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The Power and Perils of De Novo Domestication Using Genome Editing

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Keywords

genome editing, plant developmental genetics, climate change, ethnobotany, plant domestication

Abstract

There is intense interest in using genome editing technologies to domesticate wild plants, or accelerate the improvement of weakly domesticated crops, in de novo domestication. Here, we discuss promising genetic strategies, with a focus on plant development. Importantly, genome editing releases us from dependence on random mutagenesis or intraspecific diversity, allowing us to draw solutions more broadly from diversity. However, sparse understanding of the complex genetics of diversity limits innovation. Beyond genetics, we urge the ethical use of indigenous knowledge, indigenous plants, and ethnobotany. De novo domestication still requires conventional breeding by phenotypic selection, especially in the development of crops for diverse environments and cultures. Indeed, uniting genome editing with selective breeding could facilitate faster and better outcomes than either technology alone. Domestication is complex and incompletely understood, involving changes to many aspects of plant biology and human culture. Success in de novo domestication requires careful attention to history and collaboration across traditional boundaries.

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1. INTRODUCTION

1.1. Domestication, Crop Improvement, and De Novo Domestication

Crop domestication is the evolution of wild plants into cultivated crops through human selection. As this is an evolutionary process, crop species vary in their degree of change from their wild ancestors. We consider fully domesticated species to be those that are largely dependent on humans for survival and have highly modified traits (44). Partially domesticated species have experienced artificial selection but changed somewhat less from their wild ancestors. Variation in the extent of domestication can be attributed to the amount of time since the start of the domestication process as well as the consistency and strength of artificial selection (80). In contrast with domestication, which is a slow process occurring over thousands of years, crop improvement is the deliberate and intensive effort to improve established crops through selective breeding, primarily to advance yield in the context of intensive industrial-scale agriculture but more recently to adapt varieties to new abiotic or biotic stresses. From the early twentieth century, scientific approaches to crop improvement dramatically accelerated the rate of change in some domesticated species and contributed

Crop domestication:
the evolution of wild
plants into cultivated
crops through human
selection

Crop improvement:
the modern process of
intensive and
deliberate selective
breeding of
domesticated species

to increases in crop yields per cultivated area (36). Here, we explore a third process enabled by genome editing technologies termed *de novo* domestication, which is the directed modification and accelerated improvement of wild species or weakly domesticated crops (150). We also explore the use of genome editing technologies in trait modifications and targeted breeding of fully domesticated species.

Crop domestication is a globally varied and complex process, and it remains incompletely understood for most crops. In most cases, the path from wild ancestor to domesticated crop was not linear. Take maize, for example: People living in México domesticated maize about 9,000 years ago from the bushy wild grass *Zea mays* ssp. *Parviglumis* (teosinte) (117) (**Figure 1**). Unlike many other domesticated species, maize was domesticated only once. However, postdomestication gene flow from teosinte was instrumental in maize adaptation and diversification (50). While there were a few large-effect genetic variants strongly selected during maize domestication, many additional traits and regions of the genome were selected (28, 117). As humans moved maize from the tropics into temperate regions (**Figure 1d**), selection on morphological, physiological, and metabolic traits led to extensive diversity within maize (1, 119). Maize and many other examples demonstrate that while domestication is often presented as a linear process from a wild plant to a cultivated crop, the reality is more complex.

1.2. Genome Editing Technologies

Genome editing technologies, coupled with the discovery and mechanistic understanding of domestication genes, offer the opportunity for targeted and thus accelerated domestication and crop improvement. Although a few different genome editing technologies have been developed, the clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein (Cas) system is the most widely employed in plants. Cas proteins are bacterial DNA endonucleases that use a programmable guide RNA sequence to direct their activity. Following CRISPR/Cas characterization, the system was quickly engineered to be deployed in heterologous systems, wherein the guide RNA can be programmed to target any genomic locus, where it induces double-stranded DNA breaks. Due to error-prone nonhomologous end joining, these double-stranded DNA breaks can cause frameshift mutations by introducing small insertions or deletions in target genes during repair (30) (**Figure 2a**). Catalytically impaired Cas variants fused with domains encoding other types of proteins have allowed for more sophisticated gene manipulation in plants, such as targeted single-base editing (**Figure 2b**) and prime editing to modify multiple nucleotides (**Figure 2c**), as well as promoter activation or repression (6, 54, 70, 75, 121) (**Figure 2d**). Targeted local epigenetic modification has been used to adjust the expression of plant genes (65, 90) (**Figure 2e**). More complex inducible systems are also being explored and are likely to function in plants (134, 140) (**Figure 2f**). Subsequent engineering efforts have expanded the CRISPR/Cas tool kit considerably. Recent reviews cover this diversity more extensively (84, 129).

Improvements to crop characteristics using genome editing include examples such as soybean fatty acid ratio adjustments, tomato fruit size increases, watermelon tolerance to herbicide, and additional kernel row number in maize (5, 71, 99, 124). The above examples may represent the low-hanging fruit of improvements, as most traits have complex genetic underpinnings involving the interaction of multiple alleles and loci that are only partially understood. A particular advantage of CRISPR is that multiple guide RNAs can be multiplexed into a single transformation event, allowing engineers to target multiple loci simultaneously in a single generation (99, 145). Furthermore, the genome editing machinery may be removed in the final product, using techniques such as transient transformation, crossing away the stable transgenes after editing, or even delivery as ribonucleoproteins, potentially side-stepping controversial genetically modified organism (GMO)

De novo domestication: the directed modification and accelerated improvement of species, including wild relatives of crops and partially domesticated species, facilitated by genome editing technologies

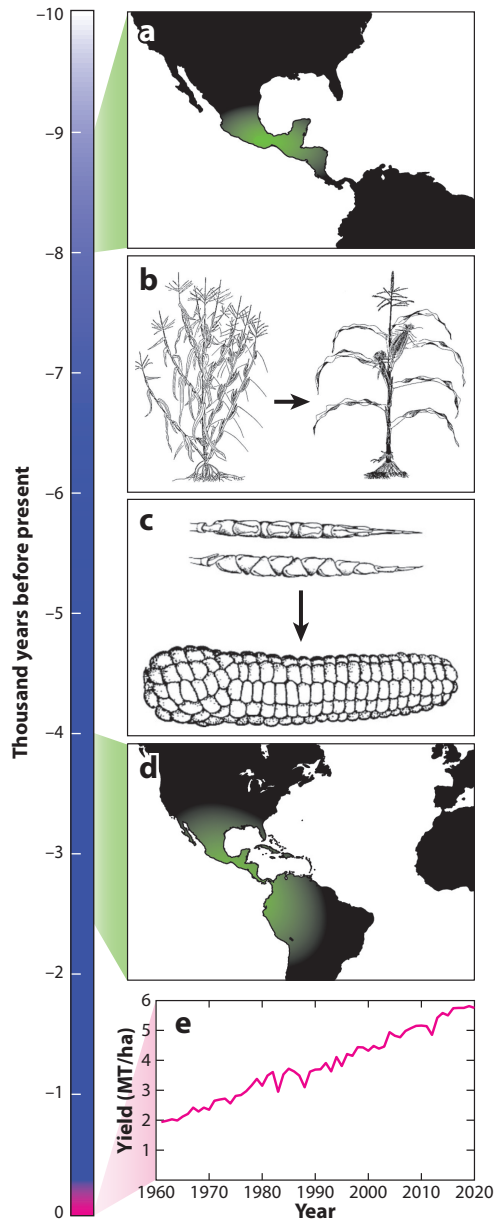


Figure 1

The process of domestication (*blue*) was long and complex for most species, as shown here for maize. Over thousands of years, maize changed morphologically (*b,c*) and expanded to agricultural environments across continents (*a,d*) under temporally and geographically varying selection (117, 119). By contrast, crop improvement (*pink*, *e*) is a modern, intensive process primarily focused on increasing yields. Panels *b* and *c* adapted with permission from Reference 28. Abbreviations: ha, hectare; MT, metric tons.

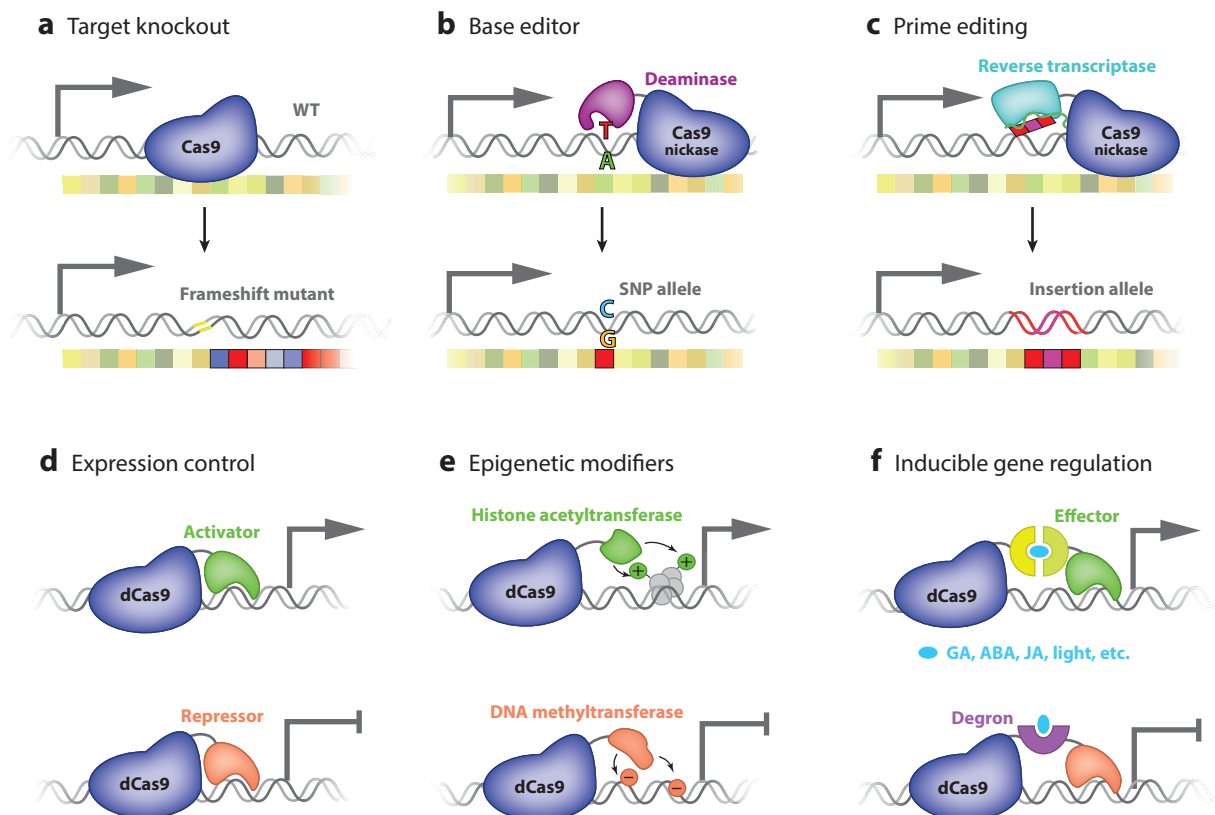


Figure 2

Genome editing technologies based on CRISPR/Cas systems. (a) The WT Cas9 protein is often used to induce targeted double-stranded breaks, which are repaired erroneously by endogenous cellular machinery that stochastically introduces small insertions or deletions, leading to frameshift mutations. (b) Cas9 variants with only single-strand nuclease activity (nickase) are used with other proteins such as deaminases to produce specific nonsynonymous SNPs. (c) Nickases can also be fused with reverse transcriptase variants and a modified guide RNA to introduce larger specific insertions or deletions. Other variants of Cas proteins are catalytically dead (dCas) and used only to guide the activity of other proteins to which they are fused (*d-f*). (d) Translational activators and repressors can be targeted to a gene's promoter region to alter expression levels. (e) Epigenetic modifiers such as histone acetyltransferases and DNA methyltransferases fuse to dCas proteins to alter chromatin and gene expression. (f) Cas constructs can be inducibly regulated, such as variants coexpressed with effectors that bind only in the presence of specific ligands. These ligands can be synthetic or endogenous, such as plant hormones, to impart temporal/spatial regulation. Degrons built into the Cas constructs can similarly eliminate the protein from cells containing the target ligand, allowing negative temporal/spatial regulation. Abbreviations: ABA, abscisic acid; Cas, CRISPR-associated protein; CRISPR, clustered regularly interspaced short palindromic repeats; GA, gibberellic acid; JA, jasmonic acid; SNP, single nucleotide polymorphism; WT, wild type.

labeling (74). These innovations offer opportunities to bring engineering solutions to market that would be otherwise infeasible using only conventional technologies.

1.3. Selective Breeding Coupled with Genome Editing Has the Potential to Be Transformative

The single most successful approach to domestication and crop improvement continues to be selective breeding. Selective breeding is the process in which breeders first assemble or generate a variable population and then select a subset of that population variation to advance to the next

generation. Direct selection on yield is accompanied by extensive indirect selection on many other traits. For example, during maize improvement in the United States and China, direct selection on yield led to indirect selection on leaf angle and tassel size (130). In this way, selective breeding offers humans the opportunity to facilitate crop adaptation to particular environments without knowing what traits are most important by “asking” the plant. Crop improvement harnessed selective breeding to the fundamentals of evolutionary theory (i.e., the modern synthesis) in the twentieth century. This is illustrated by the Illinois Long-Term Selection Experiment, which has studied continuous response to selective breeding in maize for over 100 years (85). Selective breeding has also been successful in de novo domestication, where random mutagenesis followed by selection altered domestication traits in the Australian drought-adapted grass *Microlaena stipoides* (108). Given the complexity of adaptation, selective breeding remains a powerful method for adapting species to new environments (48).

Selective breeding is a powerful technique but has limitations that may, in part, be overcome by specific advantages offered by genome editing. Selective breeding on its own can only draw from genetic diversity within a crop or closely related species and proceeds much more slowly in perennial or vegetatively propagated species than in annuals. Available genetic diversity may constrain the ability of crops to diversify and adapt to novel environments (16, 139). Genome editing technologies allow us to engineer diversity by modifying endogenous loci with intention, including the design of novel alleles that are not present in any intraspecific gene pool or, indeed, natural systems (35, 62, 99). This ability, coupled with the knowledge of plant functional genetic diversity, promises novel strategies for future crop adaptations. While genome editing technologies are still limited, their precision allows for targeted modifications that can accelerate crop improvement and domestication and, in vegetatively propagated plants, partially uncouple crop development from selective breeding (72). Thus, selective breeding and genome editing, used together, could allow for crop domestication and improvement that is faster and more successful than either technology alone.

1.4. Genome Editing Technologies Are Not a Panacea

Genome editing technologies may hold great promise to address global challenges, but as with any new technology there are potential pitfalls and limitations in their use. A recent flurry of publications (e.g., 37, 48, 144) have explored various possible benefits, as we do here. This optimism is spurred by our new capacity to enact more rapid and precise changes in plants than ever before. However, many of the problems facing our agricultural systems are not easily addressed by technological solutions, especially not on a global scale. Given that the reach of many life-saving technologies barely extends beyond a few wealthy developed nations now, de novo domesticates will likely be similarly limited unless cultural and economic issues are addressed (127). Genome editing technologies are labor- and resource-intensive and therefore limited: While we recommend that any genome editing project work to avoid genetic bottlenecks, achieving edited population sizes as diverse and numerous as their source populations is practically impossible (86). In addition, domestication is a long-term, complex process that took thousands of years in most cases (80). While crop improvement in the twentieth century has accelerated the rate of crop transformation and adaptation (**Figure 1e**), true de novo domestication, and the transformation of existing food systems, is likely to take many decades (127). However, given the profound challenges to food production we are facing because of climate change, no technology should be dismissed out of hand. De novo domestication and crop improvement using genome editing remain one important path forward in working for global food security.

Here, we discuss strategies and considerations in de novo domestication and crop improvement using genome editing. These include genetic strategies, considerations in selecting plants to focus

on in de novo domestication efforts, and ethical and ethnobotanical considerations. In addition, we briefly discuss drawing solutions from natural diversity in de novo domestication and crop improvement.

2. GENETIC STRATEGIES INFORMED BY DOMESTICATION AND EVOLUTION

2.1. Conserved Developmental Genes Are Promising Targets in Engineering Crop Architecture

Both domestication and crop improvement are complex processes that involve many modifications to plant form and physiology (1). Here, we focus on the modification of plant form, which occurs through changes in the genes and mechanisms regulating plant development. The dynamics of development, from seedling establishment to leaf initiation to inflorescence branching, impact final plant form and, in turn, crop productivity and yield (11). For example, in maize, alterations to plant development have enabled massive yield gains over the last 50 years (**Figure 1e**). Most pertinent to yield, the morphology of the maize female inflorescence has been transformed by domestication, leading to striking differences in size, flower number, and ultimately fruit (kernel) number between teosinte and maize ears (117) (**Figure 1c**). Changes to other plant traits have also been crucial in maize improvement. For example, selection acting on leaf angle has led to plants with more upright leaves, which can be planted at higher density without decreasing yield (130). As with other morphological traits, leaf angle is established over the course of development and specifically controlled by developmental genes (118). Genome editing technologies allow us to make precise changes to developmental genes and, in turn, alter plant form and improve crop yield (11).

One developmental trait that has been the focus of de novo domestication and crop improvement efforts, and that illustrates some important considerations in future efforts, is shoot apical meristem (SAM) size. The SAM is a cluster of stem cells that generates all aerial organs in vascular plants, including flowers and fruits. Meristem size is correlated with organ size and number in many plants and thus impacts yield in crops (12, 105, 141). Critically, this deeply conserved correlation between meristem size and organ size and number is mirrored by deep conservation of gene function (115). In *Arabidopsis thaliana*, the small signaling peptide CLAVATA3 (CLV3) binds to its receptor CLV1 and negatively regulates the proliferation of stem cells in the SAM (**Figure 3a**). *CLV3* and *CLV1* homologs have similar roles in deeply divergent lineages (**Figure 3b**), including tomato (separated from *A. thaliana* by more than 100 million years) and the grasses maize and rice (separated from *A. thaliana* by more than 160 million years) (61, 115). In addition, the *CLV* network has been a target of selection under domestication; an allele of a tomato *clv3* homolog is a major domestication locus (49, 141). Deep conservation of gene function means that, even in taxa where *CLV* gene function has not been determined, the *CLV* genes are reasonable targets for genome editing in many lineages, following evolution and domestication's lead.

Beyond meristem size, several conserved genetic pathways have been repeated targets of selection in domestication and improvement. Within maize, molecular parallelism underlies the convergent adaptation of different maize cultivars to highland conditions and to modern agricultural systems (130, 131). Maize and rice show substantial evidence of convergent evolution of orthologous genes, including regulators of grain production (19). During the Green Revolution, breeders targeting semidwarf stature in maize, rice, barley, and wheat repeatedly selected for variants in the gibberellin biosynthesis pathway (11). Orthologs of the stay-green *G* gene in soybean also show evidence of selection in rice and tomato, with a functional role in seed dormancy through the modulation of abscisic acid synthesis (133). Beyond domesticates, many developmental genes

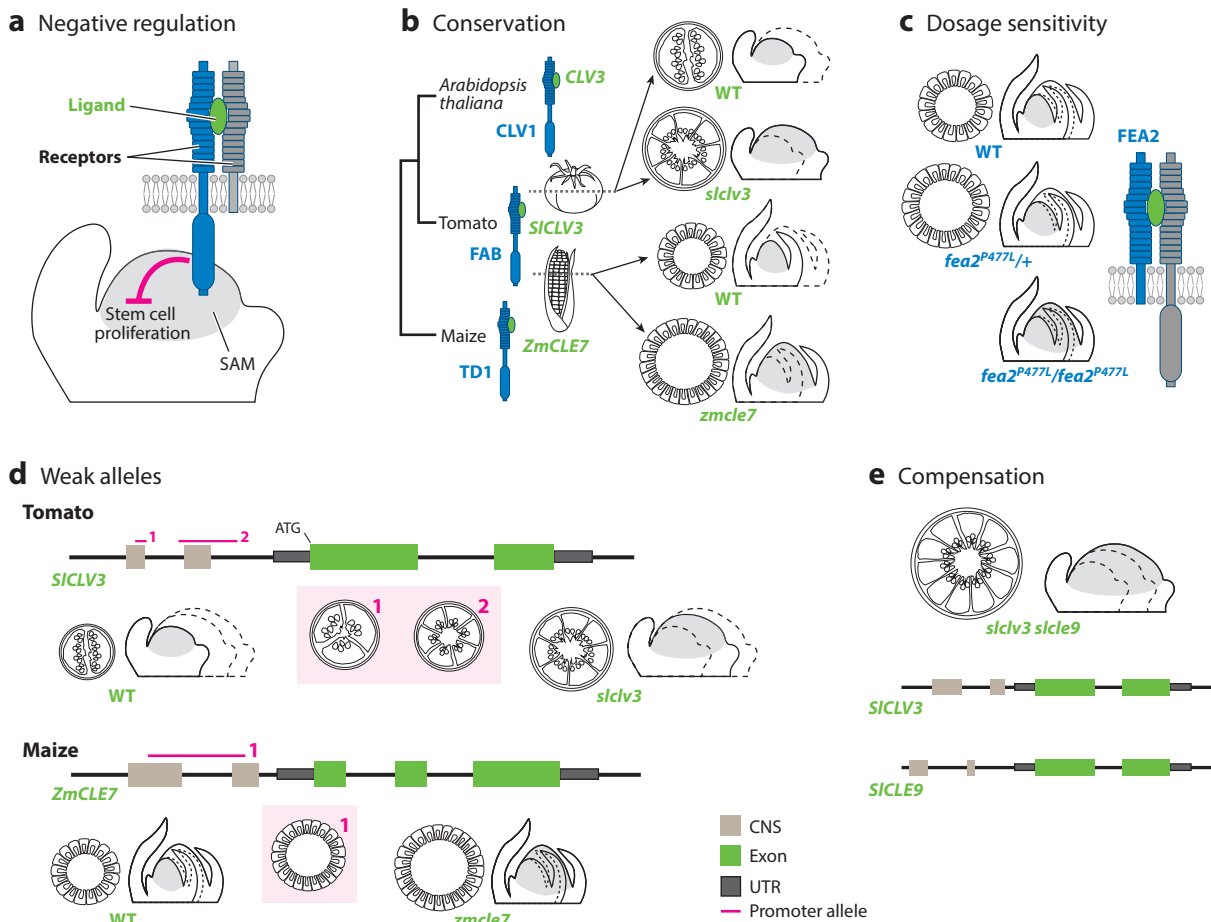


Figure 3

Genetic strategies in de novo domestication and crop improvement. (a) Negative regulators are most useful because negatively affecting gene function is easier than enhancing gene function with present genome editing technologies. The CLV3 peptide binds to its receptors, which include the leucine-rich repeat receptor-like kinase CLV1, to negatively affect stem cell proliferation in the SAM. (b) Critically, the function of CLV3 and CLV1 homologs is deeply conserved. (c) An allele of FEA2, the maize ortholog of CLV2, increases meristem size and kernel row number in the heterozygous state. (d) Editing *cis*-regulatory sequences, often detectable as CNSs in genomes, can create weak alleles and phenotypic variation that is useful in agriculture. Magenta lines indicate regions disrupted in particular alleles. Numbers indicate individual alleles and resulting phenotypes. (e) Compensating paralogs can affect the outcomes of editing focal genes. SICL9 is a close duplicate of SICLV3 that compensates for its loss. *slclv3 slcl9* double mutants have extremely fasciated meristems. Abbreviations: CLE, CLAVATA3/EMBRYO-SURROUNDING REGION; CLV, CLAVATA; CNS, conserved noncoding sequence; FAB, FASCIATED AND BRANCHED; FEA2, FASCIATED EAR2; SAM, shoot apical meristem; SICL, *Solanum lycopersicum* CLE; SICLV, *Solanum lycopersicum* CLAVATA; TD1, THICK TASSEL DWARF; UTR, untranslated region; WT, wild type; ZmCLE7, *Zea mays* CLE7.

function in similar processes across lineages. For example, the MADS-box transcription factors regulate floral organ identity in many angiosperm lineages. However, while these genes regulate similar processes, lineage-specific variation modifies precise gene function (59). Thus, detailed dissection of developmental gene function in as many lineages as possible is critical for attaining predictability in crop improvement and de novo domestication using genome editing.

Notable exceptions are found where domestication syndromes are similar between species but the responsible loci differ. For example, *TB1* is a major domestication locus in maize, but not in *Setaria italica* (foxtail millet) or rice (18, 27, 31), which has been interpreted as indicating that common mechanisms do not underlie domestication in foxtail millet and maize (37). However, *TB1* gene function is deeply conserved—well beyond the group of grasses to which maize and foxtail millet belong. *TB1* orthologs regulate axillary meristem dormancy and outgrowth in grasses and eudicots (78, 89, 132, 147). Indeed, in *A. thaliana* and maize, separated by more than 190 million years of evolution, *TB1* orthologs target orthologous genes, indicating that gene function is conserved through the deep conservation of molecular function (29, 42). Thus, *TB1* likely functions in axillary meristem dormancy and outgrowth in *Setaria italica*, but the complexity of the genetic network regulating this trait means that even when single gene mutants emerge, they may not produce phenotypes that are strong targets for selection under domestication (18). Although the nodes of genetic networks may be maintained (such as *TB1* and other conserved developmental genes), the interactions between the genes at these nodes may differ, leading to domestication loci differing between crops (18). In considering potential targets in future de novo domestication and crop improvement efforts, an in-depth view of genetic architecture and genetic interactions is important.

Null allele:

a nonfunctional gene variant

Hypomorphic allele:

a gene variant with partially reduced function

2.2. Weak Alleles Can Be Generated by Targeting Regulatory Sequences

Reducing gene function is straightforward with present technologies, whereas enhancing function is often more complex. Therefore, negative regulators are particularly attractive targets for de novo domestication and crop improvement. Again, *CLV* genes serve as a useful example because they are negative regulators of stem cell proliferation; *clv* mutants have bigger meristems and thus produce more and bigger aerial organs, including flowers and fruits (115). However, null alleles that abrogate conserved developmental gene function often result in pleiotropic, extreme phenotypes that impact many aspects of plant form. These alleles often reduce plant fitness and may not be useful in agriculture. Thus, weak (hypomorphic) alleles are often more desirable in agriculture than strong or null alleles (**Figure 3d**). Mutations that impact gene function can occur in either the coding (protein-encoding) or noncoding (gene regulatory) sequence. Weak coding sequence alleles have arisen over the course of evolution, but these are rare, in part because of negative pleiotropy associated with coding sequence alleles and because the coding sequence space of eukaryotic genomes is much smaller than noncoding sequence space. Thus, as compared to coding sequences, noncoding sequences harbor far more potential mutational targets for modulating and reducing gene expression. Indeed, noncoding alleles that impact gene expression rather than protein function have likely been much more important in natural evolution and domestication than coding alleles (81, 138). For example, noncoding alleles of the tomato *clv3* ortholog *slclv3*, created through genome editing, increase carpel number and fruit size in tomato along a phenotypic gradient, providing valuable quantitative variation likely to be useful in selective breeding (98). Similarly, weak promoter alleles of *clv3* homologs in maize increase kernel row number (71). Beyond the *clv* genes, promoter editing has been used successfully on a number of conserved developmental genes in tomato as well as on a pathogen resistance gene in grapefruit (52, 99).

Accurate detection of *cis*-regulatory elements is starting to allow for the more precise engineering of promoter alleles of developmental genes (47). *Cis*-regulatory elements conserved over deep time have the potential to be particularly useful in agriculture. These deeply conserved regulatory elements, detected as conserved noncoding sequences (CNSs), are likely to impact gene function and may allow for the creation of weak alleles even in species where mechanistic studies of gene and allele function are intractable. While these deeply conserved elements are difficult to detect in

Heterosis: larger phenotype of hybrid progeny (for example, in terms of yield or size) relative to either parent

plant genomes, the recent rapid increase in high-quality genome sequences from across the land plant phylogeny (60), coupled with new algorithms for detecting CNSs, has revealed elements conserved between *A. thaliana* and tomato (47). Future efforts are likely to reveal more of these elements, conserved over broader swathes of plant diversity, that may be appropriate targets for genome editing in de novo domestication.

2.3. Gene Duplication, Retention, and Functional Evolution Can Impact the Effects of Engineered Alleles

Variation in gene content within species and families is another important factor in engineering weak alleles. For example, *SICLV3* in tomato has a duplicate, *SICLE9*, that arose from a duplication event in a lineage leading to the Solanaceae. *SICLE9* is highly upregulated in *slc3* mutants and partially compensates for the loss of *SICLV3* function (99). This is not the case in tobacco, which has lost its *SICLE9* ortholog. Therefore, *clv3* homolog single mutants are much stronger in tobacco than they are in tomato and resemble tomato *slc3 slc9* double mutants (**Figure 3e**). The peptide encoded by *SICLV3* has also diverged in function in tomato as compared to tobacco (63). This variability in gene duplication, retention, loss, and functional evolution is likely to impact the effects of engineered *CLV3* ortholog alleles in the Solanaceae. Given rampant whole-genome duplication and polyploidy in the angiosperms (114), this variability is also likely to extend beyond the *CLV3* gene family. Predicting compensation remains challenging, but high-quality genomes that reveal structural variation, analyses of expression in relevant tissues, and analyses of gene family evolution can all be important tools that guide effective target selection in de novo domestication (99).

2.4. Dosage Sensitivity and Dominant Negatives Are Useful in Hybrid Breeding

Hybrid vigor or heterosis has been critical in crop improvement and is likely to remain so. Therefore, alleles that impact traits in the heterozygous state are useful in crop engineering. For example, dominant negative alleles have been critical in twentieth-century crop improvement. One key characteristic of green revolution crops is decreased height, which reduces lodging susceptibility (56). In wheat, this decreased height is because of mutations in the *DELLA* transcription factor genes, which regulate transcriptional responses to gibberellins. Two of the major wheat *DELLA* alleles are dominant negatives, overcoming the genetic redundancy inherent in hexaploid wheat (91). In the case of the *CLV* genes, an allele of *FASCIATED EAR2*, the maize ortholog of *CLV2*, increases kernel row number in the heterozygous state but results in extreme fasciation and decreased kernel row number when homozygous (12, 125) (**Figure 3d**). This particular allele arose by chance, but in-depth knowledge of protein and gene function could allow for the precise design of dosage-sensitive alleles.

2.5. Genome Editing for Large Effects and Selective Breeding for Fine-Tuning

While domestication often involves a few large-effect genes, there are many loci involved in domestication (55). Genetic architecture of human disease is similar, where a few core genes have large effect sizes, but many genes contribute to disease heritability. Core genes often have clear functional connections to the phenotype, such as developmental transcription factors in domestication. However, interconnectedness and the properties of cellular networks mean that every gene in a cellular network is connected to every other gene by only a few steps (14). Thus, small-effect loci impact the expression and function of core genes. In addition, core gene function may be under strong negative selection and thus less likely to accumulate the extensive intraspecific variation useful in selective breeding. This may be the case for the *CLV* genes in maize, where

engineered variation in *CLV3* homologs impacted kernel row number (71), but only one *CLV* network gene has been found to be associated with intraspecific variation in meristem size (12, 66). Genome editing can modify small numbers of large-effect loci contributing to desired traits, but it is limited by our lack of knowledge of interconnectedness and the identity and large number of small-effect loci and by the impracticality of editing all the genes that contribute to a trait, even if we knew what they were. Thus, engineering variation into a few core genes followed by fine-tuning with selective breeding may succeed where either strategy alone cannot (35). Because CRISPR guides can be multiplexed, a single construct could be introduced to edit a few core genes in a selection of successful varieties (in crop improvement) or into a few genetically distinct lineages (in de novo domestication) (35, 37). Indeed, editing multiple genes to modify plant architecture has been successful in tomato (62); an African accession of *Oryza sativa* (rice) (64); the weakly domesticated tomato relative, *Physalis* (67); and the wild crop relatives *Oryza alta* (145) and *Solanum pimpinellifolium* (149).

While we focus on meristem size here, many morphological traits and genes contribute to domestication and yield, representing excellent candidates for this approach. Variations in shoot production and branching, flowering time, reduced seed dispersal (shattering), and reduced seed dormancy are among the traits associated with domestication syndrome, many of which are regulated by conserved genes (37, 81). Critically, once a gene has been identified that represents a potential target for genome editing, domestication, evolution, and pioneering efforts in de novo domestication and crop improvement all provide useful road maps for designing successful genome editing strategies.

3. STRATEGIES IN SELECTING PLANTS FOR DE NOVO DOMESTICATION AND IMPROVEMENT

3.1. Indigenous Knowledge Systems and Ethnobotany

Ethnobotanical leads based on indigenous knowledge systems allow for a targeted approach to select plant species, genotypes, and populations for de novo domestication. Ethnobotanical records, including extensive documentation of indigenous crops (95), provide valuable information for determining which plants to select. Indigenous knowledge is ancient information that has traversed generations, often through oral histories (33). Although linked to past generations, indigenous knowledge is dynamic. Indigenous knowledge holders are thus able to tap into a deep knowledge base but also to be experimental in offering innovative solutions that are “reconstructed in response to contemporary realities” (9). The ethnobotany-driven approach has had some successes with medicinal plants in new drug discovery (8, 43). A prime example is linked to how artemisinin, extracted from *Artemisia annua* L., found its way from traditional Chinese medicine to being an important antimalarial drug in allopathic medicine (68). Ethnomedical information has been foundational in making decisions about which plants to evaluate in drug screening programs. A similar approach that is informed by ethnobotany and that works with indigenous knowledge holders could also be similarly successful in the selection of food crops for de novo domestication.

In Africa, over 2,000 plant species are consumed as food (88). In the Cape Floristic Region, an epicenter for floral diversification (with approximately 9,000 species) characterized by many endemic plants (41), at least 250 plant species are used as bush medicine (7). In 2011, Van Wyk (128) noted 120 species from South Africa as potential new foods and beverages, some of which were first documented by ethnobotanists. Such examples provide impetus for the prioritization of the documentation of indigenous knowledge and the use of ethnobotanical records as a resource in choosing plants for de novo domestication.

Indigenous knowledge:

an assembly of knowledge linked to philosophies, understandings, practices, and skills developed by people throughout history, resulting from experiences of interacting with natural systems

Ethnobotany:

the interdisciplinary study of the relationships between plants and people

3.2. Avoiding Exploitation and Engaging Stakeholders

Critically, such endeavors should only take place with adherence to cultural protocols dictated and directed by indigenous people and with their consent, especially in the context of sacred knowledge. Researchers should thus be aware of indigenous peoples' rights, stipulated in the United Nations Declaration on the Rights of Indigenous Peoples (15), and cognizant and respectful of concerns and boundaries set in place by knowledge holders in terms of the disclosure, sharing, and use of such knowledge (122). It is imperative that indigenous knowledge holders "define and control rights and access" to digitized secret and sacred information in instances where such information can lead to illicit application and misuse (51, p. 1).

Working with indigenous knowledge holders should be collaborative, not extractive. Despite globalization, deep-seated indigenous knowledge still resides in communities all over the world. This indigenous knowledge is often localized in regions that are socioeconomically impoverished and marginalized, particularly in rural settings (77). The Convention on Biodiversity and the Nagoya Protocol duly acknowledge the role of indigenous knowledge and the ethnobotanical information attached to it in shaping scientific discovery and policy as a means to ensure "fair and equitable benefitiation" (<https://www.cbd.int/abs/>) with indigenous groups and knowledge holders. In some biodiversity-rich countries with a long-standing history of ethnobotanical exploitation, particularly in the use of phytomedicines, national strategies have been promulgated, aiming to ensure fair benefit-sharing practices from bioprospecting linked to biological resources and the indigenous knowledge attached to it. These strategies need to be inclusive of all stakeholders (scientific researchers, indigenous groups, and the private sector) with a framework that can be attractive to researchers and industry partnerships without being ambiguous or plagued with complex regulatory hurdles (46). Otherwise, unfavorable environments that are difficult to navigate from ethical and legal standpoints become overly prohibitive for the implementation and adoption of scientific technologies.

It is critical to engage stakeholders from the very beginning of projects and avoid so-called helicopter science or project design failures because indigenous knowledge and opinions were not considered or integrated from the outset. Even when consultations with indigenous tribes and benefit-sharing agreements are in place and there is an overall positive sentiment toward a cross-cultural collaboration between indigenous people and scientists, project failures are sometimes unavoidable. Several pharmaceutical bioprospecting projects in the 1990s failed dismally. For example, the International Cooperative Biodiversity Group (ICBG)-Maya and ICBG-Aguaruna projects in Mexico and Peru, respectively, were placed on hold due to strong opposition from non-governmental organizations presenting arguments of economic colonialism and biopiracy (10).

3.3. Domesticating Locally Adapted Plants

Plants from particular biomes are likely to be preadapted to particular agricultural environments or regimes (83, 136, 150). For example, the Ethiopian oil crop *Guizotia abyssinica* (noug) may have been selected for resilience to harsh environmental conditions. Noug is phenotypically plastic, which may allow it to produce a crop despite extreme variations in weather such as drought and floods (26). Similarly, the particular architectures of the African cereals t'ef (*Eragrostis tef*) and fonio (*Digitaria exilis* and *Digitaria iburua*) may have allowed for adequate harvests under harsh and variable environmental conditions (24, 136). Climate-resilient crops like these present strong targets for engineering and accelerated yield improvement. However, climate-resilient semidomesticated crops such as t'ef, fonio, and noug often are low-yielding when grown en masse using conventional monoculture methods. Thus, the translation of subsistence farming practices of these and other low-yielding indigenous crops to mass markets is difficult. Both indigenous knowledge

and scientific knowledge should interface more strongly when guiding decision-making to develop and promote indigenous crops. Research should prioritize both the increased application of biotechnology for improved yields and nutritional value and intensive modeling of future impacts of climate change (76).

Medicinal plants may be highly advantageous as selection starting points in de novo domestication. Medicinal plants are critical components of primary healthcare systems, which serve approximately 80% of people in the developing world (87). Natural product research to characterize phytochemical components, safety and toxicity profiles, and, in some instances, the nutritional value of these plants is ongoing. However, medicinal ethnobotanicals derive their pharmacological properties from specialized metabolites produced from diverse (and complex) pathways that allow for metabolic plasticity as plants respond to their environments (94). Phenological and phenotypic responses to environmental stresses may be unique and lineage specific, and the intrinsic mechanisms that drive these responses remain poorly resolved for many species (2). Also, some metabolites may be phylogenetically restricted and specific to certain taxa (79, 137). This complexity makes it difficult to identify genes that allow for functional adaptive responses that are sought after in de novo domestication and crop improvement. Focusing on engineering and yield improvement in these locally adapted plants may be more successful than introducing their adaptive traits into domesticated crops.

3.4. Challenges to the Ethnobotany-Driven Approach

Urbanization and modernization threaten both indigenous knowledge and plant diversity. In many countries with high biodiversity and species richness, such as South Africa, traditional knowledge on partial domesticates and other indigenous species is fragmented due to modernization and urbanization. Substantial knowledge still resides with subsistence farmers in rural environments, but accessing this knowledge requires many ethical considerations (particularly in relation to biopiracy and biocolonialism) and an understanding of and respect for regional community protocols and customary laws. A further complication is that many species are threatened because of agricultural expansion (32), the financialization of agriculture (22), sprawling urban developments, competition from invasive species (13), and disruption of plant life cycles from climate change (135). Conservation management of plant biodiversity and the systematic documentation of threatened and nearly extinct species cannot always keep up with biodiversity losses and their unique germplasm.

We have limited knowledge concerning the genetic diversity of endemic and indigenous species, including neglected and underutilized crops (76), but our knowledge will increase with the application of next-generation sequencing tools to native species and data deposition into gene banks (127). The large and complex nature of many indigenous crop genomes adds another dimension of difficulty (142), but genome sequencing, assembly, and annotation tools have advanced considerably in the recent past, allowing for the sequencing and assembly of even the hexaploid domesticated oat (*Avena sativa*) genome (53). Genetic transformation and gene editing technologies for ethnobotanicals are not always possible due to a lack of transformation protocols, low transformation efficiencies (67), and a lack of annotated reference genomes and information to select suitable domestication-related genes for beneficial traits (38, 96). In vitro plant propagation with reliable plant regeneration protocols is generally needed to apply the current technology used for de novo domestication (23). For many semidomesticated crops and indigenous plant species that may be consumed as foods and medicines, reliable micropropagation regimes may not always be available. This lack of foundational knowledge about most plants used by humans hampers innovation and limits de novo domestication.

Partial domesticate:
a species that has experienced artificial selection but remains similar to its wild ancestors and is capable of surviving and reproducing independently of humans

3.5. Translation of Foundational Knowledge from Well-Studied Relatives

While foundational knowledge about de novo domesticates may be lacking, information from closely related species that have been more intensively studied can be translatable. Genetic conservation between de novo domesticates and other model species or well-studied crops can make the transfer of fundamental knowledge of genes and gene function more predictable. Phylogenetic relatedness and biological similarity can also accelerate tool development (e.g., transformation protocols, genetic reagents, and tools). Notably, there is prolific scientific literature on the micropropagation of medicinal and horticultural plants, with new and improved protocols being published for a wide range of taxa. This broad knowledge base could be transferable to related food crops (127). Translation of basic understanding from cultivated rice has been successful for modifying an African *O. sativa* accession and the undomesticated wild rice relative *O. alta* (64, 145). Beyond the grasses, similar strategies have been successful in the Solanaceae (tomato family) (67, 149) and the Brassicaceae (*Arabidopsis* family) (21). Similarly, people from different regions and cultures have a tendency to use plants from related phylogenetic groupings for similar medical conditions, and phylogeny-driven pharmacological screening is also being explored (101). Extensive analyses of indigenous crop/crop model pairs (25) and analyses of crop phylogenetic relationships (82, 83) thus have the potential to be powerful resources for selecting plants and genes to focus on in de novo domestication efforts.

4. ETHICAL CONSIDERATIONS IN DE NOVO DOMESTICATION

Just as deep time instructs us on how to approach the biology of crop improvement, so human history reveals the many potential pitfalls in crop engineering and de novo domestication (97, 104, 146). First, the very premise of new agricultural technologies is rationalized around the need to feed a growing global population (48, 144). There is by now a robust critique of the logic of overpopulation (45, 102). Even though we currently have (and have had in the recent past) more than enough food to feed all in the world, we fail to do so. Undernourishment, malnourishment, and, indeed, starvation persist within and across countries. Rather than expanding technology, the urgent need is to alleviate poverty and ensure the distribution of food. If the goal is to end world hunger, new technologies cannot solve this fundamental problem of inequality.

Second, the history of agricultural technology should teach us some important lessons. Often, these technologies are universal; that is, one solution fits all global contexts. Hybrid seeds, GMOs, pesticides, and herbicides have a global reach, sometimes with disastrous consequences (4, 100). For example, the environmental impact decades after the much-heralded Green Revolution that celebrated food self-sufficiency in India is sobering (40, 110). We see severe environmental degradation of soil, vegetation, and water resources and the need for increasing chemical inputs (111). During the Green Revolution, the state of Punjab, once considered the breadbasket of India, shifted from diversified climate-adapted crops into a predominantly rice-wheat crop rotation with much higher water use. With the severe loss of the water table, the state faces increasing desertification. Clearly, any new technology must work within the ecological and social contexts of agriculture (127).

Third, most innovative technologies are fueled by commerce—private sector work and a funding-driven academic reward system. Intellectual property regimes through patents and trademarks ensure the continued dependence of farmers on seed companies. Erratic weather patterns and a lack of infrastructure to support innovative seed technologies have resulted in crop failures and farmer debt and suicide (109). These histories remind us that the economic consequences of any technology are critical. Also, much (free) research on the sustainable ecological management of crops is systematically ignored in order to promote the commercialization of

technology (92, 123). Before the pursuit of any technological innovation, the first question that must be asked is whether there is a need for new technology.

Fourth, the history of technology reminds us that when technologies fail, the solution is always a new technology (106, 112)! We are caught up in an endless loop of technological determinism. Much scientific and technological innovation continues to reside in wealthy Western nations and multinational corporations (69). We risk the continuation of an extractive, Eurocentric colonial legacy in crop improvement. Genuine partnerships across developed and developing nations are urgently needed. Technological innovation that grounds local contexts (economic, social, ecological) and that includes scientists and farmers from the Global South from the very beginning will go a long way to prevent history from repeating itself.

Fifth, the Eurocentrism of science has erased, ignored, and marginalized knowledge from colonized and indigenous communities. Recent work in indigenous sciences reminds us of centuries of tried and tested cosmologies and technologies (57, 120). At the heart of this literature are innovations that are grounded in local ecologies and that recognize the interconnected human and nonhuman worlds. Ethnobotanical knowledge promises us much, but we must be careful to avoid recolonizing indigenous communities to yet again appropriate and extract knowledge. Much of the work in indigenous studies offers models of ethical and respectful collaborations.

5. MODIFYING CROPS FOR WHAT THE FUTURE HOLDS

Climate change is bringing unprecedented shifts in the environmental conditions to which our crops must adapt. These shifts are predicted to be faster and more extreme than the pace of evolution, and the ability of populations to adapt to new climate regimes may be constrained (16, 139). Importantly, genome editing in de novo domestication and crop improvement allows us to accelerate crop adaptation and engineer plants adapted to the environmental conditions we predict will exist under climate change. In addition, it allows us to look beyond crop plants for solutions to ecological problems. Angiosperms have diversified to occupy, and in many cases dominate, every biome on land. Thus, adaptations to deal with most looming problems already exist in natural diversity. In addition, aerial plant organs are all leaf homologs, and decades of molecular genetics have revealed that the functions of many core developmental genes are conserved (11, 59), meaning that knowledge of the molecular genetics underpinning plant adaptation could be translatable to crop plants.

5.1. Drawing Solutions from Diversity

Efforts are already underway for the radical modification of crop form and function in response to climate change. Engineering C₄ photosynthesis into rice is a crop-engineering strategy informed by natural diversity and was developed in response to climate change (34). Increasing temperatures, unpredictable weather patterns, decreased freshwater availability (103), pollinator decline (39), and soil erosion (93) continue to mount increasing challenges to outdoor agriculture, while rising sea levels and development on farm land reduces arable land. Indoor agriculture is generating interest for its potential solutions to these problems (126). After 10,000 years of breeding for plants grown outdoors, we now face the daunting challenge of fitting crops into an entirely alien system for which they are not adapted. To meet this challenge, Kwon et al. (62) simultaneously edited multiple genes in tomato, reducing time to flowering, introducing determinacy, reducing internode lengths, and modifying branching architecture.

Future efforts could look to diversity. For example, if vertical farming is to become widespread, we might look to the architecture of cliff- or wall-growing plants, such as *Parthenocissus tricuspidata* (Boston ivy), that can efficiently grow up vertical surfaces with specialized adhesive pads and create

a uniform foliage layer (116). Many aquatic plants have evolved highly modified root systems, or even lost their roots, to thrive in aquatic environments, such as duckweed (*Lemna*, *Spirodela*, *Wolffia* spp.), which may be better suited to hydroponic systems than roots from soil-dwelling plants (3). However, large-scale indoor growing is at a phase of innovation and may change considerably over the next few years. Thus, investigating the developmental and evolutionary basis of diversity should be a focus for the plant biology community so that this knowledge is available when it becomes advantageous to engineer crops for new environments.

5.2. Engineering Flowers to Facilitate Breeding

Selective breeding is a powerful technology that is likely to remain important in agriculture. Therefore, considering or engineering traits that facilitate breeding is an important aspect of de novo domestication and crop improvement. Critical in selective breeding is the ability for humans to develop genetic lines (often through selfing) and then to cross together different genotypes to combine traits or to take advantage of heterosis (**Figure 4a,b**). Thus, both self-pollination and the ability of humans to make controlled crosses quickly and easily are important.

One trait common to many crops, which may have been either a preadaptation to domestication or selected for under domestication and improvement, was the loss of self-incompatibility and morphological adaptations to selfing (20). Domestication and improvement in rice involved a switch from outcrossing to highly selfing, in part because of reduced stigma exertion (58). Similarly, in tomato, stigma exertion and the loss of self-incompatibility have been critical in domestication and improvement (17, 107). In potato, editing self-incompatibility loci has allowed for the generation of self-compatible lines that could be used in breeding programs (143). While the genes regulating stigma exertion are likely to be functionally conserved between potato and

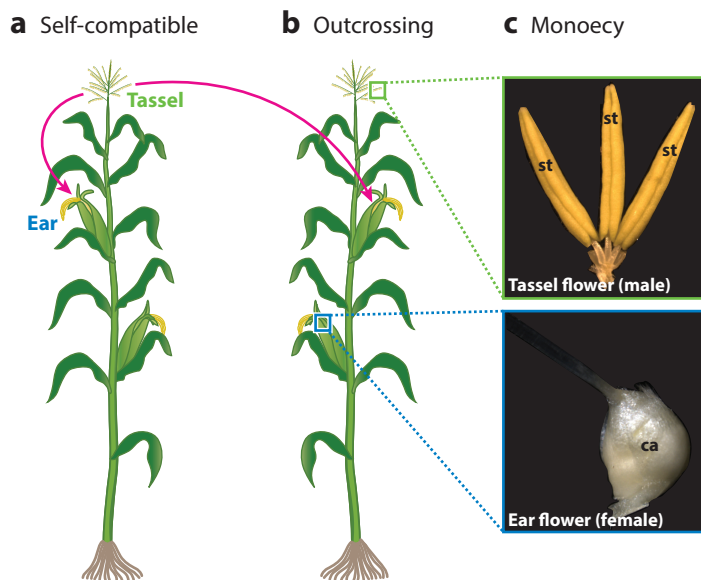


Figure 4

Floral traits that facilitate breeding, as exemplified by maize. (a) Self-compatibility coupled with (b) the ability to make outcrosses quickly and easily is important in selective breeding. Outcrossing is facilitated by separated male and female floral function. (c) In monoecy, this separation is spatial, with male and female flowers borne in separate inflorescences. Abbreviations: ca, carpel; st, stamen.

tomato, thus providing clear targets for editing and modifying potato floral morphology, there are likely many genes that impact the relative lengths of stamens versus stigmas. Thus, detailed, fundamental knowledge of the genes regulating the development of floral form in many taxa is critical for identifying targets in many de novo domestication efforts.

Floral sexuality is another floral trait that impacts breeding programs and crop productivity. Some separation of staminate and ovulate floral function is preferable to obligate selfing of hermaphroditic flowers because, although selfing allows for development of stable inbred lines, outcrossing facilitates hybrid development. In addition, extensive selfing may lead to a high genetic cost of domestication, as was likely the case in rice (73). Monoecy (i.e., separate male and female flowers on the same plant), as in maize (**Figure 4c**), allows for easy crossing and selfing. In contrast to dioecy (i.e., separate staminate and ovulate plants), every plant has the capacity to make fruit and seed, thus maximizing potential crop productivity. In the Cucurbitaceae, monoecy may have been a domestication enabler. Although dioecy is ancestral in the family, most major cucurbit crops, including cucumbers, are monoecious annuals (20). Similarly, a transition to hermaphroditic flowers (away from dioecy) occurred during grape domestication (148). Either selecting monoecious plants for de novo domestication or engineering monoecy has important consequences for downstream selective breeding.

5.3. Challenges to Drawing Solutions from Diversity

The biggest hurdle in drawing solutions from diversity continues to be the large knowledge gaps in the genetics of plant development outside of a few well-studied experimental systems. Even within well-studied systems, the functions of most genes have been defined on the basis of a few (null) alleles. The mechanistic connections between protein structure, regulatory architecture, and phenotype remain largely unknown for most genes and proteins. Epistasis and intraspecific genetic diversity also mean that even if we do know which particular *cis*-regulatory sequence or amino acid to edit, the effects of particular edits remain unpredictable in most genotypes (99). Many plants that are attractive targets in de novo domestication, or that have traits that could be useful in agriculture, are not amenable to the tools and techniques of genetics. Thus, drawing on comparative methods that consider the evolution of traits over deep time may be important for determining the genetic underpinnings of particular traits (113). Importantly, extensive gene editing as part of de novo domestication efforts in many species is likely to not only improve crop plants but also provide important functional data about the genes that regulate domestication traits. Lastly, while fundamental knowledge of the genes that regulate particular traits is important, fundamental knowledge of plant diversity remains equally important. Expertise in taxonomy and systematics, ethnobotanical expertise, and indigenous knowledge all remain critical in any de novo domestication efforts.

SUMMARY POINTS

1. Genetic strategies informed by domestication and evolution have been fruitful. Ongoing efforts should continue to draw from the examples we have in agriculture and nature. Genome editing releases us from dependence on random mutagenesis, or on intraspecific diversity, and can draw solutions more broadly from plant diversity.
2. Our understanding of the genetics underlying many plant traits that are critical for future crop engineering is sparse, which limits innovation.

3. Domestication is a complex process, incompletely understood for most crops and involving changes not only to plant form but also to many other aspects of plant biology and human culture. Genome editing is one tool that can accelerate domestication, but it is not a panacea.
4. De novo domestication and crop improvement using genome editing will still require selective breeding, especially for developing crops for different geographic areas, cultures, and environments. Therefore, focusing on traits that facilitate the breeding of wild plants or of weakly domesticated plants is likely to be fruitful.
5. Indigenous knowledge and ethnobotanical expertise have the potential to provide strong leads in selecting plants for engineering and de novo domestication. However, indigenous knowledge and communities must be respected and protected in this process.
6. Social and ethical considerations are critical. Success, and not repeating past mistakes, requires collaboration across traditional boundaries.

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LITERATURE CITED

1. Abraham-Juárez MJ, Barnes AC, Aragón-Raygoza A, Tyson D, Kur A, et al. 2021. The arches and spandrels of maize domestication, adaptation, and improvement. *Curr. Opin. Plant Biol.* 64:102124
2. Acasuso-Rivero C, Murren CJ, Schlichting CD, Steiner UK. 2019. Adaptive phenotypic plasticity for life-history and less fitness-related traits. *Proc. R Soc. B* 286:20190653
3. Acosta K, Appenroth KJ, Borisjuk L, Edelman M, Heinig U, et al. 2021. Return of the Lemnaceae: duckweed as a model plant system in the genomics and postgenomics era. *Plant Cell* 33(10):3207–34
4. Aga A. 2021. *Genetically Modified Democracy: Transgenic Crops in Contemporary India*. New Haven, CT: Yale Univ. Press
5. Al Amin N, Ahmad N, Wu N, Pu X, Ma T, et al. 2019. CRISPR-Cas9 mediated targeted disruption of *FAD2-2 microsomal omega-6 desaturase* in soybean (*Glycine max.*L). *BMC Biotechnol.* 19(1):9
6. Anzalone AV, Randolph PB, Davis JR, Sousa AA, Koblan LW, et al. 2019. Search-and-replace genome editing without double-strand breaks or donor DNA. *Nature* 576(7785):149–57
7. Aston Philander LE, Makunga NP, Esler KJ. 2014. The informal trade of medicinal plants by Rastafari bush doctors in the Western Cape of South Africa. *Econ. Bot.* 68(3):303–15
8. Balunas MJ, Kinghorn AD. 2005. Drug discovery from medicinal plants. *Life Sci.* 78:431–41
9. Beckloff RD. 2008. The conservative and dynamic nature of indigenous knowledge: a case study from Kenya. In *2008 Adult Education Research Conference*, St. Louis, MO. <https://newprairiepress.org/aerc/2008/roundtables/1>
10. Berlin B, Berlin EA. 2004. Community autonomy and the Maya ICBG Project in Chiapas, Mexico: how a bioprospecting project that should have succeeded failed. *Hum. Org.* 63(4):472–86

11. Boden SA, Østergaard L. 2019. How can developmental biology help feed a growing population? *Development* 146(3):dev172965
12. Bommert P, Nagasawa NS, Jackson D. 2013. Quantitative variation in maize kernel row number is controlled by the *FASCIATED EAR2* locus. *Nat. Genet.* 45(3):334–37
13. Boscutti F, Lami F, Pellegrini E, Buccheri M, Busato F, et al. 2022. Urban sprawl facilitates invasions of exotic plants across multiple spatial scales. *Biol. Invasions* 24(5):1497–510
14. Boyle EA, Li YI, Pritchard JK. 2017. An expanded view of complex traits: from polygenic to omnigenic. *Cell* 169(7):1177–86
15. Bruchac M. 2014. Indigenous knowledge and traditional knowledge. In *Encyclopedia of Global Archaeology*, ed. C Smith, pp. 3814–24. New York: Springer
16. Cang FA, Wilson AA, Wiens JJ. 2016. Climate change is projected to outpace rates of niche change in grasses. *Biol. Lett.* 12(9):20160368
17. Chen K-Y, Cong B, Wing R, Vrebalov J, Tanksley SD. 2007. Changes in regulation of a transcription factor lead to autogamy in cultivated tomatoes. *Science* 318(5850):643–45
18. Chen Q, Li W, Tan L, Tian F. 2021. Harnessing knowledge from maize and rice domestication for new crop breeding. *Mol. Plant* 14(1):9–26
19. Chen W, Chen L, Zhang X, Yang N, Guo J, et al. 2022. Convergent selection of a WD40 protein that enhances grain yield in maize and rice. *Science* 375(6587):eabg7985
20. Chomicki G, Schaefer H, Renner SS. 2020. Origin and domestication of Cucurbitaceae crops: insights from phylogenies, genomics and archaeology. *New Phytol.* 226(5):1240–55
21. Chopra R, Johnson EB, Emenecker R, Cahoon EB, Lyons J, et al. 2020. Identification and stacking of crucial traits required for the domestication of pennycress. *Nat. Food* 1(1):84–91
22. Clapp J, Ryan Isakson S. 2018. *Speculative Harvests: Financialization, Food, and Agriculture*. Halifax, Can.: Fernwood Publ.
23. Curtin S, Qi Y, Peres LEP, Fernie AR, Zsögön A. 2022. Pathways to de novo domestication of crop wild relatives. *Plant Physiol.* 188(4):1746–56
24. D’Andrea AC. 2008. Tef (*Eragrostis tef*) in ancient agricultural systems of Highland Ethiopia. *Econ. Bot.* 62(4):547–66
25. Dawson IK, Powell W, Hendre P, Bančić J, Hickey JM, et al. 2019. The role of genetics in mainstreaming the production of new and orphan crops to diversify food systems and support human nutrition. *New Phytol.* 224(1):37–54
26. Dempewolf H, Tesfaye M, Teshome A, Bjorkman AD, Andrew RL, et al. 2015. Patterns of domestication in the Ethiopian oil-seed crop noug (*Guizotia abyssinica*). *Evol. Appl.* 8(5):464–75
27. Doebley J, Stec A, Hubbard L. 1997. The evolution of apical dominance in maize. *Nature* 386(6624):485–88
28. Doebley J, Stec A, Wendel J, Edwards M. 1990. Genetic and morphological analysis of a maize-teosinte F2 population: implications for the origin of maize. *PNAS* 87(24):9888–92
29. Dong Z, Xiao Y, Govindarajulu R, Feil R, Siddoway ML, et al. 2019. The regulatory landscape of a core maize domestication module controlling bud dormancy and growth repression. *Nat. Commun.* 10(1):3810
30. Doudna JA, Charpentier E. 2014. The new frontier of genome engineering with CRISPR-Cas9. *Science* 346(6213):1258096
31. Doust AN, Devos KM, Gadberry MD. 2004. Genetic control of branching in foxtail millet. *PNAS* 101(24):9045–50
32. Dudley N, Alexander S. 2017. Agriculture and biodiversity: a review. *Biodiversity* 18(2–3):45–49
33. Emeagwali G. 2020. African indigenous knowledge systems and the legacy of Africa. In *Indigenous Knowledge Systems and Development in Africa*, ed. S Oloruntoba, A Afolayan, O Yacob-Haliso. Cham, Switz.: Palgrave Macmillan. https://doi.org/10.1007/978-3-030-34304-0_3
34. Ermakova M, Danila FR, Furbank RT, von Caemmerer S. 2020. On the road to C₄ rice: advances and perspectives. *Plant J.* 101(4):940–50
35. Eshed Y, Lippman ZB. 2019. Revolutions in agriculture chart a course for targeted breeding of old and new crops. *Science* 366(6466):eaax0025

30. Reflects on the CRISPR system, its discovery, and its development into a genome editing tool.

36. Evenson RE, Gollin D. 2003. Assessing the impact of the green revolution, 1960 to 2000. *Science* 300(5620):758–62
37. Fernie AR, Yan J. 2019. *De novo* domestication: an alternative route toward new crops for the future. *Mol. Plant* 12(5):615–31
38. Gepts P. 2014. The contribution of genetic and genomic approaches to plant domestication studies. *Curr. Opin. Plant Biol.* 18:51–59
39. Giannini TC, Costa WF, Cordeiro GD, Imperatriz-Fonseca VL, Saraiva AM, et al. 2017. Projected climate change threatens pollinators and crop production in Brazil. *PLOS ONE* 12(8):e0182274
40. Glaeser B. 2010. *The Green Revolution Revisited: Critique and Alternatives*. New York: Routledge
41. Goldblatt P, Manning JC. 2002. Plant diversity of the Cape region of Southern Africa. *Ann. Mo. Bot. Gard.* 89(2):281–302
42. González-Grandío E, Pajoro A, Franco-Zorrilla JM, Tarancón C, Immink RGH, Cubas P. 2017. Absciscic acid signaling is controlled by a *BRANCHED1/HD-ZIP I* cascade in *Arabidopsis* axillary buds. *PNAS* 114(2):E245–54
43. Gyllenhaal C, Kadushin MR, Southavong B, Sydara K, Bouamanivong S, et al. 2012. Ethnobotanical approach versus random approach in the search for new bioactive compounds: support of a hypothesis. *Pharm. Biol.* 50(1):30–41
44. Harlan JR. 1992. *Crops and Man*. Madison, WI: Am. Soc. Agron. Crop Sci. Soc. Am.
45. Hartmann B. 1995. *Reproductive Rights and Wrongs: The Global Politics of Population Control*. Boston: South End Press
46. Heinrich M, Scotti F, Andrade-Cetto A, Berger-Gonzalez M, Echeverría J, et al. 2020. Access and benefit sharing under the Nagoya Protocol—Quo vadis? Six Latin American case studies assessing opportunities and risk. *Front. Pharmacol.* 11:765
47. Hendelman A, Zebell S, Rodriguez-Leal D, Dukler N, Robitaille G, et al. 2021. Conserved pleiotropy of an ancient plant homeobox gene uncovered by *cis*-regulatory dissection. *Cell* 184:1724–39.e16
48. Hickey LT, Hafeez AN, Robinson H, Jackson SA, Leal-Bertioli SCM, et al. 2019. Breeding crops to feed 10 billion. *Nat. Biotechnol.* 37(7):744–54
49. Huang Z, van der Knaap E. 2011. Tomato *fruit weight 11.3* maps close to *fasciated* on the bottom of chromosome 11. *Theor. Appl. Genet.* 123(3):465–74
50. Hufford MB, Lubinsky P, Pyhäjärvi T, Devengeno MT, Ellstrand NC, Ross-Ibarra J. 2013. The genomic signature of crop-wild introgression in maize. *PLOS Genet.* 9(5):e1003477
51. Hunter J, Koopman B, Sledge J. 2003. Software tools for indigenous knowledge management. In *Museums and the Web 2003: Selected Papers from an International Conference, Charlotte, NC, March 19–22, 2003*. <https://eric.ed.gov/?id=ED482117>
52. Jia H, Orbovic V, Jones JB, Wang N. 2016. Modification of the PthA4 effector binding elements in Type I CsLOB1 promoter using Cas9/sgRNA to produce transgenic Duncan grapefruit alleviating XccΔpthA4:dCsLOB1.3 infection. *Plant Biotechnol. J.* 14:1291–301
53. Kamal N, Tsardakas Renhuldt N, Bentzer J, Gundlach H, Haberer G, et al. 2022. The mosaic oat genome gives insights into a uniquely healthy cereal crop. *Nature* 606:113–19
54. Kang B-C, Yun J-Y, Kim S-T, Shin Y, Ryu J, et al. 2018. Precision genome engineering through adenine base editing in plants. *Nat. Plants* 4:427–31
55. Kantar MB, Nashoba AR, Anderson JE, Blackman BK, Rieseberg LH. 2017. The genetics and genomics of plant domestication. *Bioscience* 67(11):971–82
56. Khush GS. 2001. Green revolution: the way forward. *Nat. Rev. Genet.* 2(10):815–22
57. Kimmerer R. 2013. *Braiding Sweetgrass: Indigenous Wisdom, Scientific Knowledge and the Teachings of Plants*. Minneapolis, MN: Milkweed Ed.
58. Kovach MJ, Sweeney MT, McCouch SR. 2007. New insights into the history of rice domestication. *Trends Genet.* 23(11):578–87
59. Kramer EM. 2019. Plus ça change, plus c'est la même chose: the developmental evolution of flowers. *Curr. Top. Dev. Biol.* 131:211–38
60. Kress WJ, Soltis DE, Kersey PJ, Wegrzyn JL, Leebens-Mack JH, et al. 2022. Green plant genomes: what we know in an era of rapidly expanding opportunities. *PNAS* 119(4):e2115640118

61. Kumar S, Stecher G, Suleski M, Hedges SB. 2017. TimeTree: a resource for timelines, timetrees, and divergence times. *Mol. Biol. Evol.* 34(7):1812–19
62. Kwon C-T, Heo J, Lemmon ZH, Capua Y, Hutton SF, et al. 2020. Rapid customization of Solanaceae fruit crops for urban agriculture. *Nat. Biotechnol.* 38(2):182–88
63. Kwon C-T, Tang L, Wang X, Gentile I, Hendelman A, et al. 2022. Dynamic evolution of small signalling peptide compensation in plant stem cell control. *Nat. Plants* 8(4):346–55
64. Lacchini E, Kiegle E, Castellani M, Adam H, Jouannic S, et al. 2020. CRISPR-mediated accelerated domestication of African rice landraces. *PLOS ONE* 15(3):e0229782
65. Lee JE, Neumann M, Duro DI, Schmid M. 2019. CRISPR-based tools for targeted transcriptional and epigenetic regulation in plants. *PLOS ONE* 14(9):e0222778
66. Leiboff S, Li X, Hu H-C, Todt N, Yang J, et al. 2015. Genetic control of morphometric diversity in the maize shoot apical meristem. *Nat. Commun.* 6:8974
67. Lemmon ZH, Reem NT, Dalrymple J, Soyk S, Swartwood KE, et al. 2018. Rapid improvement of domestication traits in an orphan crop by genome editing. *Nat. Plants* 4(10):766–70
68. Liao F. 2009. Discovery of Artemisinin (Qinghaosu). *Molecules* 14(12):5362–66
69. Li F-W. 2021. Decolonizing botanical genomics. *Nat. Plants* 7:1542–43
70. Li Z, Zhang D, Xiong X, Yan B, Xie W, et al. 2017. A potent Cas9-derived gene activator for plant and mammalian cells. *Nat. Plants* 3(12):930–36
71. Liu L, Gallagher J, Arevalo ED, Chen R, Skopelitis T, et al. 2021. Enhancing grain-yield-related traits by CRISPR–Cas9 promoter editing of maize *CLE* genes. *Nat. Plants* 7:287–94
72. Liu Q, Yang F, Zhang J, Liu H, Rahman S, et al. 2021. Application of CRISPR/Cas9 in crop quality improvement. *Int. J. Mol. Sci.* 22(8):4206
73. Liu Q, Zhou Y, Morrell PL, Gaut BS. 2017. Deleterious variants in Asian rice and the potential cost of domestication. *Mol. Biol. Evol.* 34(4):908–24
74. Liu W, Rudis MR, Cheplick MH, Millwood RJ, Yang J-P, et al. 2020. Lipofection-mediated genome editing using DNA-free delivery of the Cas9/gRNA ribonucleoprotein into plant cells. *Plant Cell Rep.* 39(2):245–57
75. Lowder LG, Zhou J, Zhang Y, Malzahn A, Zhong Z, et al. 2018. Robust transcriptional activation in plants using multiplexed CRISPR-Act2.0 and mTALE-Act systems. *Mol. Plant* 11(2):245–56
76. Mabhaudhi T, Chimonyo VGP, Chibarabada TP, Modi AT. 2017. Developing a roadmap for improving neglected and underutilized crops: a case study of South Africa. *Front. Plant Sci.* 8:2143
77. Mabuza MJ. 2021. The economic value of medicinal plant species: How rural people can benefit. In *Culture and Rural–Urban Revitalisation in South Africa: Indigenous Knowledge, Policies, and Planning*, ed. M Sirayi, M Kanyane, G Verdini. London: Routledge. <https://doi.org/10.4324/9781003145912>
78. Maurya JP, Singh RK, Miskolczi PC, Prasad AN, Jonsson K, et al. 2020. Branching regulator *BRC1* mediates photoperiodic control of seasonal growth in hybrid aspen. *Curr. Biol.* 30(1):122–26.e2
79. Mawalagedera SMUP, Callahan DL, Gaskett AC, Rønsted N, Symonds MRE. 2019. Combining evolutionary inference and metabolomics to identify plants with medicinal potential. *Front. Ecol. Evol.* 7:267
80. Meyer RS, DuVal AE, Jensen HR. 2012. Patterns and processes in crop domestication: an historical review and quantitative analysis of 203 global food crops. *New Phytol.* 196(1):29–48
81. Meyer RS, Purugganan MD. 2013. Evolution of crop species: genetics of domestication and diversification. *Nat. Rev. Genet.* 14(12):840–52
82. Milla R. 2020. Crop Origins and Phylo Food: a database and a phylogenetic tree to stimulate comparative analyses on the origins of food crops. *Glob. Ecol. Biogeogr.* 29(4):606–14
83. Milla R, Osborne CP. 2021. Crop origins explain variation in global agricultural relevance. *Nat. Plants* 7(5):598–607
84. Molla KA, Sretenovic S, Bansal KC, Qi Y. 2021. Precise plant genome editing using base editors and prime editors. *Nat. Plants* 7(9):1166–87
85. Moose SP, Dudley JW, Rocheford TR. 2004. Maize selection passes the century mark: a unique resource for 21st century genomics. *Trends Plant Sci.* 9(7):358–64
86. Moyers BT, Morrell PL, McKay JK. 2018. Genetic costs of domestication and improvement. *J. Hered.* 109(2):103–16

80. Comprehensively reviews crop domestication processes and finds substantial variation within spatial and temporal patterns.

98. Demonstrates promoter editing of an important regulator of meristem and tomato fruit size to generate quantitative phenotypic variation.

100. A classic collection that chronicles the failure of development projects, revealing that greater agricultural innovation and output does not alleviate poverty.

104. Explores the “extractive logics” underlying the epic imperial voyages to explore the natural riches of the New World and uncover the botanical secrets of its people.

87. Moyo M, Aremu AO, Van Staden J. 2015. Medicinal plants: an invaluable, dwindling resource in sub-Saharan Africa. *J. Ethnopharmacol.* 174:595–606
88. Natl. Res. Counc. 1996. *Lost Crops of Africa*, Vol. 1: *Grains*. Washington, DC: Natl. Acad. Press
89. Nicolas M, Torres-Pérez R, Wahl V, Cruz-Oró E, Rodríguez-Buey ML, et al. 2022. Spatial control of potato tuberization by the TCP transcription factor BRANCHED1b. *Nat. Plants* 8(3):281–94
90. Papikian A, Liu W, Gallego-Bartolomé J, Jacobsen SE. 2019. Site-specific manipulation of *Arabidopsis* loci using CRISPR-Cas9 SunTag systems. *Nat. Commun.* 10(1):729
91. Peng J, Richards DE, Hartley NM, Murphy GP, Devos KM, et al. 1999. “Green revolution” genes encode mutant gibberellin response modulators. *Nature* 400(6741):256–61
92. Peschard K, Randeria S. 2020. “Keeping seeds in our hands”: the rise of seed activism. *J. Peasant Stud.* 47(4):613–47
93. Pimentel D, Harvey C, Resosudarmo P, Sinclair K, Kurz D, et al. 1995. Environmental and economic costs of soil erosion and conservation benefits. *Science* 267(5201):1117–23
94. Rai A, Saito K, Yamazaki M. 2017. Integrated omics analysis of specialized metabolism in medicinal plants. *Plant J.* 90(4):764–87
95. Ramirez-Villegas J, Khoury CK, Achicanoy HA, Diaz MV, Mendez AC, et al. 2022. State of ex situ conservation of landrace groups of 25 major crops. *Nat. Plants* 8:491–99
96. Razzaq A, Wani SH, Saleem F, Yu M, Zhou M, Shabala S. 2021. Rewilding crops for climate resilience: economic analysis and de novo domestication strategies. *J. Exp. Bot.* 72(18):6123–39
97. Rodney W. 2018. *How Europe Underdeveloped Africa*. London: Verso Books
98. Rodríguez-Leal D, Lemmon ZH, Man J, Bartlett ME, Lippman ZB. 2017. Engineering quantitative trait variation for crop improvement by genome editing. *Cell* 171(2):470–80.e8
99. Rodríguez-Leal D, Xu C, Kwon C-T, Soyars C, Demesa-Arevalo E, et al. 2019. Evolution of buffering in a genetic circuit controlling plant stem cell proliferation. *Nat. Genet.* 51(5):786–92
100. Sainath P. 1996. *Everybody Loves a Good Drought: Stories from India's Poorest Districts*. Gurgaon, India: Penguin Books India
101. Saslis-Lagoudakis CH, Savolainen V, Williamson EM, Forest F, Wagstaff SJ, et al. 2012. Phylogenies reveal predictive power of traditional medicine in bioprospecting. *PNAS* 109(39):15835–40
102. Sasser JS. 2018. *On Infertile Ground*. New York: NYU Press
103. Scanlon BR, Faunt CC, Longuevergne L, Reedy RC, Alley WM, et al. 2012. Groundwater depletion and sustainability of irrigation in the US High Plains and Central Valley. *PNAS* 109(24):9320–25
104. Schiebinger L. 2021. *Plants and Empire*. Cambridge, MA: Harvard Univ. Press
105. Schnablová R, Herben T, Klimešová J. 2017. Shoot apical meristem and plant body organization: a cross-species comparative study. *Ann. Bot.* 120(5):833–43
106. Scott D. 2011. The technological fix criticisms and the agricultural biotechnology debate. *J. Agric. Environ. Ethics* 24(3):207–26
107. Shang L, Song J, Yu H, Wang X, Yu C, et al. 2021. A mutation in a C₂H₂-type zinc finger transcription factor contributed to the transition toward self-pollination in cultivated tomato. *Plant Cell* 33(10):3293–308
108. Shapter FM, Cross M, Ablett G, Malory S, Chivers IH, et al. 2013. High-throughput sequencing and mutagenesis to accelerate the domestication of *Microlaena stipoides* as a new food crop. *PLOS ONE* 8(12):e82641
109. Shiva V. 2016. Defending farmers’ seed freedom. *ANTYAJAA Indian J. Women Soc. Change* 1(2):205–20
110. Siegel BR. 2018. *Hungry Nation: Food, Famine, and the Making of Modern India*. Cambridge, UK: Cambridge Univ. Press
111. Singh RB. 2000. Environmental consequences of agricultural development: a case study from the Green Revolution state of Haryana, India. *Agric. Ecosyst. Environ.* 82:97–103
112. Smith MR, Marx L. 1994. *Does Technology Drive History?: The Dilemma of Technological Determinism*. Cambridge, MA: MIT Press
113. Smith SD, Pennell MW, Dunn CW, Edwards SV. 2020. Phylogenetics is the new genetics (for most of biodiversity). *Trends Ecol. Evol.* 35(5):415–25
114. Soltis DE, Albert VA, Leebens-Mack J, Bell CD, Paterson AH, et al. 2009. Polyploidy and angiosperm diversification. *Am. J. Bot.* 96(1):336–48

115. Somssich M, Je BI, Simon R, Jackson D. 2016. CLAVATA-WUSCHEL signaling in the shoot meristem. *Development* 143(18):3238–48
116. Steinbrecher T, Beuchle G, Melzer B, Speck T, Kraft O, Schwaiger R. 2011. Structural development and morphology of the attachment system of *Parthenocissus tricuspidata*. *Int. J. Plant Sci.* 172(9):1120–29
117. Stitzer MC, Ross-Ibarra J. 2018. Maize domestication and gene interaction. *New Phytol.* 220(2):395–408
118. Strable J, Wallace JG, Unger-Wallace E, Briggs S, Bradbury PJ, et al. 2017. Maize *YABBY* genes *drooping leaf1* and *drooping leaf2* regulate plant architecture. *Plant Cell* 29(7):1622–41
119. Swarts K, Gutaker RM, Benz B, Blake M, Bukowski R, et al. 2017. Genomic estimation of complex traits reveals ancient maize adaptation to temperate North America. *Science* 357(6350):512–15
120. TallBear K. 2014. Standing with and speaking as faith: a feminist-indigenous approach to inquiry. *J. Res. Pract.* 10(2):N17
121. Tang X, Lowder LG, Zhang T, Malzahn AA, Zheng X, et al. 2017. A CRISPR-Cpf1 system for efficient genome editing and transcriptional repression in plants. *Nat. Plants* 3(3):17018
122. Thomas PN. 2010. Traditional knowledge and the Traditional Knowledge Digital Library: digital quandaries and other concerns. *Int. Commun. Gaz.* 72(8):659–73
123. Thrupp LA. 1989. Legitimizing local knowledge: from displacement to empowerment for third world people. *Agric. Hum. Values* 6(3):13–24
124. Tian S, Jiang L, Cui X, Zhang J, Guo S, et al. 2018. Engineering herbicide-resistant watermelon variety through CRISPR/Cas9-mediated base-editing. *Plant Cell Rep.* 37(9):1353–56
125. Trung KH, Tran QH, Bui NH, Tran TT, Luu KQ, et al. 2020. A weak allele of *FASCIATED EAR 2 (FEA2)* increases maize kernel row number (KRN) and yield in elite maize hybrids. *Agronomy* 10(11):1774
126. van Delden SH, SharathKumar M, Butturini M, Graamans LJA, Heuvelink E, et al. 2021. Current status and future challenges in implementing and upscaling vertical farming systems. *Nat. Food* 2(12):944–56
127. Van Tassel DL, Tesdell O, Schlautman B, Rubin MJ, DeHaan LR, et al. 2020. New food crop domestication in the age of gene editing: Genetic, agronomic and cultural change remain co-evolutionarily entangled. *Front. Plant Sci.* 11:789
128. Van Wyk B-E. 2011. The potential of South African plants in the development of new food and beverage products. *S. Afr. J. Bot.* 77(4):857–68
129. Wada N, Osakabe K, Osakabe Y. 2022. Expanding the plant genome editing toolbox with recently developed CRISPR-Cas systems. *Plant Physiol.* 188(4):1825–37
130. Wang B, Lin Z, Li X, Zhao Y, Zhao B, et al. 2020. Genome-wide selection and genetic improvement during modern maize breeding. *Nat. Genet.* 52(6):565–71
131. Wang L, Josephs EB, Lee KM, Roberts LM, Rellán-Álvarez R, et al. Molecular parallelism underlies convergent highland adaptation of maize landraces. *Mol. Biol. Evol.* 38:3567–80
132. Wang M, Le Moigne M-A, Bertheloot J, Crespel L, Perez-Garcia M-D, et al. 2019. BRANCHED1: a key hub of shoot branching. *Front. Plant Sci.* 10:76
133. Wang M, Li W, Fang C, Xu F, Liu Y, et al. 2018. Parallel selection on a dormancy gene during domestication of crops from multiple families. *Nat. Genet.* 50(10):1435–41
134. Wang X, Dong K, Kong D, Zhou Y, Yin J, et al. 2021. A far-red light-inducible CRISPR-Cas12a platform for remote-controlled genome editing and gene activation. *Sci. Adv.* 7(50):eabh2358
135. Williams TM, Schlichting CD, Holsinger KE. 2021. Herbarium records demonstrate changes in flowering phenology associated with climate change over the past century within the Cape Floristic Region, South Africa. *Clim. Change Ecol.* 1:100006
136. Wilson ML, VanBuren R. 2022. Leveraging millets for developing climate resilient agriculture. *Curr. Opin. Biotechnol.* 75:102683
137. Wink M. 2003. Evolution of secondary metabolites from an ecological and molecular phylogenetic perspective. *Phytochemistry* 64(1):3–19
138. Wray GA. 2007. The evolutionary significance of *cis*-regulatory mutations. *Nat. Rev. Genet.* 8(3):206–16
139. Wu Y, Colautti RI. 2022. Evidence for continent-wide convergent evolution and stasis throughout 150 y of a biological invasion. *PNAS* 119(18):e2107584119

119. Uses ancient DNA sequencing to illuminate the slow complexity of the domestication process.

150. Demonstrates the potential of genome editing for de novo domestication in one of the first experimental explorations.

140. Wu Y, Yang L, Chang T, Kandeel F, Yee J-K. 2020. A small molecule-controlled Cas9 repressible system. *Mol. Ther. Nucleic Acids* 19:922–32
141. Xu C, Liberatore KL, MacAlister CA, Huang Z, Chu Y-H, et al. 2015. A cascade of arabinosyltransferases controls shoot meristem size in tomato. *Nat. Genet.* 47(7):784–92
142. Ye C-Y, Fan L. 2021. Orphan crops and their wild relatives in the genomic era. *Mol. Plant* 14(1):27–39
143. Ye M, Peng Z, Tang D, Yang Z, Li D, et al. 2018. Generation of self-compatible diploid potato by knockout of *S-RNase*. *Nat. Plants* 4(9):651–54
144. Yu H, Li J. 2022. Breeding future crops to feed the world through de novo domestication. *Nat. Commun.* 13(1):1171
145. Yu H, Lin T, Meng X, Du H, Zhang J, et al. 2021. A route to *de novo* domestication of wild allotetraploid rice. *Cell* 184(5):1156–70.e14
146. Zerner C, ed. 2000. *People, Plants, and Justice: The Politics of Nature Conservation*. New York: Columbia Univ. Press
147. Zhang F, Rossignol P, Huang T, Wang Y, May A, et al. 2020. Reprogramming of stem cell activity to convert thorns into branches. *Curr. Biol.* 30(15):2951–61.e5
148. Zou C, Massonnet M, Minio A, Patel S, Llaca V, et al. 2021. Multiple independent recombinations led to hermaphroditism in grapevine. *PNAS* 118(15):e2023548118
149. Zsögön A, Čermák T, Naves ER, Notini MM, Edel KH, et al. 2018. *De novo* domestication of wild tomato using genome editing. *Nat. Biotechnol.* 36:1211–16
- 150. Zsögön A, Čermák T, Voytas D, Peres LEP. 2017. Genome editing as a tool to achieve the crop ideotype and *de novo* domestication of wild relatives: case study in tomato. *Plant Sci.* 256:120–30**