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THERAPEUTICS

siRNAs jump the hurdle

> *PLK1* siRNAs in a complex with F5-P … significantly slowed tumour growth

The specific delivery of small interfering RNAs (siRNAs) to tumour cells, especially those that are disseminated, is a major hurdle for the development of these molecules as therapeutics. Yao *et al.* have shown that this is possible by delivering siRNAs with a fusion protein, which is comprised of a single-chain fragmented antibody (ScFv) that targets tumour cells and a positively charged peptide that binds RNA.

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The Polo-like kinase 1 (PLK1) serine/threonine kinase is overexpressed in several cancer types and can promote proliferation and survival of tumour cells. Specific delivery *in vitro* of an siRNA targeting *PLK1* into ERBB2 (also known as HER2)-expressing breast cancer cell lines and cells derived from surgically removed breast tumours was accomplished using a protamine peptide fused to an ScFv that binds ERBB2 (F5-P). F5-P-mediated delivery of *PLK1* siRNAs effectively reduced PLK1 expression, and reduced proliferation and increased apoptosis of ERBB2$^+$ breast cancer cell lines and primary breast cancer cells *in vitro*. The expression of a PLK1 mutant that was unable to bind the *PLK1* siRNA restored proliferation and prevented apoptosis, indicating that the observed effects are likely to be a direct result of PLK1 silencing.

F5-P was also capable of delivering *PLK1* siRNAs to ERBB2$^+$ cell lines or primary breast tumour cells grown as xenografts in nude mice. In these models, tail vein injection of PLK1 siRNAs in a complex with F5-P twice weekly for 4 weeks significantly slowed tumour growth (followed for 7 weeks); ERBB2$^-$ tumours were insensitive to this treatment. In addition to evaluating primary tumour growth, the authors investigated whether F5-P-mediated delivery of PLK1 siRNAs could effectively suppress the growth of metastatic cells. Indeed, PLK1 siRNA–F5-P complexes reduced the number of experimental metastases following tail vein injection of ERBB2$^+$ breast cancer cells in nude mice, resulting in significantly increased survival of the mice.

In additional experiments, the authors showed that F5-P could effectively deliver a cocktail of three siRNAs (targeting *PLK1*, cyclin D1 (*CCND1*) and *AKT*), and that this cocktail more effectively suppressed tumour growth than *PLK1* siRNAs alone. Furthermore, injection of F5-P–siRNA complexes did not induce an interferon response in immunocompetent mice, and did not affect serum indicators of cardiac damage, liver damage or renal function. Although it will be important to assess whether repeated dosing of 5-FP–siRNA complexes induces immune responses, and optimization of targeting antibodies, siRNAs and dosing regimens are needed, these data indicate that this is a promising strategy for delivering siRNAs as cancer therapeutics.

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ORIGINAL RESEARCH PAPER Yao, Y. *et al.* Targeted delivery of PLK1-siRNA by ScFv suppresses Her2$^+$ breast cancer growth and metastasis. *Sci. Transl. Med.* **4**, 130ra48 (2012)