20th International p53 Workshop- Abstract Submission Template

Submission Deadline: December 31, 2025 (5pm EDT)
Notification of acceptance: January 30, 2026

Title of study/project:

Design of Pharmacological Chaperones for Mutated p53

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Year of training:

3

Abstract:

Purpose

The thermally destabilising Y220C mutation in p53 inactivates the protein at physiological temperatures, disrupting crucial functions such as tumour suppression. However, this mutation also presents an opportunity for therapeutic intervention by creating a transient surface pocket that can be targeted by small molecules. This work aims to develop and evaluate an active-learning (AL) framework to prioritise compounds for alchemical free energy calculations, reducing computational expense while accelerating the identification and optimisation of hit and lead ligands targeting p53-Y220C.

Materials & Methods

We developed an iterative AL workflow to benchmark combinations of molecular representations, machine-learning models, and acquisition strategies for relative binding free energy (RBFE) calculations. Candidate molecules were generated via reaction-based enumeration, with an emphasis on synthetically accessible transformations. In each iteration, a subset of compounds was selected for RBFE evaluation, and the resulting affinity change estimates were used to update the predictive model. Performance of the different strategies was assessed against random selection using top-k recall metrics under fixed computational budgets representative of practical RBFE campaigns.

Results

Across multiple independent runs, the AL strategy consistently identified high-affinity ligands more efficiently than random selection. The approach enabled faster and more directed exploration of chemical space while avoiding the prohibitive computational cost of exhaustive RBFE screening, and without compromising the robustness of free energy predictions. Selected top predicted binders found with these methods were synthesised and experimentally validated.

Conclusions

These results demonstrate that active learning can substantially improve the efficiency of RBFE-driven ligand discovery for challenging p53 mutants such as Y220C. By reducing computational cost while maintaining effective identification of affinity-enhancing ligand modifications, this framework enables more tractable chemical space exploration and provides a scalable strategy for integrating physics-based free energy methods into early-stage drug discovery.

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