Viewpoint: Why we shouldn’t be deterred by CRISPR’s ‘rollercoaster year’

Despite spooking investors, new insights into DNA repair and the CRISPR gene-editing system are part and parcel of its progress from research tool to human therapy.

It’s been a rollercoaster year for companies developing CRISPR gene-editing therapies. In January, a study posted on the preprint server bioRxiv raised concerns about the potential immunogenicity of CRISPR–Cas9. In March, Nature Methods retracted a study that had suggested unexpected extensive off-target mutations arising from Cas9 activity in mice. In June, two studies in Nature Medicine revealed a role for the tumor suppressor protein p53 in antagonizing Cas9 genome editing. Now a study published in our pages by Allan Bradley and colleagues reports that in addition to off-target mutations, Cas9 can sometimes induce extensive on-target DNA damage, including large deletions, inversions and insertions.

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Many companies are already exploring solutions to these concerns. At UMass’ RNA Therapeutics meeting in May, Caribou Biosciences disclosed efforts to address off-target issues by chemical modifications and base substitutions in the guide RNA. Others are improving the specificity of Cas9 through combined rational design, directed evolution and screening for more selective variants.

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[O]ur knowledge of CRISPR–Cas gene editing and DNA repair is progressing. The picture may not be as clear as we would like. But rarely in biology does anything turn out to be as neat and simple as we imagine.

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