20th International p53 Workshop- Abstract Submission Template

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

Title of study/project: Activating p53^{Y220C} with a Mutant-Specific Small Molecule
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Year of training: 2

Abstract:

Purpose

Cancer is a complex and highly dreaded disease characterized by the uncontrolled growth and spread of abnormal cells, often driven by genetic mutations. The most frequently mutated gene in human cancers is the tumor suppressor gene *TP53*, which encodes the transcription factor and tumor suppressor protein p53. Tumor suppressor functions of wild-type p53 are lost in many mutant p53 proteins, leading to uncontrolled cellular proliferation. Currently, there are no approved therapies that directly target mutant p53 and restore its wild-type activity. One such mutant, $p53^{Y220C}$,detected in approximately 100,000 patients per year, has emerged as a tractable target for small-molecule “correctors.”

Materials & Methods

We synthesized and characterized a small-molecule chemical inducer of proximity, termed TRanscriptional Activator of p53 (TRAP-1), designed to engage mutant $p53^{Y220C}$ and the transcriptional co-regulator BRD4 in a ternary complex. Biochemical, cellular, and structural approaches were employed to evaluate ternary complex formation, transcriptional activation, and downstream cellular outcomes. Structural insights were obtained using X-ray crystallography and cryo-electron microscopy (cryo-EM).

Results

TRAP-1 formed a stable ternary complex with $p53^{Y220C}$ and BRD4, leading to potent activation of mutant p53. Treatment of $p53^{Y220C}$-expressing cell lines with TRAP-1 resulted in rapid upregulation of p21 and other p53 target genes and induced cellular senescence and apoptosis. Negative control compounds that are unable to form a ternary complex lack these activities, demonstrating the necessity of chemically induced proximity for the observed pharmacology.Crystal structure of mutant p53 protein bound with B-1 linker (functionalised p53 binder) was solved at reslution of 2.63 Å and cryo-EM analysis resolved the structure of the $p53^{Y220C}$ tetramer bound to DNA at 3.2 Å resolution, providing mechanistic insight into restored transcriptional activity.

Conclusions

This study establishes TRAPs as a novel class of bifunctional small molecules capable of restoring the transcriptional activity of mutant p53. The approach described in this work provides mechanistic detail on how chemically induced proximity can be leveraged to restore p53 function and contributes to the development of new mutant specific p53-directed therapeutics.