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Target Article

CRISPR Critters and CRISPR Cracks

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This essay focuses on possible nonhuman applications of CRISPR/Cas9 that are likely to be widely overlooked because they are unexpected and, in some cases, perhaps even "frivolous." We look at five uses for "CRISPR Critters": wild de-extinction, domestic de-extinction, personal whim, art, and novel forms of disease prevention. We then discuss the current regulatory framework and its possible limitations in those contexts. We end with questions about some deeper issues raised by the increased human control over life on earth offered by genome editing.

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> Don't blame the Martians. The human race would have developed plasto-biology in any case. Look at the older registered Kennel Club breeds—glandular giants like the St. Bernard and the Great Dane, silly little atrocities like the Chihuahua and the Pekingese. Consider fancy goldfish. (Heinlein 1947, 243)

So science fiction writer Robert A. Heinlein began his 1947 satirical story, "Jerry Was a Man," before proceeding to introduce an intelligent pet dwarf elephant, a (nonflying) winged horse, and millions of cognitively enhanced chimpanzee farm workers (Greely 2012). These beasts were created by B'na Kreeth, a Martian geneticist employed to work on (to his mind) semibarbaric Earth. Today, we may be on the verge of a similar explosion of biological fancies and freaks, coming not from Martians but a compound acronym: CRISPR/Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats).

CRISPR/Cas9 and its successors appear likely to do wonderful things—and to be able to do terrible ones. Human germline genome editing has gotten the most attention (though into which category it would likely fall remains disputed) (Baltimore et al. 2015). The use of CRISPR would be met with a variety of responses. On the one hand, using CRISPR to cure disease by human somatic cell genome editing would be universally applauded, to make better biofuel sources would be widely endorsed, and to make more animals like today's goats engineered to make drugs would be confusing but still tolerated (Pollack 2009). On the other hand, to make yet more engineered plant and animal foods would be controversial, and to make "better" biological weapons would simply be reviled.

In this short and somewhat tongue-in-cheek essay, we focus on possible uses of this powerful technology that are likely to be widely overlooked because they are unexpected and, in some cases, perhaps even "frivolous." But they are still fascinating . . . and not entirely unimportant. Because CRISPR is easier and cheaper to use than older forms of genetic engineering, often they are things that could be done outside the traditional laboratory setting. Already so-called DIY (do-it-yourself) "biohackers" are exploring possibilities such as changing blue flowers back to their original white, or producing the protein needed for "vegan" cheese, all in their own homes or informal community labs (Ledford 2015). We ask whether the current regulatory framework will let some of these creations fall into the cracks (and whether that is a problem). We end with some brief thoughts on possible deeper implications in such nonhuman applications of CRISPR/Cas9.

CRISPR CRITTERS[1]

If you could wish into existence any animal, plant, or microbe you wanted, what would you make? CRISPR/Cas9 does not promise that, quite. It will not repeal the laws of physics—no flying horses—and biology may just not permit some variations—perhaps no large animals with functioning wheels. But given enough advances (not so much in the genome editing technologies as in our understanding of how DNA sequences translate into phenotypes), it is not at all clear what kinds of living things could be created. We present five rough categories: wild de-extinction, domestic de-extinction, personal whim, art,

1. One of us (HTG) heard a man somewhere in spring 2015 refer to animals created through CRISPR/Cas9 as "CRISPR critters" and would like to credit him, but he has not been able to remember, or to find out, who it was. The phrase appears as early as 2010 (Yarris 2010) and the combined words have been trademarked by a company (Applied Stem Cell, Inc.).

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and novel forms of disease prevention—but we invite you to let your imaginations range further than ours.

WILD DE-EXTINCTION

In the last three years, de-extinction—the revival of extinct species—has gone from science fiction to a real subject of discussion, research, and even planning (Sherkow and Greely 2013; Zimmer 2013). Much of the activity has been led by Stewart Brand, Ryan Phelan, and their organization, Revive and Restore (Long Now Foundation n.d.).

Although groups have been exploring several other methods for reviving extinct organisms, such as back-breeding and cloning, genome editing offers the broadest possibilities. Genome editing requires the whole genome sequence from the extinct species, as well whole genome sequences from closely related existing species. The sequences can then be compared and the differences between them noted. A cell line would be created from the living species, and CRISPR/Cas9 would be used to edit the sequence of genes of the living species into the sequence of its extinct relative. Those cells would have to be transformed into embryos and, again, at least in mammals, transferred to the uterus of a female animal in which the embryo could establish a pregnancy and be carried to term.

Jurassic—or, less distantly, Cretaceous—Park seems impossible using this strategy, as no one can figure a plausible way that DNA could survive from 66.4 million years ago. On the other hand, DNA has been found, and sequenced, for wild horses as old as 700,000 years, making Pleistocene Park a real possibility (Telis 2013). Groups have already begun to explore the possibilities for using genome editing to "revive" the passenger pigeon, the heath hen, the great auk, and the woolly mammoth, among many others (Long Now Foundation n.d., Candidates). Even if successful, in some cases the resulting revived species might be found only in zoos or animal parks, but in others they might be reintroduced into the broader environment.

De-extinction would raise a wide range of issues. One of the intellectually interesting questions is applicability of the Endangered Species Act; does an already extinct species become endangered when in fact one has actually resurrected it, and offered it a chance to thrive rather than diminish to the brink of disappearance? Other issues would include the patentability of the "revived" animals, various legal restrictions on the introduction of "exotic" species into a jurisdiction (perhaps even if the species had lived there 200, or 20,000, years ago), the role of the National Environmental Policy Act (even for private actions if they required federal permission), tort liability, and many more (Carlin, Wurman, and Zakim 2014).

CRISPR/Cas9 is likely to be crucial to any realistic de-extinction. Geneticist George Church is already using it in his Harvard lab to edit Asian elephant cell lines to give them some woolly mammoth genes (Lewis and Maslin 2015).

DOMESTIC DE-EXTINCTION

"De-extinction" sounds like something that should happen with big animals, but consider more mundane extinctions, like that of the great-tasting tomato. Many domestic varieties of various plants have "gone extinct" over the years because they failed various tests of the market. If we can get DNA samples—or (eventually) understand enough about the genomic determinants of taste—we can bring them back, in whole or as reengineered, perhaps by adding genes from wild varieties of the plant, a process some have called "re-wilding" (Anderson et al. 2015)—not to be confused with turning the Dakotas back over to the bison.

The tomato is a good example. About 70 years ago a variant was found that ripened in a uniform manner, which made commercial cultivation much better—but the taste much worse. Recently, researchers have deciphered the various genotypes that lead to various qualities of taste (Stamp 2013), opening the door to "recreating"—or engineering—great-tasting tomatoes through genome editing. And what could be done for the tomato might be possible for any number of other foods. Even for those for which there are no heirloom samples to test for gene sequences, a fair idea of what's needed might be found in things as unlikely as works of art from centuries past, depicting fruits and vegetables with shapes, colors, and textures far different than their modern kin (Thomas 2015).

Of course, as a food item, the Food and Drug Administration (FDA) would have jurisdiction, and could hold it off the market for agency review unless it was considered "generally recognized as safe," a view unlikely to be held for the very first experiments. But if indeed the foods are identical to their former, heirloom varieties—all of which were considered safe—then these versions should eventually be able to enter the market without premarket review or special labeling.

The most interesting thing about these experiments in recovering heirloom varieties with modern biotechnology, such as genome editing, is the way they force opponents of genetically engineered foods to explain whether their objection is to the product or the process. If the product truly is identical to a beloved, lost heirloom version of a food, is it unnatural or natural? Organic? And does it matter? This goes to the heart of the trans-Atlantic split on whether to regulate based on the properties of a product or the method by which it is produced (Kolata 2015).

PERSONAL WHIM

This category encompasses a variety of possibilities, from personal pets to new garden species to novel species created for display. The personal pet has already happened with the GloFish, several species of tropical fish for aquariums that have had fluorescent proteins added to their genomes, causing them to glow red, green, orange, blue, purple, or pink when illuminated with ultraviolet light (GloFish n.d.). Surprisingly, though, the GloFish escaped regulation. The U.S. Environmental Protection Agency (EPA), U.S. Department of Agriculture

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(USDA), and U.S. Fish and Wildlife Service (FWS) all said they had no jurisdiction, and FDA, which could have regulated the genetic construct as a "new animal drug" that must be tested for safety for the fish and the environment before approval, declined to review it (Nature *Biotechnology* 2004). The agency explained its decision by noting that the fish are not used for food, and they have no reason to be any more of a threat to the environment than their unmodified, long-marketed counterparts. Absent a reason to view them as a possible public health hazard, FDA simply walked away (Bratspies 2005).

This, however, did not prevent the California Fish and Game Commission from "protecting" the people of California, and its waters (far too cold for the survival of any escaped tropical fish), from the nonexistent threat of GloFish. The fish, from two species and in six colors, are now legally sold throughout the United States and in several other countries ... but not in California (Bratspies 2005).

Interestingly, GloFish did wind up as food, in a small but dramatic way, when the website http://www.glowingsushi.com was created, with video demonstrations of recipes for using GloFish in sushi rolls, such as "Stop and Glow Nigirizushi" (using red and yellow fluorescing fish) and "Kryptonite Roll" (using green fluorescing fish). But the website's authors warn that traveling abroad with these fish "gets you into murky legal territory. It all comes down to labeling—are you transporting food, a pet, or a GMO? Each of these categories are handled differently by customs officers and are subject to different laws in various nation states" (Glowing Sushi n.d.).

Considering, as Heinlein did, what humans have done in the last 10,000 years to wolves and their descendants—and continue to do, as in the labradoodle—why should we not expect dwarf elephants, giant guinea pigs, or genetically tamed tigers? Or—dare we wonder—the billionaire who decides to give his 12-year-old daughter a real unicorn for her birthday?

Gardening is another possibility. Consider all the rose varieties and the small number of preexisting types that have given rise to them. As opposed to the Japanese, genetically engineered "blue rose" that is really more lilac in color, the long search for a truly blue rose might end not through a long process of breeding but through the insertion of a few more genes (Nosowitz 2011).

Again, reality is already intruding into this fantasy. A company called Revolution Bioengineering is working on plants that change color during the day (Rawat 2014). A Kickstarter campaign raised over $480,000 to create glow-in-the-dark houseplants (Kickstarter 2015). In July 2015 the sponsors reported substantial success and the hope to ship soon (Kickstarter 2015). Companies have already formed to create glow-in-the-dark sidewalks, and it is hardly a jump to imagine the same concept extended to gardens and public parks using biological tools (Antoniades 2013).

New plants are subject to regulation if they constitute a "plant pest" (Plant Protection Act of 2000), but that, in turn, requires a finding that they are harmful to other plants or the environment, or pose a greater risk than the risks of the organisms from which they were derived. For this reason, seemingly benign changes in such things as the color of petals might very well escape regulation. Whether this is wise or foolish, it is certainly different from systems like that used in Europe, where the merest hint of a transgenic change will trigger special scrutiny.

Then there are the possibilities of spectacles: animals and plants not created for personal use but to be exhibited. Consider, for example, the dragon. Basic physics will almost certainly combine with biological constraints to prevent the creation of flying dragons or fire-breathing dragons—but a very large reptile that looks at least somewhat like the European or Asian dragon (perhaps even with flappable if not flyable wings) could be someone's target of opportunity.

Even if the laws of physics do not apply, it is possible that some of the laws of the United States will. Unfortunately, experience has demonstrated that there is a fair amount of uncertainty about exactly which laws can and will be applied.

ART

Lois McMaster Bujold, a science fiction author with strong biological interests, created the long-running Vorkosigan series, which includes an empire called Cetaganda, where genetic manipulation is common. Young geneticists compete in contests to produce the most artistic plants and animals (and, in the case of the kitten bush, "plant-animals") (Bujold 1996). Again, reality has intruded on science fiction. Bioart, and even geno-art, already exists (Caulfield and Caulfield 2009).

Artists have long used traditional breeding to create living art forms, such as gorgeously variegated ears of corn (NativeSeeds n.d.). And some have used earlier genome editing tools. Probably the most notorious example is Eduardo Kac's creation of (or order to a genetics laboratory for) a green fluorescent protein rabbit created by injecting GFP protein into fertilized rabbit eggs and then breeding any rabbits that had taken up the gene. The full story of Kac and Alba is unclear. The French laboratory seems to have been producing GFP rabbits for several years before Kac requested one, and the rabbits did not glow very green. The eyes were green and the skin had some green glow, but the skin was obscured by the (white) fur (Dickey 2001).

It should be no surprise if artists gravitate toward this powerful new tool called CRISPR/Cas9, just as they gravitated toward computer graphics in the 1980s and 1990s. And with that tool, just what creations might geno-artists attempt? Remember that unlike most scientists or pet and garden breeders, some artists are happy to achieve fame through sometimes shocking transgressions.

NOVEL FORMS OF DISEASE PREVENTION

Pity the poor mosquito. Or more to the point, pity the poor company that wants to reduce the scourge of

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dengue fever by engineering a mosquito. Half the world's population is at risk for this disease, and tens of thousands of children die from dengue fever every year. It is spread by the *Aedes aegypti* mosquito, and a company called Oxitec wants to change that, by changing the mosquito to make it effectively sterile. Genetically (Hickey 2015; Oxitech n.d.).

Other groups are working on ways to modify the genes of mosquitoes in the *Anopheles* genus in ways that prevent the malaria plasmodium from reproducing within the mosquitoes (Clark 2012). No plasmodium reproduction in mosquitoes, no malaria in humans.

The malaria effort is taking advantage of a CRISPR-related invention called "gene drive" by which all of the offspring of one edited parent end up with two copies of the edited gene. A major article about gene drive (Gantz and Bier 2015) was prepublished online in *Science* on the same day as the call for a temporary moratorium on human germline genome modification (for which we were among the co-authors) (Baltimore et al. 2015). Already, concerns about gene drive (Oye et al. 2014) have led to a National Academy of Sciences committee that is identifying risk-mitigation strategies like reversal drive and developing guidelines for responsible gene drive research (National Academies n.d.). These disease prevention efforts, though quite novel for today's public health measures, can be fit into the current regulatory framework for biotechnology. Sort of. Which leads us into that mosquito-infected swamp.

THE REGULATORY FRAMEWORK—AND ITS CRACKS

In the 1980s, the Office of Science and Technology Policy (OSTP) within the Reagan administration developed the Coordinated Framework for Regulation of Biotechnology (OSTP 1986). Rather than treat biotechnology as a thing unto itself, to be regulated specifically because of the use of recombinant DNA (rDNA) techniques, the framework focused on the end products and their intended uses. That is, regardless of whether rDNA was involved, drugs would be regulated as drugs under existing rules for drug approval, pesticides under existing rules for pesticide approval, and so on.

Three agencies—the Department of Agriculture (USDA), the Food and Drug Administration (FDA), and the U.S. Environmental Protection Agency (EPA)—would most often be in charge of regulating products that used rDNA techniques for production, with the Centers for Disease Control and Prevention (CDC) coming into play when public health was threatened. Each has a different area of jurisdiction, and for major federal actions with possible environmental consequences, the National Environmental Policy Act (NEPA) can overlay all the agency actions, with its extensive public consultation requirements. For example, USDA regulates plant pests but the EPA regulates pesticides and FDA regulates most foods. When USDA was considering whether to loosen the controls on planting of a genetically engineered beet, there was litigation about just how intense the environmental review had to be under NEPA.

But because FDA uses a voluntary consultation process for most genetically engineered foods, there was no major action by that agency to trigger a NEPA review. By contrast, the tortured history of the AquAdvantage salmon, designed to grow more quickly to full size, required FDA to create new regulatory pathways, involving a review of the genetic construct, animal welfare, and food safety by one part of the agency, review of the food labeling by another, consultation with the EPA, and possible application of NEPA (though with yet more subtleties about its application when the possible environmental effects may be felt only outside the United States) (FDA n.d.). Adding to the complexity, the genetic construct used to engineer the salmon eggs is considered a "veterinary drug," which has led critics to claim (misleadingly) that FDA is calling the salmon itself a kind of drug. It sounds ludicrous, and has only added to the difficulty of reviewing and, perhaps, approving this first example of an engineered food animal.

Sometimes this overlapping jurisdiction can cause confusion about which agency should lead, a situation one NPR (National Public Radio) reporter deemed a "regulatory morass" (Palca 2012). At other times, there is little or no jurisdiction, due to the nature of the product and its intended use. It is here that one finds the regulatory cracks. And while these cracks exist for biotechnology in general, the introduction of faster and easier methods for gene editing, through the use of CRISPR-Cas9, will only heighten interest in a variety of changes in plants and animals, beyond the imagination of the drafters of laws governing pests, animal welfare and veterinary drugs.

Let's look at an example. The mosquito is a creature that falls into the overlap area of FDA and USDA. For FDA, the genetic construct used to engineer the mosquito is an "animal drug," because it is something used to "treat" the mosquito to limit its infection with the dengue fever virus. Animal drugs require a host of premarket steps for approval (Animal Drug Act 1968; Animal Drug Availability Act 1996; Animal Medicinal Drug Use Clarification Act 1994). But this is not the kind of animal that drafters had in mind when writing the law governing animal drugs. Chances are they were thinking of cattle and pets and such.

So in some ways it seemed more likely that the Animal and Plant Health Inspection Service (APHIS) within USDA would be the place to go for oversight, under either the Animal Health Protection Act (7 U.S.C. § 8301) (for quarantine, if the mosquito poses a threat to animal health) or the Plant Protection Act (7 U.S.C. § 7701) (if the insect posed a threat to plants). The Animal Welfare Act might also have been a candidate, except that it only protects a limited number of species, with the mosquito not among them. The question of FDA versus USDA jurisdiction circled for years, until finally an understanding was reached: The Food and Drug Administration Center for Veterinary

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Medicine (FDA-CVM) would be the lead agency coordinating other federal and state agencies such as the Centers for Disease Control and Prevention (CDC), U.S. Environmental Protection Agency (EPA), and U.S. Department of Agriculture (USDA). By then, Oxitec had begun trials in South America and the Caribbean.

Of course, in changing entire populations of *Aedes aegypti*, it would seem that the U.S. Environmental Protection Agency might also have a say. The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) (7 U.S.C. § 136 et seq.) allows the U.S. EPA to regulate pesticides, defined as any substance intended to prevent, destroy, repel, or mitigate any pest. The subtlety here is that Oxitec is not adding a pesticide to a nonpest plant or animal (as, for example, in btCorn) but rather is treating the mosquito itself as the pest, which will be killed by changing the animal itself. Assuming it does propose to permit this genetic change in the population, NEPA would also apply, with its extensive public consultation and agency response procedures.

Overall we have three agencies and multiple statutes coming into play to consider the downstream effects on the environment of engineering an entire population of mosquitos. This might be reassuring, but it also may mean there will be a morass each time a critter seems to fall between the cracks.

If nothing else, the experience with the Oxitec mosquito and the AquAdvantage salmon has confirmed that FDA can regulate the genetic constructs, looking to see whether they are safe for the environment, for a resulting animal, and for foods derived from them. But it also points to the need for much clearer and effective collaboration among among FDA, USDA, and EPA if there is to be a transparent, defensible, and consistent view of how cautious we ought to be, as well as how we can adjust the genetic construct or environmental setting to increase confidence in our safety measures. In the spring of 2015, the White House Office of Science and Technology Policy called for a reexamination of the range of laws that govern biotechnology research and products, and asked for help from the National Academy of Sciences (Holdren et al. 2015). But at least until (and unless) that is completed, the unpredictability of agency jurisdiction and discretion will leave some of the plants and animals living in a regulatory zone of uncertainty.

ETHICAL ISSUES

The regulatory issues already discussed focused on limiting the possibilities of concrete harms from CRISPR critters. This final section briefly asks whether widespread creation of such novel organisms should raise other concerns, particularly when they are not created for the purposes of saving lives, preventing climate change, feeding a growing humanity, or other valuable goals. We are not scholars of environmental ethics or philosophy; this section just lays out some questions, starting with, how would our views of nature, ecosystems, and the relationship of humans to them change in such a world—and would such changes be bad . . . or even, at this point, avoidable?

Some decry the "end of nature" and the loss of the sense of a reality outside ourselves, whether created by God or by nature. "In wildness is the preservation of the world," said Henry Thoreau, expressing sentiments echoed by many who feel impoverished by the increasing human footprint on the world. With CRISPR critters, that footprint could become even larger, and more obvious.

But, of course, that footprint has long been there. Geologists and others are actively debating the idea of declaring a new Anthropocene epoch, a new geologic division characterized by thoroughgoing human modification of the world and its living things. A major dispute has been over when the Anthropocene should be seen as starting (Certini and Scalenghe 2015; Lewis and Maslin 2015; Ruddiman et al. 2015). Some would date it from the widespread accumulation in sediments around the world of radioactive isotopes between 1945 and the end of aboveground nuclear testing (mainly in 1962 with the cessation of above ground testing by the United States and the USSR but continuing until 1980 by France, China, and [once] South Africa). Others argue it should be dated from 1610 and atmospheric changes resulting from European invasions of the Western Hemisphere. Still others would go back tens of thousands of years, to human impacts through hunting and the use of fire.

Although the human role in the large mammal extinctions at the end of the last Ice Age remains controversial, the human cause of myriad extinctions and vast changes in land use is not. We have been changing the biosphere constantly, not least by our own expansion from 100,000 or so individuals just a few tens of thousands of years ago to 1 billion in 1800 and 7.3 billion today. And now human-caused changes in the atmosphere's composition are affecting, in largely unknown ways, all life on Earth.

Are CRISPR critters different from the unexpected effects of our expansion? Are they different from the changes we have made in cattle, sheep, and goats—not to mention rice, wheat, and corn—that have vastly expanded the range of our genetically changed versions? Even those not reflexively against "unnatural" changes through biotechnology might find something unsettling about altering the biosphere with uses that are recreational, whimsical, or even Disneyfied.

CONCLUSION

Humans are terrible laboratory animals. We don't follow instructions, we have long generation times, and we can hire lawyers. The possibility of (eventual) human germline genome editing, with the furor it has created, is interesting. The possibility of greatly improved human somatic cell editing, with the lives it might save, is promising. But each has a gantlet of statutes, regulations, bureaucracies, and (potentially) courts that it must run.

Some engineered products have suffered from a confusing confabulation of regulations and laws, but nontraditional gene-editing applications such as bringing back the mammoth or growing a psychedelic garden might face only limited scrutiny if they fall into the cracks. This essay is, in essence, a plea—let's not ignore the nonhuman part of the biosphere. Not only is it much larger than the human part, but it is much more susceptible to unobserved or unfettered—but not unimportant—changes. We are not prepared to offer solutions now, but we do agree that these possibilities should spark not only the imagination, but also critical policy and ethical analysis—to say nothing of ideas for some truly excellent science fiction. ■

REFERENCES

Anderson, M. M., X. Landes, W. Xiang, et al. 2015. Feasibility of new breeding techniques for organic farming. *Trends in Plant Sciences* 20(7): 426–34.

Animal Drug Act. 1968. 82 Stat. 342, 1968, Animal Drug Availability Act. 1996. 110 Stat. 3151, 1996. Animal Medicinal Drug Use Clarification Act. 1994. 108 Stat. 4153, 1994.

Antoniades, A. 2013. Could sparkling glow-in-the-dark pavement replace street lights? TakePart. Available at: http://www.takepart.com/article/2013/10/30/starpath-glow-in-the-dark-roads-provide-energy-free-illumination.

Applied Stem Cell, Inc., Genome-wide CRISPRCRITTERS™ Custom Mouse Injection-Ready Kit (Validated). Available at: http://www.appliedstemcell.com/products/crispr-kits/crispr-critters/crispr-mouse-model-kit

Baltimore, D., P. Berg, M. Botchan, et al. 2015. A prudent path forward for genomic engineering and germline gene modification. *Science* 348: 36–38.

Bratspies, R. M. 2005. How America's first transgenic animal escaped regulation. *Minnesota Journal of Law, Science & Technology* 6: 457–504.

Bujold, L. M. 1996. *Cetaganda*. Wake Forest, NC: Baen Books.

Carlin, N. F., I. Wurman, and T. Zakim. 2014. How to permit your mammoth: Some legal implications of "de-extinction." *Stanford Environmental Law Review* 33: 3–57.

Caulfield S., and Caulfield T., eds. 2009. *Imagining science: Art, science, and social change*. Edmonton, AB, Canada: University of Alberta Press.

Certini, G., and R. Scalenghe. 2015. Holocene as Anthropocene. *Science* 349: 246.

Clark, L. 2012. Genetically-mosquito designed to avoid malaria spread. *Wired UK*. Available at: http://www.wired.co.uk/news/archive/2012-06/13/genetically-modified-mosquitoes

Dickey, C. 2001. I love my glow bunny," *Wired* 9(04). Available at: http://archive.wired.com/wired/archive/9.04/bunny.html.

Food and Drug Administration. n.d. AquAdvantage salmon. Available at: http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/GeneticEngineering/GeneticallyEngineeredAnimals/ucm280853.htm (accessed November 4, 2015).

Gants, V. M., and E. Bier. 2015. The mutagenic chain reaction: A method for converting heterozygous to homozygous mutations. *Science* 348: 442–44.

GloFish. n.d. Experience the glow. Available at: http://www.glofish.com (accessed November 4, 2015).

Glowing sushi. n.d. Cooking with GloFish®. Available at: http://www.glowingsushi.com/ (accessed November 4, 2015).

Greely, H. T. 2012. Biosci Fi: Jerry was a man, R. A. Heinlein, 1947. Stanford Center for Law and the Biosciences Blog. Available at: http://blogs.law.stanford.edu/lawandbiosciences/2012/10/17/science-fiction-law-and-biosciences-jerry-was-aman-robert-a-heinlein-1947 (accessed November 4, 2015).

Heinlein, R. A. (1947) 2012. Jerry was a man. In *Assignment in eternity*, 243–76. Riverdale, NY: Baen Press.

Hickey, S. 2015. The innovators: The biotech firm hoping to breed an end to dengue fever. *The Guardian blog: Business*. Available at: http://www.theguardian.com/business/2015/may/24/the-innovators-biotech-firm-oxitec-breed-end-dengue-fever.

Holdren, J. P., H. Shelanski, D. Vetter, and C. Goldfuss. 2015. Memorandum for heads of Food and Drug Administration, Environmental Protection Agency, and Department of Agriculture. Available at: https://www.whitehouse.gov/blog/2015/07/02/improving-transparency-and-ensuring-continued-safety-biotechnology.

Kickstarter. 2015. Glowing plants: Natural lighting with no electricity. *Kickstarter*. Available at: https://www.kickstarter.com/projects/antonyevans/glowing-plants-natural-lighting-with-no-electricit/posts/1290860

Kolata, G. 2015. A proposal to modify plants gives G.M.O. debate new life. *New York Times*, May 29, p. A3.

Ledford, H. 2015. Biohackers gear up for genome editing. *Nature* 524: 398–99.

Lewis, S. L., and Maslin, M. A. 2015. Geological evidence for the Anthropocene. *Science* 349: 246–47.

Long Now Foundation. n.d. Revive and restore. Available at: http://longnow.org/revive/ (accessed November 4, 2015).

National Academies of Sciences, Engineering, and Medicine. n.d. Current projects: Gene drive research in non-human organisms: Recommendations for responsible conduct. Available at: https://www8.nationalacademies.org/cp/projectview.aspx?key=49717 (accessed November 4, 2015).

NativeSeeds. n.d. Glass gems. Available at: http://shop.nativeseeds.org/products/ts363 (accessed November 4, 2015).

Nature Biotechnology. 2004. The one that got away. 22: 1.

Nosowitz, D. 2011. Suntory creates mythical blue (or, um, lavender-ish) rose. *Popular Science blog*. Available at: http://www.popsci.com/science/article/2011/09/suntory-creates-mythical-blue-or-um-lavender-ish-rose.

Office of Science and Technology Policy. 1986. Coordinated framework for regulation of biotechnology. *Federal Register* 51: 23302.

Oxitec. n.d. Health. Available at http://www.oxitec.com/health/ (accessed November 4, 2015).

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Oye, K. A., K. Esvelt, E. Appelton, et al., 2014. Regulating gene drives. *Science* 345: 626–28.

Palca, J. 2012. Biotech firms caught in regulatory no man's land. *National Public Radio*. Available at: http://www.npr.org/2012/01/02/144330629/biotech-firms-caught-in-regulatory-no-mans-land

Plant Protection Act of 2000. 2000. Pub. L. 106–224, codified at 7 U.S.C. 7701 *et seq*.

Pollack, M. and G. C. Shaffer. 2009. *When cooperation fails: The international law and politics of genetically modified foods*. Oxford, UK: Oxford University Press.

Rawat S. 2014. Are you ready for plants that change color? *Synbiobeta*. Available at: http://synbiobeta.com/ready-plants-change-color/

Ruddiman, W. F., E. C. Ellis, J. O. Kaplan, and D. Q. Fuller. 2015. Defining the epoch we live in. *Science* 348: 38–39.

Sherkow, J., and H. T. Greely. 2013. What if extinction is not forever? *Science* 340: 32–33.

Stamp. N. 2013. Restoring tomato flavor. *The Scientist Blog, Opinion*. Available at: http://www.the-scientist.com/?articles.view/articleNo/37271/title/Opinion–Restoring-Tomato-Flavor

Telis, G. 2013. 700,000 Year old horse becomes oldest creature with sequenced genome. *Science Blog, Evolution* Available at: http://news.sciencemag.org/plants-animals/2013/06/700000-year-old-horse-becomes-oldest-creature-sequenced-genome.

Thomas, H. 2015. This renaissance painting of fruit holds a modern-day science lesson. Available at: http://www.smithsonianmag.com/smart-news/what-renaissance-painting-can-tell-us-about-modern-watermelons-180956155/?utm_source=smithsoniantopic&no-ist

Yarris, L. 2010. CRISPR critters: Scientists identify key enzyme in microbial immune system. Berkeley Lab, News Center. Available at: http://newscenter.lbl.gov/2010/09/09/crispr-critters/.

Zimmer, C. 2013. Bringing them back to life. *National Geographic* 223(4): 28–41.

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