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MOUSE MODELS

An easier option

Genetically engineered mice have contributed significantly to our understanding of cancer, but they are expensive and time-consuming to produce. Zena Werb and colleagues have developed an efficient lentiviral method for transducing mammary stem cells (MaSCs), which can be transplanted into syngeneic mice and used to replicate the phenotype of a transgenic mouse model of breast cancer.

Virus-mediated gene transfer into stem cells can potentially provide a system for high-throughput testing of gene function *in vivo*. Unlike in genetically engineered mice, tissue-specific promoters are not required. However, success to date has been limited by the low efficiency of transduction and has been restricted to genes that confer a growth advantage on the recipient cells.

The key innovation in this study was transduction in suspension rather than on solid plates, which is more efficient for several reasons, including an increase in accessible cell surface area. The authors chose an HIV-based lentiviral construct and showed that they could efficiently transduce cells with a fluorescent gene construct even in the absence of a transforming oncogene. The resulting transgenic MaSCs contributed to all epithelial lineages when transplanted into the mammary gland of syngeneic mice, and, importantly, this effect was still observed when the cells were serially transplanted to other host individuals — the stem cells were self-renewing.

The authors tested the value of their system by transducing MaSCs with a lentivirus expressing *Wnt1*. Mice that were transplanted with these cells developed hyperplasias and adenomas, followed by adenocarcinomas, that replicated the phenotype of the mouse mammary tumour virus–*Wnt1* transgenic model of breast cancer.

This technology is likely to provide a useful alternative to transgenic models that require germline modifications, and the authors' preliminary results show that stem cells from other organs can also be transduced in this way. Further work is needed to allow large genes to be transduced with lentiviral vectors, and inducible constructs are needed for those genes for which expression is detrimental to growth.

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ORIGINAL RESEARCH PAPER Welm, B. E., Dijkgraaf, G. J. P., Bledau, A. S., Welm, A. L. & Werb, Z. Lentiviral transduction of mammary stem cells for analysis of gene function during development and cancer. *Cell Stem Cell* **2**, 90–102 (2008)

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