

# Large-scale approach reveals imperfect actor in plant biotechnology

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Scientist picking molecules from a tree. Credit: Steven Lee/Whitehead Institute

A research team led by Whitehead Institute for Biomedical Research has

harnessed metabolomic technologies to unravel the molecular activities of a key protein that can enable plants to withstand a common herbicide. Their findings reveal how the protein—a kind of catalyst or enzyme, first isolated in bacteria and introduced into plants, including crops such as corn and soybeans, in the 1990's— can sometimes act imprecisely, and how it can be successfully re-engineered to be more precise. The new study, which appears online in the journal *Nature Plants*, raises the standards for bioengineering in the 21st century.

"Our work underscores a critical aspect of bioengineering that we are now becoming technically able to address," says senior author Jing-Ke Weng, a Member of the Whitehead Institute and an assistant professor of biology at the Massachusetts Institute of Technology. "We know that enzymes can behave indiscriminately. Now, we have the scientific capabilities to detect their molecular side effects, and we can leverage those insights to design smarter enzymes with enhanced specificity."

Plants provide an extraordinary model for scientists to study how metabolism changes over time. Because they cannot escape from predators or search for new food sources when supplies run low, [plants](#) must often grapple with an array of environmental insults using what is readily available—their own internal biochemistry.

"Although they appear to be stationary, plants have rapidly evolving metabolic systems," Weng explains. "Now, we can gain an unprecedented view of these changes because of cutting-edge techniques like metabolomics, allowing us to analyze metabolites and other biochemicals on a broad scale."

Key players in this evolutionary process—and a major focus of research in Weng's laboratory—are enzymes. Traditionally, these naturally occurring catalysts have been viewed as mini-machines, taking the proper starting material (or substrate) and flawlessly converting it to the

correct product. But Weng and other scientists now recognize that they make mistakes—often by latching on to an unintended substrate. "This concept, known as [enzyme](#) promiscuity, has a variety of implications, both in enzyme evolution and more broadly, in human disease," Weng says.

It also has implications for bioengineering, as Bastien Christ, a postdoctoral fellow in Weng's laboratory, and his colleagues recently discovered.

Christ, then a graduate student in Stefan Hörtensteiner's lab at the University of Zurich in Switzerland, was studying a particular strain of the flowering plant *Arabidopsis thaliana* as part of a separate project, and he made a puzzling observation: two biochemical compounds were found at unusually high levels in their leaves.

Strangely, these compounds (called acetyl-aminoadipate and acetyl-tryptophan) weren't present in any of the normal, so-called "wildtype" plants. As he and his colleagues searched for an explanation, they narrowed in on the source: an enzyme, called BAR, that was engineered into the plants as a kind of chemical beacon, enabling scientists to more readily study them.

But BAR is more than just a tool for scientists. It is also one of the most commonly deployed traits in [genetically modified crops](#), such as soybeans, corn, and cotton, enabling them to withstand a widely-used herbicide (known as phosphinothricin or glufosinate).

For decades, scientists have known that BAR, originally isolated from bacteria, can render the herbicide inactive by tacking on a short string of chemicals, made of two carbons and one oxygen (also called an acetyl group). As the researchers describe in their *Nature Plants* paper, it has a promiscuous side, and can work on other substrates, too, such as the

amino acids tryptophan and amino adipate (a lysine derivative).

That explains why they can detect the unintended products (acetyl-tryptophan and acetyl-amino adipate) in crops genetically engineered to carry BAR, such as soybeans and canola.

Their research included detailed studies of the BAR protein, including crystal structures of the protein bound to its substrates. This provided them with a blueprint for how to strategically modify BAR to make it less promiscuous, and favor only the herbicide as a substrate and not the [amino acids](#). Christ and his colleagues created several versions that lack the non-specific activity of the original BAR protein.

"These are natural catalysts, so when we borrow them from an organism and put them into another, they may not necessarily be perfect for our purposes," Christ says. "Gathering this kind of fundamental knowledge about how enzymes work and how their structure influences function can teach us how to select the best tools for bioengineering."

There are other important lessons, too. When the BAR trait was first evaluated by the U.S. FDA—in 1995, for use in canola, and in subsequent years for other crops—metabolomics was largely non-existent as a technology for [biomedical research](#). Therefore, it could not be applied toward the characterization of [genetically engineered plants](#) and foods, as part of their regulatory review. Nevertheless, acetyl-amino adipate and acetyl-tryptophan, which are normally present in humans, have been reviewed by the FDA and are safe for human and animal consumption.

Weng and his colleagues believe their study makes a strong case for considering metabolomics analyses as part of the review process for future [genetically engineered crops](#). "This is a cautionary tale," Weng says.

**More information:** Bastien Christ et al, Non-specific activities of the major herbicide-resistance gene BAR, *Nature Plants* (2017). [DOI: 10.1038/s41477-017-0061-1](https://doi.org/10.1038/s41477-017-0061-1)

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