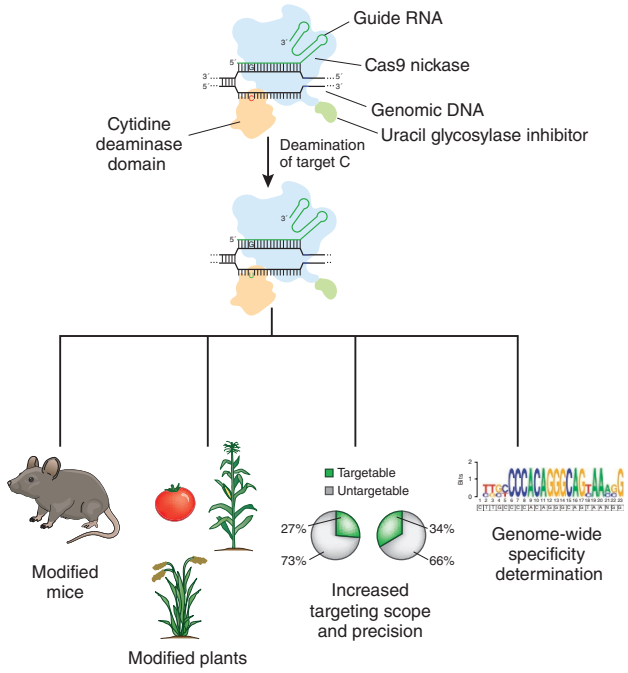

Figure 1 New developments in base editing technology. Point mutations are introduced into mice[7] and plants (maize[6], rice[5,6], tomato[5], wheat[6]). The targeting scope and precision of base editors are improved using orthologous and engineered proteins[3]. Potential off-target activity is measured genome-wide[4].

created by the base editor deaminase are converted to DNA breaks with uracil DNA glycosylase and endonuclease VIII. They identify biochemically, on average, fewer potential off-target sites for the base editor than the equivalent Cas9 nuclease, but similar numbers of sites show activity in cells for both methods. They also find sites that are uniquely modified by either the base editor or nuclease, suggesting mechanistic differences in the way that DNA is recognized and modified.

Future experiments exploring background genome-editing activity in different cell types, particularly those that activate deaminases during somatic hypermutation or during an anti-viral response, will be of great interest. Ultimately, the measure of whether any genome editing system can be considered safe for therapeutic development will rely on relevant functional assays run using appropriate cell types and animal models.

Finally, Shimatani *et al.*[5], Zong *et al.*[6], and K. Kim *et al.*[7] provide the first evidence that base editing can be used to engineer mutations into whole organisms. Shimatani *et al.*[5] introduce herbicide resistance into rice by mutating one nucleotide in the acetolactate synthase (*ALS*) gene, and insert heritable homozygous mutations into two hormone-regulating genes (*DELLA* and *ETR1*) in tomatoes. Zong *et al.*[6] make point mutations in multiple genes in rice, wheat, and maize protoplasts, some of which contain multiple C to T substitutions within the active 5-base window; plants regenerated from these cells contain similar distributions of mutations. In both studies[5,6], insertions and deletions are only rarely detected, and C to T substitutions are the predominant form of mutation.

These two reports raise exciting prospects for creating new plant varieties with improved properties. But for rapid commercial development it will be necessary to provide base editors to cells not on plasmids, as demonstrated, but in the form of ribonucleoproteins or mRNA, to ease regulatory concerns around integration of exogenous DNA into the genome.

Delivery of base editors as pre-assembled ribonucleoproteins or mRNA–sgRNA pairs is demonstrated by K. Kim *et al.*[7]. They incorporate disease-associated mutations into the dystrophin and tyrosinase genes of mouse embryos and, as with Cas9 nuclease in the form of ribonucleoprotein or mRNA, the efficiencies achieved are very high (40–100%). Importantly, unlike animals created with nucleases, there is very little evidence of mosaicism in F0 animals. This is a key advantage of base editing and should facilitate the generation of animal disease models and engineering of desired traits into livestock.

The high editing efficiency and low background activity in this study also lead K. Kim *et al.*[7] to raise the possibility of using base editing to correct disease-related genetic variants in human embryos. As genome editing tools continue to improve, the impetus to use them in human embryos both for therapeutic purposes and for research into the genetics of early development will increase. The controversial nature of these applications will require rigorous ethical oversight.

Base editing looks set to follow the same path of rapid technology development as occurred with Cas9, but with the benefit of lessons learned over the past five years. Optimization of editing activity and specificity should lead to therapeutic applications in the not-too-distant future. In the research arena, applications to pooled genetic screens, to engineering cells containing multiple mutations, and to gain- and loss-of-function *in vivo* models will accelerate progress toward unraveling mechanisms of complex genetic diseases.

COMPETING FINANCIAL INTERESTS
The author declares competing financial interests: details are available in the online version of the paper.

1. Komor, A.C., Kim, Y.B., Packer, M.S., Zuris, J.A. & Liu, D.R. *Nature* **533**, 420–424 (2016).
2. Nishida, K. *et al. Science* **353**, 919–921 (2016).
3. Kim, Y.B. *et al. Nat. Biotechnol.* **35**, 371–376 (2017).
4. Kim, D. *et al. Nat. Biotechnol.* **35**, 475–480 (2017).
5. Shimatani, Z. *et al. Nat. Biotechnol.* **35**, 441–443 (2017).
6. Zong, Y. *et al. Nat. Biotechnol.* **35**, 438–440 (2017).
7. Kim, K. *et al. Nat. Biotechnol.* **35**, 435–437 (2017).
8. DeWitt, M.A. *et al. Sci. Transl. Med.* **8**, 360ra134 (2016).
9. Dever, D.P. *et al. Nature* **539**, 384–389 (2016).

Research Highlights

Papers from the literature selected by the Nature Biotechnology editors. (Follow us on Twitter, @NatureBiotech #nbtHighlight)

A DNA-based T cell receptor reveals a role for receptor clustering in ligand discrimination
Taylor, M.J., Husain, K., Gartner, Z.J., Mayor, S. & Vale, R.D. *Cell* **169**, 108–119.e20 (2017)

Temporally precise labeling and control of neuromodulatory circuits in the mammalian brain
Lee, D. *et al. Nat. Methods* doi:10.1038/nmeth.4234 (2017)

Self-assembly of genetically encoded DNA-protein hybrid nanoscale shapes.
Praetorius, F. & Dietz, H. *Science* **355**, eaam5488 (2017)

Antisense oligonucleotide therapy for spinocerebellar ataxia type 2
Scoles, D.R. *et al. Nature* **544**, 362–366 (2017)

Therapeutic reduction of ataxin-2 extends lifespan and reduces pathology in TDP-43 mice
Becker, L.A. *et al. Nature* **544**, 361–371 (2017)