

 THERAPY

Special delivery

The ability to specifically target therapeutic agents to the tumour and avoid exposure of normal tissues should substantially reduce cancer therapy-associated side effects. A paper published in *Nature Biotechnology* indicates that the use of tumour-targeted minicells (400 nm particles derived from bacteria) is one potential route to achieving specificity.

Himanshu Brahmbhatt, Jennifer MacDiarmid and colleagues previously showed that minicells can deliver chemotherapy to tumour cell xenografts with the aid of bispecific antibodies (one arm is bound to the outer membrane of the minicell and the other is specific for a tumour antigen). Given the potential therapeutic use of small interfering RNAs (siRNAs) and the difficulties associated with targeting these agents to tumours, the authors investigated whether minicells could be effective siRNA vectors. They established that siRNAs can passively accumulate in minicells and that plasmids containing short hairpin RNAs (shRNAs) can be transfected into minicells. *In vitro*, these minicells, which are coated with epidermal growth factor receptor (EGFR)-bispecific antibodies, are taken up by EGFR-expressing human tumour cells through receptor-mediated

endocytosis. Degradation of the minicell through the lysosomal pathway results in the release of active siRNAs. Indeed, minicells containing siRNAs that target the cell cycle genes polo-like kinase 1 or cyclin-dependent kinase 1 resulted in cell death *in vitro*. These minicells also proved effective in mouse xenograft models, in which they substantially suppressed tumour growth. Importantly, mice bearing tumours treated with minicells containing scrambled siRNA or minicells with CD33-bispecific antibodies did not respond, indicating that non-specific siRNA effects were not important and that tumour targeting using the EGFR-bispecific antibody was essential.

A major clinical problem for cancer therapy is drug resistance, so the authors investigated, as an example, whether shRNAs could be used to suppress expression of multidrug resistance protein 1 (MDR1). The authors treated a variant of human colon cancer Caco-2 cells that express MDR1 (and EGFR) with EGFR-targeted minicells containing shRNAs to *MDR1*. They then treated the cells with EGFR-targeted minicells containing irinotecan or 5-fluorouracil, which are exported from the cell through MDR1. Cells treated sequentially

with these agents showed significant ($P < 0.0001$) levels of cytotoxicity compared with untreated cells. Similar results were evident *in vivo*: Caco-2-MDR1 xenografts completely regressed, as did MDR1 breast cancer xenografts treated first with EGFR minicells containing *MDR1* shRNAs and then with EGFR minicells containing doxorubicin.

These results show that targeting siRNA to tumours can be achieved using tumour-targeted minicells and that the sequential deployment of siRNA and then chemotherapy might prove effective for overcoming MDR1-related drug resistance. The targeted delivery of chemotherapy also substantially reduced the amount of drug needed to elicit a cytotoxic response in the tumour cells.

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ORIGINAL RESEARCH PAPER MacDiarmid, J. A. *et al.* Sequential treatment of drug resistant tumors with targeted minicells containing siRNA or a cytotoxic drug. *Nature Biotech.* 28 Jun 2009 (doi:10.1038/nbt.1547)



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