STEM CELL INNOVATION CONTEST 2026

11TH EDITION | THEME: STEM CELLS & AI

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VERITAS

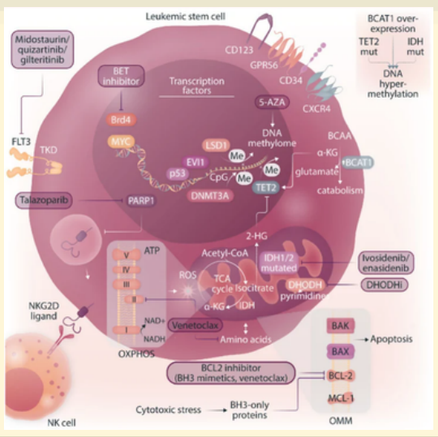
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Eradicating Venetoclax-Resistant Leukemia Stem Cells via Generative AI-Engineered BCL-xL-Targeted Peptides

I. INTRODUCTION

Relapse in acute myeloid leukemia (AML) is primarily driven by leukemia stem cells (LSCs) that evade apoptosis during Venetoclax therapy. Upon developing resistance, a Venetoclax-resistant LSC subpopulation exhibits heightened reliance on BCL-xL, making the BCL-xL–BH3 interface a compelling computational target for proof-of-concept PPI inhibitor design. To address this challenge, our rational strategy leverages generative AI to precisely design peptide inhibitors capable of competitively blocking the BCL-xL–BH3 interaction to overcome drug resistance.



II. OBJECTIVES

This study aims to establish a reproducible, anchor-guided generative AI framework for designing Bim-derived BH3 peptide variants from 15 to 30 amino acids targeting BCL-xL. By enforcing fixed spatial constraints, candidates are precisely engineered to occupy the canonical h1–h4 binding groove. Generated leads are prioritized through multi-metric structural profiling benchmarked against reference PDB 3FDL.

III. METHODOLOGY

PDB 3FDL BCL-xL complex with Bim-BH3 peptide



Interface Hotpot Analysis (Distance cutoff)

Baseline Extraction (h1-h4 Pockets & Salt-Bridges Residues)

Target BCl-xL residues 1-212, full-length

+

AI Transformer Model Anchor-Guided Conditional Generation (ESM-2/ PepMLM) with Fixed Anchors: h2 Leucine, Salt-Bridge Aspartate

Generated Peptide Sequence Library (15-30 aa)

Physicochemical Screening Filter (Cys, GRAVY, Charge)

AlphaFold2-Multimer v3 Batch Prediction

Multi-Matrix Scoring (ipTM.Score from Score Logs, Peptide Mean pLDDT, Groove Prioritized Overlap mapping with reference)

Prioritized Candidate Shortlist

IV. EXPECTED RESULT

Based on our in silico proof-of-concept screening (n = 10 candidates), the proposed generative framework demonstrates the capacity to prioritize BH3-mimetic peptide leads targeting BCL-xL.

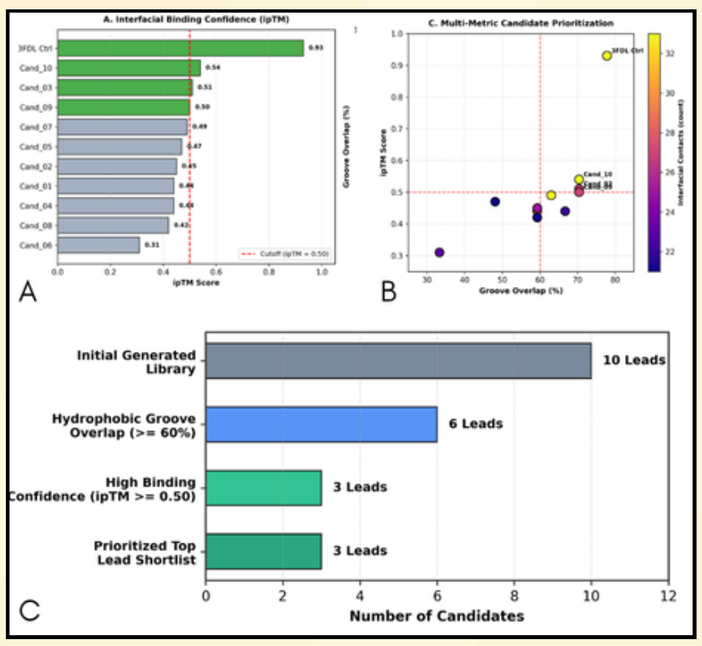


Figure 1: (A) Candidate ranking by peptide-specific mean pLDDT and ipTM score relative to 3FDL benchmark (dashed red line: coarse structural confidence cutoff ipTM=0.50) ; (B) Multi-metric prioritization (ipTM vs. Groove Overlap %; color scale = contact count); (C) Sequential screening funnel from initial library (n=10 proof-of-concept) to top leads.

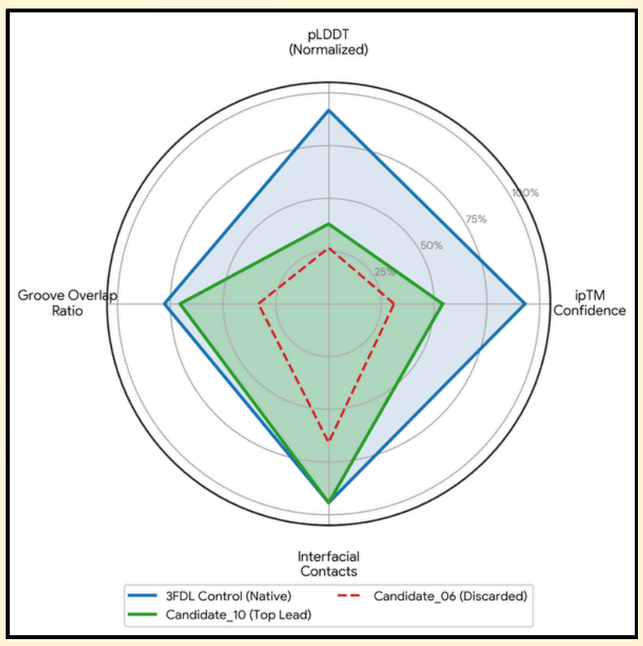


Figure 2: Multi-dimensional structural profiling comparing Candidate_10 (green) against 3FDL experimental control (blue). Candidate_10 maintains key interface contacts and spatial overlap while offering a novel sequence distinct from native Bim.

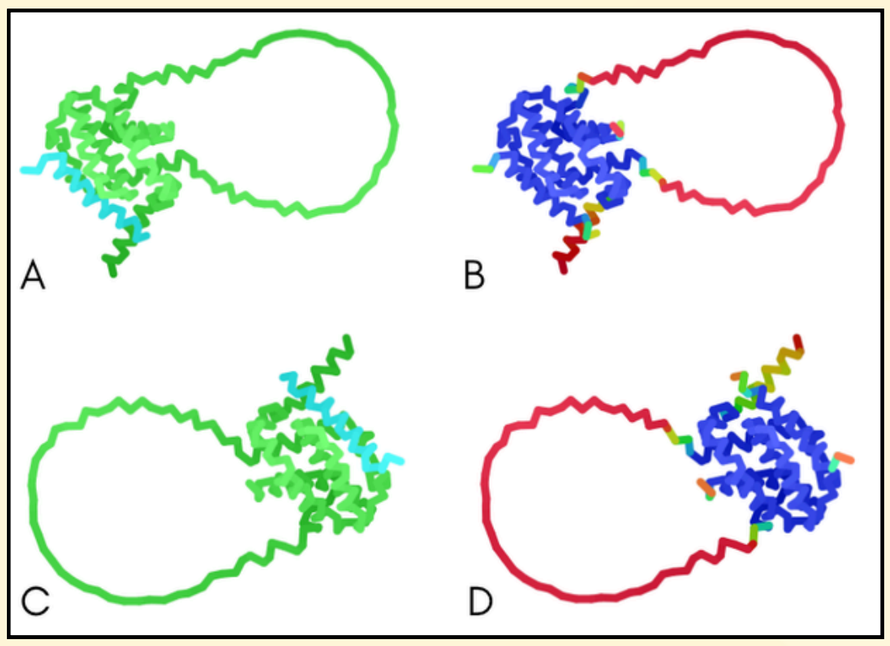


Figure 3: AlphaFold 2 predicted 3D structures colored by chain identity (left: A, C) and per-residue pLDDT confidence (right: B, D). (A-B) Top Lead Candidate_10 (cyan helix, peptide pLDDT > 80) docked tightly into BCL-xL BH3 groove. Unstructured flexible loop of BCL-xL (residues 27-82) is predicted with low confidence (pLDDT < 50, red loop). (C-D) Failed candidate showing non-groove occupied pose)

References

Waclawiczek A, Leppä A, Renders S ...Leukemic stem cell subtypes determine venetoclax resistance and therapeutic vulnerabilities in AML Cell Stem Cell, 2026; 33, 982-999.e8

Lagadinou, E. D., Sach, A., Callahan, K., Rossi, R. M., Neering, S. J., Minhajuddin, M., ... & Jordan, C. T. (2013). BCL-2 inhibition targets oxidative phosphorylation and selectively eradicates quiescent human leukemia stem cells. Cell Stem Cell, 12(3), 329-341.

Evans, R., O'Neill, M., Pritzel, A., Antropova, N., Senior, A., Green, T., ... & Hassabis, D. (2021). Protein complex prediction with AlphaFold-Multimer. bioRxiv, 2021-10.

Lee, E. F., Czabotar, P. E., Smith, B. J., Deshayes, K., Zobel, K., Colman, P. M., & Fairlie, W. D. (2009). Crystal structure of BCL-xL in complex with a BIM BH3 peptide variant. Protein Science, 18(6), 1211-1219. (PDB ID: 3FDL).