(3549) The Successor to CRISPR May Be Even More World Changing - YouTube

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Transcript:

(00:00) CRISPR is one of the biggest biotech game changers of all time, right up there with figuring out the structure of DNA in the first place. In a little over a decade, scientists went from wondering if this gene editing tool could even work in humans to rewriting a living infant's DNA to administer a life saving treatment.

(00:19) But CRISPR didn't start with a grand plan to solve genetic disorders. It started with a curiosity about how bacterial immune systems worked. A scientist named Feng Zhang was one of the people studying an element of those immune systems, and he would use what he learned to help pioneer CRISPR gene editing in human cells.

(00:39) But apparently he was just getting started because Zhang is back in the lab studying another seemingly niche area of molecular biology that may have even bigger implications. It's a set of genes called TIGR that are found in some viruses and single-celled organisms, and they may be an even more powerful tool than CRISPR for certain kinds of gene editing.

(01:03) And that sounds like a story big enough to tell in person. And that's why we created a new series called SciShow Field Trips. Each episode we get out of the studio and we visit a lab where cutting edge science is happening. Our good friend Jaida Elcock talked to Zhang in Boston, and she has the scoop on a scientist who reverse engineers life itself.

(01:28) Thanks, Hank. On any given day, you might find Feng Zhang meeting with colleagues to discuss data in a lecture hall, teaching at MIT or right here at the Broad Institute in Cambridge, Massachusetts. Although he's won countless awards, including the National Medal of Technology and Innovation, he still loves the thrill of everyday lab work.

(01:46) You can actually see with your eyes how something is changing, or how a cell or an animal is behaving. Sometimes maybe you make an observation that's not exactly related to the original question, but it can sort of inspire you to think about something new. And oftentimes in science is the least expected result that really inspires you to come up with something novel and new.

(02:12) Zhang's work often falls under what's called basic science or basic research. This tends to mean figuring out how stuff works at a fundamental level without an immediate application, like a blockbuster drug or a new kind of rocket engine. But Zhang usually has a vision of where such things could lead.

(02:27) When we are trying to do research, we have some hypotheses. So, for example, we want to know if there is a system in a bacteria that might be able to recognize DNA, or maybe it can recognize proteins, maybe they don't recognize DNA or recognize protein, but they do something else. So we just want to know everything.

(02:49) And then if we find something that does what we are looking for, we try to turn it into a tool. But before you can do any of that, well, you have to understand how things work

at the most fundamental level. And Zhang has been doing that since he was a kid. His parents were both computer scientists who took an active interest in his education.

(03:05) Rather than rote learning, Zhang was encouraged to take things apart, break them down and figure it out. Maybe it's not surprising then that his first foray into science was through computers and coding. As a pre-teen, he took apart his PC and used the parts to build other computers. But like many childhood obsessions, that quickly changed.

(03:21) The turning point really came when I was, I think, in seventh grade. I went to a Saturday enrichment class and the topic was molecular biology. What biology meant completely changed for me. Because the thought is that there are these underlying principles of how there's DNA, and the DNA has a code, and the code can be then turned into protein.

(03:47) And so you have all these different components of a biological system of a cell that work together. And if you change the code you change how the cell behaves. You can put a gene like a unit of instruction into a cell. And you can get a cell to do something different than they did before. So that made it seem like a computer. And just like there were logical principles to writing code, there were logical, fundamental principles to how the natural world was built.

(04:13) Once Zhang realized this, he began looking for ways to tinker with the building blocks of life, starting in high school when he volunteered at a local gene therapy lab. There he studied green fluorescent protein, a protein from jellyfish that glows under certain circumstances. You can attach it to other proteins and follow the glow around.

(04:29) So Zhang used it to track proteins in viruses and figure out how they infect cells and make copies of themselves. Later, as an undergraduate at Harvard, he would use GFP to reveal how the influenza virus enters cells. But other scientists would take their basic research on green fluorescent protein even further.

(04:44) So one way that you might imagine using this is if you want to study how cancer cells spread in the body, how it metastasizes. You can take a cancer cell, you can put this green fluorescent protein gene into that cancer cell. The cell will start to make it and it will be able to glow green. Then you put this GFP labeled cell into a mouse.

(05:07) And this cancer cell will start to divide, replicate and will start to spread. So now you take the mouse, you just image it, and you just look for where there are green cells. And you can get a sense of how widely this cancer cell is able to grow and spread. Zhang continued to seek out other biological systems that answered the questions he had about how life functions.

(05:30) He went on to Stanford to get his PhD, but in 2009, he made his way back to Harvard and started toying with different ways of editing genes. There, he began work on something that would change his life and biotechnology forever. We humans have immune systems to protect us from harmful organisms. Well, microbes like bacteria and archaea are no different.

(05:48) They have sequences of DNA that help defend them against viruses. Those sequences are called, you guessed it, CRISPR. The term describes their OG biological definition. It's short for clustered regularly interspaced short palindromic repeats, and they work a little like a molecular cut and paste tool. First, a snippet of RNA, DNA's one-stranded twin, acts like a

little tour guide by matching the sequence it targets, enabling it to enter the nucleus of a cell and latch on to a section of matching DNA.

(06:14) It brings along an enzyme called a CRISPR associated protein, or CAS, that then cuts the section of DNA out. Several other researchers around the world were figuring out how CRISPR works, including Emmanuelle Charpentier and Jennifer Doudna, who won the Nobel Prize for its discovery. But a lot of the early research was focused on how it works in bacteria.

(06:35) Zhang was in awe of this biological system and wanted to see if he could co-opt it to edit bigger genomes. So one of the things that is really exciting that has happened in biology is the mapping of the human genome. Scientists have been able to map the genome of healthy people and people who are affected by specific diseases.

(06:55) And by comparing their DNA, you can start to identify genetic differences or mutations that cause disease. If you know the genetic cause for disease, the tantalizing idea is if you can go into those cells and be able to reverse that mutation back to the normal DNA sequence. And so this is a holy grail for medicine.

(07:20) This can, you know, undo the underlying cause so that you make the cell healthy again. The way to do that is through gene editing. So these are DNA sequencing machines. Oh. Whoa. Each one of these machines, we can put in many, many molecules of DNA. We can study what the sequence of DNA is. And these are larger capacity machines. For example, this can do a whole human genome in a day.

(07:43) Woah. The human genome has, like, how many base pairs? 3 billion. 3 billion base pairs. And that can sequence that in a day. This sequence that in a day. Yeah. That's right. Science is amazing. Wow. Okay. Zhang tinkered with a system called CRISPR Cas9, named for the protein it uses to cut out DNA.

(08:03) And he was the first to get it to work in eukaryotes, specifically mice and humans. Over the next eight years, Zhang and his team hunted down new Cas systems from different bacteria, then engineered them to seek out different sections of DNA. Cas12a, for example, is smaller than Cas9 since it only needs a single RNA to guide it instead of the two that Cas9 has.

(08:23) Its smaller size means it's easier to get into cells. There are only so many ways to break through the cell membrane, and the smaller the better. Cas12a also makes kind of a jagged cut, which in the gene editing world is a good thing, since cutting DNA straight leaves a blunt end that can mutate more easily. Understanding those CRISPR systems soon led to treatments.

(08:43) Once you sort of understood how CRISPR works, how did you translate that into treatments for different disorders? Basically, how did you go from sort of this gene splicing stage to implementing that into living cells? The first thing to do is try to figure out what are all of the pieces that constitute a CRISPR system, and then we have to engineer them to get them to work in a human cell.

(09:05) What is the genetic mutation that you're trying to repair? Once you identify that then you can go to the computer. You can design the guide RNA to reprogram the CRISPR system to be able to recognize that mutation in the human cell. Once you have the RNA sequence, you can use chemical synthesis to make it.

(09:26) So you just go online, open up a website, you can type in the sequence, submit the order, usually maybe $20 or something like that. And then in a couple of days you get a Fedex envelope with a little tube. In the tube is the guide RNA. And so that's all you have to do. I don't even have words. That is so - that's fascinating.

(09:48) So you're quite literally just ordering the parts that you need to fix certain pieces of the DNA? Right. Now, once you get that working, that's on the inside of a human cell, right? So then you had to figure out, how do you deliver this into enough cells? Like, for example, if you want a target muscle to be able to treat muscular disorder, you have to get it into all of the muscle cells, right? So there are different delivery systems that researchers have been developing.

(10:20) The results have been amazing. So far, CRISPR has been investigated as a treatment for at least 18 different disorders, from sickle cell to leukemia. Usually, scientists edit the cellular DNA in the lab and then return those cells to the people affected where the cells replicate. But in a stunning story in 2025, it was used for the first time to rewrite DNA in a living person: that infant Hank mentioned earlier.

(10:45) It was a life-saving miracle that probably won't be the last of its kind. For all its triumphs, though, CRISPR isn't perfect. CRISPR is a gene editing method. And so for diseases where we know the underlying genetic cause, CRISPR is a good way to treat it. But there are diseases where it's more complicated.

(11:05) It's not caused by a single genetic mutation. And those are much harder to treat with CRISPR. Because you don't really know where in the genome to change to be able to restore the function of that cell or that tissue. So we need new delivery capabilities that can allow CRISPR to access these other parts of the body. Those limitations meant something better had to be out there.

(11:29) So he went back to the drawing board, back to pulling life apart to see how it works. He began studying a curious set of genes he and his colleagues discovered just a few years ago. Like CRISPR, they were made up of short repeating sequences of genetic information, plus a protein that can cut DNA, although this time they were mostly found in viruses rather than bacteria. Zhang and his team called the genetic sequences TIGR.

(11:49) Can you tell me what TIGR the acronym stands for, and what exactly does all of that mean? Yeah. TIGR. T-I-G-R stands for tandem interspaced guide RNA. And so it's a long stretch of DNA that is kind of repetitive. So it repeats itself over and over and over again, but it's not an exact repeat because there are snippets of it or stretches of it that are not repeated.

(12:20) And those happen to be the guide sequences that direct the TIGR-Tas system to different targets. Just like CRISPR was serving as an immune system for bacteria under our noses for a long time, TIGR-Tas has just been hanging out, waiting to be discovered, but the team doesn't totally know what it does yet.

(12:42) Viruses are pretty simple things, and it's not really clear why they need such a sophisticated DNA targeting system when their job is usually just to get into a cell and reproduce. We see the system in both bacteria and also viruses that infect bacteria. And it may be a system that's involved in bacterial and also viral warfare. You know, they are fighting against each other in nature.

(13:08) So it may be a system where viruses use a TIGR system to direct itself to be able to insert into a bacteria's genome, as a way to find a home and land there. And then bacteria may use it as a way to fight off the viruses, to degrade it before it's able to insert itself. So it's probably involved in some processes like this. That's really interesting.

(13:32) Yeah. And that's what's really cool about nature is that you have these competitive situations. Because it's life or death they try really hard to come up with a lot of really powerful solutions. Looking at these things and understanding how they work, I think we can discover a lot of interesting biology, and probably many of them we can harness and engineer into useful biotechnology.

(13:55) Regardless of what TIGR-Tas does in viruses, the team thinks this system has the potential to do a lot of the things CRISPR does for us, only better. Unlike CRISPR, TIGR-Tas reads both sides of the DNA double helix when deciding where to target, potentially making it more accurate in where it decides to make a cut.

(14:14) TIGR-Tas is also smaller, which could help it sneak into more places in the body. And those aren't the only advantages. There are cases where CRISPR is trying to achieve single letter precision modification, but because it opens up a 5 to 8 letter long window, you cannot have a single letter precision. Oh, okay. Whereas with TIGR-Tas, because it can make smaller windows of DNA accessible, it can overcome that limitation.

(14:43) Yeah. Continuously we have to look for new things either from nature or try to engineer CRISPR and combine CRISPR with other things, to enable these new sort of capabilities. Zhang and his team still need to learn more about how TIGR operates in viruses and other microbes to know exactly what it can do for us.

(15:06) Can you explain some of the experiments that you do with TIGR-Tas, and what exactly you hope to learn from them? When we find TIGR-Tas, one of the first things we'll do is we'll synthesize the DNA sequence for the entire TIGR-Tas system, and then we'll transplant that into a bacteria.

(15:27) And so we'll take the synthesized TIGR-Tas genes, and we'll transfer into E. coli, and we'll grow up the bacteria in the lab. We might try to purify the protein from the bacteria so that we can study the TIGR-Tas protein in a very well controlled test tube environment. Or, we'll try to put it into a human cell. So these are sort of cells growing in petri dishes, and we grow them in the incubator, and then we can transfer the TIGR-Tas system into those cells, and then we can measure to see what happens.

(15:57) And the lab is doing all sorts of experiments to that end. So these are centrifuges, we use them to spin down things that we're trying to study. So, for example, to get a gene delivered into a mouse, we might use a viral vector. So this is a hollowed out virus always sticking to the top. Oh, okay.

(16:19) And then, to concentrate it, we have to spin it really fast because there are very small particles. And you have to spin a very, very high, sort of, multiple of gravity in order for it to come down. So this is what we do. So we take one of these rotors and we put it into the machine, like this. And then we'll just close the lid and it'll start to spin. And it'll spin very fast.

(16:45) How fast? This can be as fast as 100,000 times gravity. Yeah. So if it's a human that would be smushed down. Oh my gosh, I'm - because as a marine scientist, my reference

is, like, pressure at the bottom of the ocean. And I'm assuming that this spinning this fast, that this is significantly higher pressure.

(17:07) That's right. How many times gravity.? 100,000 times gravity. That's not real. All of this is still in the "pull it apart to see how it works" phase. Once they understand that, they'll have a better idea of how it might be used therapeutically. But potentially this TIGR system could make CRISPR look like an opening act.

(17:28) That groundbreaking CRISPR treatment in 2025 rewrote the DNA of cells in the infant's liver, and it seemed to have worked incredibly well. But it's easy to get treatments to go to the liver. The liver detoxifies things, so whenever the body sees something weird, it's off to the liver with you. And cells in the liver divide a lot, which is required for CRISPR to do its thing.

(17:45) So imagine a disease where the problematic cells are harder to reach or dividing less. Think of something like Alzheimer's or Parkinson's or other diseases of the brain. What potential does TIGR-tas have for treating different diseases of the nervous system? The TIGR-Tas system is a compact system which makes delivery of the TIGR-Tas system more convenient than a bigger system like Cas9.

(18:12) So, things like ALS, or Huntington's disease, or other things where there is a known, genetic basis that we might be able to use it to treat. We're working on trying to further improve the TIGR-Tas system so that it's more effective. And also doing studies to understand, how do we best deliver them into the brain, to be able to treat different things? Nature is very wise, you know, it has all these really cool innovations and solutions to all of these different problems that plants and animals and organisms have faced over the, you

(18:49) know, millions and billions of years of evolution. And so, so, yeah, we just want to go and learn. What is the enjoyment that you get from doing all of this really cool work? I think the whole process is enjoyable. Yeah. Okay. Awesome. Like getting answers to questions is very satisfying.

(19:06) Because it makes you understand something. And oftentimes because we're working on research, so we're working on questions that no one knows the answer about before, when we find the answer we're the first person in the world to know the answer to something. And that is satisfying because you are kind of pushing the frontier.

(19:22) What are your ultimate goals for the work that you're doing? Thinking that there are these biological problems and we can take an engineer's approach to understand what is wrong with the system, how do we fix it? And then use these sort of fundamental, basic principles of DNA, and genetics to develop new solutions.

(19:43) There's still much more to do. But I think it's just rewarding that we can make progress and make, you know, treatments for diseases that people couldn't treat before. If the results are anything like the last time Zhang got interested in something, it could be world changing. SciShow Field Trips are made with our friends at HHMI's Tangled Bank Studios.

(20:05) We've come together to bring you face to face with researchers at the cutting edge of scientific discovery. You can watch more of Tangled Bank's science content at tangledbankstudios.org.