ANGIOGENESIS

A less bitter pill

The broad-spectrum angiogenesis inhibitor TNP-470 is a potent suppressor of tumour growth and metastasis, but its use is limited because it requires lengthy bouts of parenteral administration. To remove this limitation, Folkman and colleagues have enclosed TNP-470 in nanopolymeric micelles and shown that in mice it retains the potency of the free drug.

TNP-470 is a fungal derivative that was one of the first angiogenic drugs to be tested in clinical trials. Despite its efficacy, the drug caused reversible neural toxicity, leading to termination of the trials. In addition, the drug has low water solubility and poor oral availability, so requires hours of intravenous infusions several times a week. The neural side effects have been avoided by conjugating the drug to a polymer to create Caplostatin, which cannot penetrate the blood–brain barrier. Folkman and colleagues have now used a similar polymer-based approach to avoid the oral bioavailabilty limitation. They created Lodamin by conjugating TNP-470 to an amphiphilic polymer, causing the assembly of micelles in which the drug is enclosed, and which can therefore protect the drug in the stomach before absorption in the intestine.

After testing the chemical and physical properties of Lodamin, the authors evaluated the uptake of the micelles by human cells *in vitro*. The micelles were taken up by endocytosis within 20 minutes, and within 48 hours had inhibited the proliferation of endothelial cells by ~90%. The authors then looked at the biodistribution of the polymeric micelles in mice. After 2 hours the micelles were being taken up by endocytosis in the small intestine, and feeding mice with fluorescently labelled Lodamin for three days showed that it was concentrated in the stomach, the intestine and particularly the liver, but was not found in the brain. The significance of this was demonstrated by the fact that Lodamin-treated mice did not show behavioural abnormalities whereas those treated with free TNP-470 did. Furthermore, *in vivo*, mice treated with Lodamin for 6 days showed 30–40% inhibition of vessel formation in an angiogenesis assay in the eye.

Having demonstrated that Lodamin is successfully delivered orally and can effectively inhibit physiological angiogenesis, the authors tested its anti-tumour effects. When used to treat lung carcinoma and melanoma mouse models, Lodamin caused an ~80% inhibition of tumour growth, and the tumours formed only small and undeveloped blood vessels. Moreover, Lodamin was particularly effective against liver metastases, more so than TNP-470. This might be because oral delivery results in higher drug concentration in the liver.

These results show that Lodamin is a good candidate for clinical trials as it retains the anti-angiogenic properties of free TNP-470 in mouse models yet successfully overcomes prior hurdles associated with toxicity and drug administration. It could be particularly useful in cancer patients for the long-term prevention of tumour recurrence.

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ORIGINAL RESEARCH PAPER Benny, O. *et al.* An orally delivered small-molecule formulation with antiangiogenic and anticancer activity. *Nature Biotechnol.* 29 Jun 2008 (doi:10.1038/nbt1415)

FURTHER READING Duncan, R. Polymer conjugates as anticancer medicines. *Nature Rev. Cancer* **6**, 688–701 (2006)

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