DARPA's Safe Gene editing program aims to prevent Global Bioerror and Biothreat

CRISPR allows removing a single (defective) gene from a genome and replacing it with another one, to prevent genetic diseases. CRISPR "has transformed labs around the world," says Jing-Ruey Joanna Yeh, a chemical biologist at Massachusetts General Hospital's Cardiovascular Research Center, in Charlestown, who contributed to the development of the technology. "Because this system is so simple and efficient, any lab can do it." Editing with CRISPR is like placing a cursor between two letters in a word processing document and hitting "delete" or clicking "paste." And the tool can cost less than US $50 to assemble.

Recently, China announced it was genetically engineering hyper-muscular SUPER-DOGS. The dogs, which are test tube bred in a lab, have twice the muscle mass of their natural counterparts and are considerably stronger and faster. An army of super-humans has been a staple of science fiction and superhero comics for decades – but the super-dog technology brings it closer to reality. The beagle puppy, one of 27, was genetically engineered by 'deleting' a gene called myostatin, giving it double the muscle mass of a normal beagle.

The advance genetic editing technology has been touted as a breakthrough which could herald the dawn of 'superbreeds', which could be stronger, faster, better at running and hunting. The Chinese official line is that the dogs could potentially be deployed to frontline service to assist police officers. Dr Lai Liangxue, researcher at Guangzhou institute

of biological medicine and health, said: “This is a breakthrough, marking China as only the second country in the world to independently master dog-somatic clone technology, after South Korea.”

US DOD is also applying gene editing technology for military applications. During the second biennial Department of Defense Lab Day May 18, 2017, One AFRL exhibit, highlighted research into how geneticists and medical researchers edit parts of the genome by removing, adding or altering sections of the DNA sequence in order to remove a virus or disease caused by harmful chemical, biological or environmental agents a warfighter may have contact with.

Yet without careful precautions, a gene drive released into the wild could spread or change in unexpected ways. Accidently, a lethal gene engineered into a pest species, say, might jump (or, as biologists put it, “horizontally transfer”) into another species that’s a crucial part of an ecosystem.

Kevin Esvelt, head of the Sculpting Evolution lab at MIT Media Lab, which is applying for Safe Genes funding in collaboration with eight other research groups, predicts that eventually, perhaps around 15 years from now, an accident will allow a drive with potential to spread globally to escape laboratory controls. “It’s not going to be bioterror,” he says, “it’s going to be ‘bioerror.’”

This summer, the Daily Star warned that the terrorist group ISIS is using gene drives to make “supercharged killer mosquitoes.” Experts regard that as unlikely. But the idea that gene drives pose a biosecurity threat is anything but.

Because the technology to create a gene drive is widely accessible and inexpensive, biologist Kevin Esvelt of the Wyss Institute for Biologically Inspired Engineering at Harvard University warned the scientific panel at an earlier meeting, “We have never dealt with anything like this before,” as reported by Sharon Begley Senior Writer, Science and Discovery.

The possibilities for “weaponizing” gene drives range from suppressing pollinators, which could destroy an entire country’s agriculture system, to giving innocuous insects the ability to carry diseases such as dengue, said MIT political scientist Kenneth Oye, who briefed the bioweapons office. Gene drive is particularly worrisome because “it’s not just one or two labs that are capable of doing the work,” Oye said – and the “capable” could include do-it-yourself “garage biologists.”

The U.S. Defense Advanced Research Projects Agency (DARPA) has awarded a combined $65 million over four years to seven research teams toward projects designed to make gene editing technologies safer, more targeted and potentially even reversible. The DARPA’s Safe Genes program aims to deliver novel biological capabilities to facilitate the safe and expedient pursuit of advanced genome editing applications, while also providing the tools and methodologies to mitigate the risk of unintentional consequences or intentional misuse of these technologies.

Setting a Safe Course for Gene Editing Research: DARPA

Gene editing technologies have captured increasing attention from healthcare professionals, policymakers, and community leaders in recent years for their potential to selectively disable cancerous cells in the body, control populations of disease-spreading mosquitos, and defend native flora and fauna against invasive species, among other uses. The potential national security applications and implications of these technologies are equally profound, including protection of troops against infectious disease, mitigation of threats posed by irresponsible or nefarious use of biological technologies, and enhanced development of new resources derived from synthetic biology, such as novel chemicals, materials, and coatings with useful, unique properties, says DARPA.

Achieving such ambitious goals, however, will require more complete knowledge about how gene editors, and derivative technologies including gene drives, function at various physical and temporal scales under different environmental conditions, across multiple generations of an organism. In parallel, demonstrating the ability to precisely control gene edits, turning them on and off under certain conditions or even reversing their effects entirely, will be paramount to translation of these tools to practical applications. By establishing empirical foundations and removing lingering unknowns through laboratory-based demonstrations, the Safe Genes teams will work to substantially minimize the risks inherent in such powerful tools.

A new DARPA program could help unlock the potential of advanced gene editing technologies by developing a set of tools to address potential risks of this rapidly advancing

field. The Safe Genes program envisions addressing key safety gaps by using those tools to restrict or reverse the propagation of engineered genetic constructs.

“Gene editing holds incredible promise to advance the biological sciences, but right now responsible actors are constrained by the number of unknowns and a lack of controls,” said Renee Wegrzyn, DARPA program manager. “DARPA wants to develop controls for gene editing and derivative technologies to support responsible research and defend against irresponsible actors who might intentionally or accidentally release modified organisms.”

Safe Genes was inspired in part by recent advances in the field of “gene drives,” which can alter the genetic character of a population of organisms by ensuring that certain edited genetic traits are passed down to almost every individual in subsequent generations. Scientists have studied self-perpetuating gene drives for decades, but the 2012 development of the genetic tool CRISPR-Cas9, which facilitates extremely precise genetic edits, radically increased the potential value of—and in some quarters the demand for—experimental gene drives.

Traditional biosafety and biosecurity measures including physical biocontainment, research moratoria, self-governance, and regulation are not designed for technologies that are, in fact, explicitly intended for environmental release and are widely available to users who operate outside of conventional institutions. The goal of Safe Genes is to build in biosafety for new biotechnologies at their inception, provide a range of options to respond to synthetic genetic threats, and create an understanding of what is possible, probable, and vulnerable

with regard to emergent gene editing technologies. “DARPA is pursuing a suite of versatile tools that can be applied independently or in combination to support bio-innovation or combat bio-threats,” Wegrzyn said.

From a national security perspective, Safe Genes addresses the inherent risks that arise from the rapid democratization of gene editing tools. The steep drop in the costs of genomic sequencing and gene editing toolkits, along with the increasing accessibility of this technology, translates into greater opportunity to experiment with genetic modifications. This convergence of low cost and high availability means that applications for gene editing—both positive and negative—could arise from people or states operating outside of the traditional scientific community.

DARPA Awards $65M to Improve Gene-Editing Safety, Accuracy

The U.S. Defense Advanced Research Projects Agency (DARPA) has awarded a combined $65 million over four years to seven research teams toward projects designed to improve the safety and accuracy of gene editing.

The funding is being awarded under DARPA’s Safe Genes program, designed to gain fundamental understanding of how gene-editing technologies function; devise means to safely, responsibly, and predictably harness them for beneficial ends; and address potential health and security concerns related to their accidental or intentional misuse.

Efforts funded under the Safe Genes program fall into two broad categories: gene drive and genetic remediation technologies, and in vivo therapeutic applications of gene editors in mammals. Much of the research will look at ways to inhibit gene drive systems. The obvious concern with gene drive techniques is that it’s impossible to know the full ramifications of releasing a genetic modification into the environment until it is actually happening.

DARPA said the seven teams chosen for the funding will be pursuing one or more of three technical objectives:

- Develop genetic constructs—biomolecular “instructions”—that provide spatial, temporal, and reversible control of genome editors in living systems;
- Devise new drug-based countermeasures that provide prophylactic and treatment options to limit genome editing in organisms and protect genome integrity in populations of organisms; and
- Create a capability to eliminate unwanted engineered genes from systems and restore them to genetic baseline states.

1. A team led by Dr. Amit Choudhary (Broad Institute/Brigham and Women’s Hospital-Renal Division/Harvard Medical School) is developing means to switch on and off genome editing in bacteria, mammals, and insects, including control of gene drives in a mosquito vector for malaria, Anopheles stephensi. The team seeks to build a general platform for the rapid and cost-effective identification of chemicals that will block contemporary and next-generation genome editors. Such chemicals could propel the development of therapeutic applications of genome editors by limiting

off-target effects or protect against future biological threats. The team will also construct synthetic genome editors for precision genome engineering.

2. A Harvard Medical School team led by Dr. George Church seeks to develop systems to safeguard genomes by detecting, preventing, and ultimately reversing mutations that may arise from exposure to radiation. This work will involve creation of novel computational and molecular tools to enable the development of precise editors that can distinguish between highly similar genetic sequences. The team also plans to screen the effectiveness of natural and synthetic drugs to inhibit gene editing activity.

3. A Massachusetts General Hospital (MGH) team led by Dr. Keith Joung aims to develop novel, highly sensitive methods to control and measure on-target genome editing activity—and limit and measure off-target activity—and apply these methods to regulate the activity of mosquito gene drive systems over multiple generations. State-of-the-art technologies for measuring on- and off-target activity require specialized expertise; the MGH team hopes to enable orders of magnitude higher sensitivity than what is available with existing methods and make this process routine and scalable. The team will also develop novel strategies to achieve control over genome editors, including drug-regulated versions of these molecules. The team will take advantage of contained facilities that simulate natural environments to study how drive systems perform in mosquitos under conditions approximating the real world.

4. A Massachusetts Institute of Technology (MIT) team led by Dr. Kevin Esvelt has been selected to pursue modular “daisy drive” platforms with the potential to safely, efficiently, and reversibly edit local sub-populations of organisms within a geographic region of interest. Daisy drive systems are self-exhausting because they sequentially lose genetic elements until the drive system stops spreading. In one proposed variant, natural selection is anticipated to favor the edited or original version depending on which is in the majority, keeping genetic alterations confined to a specified region and potentially allowing targeted populations of organisms to be restored to wild-type genetics. MIT plans to conduct the majority of its work in nematodes, a simple type of worm that reproduces rapidly, enabling high-throughput testing of different drive configurations and predictive models over multiple generations. The team then aims to adapt this system in the laboratory for up to three key mosquito species relevant to human and animal health, gradually improving performance in mosquitos through an iterative cycle of model, test, and refine.

5. A North Carolina State University (NCSU) team led by Dr. John Godwin aims to develop and test a mammalian gene drive system in rodents. The team’s genetic technique targets population-specific genetic variants found only in particular invasive communities of animals. If successful, the work will expand the tools available to manage invasive species that threaten biodiversity and human food security, and that serve as potential reservoirs of infectious diseases affecting native animal and human populations. The team also plans to develop mathematical models of how drives would function in mice, and then perform testing in contained,

simulated natural environments to gauge the robustness, spatial limitation, and reversibility of the drives.

6. A University of California, Berkeley team led by Dr. Jennifer Doudna will investigate the development of novel, safe gene editing tools for use as antiviral agents in animal models, targeting the Zika and Ebola viruses. The team will also aim to identify anti-CRISPR proteins capable of inhibiting unwanted genome-editing activity, while developing novel strategies for delivery of genome editors and inhibitors.

7. A University of California, Riverside team led by Dr. Omar Akbari seeks to develop robust and reversible gene drive systems for control of Aedes aegypti mosquito populations, to be tested in contained, simulated natural environments. Preliminary testing will be conducted in high-throughput, rapidly reproducing populations of yeast as a model system. As part of this effort, the team will establish new temporal and environmental, context-dependent molecular strategies programmed to limit gene editor activity, create multiple capabilities to eliminate unwanted gene drives from populations through passive or active reversal, and establish mathematical models to inform design of gene drive systems and establish criteria for remediation strategies. In support of these goals, the team will sample the diversity of wild populations of Ae. aegypti.

“Part of our challenge and commitment under Safe Genes is to make sense of the ethical implications of gene-editing technologies, understanding people’s concerns, and directing our research to proactively address them so that stakeholders

are equipped with data to inform future choices," Renee Wegrzyn, Ph.D., manager of the Safe Genes program, said in a statement.

"As with all powerful capabilities, society can and should weigh the risks and merits of responsibly using such tools. We believe that further research and development can inform that conversation by helping people to understand and shape what is possible, probable, and vulnerable with these technologies."

References and resources also include:

http://www.darpa.mil/news-events/2016-09-07

https://www.darpa.mil/news-events/2017-07-19

https://www.statnews.com/2015/11/12/gene-drive-bioterror-risk/

http://idstch.com/home5/international-defence-security-and-technology/technology/biosciences/chinese-scientists-pioneering-dna-engineering-humans-plan-first-human-crispr-trial/