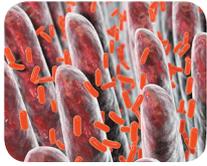


IN this section



**Gut microbes
rev up immuno-
therapy responses**
p121



**First tumor
profiling multiplex
gene panel
approval** p124



**What does
CIRM's future
hold?** p126

FDA warns public of dangers of DIY gene therapy

People are experimenting on themselves with unlicensed gene therapies and publicizing the events widely, prompting the US Food and Drug Administration (FDA) to issue a statement on November 21 cautioning against do-it-yourself (DIY) gene therapies. But even as the agency's statement also warned that selling gene editing kits aimed at homemade therapeutics is illegal, CRISPR-Cas9 kits are available to buy online, and the number of providers is growing, raising concerns that DIY gene therapy enthusiasts could be putting themselves and others at risk.

The FDA first took note in October when Tristan Roberts, who is HIV-positive, injected himself with an unregulated HIV gene therapy designed to eliminate the virus from his body, and live-streamed the event on Facebook. The experimental therapy was devised by Ascendance Biomedical of Singapore, a company that offers to help people access therapies quickly and cheaply, using a digital platform based on blockchain technology (the system behind bitcoin) to “decentralize medicine.” Ascendance Biomedical helped three biohackers develop the HIV gene therapy, a DNA plasmid that, according to the company, once injected, transfects fat cells, inducing them to produce HIV-neutralizing N6 antibodies. One month after injection the results were mixed. Roberts reported that his viral load had risen, but that his CD4⁺ T-cell count had also increased. Roberts, who developed Ascendance Biomedical's digital platform, plans to inject himself a second time with a much higher dose of the HIV therapy, according to Ascendance Biomedical's CEO Aaron Traywick. The company can produce 5,000-10,000 doses for under \$10,000 and depending on the results of Roberts' second treatment, will mass produce and distribute it at no cost in Venezuela, says Traywick, who is inviting documentary film crews to join in its Venezuelan mission.

“Everything that we do is in direct accordance with the law,” Traywick says. The company labels its therapies as research compounds not for human consumption, but points out that members of the public have the right to experiment with unapproved compounds. “An unapproved compound is not an illegal



George Church, professor of genetics at Harvard Medical School, is also business and science advisor for The Odin, a company selling genetic engineering home lab kits.

compound. It is simply a compound that has never been submitted for approval,” he adds. Self-experimentation is indeed legal and has taken place throughout history.

Even so, bioethicists, researchers and people in industry are calling for the FDA to take action. It's appropriate for the federal government to issue warnings about DIY gene therapy self-administration, on the grounds of safety but also questionable efficacy, says Keith Yamamoto, vice chancellor for science policy and strategy and a cellular and molecular pharmacology professor at the University of California, San Francisco.

What the FDA can do is regulate the sale of DNA-modifying kits and materials—if used for therapeutic purposes. The agency's position is that selling a package used to cure a disease is illegal because it should conform to the agency's oversight for drugs. The FDA requires all companies developing drugs for clinical use to first obtain permission for their experimental agents in the form of an investigational new drug application (IND) before testing in humans. The kits used for gene therapy, the FDA argues, are effectively unapproved drugs and administering them without an IND is illegal. “The [FDA's] biggest concern is that the

safety of these kits has never been established, and the lack of control over the processing and handling of the gene therapy product adds an additional level of risk,” an FDA spokesperson said in email.

What laws are being violated remains unclear, says Yamamoto. “Sale of materials for CRISPR-Cas9 technology is not itself illegal or subject to heavy regulatory oversight, so [this implies that] the stated use for self-administration is being challenged,” he says. “Marketing language could be regulated, but off-label self-administration would be hard to control.”

Another biohacker case illustrates that trying to control how the kits are used will prove difficult, if not impossible. Josiah Zayner, in October, injected himself with a CRISPR-Cas9 gene therapy designed to knock out the gene encoding myostatin, which limits muscle cell growth. Zayner, who founded The Odin, a company based in Oakland, California, which sells bacterial DNA online, including through Amazon.com, posted a video online injecting his forearm with a preparation targeting exon 1 of the gene, aiming to bulk out his muscles. The Odin sells a plasmid containing human myostatin knockout CRISPR-Cas9, and the company's

Table 1 Selected CRISPR–Cas9 kit providers

Company	Location	Product	Species	Price
Addgene	Cambridge, Massachusetts	Multiplex CRISPR–Cas9 Assembly System Kit	Human cells	\$330
Applied StemCell	Milpitas, California	CRISPRCLEAR and CRISPRCRITTER CRISPR–Cas9 genome editing kits	Mice, rats, and human and mouse cell lines	\$1,000–\$3,000
Agilent Technologies	Santa Clara, California	SureGuide CRISPR–Cas Complete Kit	Human and mouse	\$662
Canopy Biosciences	St. Louis	TUNR Flexible Gene Editing System	Human, mouse, rat, fruit fly, nematode, Chinese hamster ovary cells and more	\$1,990–\$4,990
Creative Biogene	Shirley, New York	All-in-One CRISPR–Cas9 KO Kit	Most mammalian cells	\$1,380
OriGene Technologies	Rockville, Maryland	CRISPR Products and Services	Human	\$1,290
Synthego Corporation	Redwood City, California	Gene Knockout Kit	Human	\$1,495

Note that numerous scientific supply companies provide CRISPR–Cas9 genome editing reagents individually and in partial kits, including Applied Biological Materials, Dharmacon, Genaxxon Bioscience, GeneCopia, GenScript, Integrated DNA Technologies, MilliporeSigma, New England Biolabs, OZ Biosciences, System Biosciences, Takara Bio Company and ThermoFisher Scientific.

website includes a do-it-yourself CRISPR human gene editing guide. Zayner published a blog post in which he appeared to encourage people to replicate his self-experiment. Though the knockout plasmid sold by The Odin is not ready to inject directly, buyers can “replicate it indefinitely in bacteria and grow up as much as they want and share it,” Zayner wrote. (Zayner was contacted for this article but failed to respond to requests for comment.)

It's not clear if the FDA can or should take action against Zayner, and The Odin is otherwise a reputable company. Its products are aimed at amateur molecular biologists, which could be seen as helping to boost interest in the technology. Harvard University's George Church serves as the company's business and scientific advisor.

The Odin's products include a CRISPR bacterial gene editing kit for \$159. The CRISPR kit includes a strain of non-pathogenic *Escherichia coli* bacteria and template DNA, and plasmids containing Cas9, tracrRNA and crRNA. It enables the buyer to make a K43T mutation to the *E. coli*'s *rpsL* gene, which allows the *E. coli* to survive on media with streptomycin, also provided in the package. In Germany, the government banned all imports from The Odin prompted by contamination of its kit with pathogenic bacteria, although the European Centre for Disease Prevention and Control determined that the risk from the kits was low. A December 20 editorial in *Nature* argued that the German government's reaction could limit the biohacker community's ability to promote biology.

DIYers are unlikely to develop dangerous untested gene therapies, let alone bioweapons or gene drives, says Yamamoto. These methods still require expertise, even with today's CRISPR gene editing kits and online how-to guides, he says. “I'm not concerned

that that's happening.” Those tasks require advanced knowledge and laboratory skills beyond simply being able to follow the directions of gene editing kits, says Louise Baskin, a product manager at the Dharmacon unit of Cambridge, UK–based Horizon Discovery Group. “These can't happen on a kitchen counter.”

Even so, as an editing tool, the CRISPR technique is much easier to use and cheaper than anything that has come before. It lowers the bar to entry for people developing gene therapies, and it is foreseeable that self-administration could be increasingly used to skirt regulations governing human experimentation. “The US' regulatory structure got built in response to and in the aftermath of the misuse of people” by the Nazis, according to Jeffrey Kahn, a bioethics professor at Johns Hopkins University. There is also a substantial history of human exploitation for medical research in the US from the mid-nineteenth to the mid-twentieth centuries. “Certainly there's a conversation to be had about how far in the protection-to-access arc the pendulum ought to be,” says Kahn. “There's an argument that it has been overly protective in the past, which I would agree with. But if we push too far towards access for all to research, that's also not ethically acceptable.”

Biomedical research could itself be harmed by a laissez-faire attitude to self-experimentation. To accrue knowledge, research needs to happen in a controlled, consistent way, otherwise the data are not worth collecting says Kahn.

Harvard's Church is strongly in favor of double-blind, placebo-controlled, randomized trials, even for food additives, nutritional supplements, probiotics and other products for which the FDA does not require clinical trials because they are considered safe. Church, however, makes a distinction between self-experimentation and marketed

therapies. “Self-experimentation has an interesting history and is compatible with [institutional review board] ethics approval,” he says. “But in the case of new therapies, it should be done in the context of an FDA-approved IND.”

Companies offering easy-to-use CRISPR–Cas9 gene editing kits are growing in number (Table 1). Most view research laboratories as their main consumers. Research laboratories on a budget are the main customers for Dharmacon of Lafayette, Colorado, which sells inexpensive CRISPR gene editing reagents not for use in human subjects. “When we in the research space talk about DIY, we tend to talk about people who might work in a lab and purchase Dharmacon products to do their own gene editing as opposed to purchasing a service from someone else,” says Baskin.

Packaging CRISPR–Cas9 reagents into a kit is also about making the technology accessible. Because, although the technique has revolutionized gene editing, the learning curve for working with the technology from scratch is still fairly steep, says Edward Weinstein, CEO of Canopy Biosciences in St. Louis. “Researchers simply tell us the gene they want to modify and what mutation they want to make, and then we custom design and assemble all the reagents they need, and send everything in a single kit,” says Weinstein.

Canopy Biosciences' label license prohibits any use other than R&D, Weinstein adds. The company also vets all purchase requests, investigates requests from institutions it isn't familiar with, won't deliver to non-laboratory addresses and doesn't respond to emails from personal accounts, he says. “These are all very standard practices that responsible companies in this industry use,” says Weinstein.

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