Exploring Gene Therapy
Clinical Trials through Webquest and Role Play

Lesson Summary:
In this lesson, students will learn about the benefits, dangers, and ethical dilemmas associated with gene therapy clinical trials through a webquest. They will then participate in a role play, depicting various stakeholders at an RAC meeting to decide the fate of a gene therapy trial. This activity serves as a wrap-up to the entire unit.

Student Learning Objectives:
The student will be able to…
1. Evaluate the impact of biotechnology on the individual and on society through role play.
2. Critique the ethical and morals standards of the stakeholders involved in conducting gene therapy trials.
3. Synthesize an educated stance on the controversial topic of gene therapy.
4. Explain the significance of genetic factors to health from the perspective of both individual and public health.
5. Describe how viruses transfer genetic material between cells and the role of this process in biotechnology.
6. Discuss how basic DNA technology is used to construct recombinant DNA molecules.
7. Describe the basic molecular structures and primary functions of DNA and proteins.
8. Recognize that the strength or usefulness of a scientific claim is evaluated through scientific argumentation, which depends on critical and logical thinking, and the active consideration of alternative scientific explanations to explain the data presented.
9. Explain how scientific knowledge and reasoning provide an empirically-based perspective to inform society’s decision making.
10. Weigh the merits of alternative strategies for solving a specific societal problem by comparing a number of different costs and benefits, such as human, economic, and environmental.

SC.912.L.14.6  SC.912.L.16.10  SC.912.L.18.1  SC.912.N.4.1
SC.912.L.16.7  SC.912.L.16.12  SC.912.N.1.3  SC.912.N.4.2
Materials:

- Student gene therapy webquest pages (1 per student)
- Student Handout: Gene Therapy Role Play (1 per student)
- Role Play Cards (1 per student in each stakeholder group)
- Student Worksheet: Gene Therapy Role Play (1 per student)
- Markers (1 per stakeholder group)
- Cardstock (1 per stakeholder group, to make name plate)

Background Information:

Gene therapy is the use of DNA as a pharmaceutical agent to treat disease. It derives its name from the idea that DNA can be used to supplement or alter genes within an individual’s cells as a therapy to treat disease. The most common form of gene therapy involves using DNA that encodes a functional, therapeutic gene in order to replace a mutated gene. In gene therapy, DNA that encodes a therapeutic protein is packaged within a “vector”, which is used to get the DNA inside cells within the body. Once inside, the DNA becomes expressed by the cell machinery, resulting in the production of therapeutic protein, which in turn treats the patient’s disease.

Early work with gene therapy began in the 1970s as researchers started developing the idea. The first clinical trials began in the 1990s. Gene therapy has suffered major setbacks, with the death of patients in two separate trials, resulting in very tight control of the approval and reporting process.

In 2010, researchers at the University of Florida began enrolling participants for a Phase I/II gene therapy clinic trial. Scientists have incorporated the correct gene to produce the enzyme GAA into an adeno-associated virus, which already exists in most people, and during the clinical trial, inject it into each patient’s diaphragm. The intent is to “infect” cells of Pompe patients with the genetic machinery they have been missing since birth. If successful, this method would not be a cure for Pompe disease, but could drastically increase the quality of life for people with the disease.
Advance Preparation:

(10 min)
• Reserve computer lab if completing webquest during class time.
• Print and cut out role play cards.

Implementation Note: While this role play is loosely based on the proceeding at the RAC meetings, the role card information is fictional. In particular, the statement about the death of animal models is not published data. This has been added to cause the students to realize animal models are used in early phases of research and often there are losses while dosing curves are determined. Additionally, pharmaceutical companies are businesses. While they fund many clinical trials, it is to promote their own product for the good of the business. They do not have a place at the scientific hearing to determine if clinical trials should begin. The RAC does exist, but the meetings are not open to all members of the public to plead their case. The meetings are to determine if the science is sound, the procedure shown to be safe, and if the investigator is competent to conduct a human trial.

There is not much controversy with somatic gene therapy, so this activity shouldn’t lead to harsh words or disruptive behavior. If your students are unaccustomed to role play or engaging in socioscientific discussions, this role play will help by engaging them in a relatively uncontroversial topic. Ethics is a vital component of medicine and this activity should open the door for students to engage in more difficult topics such as germ line gene therapy. Our students today will be faced with these issues in the very near future.

Procedure and Discussion Questions with Time Estimates:

Webquest (50 min if completed in class)
1. The webquest from the Genetic Science Learning Center is a great introduction to gene therapy. They provide a complete lesson plan on their website (http://teach.genetics.utah.edu/content/tech/genetherapy/Exploring%20Gene%20Therapy%20.pdf). The webquest could be assigned for homework before introducing the role play or completed in the school computer lab. If completing during class, allow 45 minutes.

*Implementation note: the companion teacher website has answers listed. These are accessible to anyone, even the students. There is a vector worksheet with the activity that you may wish to omit. For the purposes of this lesson, students only need to know generally that there are different vectors used to target different cells and deliver different genes. This is covered on the primary worksheet which accompanies the webquest.

Introduction to Role Play (30 min)
1. The class period before the role play should be used to introduce and summarize the role play activity that the students will be conducting the next day.
2. Ensure all students have a general understanding of gene therapy and all aspects of Pompe disease including the cause, symptoms, and treatment options for patients. This can be accomplished by reviewing the gene therapy webquest answers and relating it to what they have learned about Pompe or briefly lecturing on the concept. Very brief presentation from PBS DNA website could be used in lieu of a short ppt to introduce gene therapy if webquest not done: http://www.pbs.org/wnet/dna/pop_gene_therapy/index.html. Additionally, part of the webinar by Dr. Byrne, listed below, could be shown to the students.
3. Divide the students into 6 groups. Each group will represent a stakeholder group during the round-table discussion. One group will represent the RAC committee. For simplicity, have an odd number of students in this group so their vote does not end in a tie.
4. Provide each group with their respective role card which details their stakeholder group’s stance on implementing gene therapy clinical trials in an effort to find a better treatment for Pompe disease. At this time, distribute the Student Handout: Gene Therapy Role Play.
5. Have each stakeholder group create a name plate that they will display in front of their group during the round-table discussion.
6. Allow the remaining time (approximately 15 minutes) for the groups to:
   a. Review the student handout/become acquainted with the role play scenario and procedures.
   b. Read their role card and discuss how they will portray their group during the role play

**ROLE PLAY DAY:**

Role Play Activity (50 Min)

- Arrange the student desks in a way that all the stakeholder groups are able to see one another. A circle/U-shape is recommended.
- Follow the procedures outlined on the Student Handout: Gene Therapy Role Play to conduct the role play. Note: The teacher assumes the role of a moderator in this role play activity.
- Pass out the Student Worksheet: Gene Therapy Role Play to the students. This worksheet should be completed for homework.

**Assessment Suggestions:**
- Student Worksheet: Gene Therapy Role Play

**EXTENSIONS:**

**Activities**

Have the student consider gene therapy with germ cells. The role play involves gene therapy of somatic cells. What if a patient is treated with gene therapy successfully and 20 years in the future the patient would like to have children? In that case, the sperm or egg would need to be genetically manipulated to correct the mutant GAA allele. Should this be permitted?

**Literature**


**RESOURCES:**

Gene therapy web quest:
- Teacher pages: [http://teach.genetics.utah.edu/content/tech/genetherapy/Exploring%20Gene%20Therapy%20.pdf](http://teach.genetics.utah.edu/content/tech/genetherapy/Exploring%20Gene%20Therapy%20.pdf)
- Student pages: [http://learn.genetics.utah.edu/content/tech/genetherapy/](http://learn.genetics.utah.edu/content/tech/genetherapy/)

Very brief presentation from PBS DNA website (could be used in lieu of a short ppt to introduce gene therapy if webquest not done): [http://www.pbs.org/wnet/dna/popgene_therapy/index.html](http://www.pbs.org/wnet/dna/popgene_therapy/index.html)


University of Florida: [http://www.peds.ufl.edu/research/teams/byrne.asp](http://www.peds.ufl.edu/research/teams/byrne.asp)

Government Clinical Trials Website: [http://www.clinicaltrials.gov](http://www.clinicaltrials.gov)

REFERENCES:

Minutes from the September 2008 RAC meeting where this clinical trial was discussed: [http://oba.od.nih.gov/oba/RAC/meetings/Sept2008/RAC_Minutes_09-08.pdf](http://oba.od.nih.gov/oba/RAC/meetings/Sept2008/RAC_Minutes_09-08.pdf)


The concept of “fixing” someone’s genes to a cure for a genetic disease once seemed unattainable and like something out of a science fiction movie, but the possibility is much closer than we ever imagined. The novelty of this grand idea, however, was tarnished when an eighteen year old boy died in a gene therapy clinical trial in 1999. Since this incident, there has been much scrutiny about the safety and ethics behind gene therapy. Now, gene therapy clinical trials are monitored more closely than ever by the Recombinant DNA Advisory Committee (RAC) which advises the National Institute of Health (NIH). The RAC reviews human gene transfer research approaches. Protocols that raise any particularly important scientific, safety or ethical considerations are discussed by the RAC at one of its quarterly public meetings. It can take years to have a protocol approved and clinical trials to start.

Today we are at one of the RAC’s quarterly meetings in Bethesda, Maryland to discuss if scientists at the University of Florida should be granted permission to conduct a gene therapy clinical research trial on patients with Pompe disease. Here today we have a diverse group of representatives to share their professional and personal opinion on the topic. At the conclusion of today’s meeting a vote will be conducted to determine if the clinical trial should be allowed.

RAC Meeting Rules:
- You must be seated with all the members of your stakeholder group while the meeting is in progress.
- A group member must raise their hand to indicate they would like to speak. You must then wait to be recognized by the moderator (your teacher).
- Everyone must be respectful and listen when a stakeholder group is sharing their position. Any individual not in accordance with these rules will be asked to leave.

1. You will have 5 minutes to meet with your fellow group members. This time should be used to find a place to sit and set up your name plate. Also, use this time to determine one speaker for your case.
2. (10 min) Once the meeting has begun, each group will be permitted 2 minutes to introduce their group and provide a brief synopsis on their position. The moderator (your teacher) will call upon your group when it is time to speak. The moderator will select a group to go first and move in a clockwise fashion from that group on.
3. (10 min) The RAC committee members will be given a chance to ask one question of each group. The moderator will call on speakers who raise their hands.
4. (5 min) Intermission
   a. Part 1: During this intermission time stakeholders are allowed to interact with each other and learn more about the motives and ethical values of the other groups. Individuals may want to share information they learned in previous lessons.
   b. Part 2: Using the remaining time to rejoin your group and share any new information you have learned about the other stakeholder groups and formulate your closing argument.
5. (10 min) Meeting will commence. Each group will be given a 2 minute time period to present a closing statement. The groups will be called on in the order they were at the beginning of the meeting.
6. (5 min) The RAC group will have time to confer and reach a decision. Each member of the RAC will be allowed one vote: either for or against gene therapy clinical trials.
7. The moderator will call on the RAC to reveal its decision. The RAC spokesperson will indicate if your group is for or against clinical trials starting. Indicate what evidence led to the decision. If the vote is against, recommendations should be given (what is needed to show gene therapy for Pompe disease is safe and effective in human patients).
CLINICIANS. Since Pompe disease is so rare and finding a doctor who is exclusively specialized in treating patients with the disease is nearly impossible your group is made up of a variety of doctors. You have a neurologist, pulmonologist, cardiologist, oncologist, registered dietician, physical therapist, and an entire staff at a cardio-pulmonary rehab gym. Each of you attempts to improve your Pompe patient’s quality of life by relieving some of their symptoms. Despite your varying specialties you must collaborate to determine what the best treatment options are for your patients prior to implementing them. You are eager to hear and learn more about the possibilities of gene therapy clinical trials for Pompe disease and have a long list of questions to ask the researchers about the safety of this procedure. You are a strong supporter of translational research but want to ensure your patients will be safe. At the meeting you ask the principal investigator and his research team questions about their laboratory work and results thus far.

PATIENTS WITH POMPE DISEASE. Your group is composed of individuals that have been clinically diagnosed with Pompe Disease. You range in age from 3-16 years old and are all experiencing a variety of symptoms associated with the disease including muscle weakness (cardiac and skeletal), complications walking and breathing, and organ enlargement. For many of you the disease is progressing at a fast rate and you now are confined to a wheelchair and require a respirator. You are aware that these symptoms will become more severe over time and will ultimately shorten your life. The possibility of being a participant in a gene therapy clinical trial that may reduce the burdensome symptoms that you are experiencing and extend your life expectancy is very exciting but also scary. You are nervous about participating in a clinical research study, but see few alternatives for treatment. You are unsure if you should participate in the study and seek your parents and doctors for guidance on this issue.

PARENT OF PATIENTS WITH POMPE. Everyone in your group has at least one child with Pompe disease. You are constantly conducting searches seeking new scientific findings and information on the disease and actively fundraising to provide monetary assistance for scientists researching Pompe disease. Despite your enthusiasm for translational research you are still hesitant to allow your child to participate in the study without being fully informed on the potential for negative reactions in response to the treatment. You are aware, that your child already has a decreased lifespan, but are nervous about complications that may arise during the trial that could end their life even more prematurely. To make matters worse you recently heard about a teenager who died due to complications associated with a gene therapy clinical trial he was participating in. You want reassurance from the doctors, nurses, and researchers before you can comfortably encourage your child to participate in a clinical trial. At the RAC meeting you will ask the principle investigator to share the results of all the gene therapy trials that were conducted on animals in the laboratory.
PRINCIPLE INVESTIGATOR. As the principle investigator you hold a very prestigious position that also comes with great responsibility. You manage your group of researchers in the laboratory, monitor the progress of the clinical trials, and represent the University of Florida. You dedicated your career to researching the genetic mechanisms of Pompe disease and have been relentless in your quest to find a treatment for this rare condition. Along the way you have encountered difficulty obtaining funding to continue your research. Finally, however, you think you have it! You know that you will have to convince the RAC, and the families and patients with Pompe that your treatment procedure is safe and will work. At the meeting you must present evidence that you performed successful gene therapy trials on an animal model in the laboratory. You share that you have had some deaths related to the treatment; however, this occurred only when the mice were administered a treatment dosage 20 times higher than what they patient would be given. You reassure the panel that when the dosage that would be used in the human trials was administered it was tolerated by all the animal models. You also reassure all parties that each patient will be assessed prior to treatment to ensure they meet the requirements and health conditions necessary to be admitted into the trial.

PHARMACEUTICAL COMPANY. Your group represents a successful pharmaceutical company that is very interested in funding and patenting the principle investigator’s work. You have previously been in contact with him and his research team. He has submitted his research findings to your company and you are optimistic that his treatment will work. While your company produces many different types of medicines to cure common diseases and conditions, you are allured by the potential to have your company’s name associated with a treatment that can remedy Pompe disease even better than enzyme replacement therapy. At the RAC meeting you are interested to see how the panel and other stakeholders react when discussing the implementation of these gene therapy clinical trials. Overall, you are in strong support of clinical trials starting.

RECOMBINANT DNA ADVISORY COMMITTEE (RAC). Your group advises the National Institute of Health (NIH). The RAC reviews human gene transfer research approaches. Protocols that raise any particularly important scientific, safety or ethical considerations are discussed by the RAC at one of its quarterly public meetings. It can take years to have a protocol approved and clinical trials to start. You are all experts in the recombinant DNA research and clinical applications and understand the great responsibility you have as you determine the fate of a potential life saving therapy. You must also weigh the potential harm that may be done if the technology is not ready. Patient lives are at stake. Although this is a devastating disease, you cannot allow humans to be used in an experimental manner that might cause more damage. You are interested to hear from the patients and parents who live with the disease everyday and learn more about their quality of life. You also are very impressed with the lead investigator and the careful experimental approach he has taken thus far. Not only is he a researcher, but he is also a leader in the clinical care of Pompe patients.
Instructions: This worksheet is to be completed individually following the Gene Therapy Role Play activity. Use your stakeholder card and information you learned at the meeting to answer the following questions.

1. What stakeholder group did you represent?

2. What was your group’s position on allowing gene therapy clinical trials to begin?

3. Explain if you personally agree/differ with the beliefs and ethical standards of your stakeholder group.

4. Imagine if you had a moderate case of Pompe Disease. Would you enroll yourself in a gene therapy clinical study? Explain the thought process behind your decision.

5. The clinical trial under consideration in this activity only affected somatic cells. Therefore, any modification to the individual would not be passed on to offspring. Consider the case 25 years in the future. One of our Pompe patients has successfully been treated with gene therapy and is living a very normal, happy life. He is married to a wonderful person, and they long to start a family. However, the man will pass mutations for Pompe along to his children. His wife has been tested and carries some of the mutations as well, although she does not exhibit symptoms of Pompe disease. What is your position on germ line (inheritable modification to sperm or egg) gene therapy to correct the mutant GAA gene? Are you for or against? Explain thoroughly your position on the back.