**Building the Safe Genes Toolkit**

*Seven teams aim to develop new knowledge and tools to support responsible innovation in gene editing and protect against threats to genome integrity*

[DARPA created the Safe Genes program](http://www.darpa.mil/news-events/2016-09-07) to gain a 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. Today, DARPA announced awards to seven teams that will pursue that mission, led by: The Broad Institute; Harvard University; Massachusetts General Hospital; Massachusetts Institute of Technology; North Carolina State University; University of California, Berkeley; and University of California, Riverside. DARPA plans to invest $65 million in Safe Genes over the next four years as these teams work to collect empirical data and develop a suite of versatile tools that can be applied independently or in combination to support bio-innovation and combat bio-threats.

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.

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.

“The field of gene editing has been advancing at an astounding pace, opening the door to previously impossible genetic solutions but without much emphasis on how to mitigate potential downsides,” said [Renee Wegrzyn](http://www.darpa.mil/staff/dr-renee-wegrzyn), the Safe Genes program manager. “DARPA launched Safe Genes to begin to refine those capabilities by emphasizing safety first for the full range of potential applications, enabling responsible science to proceed by providing tools to prevent and mitigate misuse.”

Each of the seven teams will pursue 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. Safe Genes research will not involve any releases of organisms into the environment; however, the research—performed in contained facilities—could inform potential future applications, including safe, predictable, and reversible gene drives.

During the course of the program, teams will engage with potential stakeholders, including government regulators, to increase the value of the science and to shape experiments around their questions and concerns. Additionally, as an aid to policymakers, the teams will establish models for incorporating stakeholder engagement into future decisions on whether and how to apply such tools.

“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,” Wegrzyn said. “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. Gene editing is truly a case where you can’t easily draw a line between ethics and pure technology development—they’re inextricable—and we’re hopeful that the model we establish with Safe Genes will guide future research efforts in this space.”

The 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.

* A team led by Dr. Amit Choudhary ([Broad Institute](https://www.broadinstitute.org/)/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 protecting against future biological threats. The team will also construct synthetic genome editors for precision genome engineering.
* A [Harvard University](http://arep.med.harvard.edu/) 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.
* A [Massachusetts General Hospital (MGH)](http://www.massgeneral.org/pathology/research/researchlab.aspx?id=1271) 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.
* A [Massachusetts Institute of Technology (MIT)](https://www.media.mit.edu/people/esvelt/projects/) 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.
* A [North Carolina State University (NCSU)](https://godwin.wordpress.ncsu.edu/john-godwin/) 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.
* A [University of California, Berkeley](http://rna.berkeley.edu/) 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.
* A [University of California, Riverside](http://www.akbarilab.com/) 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*.

The teams intend to refine their research over the course of the program, building initial mathematical models of gene editing systems, testing them in insect and animal models to validate hypotheses, and feeding the results back into the simulations to tune parameters. Teams will also incorporate insights garnered from engagement with regulators and in some cases from local communities considering gene editing applications, and may run additional experiments to collect data that address concerns and could inform future regulatory reviews.

Given the potential of gene editing systems to broadly impact national security, health, and the environment, DARPA is committed to a high level of transparency and engagement in its Safe Genes research. The program will work with independent experts to help DARPA and the teams think through Legal, Ethical, Environmental, Dual-Use, and Responsible innovation (LEEDR) issues. In a separate but related effort, DARPA previously co-funded a [National Academies of Sciences, Engineering, and Medicine report on gene drives](https://www.nap.edu/catalog/23405/gene-drives-on-the-horizon-advancing-science-navigating-uncertainty-and) to help initiate the development of a framework for considering the implications of advances in gene editing, and to make recommendations on a responsible way forward.

“One aspect of Safe Genes that I’m most proud of is that we’re involving potential stakeholders from the beginning, many of whom are already considering gene editing technologies as options for responding to different health and environmental challenges but who have questions about how solutions involving gene editors would actually work,” said Wegrzyn. “DARPA sees their involvement in the Safe Genes program as invaluable for developing a model in which consideration of societal impact isn’t an afterthought, but instead a foundation on which science advances.”