fascicle of the temporalis muscle that arises from the infratemporal crista and the infratemporal spine of the sphenoid bone. In 1955 a detailed study of the origin, insertion and function of the temporalis muscle was published by W. Zenker[5]. He dissected cadaveric heads in both the frontal and horizontal planes and showed that the most medial attachment of this muscle extends over the maxillary surface of the sphenoid bone toward the foramen rotundum. It was named "the medial portion of the temporalis muscle." Other descriptions of the muscle including functional studies also exist (in German)[6–8].

Times have changed. Whereas today the vast majority of research papers are published in English, this was not always the case — something we should remember when researching all fields but particularly those that were active so many years ago.

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Retrovirus-mediated *p53* gene therapy

To the editor — We read with interest the report of partially successful retrovirus-mediated wild-type *p53* gene therapy for lung cancer[1] and wish to draw attention to our own observations on the fate of retrovirally transduced wild-type *p53* sequences.

p53-null mouse embryo fibroblasts were infected with a retrovirus expressing wild-type human *p53*, selected in puromycin and tested at regular intervals with a *p53* functional assay that quantitatively measures mutant *p53* RNA content[2,3]. Two days after infection we observed background values of mutant *p53* content. The mutant content then rose rapidly with each passage, reaching 60–80% at passage five. The simplest explanation for this rapid counter selection of wild-type *p53* expression is that RNA polymerase II and reverse transcriptase introduced mutations into the *p53* in the virus and that cells transduced with these mutants have a significant survival or growth advantage. The fraction of input virus containing inactivating *p53* mutations is difficult to infer from our data, but it could plausibly exceed 1% (ref. 4, 5). This is an irreducible mutant burden, and given the rapid selection of these mutants in our model system, the wisdom of using retroviruses for *p53* gene therapy is questionable. Indeed, one predicted late side effect of introducing mutant *p53* into large populations of normal cells would be to promote the development of new tumors through a trans-dominance mechanism.

We conclude that the use of retroviruses for any form of gene therapy where there is strong selection against wild-type protein activity is unlikely to produce lasting benefit.

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Roth replies — The relevance of the model system used by Estreicher and Iggo to human cancer is questionable at best. The use of the easily transformed mouse embryo fibroblasts combined with puromycin selection would be expected to result in cells that inactivate *p53* by mutation or deletion. Others have shown that when wild-type *p53* is transfected into cells and those cells are placed under selective pressure, the few colonies that result are able to grow because of induced mutations in *p53* (ref. 6).

However, the situation in studies of gene transfer *in vivo* and in clinical trials is quite different. Short-term expression of wild-type *p53* is sufficient to induce apoptosis. Bystander effects also apparently contribute to amplified tumor cell death. Production of retroviral vectors expressing *p53* has shown no accumulation of transforming mutants as shown by an NIH 3T3 focus-forming assay or inactive vector preparations that would indicate overgrowth of retroviruses with mutant or deleted *p53*. Estreicher and Iggo should recall that *p53* is a tumor suppressor gene and not a dominant oncogene. Its mutant form alone does not have transforming activity except for a very limited number of mouse cell lines[7]. Their observations also highlight the usefulness of *in vivo* experiments and clinical trials to assess safety and efficacy in the most relevant context.

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LETTERS TO THE EDITOR

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