Opinion

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Current challenges and future perspectives of plant and agricultural biotechnology

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Advances in understanding plant biology, novel genetic resources, genome modification, and omics technologies generate new solutions for food security and novel biomaterials production under changing environmental conditions. New gene and germplasm candidates that are anticipated to lead to improved crop yields and other plant traits under stress have to pass long development phases based on trial and error using large-scale field evaluation. Therefore, quantitative, objective, and automated screening methods combined with decision-making algorithms are likely to have many advantages, enabling rapid screening of the most promising crop lines at an early stage followed by final mandatory field experiments. The combination of novel molecular tools, screening technologies, and economic evaluation should become the main goal of the plant biotechnological revolution in agriculture.

Plant biotechnology and agriculture: targets, plant resources, and scientific tools

The potential contribution of plant and agricultural biotechnologies to solve some of the major issues of world population, food supply, and climatic–environmental changes are discussed elsewhere [1]. This is further emphasized by a recent report [2] clearly revealing that world population is unlikely to stop growing this century, contrary to previous estimations. Production of novel plant-based biomaterials, an additional target for plant agriculture, is discussed here separately.

While agricultural production advanced impressively during past decades due, among other factors, to the implementation of biotechnological tools, several remaining important issues must be addressed. The major current missions of plant and agricultural biotechnology are mentioned below and are further discussed in this opinion article:

- the contribution of new plant biotechnological tools to advanced crop breeding;
- bottlenecks holding back the translation of genomic data to crop plant traits (i.e., the genotype–phenotype gap);
- the crucial importance of plant adaptation and tolerance to abiotic and biotic stress for sustainable agricultural production;
- the role and significance of epigenetics for plant development under changing environmental conditions; and
- plant biomaterials and biofuels as a novel scope of agricultural biotechnology.

The major targets of plant and agricultural biotechnologies, which are illustrated as the processing and screening funnel (Figure 1), include sustainability (practicing agriculture *vis-à-vis* taking care of our environment and keeping a proper ecological balance), food security (i.e., yields – both quantity and quality – supplying caloric needs, proteins, lipids, vitamins, and all other nutritional factors), and the production of novel biomaterials (e.g., plant-based pharmaceuticals, bioplastics, biofuels). The wide reservoir of millennia-old plant and gene resources (at the top of the funnel), emanating from ancient plant evolution and domestication since the first agricultural revolution, were followed by gradual, long-term changes in crop qualitative and quantitative traits through continuous natural and human-directed breeding and selection. It is noteworthy that of a total of approximately 400 000 species of flowering plants, less than 200 have been domesticated as food and feed plants and only 12 species provide 75% of the food eaten [FAOStat (2010) *Production Data Relating to Food and Agriculture* (http://faostat.fao.org) Figure I]. This science-based traditional plant breeding has produced most of the crop varieties that we use today. However, the traditional techniques are no longer sufficiently powerful to satisfy current and future needs for the three targets mentioned above. Understanding of genomics paradigms has advanced considerably in the past decade. This resulted in a more integrative and deeper comprehension of how genetic and epigenetic processes regulate plant growth and development and response to the environment. The era of omics, including genomics, transcriptomics, epigenomics, proteomics, and metabolomics, is poised to facilitate biotechnological improvement of crops, particularly for physiological phenotypes that are controlled by

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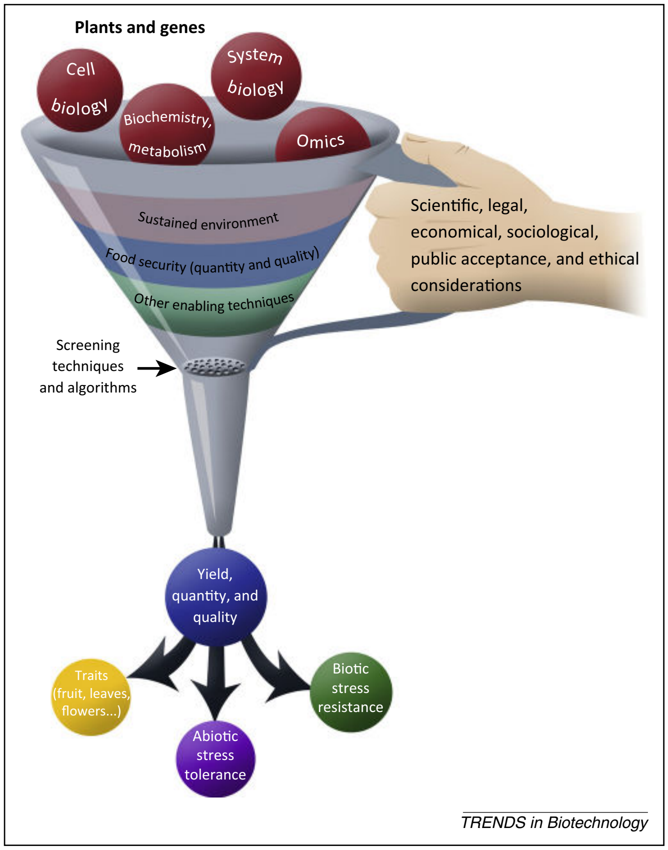


Figure 1. The agricultural biotechnology processing and screening funnel. The agricultural biotechnology landscape is presented here as a processing and screening funnel comprising the major targets of plant and agricultural biotechnologies. The funnel is nourished by the various 'ingredients'; that is, diverse scientific inputs in addition to plants and their genomes. Following appropriate screening techniques, the various agricultural products and traits are expressed and released for consumers. The hand holding the funnel emphasizes that all biotechnological applications should be evaluated with respect to their contribution to global food security and judged by economic, sociological, legal, and ethical criteria.

complex genetic and epigenetic mechanisms. Since many developmental and environmental responses are known to be regulated by epigenetics, it is predicted that reprogramming of the epigenome will be a substantial factor in crop breeding and cultivar development [3]. Abiotic stress might induce epigenetic changes as well, and epigenetic regulators might have an adaptive advantage – although we must consider a negative impact on crop yield by preventing the plant from growing to its full potential [4].

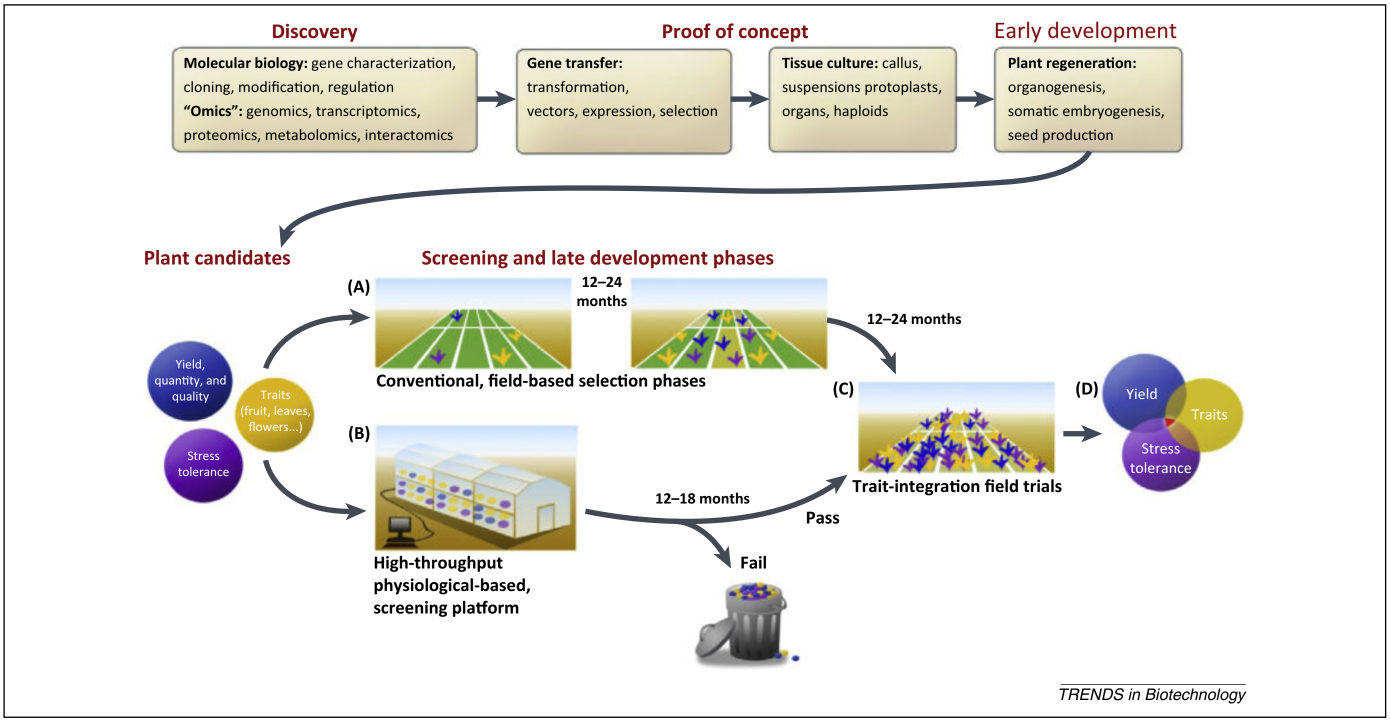
Further advances in plant biotechnology and agriculture depend on the efficient combination and application of diverse scientific inputs (Figure 1) as the ingredients going into the biotechnology processing funnel: cell biology, biochemistry, and metabolism, the various omics, systems and synthetic biology approaches, and other, enabling techniques (e.g., tissue culture, transformation, informatics). Additional major achievements in plant biology are the new methods of plant genome engineering. For example, the bacterial RNA-directed CRISPR–Cas9 endonuclease is a versatile tool for site-specific genome modification in eukaryotes. This method is applicable for genome editing of any model organism and minimizes confounding problems of off-target mutations [5] and is expected to become a method of choice, in addition to other novel technologies, for allelic modifications, gene replacement, structural characterization of the proteome, and post-translational modifications [6]. This rapidly expanding genome engineering toolkit may provide unprecedented control over the genetic information of plant genomes [7] and is important for elucidating plant metabolic, physiological, and morphological traits and therefore for better controlling and modifying biological structure and function [8,9].

Unlike laboratory studies, the realization of plant biotechnologies in the field cannot be translated and applied to agricultural practices without rigorous testing procedures and screening techniques employing reliable algorithms, as depicted by the funnel screen. Multinational research is already taking into account the biology–agriculture crosstalk, paving the way to more effective and productive development of new cultivars (Figure 2).

Once the screening parameters have been satisfied, the products of plant and agricultural biotechnologies are released from the processing and screening funnel into the field and the market (Figure 1). The variety of products and traits include agricultural products for direct human consumption (e.g., grains, fruits, tubers, bulbs, corms, leaves, flowers, fibers, cork, timber). Both product yield and quality (e.g., nutritional value, market and storage ability, taste, color, aroma) and botanical traits of importance to plant development (e.g., shoot and root architecture, growth and elongation, genetic control of flowering) [10–14] must be considered. Most important in view of the detrimental changes in climatic conditions are tolerance and adaptation to abiotic (drought, salinity, extreme temperatures, pollution) and biotic (e.g., fungal and bacterial diseases, insects) stresses. Seed companies are investing enormous effort into developing crops with higher tolerance to drought, heat, cold temperatures, and salinity [15]. Recent studies have identified a large number of genetic and molecular networks underlying plant adaptation to adverse environmental growth conditions [16]. All of these studies emphasize the complexity of the various traits and their polygenic nature (Box 1). Finally, as depicted by the hand holding the funnel, all biotechnological applications should be scrutinized with respect to global food security, economic, sociological, legal, and ethical considerations, aiming at public acceptance [17–21].

Bridging the genotype–phenotype gap

Pre-field phenotyping to increase the proportion and number of high-potential crop candidates, thus saving time and money and bridging the genotype–phenotype gap, is one of the major agrotechnology visions (Figure 2). Gene discovery integrates molecular biology and omics tools and procedures, as depicted in the discovery panel. This is followed by the proof of concept panel, which includes gene transfer stages and various tissue culture operations. Early development of transformed plant candidates occurs following *in vitro* plant regeneration, yielding plant candidates for various traits. The plant candidates that have passed the discovery and proof-of-concept phases undergo several additional evaluation and assessment steps throughout the screening and development phases, selecting the lines



TRENDS in Biotechnology

Figure 2. Bridging the genotype–phenotype gap. Production of novel, field-acceptable crop plants by either traditional breeding or genetic engineering depends on first creating a new genotype, followed by selection of the appropriate phenotypes. The process starts with gene discovery (the discovery panel), followed by gene transfer (the proof-of-concept panel) and the production of plant candidates (the early development panel). The resulting new plant candidates undergo several assessment, screening, and development steps aimed at the selection of lines with improved stress tolerance, yield, and development. The final evaluation of trait integration must be performed under field conditions, using efficient, high-throughput phenotyping platforms.

that present good stress tolerance while maintaining other desirable traits such as yield (quantity and quality), growth, and development [22,23] (Box 1).

The predominant procedure today is the selection of few plants from thousands using conventional, field-based selection processes that require whole seasons and repeated large-scale field trials. This long process may last several years and requires considerable resources, limiting the number of promising candidates that can be screened simultaneously [24–26]. We envision the development of a high-resolution, high-throughput diagnostic screening platform for the study of whole-plant physiological performance that serves as phenotypic screening – 'physiolomics' (Figure 2) – thereby bridging the existing genotype–phenotype gap. Hundreds of plants subjected to multiple combinations of stressful conditions may be screened simultaneously at particular stages of their life cycles. The phenotyping screening system can dramatically accelerate the development process and allow continuous measurement of crop behavior under controlled standard and stress conditions, to eliminate at an early stage in the greenhouse those candidates that are unlikely to perform well in field trials [27–29]. The costs of the phenotyping process are an important issue; however, the technology is rapidly developing and as yet it is difficult to estimate the costs.

Candidates passing this phase will go directly to the obligatory trait-integration field trials that will always be required before market launch. This final verification stage should integrate expected environmental conditions with the desired traits, leading to the selection of a few superior candidates that exhibit good stress tolerance as well as other desirable traits.

Plants as factories for biomaterials and biofuels

Plants produce more than 500 000 secondary metabolites with relatively low and cheap inputs [1,30,31]. Novel gene discoveries and the availability of improved metabolomics data, plant engineering procedures, and industrial platforms enable improved production not only of food and traditional plant-derived products such as fiber and cork but also of novel non-plant compounds (Figure 3). These include several major categories, briefly mentioned below, some of which are potentially attractive substitutes for petrochemical-based materials and can be produced in transgenic plants [32–34].

Plant-based biopolymers and industrial enzymes

These include many novel polymers produced in transgenic plants, such as biodegradable thermoplastics, polysaccharides for bioaffinity purification, temperature and salt-resistant enzymes for the food, paper, detergent, and other industries (e.g., cellulases, trypsin, amylases), and fibrous proteins (e.g., elastin, silk) with important material properties [34,35].

Therapeutic products

The use of plants as bioreactors for the production of 'foreign', non-plant biopharmaceuticals includes the production of bioactive peptides, vaccines, antibodies, and many therapeutic products such as hyaluronic acid and collagen [34,36–39]. The concept of 'molecular pharming' – that is, the production of edible vaccines in engineered plants that are consumed by people [40] – has been recently combined with efficient pharmaceutical production using plant-based industrial platforms [40,41]. This is based on

Box 1. Growth, development, and stress tolerance

The physiological and molecular control of root and shoot development and architecture, as well as flowering programs and fruit development, are major targets for both traditional and biotechnological advances. For example, the roots can influence the developmental processes of the shoot, including the regulation of shoot system architecture, via hormone transport. The three classes of hormone implicated in the regulation of bud outgrowth are cytokinins, strigolactones, and auxin. The first two are produced in the roots and transported to the shoot via the xylem and are central to the control of bud activation, apical dominance, and shoot branching as well as being involved in other mechanisms controlling flowering and panicle branching that are important for crop yields. Moreover, flowering is the most stress-sensitive phase in many crops; maize plants, for example, showed much greater yield losses following prolonged water stress during tasseling and ear formation stages than after similar stresses at any other growth stage. Currently, a major focus is how these organs interact with each other and how they are affected by the environment. Understanding of these interactions and their organization, development, and modulation by the environment is likely to be a decisive factor in designing future agricultural crops with an improved harvest index that are less susceptible to changing environments.

The current notion is that the defense mechanisms of plant genotypes against environmental stress conditions are tightly associated with their growth habits (genotype × environment interaction) and hence every claim of tolerance enhancement needs to be evaluated on a crop-yield basis for its agricultural economic significance. As yet, efforts to improve plant stress tolerance by genetic transformation have resulted in few important achievements. Unlike the limited success in developing abiotic stress-resistant crops, there are more examples of how basic research has contributed to breeding for crop resistance to biotic stress. This is also largely due to the fact that, in many cases, plant responses to diseases and insects are controlled by only a few genes. However, the response to abiotic stress conditions involves a large number of genetic and molecular networks, emphasizing the complexity of the various traits and their polygenic nature, which has made it difficult to achieve substantial effects in crops without side effects on yield. For this reason, biotechnology should be fully integrated with appropriate screening techniques and with classical physiology and breeding.

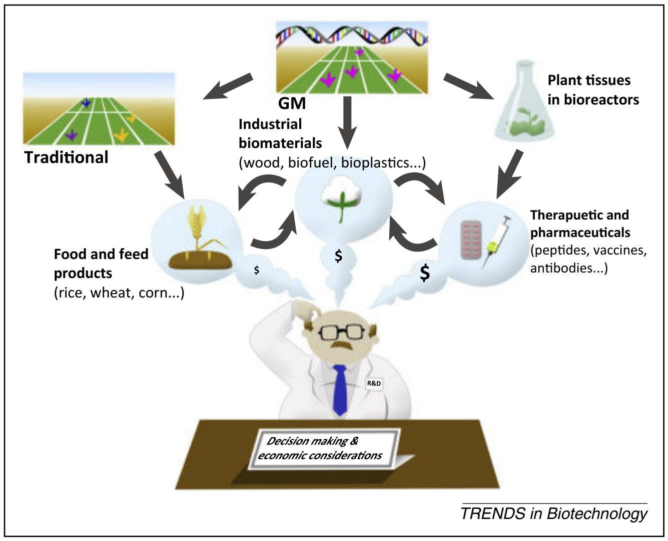
new technologies involving stable nuclear genetic transformation and the use of plastid transformation as well as transient expression technologies [41]. The new technologies and processing systems resulted recently in FDA approval of the first plant-derived recombinant pharmaceutical protein for human use – Elelyso for Gaucher disease [42] – and the production of several clinical-grade proteins.

Nutritional components

Often referred to as nutraceuticals, these are various nutritional components that improve the nutritional value and quality of foods and can be produced in transgenic plants. Included are specific amino acids, vitamins, flavonoids and other antioxidants, and increased bioavailability of essential minerals (e.g., iron) and others substances beyond the scope of this opinion article.

Biofuel and biodiesel

Most biofuel production is ethanol derived from starch or sugar feedstocks such as corn or sugarcane [1,43,44]. Increased biofuel production from food crops can negatively affect food market prices and therefore crop plants tend to be replaced by the lignocellulosic biomass of second-generation plants (mainly forest trees) and grasses such as switch grass (*Panicum virgatum*), *Miscanthus giganteus*, and sorghum grown on marginal soils [45]. Moreover, energy derived from plants has a much lower CO_2 footprint than petroleum or gas and thus plants can be considered 'CO_2 mitigators'. Biodiesel is currently produced mainly from soybean and canola, but oils from seeds of non-food plants such as castor bean (*Ricinus communis*) are possibly a good alternative.



TRENDS in Biotechnology

Figure 3. Plants as factories for biomaterials. Both traditional food and feed products and common industrial materials are produced by field-grown traditional agricultural plants or by field-grown plants that were previously engineered for improved production of the required product. Novel non-plant 'foreign' biomaterials (e.g., pharmaceuticals, industrial biomaterials) are produced by plant cells and tissues that were previously engineered to produce the desired product, most often in vials/bioreactors in industrial laboratories but sometimes also in the field. The decision-making stages and economic feasibility include several critical considerations, including which plants to employ and which biocompounds to produce and which industrial platforms fit best depending on operational costs, yield efficiency, and the market value of the compound.

Appropriate targets for the production of novel biomaterials in plants are compounds that can be produced more efficiently in plants, can be produced reliably without negatively affecting crop yields, have better physical/chemical properties when produced in plants, or are needed as a bulk material at low cost via photosynthesis [32,33]. However, while technically possible, the practical acceptance of plant biotechnologies depends also on economic/commercial considerations that may limit market acceptance, as further discussed below.

Culture systems and product types

Food and feed products, as well as novel biomaterials, are produced by field-grown traditional agricultural crops or trees or in field-grown plants that were previously engineered to improve production of a specific natural product or to produce foreign, non-plant compounds (e.g., pharmaceuticals, industrial biomaterials). Alternatively, the latter can be produced by plant cells and tissues are grown in vials/bioreactors in industrial laboratories after being engineered to produce the desired product and/or its production being elicited by modifying growth conditions or by exposure to chemical elicitors.

Decision-making strategies and economic/commercial considerations

These include first analyzing which of the many biomaterials are relevant (depending on the market price of the product, with preference for the more expensive) followed by considering which plants fit better based on their yield efficiency, natural production characteristics (e.g., is the desired metabolite produced in leaves, roots, storage organs, or seeds), culture conditions, and yield (preferring non-food plants to avoid increasing market food prices). This is followed by evaluating whether to prefer field-grown plants (usually for cheaper products) or laboratory-type facilities (usually in the case of expensive products that are difficult to produce in the field). Appropriate growth conditions for the selected plants or compounds should be tailored for each case to increase production and decisions should be made regarding the plant organ and harvesting procedures as well as compounding downstream processing including isolation, purification, and formulation techniques. Crucially important for accurate determination of the economic feasibility are the overall biomass of the plant (fresh or dry weight/day), the yield (g product/g weight or l medium) of the specific compound, and the productivity (g product/unit field area or medium volume/day or growing season). Finally, the market competitive edge of all former steps should be evaluated and improvements and adjustments made.

The future commercial acceptance of novel biomaterials is difficult to predict at this stage and very few economic evaluations have been published. The best available examples are related to plant-derived novel pharmaceuticals [46,47]. It is generally accepted that in many cases it remains cheaper to produce some materials in traditional pharmaceutical platforms where industrial processes have been optimized for many years. However, plant-based platforms, either using cell bioreactors or directly in field-grown transgenic plants, especially seeds, have many unique advantages for specific niche markets. These include: (i) unique plant-specific metabolic capacities combined with a large number of specific metabolite intermediates that can be used for therapeutic purposes and that are not produced by microbial or mammalian cell production systems; (ii) plants offer considerably less expensive and rapidly scalable possibilities to meet the demand for low-cost and large-scale production; (iii) ongoing improvements in the yield of plant products due to novel gene expression and transient expression systems; (iv) development in plants of cost-effective downstream processing, which is a significant part of production costs; and (v) glycosylation of the product can affect its pharmaceutical quality, yet some glycosylation patterns in plants are similar to those in mammalian cells while others differ, and in a few cases it has been demonstrated that the glycan profiles of plants can improve the performance of pharmaceutical proteins [46,47].

Concluding remarks and future perspectives

While plant agricultural biotechnologies have come to fruition due to the implementation of novel molecular marker-assisted crop breeding and genetic engineering, it is important to distinguish the many considerable achievements from several remaining questions and to point out future R&D needs.

At the genotype level, the use of genome mapping and omics markers resulted in impressive advances and became routine in the breeding of several field, horticultural, and forest plants. At the phenotype level, improved agricultural techniques (e.g., precision agriculture) are continuously being developed, resulting in enhanced agricultural, horticultural, and forestry yields and quality traits. In addition, novel high-throughput selection systems are being developed to enable rapid pre-field screening for specific traits and may eventually become routine.

Future directions, the prospects for which seem promising, should be aimed at solving the current major hurdles to agricultural biotechnology. (i) Bridging the genotype–phenotype gap by improving quantitative and automated selection and screening methods that focus on whole-plant physiology (e.g., transpiration, photosynthesis) and quality traits. These traits, combined with decision-making algorithms, will enhance the release of newly bred varieties to farmers and avoid long development phases and large-scale field studies. (ii) Bridging the genome–environment gap: since many desired plant traits depend on the interaction of many genes and metabolic pathways with the environment, enhanced adoption of translational and interactome research at all R&D stages (viz., continuously relating molecular data and breeding parameters to field performance) should preferably use more model crop plants. (iii) More attention should be given to epigenetic molecular events that are evolutionarily most relevant to plant adaptation to changing environments. (iv) Improving the biotechnological procedures of novel biomaterial production. (v) Promoting transparent dialog between molecular biologists and plant physiologists on the one hand and farmers, breeding companies, and the public on the other hand to solve jointly the economic, sociological, legal, and ethical hurdles.

We thus urge the adoption of a systems bioagriculture integrated approach (as in systems biology), also considering the plant microbiome, to achieve substantial progress in plant biotechnology and agriculture in the 21st century.

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