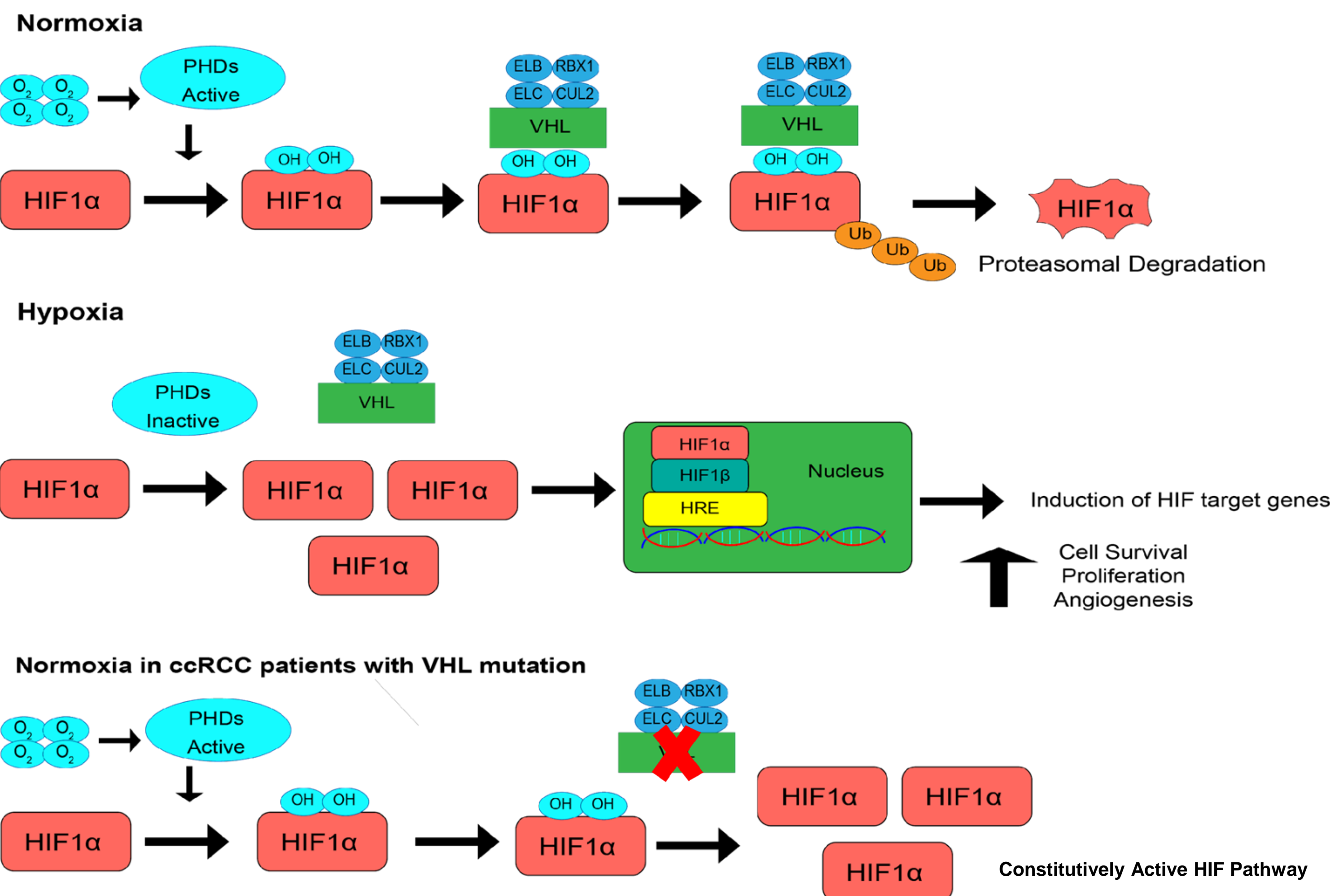


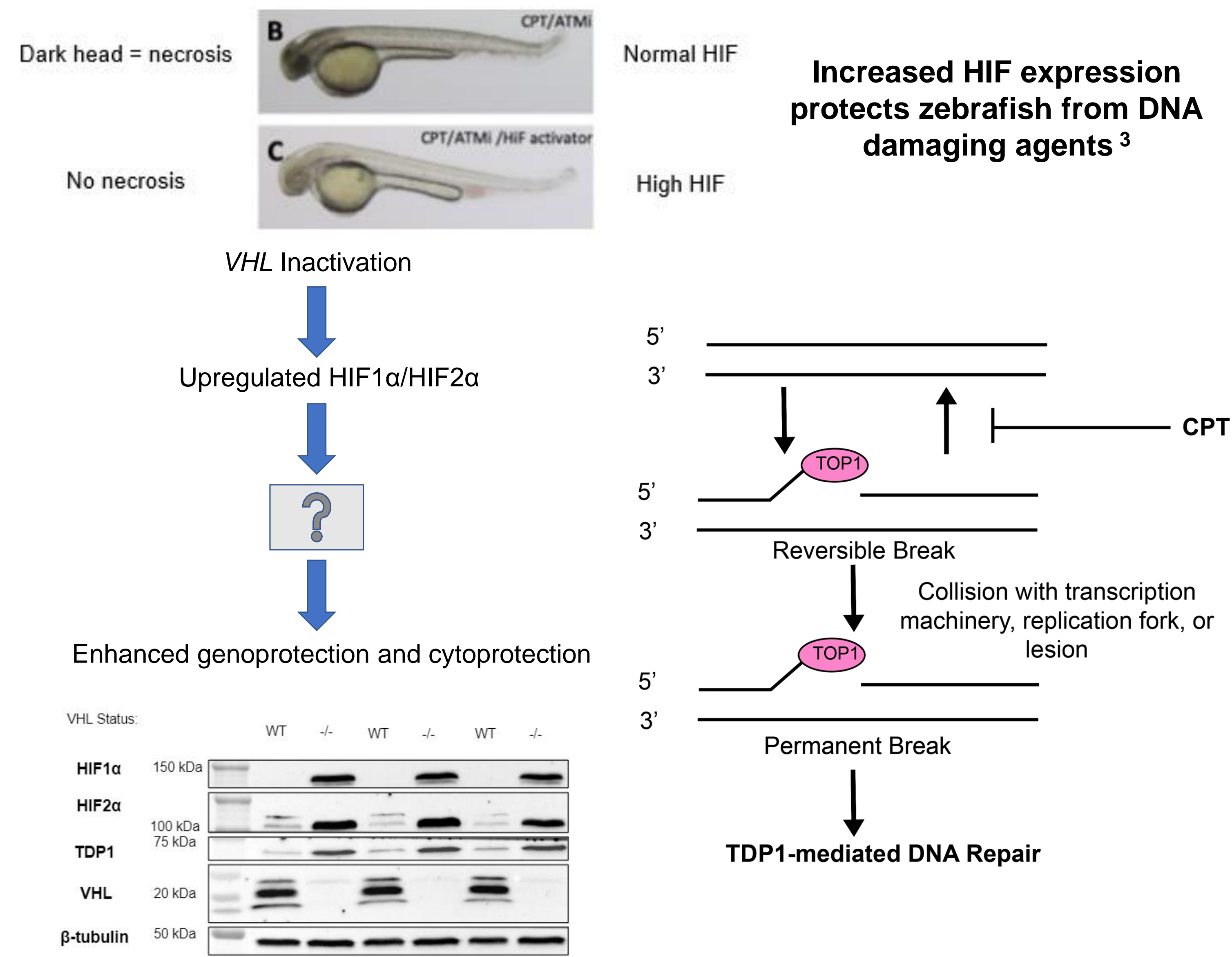


The VHL/HIF Pathway

- Clear cell renal cell carcinoma (ccRCC) accounts for 70% of all RCCs and are commonly caused by mutations in *VHL*, a key regulator of the hypoxia inducible pathway (activated under low oxygen)¹
- Hypoxic cores are a common marker of tumours²
- High levels of hypoxia-inducible factors (HIFs) present in hypoxic cores are thought to provide a protective effect³



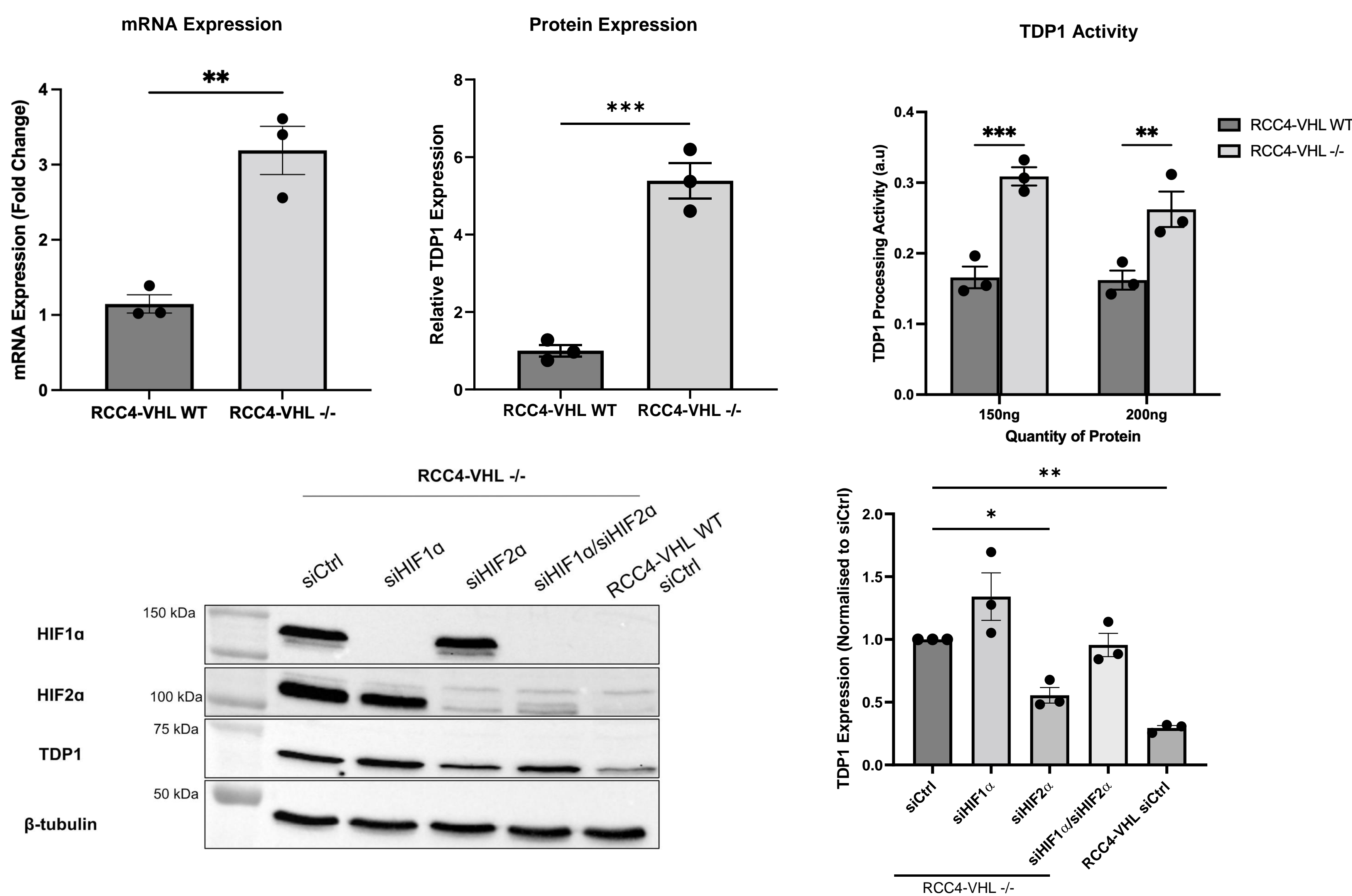
Objectives and Methods



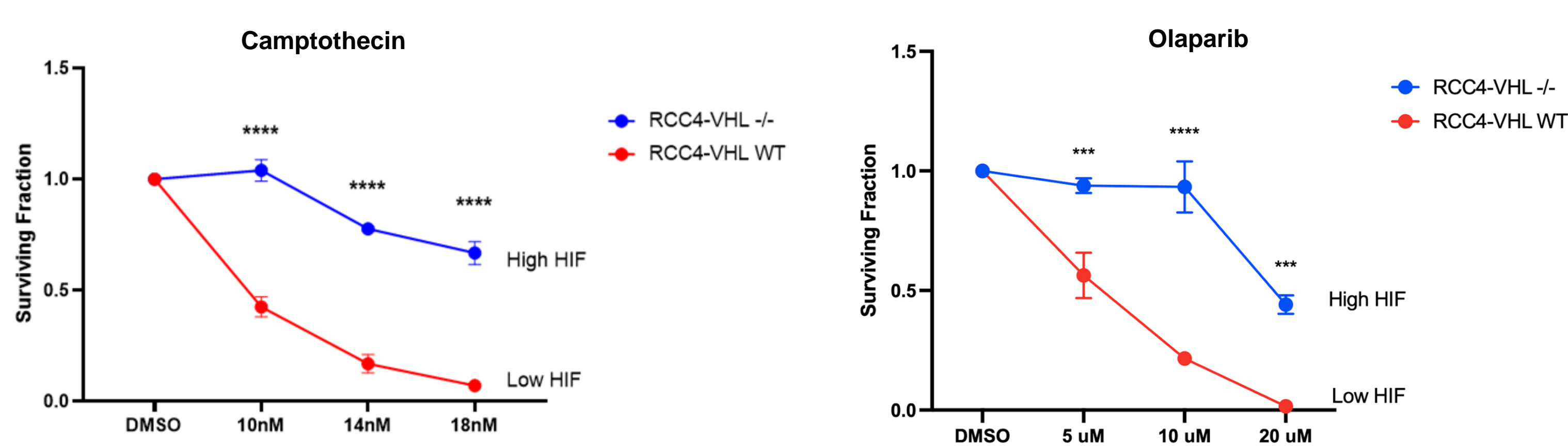
Is TDP1 a key regulator of HIF-mediated resistance?

Results

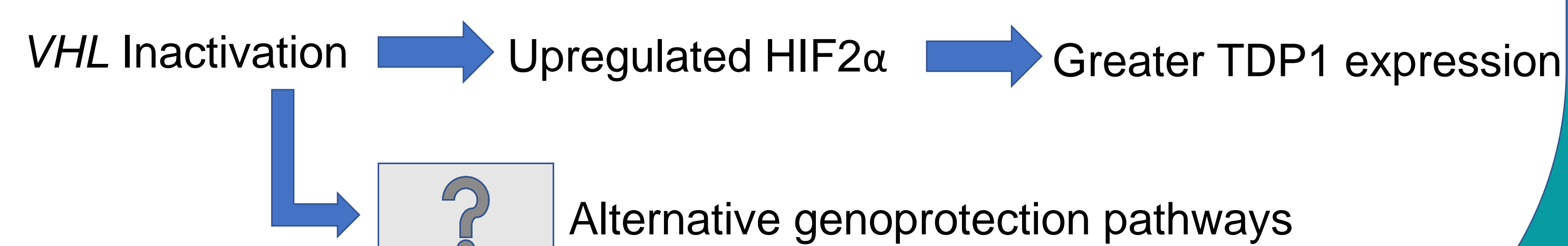
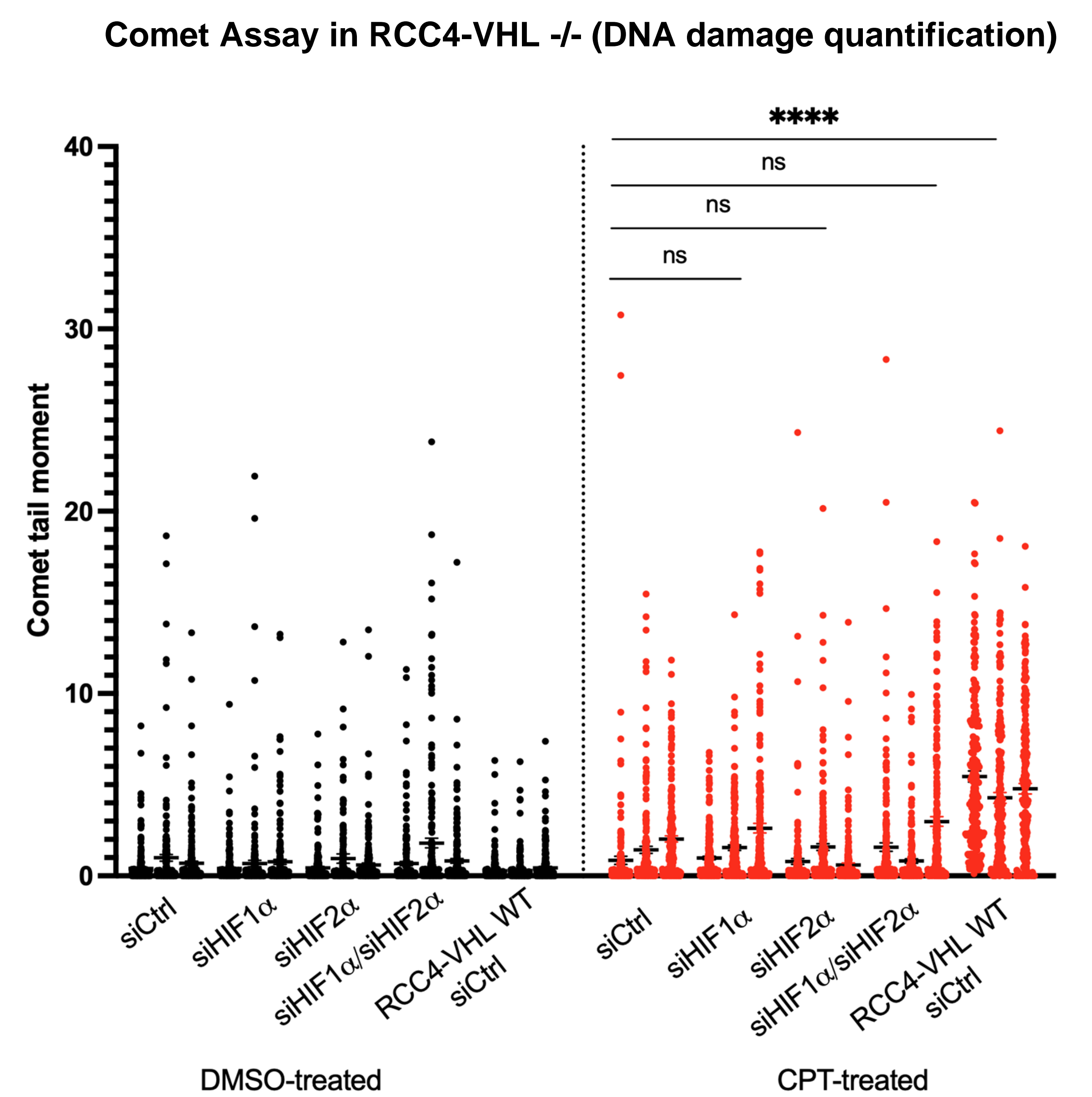
1) TDP1 Expression and activity is upregulated in RCC4-VHL -/- cells and can be reduced via HIF2α knockdown



2) RCC4-VHL -/- cells are more resistant to camptothecin and olaparib treatments

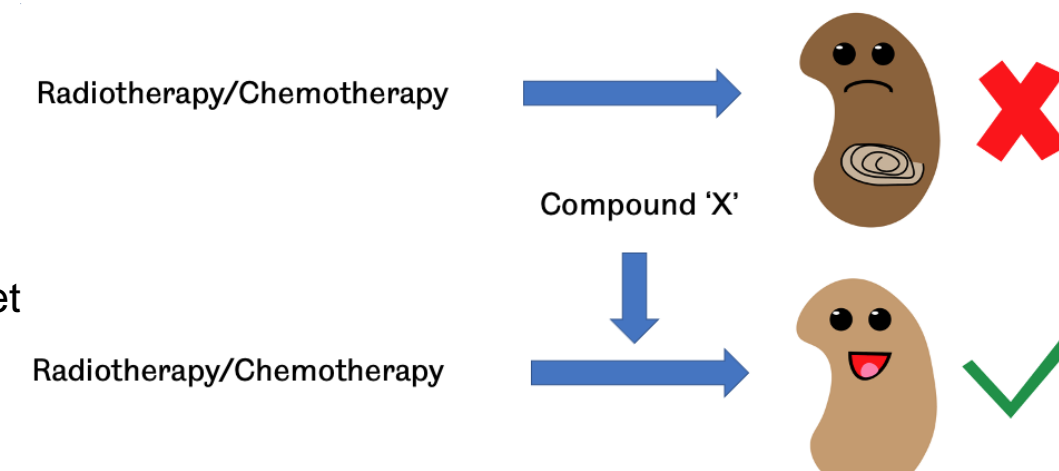


3) Resistance to CPT treatment in comet assays cannot be overcome by HIF knockdowns alone



Conclusions and Future Work

- RCC4 cells lacking functional VHL are more resistant to DNA damaging agents
- TDP1 expression and activity is upregulated in RCC4-VHL -/- cells, suggesting that ccRCC patients may also have greater TDP1 expression
- Increased expression of HIF2α may play a significant role in the upregulated of TDP1
- Decreasing HIF1α/HIF2α is not sufficient to resensitise RCC4-VHL -/- cells to camptothecin in a comet assay
- Further work is required to understand what pathways are influenced by loss of functional VHL



References

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