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# Gene therapy by mRNA stabilization?

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Successful gene therapy for cancer requires effective targeting of viruses that replicate only in tumor cells, but selective gene expression with adenoviral vectors has been difficult to achieve. Expression of various tumor-associated proteins is significantly enhanced in many tumors, partly by stabilization of their mRNAs through adenosine-uridine rich sequences in the 3' untranslated regions (UTRs). In a June 8 advanced online publication from Nature Biotechnology, Atique Ahmed and colleagues at the Mayo Clinic show that tumor-cell-selective stabilization of mRNA can be used to control therapeutic gene expression in viral vectors used for cancer gene therapy (*Nature Biotechnology,* DOI:10.1038/nbt835, June 8, 2003).

Ahmed *et al.* created a conditionally replication-competent adenoviral vector in which expression of the essential E1A gene is regulated by ligation of its mRNA to the 3' UTR of PTGS2 (also known as COX2), allowing stabilization of the mRNA specifically by activated Ras/ MAP kinase signalling. They observed that the Ad-E1A-COX virus is preferentially oncolytic *in vitro* in human tumor cells with high MAP kinase activity. *In vivo*, the Ad-E1A-COX virus was at least as effective as wild-type viruses in tumors expressing high levels of MAP kinase, but it generated no significant therapeutic effects in tumors expressing low levels of MAP kinase.

"To our knowledge a replicating (adeno)virus whose tumor selectivity is based upon control of gene expression at the level of mRNA stability has not been described previously. This strategy has great potential for expansion, because there are many different genes whose 3' UTRs control selective mRNA stability under different physiological, pathological and tumor-associated conditions," conclude the authors.

# References

1. Post-transcriptional regulation of gene expression by degradation of messenger RNAs.

2. *Nature Biotechnology*, [http://www.nature.com/nbt/]

3. Mayo Clinic, [http://www.mayo.edu/]