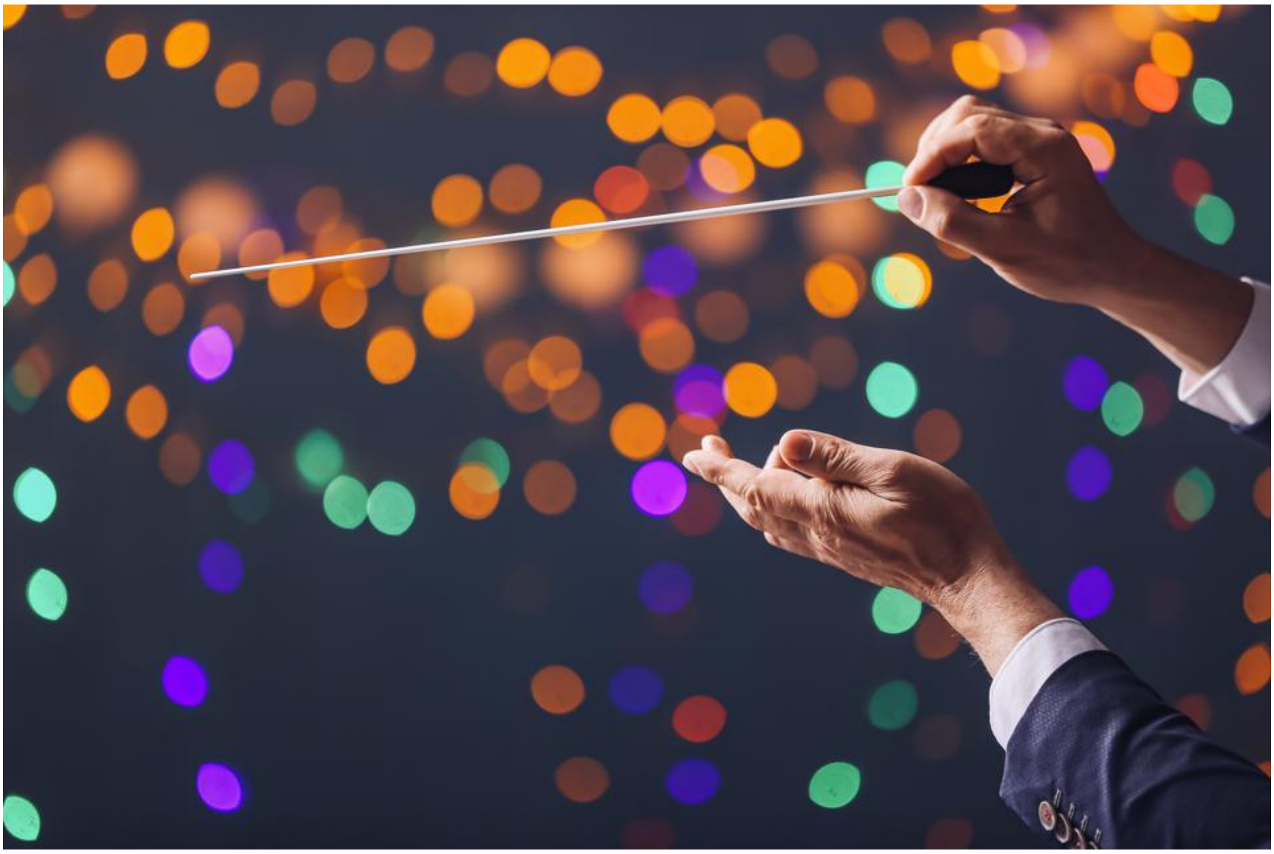
Epigenetics: Conducting The Symphony Of Genetics

Michael Helmstetter



Epigenetics is like a symphony conductor, who with just a gesture of the baton, conveys the message to quiet the strings while turning up the horns. The symphony as a whole remains intact, but the sound changes entirely.

For all the hype, fear and misinformation that surrounds the application of gene editing, there is an equally powerful technology that offers much the same in potential benefit. This technology, epigenetics, is a natural process that has gone largely unremarked by consumers.

Yet epigenetics is introducing incredible promise in the search for ways to deliver sustainable food to a growing population on a planet increasing challenged by climate change.

It's time for an examination of epigenetics and the opportunities it brings, in contrast to GMO and gene editing technologies. The overall epigenetics market is projected to grow to a USD 35 billion market by 2028, largely on the basis of human health products in diagnosis and treatment. Yet the application of epigenetics to crop enhancement, animal health and aquaculture may be closer to fruition. Let's explore what we see as significant (if underappreciated) opportunities.

A simple explanation of epigenetics

Let's start with genetics, the study of genes, the DNA code containing the instructions to cells to create the many functions of the organism. The human genome contains about 3 billion base pairs of DNA – the code that makes each person unique. This DNA code resides in every cell, essentially the same code in every cell in your body.

Epigenetics explains how the same DNA code can guide some cells to behave differently from others. Epigenetics studies the chemical compounds and proteins that can attach to DNA and direct the actions to turn a specific gene "on" or "off" – expressing or silencing a gene.

Think of a symphony orchestra. Epigenetics would be the conductor, who with just a gesture of the baton, conveys the message to quiet the strings while turning up the horns. The symphony as whole remains intact, but the sound changes entirely.

The term was coined in the mid-twentieth century by British biologist Conrad Waddington, who used it to describe the way cells gradually take on more specialized roles during the development of an embryo – how some cells become blood, others bone and still others turn into nerves, for example. The prefix "epi" comes from the Greek and means "on top of" or "above." So in this word, *epigenetic*, it describes the factors beyond the code that regulate the activity of the cells.

But importantly, throughout epigenetic changes, the DNA sequence never changes.

In Nobel-prize winner Paul Nurse's new book, What is life? Five great Ideas in Biology, he explains epigenetics as "the set of chemical reactions that cells use to turn genes either on or off in fairly enduring ways." As part of his chapter on "Life as Information," he continues: "These epigenetic processes do not change the DNA sequence of the genes themselves; instead, they often work by adding chemical 'tags' to the DNA, or to the proteins that bind to that DNA. This creates patterns of gene activity that can persist through the lifespan of a cell and sometimes even longer, through many cell divisions."

Epigenetic changes are especially important because they are naturally occurring and happen continuously. Epigenetics is different from gene editing, which makes an irreversible alteration in DNA sequence by removing or inserting DNA. In some cases, like in a GMO or genetically modified organism, DNA from another source may be added. But epigenetic changes do not alter DNA and can happen in a reversible way, although some epigenetic changes can persist into later generations.

A new tool

In recent decades, we've learned about other factors that influence epigenetic switches, such as age, behavior and environment, for example. Additionally, now we know the chemical processes that can turn a specific gene on or off – DNA methylation, histone modification, acetone methylation and RNA interference or RNAi are the most common.

A particular breakthrough occurred when Dr. Sally Mackenzie, professor at Penn State University, found a plant gene, MSH1, that can trigger a plant to behave as though it is under stress. The reprogrammed plant invokes the mechanisms to manage its growth, producing greater resilience. When these epigenetically impacted plants are bred or grafted, their offspring produce higher yields and greater resiliency too.

Dr. Mackenzie's findings became the basis for the company Epicrop Technologies Inc., which is one of the companies in which my firm, TechAccel, has invested. Our relationship with Epicrop has produced two subsidiaries that are advancing Dr. Mackenzie's method to produce reprogrammed canola and berry crops with higher yields and greater resiliency.

Why now

The introduction of CRISPR and other gene editing tools opened new opportunities for breeding and trait selection, fueled by the rapid development of ultra-high throughput sequencing technologies and their sharply declining costs. These same technologies support the blossoming study of the epigenome. With each new advance, we come closer to understanding the on-off switches in the genome that can increase yield, combat stress, enhance flavor or nutrition, retard spoiling or aging, and influence many more characteristics.

The use of epigenetics has become more popular for another reason: the friendlier regulatory environment. Since epigenetic changes occur continually, naturally, there is a lesser role for regulatory oversight than in gene-edited or GMO products. The epigenetic process doesn't change the genetic code, the only engineering is the method to induce a gene to switch on or off.

And there are advances in applying epigenetic inducements in an accelerated way, vastly faster than conventional cross-breeding techniques. Sound Agriculture, for example, has a novel and relatively simple oligonucleotide-based strategy for epigenetically silencing individual genes. (Sound Ag is another of TechAccel's select investments and a partner in proof-of-concept studies in grape.)

New frontiers for epigenetics

The combination of advancing new methods of activating or silencing genes, the availability of high-speed sequencing for phenotypic analysis, and the likelihood of a simpler regulatory route to market are all factors that make epigenetics so promising.

Beyond that, there is a wide horizon of opportunity, with work underway in many fields for social and environmental benefit:

Agriculture: Significant advances have already been achieved in understanding how to use epigenetic modifications to improve a plant's resistance to pathogens and stress, making it more able to adapt to heat and drought. RNAi, which I've previously discussed, has been successfully applied to increase protein content, suppress starches, increase flavonoids and confer pesticidal benefits.

Behind the sunflowers, a field of epigenetically enhanced canola grows in field trials.

In our own epigenetics programs, we are focused on two crops: the strawberry, which is notoriously vulnerable to soil-borne pathogens and limited in environmental range, and canola. In the strawberry, epigenetic breeding – with selection for environmental stability, enhanced disease resistance and additional phenotypes – is an attractive non-GMO alternative to enhance complex traits. In canola, a crop of growing importance (global demand estimated to reach 250 million tons by 2025, up from 150 million in 2015), we focus on improving yield.

Aquaculture: Research is exploring methods of using epigenetics to confer heat tolerance to coral reefs, as well as improving feed and selecting traits for adaptation to pathogens, disease and impacts of climate change. The idea is to tailor the fish to its aquaculture environments, and so maximize commercial production in a safe, effective and sustainable way.

Animal health: Livestock nutrition is an emerging area for epigenetic research, examining ways to help animals increase their nutrient uptake or better process feeds. Additionally, the entire application of epigenetics to inducing desired traits is an important area of discovery. As noted in a recent Frontiers journal article, “Epigenetics is also attractive for animal breeding because it may help identifying part of the missing causality and missing heritability of complex traits and diseases.

In addition to these research areas, applications from human health – in precision nutrition and personalized medications, monitoring of disease, and therapeutic treatments (epidrugs) – will almost certainly be modeled for other plant and animal species.

This is why epigenetics advances deserve more attention, from researchers, investors and consumers alike. It's worth educating consumers on the opportunities of epigenetics as a tool to build resiliency in the face of climate change. It's up to us to use all available tools to improve our food supplies in ways that nourish, sustain and protect our planet. The race is on.

Michael Helmstetter

I am the co-founder, president and chief executive of TechAccel (Technology Acceleration Partners). TechAccel is a technology and venture development enterprise in the agriculture and animal health sector. We identify promising innovations in key technology areas, and then make equity investments and fund science advancement research. Through our network of research universities and institutes, we expand the innovation by applying it to adjacent markets, giving the innovator another shot on goal. I also serve as managing partner of Covenant Animal Health Partners, a TechAccel subsidiary that focuses on development of "revenue-ready" animal health products for companion and farm animals. I have more than 30 years of start-up, spin-off and technology advancement expertise in sectors including agriculture, defense and biotechnology. My research and development experience covers biotechnology, toxicology, chemical instrumentation, sampling designs and complex data analysis.