

## Previews

# CRISPR meets AI-based robotics: Advancing sustainable agriculture

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In this issue of *Cell*, Xu and colleagues develop an approach integrating genome editing, artificial intelligence, and robotics to enhance crop improvement. By reconfiguring reproductive traits for automated pollination in crops such as tomatoes and soybeans, their approach accelerates hybrid seed production and yields crops with better stress tolerance, flavor, and resilience, supporting sustainable agriculture and crop diversity.

Global food security is increasingly challenged as population growth, climate change, and emerging biotic and abiotic stresses place rising demands on agricultural systems. One of the most successful strategies in plant breeding to boost yields has been the exploitation of hybrid vigor, also known as heterosis. First described by Kölreuter in 1761,<sup>1</sup> heterosis results from crosses between distinct varieties, producing F1 hybrids with enhanced agronomic traits. However, this effect is largely confined to the F1 generation, necessitating continuous and labor-intensive emasculation and crossing to maintain superior hybrid seed stocks. Yet despite its long history of application, the molecular basis of heterosis remains only partially understood.<sup>2</sup> Addressing today's challenges requires moving beyond conventional methods by combining decades of breeding expertise with innovative technologies to support sustainable crop improvement and cultivation systems. Among the most significant recent advances in biotechnology is the application of sequence-specific nucleases, with CRISPR-Cas9 emerging as the pivotal tool to engineer plant genomes for contemporary agricultural challenges.<sup>3</sup> Complementing advances in genome optimization, precision-farming robotics are being developed to automate pollination, harvesting, and resource management, though their effectiveness remains constrained by complex plant architecture. In parallel, artificial intelligence (AI) has become a powerful approach to integrate genomic and phenotypic datasets, revealing patterns of growth, develop-

ment, and stress responses.<sup>4</sup> By converting raw data into biological insight, AI is beginning to deepen our understanding of adaptation, selection, and heterosis while, in combination with gene editing, paving the way for more efficient breeding strategies.

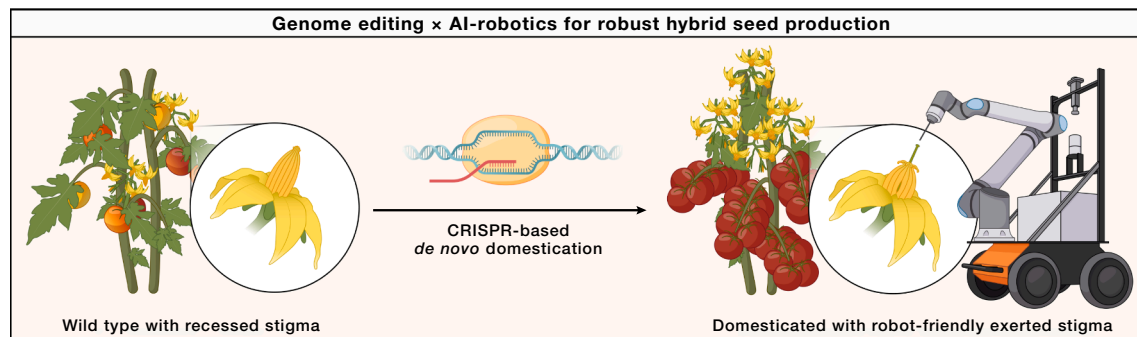
The pioneering study by Cao Xu and colleagues in this issue of *Cell* now shows that the synergistic combination of classical breeding strategies with modern technologies can significantly improve hybrid seed production. To move toward precision agriculture, they introduce a crop-robot co-design strategy in tomato that integrates genome editing with AI-driven robotics (GEAIR), enabling faster, automated breeding of climate-resilient crops while enhancing yield, cost efficiency, and sustainability (Figure 1).<sup>5</sup> In this proof-of-concept, the authors demonstrate that crop traits can be converted into robot-compatible features, exemplified by editing the phenotype of recessed stigmas in cultivated tomato—an outcome of artificial selection to preserve inbred purity but now a major barrier to robotic cross-pollination and a driver of high hybrid seed production costs. To generate a robot-friendly, stigma-exserted male-sterile floral morphology, a CRISPR-Cas9-based multiplexing strategy targeted the B-class MADS-box gene *GLO2*, a key component of the ABC model of flower development, in the elite tomato cultivar Ailsa Craig (AC). In particular, the *glo2*-inver line, harboring a 2,795 bp inversion with a concurrent 420 bp translocation spanning intron 2 to the 3' UTR, demonstrated optimal stigma exertion and complete

male sterility with minimal impact on yield and seed quality. In manual crossing, *glo2*-inver reduced pollination time by more than half without affecting fruit set, demonstrating practical utility and providing the basis for subsequent development of an autonomous robotic pollination system.<sup>5</sup>

With the barrier of recessed stigmas genetically removed, the GEAIR system was established as an autonomous platform for robotic pollination in tomato hybrid breeding. Flower identification and precise pollen delivery were achieved through the deep-learning model YOLACT\_Orient combined with pseudo-binocular 3D localization and a robotic arm capable of gently brushing pollen onto the stigma tip. In greenhouse trials, GEAIR matched manual efficiency on stigma-exserted lines, ensuring routine, continuous, and consistent performance, although its success rate was somewhat lower. To demonstrate its use in hybrid seed production, *glo2*-inver plants served as female parents in crosses with five diverse inbreds, producing F1 hybrids that displayed heterosis for yield, fruit weight, and Brix, including cases exceeding the best parental line.<sup>5</sup>

While inbreeding has narrowed the genetic base of modern tomato, wild relatives retain valuable traits that are difficult to exploit. A pioneering study by Dan Voytas and colleagues demonstrated that CRISPR-Cas9-based *de novo* domestication can be achieved through simultaneous editing of six loci in *Solanum pimpinellifolium*, rapidly generating plants with increased fruit size, number, and nutritional value.<sup>6</sup> Building on this potential to convert





**Figure 1. Genome editing-artificial intelligence-robotics (GEAIR) to support sustainable crop improvement and cultivation systems**

By reconfiguring floral and architectural traits for robotic pollination, GEAIR exemplifies how integrative strategies that unite genome editing with AI and robotics can accelerate hybrid seed production, enable *de novo* domestication, and expand agricultural diversity.

wild species into agronomically valuable crops, Xu et al. then combined genome editing and GEAIR robotics under speed-breeding conditions into a unified pipeline.<sup>5</sup> Editing *SELF PRUNING (SP)* and *SELF PRUNING 5G (SP5G)* in the wild species *S. pimpinellifolium* generated compact, photoperiod-insensitive male-parent lines, which were crossed with the *glo2*-inver line. Within one year, a stable F6 parental line was obtained that combined saline-alkaline and disease tolerance with enhanced flavor, lycopene, and Brix. Crosses with modern accessions yielded F1 hybrids, including one suited for vertical farming with elevated Brix and another with strong stress tolerance and increased yield.<sup>5</sup> Although limited in scale, this proof-of-concept demonstrates the value of integrating GEAIR robotics with *de novo* domestication and speed breeding to accelerate variety development in controlled environments.

Building on the successful engineering of an AI-robotic-compatible trait in the elite tomato cultivar AC, Xu and colleagues showed that the high conservation of *GLO2* allowed the same CRISPR construct to generate stigma-exserted male-sterile lines across diverse tomato varieties. Moreover, comparative analysis across *Solanaceae* identified conserved B-class MADS-box complexes as tractable targets for floral engineering, indicating the broader potential of this strategy and motivating evaluation in more distant crops. Applied to the cleistogamous legume soybean, genome editing produced stigma-exserted male-sterile mutants that reduced manual pollination time by 76% without affecting female fertility, demon-

strating the applicability of GEAIR across plant families.<sup>5</sup>

By providing a solution for converting recessed stigmas into AI-robotic-compatible floral morphology, this work provides a foundation for precision breeding and illustrates how genome editing can be integrated with cultivation systems designed for automation.<sup>5</sup> The next challenge is to expand such strategies to a wider set of crop traits that define compatibility with automation and large-scale cultivation. Morphological features such as clustered growth, dense foliage, and irregular root systems continue to limit progress, underscoring the need to better understand and reconfigure plant architecture. Important first advances have been made in this direction, spanning modifications of branching angles, tiller number, root systems, and fruit morphology—for instance, the *fs8.1* allele in tomato confers elongated, compression-resistant fruits suitable for mechanical harvesting without loss of quality.<sup>7,8</sup> Yet, more complex traits remain difficult to engineer, as shown by a recent study on tomato inflorescence development, where mobilizing cryptic genetic variation within regulatory networks diversified architectures and revealed how dosage-dependent and epistatic interactions reshape floral morphology to expand the design space for crop improvement.<sup>9</sup> Such complexity points to the need for integrative strategies that bring together omics, genome editing, protein design, and high-throughput phenotyping, with AI accelerating genotype-phenotype decoding and predictive trait engineering<sup>4</sup>—an approach that will be essential not only for improving existing crops but also for

advancing *de novo* domestication and rational redomestication to expand agricultural diversity.<sup>10</sup> Beyond single-nucleotide edits, chromosome engineering offers the possibility to deliberately reprogram recombination landscapes, opening routes to rearrange genomes in ways that were previously accessible only to natural evolution.<sup>3</sup> These advances open opportunities for more complex strategies, including guided mimicry of evolutionary processes, stacking of complex traits on plant artificial chromosomes, and the deliberate restructuring of plant genomes.<sup>3</sup> Realizing this vision will require interdisciplinary efforts that unite genome engineering, digital technologies, and systems-level crop design, marking a transition toward future-oriented agricultural innovation.

#### DECLARATION OF INTERESTS

The authors declare no competing interests.

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## Don't forget to floss! An innovative approach for vaccine delivery

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<https://doi.org/10.1016/j.cell.2025.09.008>

In a recent issue of *Nature Biomedical Engineering*, Ingrole et al. explore a new approach for needle-free vaccine delivery through the mouth. They devise and test a dental-floss-based flu vaccine as an alternative mode of mucosal vaccination.

Will flossing be more exciting if it delivers a vaccine at the same time? Ingrole et al.<sup>1</sup> think so! They introduce flossing as a new route for mucosal vaccination through the gums (the mucosal area adjacent to teeth) in the oral cavity and demonstrate efficacy of their delivery system for a variety of vaccine modalities delivering protein, inactivated virus, peptide-presenting immunogenic nanoparticles, and messenger RNA. They establish that floss vaccination induces robust systemic and mucosal recall responses, superior to those elicited by sublingual vaccination, and confers protection in a mouse model of influenza virus infection.

The authors implement an innovative, needle-free approach targeting a unique interphase of the oral mucosa,<sup>1</sup> the junctional epithelium (Figure 1). Oral/sublingual vaccination has been strongly considered in the past due to the accessibility of the oral cavity. Sublingual vaccination works by placing the vaccine under the tongue, where it is absorbed through

the blood-rich tissue without using a needle.<sup>2</sup> However, sublingual vaccination has not been broadly established due to lower delivery and efficacy of the vaccine components as well as the possibility of tolerance induction, as antigens delivered via this route may promote the development of suppressive regulatory T cells.<sup>2,3</sup> However, the authors realized that the most permeable and open site of the oral barrier, the junctional epithelium on the inside surface of the gums, had not been considered as a potential site for vaccine delivery. They recognized that the junctional epithelium is a unique mucosal interface with “anomalously high permeability,” which creates a “leaky open system for bi-directional transmigration of substances.” As such, microbial elements can pass through the barrier, while host cells (particularly neutrophils) and serum exudate from local vasculature constitutively exit through the intraepithelial connections. Beneath the epithelium at this interphase, a complex immunolog-

ical network constantly patrols this barrier, even in the setting of pristine health.<sup>4</sup> The authors consider the unique architecture of this area as a missed opportunity for vaccine delivery. They utilize a floss system to gain access to the junctional epithelium at deeper areas of the crevice and bypass the flow of fluid that exits the area (crevicular fluid; Figure 1) as they deliver the vaccine. This approach allows for delivery of vaccines in experimental mouse models and shows promise toward delivery for human vaccination.

Influenza vaccination remains a cornerstone of global public health, yet current vaccines face continued challenges. Most licensed influenza vaccines contain inactivated virus and are delivered by injection into the muscle, which induces strong systemic immunity but often limited mucosal protection. Because influenza viruses infect and spread via the respiratory mucosa, eliciting local immune responses in the airways is increasingly recognized as an important vaccine

