generation" around which a new forest will grow by itself. A comparison of 13 experimental sites in Costa Rica by Andy Kulikowski and Karen Holl of the University of California, Santa Cruz, showed this approach, called "applied nucleation," can be as good or better at promoting the regrowth of a diverse forest than densely planting an entire area with one or just a few species. Nucleation allows more space for the trees as well as light, says forest ecologist Robin Chazdon of the University of the Sunshine Coast (USC), a co-editor of the special issue: "Trees like that!" But forests can even recover all on their own. Since 1997, Chazdon has monitored a former pasture in northern Costa Rica where not a single tree was planted. A healthy natural forest has sprung up.

How reforestation affects local people—and vice versa—is an important factor in planning a project. Reforestation can reduce the land available for farming, but local communities can be compensated—and the new forest can provide timber, wildlife hunting opportunities, and other sources of income. "We need to make sure restoration is beneficial and wanted by local communities," Banin says.

University of York conservation scientists Robin Loveridge and Andrew Marshall, also at USC, studied the well-being of people involved in reforestation projects in eastern Tanzania. They compared the satisfaction of people who sell timber certified as sustainable with that of communities that did not have a sustainability program. The better a forest was managed, the happier those doing the managing were, the team found. "It's not just about getting the ecological dynamics right, but also the social and economic dynamics," Cook-Patton says.

Many other issues need attention as well, says Marshall, also a co-editor of the theme issue. They range from the role of lianas and vines—which can both hamper reforestation by hindering light and help it by offering protection from storms—to how to measure success and manage the projects. The answers will depend on local conditions. "You can have a trillion dollars," says Bill Laurance, a forest ecologist at James Cook University, Cairns, "but there's no simple answer that fits all."

Forest ecologist Simon Lewis of University College London is excited about the momentum behind reforestation but worries about the quality of the new forests. "There is a risk that as countries try to meet tough targets on curbing deforestation, old-growth forests are still cut but are replaced elsewhere," Lewis says. That means no net deforestation, "but a high-carbon, high-biodiversity forest is replaced by lower carbon and lower diversity forest." ■

GENE EDITING

'Ancestry problem' sends CRISPR astray in some people

Reference genomes used to direct the gene editor fail to account for human diversity in those of African descent

By **Jocelyn Kaiser**

The 10-year-old gene-editing tool known as CRISPR is indispensable for engineering plants, tailoring lab animals, and probing basic biology. But there's a caveat when it is used to tweak human genes: Unlike lab mice, which are usually inbred and genetically identical, people's genomes differ individually and by ancestry.

These ancestry differences mean CRISPR doesn't always edit some genomes as intended, particularly in people of African descent, whose genomes are most likely to differ from those used to steer CRISPR to a specific gene. A new analysis finds that failing to account for ancestry slightly skewed a massive sweep for cancer genes, causing it to miss genes important as drug targets in those of recent African descent.

The study, posted online, "shows a clear example of this [ancestry] problem," says computational biologist Luca Pinello of the Harvard University–affiliated Massachusetts General Hospital, who has also studied the issue. He and the scientists behind the new work propose tools to avoid it.

To edit a human gene, scientists first design a short strand of RNA to match part of the gene's DNA sequence. This guide RNA then leads CRISPR's DNA-snipping enzyme to the right spot. If the guide RNA doesn't closely match the genome being edited, CRISPR may not make the desired cut.

The guide RNAs are usually based on a reference genome compiled from just a few people's DNA that doesn't fully capture human diversity. And people with African ancestry are more genetically diverse than Europeans or Asians, whose ancestors left Africa and spread across the globe only relatively recently.

Ancestry issues with CRISPR were first reported 5 years ago, but Sean Misek, a postdoc at the Broad Institute of MIT and Harvard and lead author of the new preprint, wanted to explore them in cancer biology. His team turned to the Cancer Dependency Map, a collaboration that used CRISPR to systematically knock out roughly 18,000 genes in 1000 lines of cancer cells grown from individual human tumors. The project looked for genes involved in cancer growth or survival that could be targeted with drugs.

The team, which included senior authors Jesse Boehm at the Massachusetts Institute of Technology and Broad and Rameen Beroukhim of Broad and the Dana Farber Cancer Institute, found CRISPR failed to knock out 2% to 5% of the 18,000 genes in an individual cell line. These errors were about 20% more common in the 41 cell lines from people with recent African ancestry than in other groups, the team reports. As a result, "We're missing [cancer drug] targets in individuals of African descent," Misek says.

Similarly, Pinello's lab and others have shown how ancestry mismatches can cause CRISPR to cut the genome in the wrong spot when it is used to treat diseases such as sickle cell disorder, which mainly affects people of African ancestry. Such off-target cuts could lead to cancer. The CRISPR ancestry problem is an example of how excluding diverse populations in genomics studies "may inevitably contribute to cancer health inequity," says translational cancer biologist Olorunseun Ogunwobi of Hunter College of the City University of New York.

Both teams have built free web tools that compare a proposed guide RNA with tens of thousands of genomes procured from diverse populations. Ancestrygarden.org from the Boehm and Beroukhim labs lets users assess the impact of ancestral diversity on standard CRISPR guide RNAs. And CRISPRme from Pinello's team checks for off-target matches. "The hope here is that we push people to rethink how they're using CRISPR in the laboratory," Misek says.

"This is an important issue," and the web tools should help, says Melissa Davis, a genomicist who studies disparities in breast cancer at Weill Cornell Medicine. Adam Phillippy of the National Human Genome Research Institute agrees. "It is exactly tools like this—tools that make human genomic variation easy to explore and understand—that can help alleviate the bias in the first place." ■

Downloaded from https://www.science.org at Shanghai Normal University on November 25, 2022

Science

‘Ancestry problem’ sends CRISPR astray in some people

Jocelyn Kaiser

Science, 378 (6622), • DOI: 10.1126/science.adf8991

View the article online
https://www.science.org/doi/10.1126/science.adf8991
Permissions
https://www.science.org/help/reprints-and-permissions

Downloaded from https://www.science.org at Shanghai Normal University on November 25, 2022

Use of this article is subject to the Terms of service

Science (ISSN 1095-9203) is published by the American Association for the Advancement of Science. 1200 New York Avenue NW, Washington, DC 20005. The title *Science* is a registered trademark of AAAS.
Copyright © 2022 The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. No claim to original U.S. Government Works