

COMMENTARY

PERSPECTIVES

BIOTECHNOLOGY

Driving forward the restoration of an American icon

Genome-informed breeding and new transformation approaches could improve disease resistance of the American chestnut tree

Steven H. Strauss and Gancho T. Slavov

The American chestnut tree (*Castanea dentata*) nearly died off a century ago when the fungal pathogen *Cryphonectria parasitica* decimated chestnut forests across the eastern United States. The loss had large effects on Indigenous and European settler populations as well as on numerous wild species. Restoration efforts have been nearly as long, pursued by scientists and advocated by rural and urban forest lovers alike. Early attempts focused on traditional hybridization-based breeding methods with disease-resistant Asian chestnuts. Over the past several decades, genetic engineering became a prominent approach to producing blight-resistant trees. On page 730 of this issue, Westbrook *et al.* (1) report the genomic and physiological basis of blight resistance and describe how genes and genomes that contribute to resistance could be bred or transformed into the American chestnut. The analyses point to ways of accelerating the repopulation of the Appalachian forests where the American chestnut once thrived.

The main approach used over the past century has been hybridization of the American chestnut to the blight-resistant Asian chestnuts, *Castanea mollissima* and *Castanea crenata*. This strategy has been invigorated by the incorporation of advanced omics tools, including comparative genomics, transcriptomics, and metabolomics. Such studies have identified a wide variety of genes and associated metabolites or mRNAs—many with a known function in biotic resistance (to a biological threat, such as a microbe or insect)—that are differentiated in their presence or expression between the two species. For example, among the many differentially expressed metabolites, lupeol, a triterpene sterol present in the bark of the Chinese chestnut species, almost completely inhibited chestnut blight fungal growth in laboratory assays. Given the widespread success of terpenoid engineering in diverse plants (2), it is possible that editing of the lupeol

Restoring the American chestnut requires a multifaceted approach to revive a species that was wiped out by a blight in the early 20th century.

pathway-associated genes in the American chestnut, and/or engineering the Chinese strain's genes into the American chestnut genome, could enhance this potential mechanism of resistance.

Using both family-based linkage mapping and population-based association mapping (3) with a genome-wide set of markers (of specific and variable DNA sequences), Westbrook *et al.* studied the associations of chromosome segments with blight resistance. Although some significant associations between genomic regions and blight resistance (called quantitative trait loci) were discovered because of small and variable effect sizes, the specific markers for these regions would not be very useful in breeding programs. It is also very difficult to conclusively determine the causative genes in these regions. Westbrook *et al.* conducted a genome-wide association study (GWAS) for this purpose, but gene identification is challenging in chestnut and other forest trees because sample sizes are typically too small to detect the inherently weak effects of loci underlying complex traits, and genetic architectures usually differ among families and populations (4). By contrast, indirect selection using a large set of random genome markers rather than phenotypes (“genomic selection”) tends to be more useful. However, this will be effective only in the presence of strong population structure (when a population is not a homogeneous mix but has distinct genetic subgroups, as is found in most natural populations of forest trees), or if there is genetic relatedness, as is typical for breeding populations (5). Moreover, because breeding and phenotyping of partially resistant trees is slow, imprecise, and costly—requiring several years to assess the relevant age-related susceptibility in the field—genomic selection could potentially enhance the rate and efficiency of breeding. This benefit could be amplified by recently developed “speed breeding” methods effective in chestnut trees (6). Although the economic feasibility of genomic selection in tree breeding remains

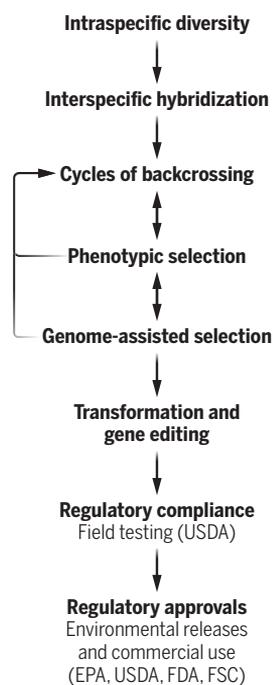
an open question because of the high cost of genotyping, the results of Westbrook *et al.* clearly indicate that even a small to moderate set of genome-wide markers (e.g., below 10,000) could be used effectively to trace Asian chestnut ancestry and thus speed advanced-generation breeding for genetic resistance to the blight.

The genes identified by Westbrook *et al.* also provide a path forward for expanding transformation-based approaches, including gene editing and gene transfer. Starting in 1997 (7), studies on the overexpression of a gene encoding oxalate oxidase (OxO), an enzyme that breaks down the potent fungal toxin oxalic acid, suggested that it could be an avenue for producing fully resistant trees (8). The gene came from wheat, but the enzyme is widely present among plants, which ensures a high degree of nutritional safety for consumption of the chestnuts. The mechanism of OxO action also suggests that it may provide sustainable resistance because the OxO-encoding gene does not prevent the blight fungus from living on dead tissues, such as outer bark and discarded branches. Unfortunately, data presented by Westbrook *et al.* suggest that resistance in the field might be unstable or incomplete—and interfere with plant growth—casting doubt on the effectiveness of this approach. Fortunately, the findings of Westbrook *et al.* suggest several other potential genes to explore. For example, analysis of genes with increased expression in response to blight inoculation showed the involvement of diverse physiological pathways, including folate transporters and monoterpene, panthothenate, and flavonoid biosynthesis, among others. Modifying the activity of one or several of these pathways could be accomplished through various transformation approaches. Surveys show that most of the public and forest-interested parties in the United States support breeding and biotechnology-based approaches to American chestnut restoration (9).

What is perhaps most exciting about the study of Westbrook *et al.* is the proposal to pursue not one but any and all methods that make biological sense—transgenic, gene-edited, genomic, conventional breeding, or otherwise—to restore this nearly extinct and beloved keystone species (see the figure). There may not be a “silver bullet” for resistance as OxO was once thought to be; given the complexity of the resistance mechanisms that Westbrook *et al.* have uncovered, multiple transgenes and/or gene edits may need to be used in combination with diverse breeding products. However, advanced gene editing and transgenic approaches face serious obstacles. The chestnut tree genome remains difficult to transform or edit, and required containment makes it difficult to conduct experimental field trials at the scale needed to explore diverse transformation products and integrate them into breeding programs in a timely manner. Although the commercial release of American chestnut trees with the OxO gene in the United States has been intensively discussed with regulators for decades, and petitions for commercial use have been awaiting decisions by the US Department of Agriculture, the Environmental Protection Agency, and the Food and Drug Administration for several years, it is unclear whether and when all final approvals will be granted (and this would only be for a single OxO gene insertion). Currently, genetically modified organisms that contain any DNA from outside the sexual gene pool, or those that contain more than simple edits of native genes, must be fully contained and intensively inspected

An integration framework

The scheme depicts a pathway to efficiently produce disease-resistant American chestnut trees. It combines breeding with resistant Asian chestnuts, genomic analysis, advanced tools of gene editing and gene transfer, and calls for regulations and market reforms in the United States that allow open field trials and enable rapid commercial use.



EPA, Environmental Protection Agency; FDA, Food and Drug Administration; FSC, Forest Stewardship Council; USDA, United States Department of Agriculture.

by federal regulators during development. Yet in 2016, the US National Academy of Sciences (10) again stated that the method is no more concerning than conventional and unregulated forms of genetic modification. The continued focus on the method in regulation, rather than the trait and its value-risk proposition, severely hampers research and breeding with transformation-based innovations of all types.

The requirement for containing nearly all forms of genetically modified plants puts large constraints on field studies. Because tree pollen and sometimes seeds can disperse great distances, this generally means that only a few large trees, whose flowers can be bagged or removed, can be studied. Researchers usually cut the trees down before they are sexually mature to avoid the costs of bagging and the attendant legal risks of a missed set of flowers, which prevents evaluation of long-term effects. To evaluate the diversity of transformation-associated genes from Asian chestnuts identified by Westbrook *et al.*, regulatory and market certification (11) systems are needed in the United States that help, not hinder, extensive field research with diverse genes.

Despite decades of work, producing a blight-resistant American chestnut tree that can fully compete in natural forest settings has been unsuccessful. What is needed now are long-term, multigenerational projects that leverage the most advanced technologies available, including genomic selection, gene editing, and gene transfer. Climate change has also now put many other forest tree species under threat of loss or potential extinction, for which biotechnology-based approaches can be useful (12). Unfortunately, despite popular support (9), transformation-based approaches face major governmental and/or market barriers, even when using chestnut-derived genes

and gene edits. Establishing a new, more comprehensive model for restoring the American chestnut on the basis of all the available science—and that addresses legal and market-based obstacles—would pave the way to address a growing list of threatened species that are environmentally, economically, and culturally important. □

REFERENCES AND NOTES

1. J. W. Westbrook *et al.*, *Science* **391**, 730 (2026).
2. X. Liu, P. Zhang, Q. Zhao, A. C. Huang, *J. Integr. Plant Biol.* **65**, 417 (2023).
3. L. R. Cardon, J. I. Bell, *Nat. Rev. Genet.* **2**, 91 (2001).
4. G. T. Slavov, D. Macaya-Sanz, S. P. Difazio, G. T. Howe, *Proc. Natl. Acad. Sci. U.S.A.* **122**, e2425691122 (2025).
5. D. Grattapaglia, *Forests* **13**, 1554 (2022).
6. T. Klak *et al.*, *Plant Direct* **9**, e70129 (2025).
7. W. A. Powell, A. E. Newhouse, V. Coffey, *Cold Spring Harb. Perspect. Biol.* **11**, a034587 (2019).
8. A. E. Newhouse, W. A. Powell, *Conserv. Sci. Pract.* **3**, e348 (2021).
9. J. D. Petit, M. D. Needham, G. T. Howe, *Risk Anal.* **42**, 470 (2022).
10. National Academies of Sciences, Engineering, and Medicine, *Genetically Engineered Crops: Experiences and Prospects* (National Academies Press, 2016).
11. S. H. Strauss *et al.*, *Science* **365**, 767 (2019).
12. J. M. LeBoldus *et al.*, *Annu. Rev. Phytopathol.* **62**, 309 (2024).

ACKNOWLEDGMENTS

We thank the late William Powell for his extensive contributions to forest restoration.

10.1126/science.aee8977

College of Forestry, Oregon State University, Corvallis, OR, USA.
Email: steve.strauss@oregonstate.edu



Driving forward the restoration of an American icon

Steven H. Strauss and Gancho T. Slavov

Science **391** (6786), . DOI: 10.1126/science.aee8977

View the article online

<https://www.science.org/doi/10.1126/science.aee8977>

Permissions

<https://www.science.org/help/reprints-and-permissions>

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 © 2026 The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. No claim to original U.S. Government Works