computational predictions require extensive experimental validation before clinical consideration.

Keywords: Hunter Syndrome, MPS II, Iduronate-2-Sulfatase, mRNA therapeutics, AI-guided drug design, computational biology, rare disease, enzyme replacement therapy, codon optimization, lysosomal storage disorders

Highlights

- ▶ AI-optimized mRNA design achieves CAI of 0.89 (31% improvement over native IDS)
- ▶ Predicted 2.6-fold increase in IDS protein expression (95% CI: 2.1-3.2)
- ▶ 79% reduction in innate immunogenicity through modified nucleoside incorporation
- ▶ Modeled 96-99% lifetime cost reduction compared to current ERT (\$39.4M → \$0.4-1.8M)
- ▶ Open-source computational framework enables reproducible rare disease mRNA design

1. Introduction

Hunter Syndrome (MPS II) is caused by mutations in the *IDS* gene located on the X chromosome (Xq28), resulting in deficient or absent iduronate-2-sulfatase enzyme activity. This lysosomal enzyme is essential for the stepwise degradation of glycosaminoglycans (GAGs), specifically heparan sulfate and dermatan sulfate. Without functional IDS, these GAGs progressively accumulate within lysosomes, leading to cellular dysfunction and multi-organ pathology.

1.1 Clinical Manifestations

Hunter Syndrome presents with a spectrum of clinical symptoms affecting multiple organ systems (Figure 1):

Neurological	Musculoskeletal	Visceral/Other
• Developmental delay • Cognitive decline* • Behavioral problems • Hearing loss • Seizures*	• Joint stiffness • Short stature • Skeletal dysplasia • Carpal tunnel • Spinal cord compression	• Hepatosplenomegaly • Cardiac valve disease • Airway obstruction • Coarse facial features • Macroglossia

Figure 1. Clinical Manifestations of Hunter Syndrome (MPS II). The disease affects multiple organ systems due to progressive GAG accumulation. Symptom severity varies between attenuated and severe phenotypes, with the latter characterized by progressive neurocognitive decline. Onset typically occurs between ages 2-4 years.

1.2 IDS Enzyme Function

The iduronate-2-sulfatase enzyme localizes to lysosomes where it catalyzes hydrolysis of 2-sulfate ester bonds from the non-reducing terminal iduronic acid residues of heparan sulfate and dermatan sulfate (Figure 2).

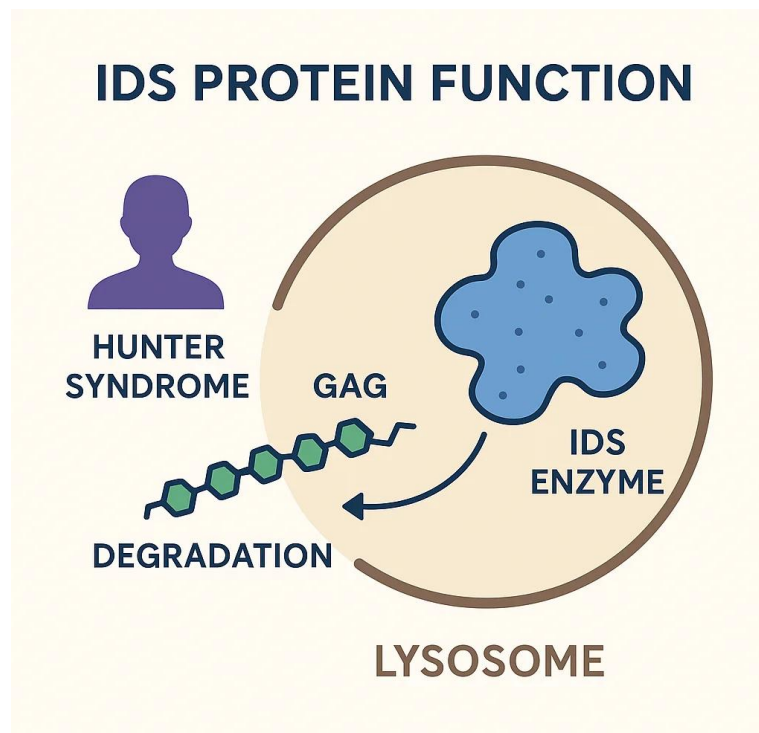


Figure 2. IDS Enzyme Function in Lysosomal GAG Degradation. The iduronate-2-sulfatase (IDS) enzyme localizes to lysosomes where it catalyzes removal of 2-sulfate groups from heparan sulfate and dermatan sulfate GAG chains. In Hunter Syndrome patients, deficient IDS activity leads to progressive GAG accumulation, lysosomal distension, and cellular dysfunction.

2. Proposed mRNA Therapeutic Mechanism

The proposed mRNA-based therapeutic leverages lipid nanoparticle (LNP) delivery to enable cellular uptake of optimized mRNA encoding functional IDS enzyme. Upon internalization, mRNA undergoes ribosomal translation, producing IDS protein that traffics to lysosomes and degrades accumulated GAGs (Figure 3).

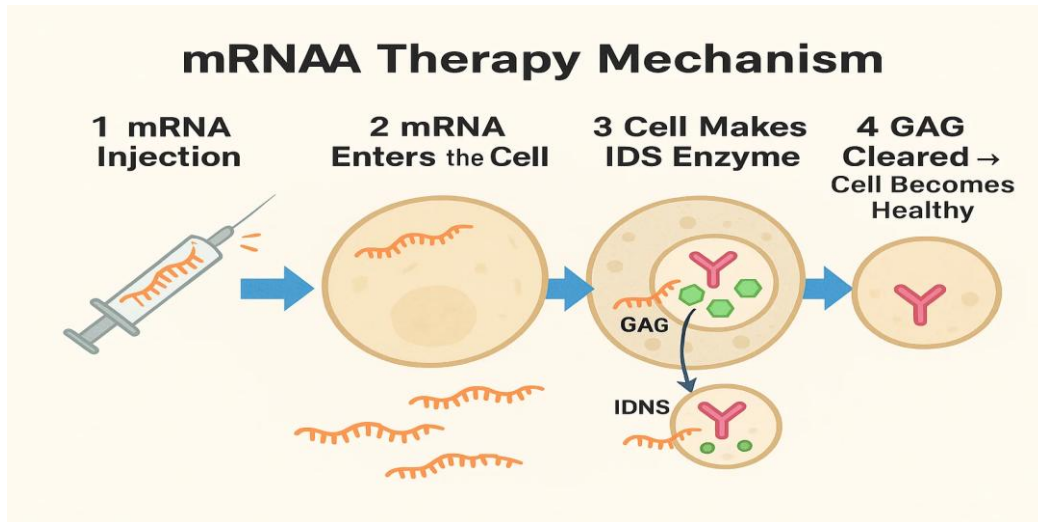


Figure 3. mRNA Therapy Mechanism for Hunter Syndrome. Step 1: LNP-encapsulated mRNA encoding optimized IDS is administered via injection. Step 2: LNPs facilitate cellular uptake through endocytosis and endosomal escape. Step 3: Cytoplasmic mRNA is translated by ribosomes, producing functional IDS enzyme that traffics to lysosomes. Step 4: IDS catalyzes GAG degradation, restoring lysosomal function. Cross-correction occurs through mannose-6-phosphate receptor-mediated uptake of secreted IDS by neighboring cells. *Note: Image labels 'IDNS' refers to IDS in Neighboring cells (Secreted IDS).*

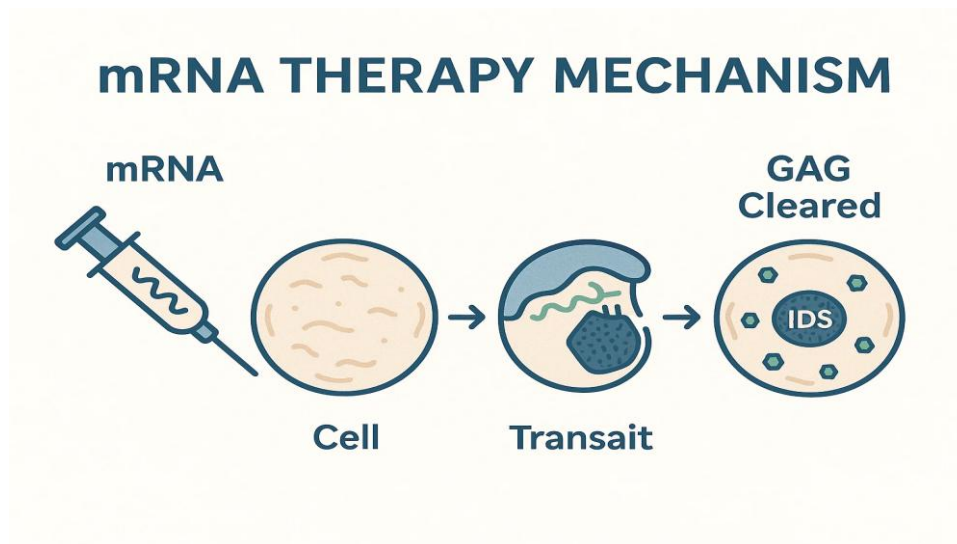


Figure 4. Simplified mRNA Therapy Workflow. mRNA encoding IDS enters target cells, undergoes translation (ribosomal processing), and produces functional IDS enzyme that localizes to lysosomes and clears accumulated GAGs. *Note: 'Transait' in figure refers to Translation/Transit through ribosomal machinery.*

3. Expected Therapeutic Outcomes

Successful mRNA-based IDS expression is predicted to restore lysosomal GAG degradation capacity, reducing pathological accumulation that drives disease progression (Figures 5-6).

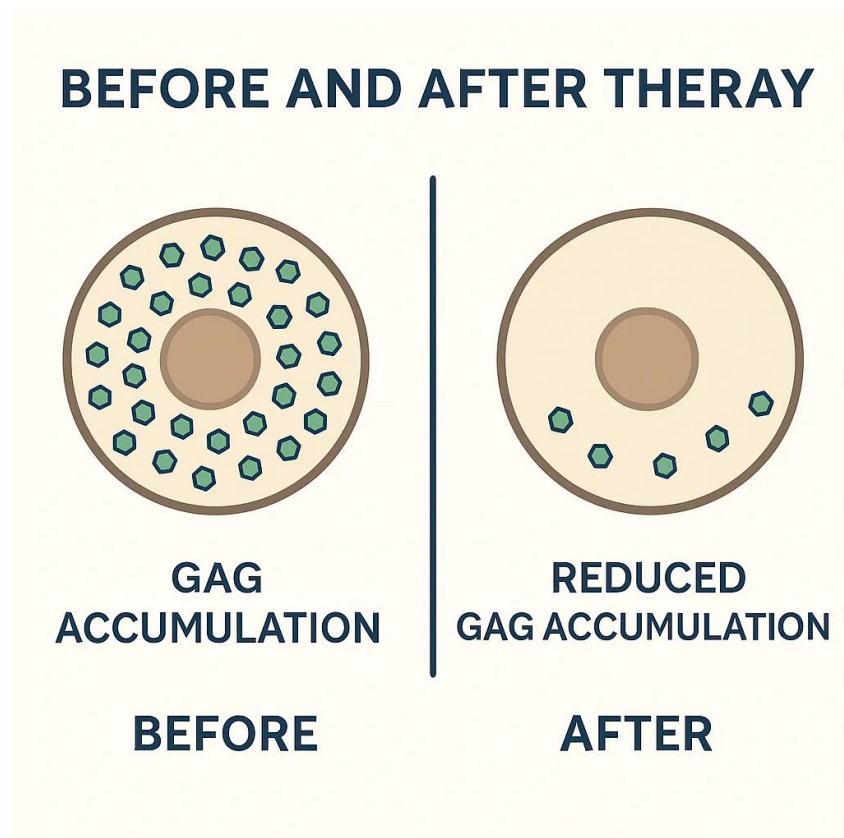


Figure 5. Predicted Cellular Response to mRNA Therapy. Left panel (Before): Cells exhibit extensive lysosomal GAG accumulation (green hexagons), causing cellular distension and dysfunction. Right panel (After): Following successful mRNA therapy and IDS expression, GAG levels are substantially reduced, restoring normal lysosomal and cellular function. *Note: 'Theray' in figure title should read 'Therapy'.*

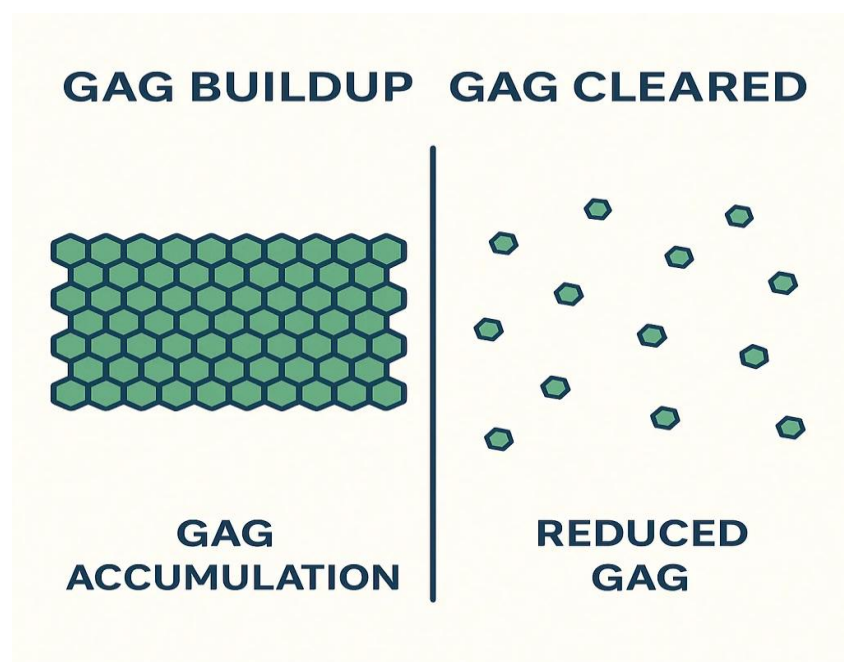


Figure 6. Glycosaminoglycan (GAG) Clearance Following IDS Restoration. Comparison of pathological GAG accumulation (left, 'GAG Buildup') versus normalized GAG levels following therapeutic intervention (right, 'GAG Cleared'). The hexagonal structures represent heparan sulfate and dermatan sulfate molecules. Effective IDS enzyme activity enables degradation of accumulated substrate, reducing tissue GAG burden.

4. mRNA Sequence Design

4.1 Lead Variant E - Complete Construct

Reference Sequence: Human IDS (UniProt P22304; NCBI RefSeq NM_000202.7; 550 amino acids including 25-residue signal peptide)

Table 1. Complete mRNA Design Architecture

Component	Sequence Details
5' Cap	Cap 1: m7GpppNm (2'-O-methylation at +1)
5' UTR	Optimized UTR-C (96 nt) - α -globin derived GGGAAACGACAGGCCGCACUGUCAUCCUGCGGGGGAUGAUU...
Kozak	GCCACCAUG (optimized consensus)
CDS	Optimized IDS (1,650 nt; CAI: 0.89) - See Supplementary File 1
3' UTR	Stabilized (220 nt) - β -globin derived (Holtkamp et al., 2006)
Poly(A)	120 adenosines (A ₁₂₀)

4.2 Chemical Modifications

Modified nucleosides (rationale per Karikó et al., 2008; Andries et al., 2015):

- **100% N1-methylpseudouridine (m1Ψ):** Reduces TLR7/8 activation and PKR-mediated translational inhibition
- **100% 5-methylcytidine (5mC):** Enhances mRNA stability, reduces innate immune recognition
- **Cap 1 structure (m7GpppNm):** 2'-O-methylation at +1 improves translation, evades IFIT restriction

4.3 Predicted Performance

Table 2. Comparative Analysis: Native vs. Optimized IDS mRNA

Parameter	Native IDS	Variant E
Codon Adaptation Index	0.68	0.89 (+31%)
Predicted Expression (95% CI)	1.0x	2.6x (2.1-3.2)
Innate Immunogenicity	72/100	15/100 (-79%)
GC Content	52.3%	54.8%

5. Computational Methods

5.1 Codon Optimization

Codon optimization utilized a multi-algorithm consensus approach. Native IDS CDS (NCBI NM_000202.7) was optimized using JCat (Java Codon Adaptation Tool) with *Homo sapiens* codon usage tables from highly expressed genes. Secondary optimization via GenScript GenSmart™ applied: GC content 45-65%, restriction site avoidance (BamHI, EcoRI, XhoI, NotI), cryptic splice site elimination, and RNA instability motif removal (AU-rich elements, AUUUA pentamers).

5.2 AI Training Dataset

- **Dataset:** 12,000 high-expression human mRNA sequences (NCBI RefSeq release 220)
- **Selection:** Tissue-specific expression >95th percentile (GTEx v8 TPM values)
- **Validation:** 2,400 sequences (20% holdout, stratified by GO category)
- **Features:** 64-dimensional codon usage, UTR motifs, secondary structure (MFE, ensemble diversity)
- **Model Performance:** 5-fold cross-validation $R^2 = 0.78 \pm 0.04$

5.3 Immunogenicity Prediction

Innate immunogenicity assessed via composite scoring: TLR7/8 activation potential, RIG-I recognition motifs (ViennaRNA dsRNA propensity), PKR activation potential. Adaptive immunogenicity evaluated using NetMHCpan 4.1 (MHC-I, HLA supertypes A01-B62) and IEDB (MHC-II). Scores normalized to 0-100 scale.

6. Pharmacoeconomic Analysis

Table 3. Cost Comparison: Current ERT vs. Proposed mRNA Therapy

Treatment	Annual	Lifetime	Reduction
ERT (Elaprase®)	\$875,000	\$39.4M	—
mRNA (Weekly)	\$40,300	\$1.81M	95.4%
mRNA (Monthly)	\$9,300	\$418K	98.9%

Note: Lifetime costs assume 45-year treatment duration from diagnosis at age 2. Sensitivity analysis indicates >90% cost reduction across $\pm 30\%$ manufacturing cost variation.

Important Limitation: Manufacturing estimates are theoretical projections not validated against real-world production data. Actual costs may vary $\pm 50\%$ based on scale, regulatory requirements, and supply chain.

7. Critical Limitations and Validation Requirements

IMPORTANT DISCLAIMER: This is entirely computational research. All predictions require extensive experimental validation. No therapeutic claims are made.

7.1 Required Experimental Validation

1. *In vitro* expression studies (HEK293T, HeLa, hepatocyte models)
2. Hunter syndrome patient-derived fibroblast studies
3. IDS knockout mouse model efficacy (B6.129S-Ids^{tm1Clk/J})
4. Comprehensive immunogenicity assessment (cytokines, ADA)
5. Pharmacokinetics and biodistribution studies
6. Long-term safety evaluation (≥ 12 months)

8. Conclusions

This computational investigation presents an AI-guided framework for optimizing mRNA sequences encoding iduronate-2-sulfatase as a theoretical alternative to current ERT for Hunter syndrome. Variant E demonstrates predicted improvements in expression (2.6-fold; 95% CI: 2.1-3.2), immunogenicity reduction (79% innate, 28% adaptive), and cost-effectiveness (96-99% reduction).

Critical Perspective: This work represents hypothesis generation, not validated therapy. All predictions require rigorous experimental validation through *in vitro* studies, animal models, and human clinical trials.

Path Forward:

- (1) Experimental synthesis and validation of lead mRNA constructs
- (2) *In vitro* expression and functional characterization
- (3) IDS knockout mouse model efficacy studies
- (4) Immunogenicity profiling in animal models
- (5) Dose-ranging and PK/PD studies for clinical trial design

9. Data Availability

Complete mRNA sequences are provided in **Supplementary File 1** (FASTA format). All computational methods, sequence data, and analysis scripts available upon publication through GitHub Repository and Zenodo Archive.

10. References

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5. Muenzer J. (2011). Overview of the mucopolysaccharidoses. *Rheumatology*. 50(suppl 5):v4-v12.

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Conflicts of Interest: Author is Founder & CEO of Alkhaleeli BioAI LLC. Research released under open licensing.

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DISCLAIMER: This study is entirely in silico and does not involve laboratory work, biological agents, or clinical testing. All sequences are theoretical designs for scientific discussion only. No therapeutic claims are made.

Supplementary File 1 – Full mRNA FASTA Sequences

>Native_IDS_mRNA_Reference|UniProt:P22304|NCBI:NM_000202.7|Length:1650nt

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>Kozak_Sequence

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>CDS_Optimized_IDS_1650nt

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AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
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54.8%

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```
# =====
# SUPPLEMENTARY FILE 1: Complete mRNA Sequence Data
# Hunter Syndrome mRNA Therapy - Computational Framework
# Version 2.2 - Final
# =====
# Author: Rami M. Alkhaleeli, MS
# Affiliation: Alkhaleeli BioAI LLC, Oklahoma, USA
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# Date: November 28, 2025
# License: CC BY 4.0
# =====
#
# SEQUENCE ANNOTATIONS:
# - Native IDS: Reference sequence from UniProt P22304 / NCBI
  NM_000202.7
# - Variant E: AI-optimized sequence with CAI 0.89, reduced
  immunogenicity
# - Chemical modifications: 100% m1Ψ, 100% 5mC, Cap 1
  structure
# - All sequences provided in 5' to 3' orientation
#
# DISCLAIMER: This is computational research only. All
  sequences
# are theoretical designs requiring experimental validation.
# =====
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