

## THERAPY

**Potential of siRNA-based therapies for pancreatic fibrosis**

Fibrosis associated with chronic pancreatitis is irreversible; no targeted therapies are currently available. Now, a new study published in *Gut* shows that an siRNA-based antifibrotic targeted therapy resolves pancreatic fibrosis in a rat model, offering hope for future antifibrotic drugs that can reverse this pancreatic damage.

Sustained activation of pancreatic stellate cells (PSCs) results in the accumulation of fibrotic tissue in the pancreas. Yoshiro Niitsu and colleagues had previously shown that vitamin-A-coupled liposomes containing siRNA

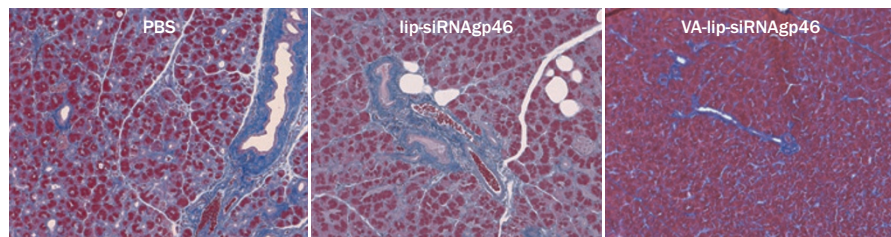
against the collagen-specific chaperone protein gp46 (VA-lip-siRNAgp46) completely resolved liver fibrosis in animal models. They therefore reasoned that a similar approach could work for pancreatic fibrosis, especially as PSCs resemble hepatic stellate cells and have similar roles in inducing fibrosis.

*In vitro* studies confirmed specific uptake of VA-lip-siRNAgp46 into activated PSCs and knockdown of gp46, with subsequent suppression of collagen secretion. Using a rat model of chronic pancreatitis (induced by dibutyltin

dichloride), the researchers confirmed specific delivery of VA-lip-siRNAgp46 directly to PSCs in fibrotic tissue *in vivo*. Moreover, 10 systemic treatments of VA-lip-siRNAgp46 (0.75 mg/kg siRNA) led to complete resolution of pancreatic fibrosis.

Pre-phase I testing of this siRNA-based agent is already underway and the authors hope to proceed to phase I trials for liver fibrosis (NASH) soon. “Then we will expand our clinical study to other organ fibrosis, including pancreatic fibrosis,” adds Niitsu. However, the investigators concede that careful testing for off-target and adverse effects of siRNA-based therapies is needed before application in the clinic.

Katrina Ray



Treatment with VA-lip-siRNAgp46 resolves pancreatic fibrosis in rats with DBTC-induced pancreatitis. Abbreviations: DBTC, dibutyltin dichloride; lip-siRNAgp46, liposome of gp46 siRNA; PBS, phosphate buffered saline; VA-lip-siRNAgp46, vitamin-A-coupled liposome of gp46 siRNA. Courtesy of Y. Niitsu.

**Original article** Ishiwatari, H. *et al.* Treatment of pancreatic fibrosis with siRNA against a collagen-specific chaperone in vitamin A-coupled liposomes. *Gut* doi:10.1136/gutjnl-2011-301746