

## Targeted Therapy

**Major finding:** Targeting the acidic tumor microenvironment enhances anti-miR delivery and oncomiR inhibition.

**Concept:** Attachment to pHLIP transports anti-miRs across the plasma membrane and escapes liver clearance.

**Impact:** This system may have therapeutic potential in both cancer and other pathologic conditions.

### TARGETED DELIVERY TO THE TUMOR MICROENVIRONMENT IMPROVES miRNA SILENCING

Overexpression of oncogenic miRNAs, known as oncomiRs, has been shown to drive tumor initiation and maintenance and results in dependency of some tumors on expression of these miRNAs. Recent studies have explored targeted inhibition of oncomiRs using antisense oligomers (antimiR) as a strategy to overcome this oncomiR addiction and suppress tumor growth. However, the anticancer activity of antimiRs is limited by suboptimal delivery into target tumor cells. To overcome this limitation, Cheng and colleagues developed a new antimiR delivery platform in which charge-neutral peptide nucleic acid antimiRs were attached to a low pH-induced transmembrane structure (pHLIP), which specifically localized to the acidic tumor microenvironment, but not the liver, and effectively transported antimiRs across the plasma membrane of various tumor cell types under acidic conditions. Treatment with pHLIP-antimiR-155 diminished the growth of subcutaneous miR-155-driven lymphoma tumors, prolonged survival, and suppressed metastatic spread more effectively than commercially available antimiRs and without systemic toxicity. Furthermore, targeted silencing of miR-155 via systemic administration

of pHLIP-antimiR-155 also effectively inhibited lymphoma growth and liver metastasis in a transgenic mouse model of miR-155-addicted lymphoma, resulting in decreased lymph node tumor burden and restoration of splenic architecture without renal damage. RNA sequencing analysis of regressing tumors following antimiR treatment compared with miR-155-addicted tumors identified putative miR-155 target genes that are differentially expressed upon oncomiR withdrawal, including genes that regulate cell adhesion and migration, as well as a number of tumor suppressor genes that represent predicted miR-155 targets. Of note, two validated miR-155 targets, *Bach1* and *Mafb*, were upregulated following pHLIP-antimiR-155 treatment. In sum, these data demonstrate the anticancer efficacy of this antimiR delivery platform and suggest that targeted miRNA silencing using this system may also be useful for other pathologic conditions. ■

Cheng CJ, Bahal R, Babar IA, Pincus Z, Barrera F, Liu C, et al. *MicroRNA silencing for cancer therapy targeted to the tumour microenvironment. Nature* 2014 Nov 17 [Epub ahead of print].

## Clinical Trials

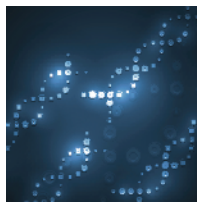
**Major finding:** The RNAi therapeutic Atu027 is well tolerated and active in patients with advanced solid tumors.

**Concept:** Atu027-mediated silencing of protein kinase N3 in endothelial cells may promote vessel normalization.

**Impact:** Treatment with Atu027 may prevent and target metastatic lesions in various advanced cancers.

### A VASCULAR-TARGETED RNAi THERAPEUTIC SHOWS ACTIVITY IN ADVANCED CANCERS

Administration of siRNA molecules enables targeted downregulation of specific genes and is being developed as a potential antitumor therapeutic strategy. Atu027 is a liposomal RNAi therapeutic agent containing siRNA directed against protein kinase N3 (PKN3), a downstream effector of the PI3K pathway that promotes tumor cell growth and angiogenesis. Preclinical studies have shown that Atu027 silences PKN3 expression in vascular endothelial cells and inhibits invasive tumor growth and metastasis in mice, and mechanistic studies suggest that Atu027 may prevent metastatic spread by enhancing vessel integrity and reducing vascular permeability. Schultheis and colleagues investigated the safety and efficacy of escalating doses of Atu027 in a first-in-human phase I study in 34 patients with advanced refractory solid tumors. Atu027 was well tolerated at all doses and a maximum tolerated dose was not reached. The majority of adverse events were grade 1 or 2, with the most frequent treatment-related adverse event being fatigue, and only one dose-limiting toxicity was observed at the highest dose. Moreover, in contrast to other liposomal RNAi therapies, administration of



Atu027 did not significantly activate innate immune responses and did not require immunosuppressive premedication. Atu027 treatment resulted in disease stabilization in 41% of patients, including 8 patients who exhibited stable disease at the end of the study and 7 patients who experienced partial or complete regressions of distant metastatic lesions. Although biopsies were not obtained as part of this trial, analysis of serum plasma proteins following treatment revealed decreased plasma concentrations of the soluble variant of VEGF receptor 1 (sVEGFR1, also known as sFLT1) in 12 of 20 patients, suggesting that sVEGFR1 may represent a potential serum biomarker of vascular response to Atu027. These results indicate that Atu027 is safe and effective in various advanced cancers and support additional clinical trials of Atu027 in combination with cytotoxic drugs. ■

Schultheis B, Strumberg D, Santel A, Vank C, Gebhardt F, Keil O, et al. *First-in-human phase I study of the liposomal RNA interference therapeutic Atu027 in patients with advanced solid tumors. J Clin Oncol* 2014 Nov 17 [Epub ahead of print].