

QnAs with Zachary B. Lippman

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Zachary B. Lippman works at the interface of plant development, genetics, genomics, and agriculture. He has used some of the latest genome-editing techniques to study the mechanisms of fundamental plant processes, such as flowering, and to harness such mechanisms for crop improvement. A professor of genetics at Cold Spring Harbor Laboratory and an investigator of the Howard Hughes Medical Institute, Lippman received the 2020 National Academy of Sciences Prize in Food and Agriculture Sciences for his contributions to crop improvement. Lippman talks to PNAS about his recent research.

PNAS: How did you become interested in plant genetics and crop improvement?

Lippman: I've been interested in plants and agriculture for a very long time. I worked on vegetable farms when I was younger and really appreciated how important farming and agriculture are for humanity. When I went to college, I majored in plant breeding and genetics, and I did research in Steven Tanksley's [laboratory], where I learned what was happening in modern quantitative genetics. For my PhD, I worked with Rob Martienssen at Cold Spring Harbor Laboratory on questions of transposons and the regulation of genes epigenetically through transposons and heterochromatin in *Arabidopsis*. That gave me a very broad view of genomics and gene-expression control and how it relates to phenotypic variation. I then moved to a postdoc with Dani Zamir in Israel, where my training focused on linking plant development with breeding. I'm always thinking about questions of evolutionary diversity in nature and in agriculture and the intersection of the two, and how natural mutations have contributed to human-driven evolutionary selections. This has led to a broader interest in quantitative variation linked to genes that control growth and development. I'm also interested in the importance of transcriptional control of genes and dosage as a driver of quantitative variation. We collaborate with many excellent colleagues on these and related topics.

PNAS: What are some of the applications of your work?

Lippman: Those of us working on crop systems in plant biology are often thinking about the translational side:



Zachary B. Lippman. Image credit: Andrew Krainer (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY).

What our research and discoveries mean for agriculture. I try to think about how to apply what we're learning from fundamental biology to agricultural problems of adaptation and productivity. When genome editing came along, we had several ideas about how to better address and link those questions. That led to the use of CRISPR/Cas9 genome editing to modify promoter sequences (1). We targeted and mutagenized the *cis*-regulatory regions of several genes controlling growth and development that are connected to productivity, and we showed that we could engineer quantitative variation.

PNAS: How did you come up with this approach?

Lippman: When I read the first papers on genome editing, obviously the first thing I thought of as a geneticist was to knock out genes. But I actually wrote

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“promoter CRISPR” on a sticky note and put it on my desk, which is exactly what we ended up doing once we got all of the pieces in place. The more fundamental root of that idea comes from a very deep appreciation for the importance of *cis*-regulatory variation in controlling quantitative traits in plants and animals, pointing to this mutational space to engineer quantitative variation. We thought a lot about how we might best go about demonstrating this at scale and in a very concrete way. In the paper that demonstrates this, we go very deep in terms of allelic diversity and quantitative trait diversity for three genes affecting three traits in tomato (1). The initial hook was the agricultural application, but perhaps the more important hook that we are focusing on now is using this approach to address questions about the relationship between *cis*-regulatory variation, transcriptional change, and phenotypic outputs. This paper followed up on another of our papers that I think was exciting, on epistasis and its role in quantitative variation in domestication and breeding (2).

PNAS: What did that paper show about epistasis in tomato plants?

Lippman: A breeding trait in tomato that first emerged in the 1950s was this “jointless” trait that allowed ease of harvestability. It was eventually transformative, but there were a lot of initial problems with breeding with that gene and mutation, which turned out to have a negative interaction with many different tomato varieties. We leveraged natural mutations as well as CRISPR/Cas9 genome editing to show that this was due to a negative epistatic relationship with a historical mutation that arose thousands of years

ago. We then dissected the entire epistasis syndrome as it relates to flower production and yield. We showed how breeding with “jointless” gave you a negative hit on yield because of this epistasis, and how breeders ultimately corrected this problem. We also showed how understanding all of the quantitative nuances of this epistasis allowed us to redirect it in a positive way to fine-tune flower production and improve yield. It was eye-opening for how complex epistasis and genetic interactions can get even in the context of something as simple as a single gene mutation that facilitates harvesting a crop like tomato.

PNAS: You have also used genome editing to improve a plant called groundcherry, which is grown in Central and South America for its berries (3). How did you achieve that?

Lippman: We wanted to look at plants that have broader agricultural potential, with the idea that we could accelerate the improvement of some of these so-called “orphan crops,” to elevate them and expand our repertoire of crop diversity. What I look for in a system like this is: Can I grow it easily? Does it produce well in the greenhouse and in the field? Can I do genetics and crosses? Is it diploid, and is the genome not too large? Groundcherry checked all these boxes. Then, you can deal with some of the more challenging things, such as the transformation protocols and the gene editing itself, and here, again, we work with excellent collaborators. There’s quite a bit of space to improve orphan crops, and genome editing really accelerates the kinds of modifications you would have trouble making in a traditional breeding program. That’s, pardon the pun, the low-hanging fruit.

1 D. Rodríguez-Leal, Z. H. Lemmon, J. Man, M. E. Bartlett, Z. B. Lippman, Engineering quantitative trait variation for crop improvement by genome editing. *Cell* **171**, 470–480.e8 (2017).

2 S. Soyk *et al.*, Bypassing negative epistasis on yield in tomato imposed by a domestication gene. *Cell* **169**, 1142–1155.e12 (2017).

3 Z. H. Lemmon *et al.*, Rapid improvement of domestication traits in an orphan crop by genome editing. *Nat. Plants* **4**, 766–770 (2018).