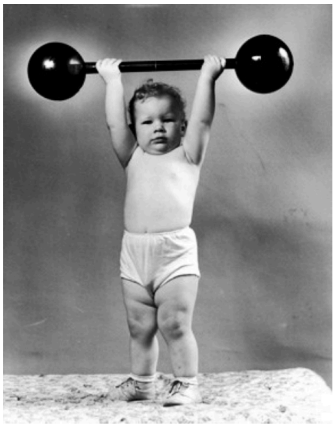
Searching for the Perfect Athlete

By Reeves Wiedeman



Superbaby was born around the turn of this century, in Berlin, emerging in a fit of twitches and shudders. Epilepsy, the doctors first thought, until one noticed that although Superbaby was roughly the size of any other newborn, his biceps were chiseled. His skin held tight around his calves and quads. The phrase “baby fat” did not apply.

The boy’s tremors calmed, and he settled into relative normalcy. But by age four, he had twice as much muscle as other boys his age, and could hold a six-pound dumbbell, horizontally, at arm’s length, a struggle for some grownups. Something was going on, and laboratory analysis found that the secret to Superbaby’s physique was more earthly than Clark Kent’s: an extremely rare genetic mutation—passed on from his mother, an accomplished sprinter—that inhibited myostatin, a protein that limits muscle growth. The genetic blueprint that keeps most of us puny, or relatively so, was missing.

Superbaby’s story is one among a number of tales of athletic irregularity in “The Sports Gene,” a new book by David Epstein, who holds a masters in environmental science but now covers the science of sports for *Sports Illustrated*. Like a good academic, Epstein weaves a thicket of studies and double-blind tests into anecdotes like Superbaby’s. Beware, those who enter seeking a quick answer to whether or not your son or daughter has an athletic scholarship in his or her future: the book is heavy on talk about stop codons and VO2 maxes and bivariate overlap zones, and short on easy answers. It is,

however, long on difficult questions. Can nature predict athletic performance? What about nurture? Is it possible to create a Superbaby from scratch? If we can, should we want to?

The answers, in brief, are “yes,” “yes,” “not quite,” and “ask your conscience.” But a bit of exploration of each proves fruitful.

The nature-versus-nurture debate that drives the book takes as its foundation the ten-thousand-hours hypothesis, offered first by a team of academics and popularized by Malcolm Gladwell. The theory maintains that it will require a basketball player ten thousand hours of concentrated jump shooting to become proficient at that task—the same for the tasks of painters, musicians, and lawyers. It’s the American dream boiled to a formula: work hard, and you can be anything you want.

Epstein offers some evidence suggesting that the claim has some merit. Take Albert Pujols, one of the greatest hitters in baseball history. (Until his struggles this season, at least.) Common sense held that Pujols’s success at the plate was due at least in part to superlative reflexes. Yet when scientists at Washington University in St. Louis tested his reaction time against a random sample of college students, Pujols landed in the sixty-sixth percentile—better than most, but hardly two hundred and forty million dollars over ten years better.

What Pujols does have is hours and hours of visually recorded memory, and the ability to “chunk” that information into useful segments. Over the years, he and other top hitters have compiled a mental database of physiological clues—how a curveball’s delivery looks compared to a fastball’s, for instance—that allow them to react to a pitch more quickly than, say, a recreational softball player can. (Speaking of softball, it’s probably for this reason, Epstein notes, that when Pujols faced Jennie Finch, a softball pitcher, in an exhibition, he quickly struck out: all of the mental information Pujols had about a baseball pitcher’s overhand motion was useless when facing a softball player throwing underhand.)

Still, Epstein acknowledges that it helps to be tall, and strong, and not need glasses: most Major Leaguers, when tested for vision, have exceptional eyesight. In any athletic endeavor, as with any intellectual one, there are some innate talents that can't be acquired. Tiger Woods's gifts with a driver have been largely credited to his willingness to practice at a young age for hours on end. That certainly helped, but, in the interest of bursting bubbles, Epstein is quick to point out Woods's ability, at six months old, to stand on his father's palm while the elder Woods walked around the house. Not quite Superbaby, but close. The most devastating quotation in "The Sports Gene," for those who harbor hopes of a second act as a professional athlete, might be this one, delivered by a scientist who has been testing inherited athleticism in rugby players: "We've tested over ten thousand boys, and I've never seen a boy who was slow become fast."

Well, bummer. There are, by Epstein's count, around a hundred thousand "naturally fit" Americans between the ages of twenty and sixty-five—those whose genetic makeups predispose them to being in shape. The book is rife with such genetic advantages that find their ways into different populations. Members of a particular ethnic group in Kenya, in addition to living at altitude, have thinner legs, which makes the pendulum effect necessary for distance running that much easier to create. An outsized number of Jamaicans from Trelawny, a region in the island's northwest, have become world-champion sprinters. Redheads from everywhere tend to have greater tolerance for physical pain.

But the disappointing reality Epstein most often presents is that there are no answers, or at least not definitive ones, to the questions of what genetic traits will guarantee athletic success, or whether training can truly overcome inborn limitations. Take ACTN3, a gene that allows for the production of alpha-actinin-3, a protein found in the fast-twitch muscles of almost every top sprinter who has ever been tested for the gene. But a properly functioning ACTN3 is not a golden ticket, merely a prerequisite for entry. "The ACTN3 gene may tell a billion or so people in the world that they won't be in the Olympics 100-meter final," Epstein writes. "But chances are they all already knew that."

Still, professional teams, which rise and fall on their ability to judge which athletes are worth spending time and money on, are starting to take genetics seriously. European soccer teams have begun employing scientists to test athletes in their youth-training academies for everything from willingness to practice to their top sprinting speed. (Those who go on to sign professional contracts are, on average, two-tenths of a second faster in a shuttle sprint as preteens than those who don't.) In 2005, a rugby team in Australia announced that it would start testing players for ACTN3 because of what it might be able to predict about sprinting speed. That same year, after the Chicago Bulls center Eddy Curry was diagnosed with a benign arrhythmia, the team offered him a new contract only on the condition that he submit to DNA testing to look for a specific gene variant that could cause Curry to suffer a sudden, possibly fatal heart attack. (Curry declined, citing privacy concerns.)

If we are beginning to understand which genetic components lead to superior athletic performance, are we at a point where humans can be bred to become athletes? Epstein takes two hundred pages to get to this question, and when he does, he starts with animals. He visits mushers in the Iditarod who claim they have bred huskies not only for speed and endurance but masochism: they claim an ability to breed dogs who are not only able to run for long periods, but who *want* to do nothing else. Thoroughbred race horses, meanwhile, have been bred for speed so successfully that their times have begun to plateau, and Epstein speculates they may have reached their peak speed—that breeders have simply run out of genetic traits to exploit.

Could the same be done with humans? Certain athletic records may seem unbeatable, but others are broken regularly, suggesting that there is still room for improvement. The technology is on the not-too-distant horizon: scientists have produced fertile eggs from mouse stem cells, allowing for the possibility that, one day soon, humans will be able to engineer their children to receive specific traits and not others. *Give him my wingspan, but not the vertical leap*. The big hope for these technologies is that they will help deal with debilitating diseases, but big-money sports are inevitably going to get involved. Human-growth hormone was initially seen as a potential way to treat growth disorders in children, but H.G.H. is now at the center of the Biogenesis scandal that got Ryan

Braun suspended, and will reportedly bring down Alex Rodriguez and other major-leaguers soon. Similarly, Superbaby's myostatin mutation, along with research in mice that found a similar result, led scientists to believe the protein could be useful in treating muscular dystrophy. But the athletic potential of "double muscle," as the condition is known, is obvious. Superbaby's family has kept his identity secret, but no one could blame the German Olympic committee for making inquiries.

Barring the creation of super athletes from a pool of genetic material—the stuff of Cold War-era movies about East German sports—your kids are stuck with what you can give them. The odds of any human possessing something approaching the perfect set of athletic gene variants, according to Epstein, is less than one in a quadrillion. He writes: "It's as if we've all played genetic roulette over and over, moving our chips around, winning sometimes and losing other times, all of us gravitating toward mediocrity." Bummer again. A slightly more uplifting take comes from a sports psychologist with whom Epstein spoke, who told him, "Maybe it's dangerous, too, to say that you're stuck where you are because you're not working hard enough." The point is ultimately a conservative one: perhaps you can't be whatever you want, and if so, maybe it's better to just accept that now. For anyone still in denial, Epstein chooses this as his book's final phrase: "Happy training."

http://www.newyorker.com/online/blogs/sportingscene/2013/07/genetics-searching-for-the-perfect-athlete.html

Chinese Scientist Claims to Use Crispr to Make First Genetically Edited Babies

By Gina Kolata, Sui-Lee Wee and Pam Belluck

- Nov. 26, 2018

Ever since scientists created the powerful gene editing technique Crispr, they have braced apprehensively for the day when it would be used to create a genetically altered human being. Many nations banned such work, fearing it could be misused to alter everything from eye color to I.Q.

Now, the moment they feared may have come. On Monday, a scientist in China announced that he had created the world's first genetically edited babies, twin girls who were born this month.

The researcher, He Jiankui, said that he had altered a gene in the embryos, before having them implanted in the mother's womb, with the goal of making the babies resistant to infection with H.I.V. He has not published the research in any journal and did not share any evidence or data that definitively proved he had done it.

But his previous work is known to many experts in the field, who said — many with alarm — that it was entirely possible he had.

"It's scary," said Dr. Alexander Marson, a gene editing expert at the University of California in San Francisco.

While the United States and many other countries have made it illegal to deliberately alter the genes of human embryos, it is not against the law to do so in China, but the practice is opposed by many researchers there. A group of 122 Chinese scientists issued a statement calling Dr. He's actions "crazy" and his claims "a huge blow to the global reputation and development of Chinese science."

If human embryos can be routinely edited, many scientists, ethicists and policymakers fear a slippery slope to a future in which babies are genetically engineered for traits — like athletic or intellectual prowess — that have nothing to do with preventing devastating medical conditions.

While those possibilities might seem far in the future, a different concern is urgent and immediate: safety. The methods used for gene editing can inadvertently alter other genes in unpredictable ways. Dr. He said that did not happen in this case, but it is a worry that looms over the field.

Dr. He made his announcement on the eve of the Second International Summit on Human Genome Editing in Hong Kong, saying that he had recruited several couples in which the man had H.I.V. and then used in vitro fertilization to create human embryos that were resistant to the virus that causes AIDS. He said he did it by directing Crispr-

Cas9 to deliberately disable a gene, known as CCR5, that is used to make a protein H.I.V. needs to enter cells.

Dr. He said the experiment worked for a couple whose twin girls were born in November. He said there were no adverse effects on other genes.

In a video that he posted, Dr. He said the father of the twins has a reason to live now that he has children, and that people with H.I.V. face severe discrimination in China.

Dr. He's announcement was reported earlier by the MIT Technology Review and The Associated Press.

In an interview with the A.P. he indicated that he hoped to set an example to use genetic editing for valid reasons. "I feel a strong responsibility that it's not just to make a first, but also make it an example," he told the A.P. He added: "Society will decide what to do next."

It is highly unusual for a scientist to announce a groundbreaking development without at least providing data that academic peers can review. Dr. He said he had gotten permission to do the work from the ethics board of the hospital Shenzhen Harmonicare, but the hospital, in interviews with Chinese media, denied being involved. Cheng Zhen, the general manager of Shenzhen Harmonicare, has asked the police to investigate what they suspect are "fraudulent ethical review materials," according to the Beijing News.

The university that Dr. He is attached to, the Southern University of Science and Technology, said Dr. He has been on no-pay leave since February and that the school of biology believed that his project "is a serious violation of academic ethics and academic norms," according to the state-run Beijing News.

In a statement late on Monday, China's national health commission said it has asked the health commission in southern Guangdong province to investigate Mr. He's claims.

Many scientists in the United States were appalled by the developments.

"I think that's completely insane," said Shoukhrat Mitalipov, director of the Center for Embryonic Cell and Gene Therapy at Oregon Health and Science University. Dr. Mitalipov broke new ground last year by using gene editing to successfully remove a dangerous mutation from human embryos in a laboratory dish.

Dr. Mitalipov said that unlike his own work, which focuses on editing out mutations that cause serious diseases that cannot be prevented any other way, Dr. He did not do anything medically necessary. There are other ways to prevent H.I.V. infection in newborns.

Richard Hynes, a cancer researcher at the Massachusetts Institute of Technology, who co-led an advisory group on human gene editing for the National Academy of Sciences and the National Academy of Medicine, said that group and a similar organization in

Britain had determined that if human genes were to be edited, the procedure should only be done to address “serious unmet needs in medical treatment, it had to be well monitored, it had to be well followed up, full consent has to be in place.”

It is not clear why altering genes to make people resistant to H.I.V. is “a serious unmet need.” Men with H.I.V. do not infect embryos. Their semen contains the virus that causes AIDS, which can infect women, but the virus can be washed off their sperm before insemination. Or a doctor can inject a single sperm into an egg. In either case, the woman will not be infected and neither will the babies.

Dr. He got his Ph.D., from Rice University, in physics and his postdoctoral training, at Stanford, was with Stephen Quake, a professor of bioengineering and applied physics who works on sequencing DNA, not editing it.

Experts said that using Crispr would actually be quite easy for someone like Dr. He.

After coming to Shenzhen in 2012, Dr. He, at age 28, established a DNA sequencing company, Direct Genomics, and listed Dr. Quake on its advisory board. But, in a telephone interview on Monday, Dr. Quake said he was never associated with the company.

https://www.nytimes.com/2018/11/26/health/gene-editing-babies-china.html

Cancer and Infectious Diseases

Scientists report that they have discovered a way to tweak genes in the body's immune cells by using electrical fields.

By Gina Kolata

- July 11, 2018

For the first time, scientists have found a way to efficiently and precisely remove genes from white blood cells of the immune system and to insert beneficial replacements, all in far less time than it normally takes to edit genes.

If the technique can be replicated in other labs, experts said, it may open up profound new possibilities for treating an array of diseases, including cancer, infections like H.I.V. and autoimmune conditions like lupus and rheumatoid arthritis.

The new work, published on Wednesday in the journal Nature, "is a major advance," said Dr. John Wherry, director of the Institute of Immunology at the University of Pennsylvania, who was not involved in the study.

But because the technique is so new, no patients have yet been treated with white blood cells engineered with it.

"The proof will be when this technology is used to develop a new therapeutic product," cautioned Dr. Marcela Maus, director of cellular immunotherapy at Massachusetts General Hospital.

That test may not be far away. The researchers have already used the method in the laboratory to alter the abnormal immune cells of children with a rare genetic condition. They plan to return the altered cells to the children in an effort to cure them.

Currently, scientists attempting to edit the genome often must rely on modified viruses to slice open DNA in a cell and to deliver new genes into the cell. The method is time-consuming and difficult, limiting its use.

Despite the drawbacks, the virus method has had some success. Patients with a few rare blood cancers can be treated with engineered white blood cells — the immune system's T-cells — that go directly to the tumors and kill them.

This type of treatment with engineered white cells, called immunotherapy, has been limited because of the difficulty of making viruses to carry the genetic material and the time needed to create them.

But researchers now say they have a found a way to use electrical fields, not viruses, to deliver both gene-editing tools and new genetic material into the cell. By speeding the process, in theory a treatment could be available to patients with almost any type of cancer.

“What takes months or even a year may now take a couple weeks using this new technology,” said Fred Ramsdell, vice president of research at the Parker Institute for Cancer Immunotherapy in San Francisco. “If you are a cancer patient, weeks versus months could make a huge difference.”

“I think it’s going to be a huge breakthrough,” he added.

The Parker Institute already is working with the authors of the new paper, led by Dr. Alexander Marson, scientific director of biomedicine at the Innovative Genomics Institute — a partnership between University of California, San Francisco and the University of California, Berkeley — to make engineered cells to treat a variety of cancers.

In the new study, Dr. Marson and his colleagues engineered T-cells to recognize human melanoma cells. In mice carrying the human cancer cells, the modified T-cells went right to the cancer, attacking it.

The researchers also corrected — in the lab — the T-cells of three children with a rare mutation that caused autoimmune diseases. The plan now is to return these corrected cells to the children, where they should function normally and suppress the defective immune cells, curing the children.

The technique may also hold great promise for treating H.I.V., Dr. Wherry said.

The H.I.V. virus infects T-cells. If they can be engineered so that the virus cannot enter the T-cells, a person infected with H.I.V. should not progress to AIDS. Those T-cells already infected would die, and the engineered cells would replace them.

Previous research has shown it might be possible to treat H.I.V. in this way. “But now there is a really efficient strategy to do this,” Dr. Wherry said.

The idea of engineering T-cells without using a virus is not new, but the immune cells are fragile and hard to keep alive in the lab, and it has always been difficult to get genes into them.

Scientists usually introduced replacement genes into T-cells with a type of virus that was disarmed so that it would not cause disease and that can insert new genes into cells. But when these viruses insert the genes into a cell’s DNA, they do so haphazardly, sometimes destroying other genes.

“We needed something targeted, something fast and something efficient,” Dr. Marson said. “What if we could just paste in a piece of DNA and avoid the viruses altogether?”

The idea would be to slip a type of molecular scissors, known as Crispr, into cells that would slice open DNA wherever scientists wanted a new gene to go. That would avoid the problem of using a virus that inserts genes pretty much at random.

And along with the scissors, they would add a piece of DNA containing the new gene to be added to the cells.

One way to do that would be to use an electrical field to make the cells permeable. It required a herculean effort by a graduate student, Theo Roth, to finally figure out the right molecular mixture of genes, gene-editing tools and electrical fields to modify T-cells without a virus.

“He tested thousands of conditions,” Dr. Marson said.

Already the scientists are talking to the Food and Drug Administration about using the new method to precisely attack solid tumors, as well as blood cancers.

“Our intent is to try to apply this as quickly as possible,” Dr. Ramsdell said.

So when they knew they had a system that worked, did they break out the champagne? Have a party?

Well, no, Mr. Roth said in an interview. He just took the data to Dr. Marson.

“We certainly had an exuberant walk to Alex’s office,” he recalled.

https://www.nytimes.com/2018/07/11/health/gene-editing-cancer.html?action=click&module=RelatedLinks&pgtype=Article

Scientists Can Design 'Better' Babies. Should They?

By Clyde Haberman

- June 10, 2018

For nine frustrating years, Lesley and John Brown tried to conceive a child but failed because of her blocked fallopian tubes. Then in late 1977, this English couple put their hopes in the hands of two men of science. Thus began their leap into the unknown, and into history.

On July 25, 1978, the Browns got what they had long wished for with the arrival of a daughter, Louise, a baby like no other the world had seen. She came into being through a process of in vitro fertilization developed by Robert G. Edwards and Patrick Steptoe. Her father's sperm was mixed with her mother's egg in a petri dish, and the resulting embryo was then implanted into the womb for normal development.

Louise was widely, glibly and incorrectly called a "test-tube baby." The label was enough to throw millions of people into a moral panic, for it filled them with visions of Dr. Frankenstein playing God and throwing the natural order of the universe out of kilter. The reality proved far more benign, maybe best captured by Grace MacDonald, a Scottish woman who in January 1979 gave birth to the second in vitro baby, a boy named Alastair. Nothing unethical was at work, she told the BBC in 2003. "It's just nature being given a helping hand."

In this installment of its video documentaries, Retro Report explores how major news stories of the past shape current events by harking back to Louise Brown's birth. If anything, more modern developments in genetics have raised the moral, ethical and political stakes. But the fundamental questions are essentially what they were in the 1970s with the advent of in vitro fertilization:

Are these welcome advances that can only benefit civilization? Or are they incursions into an unholy realm, one of "designer babies," with potentially frightening consequences?

In vitro fertilization, or I.V.F., is by now broadly accepted, though it still has objectors, including the Roman Catholic Church. Worldwide, the procedure has produced an estimated six million babies, and is believed to account for 3 percent of all live births in some developed countries. Designer-baby fears have proved in the main to be "overblown," said Dr. Paula Amato, a professor of obstetrics and gynecology at Oregon Health & Science University in Portland. "We have not seen it with I.V.F. in general," she told Retro Report. "We have not seen it with P.G.D."

P.G.D. is shorthand for pre-implantation genetic diagnosis, developed more than two decades ago and an offshoot of in vitro fertilization. Couples with family histories of serious diseases — cystic fibrosis, Tay-Sachs and Down syndrome are among the more

common — can have their lab-created embryos tested for the probability of passing the flaws to their offspring. Technology in effect gives them a measure of control over their genetic fate. An embryo that looks O.K. under a microscope can be implanted in the mother's uterus for normal development. (Typically, the others are discarded, itself a morally fraught practice for some people).

But what if the issue isn't averting a dreadful disease? What if would-be parents, rather than leaving the matter to an old-fashioned roll of the genetic dice, resort to embryonic selection to guarantee the child is of a particular sex? It can be done with pre-implantation genetic diagnosis. Dr. Jeffrey Steinberg, director of The Fertility Institutes in New York, does it as matter of course.

"The technology was out there — it was being applied only to diseases," Dr. Steinberg told Retro Report. He continued: "I've decided to open the door and expand it and say, 'Listen, this is something that people are interested in, causes no harm, makes people happy. Let's expand it.'" Though many doctors are strongly skeptical, he also offers P.G.D. to improve the odds that a baby will have a desired eye color, practically casting himself as the Benjamin Moore of the laboratory with his "choice of 30 shades of blue eyes."

Still other gene-altering techniques are now in play. Mitochondrial transfer, for one, is intended for a woman whose genetic makeup makes it likely she will bear a child with a severe birth defect. DNA is removed from her egg and implanted in an egg from another woman that contains healthy energy-generating components known as mitochondria. This has given rise to the discomfiting term "three-parent baby."

Then there is a gene-editing method called Crispr, the acronym for a mouthful of a procedure: Clustered Regularly Interspaced Short Palindromic Repeats. A team led by Shoukhrat Mitalipov, an American reproductive biologist, announced last year that it had applied the technique to change a human genome. With an enzyme called Cas9 acting as a scalpel, Crispr snipped away a mutated gene that can lead to thickened heart muscles and cause sudden death in young athletes.

In theory, it meant that if this embryo were implanted in a womb — it wasn't in this team's research — the child eventually born would not carry the mutation, and nor would any grandchildren. In short, that family's germ line, the genetic material governing cellular lineage from one generation to the next, would have been permanently altered.

As Louise Brown prepares for her 40th birthday next month, moral debates over the new capabilities echo those that swirled around her parents, both now dead.

Some ethicists see only good in the prospect of eliminating diseases that condemn families to misery. After all, don't childhood vaccinations amount to using technology for that very same purpose? Yet few people regard measles or polio shots as unacceptable fiddling with the natural world.

In a different camp are those who invoke slippery slopes, fearing unpredictable genies that may be unleashed. What, they ask, is to prevent gene editing from being used someday not to combat disease but, rather, to design people who are stronger or smarter than everyone else, able themselves to produce children programmed genetically for SAT scores of 1,600 or LeBron James point totals?

Then again, selecting genes to produce, say, a star basketball player is hardly a snap; height alone is influenced by tens of thousands of genetic variations. On the other hand (there is almost always another hand) the sheer expense of the procedures threatens to widen an already substantial gap between the wealthy and everyone else.

In 2017, an advisory group formed by the National Academy of Sciences and the National Academy of Medicine endorsed gene editing in principle, but with a proviso that it be used only to deal with "serious diseases and disability" and only when no "reasonable alternative" exists.

Some scientists say it is unwise to be paralyzed by fear of the unknown. But Marcy Darnovsky, executive director of the Center for Genetics and Society in Berkeley, Calif., is more skeptical. "We have to ask where is the stopping point," Ms. Darnovsky said, and she suggested that policy discussions include "a much broader range of voices" than just scientists.

Perhaps Shakespeare can enter the conversation. He bequeathed words often invoked to encapsulate both hope for and dread of human capability. They're from "The Tempest": "O brave new world, that has such people in't."

https://www.nytimes.com/2018/06/10/us/11retro-baby-genetics.html?action=click&module=RelatedLinks&pgtype=Article

Scientist in China defends human embryo gene editing

He Jiankui uses Hong Kong summit to reply to critics of his Crispr-Cas9 trials altering baby DNA for HIV resistance

Suzanne Sataline*in Hong Kong and* **Ian Sample**

Wed 28 Nov 2018

The Chinese scientist who claims to have altered the DNA of twin girls before birth – without going through the usual scientific channels – said he was proud of his work, and claimed another woman enrolled in his trial was pregnant with a similarly modified baby.

The scientist, He Jiankui, spoke to hundreds of colleagues and journalists on Wednesday at the International Human Genome Editing Summit at the University of Hong Kong.

He said details of the first births from the trial, which used gene-editing technology known as Crispr-Cas9, had been submitted to a scientific journal, which he did not name. Nor did he say when the results might be published.

In a planned presentation, He, an associate professor at Southern University of Science and Technology, in Shenzhen, described how he used Crispr-Cas9 to modify a gene called CCR5 in a number of embryos created through IVF for couples with HIV-positive fathers.

The modification was intended to mirror a natural mutation found in a small percentage of people which makes them resistant to the virus. Two girls named Nana and Lulu were born with the genetic changes, he said.

The researcher's 40-minute Q&A offered a charged forum for scientists to publicly question a colleague caught in controversy.

The Nobel laureate David Baltimore, an organiser of the summit, who is professor emeritus of biology at the California Institute of Technology, called He's work irresponsible. "I think there has been a failure of self regulation by the scientific community because of a lack of transparency," Baltimore said.

David Liu, a biologist at the Broad Institute in Cambridge, Massachusetts, challenged He on how the girls might benefit from having their DNA altered. The children were not at risk of contracting HIV at birth and he said there were many ways to avoid HIV infection later in life. "What was the unmet medical need for these patients in particular?" Liu asked.

He said in defence: “I truly believe that, not only for this case but for millions of children, they need this protection since an HIV vaccine is not available. For this case I feel proud.”

Matthew Porteus, professor of paediatrics at Stanford University, said: “He’s already at risk of becoming a pariah.” Scientists talked about their research plans years in advance with many colleagues, to get feedback before they set out. “Unless he starts to engage in the scientific process, it will get worse and worse,” Porteus added.

At the summit He presented slides to an audience of scientists who expressed concern that he could have brought harm to his subjects and jeopardised gene editing research.

The scientist said, however, he wanted to prevent HIV being inherited from a parent because so many children were affected by the virus in China. Eight couples had agreed to take part in the study, though one had dropped out. With each, the father was HIV positive, while the woman was clear of the virus.

He told the audience he had worked on 31 eggs and implanted two altered embryos in one woman. One of the babies had only one copy of the CCR5 gene edited, which was not enough to confer HIV resistance. The health of both children would be monitored for the next 18 years.

The gene-editing work had started three years ago, partly paid for by He, who had consulted, he said, with just a few colleagues about his plans.

In the UK and many other countries it is illegal to create genetically modified babies, and scientists in the field have reached a broad consensus that it would be deeply unethical to try. Genome editing is not considered safe, and any genetic modifications – whether beneficial or unintentionally harmful – affect not only the child, but their children and future generations.

“It is impossible to overstate how irresponsible, unethical and dangerous this is at the moment,” said Kathy Niakan, a scientist at the Francis Crick Institute, in London, who was present at the summit. “There was a worrying lack of oversight or scrutiny of his clinical plans before he started human experiments and a complete lack of transparency throughout the process.

“I found it highly troubling that He avoided questions about approval processes, and his answers on patient recruitment and consent did not reassure me. The team don’t seem to have had adequate training on proper consent processes. Offering vulnerable patients free IVF treatment presents a clear conflict of interest.”

On Tuesday it was announced that He’s work was being investigated by Chinese officials and his university in Shenzhen.

He's vague answers at the summit prompted more questions from the audience. Did He know enough about the technology to ensure that the children would be healthy, or might they contract other deadly viruses? He insisted he did know enough.

"How do you see your responsibility to these children?" asked Eben Kirksey, an associate professor of anthropology, at Deakin University, in Victoria, Australia. He replied that the children's medical care would be provided for, but offered no details.

The missing information frustrated many in the audience. "This is a red line," one conference attendee told He. "Why did you choose to cross it and conduct this in secret?"

Robin Lovell-Badge, a geneticist at the Francis Crick Institute, in London, claimed that He was misguided. "He clearly made some wrong decisions. I'm very critical of calling this a scientific breakthrough because he's messed up all along."

Lovell-Badge said he was inclined to believe that He had altered the babies' DNA, but said the scientist needed to show proof of it. The only way to convince the world would be if an independent, qualified, lab tested the DNA of the parents and the two babies to show that the genes had been edited. "Nothing that I've been shown says it's false. But the evidence I've seen is not yet good enough," he added.

https://www.theguardian.com/science/2018/nov/28/scientist-in-china-defends-human-embryo-gene-editing

China orders halt to gene-editing after scientist's claims

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Mark Schiefelbein / AP file

Nov. 29, 2018 / 4:50 AM PST

By Reuters

SHANGHAI — The Chinese government on Thursday ordered a temporary halt to research activities for people involved in the editing human genes, after a Chinese scientist said he had edited the genes of twin babies.

Scientist He Jiankui said this week that he used a gene-editing technology known as CRISPR-Cas9 to alter the embryonic genes of the twin girls born this month.

He's announcement, which has not been verified, sparked an international outcry about the ethics and safety of such research.

"The nature of this incident is extremely nasty, and relevant bodies have been ordered to temporarily halt the scientific research activities of relevant personnel," the state news agency Xinhua said, citing the health ministry, science and technology ministry and China Association for Science and Technology.

The organizers of a conference where He claimed to have edited the genes also condemned the work on Thursday, calling it "deeply disturbing" and "irresponsible."

"Even if the modifications are verified, the procedure was irresponsible and failed to conform with international norms," the organizing committee of the Second International Summit on Human Genome Editing, being held in Hong Kong this week, said in a statement.

The committee called for an independent assessment of He's claims.

He said gene editing would help protect the girls from infection with HIV, the virus that causes AIDS.

Chinese scientists have also condemned the work and the Southern University of Science and Technology, where He is on leave from his position as an associate professor, has announced an investigation.

The Guangdong province Health Commission said on its website on Wednesday it and Shenzhen city had set up a team to investigate the case.

He's filing to a Chinese clinical trials database indicates that a hospital did an ethical review of the project, but the hospital involved denied that its ethics review committee ever met to discuss the work.

He said after his presentation on Wednesday he was proud of what he had done.

The presidents of the U.S. National Academy of Sciences (NAS) and the U.S. National Academy of Medicine (NAM) also expressed concern about He's work.

"The events in Hong Kong this week clearly demonstrate the need for us to develop more specific standards and principles that can be agreed upon by the international scientific community," NAS president Marcia McNutt and NAM president Victor Dzau said in a statement.

https://www.nbcnews.com/health/health-news/china-orders-halt-gene-editing-after-scientist-s-claims-n941556

7 Diseases CRISPR Technology Could Cure

Clara Rodríguez Fernández on 25/06/2018

CRISPR technology offers the promise to cure any human genetic disease. Which are the candidates to be the first one?

CRISPR-Cas9 was first described as a gene editing tool in 2012. In just a few years, the technology has exploded in popularity thanks to its promise of making genome editing much faster, cheaper and easier than ever before.

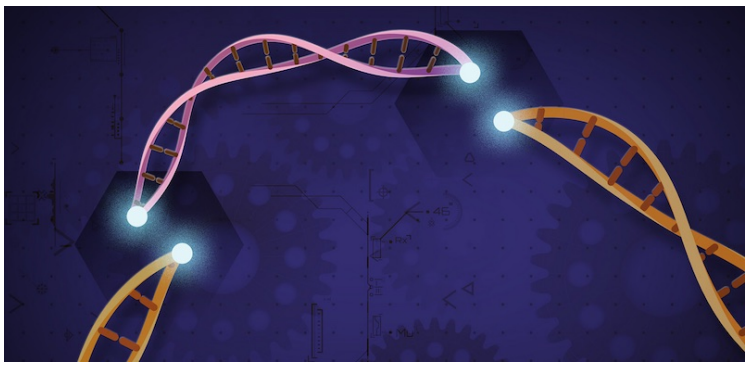
CRISPR has already changed the way scientists do research, but what everyone is expecting, either with excitement or fear, is its use in humans. In theory, CRISPR technology could let us edit any mutation at will and cure the disease it causes. In practice, we are just at the beginning of the development of CRISPR as a therapy and there are still many unknowns.

But if you had at least a chance to cure any genetic disease, what would it be? These are seven diseases that scientists are already tackling with the help of CRISPR, and which could eventually become some of the first conditions to ever be treated with this revolutionary technology.

1. Cancer

One of the first applications of CRISPR could be in cancer. One of the first and most advanced CRISPR clinical trials, which is currently running in China, is testing the potential of the gene editing tool in patients with advanced cancer of the esophagus.

The treatment being tested at the Hangzhou Cancer Hospital starts with the extraction of T cells from the patient. Using CRISPR, the cells are modified to remove the gene that encodes for a receptor called PD-1 that some tumors are able to bind to and instruct the immune system not to attack. The cells are then reinfused into the patient with a higher capacity to attack tumor cells.



So far, at least 86 people with different forms of cancer have been treated with CRISPR in China, and results should be available soon.

The first CRISPR trial planned to be run in the US will also target cancer, using CRISPR to remove PD-1 as well as a T cell receptor from T cells engineered to express a cancer-targeting receptor.

2. Blood disorders

The first CRISPR trial in Europe will seek to treat beta-thalassemia, a blood disorder that affects the oxygen transport in the blood. The therapy, developed by CRISPR Therapeutics and Vertex Pharmaceuticals, consists in harvesting hematopoietic stem cells from the patient and using CRISPR technology to make them produce fetal hemoglobin, a natural form of the oxygen-carrying protein that binds oxygen much better than the adult form.

A first trial in beta-thalassemia is expected to begin later this year after clearance from the EMA. A second trial will test the same therapy in the treatment of sickle cell diseases, another blood disorder affecting oxygen transportation. However, the FDA has put the US trial on hold to clear some safety questions before going ahead.

Hemophilia is another blood disorder that CRISPR technology could tackle. CRISPR Therapeutics is working with Casebia on an *in vivo* CRISPR therapy where the gene editing tool is delivered directly to the liver.

3. Blindness

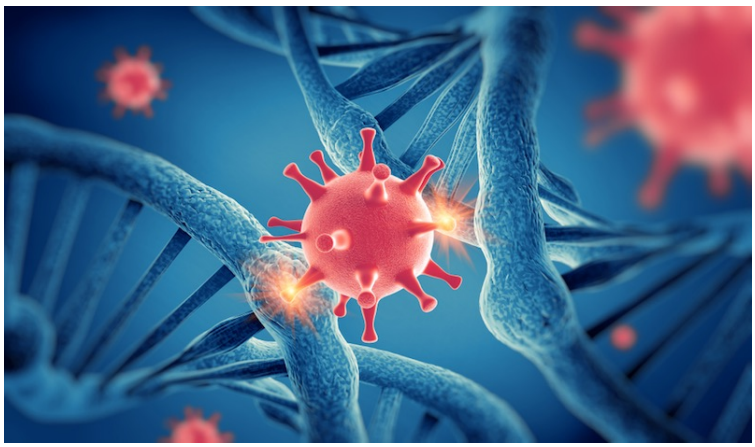
CRISPR is a great candidate to treat genetic blindness. For many hereditary forms of blindness, the specific mutations causing the disease are known making it easy to instruct CRISPR-Cas9 to target and modify that gene.

In addition, the eye is an immunoprivileged part of the body, meaning that the immune system's activity is limited there. This becomes an advantage in sight of the concerns that have recently been raised regarding the possibility that CRISPR could induce immune reactions against it that would block its activity and derive into side effects.

Editas Medicine is working on a CRISPR therapy for Leber Congenital Amaurosis, the most common cause of inherited childhood blindness, for which there is no treatment. The company aims to target the most common mutation behind the disease, using CRISPR to restore the function of the photoreceptor cells before the children lose sight completely.

4. AIDS

There are several ways CRISPR technology could help us in the fight against AIDS. One is using CRISPR to cut the HIV virus out of the DNA of immune cells. This approach could bring the key advantage of being able to attack the latent form of the virus, which is inserted into our DNA and inactive, making it impossible for most therapies to target it.



Another approach could make us resistant to HIV infections. Certain individuals are born with a natural resistance to HIV thanks to a mutation in a gene known as CCR5, which encodes for a receptor on the surface of immune cells that HIV needs to get inside the cells. The mutation changes its structure so that the virus is no longer able to bind the receptor.

Most CRISPR applications in HIV are in early stages of development, still being tested in animals before a clinical trial in humans can be planned.

5. Cystic fibrosis

Cystic fibrosis is a genetic disease that causes severe respiratory problems. Although there are treatments available to deal with the symptoms, the life expectancy for a person with this disease is only around 40 years. CRISPR technology could help us get to the origin of the problem by editing the mutations that cause cystic fibrosis, which are located in a gene called CFTR.

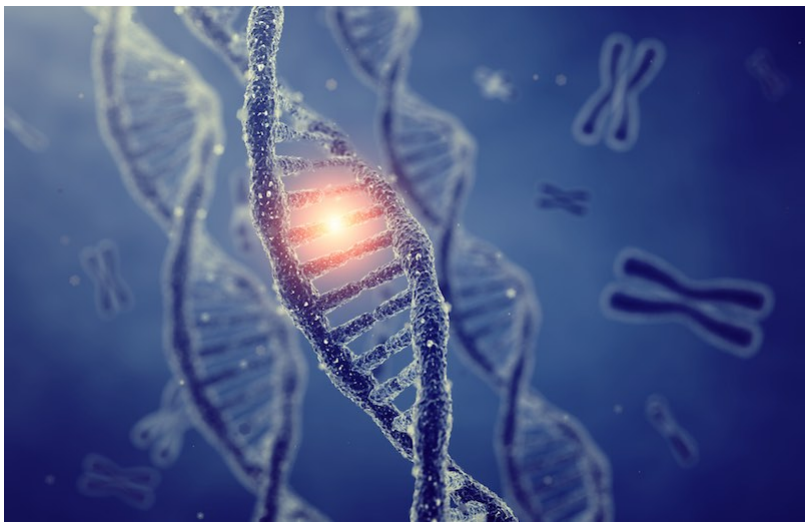
Researchers have proven that it is possible to use CRISPR in human lung cells derived from patients with cystic fibrosis and fix the most common mutation behind the disease. The next step will be testing it in humans, which both Editas Medicine and CRISPR Therapeutics are doing.

However, cystic fibrosis can be caused by multiple different mutations in the CFTR gene, meaning that different CRISPR therapies will have to be developed for different genetic defects. Editas has stated that it will be looking at the most common mutations as well as some of the rare ones for which there is no treatment.

6. Muscular dystrophy

Duchenne's muscular dystrophy is caused by mutations in the DMD gene, which encodes for a protein necessary for the contraction of muscles. Children born with this disease suffer progressive muscle dystrophy in children, and there is currently no treatment available beyond palliative care.

Research in mice has shown CRISPR technology could be used to fix the genetic mutations behind Duchenne's muscular dystrophy. Earlier this year, a group of researchers in the US revealed a method that, instead of fixing each mutation individually, used CRISPR to cut at 12 strategic "mutation hotspots" covering the majority of the estimated 3,000 different mutations that cause this muscular disease. A company called Exonics Therapeutics was spun out to further develop this approach.



Editas Medicine is also working in a CRISPR therapy for Duchenne's muscular dystrophy. It is also following a broader approach where instead of fixing mutations, CRISPR removes whole sections of the protein containing mutations that make the protein shorter but still be functional.

7. Huntington's

Huntington's disease is a neurodegenerative condition with a strong genetic component. The disease is caused by an abnormal repetition of a certain DNA sequence within the huntingtin gene. The higher the number of copies, the earlier the disease will manifest itself.

Treating Huntington's could be tricky, as any off-target effects could have more dangerous consequences in the brain than anywhere else in the body. So scientists are looking at ways to tweak the gene editing tool to make it safer.

Researchers in the US have developed KamiCas9, a version of CRISPR-Cas9 that includes a "self-destruct button" for the Cas9 enzyme. Meaning CRISPR is instructed to cut the sequence of its own Cas9 enzyme. A group of Polish researchers has opted for pairing CRISPR-Cas9 with an enzyme called nickase to make the gene editing more precise.

It's difficult to predict the outcome of these first efforts to use CRISPR as a therapy, but as these first attempts progress, more and more indications will certainly be added to the list. One of the biggest challenges to turn this research into real cures is the many unknowns regarding the potential risks of CRISPR therapy. Some

scientists are concerned about possible off-target effects, immune reactions to the gene editing tool, or that it could increase the risk of cancer. But only time will tell.

https://labiotech.eu/tops/crispr-technology-cure-disease/

ScienceNews for Students

Explainer: How CRISPR works

This technique lets scientists edit DNA in plants and animals

TINA HESMAN SAEY
JUL 31, 2017 — 6:50 AM EST

Scientists are using a tool called CRISPR/Cas9 to edit DNA.
KIRSTYPARGETER/ISTOCKPHOTO

Scientists usually shy away from using the word *miracle*. Unless they're talking about the gene-editing tool called CRISPR, that is. "You can do anything with CRISPR," some say. Others just call it amazing.

CRISPR stands for "clustered regularly interspaced short *palindromic* repeats." Those repeats are found in bacteria's DNA. They are actually copies of small pieces of viruses. Bacteria use them like collections of mug shots to identify bad viruses. Cas9 is an *enzyme* that can cut apart DNA. Bacteria fight off viruses by sending the Cas9 enzyme to chop

up viruses that have a mug shot in the collection. Scientists recently figured out how bacteria do this. Now, in the lab, researchers use a similar approach to turn the microbe's virus-fighting system into the hottest new lab tool.

This CRISPR/Cas9 tool was first described in 2012 and 2013. Science labs around the world soon started using it to alter an organism's genome — the entire set of its DNA instructions.

This tool can quickly and efficiently tweak almost any gene in any plant or animal. Researchers already have used it to fix genetic diseases in animals, to combat viruses and to sterilize **mosquitoes**. They have also used it to prepare pig organs for human transplants and to beef up the muscles in **beagles**.

So far CRISPR's biggest impact has been felt in basic biology labs. This low-cost gene editor is easy to use. That has made it possible for researchers to delve into the basic mysteries of life. And they can do it in ways that used to be difficult if not impossible.

Robert Reed is a developmental biologist at Cornell University in Ithaca, N.Y. He likens CRISPR to a computer mouse. "You can just point it at a place in the genome and you can do anything you want at that spot."

At first, that meant anything that involved cutting DNA. CRISPR/Cas9 in its original form is a homing device (the CRISPR part) that guides molecular scissors (the Cas9 enzyme) to a target section of DNA. Together, they work as a genetic-engineering cruise missile that disables or repairs a gene, or inserts something new where the Cas9 scissors has made some cuts. Newer versions of CRISPR are called "base editors." These can edit genetic material one base at a time, without cutting. They're more like a pencil than like scissors.

Here's how it works

Scientists start with RNA. That's a molecule that can read the genetic information in DNA. The RNA finds the spot in the *nucleus* of a cell where some editing activity should take place. (The nucleus is a compartment in a cell where most of the genetic material is stored.) This guide RNA shepherds

Cas9 to the precise spot on DNA where a cut is called for. Cas9 then locks onto the double-stranded DNA and unzips it.

This allows the guide RNA to pair up with some region of the DNA it has targeted. Cas9 snips the DNA at this spot. This creates a break in both strands of the DNA molecule. The cell, sensing a problem, repairs the break.

Fixing the break might disable a gene (the easiest thing to do). Alternatively, this repair might fix a mistake or even insert a new gene (a much more difficult process).

Cells usually repair a break in their DNA by gluing the loose ends back together. That's a sloppy process. It often results in a mistake that disables some gene. That may not sound useful — but sometimes it is.

Scientists cut DNA with CRISPR/Cas9 to make gene changes, or *mutations*. By comparing cells with and without the mutation, scientists can sometimes figure out what a protein's normal role is. Or a new mutation may help them understand genetic diseases. CRISPR/Cas9 also can be useful in human cells by disabling certain genes — ones, for instance, that play a role in inherited diseases.

"The original Cas9 is like a Swiss army knife with only one application: It's a knife," says Gene Yeo. He is an RNA biologist at the University of California, San Diego. But Yeo and others have bolted other proteins and chemicals to the dulled blades. That has transformed that knife into a multifunctional tool.

CRISPR/Cas9 and related tools can now be used in new ways, such as changing a single nucleotide base — a single letter in the genetic code — or adding a fluorescent protein to tag a spot in the DNA that scientists want to track. Scientists also can use this genetic cut-and-paste technology to turn genes on or off.

This explosion of new ways to use CRISPR hasn't ended. Feng Zhang is a molecular biologist at the Massachusetts Institute of Technology in Cambridge. He was one of the first scientists to wield the Cas9 scissors. "The field is advancing so rapidly," he says. "Just looking at how far we have come…I think what we'll see coming in the next few years will just be amazing."

Power Words
(for more about Power Words, click here)

application A particular use or function of something.

base (in genetics) A shortened version of the term nucleobase. These bases are building blocks of DNA and RNA molecules.

biology The study of living things. The scientists who study them are known as **biologists**.

Cas9 An enzyme that geneticists are now using to help edit genes. It can cut through DNA, allowing it to fix broken genes, splice in new ones or disable certain genes. Cas9 is shepherded to the place it is supposed to make cuts by CRISPRs, a type of genetic guides. The Cas9 enzyme came from bacteria. When viruses invade a bacterium, this enzyme can chop up the germs DNA, making it harmless.

cell The smallest structural and functional unit of an organism. Typically too small to see with the naked eye, it consists of watery fluid surrounded by a membrane or wall. Animals are made of anywhere from thousands to trillions of cells, depending on their size. Some organisms, such as yeasts, molds, bacteria and some algae, are composed of only one cell.

chemical A substance formed from two or more atoms that unite (become bonded together) in a fixed proportion and structure. For example, water is a chemical made of two hydrogen atoms bonded to one oxygen atom. Its chemical symbol is H2O.

CRISPR An abbreviation — pronounced crisper — for the term “clustered regularly interspaced short palindromic repeats.” These are pieces of RNA, an information-carrying molecule. They are copied from the genetic material of viruses that infect bacteria. When a bacterium encounters a virus that it was previously exposed to, it produces an RNA copy of the CRISPR that contains that virus’ genetic information. The RNA then guides an enzyme, called Cas9, to cut up the virus and make it harmless. Scientists are now building their own versions of CRISPR RNAs. These lab-made RNAs guide the enzyme to cut specific genes in other organisms. Scientists use them, like a genetic scissors, to edit — or alter — specific genes so that they can then study how the gene

works, repair damage to broken genes, insert new genes or disable harmful ones.

developmental (in biology) An adjective that refers to the changes an organism undergoes from conception through adulthood. Those changes often involve chemistry, size and sometimes even shape.

DNA (short for deoxyribonucleic acid) A long, double-stranded and spiral-shaped molecule inside most living cells that carries genetic instructions. It is built on a backbone of phosphorus, oxygen, and carbon atoms. In all living things, from plants and animals to microbes, these instructions tell cells which molecules to make.

engineering The field of research that uses math and science to solve practical problems.

field An area of study, as in: Her field of research was biology. Also a term to describe a real-world environment in which some research is conducted, such as at sea, in a forest, on a mountaintop or on a city street. It is the opposite of an artificial setting, such as a research laboratory.

fluorescent Capable of absorbing and reemitting light. That reemitted light is known as a fluorescence.

gene (adj. genetic) A segment of DNA that codes, or holds instructions, for producing a protein. Offspring inherit genes from their parents. Genes influence how an organism looks and behaves.

genome The complete set of genes or genetic material in a cell or an organism. The study of this genetic inheritance housed within cells is known as genomics.

muscle A type of tissue used to produce movement by contracting its cells, known as muscle fibers. Muscle is rich in a protein, which is why predatory species seek prey containing lots of this tissue.

mutation (v. mutate) Some change that occurs to a gene in an organism's DNA. Some mutations occur naturally. Others can be triggered by outside

factors, such as pollution, radiation, medicines or something in the diet. A gene with this change is referred to as a mutant.

nucleus Plural is nuclei. (in biology) A dense structure present in many cells. Typically a single rounded structure encased within a membrane, the nucleus contains the genetic information.

organ (in biology) Various parts of an organism that perform one or more particular functions. For instance, an ovary is an organ that makes eggs, the brain is an organ that interprets nerve signals and a plant's roots are organs that take in nutrients and moisture.

palindrome (adj. palindromic) A word, a name or a phrase that has the same ordering of letters when read forwards or backwards. For instance, *dad* and *mom* are both palindromes.

protein Compound made from one or more long chains of amino acids. Proteins are an essential part of all living organisms. They form the basis of living cells, muscle and tissues; they also do the work inside of cells. The hemoglobin in blood and the antibodies that attempt to fight infections are among the better-known, stand-alone proteins. Medicines frequently work by latching onto proteins.

RNA A molecule that helps "read" the genetic information contained in DNA. A cell's molecular machinery reads DNA to create RNA, and then reads RNA to create proteins.

tag (in biology) To attach some rugged band or package of instruments onto an animal. Sometimes the tag is used to give each individual a unique identification number. Once attached to the leg, ear or other part of the body of a critter, it can effectively become the animal's "name." In some instances, a tag can collect information from the environment around the animal as well. This helps scientists understand both the environment and the animal's role within it.

Citation
Journal: S. Wang et al. An RNA-aptamer-based two-color CRISPR labeling system. *Scientific Reports*. Vol. 6, May 27, 2016, p. 26857. doi: 10.1038/srep26857.

Journal: A. C. Komor et al. Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage. *Nature*. Vol. 533, May 19, 2016, published online April 20, 2016, p. 420. doi:10.1038/nature17946.

Journal: D. A. Nelles et al. Programmable RNA tracking in live cells with CRISPR/Cas9. *Cell*. Vol. 165, April 7, 2016, p. 488. doi: 10.1016/j.cell.2016.02.054.