Small Molecule–based Targeting of TTD-A Dimerization to Control TFIIH Transcriptional Activity Represents a Potential Strategy for Anticancer Therapy

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The human transcription factor TFIIH is a large complex composed of 10 subunits that form an intricate network of protein–protein interactions critical for regulating its transcriptional and DNA repair activities. The trichothiodystrophy group A protein (TTD-A or p8) is the smallest TFIIH subunit, shuttling between a free and a TFIIH-bound state. Its dimerization properties allow it to shift from a homodimeric state, in the absence of a functional partner, to a heterodimeric structure with p52 subunit in TFIIH, enabling dynamic binding to the transcription factor.

Recruitment of p8 at TFIIH stabilizes the overall architecture of the complex, whereas p8's absence reduces its cellular steady-state concentration and consequently decreases basal transcription, highlighting that p8 dimerization may be an attractive target for down-regulating transcription in cancer cells.

Here, using a combination of molecular dynamics simulations to study p8 conformational stability and a >3000-member library of chemical fragments, we identified small-molecule compounds that bind to the dimerization interface of p8 and provoke its destabilization, as assessed by NMR and biophysical studies. Using quantitative imaging of TFIIH in living mouse cells, we found that these molecules reduce the intracellular concentration of TFIIH and its transcriptional activity to levels similar to that observed in individuals with trichothiodystrophy owing to mutated TTD-A.

Our results provide a proof of concept of fragment-based drug discovery, demonstrating the utility of small molecules for targeting p8 dimerization to modulate the transcriptional machinery, an approach that may help inform further development in anticancer therapies [1].

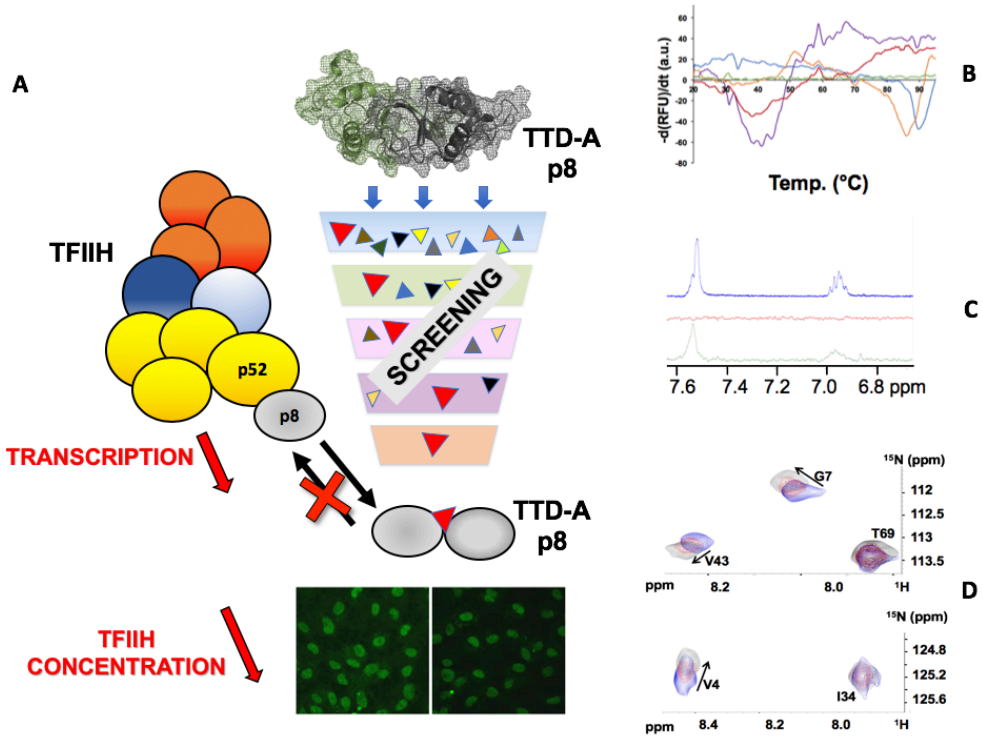

Figure 1: (**A**) An illustration of the workflow used to identify small molecules that bind to the dimerization interface of p8 and provoke its destabilization, giving rise to decrease in TFIIH concentration and transcriptional activity. The potential binders were evaluated for their capacity to (**B**) decrease the thermal stability of p8 using thermal shift assays and (**C**) to bind to p8 as assessed by Saturation transfer difference (STD) NMR experiments. (**D**) Selected view of the ^{1}H-^{15}N HSQC spectrum recorded for p8 showing chemical shift changes for residues at the interface of the dimer.

References:

[1] Gervais, V., Muller, I., Mari, P. O., Mourcet, A., Movellan, K. T., Ramos, P., Marcoux, J., Guillet, V., Javaid, S., Burlet-Schiltz, O., Czaplicki, G., Milon, A., Giglia-Mari, G. (2018) ***J. Biol. Chem.*** 28, 14974-14988