THE BILLION YEAR-OLD SCISSORS

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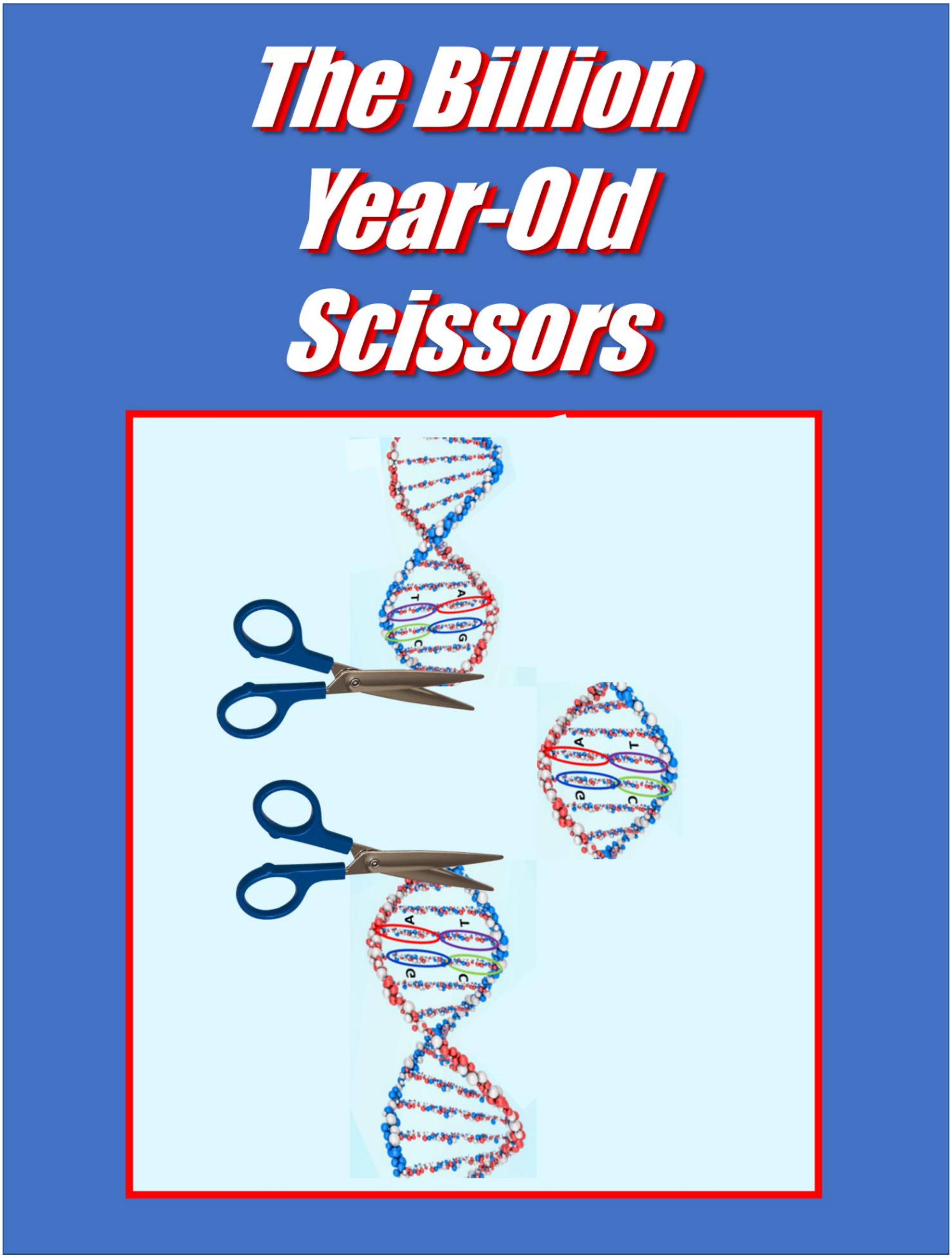


GRANDPA'S STORIES

THE BILLION-YEAR-OLD SCISSORS

(AS TOLD BY GRANDPA)

Hi, I'm Grandpa. My four grandkids, their three friends and I are going to tell you the story of *The Billion-Year-Old Genetic Scissors*. The 2020 version of the *Genetic Scissors* is the latest breakthrough in the genetic engineering technology that gave us COVID-19 vaccines in record time and has the promise to bring us vaccines for many more diseases including cancer. It can also be applied to eliminate inherited diseases like Sickle Cell Anemia.

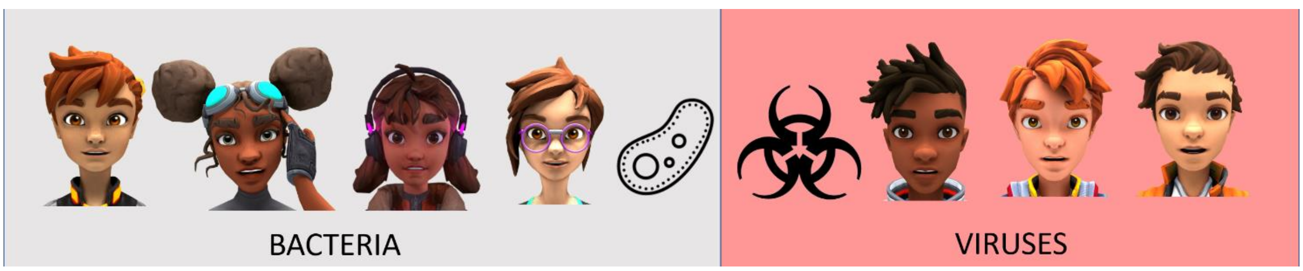
Genetic engineering is the technology that allows scientists to make changes in the basic instructions that describe all living things: single celled organisms, plants, and animals, including humans. The instructions are written in the genetic codes that are unique for each living organism. The genetic codes are like the organism's *blueprints* and *user's manual*. But the gene codes are not written in words, numbers, and diagrams. The codes are created with sequences of large molecules linked in a giant molecule called DNA.

The latest breakthrough called the CRISPR/Cas9 *Genetic Scissors* is a technology that allows precise editing (cutting and pasting) of genetic codes. It was developed by two women scientists, Jennifer Doudna and Emmanuella Charpentier. Their breakthrough won them the 2020 Nobel Prize in Chemistry. As the name implies, their development was based on CRISPR, an ancient *Genetic Scissors* developed by bacteria that was recently discovered.

A THREE BILLION YEAR OLD WAR:

The Nobel Prize is just the latest chapter in the CRISPR story. The story actually began 3 billion years ago, and the story characters are viruses at war with bacteria. To tell the story, the boys will play the part of viruses and the girls will be bacteria.

"Hey, no fair about the Nobel Prize," said Lizzy Bacterium. "Why didn't *we* get any recognition?"



"Yeah," agreed Johari B. "The *Genetic Scissors* is based on our technology."

"I agree," complained Neddy B. "It took us like a billion years to develop CRISPR."

"And those two humans get all the credit," finished VC Bacterium.

"Sorry, you are misinformed young ladies," said Milo Virus, "Nobel Prizes are only awarded to living humans. No bacteria allowed."

"Ok," I said. "Let's set the record straight. Let's tell the CRISPR *Genetic Scissors* story as it started three billion years ago."

BACTERIA

"Right," agreed Johari, we bacteria were the GOAT, the Greatest Of All Time. We started all the life on earth."

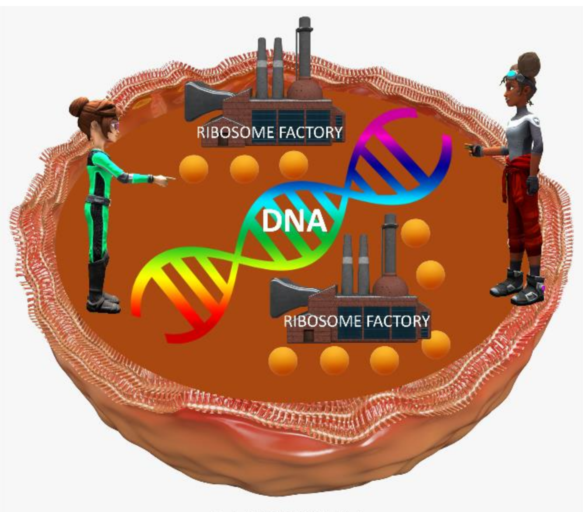
"And we did more than that," stated VC. "I am a special kind of bacterium called a cyanobacterium. My specialty is using sunlight to convert carbon dioxide in the air into oxygen gas and carbon for me to use. All the oxygen that I released into the air is responsible for Planet Earth's oxygen rich atmosphere. If it weren't for me and my cyanobacteria sisters, the oxygen breathing animals like humans wouldn't be here today."

"And," continued Lizzy, "we bacteria had all kinds of capabilities. We could gather nutrients, produce the substances that we needed to live, and we could reproduce so our kind could live for billions of years."

"Not like those virus things," added Neddy. "They didn't know how to reproduce themselves."

"That's true." agreed Jackson Virus. "We viruses did not have the ability to reproduce on our own. But we have been around for billions of years too."

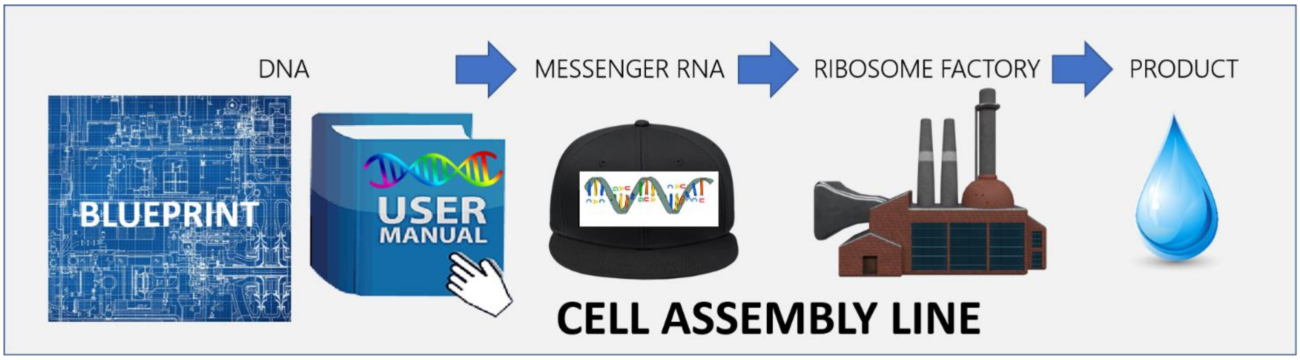
"We are very clever creatures," bragged Milo Virus. "We use you bacteria to reproduce ourselves. So, ladies, show us what you have and then we will show you how us viruses hijack your abilities to reproduce."



BACTERIUM

"Ok," said Neddy. "Johari and I will give you the tour using the cell playground in our virtual world. We are very simple single-celled organisms. We have a cell wall, DNA and Ribosomes. The DNA is our *user's manual* and *blueprints*, and the ribosomes are our factories that produce things we need. We don't have a cell nucleus to store our DNA like humans do so we are called prokaryotic organisms. Johari is pointing to our DNA and I am pointing to our ribosomes, those little yellow spheres, The factories are there just to remind you of what the ribosomes are for."

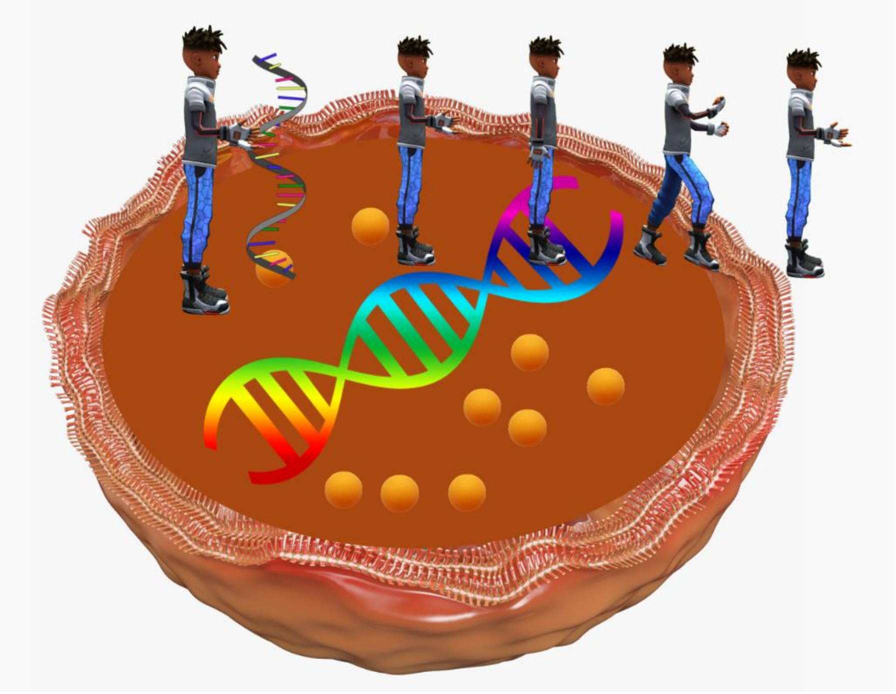
"Our DNA," added Johari pointing, "contains all the instructions for our construction and everything that we do and make. The cell knows how to transcribe the instructions for needed substances from the DNA into a small piece of RNA called messenger RNA, also called mRNA. The mRNA goes to the *Ribosome Factories* that take the mRNA instructions and produce the corresponding substances. So, if I need a chemical to use for digesting some dead waste material, my assembly line would look like this:



The product specifications and manufacturing instructions would be found in the DNA *blueprint* and *User's Manual*, and those would be transcribed into mRNA. The mRNA would be delivered to the *Ribosome Factories* that would manufacture the product."

VIRUSES

"That is a great system those bacteria have," said Richie Virus. "So why do we need our own reproduction system when we can use theirs? Here is how we do it."



Jackson took over saying, "we break into the bacteria cell and bring our RNA genetic code directly to a ribosome factory. The factory is kinda dumb and just produces whatever RNA is delivered to it."

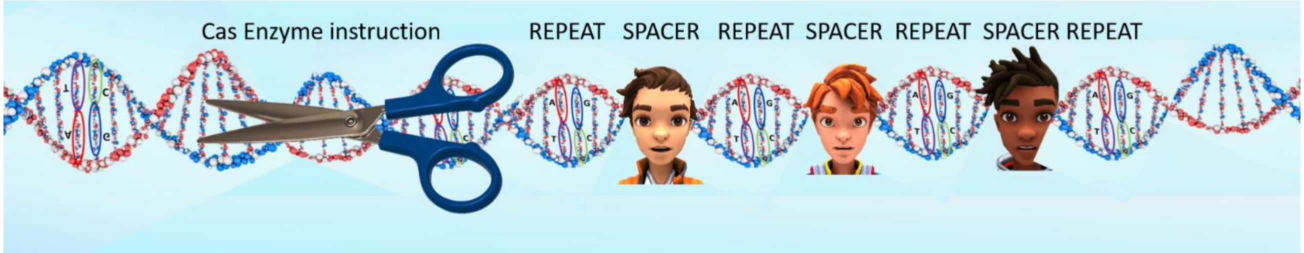
"So", concluded Milo, "they just churn out copies of the Jackson virus. And since our success with bacteria, we have learned to apply the same trick in the cells of plants and animals."

THE BACTERIA FIGHT BACK

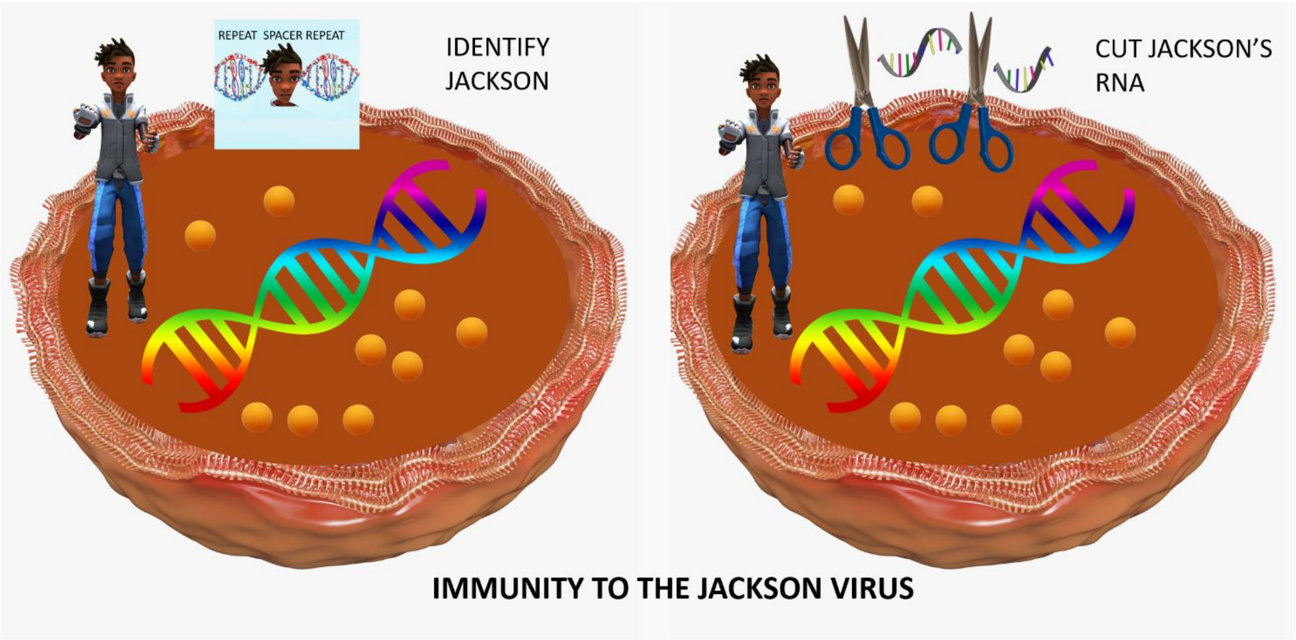
"Oh, those viruses are so clever and so sneaky," said Lizzy B. "But we bacteria are clever too. We created a defense against the viruses."

"Yeah Lizzy, we bacteria are smart," added Johari. "We modified our DNA with two things. First, we copied some of the DNA or RNA from every virus that attacked us. We put that piece of their genetic code like a wanted poster with their *mug shot* into our DNA. Each new virus has its *mug shot* posted in a section of DNA called a SPACER. The SPACERS are separated by identical DNA sequences called REPEATS. It's like the old post office wall with all the Wanted Posters. That allowed us to recognize any virus that had attacked us before by comparing their genetic code *mug shot* in our file with the genetic code *mug shot* of the new attacker."

"And the other part of our defense system was our *Genetic Scissors*," continued VC. "If we recognized a former attacker, we could use our *Genetic Scissors* to cut its genetic code and that prevented it from using our ribosomes to reproduce. Our *Genetic Scissors* is also used with a new virus attacker to cut out its *mug shot* and paste it into our DNA as a new SPACER."



"So, here is how our immune system works," said Neddy. "Jackson the virus tries to do his mean reproduction trick again. But his *mug shot* is already in our DNA as a bad guy. So, we compare his DNA to our sample DNA and voila, we have a match. The *Genetic Scissors* part of our DNA then makes short work of Jackson the virus, by cutting up his DNA or RNA. Now he can't use his genetic code in our ribosomes to make copies of himself. We are immune to the Jackson Virus."



"Isn't that an amazing system," said VC. "of course, we really don't have scissors. The cutting is done by a molecule called an enzyme. That is the kind of molecule that is used in our stomach to break down our food and is used for other things too. What is actually in our DNA is the instructions for the ribosomes to produce the enzymes."

HUMANS DISCOVER CRISPR

"OK, kids" I said. "You did a great job of explaining how viruses attack bacteria, and how the bacteria defend themselves. This is a good time for me to explain what us humans discovered about the bacteria's secrets that they named CRISPR. That is the name given to that part of the DNA shown in your diagram as REPEAT – SPACER – REPEAT – SPACER – REPEAT - SPACER – REPEAT. CRISPR is an acronym that stands for Clustered Regularly Interspaced Short Palindromic Repeat. This name, applied in a 2001 publication, refers to the unique organization of short, partially palindromic repeated DNA sequences separated by spacers found in the DNA of bacteria and other microorganisms. A palindrome is a word or sequence that reads the same backward as forward, for example the word *madam*. So, the REPEATS have that special forwards and backwards similarity, at least partially."

"But it took scientists another 7 years to figure out our immune system," said Lizzy B. "The REPEATS is what got scientists interested in our DNA samples, but the really important part was the SPACERS. In 2003, a Spanish scientist named Francisco Mojica identified the SPACERS as genes sequences from viruses that attacked the bacteria. He figured out that it was part of the bacteria's immune system. Bacteria that had a specific virus gene sequence as the SPACERS In their own genetic code appeared to be immune to that virus."

Then VC B added, "The other really important part of our immune system is the special section of DNA that is pictured as the scissors. That part of the DNA was recognized in 2008 and is called Cas for CRISPER associated. That section is the instructions for the enzymes that can cut and paste parts of virus gene sequences for future defense. They can capture and install the virus "*mug shots*" as the SPACERS. Other Cas sequences can produce the enzymes used to attack the genetic code of an invading virus. They can identify the invading virus by the SPACER *mug shot* and cut up the invading virus's genetic code so it can't reproduce."

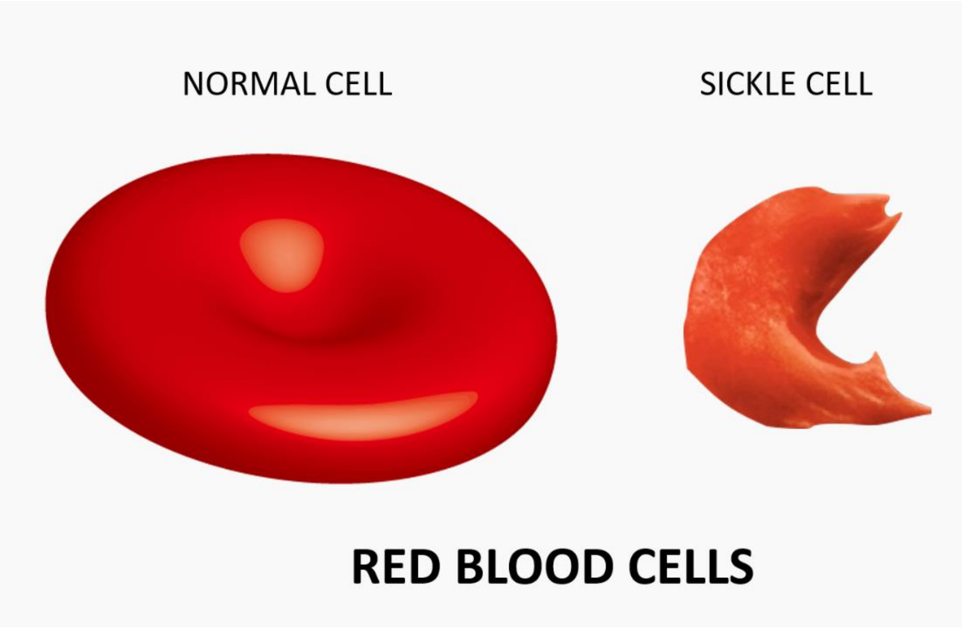
APPLICATIONS OF THE BACTERIA CRISPR IMMUNITY SYSTEM

"And then came more advances" said Neddy Bacterium. "Scientists started using our system of *mug shots* (CRISPR) and scissors (Cas genes) to do genetic engineering or gene editing on plants and animals including human beings."

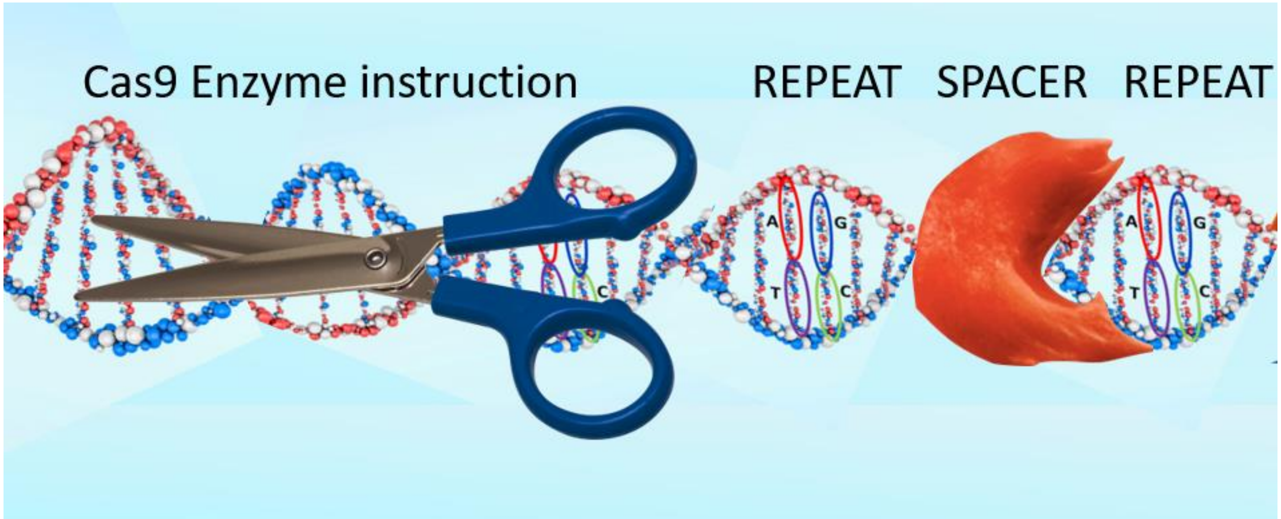
"Right, Neddy," I agreed. "The Nobel Prize to Doudna and Charpentier was awarded for a system called CRISPR/Cas9. It had all the capabilities to identify a target gene and make cuts to remove or replace parts of the gene.

"Some of the applications that have been considered are editing out the single gene that cause diseases like Huntington's, Tay-Sachs, HIV, and Sickle Cell anemia. One way to do that is to do gene editing on a fertilized egg. That allows the edited DNA to be inherited by future generations, potentially eliminating the disease.

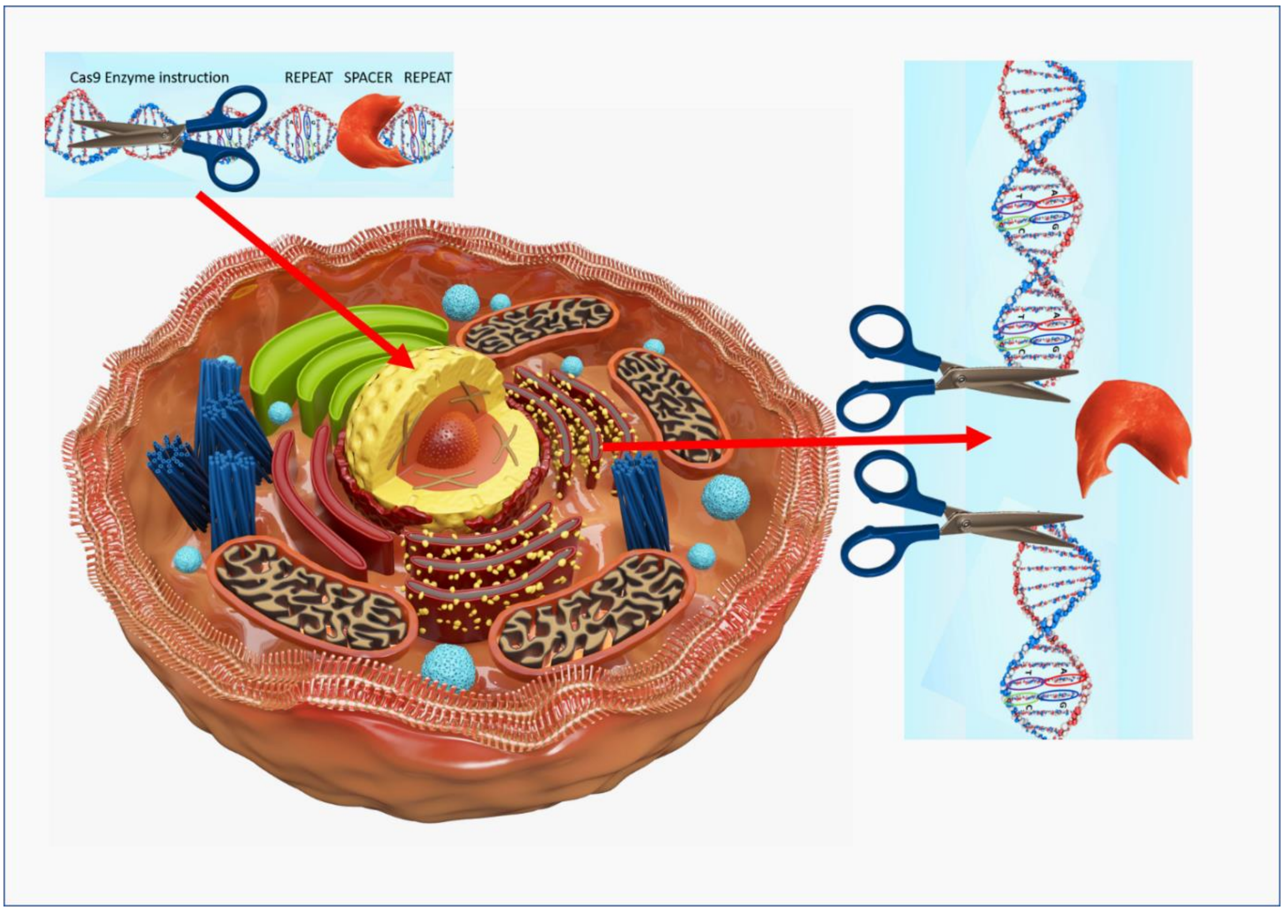
"Another way was used to treat Sickle Cell anemia. The disease is caused by a genetic mutation that leads to badly shaped red blood cells. The sickle shaped cells tend to clot in the blood stream, restricting blood flow and causing pain. As a treatment, the patient's stem cells responsible for red blood cell production were extracted from the patient, edited to remove the gene responsible for producing distorted sickle cells and then reintroduced into the patient. The edited stem cells then produced ordinary red blood cells. The treatment worked to relieve the patient from the pain. However, the treatment would be very expensive to use on a large scale.



"The CRISPR/Cas9 *genetic scissors* for sickle cells is pictured below. The SPACER gene would be the sickle cell gene *mug shot*. The Cas9 gene would have the instructions for producing the enzymes that would identify the sickle cell *mug shot* in the human DNA and edit out the sickle cell gene and replace it with stem cell genes that produce normal cells.



The CRISPR/Cas9 genetic code would be introduced to a [cell nucleus](#) (yellow sphere) where human DNA is located, and editing would take place there.



"All of this cutting and pasting sounds simple," said Johari. "We do it for words all the time with simple keystrokes on our computers with Word or Power Point documents. But the actual computer code to make it happen is much more complicated."

"That's right Jo," said Jackson. "And the gene codes that produce the enzymes that make cutting and pasting possible in genetic engineering is even way more complicated."

"Yeah," said Lizzy B. "The humans didn't just copy our cutting and pasting system. They copied the actual gene codes that make the enzyme molecules that do the cutting and pasting that we bacteria created over billions of years for our immune system."

"It could have taken the humans decades more to actually make the gene codes themselves instead of copying ours," added Neddy B. "So, even more of the credit should go to us bacteria."

"Finally, here is something to think about," I said. "We humans are the first species capable of editing our own evolution. What should we do? Gene editing to eliminate hereditary diseases like sickle cell and Huntington's appears to be a good goal. But what about *designer babies*, gene edited to select the color of hair and eyes, the height and strength, and even the baby's intelligence. What are the ethical questions which must be addressed?

"And how can the technology be controlled? Gene editing is not that hard to do. A biohacker by the name of Josiah Zayner sold a frog genetic engineering kit for $299 online. Injected into the frog, its leg muscles would double in size within a month. So, controlling such a simple to use technology will not be easy.

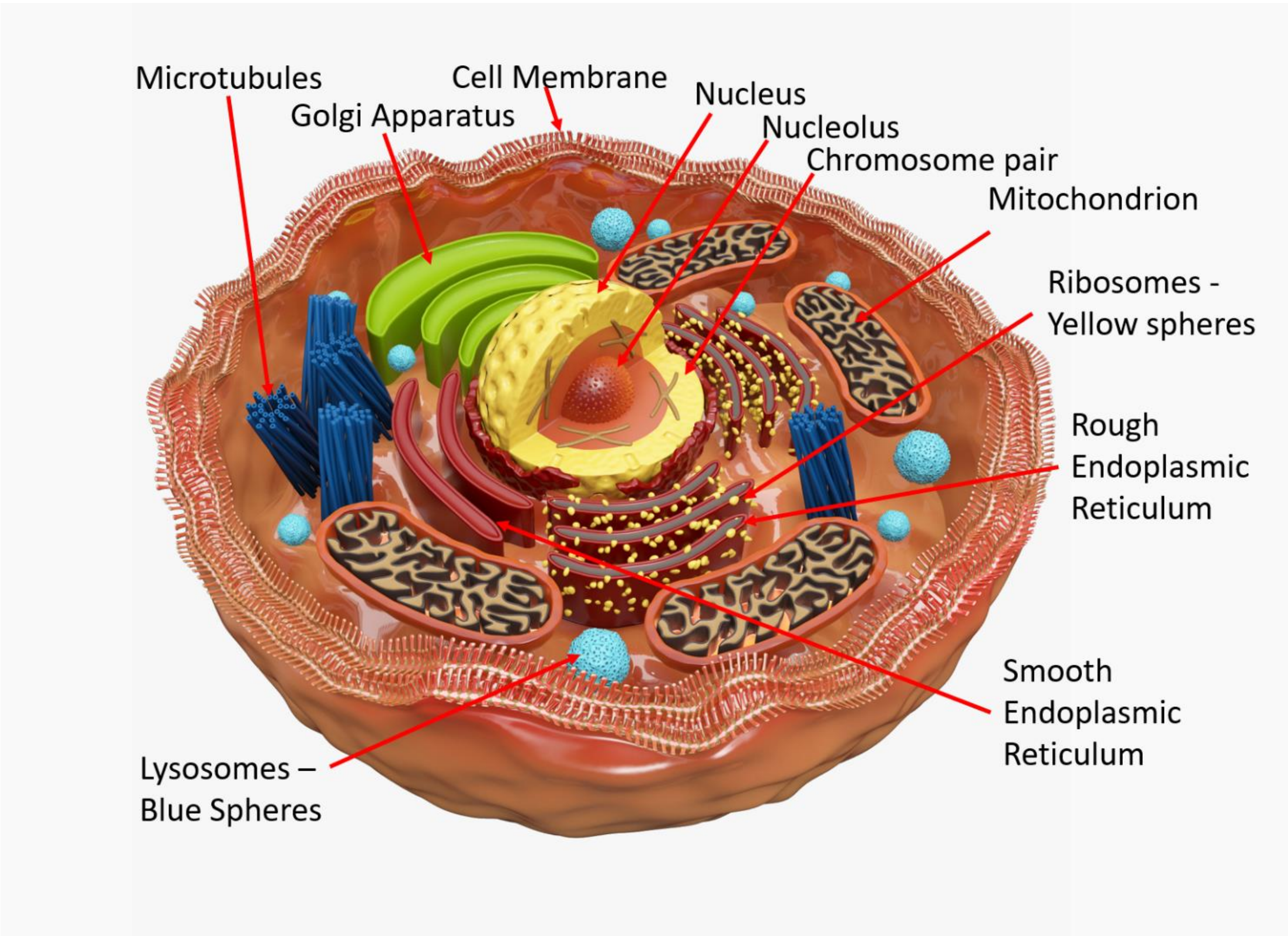
"Here is one more thought. This fantastic genetic engineering technology started with scientists' pure curiosity about why bacteria had those REPEATS in their genetic code. They were not seeking practical applications. But learning new basic things often results in important advances. That bit of curiosity may lead to improved vaccines, cures for cancer, and the elimination of hereditary diseases."

An excellent source of information on the CRISPR technology is the book *Code Breaker Jennifer Doudna, Gene Editing, and the Future of the Human Race* by Walter Isaacson.

GRANDPA'S GLOSSARY

Bacteria: Bacteria are single celled organisms that can't be seen with the naked eye but can be seen under a microscope. Bacteria can cause disease such as strep throat and pneumonia. But bacteria also have beneficial uses such as in the production of yogurt, cheese, and vinegar. Bacteria occur in the shape of spheres, rods and spirals. They were among the first life forms to appear on Earth over 3 billion years ago and are present almost everywhere on Earth.

Cells: The cell is the basic building block for all living things. The cell was discovered by Robert Hooke in 1665 from studies of living material in which he observed very small repeating structures using a microscope. He called the structures cells because they resembled cells of a honeycomb. The first living things on Earth were single-celled organisms. Each cell was able to perform all the functions necessary for life. They could feed themselves and reproduce. Multicell creatures like humans have highly specialized cells that perform specific functions, such as nerve cells which are long and can transmit signals, muscle cells which contract to move arms and legs, and killer T-cells which can attack foreign objects to protect the body. Most cells are



between 1 micron (1/1,000,000 of a meter) and 100 microns in size. The human body contains about 30 trillion cells whose size is like the thickness of a hair.

Cell Nucleus: The cell nucleus is a highly specialized structure of every cell (except for prokaryotic bacteria) that serves as the information processing and administrative center of the cell. This structure has two major functions: it stores the cell's hereditary material (the information on your body's characteristics; the blueprint and instructions for building your body) in the genes, and it coordinates the cell's activities, which include growth, metabolism, protein synthesis, and reproduction (cell division).

CRISPR: CRISPR is an acronym given to the arrangement of gene sequences observed in some bacteria. It stands for Clustered Regularly Interspaced Short Palindromic Repeat. The gene sequence was part of the bacteria's immune system's defense against viruses.

Cyanobacteria: Cyanobacteria are small, single-celled, bacteria organisms that live in water and manufacture their own food and grow by photosynthesis. They often grow in colonies large enough to see. Cyanobacteria are the oldest known fossils, 3.5 billion years old, but are still around today. They were essential in shaping the course of evolution on Earth, being responsible for the planet's oxygen gas concentration required by oxygen breathing life forms. Before the cyanobacteria generated oxygen in the oceans and atmosphere by photosynthesis, the planet was unsuitable for life as we know it today.

DNA (Deoxyribonucleic Acid): Let's say you wanted to build a robot. You look online and find a set of instructions. It would have to contain lots of things: a list of parts; specifications and drawings for each part (for size, shape, color, function, etc.); and instructions for how the parts are connected. If your friend is going to build one too, you need to copy the instructions. If you are building a complicated robot, the list could be very long, requiring a whole book full of instructions. The instructions for building you and all living things are contained in the DNA, which is reproduced in every cell. Each living thing has its own unique DNA code. The double-helix structure of DNA was identified by James Watson, Francis Crick, Maurice Wilkins, and Rosalind Franklin in separate papers in the journal *Nature* in 1953. Watson, Crick, and Wilson (but not Franklin, who died in 1958) received the 1962 Nobel Prize in Physiology or Medicine. You can see a picture of the double helix in Epilogue 2. It is two long chains of molecules that are twisted around each other, like a long rope. The molecules are built of mainly five atoms: carbon, hydrogen, oxygen, nitrogen (CHON), and phosphorus. The links between the two twisted backbones of the DNA are made up of 4 protein molecules in pairs. They are designated by the letters A paired with T, and G paired with C. The building instructions are determined by the order or sequence in which the four molecules are arranged. This is like thousands of words created with different sequences of the twenty-six letters of the English alphabet, or computer codes created with different sequences of ones and zeros.

Each cell in your body contains a complete twisted pair of chains in the form of DNA. When you started life as a single cell, one of your DNA chains came from your mother and the other from your father. As your cells multiplied, the DNA was copied so that each cell had an identical copy of your first DNA molecule. The instructions on whether you are a girl or boy, the color of your eyes and hair, how tall you will be, and every other physical thing about you are coded in your DNA. A single double strand of a human's DNA if stretched out straight would be 2 meters long. If all the DNA in a human body were stretched out and connected end to end it would be 60 billion kilometers long, long enough to extend to Pluto and back to Earth 4 times.

Enzymes: Enzymes are proteins produced by living organisms that act as catalysts. Catalysts are atomic elements or molecules that accelerate chemical reactions. A common example of an enzyme catalyst is the molecule pepsin which is used in the digestive systems of humans and many other animals, where it helps digest the proteins in food.

Genes: These are the basic arrangement of DNA molecules in the chromosomes of the cell nucleus that determines the body's individual characteristics like hair color, eye color, and height. Genes are linear sequences of nucleotide molecules along a segment of DNA that provides the coded instructions for hereditary characteristics (your body's building instructions. A gene is a basic unit of heredity. During gene expression, the DNA is first copied into RNA which transmits the instructions to the cells of the organism.

Genetic Code: The genetic code is the molecular system used by living cells to translate information encoded within genetic material into the products and substances required by the organisms. For living cellular organisms the code is created by the sequence of four molecules designated by the letters A, C, G, and T strung together in the DNA. The code for any molecular substance can be transcribed into messenger RNA in a way that the cellular factories, the ribosomes, can read them and turn them into protein molecules. In some viruses, the genetic code is written in single stranded RNA rather than the double stranded DNA.

Genetic Engineering: Genetic engineering is the process of using DNA and RNA in technology to alter the genetic makeup of an organism. Genetic engineering involves the direct manipulation of one or more genes. Sometimes, a gene from another species is added to an organism's genome to give it a desired feature.

Immune: An organism is immune to an infection if it has resistance to that infection due to the presence of specific antibodies or white blood cells. Such immunity may be naturally occurring or may be acquired from a prior infection or from a vaccine.

Immune System: In a living organism, the immune system is the organisms' mechanisms for fighting disease. In bacteria, the immune system is part of the organism's DNA capable of remembering, identifying and destroying an invading virus. In multi-celled organisms the immune system can be a network of specialized cells, tissues, organs, and substances that help the body fight infections and other diseases. Such systems can produce antibodies and specialized cells which attack an infectious substance as well as cells capable of remembering (sometimes for decades) the infection and producing new antibodies and attack cells should the infection reappear.

Messenger RNA: Messenger RNA, or mRNA, is a single-stranded molecule of RNA that contains the genetic sequence of a gene, a part of the genetic code for a specific functional product. For example, the protein spikes on the coronavirus are such functional products. The mRNA is read by a ribosome in the process of synthesizing the product. The pepsin molecule described in Epilogue 2 is another example of a functional product created by a cell's ribosomes using mRNA. The process of copying a gene from DNA into mRNA is called transcription.

Molecules: Atoms can be attached to other atoms to form a new unit called a molecule. Simple molecules can be made of the same kind of atom, like hydrogen, nitrogen, or oxygen molecules which have only two atoms each. Or different atoms can attach like two hydrogens and one oxygen to form a water molecule. Examples of bigger molecules are found in oil which consist of strings, or rings, of a few to more than twenty carbons with attached hydrogens. Then, there are very large molecules like DNA that have hundreds of millions of atoms of many different kinds.

Prokaryotic: The word prokaryotic refers to a single cell organism that does not have a cell nucleus and other distinct structures (organelles) bound by membranes. Other organisms (including humans) have cells with a distinct cell nucleus. These are called eukaryotic cells. All bacteria are prokaryotic. Bacteria are the organisms in which the CRISPR system was discovered.

Ribosomes: Ribosomes are complex structures found inside living cells. Their purpose is to produce functional products (proteins) required by the organism according to the instructions contained in messenger RNA created by the organism. Viruses have the ability to hijack a cell's ribosomes to have it make copies of itself from its RNA. The ribosomes are also used by mRNA vaccines to have it make copies of the protein spikes seen on the outside of a coronavirus. The spikes stimulate the body's immune system to prepare it to fight off the virus should it appear.

RNA: Ribonucleic acid (RNA) is a large molecule that is similar to DNA but is only a single chain rather than a double helix. The complete genetic code for the coronavirus is written in its RNA. In humans and other animals, the code for making protein substances and products needed by the body is written in RNA. These special purpose RNA molecules are copied from sections of DNA in a process called transcription. RNA consists of a single backbone chain with protruding pairs of four molecules designated by the letters A paired with U, and G paired with C. So, three of the molecules are the same as those in the connecting chains in DNA. The building instructions are determined by the order or sequence in which the four molecules are arranged. This is like thousands of words created with different sequences of the twenty-six letters of the English alphabet, or computer codes created with different sequences of ones and zeros. Messenger RNA or mRNA is used by cellular organisms to convey the information (genetic code) required for the cells to produce specific products.

Vaccine: A vaccine is a medicine that can provide immunity to an infectious disease caused by a virus or bacterium. A vaccine uses a weakened, dead, or partial form of the virus or bacterium. When exposed to the vaccine, the body's immune system reacts to destroy the foreign substance. Because the active ingredient resembles the disease-causing agent, the immune system is prepared to defend against the active agent in the future. The treatment using a vaccine is called vaccination.

Virtual World: Virtual worlds, also known as virtual environments, use computer technology to create a simulated world that a user can explore and interact with, while creating a feeling as if he or she were in that world. The representation of the user in that world is called an avatar. The user can even wear goggles to make it appear that he or she is surrounded by the 3-D virtual world. That is called virtual reality.

Viruses: A virus is an infectious particle that is too small to be seen, even under a microscope. It cannot replicate itself but can hijack living cells of an organism to produce virus copies. Viruses infect all types of life forms: animals, plants, bacteria, and other microorganisms. There are millions of types of viruses in every place on Earth. There are more viruses than any other type of biological entity. The war between viruses and bacteria has been going on for 3 billion years, with each entity developing sophisticated attack and defense strategies. Most biologists say that viruses are not living organisms. They are not made out of cells, they don't grow, they are not stable, and they can't reproduce by themselves.

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