Genetic engineering's new frontier

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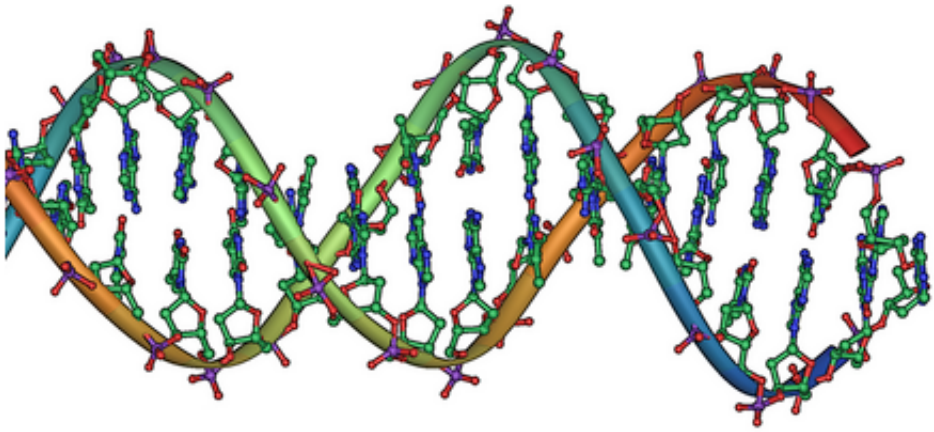

DNA double helix. Credit: public domain

Humanity's ability to alter nature, a characteristic of our species for thousands of years, has taken a big step forward.

The ability to change the genetics of life to our liking was previously confined to domesticated creatures such as livestock and crops. It now extends throughout much of the biosphere, including ourselves.

Genetic engineering on a planetary scale used to be the stuff of science fiction dreams, and sometimes nightmares. But now the potential has arrived. For the first time, discussions about quickly transforming entire

ecosystems on a large scale are no longer hypothetical.

Scientists from University of California, San Diego and the University of California, Irvine announced last week that they had genetically engineered a breed of mosquito that not only blocks infection by malaria parasites, but can quickly spread its antimalarial genes throughout its species. In some areas, a single season might be enough to change the population.

Since malaria kills hundreds of thousands of people annually, the potential benefit is obvious. Other mosquito-borne diseases could possibly be controlled in this fashion as well.

And apart from fighting disease, there's a vast potential to easily introduce desirable changes in other wild species, along with farm animals and cultivated plants. One could imagine algae engineered to grow more prolifically as a source of biofuel, disease-resistant cattle ... the list is endless.

But worries about pitfalls and mistakes are also widespread. Lessons from previous ecological disruptions resonate in the minds of scientists and bioethicists.

Unintended havoc is sometimes caused when people wittingly or unwittingly transplant a species into an environment it's not native to. Without natural predators, the invasive species can run wild and produce undesired effects.

The spread of Africanized bees in North America, snakes in Guam and rabbits in Australia all provide examples of irreparable harm from introduced species.

And for humans, there's no lack of nightmare stories from science

fiction about modifying people, whether genetically or through social conditioning.

The scientists say they recognize the potential pitfalls, and are keeping their work safeguarded in the laboratory. They're asking other scientists, governments and nongovernmental organizations to discuss how and whether this technology should be used.

In January, the J. Craig Venter Institute in La Jolla will host a workshop among these groups. That will be followed by many more meetings to develop rules and ethical guidelines people have never needed before. Questions include:

-Where to use the technology?

-How to get consent of the local population?

-What could go wrong, and how to handle it?

It appears likely that the technology will be evaluated in stages, said Robert Friedman, JCVI's chief operating officer. After laboratory testing, contained field trials would be conducted to examine how the testing works in an outdoor setting. But this could only be done once the many questions about how to handle this technology are considered, and down the line, how would a regulator actually approve such organisms.

"The workshop itself will focus on insects, but not just insect-borne human diseases," Friedman said. "It will also focus on potential agricultural applications of gene drive technologies."

Humanity reached this point because after decades of genetic engineering, scientists have devised a reliable method of pushing man-made genetic changes through wild populations. Called gene drive, this

technology has been married to the powerful gene editing technology called CRISPR-Cas9.

In traditional breeding, genes from a relatively few modified creatures tend to be swamped out in the much larger population with unmodified genes. That's why the reproduction of basset hounds, for example, must be strictly controlled to keep the breed distinct.

Gene drive changes this equation by multiplying the number of modified genes with each generation. A modified gene inherited from, say, the father, actively spreads the alteration to the corresponding gene inherited from the mother. Under ideal conditions, the genes would nearly double in frequency with each generation.

The concept has been around since at least 2003, but swiftly took flight after CRISPR technology became available about four years ago.

With the impending arrival of this technology and the potential to use it outside the lab, genetic engineering experts led by George Church of Harvard Medical School wrote a cautionary commentary in the journal *Science*. The commentary warned of potential dangers and urged strict precautions.

That was in April 2014. In March of this year, scientists led by UC San Diego's Ethan Bier and Valentino Gantz had reported, also in *Science*, that they had gotten a gene drive to work in fruit flies. They evocatively named the technology a "mutagenic chain reaction."

In the chain reaction, a mutation that's heterozygous, present in only one pair of genes, is converted into a homozygous mutation, present in both pairs. In the mosquito study published Nov. 23 by Bier, Gantz and UC Irvine researcher Anthony James, the efficiency of conversion was measured at 99.5 percent.

This chain reaction element introduces a new factor in genetic engineering, which itself was subject to a moratorium in the mid-'70s as scientists examined the risks and benefits.

Scientists and policymakers came to a consensus that genetic engineering is a legitimate tool for developing better medicines. For example, the insulin used by diabetics is made in bacteria that have been given a gene that codes for making insulin. An entire class of drugs, monoclonal antibodies, is produced from genetically engineered cells in what is now a standard part of the pharmaceutical industry.

Moving from genetically engineered drugs to foods has proven more controversial. Milk from cows given growth hormone made by genetic engineering is widely opposed, although the U.S. Food and Drug Administration has said the milk is safe to drink.

Genetically modified crops are opposed by environmental groups such as Greenpeace, and some countries have banned their importation.

Opponents say introducing food with man-made genes outside the laboratory could have dangerous or unforeseen results. In Mexico, opposition has focused on preventing the use of GM maize, which could hybridize with teosinte, corn's wild ancestor. Teosinte provides genetic diversity lost in domesticated corn. This diversity includes traits for disease resistance lost in the process of domestication.

Scientific studies have found no harm to human health from genetic modification of foods. The potential benefits include greater productivity, disease and drought resistance, and higher nutritional value.

One such food, "golden rice," has been genetically modified to produce more vitamin A. It's intended to prevent or treat vitamin A deficiency, which affects 250 million preschool children and is the leading cause of

preventable blindness in children, according to the World Health Organization.

Transnational groups such as WHO and the United Nations have issued policy statements on genetically modified crops, pointing out potential problems as well as benefits. But they do not have regulatory power, which lies in the hands of the various sovereign states. Their role is to provide research and tools to guide decision-making.

It's not clear what structure will be developed to deal with the proposed use of gene drive outside of laboratories. That will presumably be a big part at the January workshop to be held at the J. Craig Venter Institute in La Jolla.

Venter, a genomics pioneer who has worked in the field for decades, has long advocated improving on nature in the form of genetically engineered life. He led a team that created the first life form with a partly synthetic genome.

Besides JCVI, Venter-founded companies include Synthetic Genomics, a La Jolla-based company that's developing synthetic biology to develop products such as new vaccines and drugs, foods, biofuels and animal organs for human transplant. Another Venter-founded company, Human Longevity, is combining genomics and other "-omics" to develop an extremely detailed health fitness evaluation.

For its part, JCVI has been looking for several years at how the regulatory system will be able to handle powerful next-generation biotechnology, said Friedman, the institute's chief operating officer.

"We had a report in 2014 that gave an extensive overview, and unfortunately, one of the things it did not touch on was insects," Friedman said. "We focused mostly on microbes and plants."

After learning of Gantz and Biers' gene drive work in fruit flies, Friedman said he asked Bier if he would like to participate in examining how well existing regulations cover this next-generation technology. The January workshop is the result.