Structural proteomics and AI platform enables KAT6A PROTAC rational design

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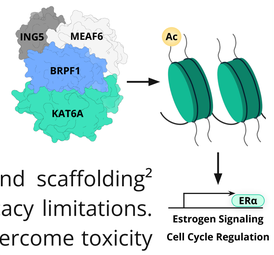
Introduction

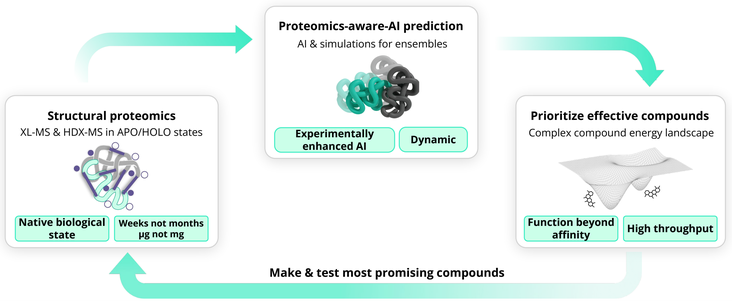
KAT6A is a histone acetyltransferase that plays a critical role in ER signaling and cell cycle regulation[1]. It is dysregulated in many cancers, acting as an oncogene that drives cell proliferation and suppresses cellular senescence.



KAT6 PROTACs can target both the enzymatic and scaffolding[2] functions of KAT6A/B, potentially overcoming efficacy limitations. In addition, selectivity towards KAT6A may help overcome toxicity adverse effects such as neutropenia and dysgeusia[3].

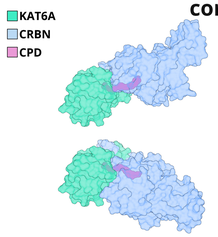
AIMS™ proteomics & AI platform for PROTAC design

The AIMS™ platform uses proteomics-aware-AI. Structural proteomics methods such as cross linking mass spectrometry (XL-MS) provide distance constraints that are used to generate a Proteomics-aware-AI structure prediction that is experimentally grounded. The model is then used to prioritize PROTAC drug designs that are predicted to be the most active.



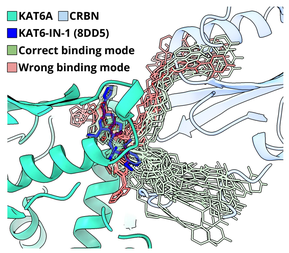
Limitations of structure prediction tools for PROTAC modeling

Boltz-2 cannot confidently separate multiple ternary complex conformations of KAT6A:CRBN:PROTAC



Structure prediction algorithms generate multiple KAT6A:CRBN:PROTAC ternary complex conformations with comparable confidence scores. The two shown examples, display distinct binding interfaces, underscoring the need for experimental structural data to resolve the correct assembly.

Incorrectly predicted binding modes for the PROTAC

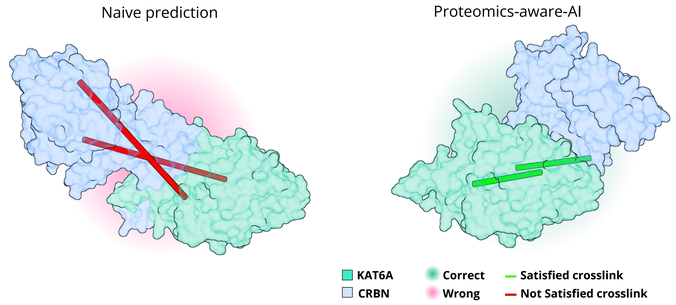


Boltz-2 predicts multiple binding modes for the KAT6 warhead of the PROTAC, several of which deviate from the expected orientation. Such inaccuracies can distort calculated binding affinities, highlighting the need for improved prediction models that integrate experimental structural data for more accurate docking results.

AIMS™ reveals KAT6A:CRBN conformation

XL-MS data for KAT6A:CRBN showed a conformational change compared to the naive method. This experimental data helped guide structure prediction to the correct conformation, allowing for accurate modeling of the complex.

Identification of correct complex conformation

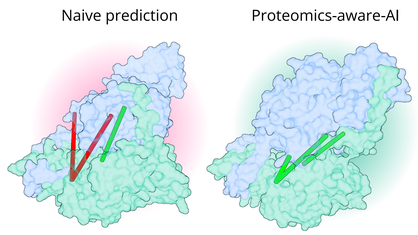


AIMS™ reveals PROTAC-dependent KAT6A:CRBN conformations

XL-MS data was generated for each KAT6A:CRBN:PROTAC ternary complex, revealing conformational differences induced by distinct PROTACs. This experimental data guided structure prediction toward the correct conformation, enabling accurate modeling of the complex for lead optimization.

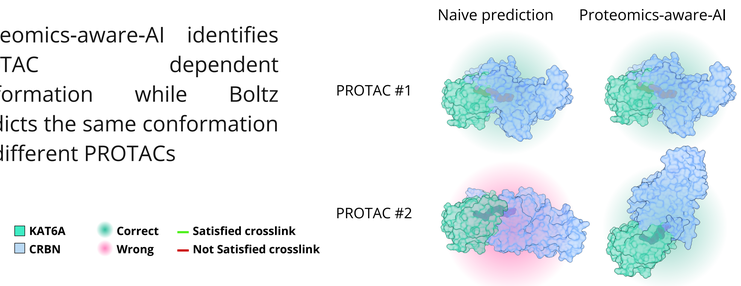
Identification of correct ternary complex conformation

Proteomics-aware-AI highlights correct and incorrect predicted ternary complex structures



Identification of correct PROTAC-dependent conformation

Proteomics-aware-AI identifies PROTAC dependent conformation while Boltz predicts the same conformation for different PROTACs

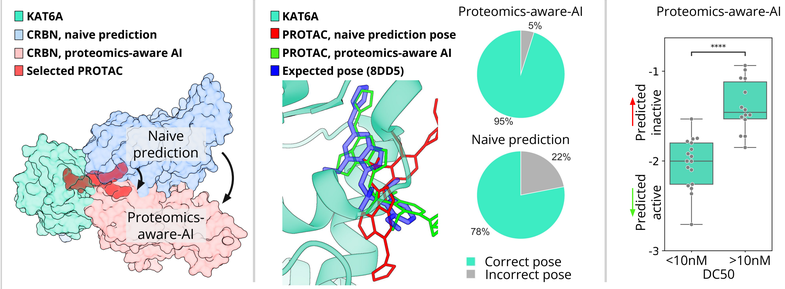


XL-MS-guided structure prediction revealed PROTAC-dependent conformations of the ternary complex that differ from the unconstrained model, underscoring the value of integrating experimental restraints.

Proteomics-aware-AI enables PROTAC design

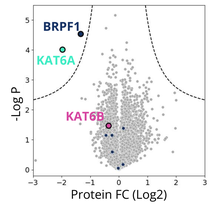
A comprehensive benchmark was established by curating PROTAC molecules and their known activity data. The Proteomics-aware-AI model was assessed by its ability to both accurately identify the correct binding pose and successfully prioritize active compounds.

Improved prioritization model by correctly predicting ternary structure and compound binding pose



AIMS™ enables design of potent & selective PROTAC

Global proteomics confirms KAT6A selective degradation

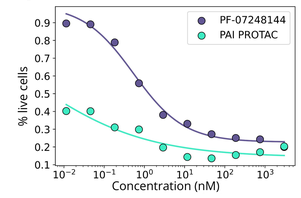


Proteomics analysis shows strong, selective degradation of KAT6A with minimal effects on related proteins such as KAT6B, demonstrating target specificity of the designed PROTAC.

Superior in vitro efficacy over PF-07248144

PROTAC shows better anti cancer efficacy compared to the clinical stage inhibitor in T47D (ER+, breast cancer) cell line.

PAI PROTAC IC50 = 0.004 nM
PF-07248144 IC50 = 1.292 nM



Summary

- **AIMS™ platform** integrates structural proteomics data with AI modeling to improve the accuracy of ternary complex predictions.
- Proteomics-aware-AI enhances the lead optimization process and better differentiate activity levels compared to naive models.
- AIMS™ platform identified potent, selective KAT6A degraders that outperform reference small molecules such as PF-07248144 in vitro.

References

1. Mukohara et al. "Inhibition of lysine acetyltransferase KAT6 in ER+ HER2− metastatic breast cancer: a phase 1 trial." Nature medicine (2024).
2. Chiho Kim et al. "Targeting Scaffolding Functions of Enzymes using PROTAC Approaches" Biochemistry 2023, 62, 3, 561-563.
3. Arad, Gali, et al. "Discovery and proteomic characterization of a novel KAT6A/B inhibitor." Cancer Research 85.8_Supplement_1 (2025): 459-459.