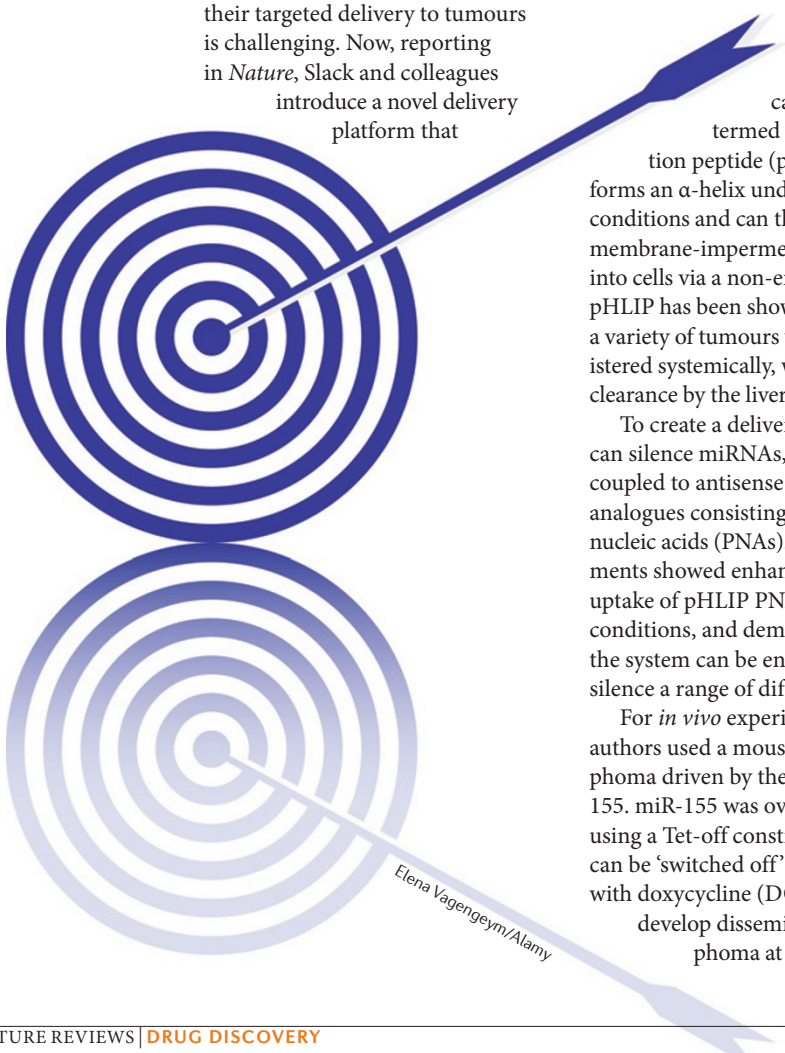
CANCER

New delivery platform targets antimirs to tumours

MicroRNAs (miRNAs) are short, non-coding RNAs that suppress the expression of target genes. Dysregulated miRNAs are known to cause pathology in a range of conditions, and oncomirs (oncogenic miRNAs; a subgroup of miRNAs) can have a causal role in cancer. Therapeutic strategies that use antisense oligomers (antimirs) to silence oncomirs are attractive, but their targeted delivery to tumours is challenging. Now, reporting in *Nature*, Slack and colleagues introduce a novel delivery platform that targets the acidic microenvironment of tumours, and demonstrate its efficacy in a mouse model of lymphoma.



Elena Vagengeym/Alamy

The *in vivo* delivery of therapeutic nucleic acid analogues can be hampered by non-specific organ distribution (such as accumulation in the liver), clearance by the reticulo-endothelial system, and destruction in endolysosomes. The authors took advantage of a previously reported carrier peptide termed pH-low insertion peptide (pHLIP), which forms an α-helix under acidic conditions and can then translocate membrane-impermeable molecules into cells via a non-endocytic route. pHLIP has been shown to home to a variety of tumours when administered systemically, while avoiding clearance by the liver.

To create a delivery vector that can silence miRNAs, pHLIP was coupled to antisense nucleic acid analogues consisting of peptide nucleic acids (PNAs). *In vitro* experiments showed enhanced cellular uptake of pHLIP PNAs under acidic conditions, and demonstrated that the system can be engineered to silence a range of different miRNAs.

For *in vivo* experiments, the authors used a mouse model of lymphoma driven by the oncomir miR-155. miR-155 was overexpressed using a Tet-off construct, which can be 'switched off' by treatment with doxycycline (DOX). The mice develop disseminated lymphoma at 2 to 3 months of age, which regresses upon DOX-induced miR-155 withdrawal. Tumour regression can also be induced with a cocktail of chemotherapeutics and steroids (CHOP), which is part of the current standard of care for the treatment of lymphoma in humans.

Delivery of a PNA-based anti-miR-155 by pHLIP (pHLIP–anti155) by intravenuous injection seemed to be tolerated well and delayed tumour growth and metastatic spread. Similar to DOX, pHLIP–anti155 treatment normalized counts of circulating lymphocytes to wild-type levels. In contrast, CHOP treatment resulted in lymphocyte levels much lower than in wildtypes — reflecting the toxicity of conventional chemotherapeutics and indicating that pHLIP–anti155 might be better tolerated. RNA sequencing analysis of pHLIP-anti155-treated tumours showed an upregulation of a number of known tumour suppressors, as well as differential expression of a range of other genes known to be involved in cancer, cell adhesion and migration pathways.

The authors point out that, in principle, every miRNA is druggable. Therefore, pHLIP–PNAs could also have therapeutic potential in other conditions that produce localized acidic environments — including ischaemia, myocardial infarctions, stroke, tissue trauma, and in sites of inflammation and infection.

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