

De Novo Domestication: An Alternative Route toward New Crops for the Future

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ABSTRACT

Current global agricultural production must feed over 7 billion people. However, productivity varies greatly across the globe and is under threat from both increased competitions for land and climate change and associated environmental deterioration. Moreover, the increase in human population size and dietary changes are putting an ever greater burden on agriculture. The majority of this burden is met by the cultivation of a very small number of species, largely in locations that differ from their origin of domestication. Recent technological advances have raised the possibility of *de novo* domestication of wild plants as a viable solution for designing ideal crops while maintaining food security and a more sustainable low-input agriculture. Here we discuss how the discovery of multiple key domestication genes alongside the development of technologies for accurate manipulation of several target genes simultaneously renders *de novo* domestication a route toward crops for the future.

Key words: *De Novo* Domestication, Redomestication, New Crops, Genome Editing, Food Security, Sustainable Agriculture

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INTRODUCTION

The majority of crops and vegetables that we currently eat were domesticated from their wild progenitors within the past 12 000 years. During the process of domestication, our ancestors simply chose what they needed for living. Such simple choices ultimately led to the pyramiding of valuable mutations and re-combinants in key genes that rendered cultivated crops easier to breed, culture, and store seeds from. Intriguingly, many different crop species share common domesticated traits such as, for example, seed shattering. In rice the seed number was greatly increased by domestication, whereas the weight of a single kernel was not (Si et al., 2016). By contrast, in tomatoes and eggplants the number of fruits per plant did not increase greatly upon domestication, but the size and weight of the individual fruit did (Zhu et al., 2018). These species represent only a few examples of the 150 or so plants commonly cultivated today. However, 70% of the calories consumed by humans come from only 15 crops, which were domesticated in different countries worldwide (Figure 1). Of these, maize, rice, and wheat grains directly contribute more than half of all calories consumed (Ross-Ibarra et al., 2007). Importantly, upward of 7000 of the 400 000 extant plant species known are regarded as semi-cultivated (Smykal et al., 2018) and could represent an important source of germplasm for the design of future crops.

Several difficulties make current crop production particularly challenging. Heavy reliance on chemical fertilizers and pesticides comes at an environmental cost and results in unsustainable productivity. Requirement for fresh water remains high in the face of its increasing scarcity. Current climate change predictions suggest that agriculture will face more extreme climate changes, including drought, heat, cold, and saline and alkaline soil. In addition, most of our crops are rich in macronutrients but poor in the micronutrients that are necessary for humans and animals. Finally, while the amount of cereal production has more than kept pace with the human population (Figure 1), production efficiency of current major crops is highly variable across the world, with some crops being very poorly suited to their area of cultivation. For example, yields of cassava in South East Asia are up to three-fold higher than those of sub-Saharan Africa (<http://www.fao.org/faostat/en/#home>), mainly because of large-scale fertilizer use in Asia, while none is applied to the nutrient-poverished soils of Africa.

The booming human population, environmental degradation, and ever increasing competition for land, alongside our unprecedented understanding of the domestication process and the

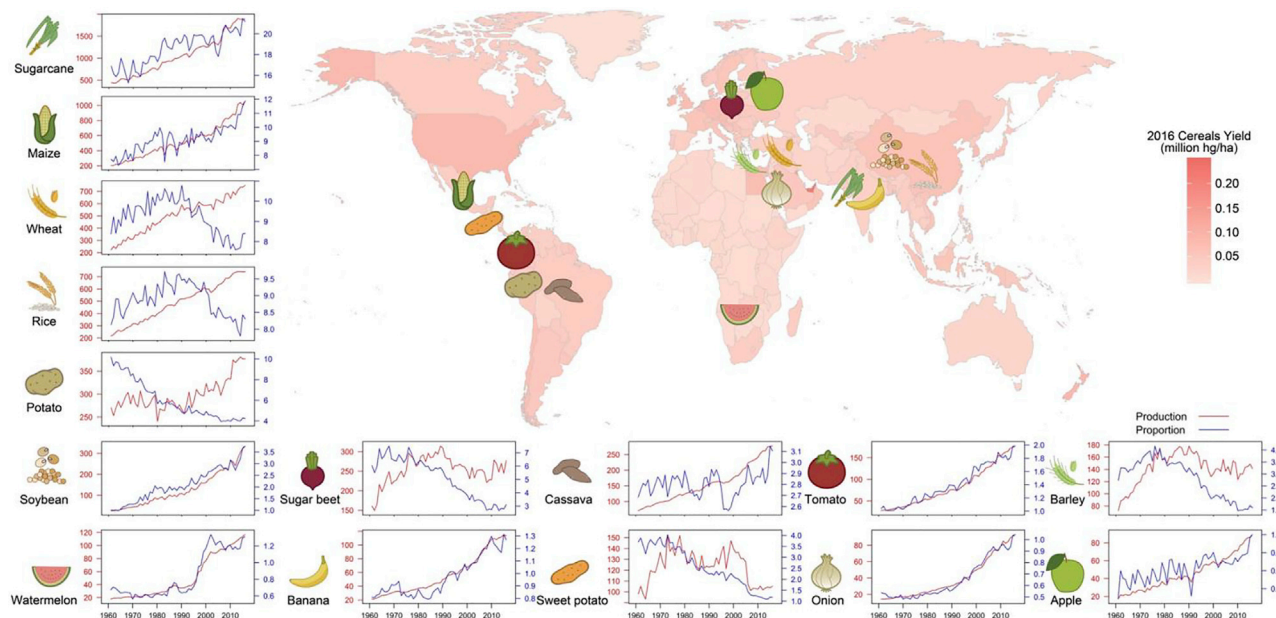


Figure 1. The Spatial and Temporal Dynamics of Global Crop Yield.

The heatmap represents the average cereal yields of countries of the world in 2016 (unit: million hg/ha). The spatial production and proportional contribution of the 15 top crops in 2016 are provided in the graphs (red lines represent million tonnes production, blue lines the proportional contribution). The positioning of the crop signals on the map indicates their place of origin.

advanced status of genotyping tools, raises the question of whether it is possible to accelerate the domestication process to create (an) ideal crop(s) for human needs. Recent developments in genome editing, which allow far more targeted and precise genetic manipulations than previously possible, alongside the shift to molecular breeding, render this a timely question.

In this article, we begin by reviewing the history of crop domestication. We then describe the first case studies that demonstrate the nascent potential for introducing domestication traits into semi-cultivated and non-cultivated plant species (Lemmon et al., 2018; Li et al., 2018b; Zsögön et al., 2018). We provide a perspective on how the combination of our current understanding of crop plant domestication and improvement could be harnessed in attempts to develop new crops to face the grand challenges facing agriculture in the 21st century.

THE HISTORY OF CROP DOMESTICATION AND IMPROVEMENT

Human-guided domestication began approximately 12 000 years ago in the Middle East and Fertile Crescent, and subsequently occurred in different parts of the world including China, Mesoamerica and the Andes, Near Oceania, sub-Saharan Africa, and eastern North America (Purugganan and Fuller, 2009; Meyer and Purugganan, 2013) (Figure 1). Based on the idea of Plant Breeding 4.0 (Wallace et al., 2019), we further extend our view to divide the history of crop improvement into four generations. First-generation (1G) breeding began with phenotype-based selection by local independent farmers, which slowly led to the dramatic changes observed in modern crops (Doebley et al., 2006; Wallace et al., 2019). With the world population massively increasing by the turn of the 20th century, until hybrid breeding

(2G) was developed in the 1980s and mating designs and statistical analyses were incorporated (Fisher, 1919; Wright, 1921), the use of fertilizer and pesticide became widespread (Carvalho, 2017), and the first “green revolution” occurred at the end of the 1950s, resulting in dwarf plants with consequently higher yields (Khush, 2001). Only 30 years ago, we entered the third generation of breeding (3G), which is also known as the second green revolution or biotechnology-based breeding. This generation involves the application of transgenic technology and the utilization of genome breeding technology, with genome-wide association studies (Risch and Merikangas, 1996; Fernie and Gutierrez-Marcos, 2019), marker-assisted breeding (Lander and Botstein, 1989) and genomic selection (Meuwissen et al., 2001) harnessed for crop improvement. Currently we are at the start of the fourth generation of breeding (4G), which promises to be the third green revolution, and involves design breeding (Figure 2). That is, genome editing and precision breeding can be combined with the mining of big data to tailor crops to demands, including local preferences and climates, as well as to create a more sustainable and climate-friendly agricultural industry.

THE PROCESS OF DOMESTICATION

Domesticated plant species span 160 taxonomic families (Meyer and Purugganan, 2013), with it being estimated that over 2500 species have undergone some extent of domestication (Meyer et al., 2012) and around 300 have been fully domesticated (Meyer and Purugganan, 2013; Salman-Minkov et al., 2016) (Supplemental Table 1). Current models based on archaeological, genetic, and genomic evidence suggest that domestication is a multi-staged process that encompasses the onset of domestication, the increase in frequency of desirable

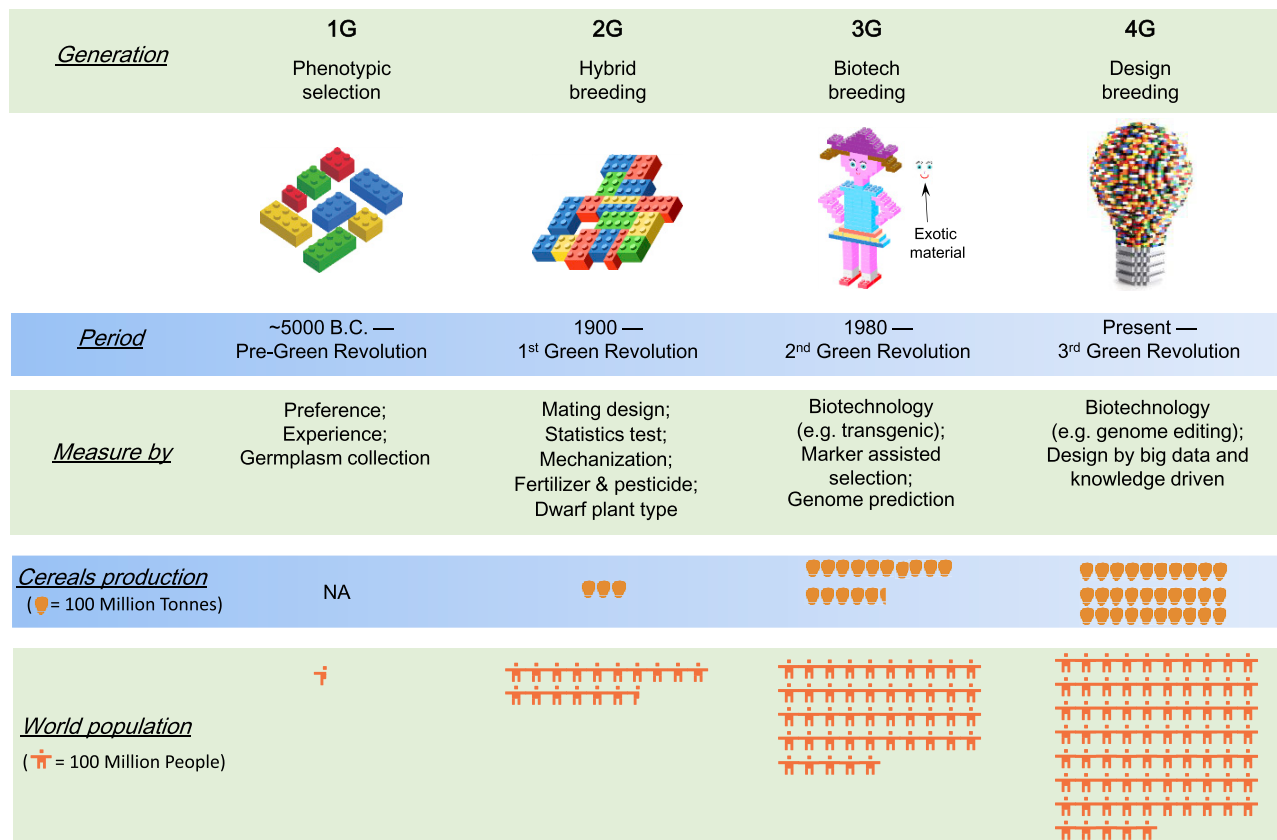


Figure 2. How Breeding History Feeds Human Civilization.

The horizontal axis summarizes four milestone generations of breeding while the vertical axis presents specific characteristics of each generation. The first generation (1G) started ~10 000 years ago, focusing on simple phenotype-based collection and wild species domestication; it had a very limited production being able to feed about 50 million people. 2G breeding is characterized by hybrid and dwarf breeding and occurred during the early 20th century. In this generation people had already incorporated statistics and design into breeding practice and applied mechanization, fertilizers, and pesticides widely, resulting in the annual production of approximately 300 million tonnes of food to feed 1.65 billion people. Several modern biotechnologies have been applied after 1980 until now in 3G breeding, which was especially characterized by the application of transgenic technologies, whole-genome prediction, and marker-assisted selection using molecular markers. Between 1980 and today cereals production increased from 1.55 to 3 billion tonnes worldwide, increasing our capacity to feed from 4.5 to 7.5 billion people. Currently 4G breeding is emerging as precision design agriculture as the integration of deep exploration on crop functional genomics, popular precision editing technologies, and big data mining are incorporated into breeding strategies.

alleles, the formation of cultivated populations and, finally, deliberate breeding. However, the delineation of domestication is complicated in many species by multiple domestication events (Bitocchi et al., 2012; Dai et al., 2012; Schmutz et al., 2014; Fang et al., 2017; Liu and Yan, 2017; Wing et al., 2018), and often post-domestication genetic exchange with progenitor species occurs (Gross and Olsen, 2010). Indeed, three major routes have been taken toward crop speciation: selection, polyploidy, and introgression (Figure 3). A striking example is the speciation that occurred in the Brassicaceae family, which has involved favorable organ-shape selection from wild mustard, including terminal bud selection (for cabbage), flower selection (for broccoli), and stem selection (for kohlrabi [Osnas, 2012]), as well as allopolyploidy via hybridization with Chinese cabbage (for rutabaga [Griffiths et al., 1999]), and introgression from *Arabidopsis lyrata* transformed non-adapted *Arabidopsis arenosa* into adapted *A. arenosa* (Arnold et al., 2016) (Figure 2). The fact that such diverse changes in morphology and physiology could be rendered via simple genetic changes

bodes well for future approaches aimed at tailoring crop production to a prespecified growth habit.

The complex of traits that commonly occurred upon domestication of diverse species has become known as the domestication syndrome, which has been extensively studied (Dillon et al., 2007; Alonso-Blanco et al., 2009; Gross and Olsen, 2010; He et al., 2011; Sakuma et al., 2011; Flint-Garcia, 2013; Abbo et al., 2014; Cornille et al., 2014; Dong et al., 2014; Avni et al., 2017; Che and Zhang, 2018; Hu et al., 2018). Many of these traits are common across different crop species, particularly within a crop type. For example, cereal species are characterized by the acquisition of modified seed shattering, seed size, and dormancy traits, while vegetable crops are characterized by the acquisition of modified fruit size and shape. Indeed, a mere 12 years ago the list of confirmed domestication genes numbered just over two dozen (Doebley et al., 2006). Since then, this number has increased about four-fold; recent examples of domestication genes include genes found to affect seed

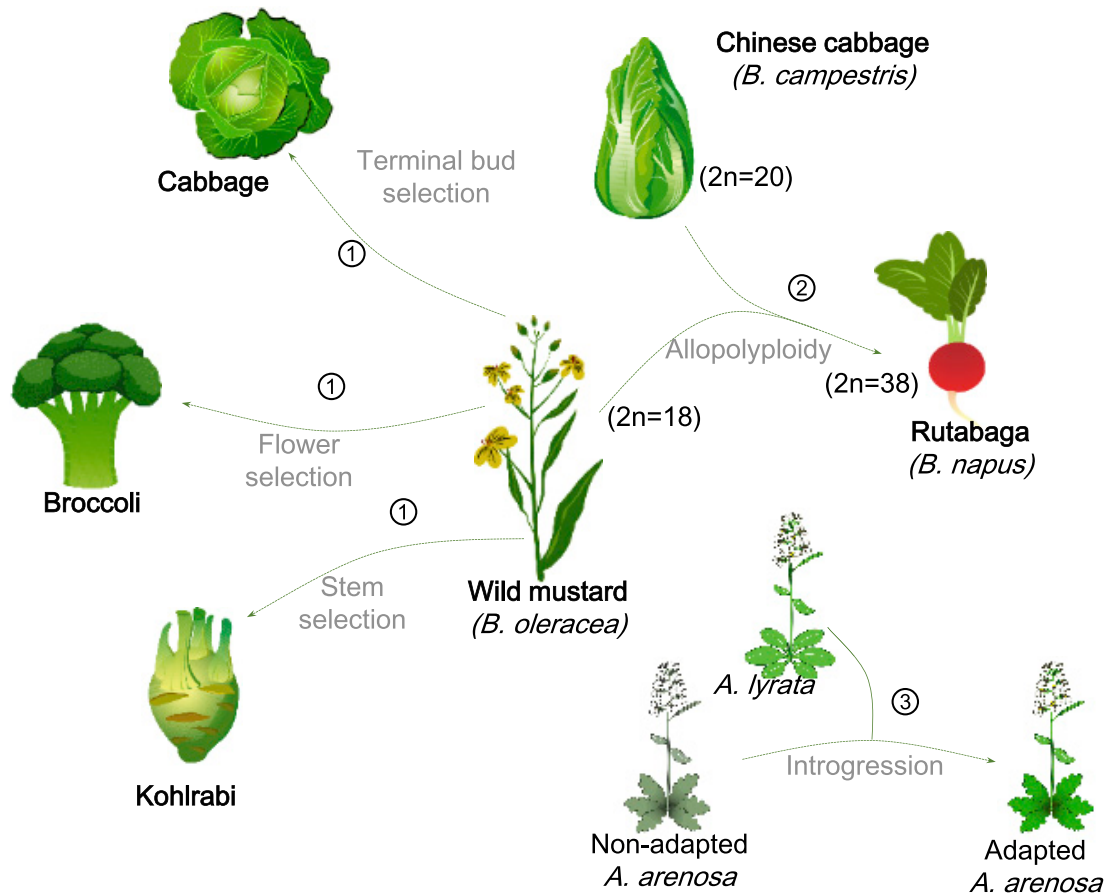


Figure 3. Routes for Crop Speciation.

A new species can be shaped in multiple ways including selection of specific organs (1, described in [Osnas, 2012](#)), allopolyploidy among subspecies (2, described in [Griffiths et al., 1999](#)), or absorbing new alleles through introgression from nearby species (3, described in [Arnold et al., 2016](#)).

dormancy in rice, soybean, and tomato ([Wang et al., 2018](#)), or grain filling in maize ([Sosso et al., 2015](#)), and genes involved in the evolution of tuberous crops ([Cheng et al., 2016](#); [Hardigan et al., 2017](#)). Indeed, there are many successful examples of this approach in a wide range of crops, including rice, maize, wheat, barley, sorghum, and tomato, and covering, but not limited to, many traits involved in plant and inflorescence architecture, yield, pigmentation, and ease of planting or harvesting ([Table 1](#)).

Collectively, these studies have allowed interesting comparative analyses of trait evolution because despite many species having similar domestication traits, both the same and different genes have been demonstrated to underlie their domestication ([Gross and Olsen, 2010](#); [Lenser and Theissen, 2013](#)). For example, some fruit weight quantitative trait loci (QTL) in tomato and pepper do map to the same loci ([Paran and van der Knaap, 2007](#)); the stay green gene *G* confers control of seed dormancy in a range of species ([Wang et al., 2018](#)), and the glutinous grain improvement traits in rice, sorghum, barley, and millet are all controlled by orthologs of the *Waxy* gene ([Meyer and Purugganan, 2013](#)). However, despite hints suggesting that the same was true for all cereal domestication traits, fine mapping revealed that these were in fact encoded by different genes ([Li and Gill, 2006](#)). Indeed, the canonical domestication gene *tb1*

of maize ([Doebley et al., 1997](#)) only has minor effects on branching in foxtail millet ([Doust et al., 2004](#)), while even within barley different genes are causal for changes in shattering within the two domesticated lineages ([Azhaguvel and Komatsuda, 2007](#)). To summarize, these data suggest that both common and convergent mechanisms underlie the domestication syndrome.

However, while the domestication syndrome of some crops such as cereals is becoming very well characterized, those of vegetable crops are less well characterized ([Meyer et al., 2012](#)) and yet others such as tree and rootstock cultivated plants remain poorly characterized ([Breton et al., 2009](#); [Warschefsky et al., 2016](#)). This is partially due to the better conservation of cereals in the fossil record, in part due to the research effort expended on the various species and largely due to the genetic tractability of the species in question. Nevertheless, genomics has revolutionized even our understanding of the evolution of crops that have historically been characterized only poorly ([Olsen and Wendel, 2013](#); [Sharma et al., 2018](#)). Two aspects have been particularly instrumental in this endeavor: the advent of next-generation sequencing ([Sharma et al., 2018](#)) and techniques that use broad natural allelic variance for assessing the genetic architecture of traits ([Zamir, 2001](#); [Olsen and Wendel, 2013](#); [Huang and Han, 2014](#)).

Trait	Crop	Domesticated gene	Function	Reference
Fruit/seed size and weight	Tomato	<i>SUN</i>	Unknown protein	Xiao et al., 2008
	Tomato	<i>fasciated</i>	TF	Cong et al., 2008
	Tomato	<i>fw2.2</i>	Similar to human RAS	Frary et al., 2000
	Rice	<i>qSW5</i>	Unknown protein	Shomura et al., 2008
Grain filling	Rice	<i>GIF1</i>	Cell-wall invertase	Wang et al., 2008
	Maize	<i>ZmSWEET4c</i>	Hexose transporter	Sosso et al., 2015
Growth habit	Soybean	<i>Dt1</i>	Signaling protein	Tian et al., 2010
Plant/inflorescence architecture	Barley	<i>INT-C (HvTB1)</i>	TF	Ramsay et al., 2011
	Barley	<i>Vrs1</i>	TF	Komatsuda et al., 2007
	Maize	<i>ra1</i>	TF	Sigmon and Vollbrecht, 2010
	Wheat	<i>Q</i>	TF	Simons et al., 2006
	Maize	<i>tb1</i>	TF	Doebley et al., 1997
	Rice	<i>PROG1</i>	TF	Jin et al., 2008; Tan et al., 2008
	Rice	<i>SD1</i>	Gibberellin biosynthetic enzyme	Asano et al., 2011
Seed casing	Barley	<i>Nud</i>	TF	Taketa et al., 2008
	Maize	<i>tga1</i>	TF	Wang et al., 2005
Seed color	Rice	<i>Bh4</i>	Amino acid transporter	Zhu et al., 2011
	Rice	<i>Rc</i>	TF	Sweeney et al., 2006
Seed dormancy	Rice	<i>Sdr4</i>	Zinc finger protein	Sugimoto et al., 2010
	Rice	<i>OsG</i>	Protease	Wang et al., 2018
	Soybean	<i>G</i>	Protease	Wang et al., 2018
	Tomato	<i>SolyG</i>	Protease	Wang et al., 2018
Shattering	Rice	<i>qSH1</i>	TF	Konishi et al., 2006
	Rice	<i>sh4</i>	TF	Li et al., 2006
	Sorghum	<i>Sh1</i>	TF	Lin et al., 2012
Style length	Tomato	<i>Style2.1</i>	TF	Chen et al., 2007
Flowering	Wheat	<i>Vrn1</i>	TF	Yan et al., 2003
	Wheat	<i>Vrn2</i>	TF	Yan et al., 2004
	Sunflower	<i>HaFT1</i>	TF	Blackman et al., 2010

Table 1. Selected Domestication Genes Spanning the Range of Traits that Have Commonly Been Described as Domestication Traits.

INSIGHTS FROM GENOME SEQUENCING

While detecting the phenotypic variance between a crop plant and its wild relatives is generally straightforward, the identification of the genetic basis for these differences has proved much more difficult. The most common approach has been the construction of segregating populations from a cross between a cultivated accession and a wild relative, followed by QTL analysis and, where possible, subsequent fine mapping of the respective domestication gene. The alternative approach is that of population genetic analysis using whole-genome profiling by direct (re-)sequencing of tens of diverse varieties of a domesticated crop and its wild progenitor. This method is largely coupled to genomic screening of artificial selection signatures to detect selective sweeps (Huang and Han, 2014).

To a large extent, next-generation sequencing has facilitated the definition of domestication genes, and crop improvement has thus been described to have been “democratized”

(Jackson et al., 2011) in that whole-genome sequences are now available for a large number of crops and their wild species (Supplemental Table 1). The availability of whole-genome sequences is a prerequisite for their use as both sources and recipients of allelic variance. As well as providing information on ortholog identities and selective sweeps, application of high-quality sequencing provides important information on three further features of domestication: genomic structural variation, transposable elements, and gene and whole-genome duplications (Olsen and Wendel, 2013; Scossa et al., 2016).

Genomic structural variation has been reported as underlying some important agricultural traits, with copy-number variation being linked to variation in wheat vernalization and flowering time (Diaz et al., 2012), as well as barley freezing tolerance (Knox et al., 2010). Moreover, transposable elements are present at high frequency throughout crop genomes (Morrell et al., 2011). Indeed a Hopscotch retroelement insertion in the

canonical domestication gene *tb1* of maize has been identified as underlying the single-stemmed maize phenotype (Studer et al., 2011). Similarly, the white berry phenotype of grapes (Walker et al., 2007) and blood orange color (Butelli et al., 2012) are both the consequence of retrotransposon insertions. The role of whole-genome duplication has been equally well documented, with a recent global survey of over 200 crop and over 2000 wild species revealing that polyploids are over-represented in crop species (Salman-Minkov et al., 2016). In addition to genome sequencing, considerable insight into domestication has also been provided by transcript profiling, epigenetics studies, and the use of metabolomics (Olsen and Wendel, 2013).

INSIGHTS FROM TRANSCRIPTOMICS, EPIGENETICS, AND METABOLOMICS

In maize a surprisingly large number of genomic regions to be involved in domestication and improvement, with genes tending to be expressed higher and exhibiting lower expression variability in maize than its progenitors (Hufford et al., 2012; Swanson-Wagner et al., 2012). Such large-scale reprogramming of transcription has also been observed in cotton (Rapp et al., 2010), tomato (Koenig et al., 2013), and common bean (Bellucci et al., 2014). This is quite likely in part a consequence of the fact that many of the domestication genes encode transcription factors that may have additional target genes to those targeted by artificial selection. A more recent genome-wide study revealed the important contribution that alternative splicing makes to regulating phenotypic variance in maize (Liu et al., 2015; Chen et al., 2018).

Several epigenetic variations have been noted to contribute to crop domestication; for example, the colorless non-ripening locus in tomato results from repression of an epiallele of a SQUAMOSA promoter binding protein-like transcription factor (Manning et al., 2006), and epialleles have been reported to associate with vitamin E accumulation in tomato. Roles for epialleles have also been reported in sex determination in melon (Martin et al., 2009), plant stature in rice (Miura et al., 2009), photoperiod sensitivity in cotton (Song et al., 2017), and somaclonal variation in oil palm (Ong-Abdullah et al., 2015). Furthermore, genome-wide studies investigating the methylome of important crop species suggest that the majority of these modifications are highly conserved within a species (Kim et al., 2015; Springer and Schmitz, 2017).

The application of metabolomics to specifically study domestication is fairly recent, although it is much used in QTL studies (reviewed in Fernie and Tohge, 2017; Fang et al., 2019) and is becoming a stalwart for studying the genetics of quality aspects of our crops (Klee and Tieman, 2018). However, two studies do explicitly address how domestication and crop improvement affect the metabolome. First, a deep evaluation of changes in primary metabolism in cultivated wheat and its progenitor species demonstrated that changes in unsaturated fatty acid and amino acid content mark the domestication of emmer and durum wheat, respectively (Beleggia et al., 2016). Second, a multiomics approach studying fruit from several hundred tomato genotypes has illustrated how features of

domestication have altered the metabolite content of this fruit (Zhu et al., 2018).

CURRENT CHALLENGES IN AGRICULTURE

In addition to ensuring that people in all parts of the world have enough to eat, future agriculture must meet a considerable number of other grand challenges, including becoming more sustainable, being tolerant to extremities of climate precipitated by climate change, and the need to bio-fortify the micronutrient content of our crops. Quantitative genetics approaches have revealed genomic regions and genes involved in water-use efficiency (Setter et al., 2011) and nitrogen-use efficiency (Li et al., 2018a) as well as disease resistance (Nelson et al., 2018). Furthermore, the use of naturally stress-resilient plants as a starting point toward high-production stress-tolerant crops has recently been postulated (Zhang et al., 2018a). In combination, these studies suggest that the tools to approach the challenge posed by climate change are already at hand. Moreover, better education of smallholder farmers in China has been demonstrated to increase yields despite a reduction in nitrogen fertilizer (Cui et al., 2018), suggesting that better agronomy remains a feature that needs to be factored into models for optimized sustainable production. A number of studies have additionally demonstrated the feasibility of enhancing the levels of micronutrients and vitamins in plants both using conventional breeding and transgenesis (Harjes et al., 2008; Yan et al., 2010; Fudge et al., 2017; Vasconcelos et al., 2017), hinting that incorporating these traits into the parts list of an ideal crop may not represent an insurmountable hurdle.

The threats to agriculture imposed by climate change are arguably more challenging to address. Many factors are associated with climate change, but four primary factors—rising temperature, an intensified hydrological cycle, increasing atmospheric carbon dioxide (CO₂), and elevated tropospheric ozone (O₃)—have affected and will continue to dramatically affect crop production (Lobell and Gourdji, 2012). While climate change is an almost universally acknowledged phenomenon, our understanding of its impact remains fragmentary, rendering predictions difficult. Despite the current lack of certainty of the exact effects of climate change, it is essential that breeding efforts continuously monitor improvements in the accuracy of projections and, in tandem with climatologists, consider traits that are currently measured and modeled in contemporary phenotyping approaches (Araus and Kefauver, 2018; Varshney et al., 2018) when planning future agriculture strategies (Henry et al., 2016).

REDOMESTICATION

Having retraced our steps to define the past domestication of our major crops, it is important to survey the current state of global agriculture and the challenges that face it in the near future. Humans currently cultivate, in large quantities, only about 150 of the estimated 30 000 edible plants worldwide (Shelef et al., 2017). These species all derive from one of the well-defined centers of origin described above (Meyer and Purugganan, 2013), yet most of them have achieved global

prominence mainly in areas in which they did not originate (Drewnowski and Popkin, 1997). This is, to a large extent, the case for the seven most globally used crops maize, rice, wheat, soybean, sugarcane, tomato, and potato (<http://www.fao.org/faostat/en/#home>; Figure 1). Intriguingly, this phenomenon is so extreme that nearly all the plants consumed by humans in the United States can be regarded as being exotic species (Pimmental et al., 2005), despite the fact that eastern North America is in itself an independent center of plant domestication (Smith, 2006; Smith and Yarnell, 2009). Of the six species of eastern Northern American domesticates, only squash (*Curcubita pepo*) and sunflower (*Helianthus annuus*) are currently still grown as crops (Smith, 2006; Smith and Yarnell, 2009). However, there is revived interest in many of the eastern Northern American domesticates (Mueller et al., 2017), as well as similarly developed species in Europe, Latin America, Africa, Asia, and Oceania (Dirzo and Raven, 2003; Smykal et al., 2018). For example, a recent review by Smykal and colleagues recommends several lost African species that could be recultivated (Council, 1996; Henry et al., 2016; Smykal et al., 2018). Furthermore, experiments have demonstrated that goosefoot cultivation can already produce harvests comparable with those of agricultural crops (Hernández Bermejo and León, 1994; Patton and Williams, 2016), suggesting that redomestication of this species via selective breeding or gene editing could render it an attractive alternative to the exotic species currently grown in North America (Mueller et al., 2017).

Alongside *de novo* domestication (i.e., the introduction of domestication genes into non-domesticated plants), such redomestications of crop wild relatives represent an important opportunity for fitting cultivated species to the climatic niche which they habit. Given the current uncertainties brought about by the changing climate, the deterioration of arable land, and the increased use of land for biofuel production, the advantages of local food production in terms of both secure and sustainable farming are manifold (Shelef et al., 2017). In this context it should not be overlooked that, in the developing world, 10%–15% of the billion hectares are farmed by traditional methods, and close to half a billion people cultivate food in smallholder farms (Shelef et al., 2017), so that restarting cultivation of lost species may be particularly valuable to such farmers since native species are often already adapted to the local environment and, as such, their farming requires less intensive input. Such strong claims have been made for Maramba bean and African Locus bean (Smykal et al., 2018) both of which have been targeted for genome sequencing by the African Orphan Crops Consortium (<http://africanorphanocrops.org/>). As a cautionary note it is important to recognize that domestication of new crops has nearly stopped; however, as we hope to convince the reader in the next two sections, new (and revisited) technological approaches for the accelerated domestication of these and food crop species are beginning to yield fruit.

DE NOVO DOMESTICATION

Collective evidence suggests that there are many ways to domesticate a plant. That said, results of the limited number of domestication experiments published to date suggest that artifi-

cial selection needs in excess of 20 generations to change the phenotypes of wild or crop wild hybrids (Hilu and Wet, 1980; Hillman and Davies, 1990; Hillman and Davis, 1990). Furthermore, studies on the genetic architecture of domestication suggest that domestication phenotypes under simple genetic control can be achieved more quickly than traits with a complex genetic basis. More problematic than the timescale of domestication is the phenomenon that has become known as the cost of domestication (Charlesworth and Willis, 2009; Gepts, 2014; Gaut et al., 2018), that is, the proposal that linked selection can drag deleterious mutants to high frequency (Chun and Fay, 2011; Zhou et al., 2017). Indeed, most crops examined to date contain considerably more deleterious allelic variants than their wild relatives (Renaut and Rieseberg, 2015; Kono et al., 2016; Liu et al., 2017; Ramu et al., 2017; Wang et al., 2017; Zhou et al., 2017), with species that are clonally propagated being particularly susceptible to accrue such mutations (Gaut et al., 2018). This phenomenon clearly needs to be carefully considered when planning future agricultural strategies.

The increasing demand for biofuels has driven increasing interest in the next wave of *de novo* domestications. For example, scientific breeding of leading candidates such as *Miscanthus* (Heaton et al., 2008) is under way, while research on close relatives of sorghum and sugarcane is booming (Paterson et al., 1995a, 1995b; Zhang et al., 2018b), as is that on alternative candidates such as tree tobacco and *J. curcas* (Montes and Melchinger, 2016; Usadel et al., 2018). Moreover, farming of aquatic plants such as duckweed (Cheng and Stomp, 2009) and seaweed (Loureiro et al., 2015) has also begun.

Although fairly few applications of *de novo* domestication of food and feed have been reported, there are several examples of how domestication genes were targeted in biotechnology approaches that predate the development and widespread adoption of genome-editing techniques (Osterberg et al., 2017). For example, the silencing of different genes (namely *LABA1* and *RAE2*) via RNA interference has been used to shorten the awns of a rice introgression with long barber awns (Hua et al., 2015; Bessho-Uehara et al., 2016). Similarly, the silencing of genes of fatty acid biosynthesis (*FAD2* and *FAE1*) improved the seed oil quality of the wild plant field cress (*Lepidium campestre*) (Ivarson et al., 2016). Mimicry of domestication has additionally been achieved by random mutagenesis followed by sequence evaluation of the “targeted” domestication gene. Examples of this approach include the shatter-proofing of weeping rice grass (*Microlaena stipoides*), an Australian wild relative of rice, via mutagenesis of the orthologs of *qSH1* and *sh4* genes (Shapter et al., 2013), while crop productivity in tomato has been improved by combining induced mutations in the florigen pathway (Park et al., 2014). Furthermore, a number of genome-sequencing studies have been initiated for species that can be regarded as currently in the process of being domesticated, including intermediate wheatgrass (*Thinopyrum intermedium*), field pennycress (*Thlaspi arvense*), tree tobacco (*Nicotiana glauca*), and apiois (*Apiose americana*) (Dorn et al., 2015; Belamkar et al., 2016; Kantarski et al., 2017; Usadel et al., 2018). These studies provide clear proof of principle that the alteration of single

domestication genes can dramatically improve the potential of little- or non-cultivated species.

Two parallel approaches have been suggested for the *de novo* domestication of wild plants: traditional breeding approaches (Runck et al., 2014; DeHaan et al., 2016) and gene editing (Altpeter et al., 2016; Kantar et al., 2016; Zsögön et al., 2017). For gene editing, the CRISPR/Cas9 approach has become the method of choice (Altpeter et al., 2016; Pacher and Puchta, 2017; Scheben et al., 2017). This genome-editing tool, which is modified from a prokaryotic immune system, induces double-stranded DNA breaks by the action of Cas9 nuclease at a genome location corresponding to a designed guide RNA (Altpeter et al., 2016) (Figure 4). Gene editing can, at least in theory, be used to: activate or suspend the function of any gene (Qi et al., 2013); create multiple different alleles of any gene (Rodriguez-Leal et al., 2017); achieve any base substitution (Gaudelli et al., 2017); add genes that do not exist in the original genome (Park et al., 2017); and delete any sequence including large chromosomal fragments or even the entire chromosome (Xiao et al., 2013). However, to date, prerequisites for the use of CRISPR/Cas9 are that the genome of the plant to be edited must be sequenced in order to identify known orthologs of domestication genes. As such, its use is currently largely restricted to cases wherein a loss-of-function mutation will lead to the domestication phenotype. That said, the number of species whose genomes have been edited is rapidly expanding (Osterberg et al., 2017), and important examples of loss-of-function mutants with beneficial effects include those enhancing rice and maize yields (Belamkar et al., 2016; Shi et al., 2017), the generation of virus-resistant cucumber (Chandrasekaran et al., 2016) and mildew-resistant wheat (Wang et al., 2014), improved soybean oil content (Haun et al., 2014), and potato storage ability (Clasen et al., 2016), as well as potentiating rubber production in dandelion (Iaffaidano et al., 2016).

Given the fact that we have in hand powerful portfolios of domestication-related genes, these techniques, or alternatively introgression breeding, provide us with an opportunity to revisit the ideotype model of Donald (1968), which posited that crop breeding should seek to achieve model characteristics rather than select against defective traits. The model was originally proposed for wheat but is equally applicable to any other domesticate. Zsögön et al. (2017) recently assessed the domestication of the world's six major crops and postulated that gene-editing techniques could be used to introduce key monogenic traits into crop wild relatives as a means of *de novo* domestication. They cover the major domestication genes of maize, rice, and wheat (Table 1), commenting that the majority of the genes identified represent modifications which could readily be targeted by available gene-editing technology and noting that one of the targets had indeed already been modified by such techniques in tomato (Livne et al., 2015). Zsögön et al. also surveyed two of the three next most important world crops, cassava and potato, arguing that potato and cassava were selected to accumulate biomass in underground sinks by alterations in the levels of cytokinins and the mobile signal SP6A, which are responsible for tuber initiation (Peres et al., 2005; Eviatar-Ribak et al., 2013). The authors suggest the disease-resistant *Solanum demissum* and *Solanum stoloniferum* as potential substitute crops for potato, and the large-rooted

and apoxic *Manihot glaziovii* and *Manihot neosana* (Nassar et al., 2008) as substitutes for cassava.

As three recent studies in the Solanaceae demonstrate, the potential of gene editing for improving domestication traits is vast—one of the studies is based on the orphan crop groundcherry (*Physalis pruinosa*) (Lemmon et al., 2018) while the other two describe *de novo* domestication of the wild tomato *Solanum pimpinellifolium* (Li et al., 2018b; Zsögön et al., 2018). The study on groundcherry focused on its undesirable characteristics for a crop, that is, its sprawling growth habit and small fruits, which drop to the ground due to strong stem abscission. It included development of a transformation procedure for this species alongside whole-genome sequencing and RNA sequencing in order to provide much-needed genome resources. Having these in hand, the researchers next examined homologs of the florigen suppressors and known tomato improvement genes, *SELF-PRUNING* (*SP*) and *SELF-PRUNING 5G* (*SP-5G*), with knockout of the first of these proving too severe and causing an extreme compactness but knockout of the second resulting in increased auxiliary flowering without changes in the primary shoot, which nevertheless resulted in enhanced fruit density (Lemmon et al., 2018). Similarly, targeting of the *CLAVATA* (*CLV*) pathway, which regulates shoot apical meristem size, resulted in increased floral meristem size, additional flower organs, and conversion from a two-locular to a larger three-locular fruit (Lemmon et al., 2018). The analogous studies in *S. pimpinellifolium* targeted *SP*, *SP-5G*, *CLV*, and a total of eight further domestication genes, looking to improve architectural traits, day-length insensitivity, fruit size and shape, and vitamin A and C content (Li et al., 2018b; Zsögön et al., 2018). Both studies were highly successful in terms of the specific traits that they targeted, doubling the yield of *S. pimpinellifolium* and increasing lycopene contents to 500% of control levels (Li et al., 2018b; Zsögön et al., 2018). A further example of the power of gene editing in breeding is provided by the recent demonstration that knocking out the self-incompatibility gene *S-RNase* allows redomestication of potato into an inbred-line based diploid crop, representing a promising alternative to traditional clonal propagation of tetraploid potato (Ye et al., 2018). The study demonstrated the utility of this approach in four different *Solanum tuberosum* clones, thus opening up the myriad possibilities in future diploid breeding, which will likely greatly facilitate both basic research and genetic improvement of potato and self-incompatible crops.

As an alternative, as well as being a powerful strategy to determine the genetic architecture of traits (Fernie et al., 2006), introgression breeding has been a staple of crop improvement over many years, with considerable gains being made in yield (Ashikari et al., 2005) and disease resistance (Nelson et al., 2018). In practice, this occurs by creating populations of near-isogenic lines in which either a single locus is introgressed via backcrossing (Belcher et al., 2012), a large number of loci can be introgressed (Liu et al., 2016), or lines at the end of the inbreeding process harboring residual heterozygous regions can be self-pollinated to produce near-isogenic lines divergent at these regions (Tuinstra et al., 1997). Taking plant yield as a case study in rice, Ashikari et al. (2005) identified the QTL *Gn1a* for grain number and combined it with other desirable traits such as plant height in a process known as QTL pyramiding. In a similar

combinatorial approach, Gur and Zamir (2004) demonstrated that by pyramiding three independent yield-promoting genomic regions from the drought-tolerant *Solanum pennellii*, they were able to elevate tomato yield dramatically. As well as yield, introgression has been commonly used in breeding late blight disease resistance in potato (Haverkort et al., 2016) and submergence tolerance in rice (Bailey-Serres et al., 2010), among many examples of traits altered by exotic introgression. Indeed introgression breeding currently benefits greatly from the vast number of available crop wild relative genome sequences (Supplemental Table 1). As yet, relatively few studies have performed introgressions in the opposite direction, that is, the introgression of domesticated alleles into exotic backgrounds. However, if genome sequences of the domesticated and wild relative are available and key domestication genes of the domesticate are known, transferring said genes into the exotic germplasm is fairly straightforward. Thus, if public concerns over the use of gene editing are not allayed, introgression breeding could prove an effective alternative tool for *de novo* domestication. Indeed, unlike current gene-editing approaches, introgression breeding is also capable of examining the effect of large structural genome variants—via the use of introgression of large chromosomal sections—which have recently been demonstrated to play an important role in the domestication process (Olsen and Wendel, 2013; Huang and Han, 2014). In addition, it can replicate other modes of action of gene editing if suitable source alleles are available (Figure 3). Moreover, as observed in the *de novo* domestication of groundcherry (Lemmon et al., 2018), knockout strategies are sometimes too extreme and more subtle changes are often required to produce the desired phenotype (Comai, 2018). This can admittedly be achieved via subtler gene-editing strategies as illustrated by the introgression of LIN5, which succeeded in enhancing agronomic yield in tomato (Fridman et al., 2004) following the failure of multiple transgenic approaches with the same aim (Sweetlove et al., 2017). Nevertheless, introgression breeding has two clear disadvantages with respect to gene editing. Firstly, the range of phenotypic variance that can be introduced is constrained by that which is available in species that are so closely related that one can cross them with one another. Secondly, the occurrence of linkage drag of deleterious alleles of nearby genes requires close attention when following the introgression approach so as to avoid paying a too heavy cost of domestication, that is, accumulation of too many linked deleterious mutations, via this approach.

For either approach, suitable species need to be found and extensive preliminary characterization performed to assess their suitability. We have collated a list of possible candidate species alongside important indicators such as ease of transformation, exhibition of one or more desirable traits, and genome sequence information, which are currently a prerequisite of this approach (Supplemental Tables 1 and 2). Following identification of an appropriate species, we suggest that it should be *de novo* domesticated via the modification of a few genes, as described in the examples above; beyond this, we suggest to optimize the resultant crop via the use of synthetic biology approaches to introduce novel pathways, such as for example high levels of provitamin A (Beyer, 2010), anthocyanins (Butelli et al., 2008), and omega-3 fatty acids (Napier et al., 2018) or even medicinally important compounds, such as artemisinin (Fuentes et al., 2016)

and resveratrol (Zhang et al., 2015). Finally, once stabilized populations exist, we propose the introduction of multiple pathways with batteries of genes, thus addressing high production efficiency, high fertilizer-use efficiency, high resistance and adaptation, balanced nutrition, and great flavor in order to create the ideocrop. Such an ideocrop can be varied by combinatorial blending of different characteristics to meet specific needs (Figure 5). A wonder crop like this would have been dismissed as a pipedream a mere few years ago, but technological advances, as well as arguably more importantly mechanistic insights into the genes displaying major influence on the above traits, have rendered this feasible. Of course we are not proposing a single ideal crop but rather several that are adapted to their growth habit and capable of producing food (or for that matter biofuel or medicine) locally. In addition, to learn from the errors of our past we suggest that the generation of these plants is done in a manner that does not introduce a genetic bottleneck, that is, either by introducing domestication genes into a range of individuals within a population or, more feasibly, by crossing the *de novo* domesticate with a broad range of individuals to circumvent the accumulation of deleterious mutations, which has hampered our current crops. As well as generating a less intensive agriculture, the tailoring of crops to their growth environment in a manner that also yields nutritious harvests may ultimately have the added bonus of reducing the environmental footprint associated with global transport.

CONCLUSIONS AND FUTURE PERSPECTIVES

The history of crop domestication parallels the most glorious era in human history in the past 12 000 years. It has produced a splendid agricultural civilization and culture, allowing human beings to transition from a nomadic hunting life to their self-sufficient modern life. Over the past 100 years, thanks to the development of modern agricultural technology, and especially the first green revolution (Figure 4), people have been able to efficiently and directionally improve crops, allowing great increases in crop yield and consequently the number of people they can sustain. While this is undeniably impressive, it is important to acknowledge that the high-input and high-output mode of the first green revolution has also brought tremendous pressure to bear on our plants, and is becoming increasingly unsustainable (Osterberg et al., 2017). Moreover, while focusing on increasing crop yields, the improvement of crop quality and acutely that of micronutrients has been largely overlooked. The consequent nutritional imbalance has brought serious health problems (Martin and Li, 2017), and as such next-generation crops enriched in micronutrients are required to address human diet-related chronic disease (Francis et al., 2017).

In fact, the process of crop domestication has been very slow. Today's knowledge tells us that this process involved only a limited number of genes, with some of these even being conserved among different species (Table 1). This opens up the possibility of knowledge-driven crop redomestication or even *de novo* domestication. Genome-editing technology has proved to be a reliable tool for rapid and accurate improvement of target traits in different plants. There have been many successful examples in the past few years (Zhang et al., 2018c). In recent cases (Lemmon et al.,

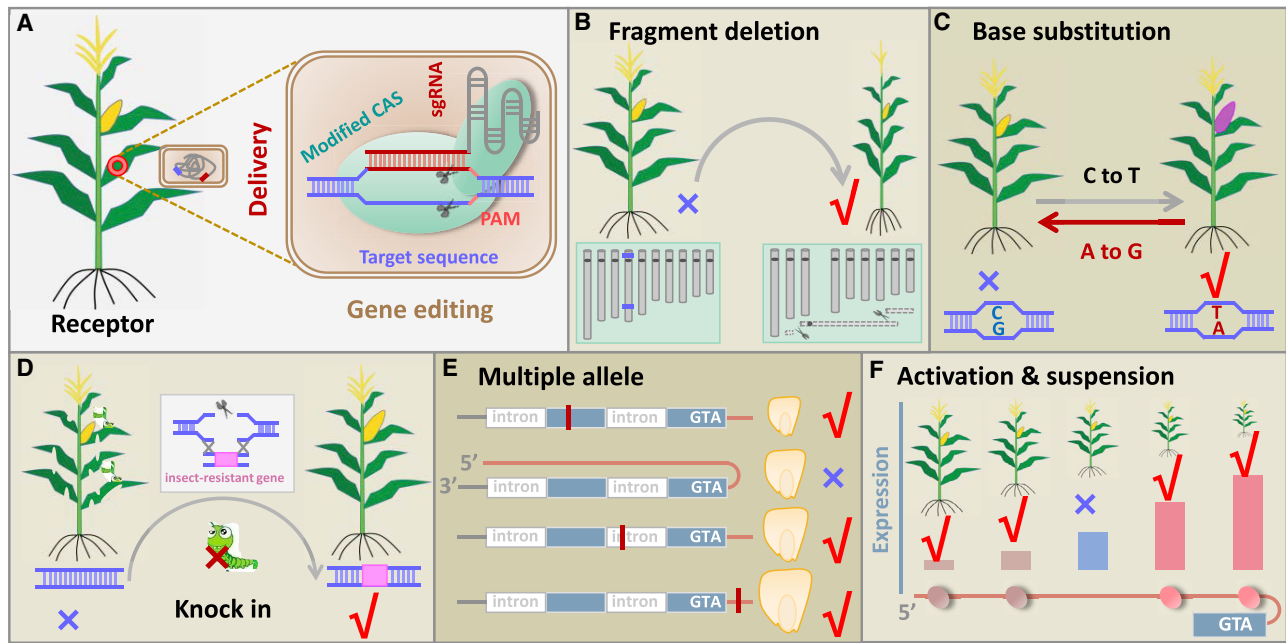


Figure 4. A Simplified Schematic Representation of Genome-Editing Techniques in Plants and Their Potential Application. (A) Gene-editing model, including editing element delivery and modified model with single guide RNA (sgRNA) and different functional CAS protein or protein complex. (B and C) Delete any sequence including large chromosomal fragments or (B) even the entire chromosome via paired sgRNA (C) to achieve any base substitution. (D–F) Add genes that do not exist in the original genome (D), create multiple different alleles of any gene (E), and activate or suspend the function of any gene (F). Ovals represent activator complex (red) and repressor complex (pink).

2018; Li et al., 2018b; Zsögön et al., 2018), wild relatives have been readily transformed into cultivated crops by several genetic changes, which show the prospect of crop redomestication. In Figure 5, we outline several key steps for future ideal crop design. Finding wild or semi-wild plants suitable for editing remains the most critical step. For this reason we defined key indicators and on their basis have suggested a list of plants that may be suitable for *de novo* domestication (Supplemental Table 1). In our opinion, those plants with one or more of the following traits (perennial grains, high nutritional value, high water-use efficiency, nitrogen

fixing, and poor soil tolerance) should be given priority. We do not mean to trivialize the difficulties inherent in achieving these goals, which will clearly additionally need a much deeper understanding of the genotype to phenotype equation. Indeed relatively few traits can be attributed directly to single genes, be they transcription factors or other genes. Network-level understanding of biological complexity will ultimately require insight into how genotypic information translates into the emergent properties of the phenotype. That said, the tools are now in hand both to investigate this complex behavior and to influence it in a beneficial

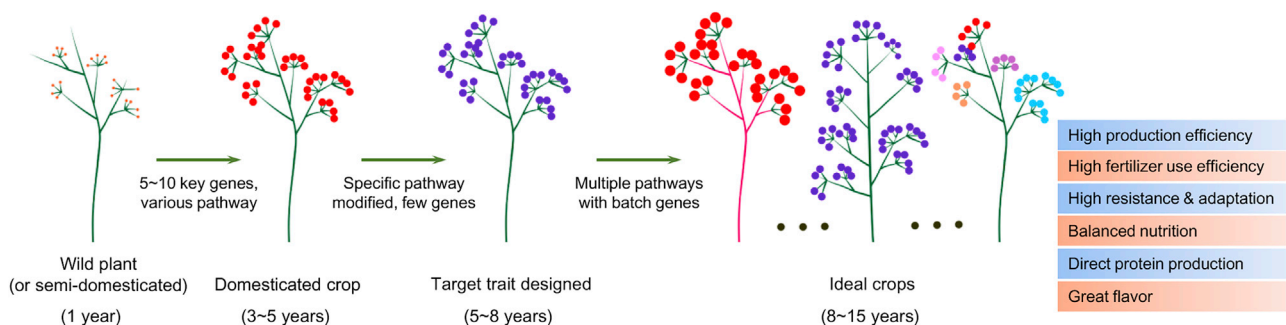


Figure 5. A Roadmap and Timeline for Ideal Crop Breeding. Ideal crops can be cultivated from wild plants or any other (semi-)domesticated crops. The process involves four major steps: (i) the collection and evaluation of a novel plant chassis (~1 year), which should include several favorable features including ease of transformation, exhibition of one or more desirable traits, and genome sequence information; (ii) *de novo* domestication via editing, or introgressing, a few genes affecting key traits (~3–5 years); (iii) reaching a given target trait by modifying a specific pathway (~5–8 years); and (iv) designing the ideal crop for any given trait with a larger number of genes edited in sophisticated, accurate, and ensemble manners (~8–15 years). Potential target traits are listed within the figure.

manner. While studies to date demonstrate the first examples of our ability to influence it, the knowledge to rationally design novel plants will take a good while longer to acquire.

Transgenesis-based approaches, while direct, are, at least in some countries, restricted due to lack of public acceptance. The recent ruling by the European Union that gene-edited plants should be considered as genetically modified organisms means that, at least in Europe, this is also the case for gene-edited lines (Callaway, 2018). However, it is important to note that the US Department of Agriculture does not consider genome-edited crops to be genetically modified organisms (Ledford, 2013). Recently, some researchers proposed five steps as the primary guiding principles for regulating genome-editing products (Huang et al., 2016), providing a basis for discussion and hopefully the development of a consensus. We believe that such a consensus will pave the way for the next ideocrop cultivation. It will, naturally, need strong regulatory control, particularly given the fact that many crop wild relatives accumulate higher levels of harmful or even toxic specialized metabolites (Osterberg et al., 2017). However, even in the case that gene editing does not find societal acceptance, introgression-based approaches (Figure 3) can be adopted for the purpose of *de novo* domestication.

In addition to policy barriers there are also technical challenges, such as those presented by transformation technology. At present, gene editing of all plants relies on transformation technology, but transformation of many plants remains an obstacle (Supplemental Table 1). High-efficiency transformation technology (Lowe et al., 2016) and pollen-based transformation technology (Zhao et al., 2017) provide new opportunities for solving this challenge. The lack of understanding of genome structure and gene regulatory networks is also a bottleneck for the realization of ideal crops at the third step shown in Figure 5. However, we advocate that knowledge-driven genetic architecture dissertation and big-data-driven machine learning, as well as technological breakthroughs from synthetic biology and other fields, will ultimately help us achieve the ambitious goal of ideocrop design.

SUPPLEMENTAL INFORMATION

Supplemental Information is available at *Molecular Plant Online*.

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