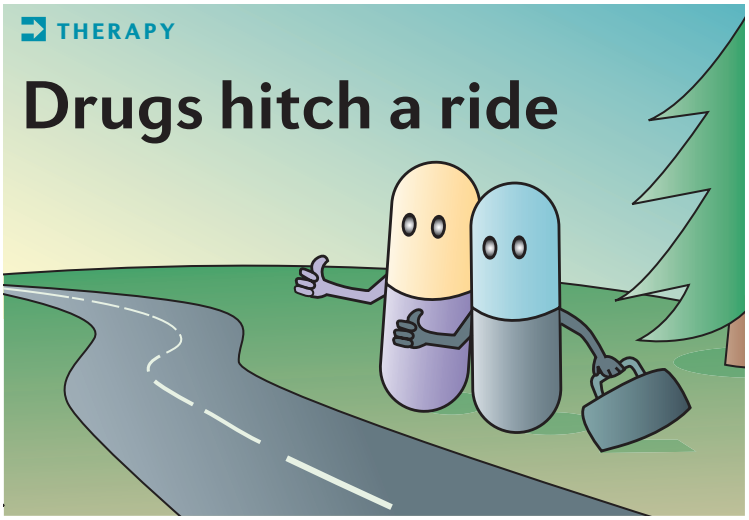

A limitation of many anticancer drugs is their inability to target and penetrate tumour tissue, leading to reduced efficacy and nonspecific adverse effects on normal cells. In a study published in *Science*, researchers led by Erkki Ruoslahti have identified a method of specifically targeting drugs to the extravascular tumour tissue, and they show that this increases drug potency.

Previously, Ruoslahti and colleagues identified a cyclic peptide, iRGD (CRGDKGPDC and closely related variants), which targets tumour cells by binding αv integrins that are specifically expressed on the tumour vessel endothelium. Once bound, iRGD is cleaved and loses much of its affinity for integrins. However, the truncated peptide shows increased binding to neuropilin 1 (NRP1), and this facilitates the penetration of the peptide into the tumour tissue. The authors exploited these properties and found that drugs chemically conjugated to iRGD are carried deep into tumours.

In this study, Kazuki Sugahara, Tambett Teesalu *et al.* showed that molecules did not have to be chemically linked to iRGD to be targeted to tumours. Compared with controls, co-administration of iRGD increased the penetration of compounds of different sizes and chemical properties as much as 40-fold in the tumour parenchyma of human tumour xenografts growing in immunodeficient mice. This tumour-specific penetration was shown to depend on the sequence of the cleaved iRGD peptide and required active transport rather than passive leakage, as drug accumulation was inhibited by NRP1-specific antibodies, sodium azide or a reduction in temperature.

Does co-administration of iRGD have similar effects on drugs currently used in the clinic? The authors tested the ability of four anticancer drugs co-administered with iRGD to penetrate and inhibit the growth of human breast and prostate xenografts in mice compared with each drug alone. iRGD combined with nab-paclitaxel, doxorubicin, liposomes containing doxorubicin or trastuzumab therapy provided equivalent or better delivery and anti-tumour efficacy, as well as an improved therapeutic index by decreasing the effective dose. Notably, tumour progression, in the form of macroscopic metastases or dissemination of tumour cells, was not observed in animals given the iRGD peptide.

The results of this study suggest that the co-administration of iRGD with approved anticancer drugs could be an effective way of enhancing their efficacy and selectivity. As this does not require chemical conjugation to the iRGD peptide, approved drugs could be used without modification, allowing straightforward regulatory compliance and avoiding the loss of efficacy that often accompanies reagent coupling.

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“the co-administration of iRGD with approved anticancer drugs could be an effective way of enhancing their efficacy and selectivity.”

ORIGINAL RESEARCH PAPER Sugahara, K. *et al.* Coadministration of a tumor-penetrating peptide enhances the efficacy of cancer drugs. *Science* 8 Apr 2010 (doi:10.1126/science.1183057)