

 GENOME ENGINEERING

# Breakneck evolution

Modifying genomes remains an arduous task that largely involves tinkering with one gene at a time. However, a new large-scale genome engineering approach — termed multiplex automated genome engineering (MAGE) — allows multiple mutations to be introduced simultaneously in a genome and promises to bring unprecedented flexibility and speed to metabolic engineering efforts and laboratory studies of evolution.

The technique simply involves introducing into cells a pool of single-stranded oligonucleotides that are complementary to a target sequence: these bind to a target on the lagging strand during DNA replication and bring about allelic replacement, which produces mismatches or indels. Because pools are varied and are introduced simultaneously during cell growth, many changes can be induced across a chromosome and across the population.

The efficiency of the allelic replacement depends on the number of sequences to be targeted, the diversity of the pool and the degree of homology between the oligonucleotide and its target — if the match is precise, mutations are introduced in a targeted manner, but if the oligonucleotide is degenerate, a more diverse set of changes is introduced.

This tunable property was tested in *Escherichia coli*, in which 24 genetic components of a biosynthesis pathway were modified simultaneously to increase lycopene production fivefold in just 3 days.

MAGE is an inexpensive way of rapidly producing vast numbers of combinatorial variants and, because it is automated and relies on widespread ssDNA interactions, it should be easy to adapt to other organisms.

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**ORIGINAL RESEARCH PAPER** Wang, H. H., Isaacs, F. J. et al. Programming cells by multiplex genome engineering and accelerated evolution. *Nature* 26 Jul 2009 (doi:10.1038/nature08187)