

Targeting TP53 nonsense mutations by Translational Readthrough: functional rescue of p53 and enhanced chemotherapy sensitivity

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INTRODUCTION

Nonsense mutations generate premature termination codons (PTCs), leading to the synthesis of truncated proteins that are frequently unstable and functionally inactive. This type of mutation accounts for 11% of genetic diseases, including hereditary cancers. Today, there is no therapy for these mutations; however, an approach is represented by TRIDs (Translational Readthrough Inducing Drugs), which allow overcoming the PTC and restoring the protein.

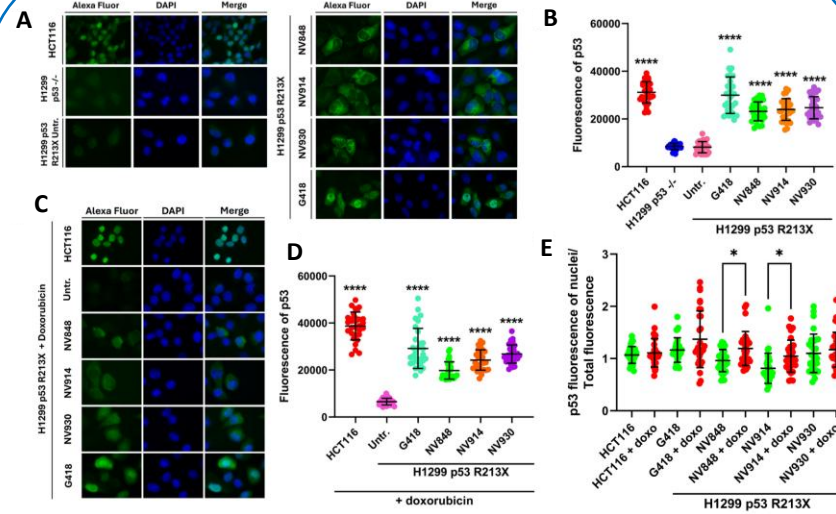


Figure 1: Immunofluorescence assay for p53 before and after DNA damage (A-D) and fluorescence of nuclei (E).

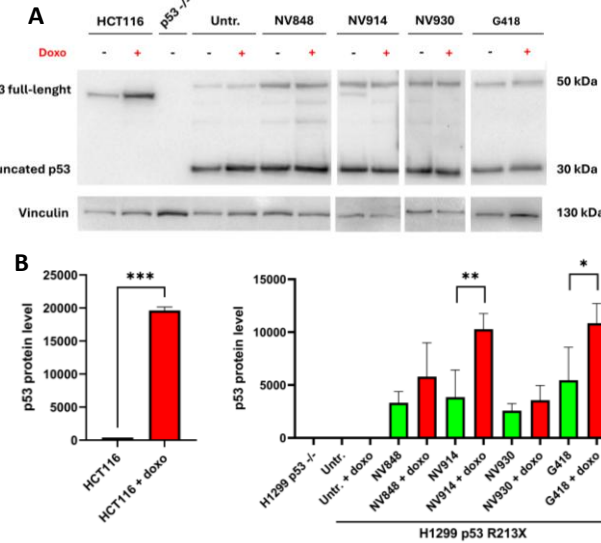


Figure 2: Western blot for p53 before and after DNA damage (A-B).

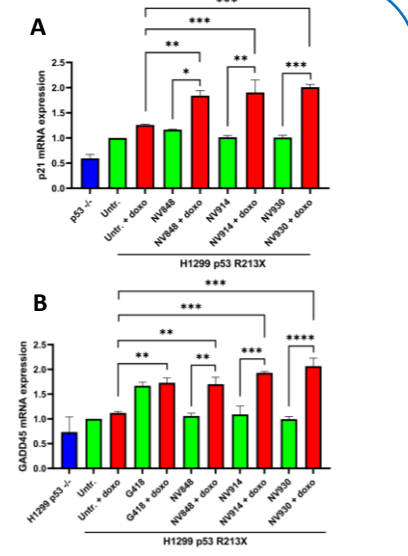


Figure 3: qPCR for p21 (A) and GADD45 (B) before and after DNA damage.

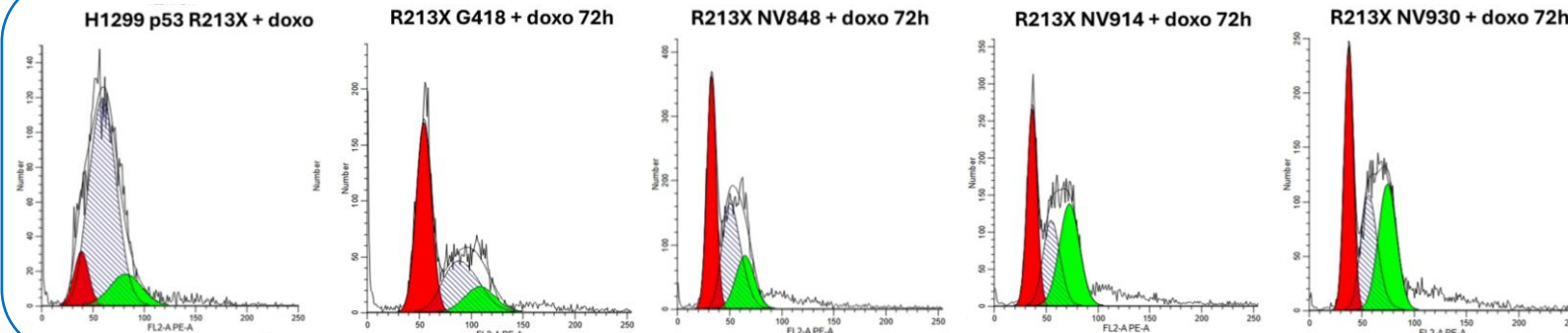


Figure 4: Flow cytometer assay after DNA damage at 72h treatment

CONCLUSIONS

We observed the rescue of p53 expression, an increase in transcripts of its target genes, and a phase G1 cell cycle arrest, thereby demonstrating a functional rescue of the protein. This study provides promising evidence that translational readthrough approaches can restore the expression and function of tumor suppressors carrying nonsense mutations, thereby enhancing the sensitivity of tumor cells to chemotherapeutic agents.