



## **Exploring CRISPR Gene Drives for Schizophrenia and Superpowers**

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### **Overview**

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Imagine being an African American living during the post-civil rights movement. Police brutality is common; African Americans are angry and protesting. Without your knowledge or permission, a government agency administers a vaccine to you and other people in the city with the intent of suppressing your aggressive behavior. However, their experiment failed. You've witnessed the kidnapping of your brothers and sisters as they exhibited strange powers, or even died because of those powers. Yet, you survive to become the city's next superhero, saving African Americans from police brutality and black-on-black crime. You temporarily retire, get married, and have two children, who actually inherit superpowers from you. Just when you think things are back to normal, crime surges and beckons your return to heroism. When the government learns of this years later, you are now hunted because the government wants to study your genetic advantage in surviving the effects of the vaccine. If this story sounds familiar, it is because this is the story of DC Comics' African American superhero, Black Lightning.

What if the technology to vaccinate people on the level of mental disorders and behavior aggression really existed? Would you believe it? The truth is, scientists are not too far from determining the genetic markers of some mental disorders. In addition, scientists have already conducted enough research to precisely cut DNA. Should humans even be in possession of that type of power? Is it okay to tamper with the human genome at the expense of human lives even if it legitimately means potentially saving many lives? I believe that these are the types of questions that will really get students engaged in learning chemistry.

I am a teacher that loves creating relevant content. However, I feel that the curriculum in the school district of Philadelphia really keeps chemistry teachers boxed into traditional lessons that have not advanced since I was first introduced to chemistry back in 2002; they barely scratch the surface of science application. Since I am in charge of molding the next generation of students, I feel obligated to teach students new ways of doing things, which translates to offering them the most up-to-date curriculum available. If I am not living up to that task, then that means my university degrees and professional accomplishments carry no weight or power because there is no impartation of my professional experiences to the next generation of scholars. Failure to impart these experiences actually sends my students back in time to a darker past contrary to advancing them toward a brighter future.

There are dual purposes for writing this unit. In my three years of teaching, I am beginning to encounter more

students who are interested in medical or nursing careers. Thus, to meet that need, I am writing this unit to give my students a taste of biochemistry. Secondly, my students will have taken the Biology Keystone examination at the culmination of their freshman year, which is required by the Pennsylvania Department of Education. In the event that students have not scored proficient on the examination, this unit offers an opportunity for students to get some review before having to retake. Due to students being required to take biology before chemistry, the biology teachers that I have worked with often wish that students had some chemistry first because the Keystone exam questions imply familiarity with chemistry content, such as the structure of fats, carbohydrates, and proteins.

After watching the Black Lightning television series, I have considered several themes worth exploring in chemistry. First, I think the prevalence of mental disorders in African Americans would interest my students. and determining if there really are genetic factors that contribute to aggression and mental health. This creates an opportunity for studying the biochemistry involved in the manipulation of DNA, including content themes of intermolecular forces, Lewis structures, amino acids, and proteins. Ultimately, students will be able to discuss the costs, benefits, and controversies involved with manipulating DNA.

## Background

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In order to understand the direction of this unit, it is important to visit several topics. First, we will examine environmental influences on genes and some mental disorders that are believed to have genetic links. Next, we will look at the possible pathways to developing a therapy, and the mechanisms by which those therapies work for treating mental disorders at the genetic level. Finally, I will address concepts that could hinder the advancement of this technology and its potential pitfalls. Throughout this section of the curriculum unit, I will go back and forth by comparing what scientists are doing in our universe with what writers between DC Entertainment and Warner Bros. Television have scripted in the Black Lightning television series. This television adaptation is essential to generating student interest in this unit.

### **Epigenetics: Environmental Influence on Genes**

The Black Lightning television series offers such a great platform to discuss genetic experimentation, but where do we begin? It begins with answering this question: What factors motivate or trigger aggressive behavior in the African Americans as portrayed in the TV show? The first thing that comes to mind is oppression from the police. Next are other things that I have noticed either in my lifetime or in my students' lives: low socioeconomic status, poor living conditions, minimal access to quality healthcare, being raised by a single parent, being orphaned, etc. This list can become quite extensive.

While we know that social and environmental factors can influence aggressive behavior, there may be underlying genetic causes for aggression in people. Aggressive behavior has been linked to attention-deficit/hyperactivity disorder and schizophrenia. There are even claims that the genes and neural circuits that activate aggression are conserved between species, meaning that the study of animal models should provide comparable evidence.<sup>1</sup> However, there is still complexity in comparing aggression research between different animals. There are non-human types of aggression such as offensive-, defensive- and predatory-subtypes. Human aggression can also be subcategorized as adolescent-onset (rebellious), reactive (impulsive), or instrumental (non-impulsive) aggression.<sup>2</sup>

There is suspicion that each psychiatric disorder may prevail in exhibiting one subtype of aggression over another. Research scientists are currently looking to zebrafish as the model organism for studies on aggressive behaviors.<sup>3</sup> Zebrafish have already been used to study the presence of impulsivity, stress and anxiety, and even social behaviors, indicating that zebrafish are suitable for studying the different subtypes of aggression.

Recent reports of schizophrenia have shown that people of African heritage have higher rates of this mental disorder.<sup>4</sup> Also, of those individuals diagnosed with schizophrenia, people of African heritage showed more severe symptoms than Caucasians.<sup>5</sup> In addition, differences in the quality and scope of hallucinations and delusions have been noted for people of differing ancestry.

In 2015, a group of scientists compared the symptoms of psychosis in schizophrenia, schizoaffective disorder, and bipolar disorder between African Americans and Caucasians.<sup>6</sup> They confirmed that diagnosis of schizophrenia was more common and the diagnosis of bipolar schizoaffective disorders was less frequent in African Americans compared to Caucasians. The same study revealed that African Americans expressed symptoms of hallucinations and delusions across the three categories of disease previously mentioned. Even African Americans with mild psychosis tended to over-endorse hallucinations and under-endorse delusions compared to Caucasians. Other symptoms did not exhibit racial bias, nor did racial bias in assessment of symptoms explain differences in the proportion of the symptoms between the two groups.

The aforementioned studies ought to make you question whether or not environments influence the manifestation of systems. Epigenetics is the study of how environmental pressures and social stressors can induce biological pathways that affect the health of organisms. Another simpler definition is this: “biochemical modifications that alter genetic expression but do not alter the DNA sequence”.<sup>7</sup> While epigenetics is more evident in plant and animal species that reproduce quickly, the search for epigenetic effects in humans is only beginning.<sup>8</sup> Due to the fact that so many variables serve as environmental pressures, it is difficult to isolate a causative effect, leaving only correlative data.

### **The Search for Aggression Genes**

Let’s return to the science fiction in the Black Lightning television series for a moment. Even though epigenetics is not well understood in humans at the moment in the real world, scientists in the DC universe seem to have some understanding. Their response to aggressive behavior in African Americans with a vaccine is quite profound. This implies that their so-called “vaccine” is not a vaccine by traditional convention. The television show does indicate that this vaccine contains genetic material, meaning that the brain was not simply medicated with a drug. They found a way to deliver genetic material to brain cells: viruses. Let’s examine the genetic material related to schizophrenia currently being studied in real life.

While the possible genetic markers of aggression are still being examined, schizophrenia is a severe mental disorder. Symptoms include hallucinations, delusions, cognitive deficits, and apathy. While inheritance patterns of the disease are complex and not completely understood, heritability has been estimated around 73-90%.<sup>9</sup>

Now, let’s review a few things about the substances that ultimately create genes: deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). They are both composed of four bases connected by a phosphate backbone. There are 5 nucleobases. DNA and RNA share 3 bases: cytosine (C), guanine (G), and adenine (A). The two bases, C and G complement each other in pairs. Adenine has two complementary bases,

depending on whether or not it is pairing with DNA or RNA. If a strand of DNA is paired with another strand of DNA, then its complementary base is thymine (T). If a strand of DNA is paired with one of RNA, then its complementary base is uracil (U). DNA codes for the genetic makeup of the organism, while RNA codes, decodes, and regulates the expression of genes. RNA can be classified into subtypes, such as messenger RNA (mRNA), guide RNA (gRNA), micro-RNA (miRNA), and long non-coding RNA (lncRNA).

Intermolecular forces ultimately drive the helical structure of DNA beginning with the bases.<sup>10</sup> The bases form hydrogen bonds, and their matching pair is based on the arrangement of the hydrogen bond donor and acceptor at the end of each base. The hydrogen bond that forms between the base pairs nearly cancels out the dipoles, making the bond nonpolar.

The expression of schizophrenia has been linked to micro-RNA (miRNA) and long non-coding RNA (lncRNA).<sup>11</sup> Reports have shown that there are several miRNAs related to schizophrenia such as miR-132/121 that affect the neuronal maturation and plasticity. miR-138/125b both affect dendritic spine size, while miR-137 affects spine maturity. miR-132 affects spine density, size, and maturity. Moreover, miR-132 influences dendritic branching and synaptic integration in newborn hippocampal neurons.

### **Targeting Aggression and Related Disorders**

Now that we've explored the possibility of genes coding for aggression and other mental disorders, we still have to figure out how a vaccination is capable of treating a mental disorder. We are so used to vaccines being used to prevent the onset of diseases such as polio, measles, mumps, chicken pox, and influenza. How could the scientists in Black Lightning actually conceive the idea of developing a vaccine to treat mental illness?

Vaccines work by supplying a host with a dead or weakened pathogen in order to generate an immune response in the host, later protecting it in the event of a true pathogen infection. Viruses are also capable of crossing the blood-brain barrier, unlike other microbes. Also, it is an immune cells job to fight viruses and generate an immune response, not the brain cell. Returning to Black Lightning's case, the vaccine could not have been a real vaccine by definition, but rather a form of virus therapy.

Since viruses are carriers of genetic information (either DNA or RNA), it is very plausible to load drugs or other genetic materials into those viruses. This is already being put into practice via the use of phages (bacteria-specific viruses). Even though bacteria can develop resistance to phages, scientists have found ways to work around that.<sup>12</sup> They are creating or discovering phages that bind to the virulence factors (typically protein structures) of bacteria to drive evolutionary trade-offs in the bacteria. Because the phages are lethal to the bacteria, they exert selection pressure for the bacteria to evolve phage resistance while simultaneously reducing their virulence (a trade-off). In some cases the result is increased sensitivity to chemical antibiotics. If scientists are able to develop phages that safely treat bacteria infecting the human body, then a "harmless" version of a virus should pose no problem if harnessed to deliver drugs and other molecules to brain cells. A group in Pasadena, CA has developed a "harmless" virus to meet that objective.<sup>13</sup> A mouse variant of a virus has been tested *in vivo* and a human variant has only been tested *in vitro*. These virus variants transduce both neurons and astrocytes more efficiently than prior variants.

### **CRISPR Technology: The Genetic Editor**

So back in the DC Comics universe, the evil scientists trying to keep African Americans in oppression via

vaccinations have finally figured out how to target the brain. We still need to know what types of molecules these viruses are pressuring our precious brain cells to uptake. The answer is quite complicated, but catchy: clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated nuclease 9 (Cas9). Sometimes, these two are referred to as a combined system called CRISPR/Cas9 gene drive system (CGD).

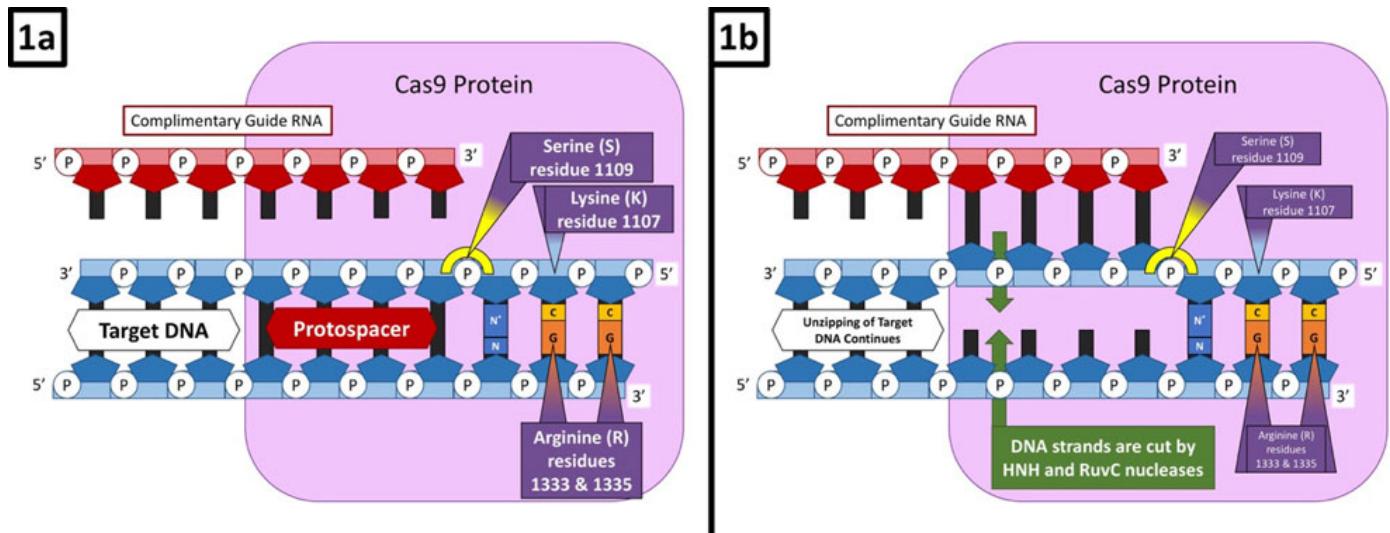
### **The History of CRISPR**

While clustered regularly interspaced short palindromic repeats (CRISPR) is relatively new in its name, its discovery dates back to the 1980s.<sup>14</sup> In the late 1980s, scientists were first observing the repeat sequences in pathogenic bacteria. The advancement of genome sequencing technologies during the 1990s really accelerated the ability to observe these repeating sequences in much of the bacterial world, but scientists did not understand the purpose of these sequences. It was not until 2002 when two groups consistently and repeatedly observed the occurrence of these repeats, coining the acronym 'CRISPR'. At that time, scientists began to realize that CRISPR could be used to separate repeating sequences or to even repair DNA. The true function of CRISPR was revealed in 2005 when research groups observed that the origin of these random sequences of CRISPRs were from viruses and plasmids, indicating that CRISPR may be a defense system in prokaryotes.

As we approach 2007, using bacterial cultures and phages, scientists conducted experiments hypothesizing that bacteria acquire these genetic spacers as a means for achieving phage resistance. As a result, several discoveries were made. First, CRISPRs can uptake phage DNA during cellular infection. Second, the contents of the CRISPR spacer determine whether or not the bacterium will gain, lose, or exchange resistances via addition, deletion, or transplantation. Finally, the Cas9 sequence was officially recognized as the adaptive immune system of bacteria.<sup>15</sup>

### **The workings of the CRISPR/Cas9 system**

The CRISPR/Cas9 system works using a Protospacer Adjacent Motif (PAM) binding to locate target sequences (Figure 1a). The most common form of the Cas9 nuclease comes from *Staphylococcus aureus* (SaCas9) and *Streptococcus pyogenes* (SpCas9), two types of bacteria responsible for staph infections and strep throat, respectively.<sup>16</sup> SpCas9 requires a PAM sequences of 5'-NGG-3', where "N" is any nucleobase that is followed by two guanine (G) bases.<sup>17</sup> The PAM interaction uses two arginine residues to bind to the major groove of the guanine bases, a lysine residue to bind to the minor groove, and serine residue to bind to the phosphate group in front of the "N" nucleobase. This will cause the DNA to unzip, allowing the complementary strand of gRNA to take its position, and Cas9 begins to rewrite the DNA using the gRNA. Two nucleases (HNH and RuvC) work to cleave the DNA specifically between the third and fourth nucleobase pairs (Figure 1b).



**Figure 1a.** Guide RNA helps Cas9 locate PAM sequence NGG.

**Figure 1b.** Two nucleases (HNH and RuvC) cleave the DNA and begin to pair it with the RNA

### CRISPR Trials on Schizophrenia

So while studies are on their way for markers of aggression, let's examine a disease related to aggression: schizophrenia. This mental disorder has mainly been treated using medications, but medications typically have adverse side effects. Patients, wanting to avoid the side effects, will come off of the medication and their disease is now left unregulated. As an alternative, scientists are looking to investigate the use of the CRISPR/Cas9 system as a means of directly correcting the mutations in DNA genomes and ncRNA genes. A group at Duke University has already used the system to treat a human disease, Duchenne muscular dystrophy, within a living mouse model by replacing mutations with substitutions.<sup>18</sup>

Using CRISPR, scientists have been able to edit the non-coding regions of genomic DNA in both human and animal cell lines, even in schizophrenia research. So far, the best use of this technology in schizophrenia research is the use of two gRNAs, allowing for two specific cuts to be made in order to delete a larger fragment of DNA.<sup>19</sup> This dual gRNA technique is favorable because schizophrenia involves multiple gene alterations of ncRNAs.

One of the main drawbacks of schizophrenia research has been the lack of translatable animal models to determine the cause. The CRISPR/Cas9 system allows for opportunity to create these animal models, target specific genes, and ultimately determine if one or a combination of ncRNAs lead to the development and progression of schizophrenia.<sup>20</sup>

### Implications of CRISPR Technology

Although many are in awe about the idea of cutting, replacing, and repairing genes with this technology, I'm sure the scientists who developed the vaccine as portrayed in *Black Lightning* were hopeful as well. Unfortunately, things did not go as planned. They accidentally altered the DNA of African Americans to the point that they developed superpowers. So let's look at some of the things that could go wrong with CGD technology in the real world.

A risk concerning CGD technology is the possibility of extra (nontarget) deletions or insertions in the genome.

Recently, a group discovered in their experiment a combination of deletions and insertions at 17 sites in the mouse genome.<sup>21</sup> The average deletion size was 9 base pairs, but some deletions approached 600 base pairs of DNA. The group observed that during simultaneous targeting of loci, sequences were often removed between loci separated by large distances. The same group concluded that the safest way to delete genes for now is through a two-step targeting mechanism.

While scientists have been optimistic about the discovery and use of CGD, there have already been reports of its resistance. One would like to believe that nearly all fruit flies readily accept CGDs, but a strain of fruit flies from Tasmania have a resistance rate as high as 56 percent.<sup>22</sup> Scientists have proposed CGD as a way to exterminate invasive species, but varying resistance means that CGD efforts may not prevail in that context. On the other hand, it has been reported that CGD systems are too invasive, meaning that it only takes a few organisms with CGD to invade a local population and then infiltrate neighboring populations.<sup>23</sup> Rather than try to control invasive species, scientists have proposed that the best application of CGD may be to prevent the spread of diseases such as malaria in mosquitos.

One issue concerning the Cas9 nuclease is that the resistance of the nuclease itself. Using blood donations, 79% of donors' blood developed antibodies against SaCas9, while 65% of donors produced antibodies against SpCas9. In addition, 46% of donors' blood contained anti-SaCas9 T-cells, while results also suggest that anti-SpCas9 T-cells may even exist. Another issue is that even our trusted model, the zebrafish, is not compatible with SpCas9.<sup>24</sup> After considering various strains of the fruit fly and bacteria, it is highly likely that scientists will have to search for a variety of Cas9 genes in order to minimize resistance in zebrafish and humans and devise a translatable model. Another alternative is to engineer Cas9 genes.<sup>25</sup>

While scientists have not found a solid method for using CRISPR in humans, these setbacks will not stop them from dreaming. Whether we like it or not, this technology is becoming our future. The backstory behind the DC Comics' superhero, Black Lightning, will no longer be just science-fiction. Our understanding of science is evolving rapidly. With Black Lightning now having to protect his neighborhood and his family from a drug war, there are still some questions. Will CRISPR be used similarly in real life to genetically enhance human beings? Or will we accidentally create superheroes similar to Black Lightning? What if CRISPR fails, edits too many genes, and begins to rob people of the life that scientists actually intended to improve, such as through healing of disease? These are all questions that my students will grapple with.

## Teaching Strategies

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### Student Audience

This unit is written for students in grade 10, who attend classes together as an advisory. Students have 60-minute class periods three days per week and 50-minute class periods twice weekly. An estimated 85% of the students are enrolled in algebra II, while the remaining students take geometry. The students enrolled in geometry are usually in the same advisory, which typically hastens the pace of the class compared to sections without geometry students. Grade 10 students are also committed to the completion of a personal project, a requirement for finishing the International Baccalaureate (IB) Middle Years Program (MYP).

## Developing the Concept

In IB MYP, key concepts are words used to paint a broad picture of learning expectations that can be observed within and across disciplines. Of the three fundamental key concepts recommended by IB (change, relationships, and systems), this unit will focus on the key concept of *relationships*.

Related concepts are more discipline-specific and allow for exploration of the key concepts in greater detail to cultivate students' conceptual understanding. The three related concepts selected for this unit's presentation are balance, form, and identity.

The conceptual phrase is a generic statement that summarizes a concept, is nonspecific, and can be applied across multiple content areas and topics. The conceptual phrase developed for this unit is as follows:

**Balanced relationships determine form and identity.** This conceptual phrase can be translated to topics, such as ion formation, acids and bases, solution chemistry, and redox reactions. Thus, students benefit from learning conceptual phrases because they potentially build continuity between old and new content.

## Inquiry-Based Learning

Inquiry questions are provided for students as a guide to their learning expectations. They are not necessarily exam questions, but they ought to provoke students into learning the content. Below are the several examples of inquiry questions that can be used throughout the unit. Other potential questions for inquiry-based learning will be listed in the classroom activities as they are needed.

### *Factual Questions*

- How do intermolecular forces differ from intramolecular forces?
- What does it mean for a molecule to be polar?

### *Conceptual Questions*

- How does the electronegativity of elements determine bond type?
- How do intermolecular forces affect melting and boiling points?
- How do intermolecular forces affect the physical properties of a substance?
- How do the forces in ionic bonds differ from London dispersion forces?
- Explain the distribution of subatomic particles in dispersion forces and dipole-dipole forces.
- How do intermolecular forces and bond types influence protein shape?
- How does CRISPR/Cas9 locate a sequence to replace?

### *Debatable Questions*

- How far will humanity go in its quest to cure diseases?
- Given the endless possibilities of human biology, will we truly be able to implement personalized medicine?
- Should research efforts be focused on finding cures or preventing onset?
- Should gene drive technology be used to enhance humans, prevent disease, or both?

### *Global Context and Inquiry Statement*

The global context is what allows me to connect my content to the real world. The IB program identifies six



areas of global context. The context of this unit is in the area of scientific and technical innovation, where students will be challenged to understand the world that they live in and examine the impact that scientific and technological advances have on communities, environments, and human activities in order to meet a specific need. The inquiry statement combines the concept together with the context to clearly point the students in the direction of their learning. Therefore, the inquiry statement of this unit will be: Balancing relationships between different molecules aids in the engineering of targets for treatment and stabilization of genetic disorders.

### **Assessment Criteria**

The IB program identifies four areas of assessment for performance-based learning in science. This unit will primarily focus on two of those criteria. The first is “knowing and understanding”, in which students are required to explain and apply scientific knowledge and understandings while analyzing and evaluating information to make scientifically supported judgments. The other is “reflecting on the impacts of science”, in which students are required to explain, discuss, and evaluate how science is applied and used to address a specific problem or issue while applying scientific language effectively.

## **Classroom Strategies**

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This unit will rely on accessing prior knowledge of electronegativity and polarity and using models to identify combinations of chemical structures and their interactions. Secondly, this unit will develop media literacy, in which students will read samples of news articles related to CRISPR. They will compare the facts that they have acquired to the Black Lightning television series. Finally, students will work in teams in a hands-on activity in order to model biochemistry at the molecular level.

Below is a suggested timeline of topics and activities. Activities marked with an asterisk (\*) are ones developed with focus on the benefits and controversies of manipulating biology.

- Day 1: Science Fact, Fiction, and Opinion: Exploring the Biochemistry in Black Lightning\*
- Day 2: Intermolecular Forces
- Day 3: Lewis Structures of Amino Acids
- Day 4: Function of Amino Acids
- Day 5: Developing CRISPR Literacy\*
- Day 6: Review of Nucleic Acids, DNA, and RNA
- Day 7: Making the Cut with CRISPR\*

The order of the topics allows me to alternate between familiar and unfamiliar information to my students. ‘Science Fact, Fiction, and Opinion’ is designed to use media from the Black Lightning television series to engage students on the topic of gene manipulation. This opens the door for me to teach the intermolecular forces and Lewis structures of amino acids so that students can gain some insight of how proteins are able to get their shapes through the intermolecular forces. Since Cas9 is a protein, students will be ready to read literature and understand how this protein works. Following their introduction to Cas9, I will tap into their prior knowledge of nucleic acids and DNA from biology. The unit will culminate with the students having to read RNA and DNA sequences to determine if Cas9 will edit a DNA given an RNA sequence. Lessons on

intermolecular forces, amino acids, and DNA can be taught according to your perspective of the content. While the suggested timeline spans seven days, I could see myself extending the unit to 10 days at most, especially if I believe my students need the extra support.

## **Classroom Activity 1: Science Fact, Fiction, and Opinion - Exploring the Biochemistry in Black Lightning**

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### **Lesson Overview**

This activity is designed to be the opener of the unit by developing interest in the topic of gene manipulation and how our understanding of chemistry can drive humanity towards gene therapy. This activity can be performed in one class period or broken up across several class periods to sustain student interest on days when the lessons are extremely content-driven. In my short teaching experience, my administrators have always encouraged me to connect the content back to the context so that students are always aware of why they are learning the content. Therefore, I will prefer using a piece of the activity on a daily basis to generate discussions on gene manipulation and build anticipation for the increasingly complex content.

### **Preparation**

This activity lends itself the students' knowledge and opinions via discussion and utility classroom technology tools such as Plickers.com or Socrative.com. I will present my students with a variety strategically crafted true/false statements along with general statements to observe students' viewpoints on biomedicine. Ultimately, I will follow through by asking for students' opinions on the statements to generate discussion. Some statements will be presented before a cutscene from the Black Lightning television series, while other statements will be presented after. Preparation here highly depends on which platform you are going to use to present these statements to students and collect their responses. I highly encourage that you download or rent the Black Lightning television series from an online service such as iTunes or purchase the DVD set, just in case your school district's firewall prevents access to streaming services such as Netflix. If needed, scripts are also available for English language learners.<sup>26</sup>

### **Implementation**

I've selected scenes from the Black Lightning television series and assigned titles to the scenes to summarize what I want students to get from those scenes. There are scenes focused on science literacy, drug abuse, gene isolation, and the decision-making process behind genetic mutations and their therapies.

Science Literacy through the Media (Season 1, Episode 5): In this scene, Anissa learns that her grandfather conducted research on the vaccine that was experimentally used on the people of Freeland. I chose this scene because this is something that everyone can relate to. We live our normal everyday lives only to find out that an health epidemic may have occurred and the truth was withheld for too long. This scene should be played after the students are surveyed.

- Agree/Disagree: I completely trust the media when it comes to informing me about medicine such as vaccines.
- Agree/Disagree: YouTube is the best place to find the truth when the news does not tell the truth.

- Post-Scene Discussion: What's your viewpoint/thoughts on the Flint water crisis?

Drugs and DNA (Season 1, Episode 8): In this scene, Lynn, Anissa's mother, discovers that her father-in-law's vaccine is chemically related to green light, a drug that has hit the streets of Freeland, causing its users to develop unstable enhanced abilities. I chose this scene because it can open up the discussion of what drugs and vaccines are used for. I can gauge my students' perspectives and debunk any misconceptions that they have about medicine concerning drugs and vaccines. This scene should be played after the students are surveyed.

- True/False: Drugs can alter the DNA of individuals who take them.
- True/False: Drugs can alter the expression of DNA.
- True/False: Both drugs and vaccines can be used to alter brain activity.
- Agree/Disagree: I believe that the government conspires to keep the truth about medicine from society.
- Agree/Disagree: Vaccines have adverse side effects that outweigh their benefits to humanity.

Drugs and DNA (Season 1, Episodes 8 and 12): In the scene from episode 8, Gambi reveals the truth about his past involvement in the circulation of the original vaccine used to domesticate the behavior of African Americans in Freeland. In episode 12, the ASA reveals to Black Lightning's nemesis, Tobias Whale, the purpose of the vaccine and the results. These scenes were selected because there are always a select group of people who believe that the government conspires against the citizens. At the same time, I can ask the students tough questions to see what they really believe and get them to start making connections between science fact and science fiction. As I mentioned in the Background of this unit, the vaccine delivered in Black Lightning could not have been a true vaccine by definition, but rather a form of therapy. These scenes should be shown prior to surveying the students.

- Agree/Disagree: Vaccinations are used to control society.
- Agree/Disagree: I believe that chemical warfare is already being used to alter our
- True/False: Aggressive behavior is genetically inherited.
- True/False: Mental disorders are genetically inherited.
- True/False: Drugs are used to give humans enhanced abilities.
- Post-Scene Discussion: Which biological components could be responsible for superhuman strength and high pain tolerance?

Gene Isolation (Season 1, Episode 12): This scene focuses on Jennifer's response to her parents after finding out that she has inherited genes for enhanced abilities. I selected this scene to hone in on the science of genetics and to assess students' prior knowledge on inheritance. This scene can be shown before surveying the students.

- True/False: Phenotypes are generally affected by a single set of genes, as demonstrated using Punnett squares.
- True/False: Scientists have effectively isolated genes and how to control them.
- Post-Scene Discussion: Where do we draw the line when it comes to isolating and/or manipulating genes?

Important Decisions about Gene Therapy (Season 1, Episode 12): This scene focuses on Jefferson and Lynn's differing viewpoints as parents of a daughter who is disturbed by having genetically enhanced abilities. I selected this scene to really focus on the mind of the Jefferson's daughter, who is a teenager trying to find her own identity only to realize she is not who she thinks she is because of a genetic mutation that she carries. I

believe that this scene will really grab my students and tie their interests to the content. The scene should be shown before the students are surveyed.

- Agree/Disagree: If a person has a genetic defect, then they are a broken individual that needs to be fixed.
- Agree/Disagree: If a DNA test could determine whether or not I am predisposed for a disease, I would want to know it immediately.
- Agree/Disagree: All genetic mutations should be corrected or suppressed.
- Agree/Disagree: I believe that the fate of children with genetic mutations should be determined by their parents alone.
- Agree/Disagree: Parents should decide the fate of their unborn child if a genetic mutation is discovered.
- Post-Scene Discussion: What should we consider when making decisions on correcting a genetic mutation?

## Classroom Activity 2: CRISPR Literacy Gallery Walk

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### Lesson Overview

In this activity, students will work in teams to summarize articles and list any pros and cons of gene drive technology on a medium-sized poster board. Once the students have finished their summaries, they will report out to the class via gallery walk. Since my classroom has eight lab tables for teams, I have selected eight articles from Science News for Students, one for each team.<sup>27</sup> Each article also contains a list of defined vocabulary that may be unfamiliar to students, but are essential to understanding the article. I will even ask students to select five vocabulary words that they want their classmates to be responsible for learning. Of course, there will be some overlap of vocabulary words, which is fine because it will show students which vocabulary words are the most important. The list of pre-selected articles are as follows:

1. Can DNA editing save endangered species?
2. New tools can fix genes one letter at a time
3. Molecular scissors fix disease-causing flaw in human embryos
4. Even some Olympic athletes cheat with drugs
5. Gene editing swats at mosquitoes
6. Expert panel approves human gene editing
7. Gene editing creates buff beagles
8. Scientists hide a real movie within a germ's DNA

I am also likely to have a few advanced students that appreciate a challenge. Therefore, I have listed three articles could substitute for the aforementioned readings from the parent publisher, Science News.<sup>28</sup>

1. Cancer cells engineered with CRISPR slay their own kin
2. Researchers say CRISPR edits to a human embryo worked. But critics still doubt it
3. Most Americans think it's OK to tweak a baby's genes to prevent disease

## Preparation

If there is technology available in the classroom, all of the cited articles are accessible on the internet. It would be wise to have printed copies of the articles in case of technological failure. Be sure to provide students with art supplies depending on how involved you want the students' class notes to be. Some teachers ask students to sketch pictures for their gallery walk, which would require an assortment of art supplies, but would also require more class time to complete.

## Implementation

Organize students into groups based on their ability levels. Assign articles based on reading levels or allow the students to pick from the selection of articles provided. Provide a medium-sized poster board or sheet (3 to 4 feet in width). Ask the students to read their assigned article, determine five (5) key points that they would use to summarize their article, and define 3-4 vocabulary words that are essential to understanding the article. This should take no longer than 20 minutes. Ask the students to hang up their posters somewhere around the classroom and select one person who will be the expert on the article. The expert will stay with the group's poster and explain any information on the poster that their visiting classmates cannot understand. The students will then visit each poster in their teams to take notes and new vocabulary. Students who volunteered to be experts ought to consult their group for notes at the end of the gallery walk. I often give extra credit to groups if their expert can recite some of the information they learned from the other groups. In this case, I would ask the experts to recite one pro or con from each of the eight articles read in class.

## Classroom Activity 3: Making the Cut with CRISPR

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### Lesson Overview

In this activity, I want the students to become the Cas9 protein. At the beginning of class, I plan to provide a short lecture (10-15 minutes) about the Cas9 protein and how it performs. At this time, I would also remind my students of the complementary base pairs of DNA and RNA. Once the lecture concludes, I will ask them to search the entire genetic sequence in the classroom and identify and label as many 5'-NGG-3' sequences possible with Cas9 sticky notes. Afterwards, I will assign schizophrenia-associated miRNA sequences to teams of students, and ask them to write the complete double-stranded DNA sequences that would match the miRNA. Then they will search the DNA sequence around the classroom for the places where Cas9 would actually create edits. By the end of the lesson, I expect students to be able to describe how Cas9 will specifically target DNA using specific amino acid residues and RNA. The activity could be used as part of a cumulative assessment.

### Preparation

Below are five miRNA sequences and their complementary DNA sequences related to schizophrenia (Table 1).<sup>29</sup>

miR-132		miR-125b	
RNA	5' -GCUGGUACCGACAUCUGACAAU-3'	RNA	5' -UCCUGAGACCCUAACUUGUGA-3'
DNA Strand 1	3' -CGACCATGGCTGTAGACTGTTA-5'	DNA Strand 1	3' -AGGGACTCTGGGATTGAACACT-5'
DNA Strand 2	5' -GCTGGTACCGACATCTGACAAT-3'	DNA Strand 2	5' -TCCCTGAGACCCTAACTTGTGA-3'
miR-137		miR-219	
RNA	5' -UUAUUGC UUAAGAAUACGCGUAG-3'	RNA	5' -UCUUAACGCAAACCUGUUAGU-3'
DNA Strand 1	3' -AATAACGAATTCTTATGCGCATC-5'	DNA Strand 1	3' -AGAATTGCGTTTGGACAATCA-5'
DNA Strand 2	5' -TTATTGCTTAAGAATACGCGTAG-3'	DNA Strand 2	5' -TCTTAACGCAAACCTGTTAGT-3'
miR-138			
RNA	5' -AGCUGGUGUUGUGAAUCAGGCCG-3'		
DNA Strand 1	3' -TCGACCACAACACTTAGTCCGGC-5'		
DNA Strand 2	5' -AGCTGGTGTGTGAATCAGGCCG-3'		

The key to this activity is having enough DNA strands posted around the classroom. To prepare, first generate each of the 5 DNA sequences and introduce a type of genetic mutation into the DNA. Then add the PAM 5'-NGG-3' to the mutated sequence. Finally, add a random nucleotide sequence. Examples can be found in Table 2. Ultimately, you want to create a DNA sandwich with the mutated DNA sequences between two random sequences, knowing that the PAM must be at the 3' end of the mutated sequence so that it is a designated marker for Cas9 to identify.

Mutation	Nucleic Acid	Sequences with mutations in DNA	PAM	Random Sequence
	<b>miR-132</b>			
	RNA	5' -GCUGGUACCGACAUCUGACAAU		
point	DNA Strand 1	3' -CG <b>CA</b> ATG <b>CT</b> GTAGACTGTTA	TCC	ATTT <b>CG</b> AGCTAGGGA-5'
	DNA Strand 2	5' -G <b>CGG</b> T <b>TAC</b> CGACATCTGACAAT	AGG	TAA <b>AG</b> CTCGATCCCT-3'
	<b>miR-137</b>			
	RNA	5' -UUAUUGC UUAAGAAUACGCGUAG		
deletion	DNA Strand 1	3' -AATAACGAAT <b>TC</b> ---TGCGCATC	ACC	GATTACCTAGTCATTTA-5'
	DNA Strand 2	5' -TTATTGCTTA <b>AG</b> ---ACGCGTAG	TGG	CTAATGGATCAGTAAAT-3'
	<b>miR-138</b>			
	RNA	5' -AGCUGGUGUUGUGAAUCAGGCCG		
insertion	DNA Strand 1	3' -TCGACCACAAC <b>AGTAGT</b> CTTAGTCCGGC	GCC	CTTAGATTCGGAT-5'
	DNA Strand 2	5' -AGCTGGTGT <b>TGTCATCA</b> GAATCAGGCCG	CGG	GAATCTAAGCCTA-3'

## Implementation

To start the activity, only give the students with the miRNA sequences. Ask them to derive the DNA associated with the miRNA. To avoid confusion, make sure that the students' top strand of DNA begins with 3' and the bottom strand begins with 5'. Focusing on strand 2 as demonstrated in Tables 1 and 2 will help the students find their DNA targets.

### Steps to Cutting with Cas9

The following are some basic instructions that you can provide the students.

1. Identify the protospacer adjacent motifs (5'-NGG-3').

2. Determine if the four nucleotides (protospacer) to the left of the PAM are complementary to the nucleotides from any of the miRNA sequences. If they don't match, then Cas9 will not try to correct the DNA.
3. Compare the DNA sequence derived from the miRNA with the DNA sequences provided.
4. Determine if the Cas9 protein will correct a mutation, add/delete nucleotides, or create further complications in the DNA.

Once the students have determined the complementary DNA sequences to the miRNA, I will ask them to revisit all of their Cas9 markers placed around the room. Then they will examine the DNA sequence to the left of the Cas9 marker to determine if the Cas9 protein will cut the DNA. If it will not cut the DNA, then students will remove the Cas9 sticky note. If the first four nucleobases (the protospacer) match the DNA, then Cas9 will know to cut the DNA and continue making repairs. Students should continue to read the sequence to determine if any mutations of nucleobases were corrected or replaced along the way. Towards the end of the activity, you can begin tell the students what specific genes are activated by the miRNA molecules that you provided to them.

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## Appendix

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### Standards - Annotated

#### Pennsylvania Department of Education: Standards Aligned System

Standard - 3.1.B.B3: Describe the basic structure of DNA, including the role of hydrogen bonding. Explain how the process of DNA replication results in the transmission and conservation of the genetic code. Describe how transcription and translation result in gene expression. Cite evidence to support that the genetic code is universal.

This unit addresses how RNA are responsible for the regulation for genes and how RNA molecules can be used to repair DNA.

Standard - 3.1.C.B3: Describe the structure of the DNA and RNA molecules.

Standard - 3.1.C.C2: Use molecular models to demonstrate gene mutation and recombination at the molecular level.

The unit focuses on how a protein originally discovered in bacteria could create a way for humans to repair genetic mutations at precise locations.

Standard - 3.2.C.A2: Draw Lewis dot structures for simple molecules and ionic compounds.

Predict the chemical formulas for simple ionic and molecular compounds.

## Common Core Standards for Science and Technical Subjects

RST.11-12.1 Cite specific textual evidence to support analysis of science and technical texts, attending to important distinctions the author makes and to any gaps or inconsistencies in the account.

WHST.9-12.9 Draw evidence from informational texts to support analysis, reflection, and research.

## Next Generation Science Standards

HS-PS2-6. Communicate scientific and technical information about why the molecular-level structure is important in the functioning of designed materials.

This standard is implemented in the lesson in which students must learn the role of the Cas9 nuclease and determine where the nuclease would alter DNA given an miRNA sequence as guide RNA.

HS-LS1-1. Construct an explanation based on evidence for how the structure of DNA determines the structure of proteins which carry out the essential functions of life through systems of specialized cells.

This unit actually addresses the idea of using RNA and proteins to reverse engineer DNA.

HS-LS3-2. Make and defend a claim based on evidence that inheritable genetic variations may result from: (1) new genetic combinations through meiosis, (2) viable errors occurring during replication, and/or (3) mutations caused by environmental factors.

This unit will examine errors during replication when learning the role of the Cas9 nuclease and discuss environmental factors that could cause mutations during the classroom discussion about science facts and fiction in the Black Lightning television series.

## Notes

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1. Kalueff et al., "Zebrafish as an Emerging Model for Studying Complex Brain Disorders."
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