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TUMOUR METABOLISM

Translating the undruggable target

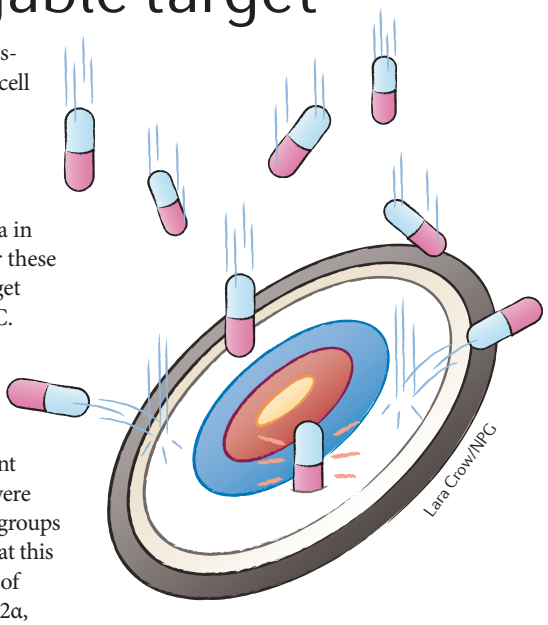
Clear cell renal cell carcinoma (ccRCC) is largely attributable to inactivating mutations in the von Hippel–Lindau tumour suppressor pVHL, which drive accumulation and activation of the transcription factor hypoxia-inducible factor 2α (HIF2α). HIF2α, like many transcription factors, was considered undruggable until the discovery of a large cavity within the HIF2α PAS-B domain capable of binding to small molecules. This breakthrough led to the identification of a series of selective HIF2α antagonists. Three studies have now evaluated the anti-tumour activity of two of these compounds, PT2399 and the closely related analogue PT2385, in preclinical models of pVHL-mutant ccRCC.

What is the mechanism of HIF2α antagonists? Using a *VHL*$^{-/-}$ ccRCC cell line, 786-O, both Cho *et al.* and Wallace *et al.* showed that treatment with PT2399 or PT2385 could disrupt the heterodimerization between HIF2α and its transcriptional partner HIF1β (also known as ARNT), thereby preventing HIF2α binding to DNA. Complementing these findings, Chen *et al.* demonstrated the same result with the treatment of patient-derived xenograft (PDX) ccRCC tumours. All three studies used quantitative PCR to show that both PT2399 and PT2385 suppressed the expression of a number of HIF2α-specific target genes, such as vascular endothelial growth factor A (*VEGFA*), cyclin D1 (*CCND1*) and erythropoietin (*EPO*), but importantly, not those of HIF1α, such as phosphoglycerate kinase 1 (*PGK1*).

What is the functional outcome of specific HIF2α transcriptional inhibition *in vivo*? Cho *et al.* and Wallace *et al.*, using 786-O xenograft mouse models, saw that extended treatment with PT2399 or PT2385 caused tumour stasis and regression coinciding with decreased cell proliferation and decreased angiogenesis. PT2399 and PT2385 also substantially reduced tumour growth and decreased tumour vascular area in *VHL*$^{-/-}$ ccRCC PDXs. Together these studies validate HIF2α as a target driving pVHL-defective ccRCC.

Could HIF2α antagonists be used as therapy for all *VHL*$^{-/-}$ ccRCCs? Surprisingly, Cho *et al.* and Chen *et al.* both observed that some VHL-mutant ccRCC cell lines and tumours were resistant to PT2399. These two groups came to the same conclusion that this resistance is probably the result of differential dependence on HIF2α, with both sensitive VHL-deficient ccRCC cell lines and PDX tumours having considerably higher HIF2α levels. However, the responsiveness of *VHL*$^{-/-}$ ccRCCs may not be exclusively ascribed to HIF2α expression; Cho *et al.* identified two resistant ccRCC cell lines with high HIF2α harbouring a p53 R248W mutation, suggesting that p53 status could also be a factor. In addition, Chen *et al.* found that even sensitive PDX tumours could gain resistance to PT2399 after prolonged exposure, with one tumour harbouring a PT2399 binding site mutation in HIF2α and another a second site suppressor mutation in HIF1β. This finding suggests that the design of complementary inhibitors may be required.

Do these HIF2α antagonists represent an improvement over current approved first-line angiogenesis inhibitors for advanced ccRCC? Chen *et al.* and Wallace *et al.* compared the activity of PT2399 or PT2385 against sunitinib. Both HIF2α antagonists were better tolerated, and showed greater efficacy than sunitinib in reducing PDX tumour growth. Chen *et al.* even found that PT2399 inhibited tumour growth in some sunitinib-resistant PDX tumours.



The potential of PT2399 and PT2385 for clinical use is already evident, as Chen *et al.* demonstrated that a patient with extensively pretreated metastatic ccRCC, subsequently treated with PT2385 in a phase I trial, had a sensitive PDX tumour and exhibited progression-free survival for more than 11 months. However, these studies also underscore the need for predictive and pharmacodynamic biomarker-driven clinical trials, as patient responses are likely to depend, at least in part, on HIF2α levels.

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> “extended treatment with PT2399 or PT2385 caused tumour stasis and regression”

ORIGINAL ARTICLES Chen, W. *et al.* Targeting renal cell carcinoma with a HIF-2 antagonist. *Nature* http://dx.doi.org/10.1038/nature19796 (2016) | Cho, H. *et al.* On-target efficacy of a HIF2α antagonist in preclinical kidney cancer models. *Nature* http://dx.doi.org/10.1038/nature19795 (2016) | Wallace, E. M. *et al.* A small-molecule antagonist of HIF2α is efficacious in preclinical models of renal cell carcinoma. *Cancer Res.* **76**, 5491–5500 (2016)