# TOOLS IN BRIEF

MODEL ORGANISMS

## Editing the fish genome

The lack of robust methods for targeted modification of the zebrafish genome has impeded many studies in this important vertebrate model organism. Engineered nucleases have been used to mutate the fish genome via the nonhomologous end-joining repair pathway, but genome editing by homology-directed repair (HDR) has so far proven elusive in this organism. Bedell *et al.* now demonstrate that transcription activator–like effector nucleases (TALENs) based on the GoldyTALEN scaffold are effective tools for editing the fish genome. They achieved biallelic mutations at several loci that recapitulate morpholino-generated loss-of-function phenotypes and that are transmitted through the germ line. In separate experiments, they used single-stranded oligonucleotides as donor templates for HDR-based introduction of sequences, including *loxP* sites, at targeted locations of the zebrafish genome.

Bedell, V.M. *et al. Nature* advance online publication (23 September 2012).

GENETICS

## Accelerated GWAS

Attempts to associate human disease with underlying genetic variation have been buoyed by a rising tide of genotyping data. At the same time, powerful methods are needed to tease out real associations from those due to the cryptic relationships and shared ancestry found in large-sample studies. Mixed models can remove these confounding effects but are computationally demanding, thus leading to recent efforts to improve their efficiency. Svishcheva *et al.* introduce GRAMMAR-Gamma, which is based on a fast approximation of the powerful FASTA method. The approach renders computational time linear rather than quadratic with respect to the number of individuals. Tests on synthetic and real data demonstrate that millions of nucleotide variants can be rapidly analyzed from large-sample data sets.

Svishcheva, G.R. *et al. Nat. Genet.* **44**, 1166–1170 (2012).

MOLECULAR ENGINEERING

## PSmOrange2

Photoswitchable fluorescent proteins (PSFPs) are widely used for tracking intracellular proteins or cells, and they are important probes for super-resolution microscopy. Most PSFPs change from emitting green to red fluorescence upon irradiation with phototoxic violet light; but recently a fluorescent protein (PSmOrange) was developed that can be photoswitched with visible light from orange to far red, which represents the most red-shifted excitation peak of all GFP-like fluorescent proteins. Building on that work, Subach *et al.* now report a new version of PSmOrange with ninefold higher photoconversion contrast and tenfold faster photoswitching kinetics. PSmOrange2 can be efficiently photoswitched with common two-photon lasers and via fluorescence resonance energy transfer (FRET) from green fluorescent donors—an effect that the authors call 'FRET-facilitated photoswitching' and that they demonstrate using several sets of interacting proteins.

Subach, O.M. *et al. J. Am. Chem. Soc.* **134**, 14789–14799 (2012).

MODEL ORGANISMS

## A comprehensive database of poly(Q) mouse models

The polyglutamine (poly(Q)) family of neurological disorders—which includes Huntington's disease, spinal muscular atrophy and spinocerebellar ataxias, among others—is characterized by the expansion of CAG repeats in the coding region of causative genes. To date, more than 100 poly(Q) mouse models have been created, which makes it difficult to find, compare and translate the information between them. To aggregate information about this valuable resource, Figiel *et al.* and Switonski *et al.* collected and analyzed the body of data related to behavioral, molecular, cellular and anatomical characteristics of poly(Q) mouse models (Figiel *et al.*, 2012) as well as the *in vivo* experimental therapeutic approaches used to treat them (Switonski *et al.*, 2012). The data have been compiled in two review articles and corresponding Excel tables for easy navigation.

Figiel, M. *et al. Mol. Neurobiol.* **46**, 393–429 (2012); Switonski, P.M. *et al. Mol. Neurobiol.* **46**, 430–466 (2012).