AI-Driven Development of Oral and Long-Acting GLP-1 Prodrug Constructs for Type 2 Diabetes and Obesity Treatment:

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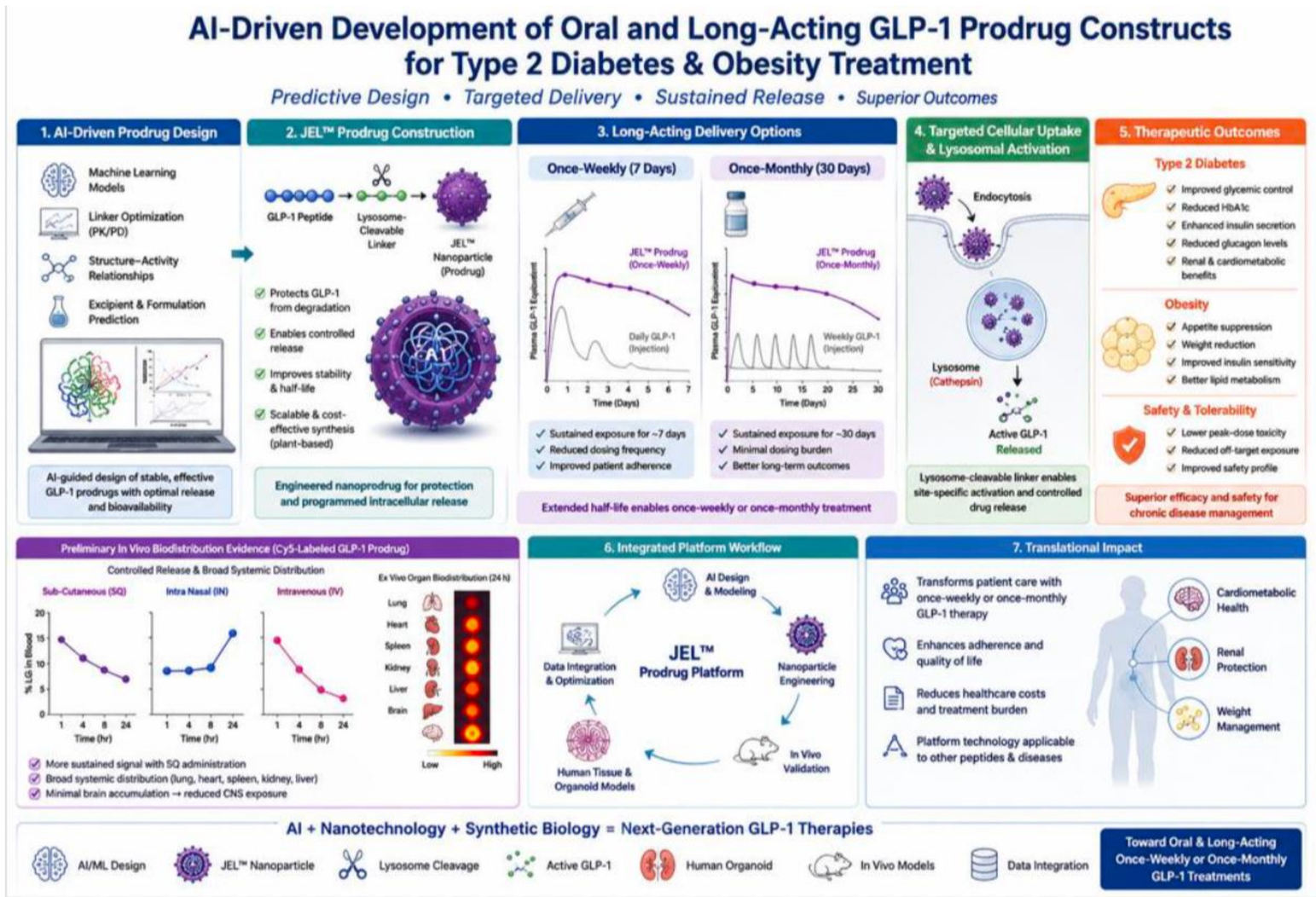
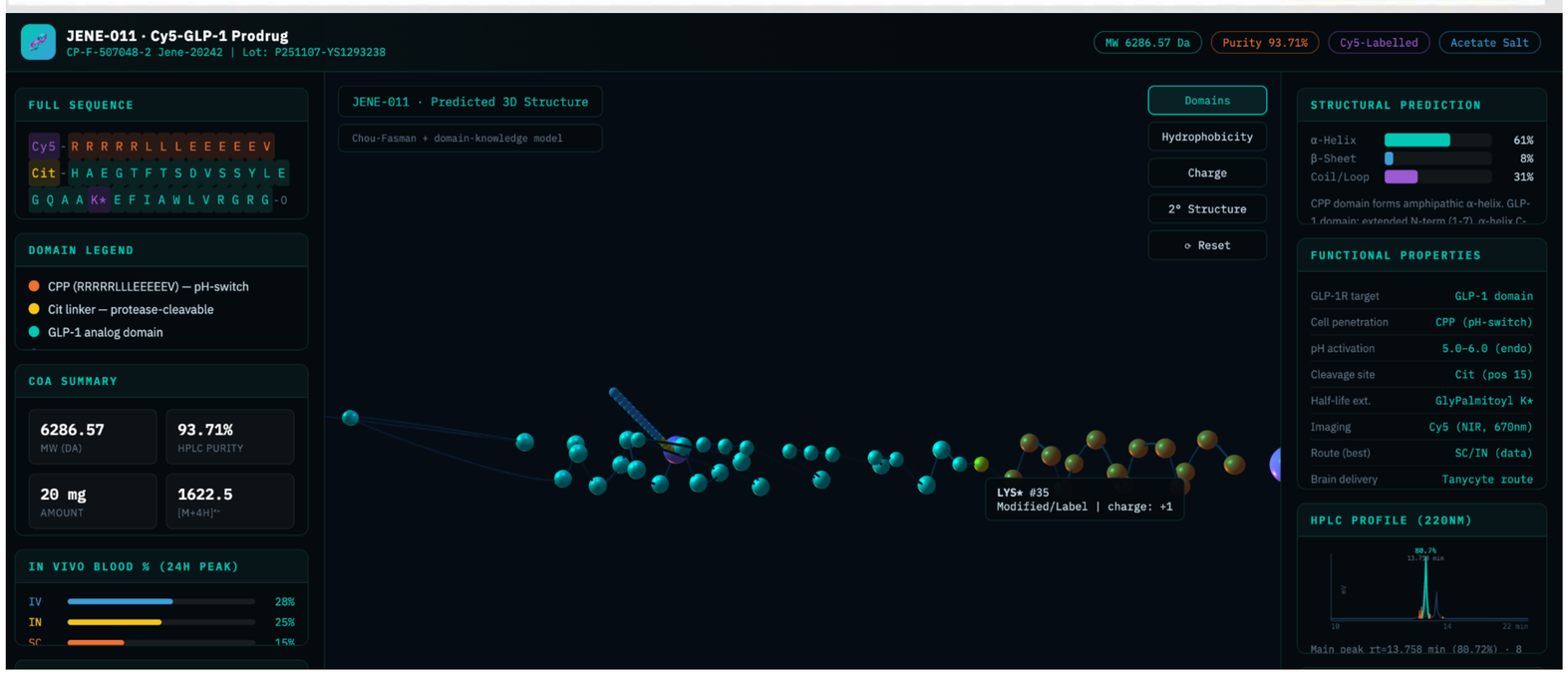




Background

Type 2 diabetes mellitus (T2DM) and obesity are major global health challenges associated with increased cardiovascular, renal, and metabolic complications. Although glucagon-like peptide-1 receptor agonists (GLP-1RAs) have demonstrated significant clinical efficacy in glycemic control and weight reduction, current therapies often require frequent administration and may exhibit variable pharmacokinetic profiles. To address these limitations, we developed JENE-011, an AI/ML-designed lysosome-cleavable GLP-1 peptide prodrug utilizing Jenetech Labs' proprietary JEL™ platform technology. The platform combines computational peptide optimization, linker engineering, and long-acting delivery strategies to improve therapeutic exposure, stability, and patient adherence.

Methods

AI/ML Design and Virtual Screening

A multi-stage AI/ML framework was employed to design and optimize GLP-1 peptide prodrug candidates. Protein language models, sequence embeddings, physicochemical descriptors, toxicity prediction algorithms, permeability prediction models, and structure-based virtual screening were integrated into a unified peptide discovery pipeline. Candidate sequences were evaluated using:

- GLP-1 receptor activity prediction models
- Toxicity prediction (ToxinPred-inspired ensemble)
- Permeability and developability assessment
- Structure prediction using peptide folding algorithms
- Docking readiness and molecular interaction scoring
- Multi-objective optimization for potency, stability, and manufacturability

Top-ranked candidates were selected based on predicted receptor activity, safety profile, developability, and pharmacokinetic potential.

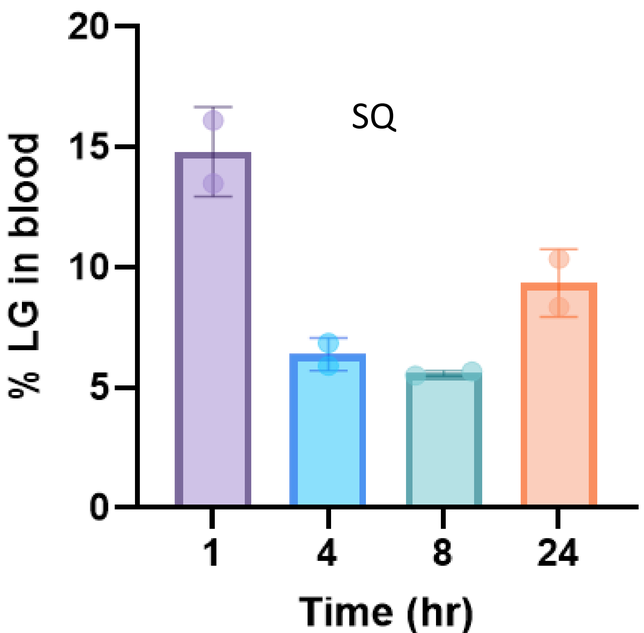
Synthesis and Characterization

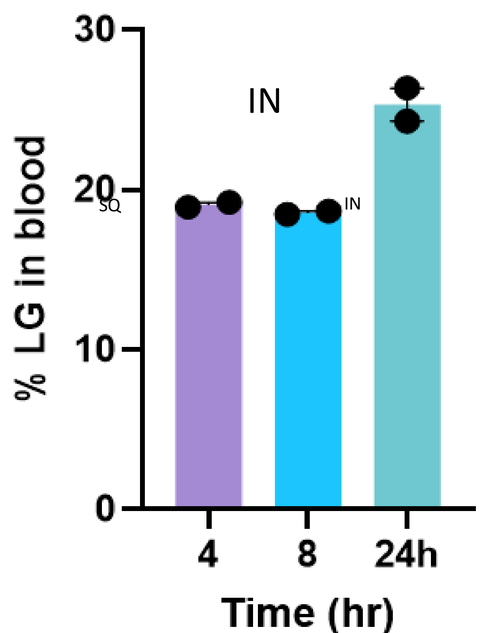
JENE-011 was synthesized using standard Fmoc solid-phase peptide synthesis (SPPS). The construct incorporated a lysosome-cleavable Val-Cit linker and a palmitoyl lipid conjugate to enhance albumin binding and extend systemic exposure. Crude products were purified by reverse-phase HPLC and characterized using LC-MS and analytical HPLC. Product identity, purity, molecular weight, and stability were confirmed prior to in vivo evaluation.

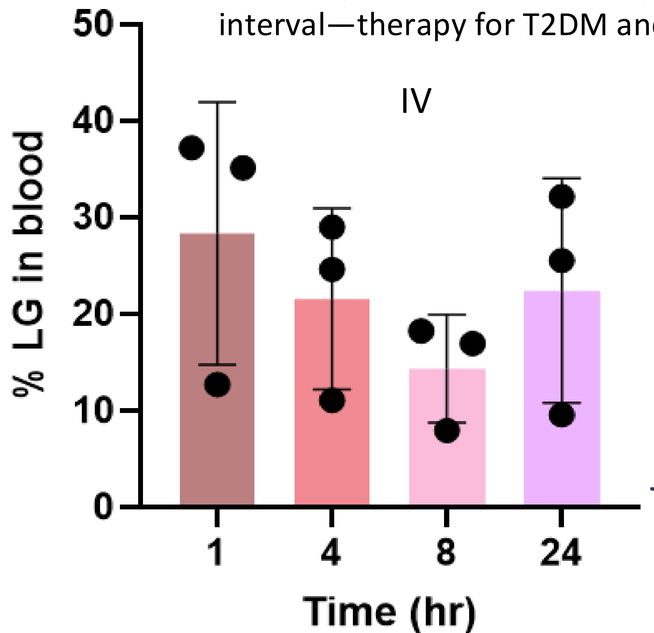
Parameter	Native GLP-1	Predicted JENE-011
Half-life	1–2 min	24–168+ h
DPP-IV degradation	rapid	largely protected
Albumin binding	none	high
Dosing frequency	daily/continuous	weekly potential
Biodistribution	limited	broad systemic
Patient adherence	low	improved

JENE-011 represents a novel AI/ML-derived long-acting GLP-1 peptide prodrug platform designed to overcome limitations of native GLP-1 therapy. Integration of computational peptide engineering, lysosome-cleavable linker technology, and lipid-mediated pharmacokinetic enhancement produced a candidate demonstrating favorable developability and prolonged in vivo exposure. These findings support further pharmacokinetic, pharmacodynamic, and efficacy studies to advance JENE-011 as a potential once-weekly—and potentially extended-interval—therapy for T2DM and obesity.

ADME area	Prediction
Absorption	Best sustained absorption predicted after **SC/SQ injection**. SQ blood signal remains detectable through 24 h, suggesting depot-like release. IN shows delayed/increasing 24 h blood signal. IV shows rapid high early exposure then decline.
Distribution	Broad systemic tissue exposure expected, with signal in **lung, heart, spleen, kidney, liver**, and low/absent brain signal under tested conditions.
Metabolism	Likely proteolytic/lysosomal cleavage of the peptide-linker construct, with palmitoyl-mediated albumin association slowing clearance. Val-Cit/citrulline-like linker suggests enzyme/lysosomal cleavage potential.
Excretion	Parent prodrug likely cleared mainly by hepatic/reticuloendothelial uptake plus proteolytic degradation; smaller peptide fragments/dye metabolites may clear renally and hepatobiliary.
Half-life	Predicted apparent terminal half-life is longer than native GLP-1. From SQ profile, practical exposure likely extends **≥24 h** in mice; true terminal t½ requires plasma LC-MS/MS.
Bioavailability	SQ predicted highest controlled exposure; IN may show meaningful systemic absorption but variable; IV gives complete input but less controlled exposure.
Once-weekly potential	The current mouse Cy5 data support **long-acting behavior**, but not yet definitive once-weekly PK. Once-weekly prediction is plausible if unlabeled JENE-011 has strong albumin binding/depot retention and exposure scales favorably.
Once-monthly potential	Not supported by this dataset alone. Would require depot formulation or nanoparticle formulation data showing multi-week release.







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