

 THERAPY

## Good old herbs

Once upon a time, around 1,800 years ago, there was a Chinese medicine known as Huang Qin Tang. It was based on four different herbs and was used to treat gastrointestinal symptoms such as diarrhoea, nausea and vomiting. Today, PHY906, a compound derived from this medicine, is in clinical trials to evaluate its effect as an adjuvant to chemotherapy in metastatic colorectal carcinoma (CRC). But how does it work? A group led by Yung-Chi Cheng has now identified several mechanisms of action for PHY906.

The authors first evaluated the ability of PHY906 to inhibit tumour growth in mice carrying colon tumour allografts. PHY906 was unable to inhibit tumour growth, but enhanced the antitumour effect of CPT-11 (irinotecan) — a compound with severe gastrointestinal adverse effects that is commonly used for the treatment of metastatic CRC — and also reduced the body weight loss that is associated with this chemotherapeutic. After 4 days of treatment, PHY906 could restore the histological structure of the small and large intestine that had been

severely damaged by CPT-11. The authors observed fewer apoptotic cells across all intestinal segments and enhanced proliferative activity of intestinal progenitor cells in the intestinal crypt. PHY906 induced expression of the stem cell markers *Lrp5*, *Cd44* and *Ascl2* on these crypt cells, confirming that they were progenitor cells. As *Lrp5*, *Cd44* and *Ascl2* are targets of Wnt signalling, the authors wondered whether PHY906 could stimulate this pathway. Treatment of HEK293 cells with PHY906 revealed that the compound itself did not activate Wnt signalling; however, when PHY906 was combined with several compounds that are present in the gastric fluid, this led to the activation of Wnt-mediated gene transcription.

PHY906 could also reduce the intestinal infiltration of neutrophils and macrophages triggered by CPT-11 by reducing the levels of expression of pro-inflammatory cytokines such as tumour necrosis factor- $\alpha$  (TNF $\alpha$ ) and macrophage chemotactic protein 1 (MCP1). The authors also observed reduced activity of inducible nitric oxide synthase



(iNOS) and cyclooxygenase 2 (COX2), which could potentially result in the inhibition of the inflammatory cascades downstream of these proteins.

These results have therefore identified several pathways targeted by PHY906 in its fundamental role of mitigating the gastrointestinal toxicity that is induced by chemotherapy.

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**ORIGINAL RESEARCH PAPER** Lam, W. *et al.*  
The four-herb chinese medicine PHY906 reduces  
chemotherapy-induced gastrointestinal toxicity.  
*Sci Trans Med.* 2, 45ra59 (2010).



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