Lesson Summary:
Working in groups, students will read Pompe fact cards and use text clues to sequence the events in the discovery and treatment of Pompe disease. This lesson illustrates scientific discovery as a collaborative effort of many individuals building on prior knowledge and developing unique ideas to explore.

Student Learning Objectives:
The student will be able to...
1. Sequence scientific discoveries
2. Discover that science is a collaborative effort
3. Consider the role technology has played in the rapid advances in biomedical science during the last twenty years

Standards:

Materials:
• Student Page: The Road to Treatment Timeline Cards (1 set per group)
• Teacher Page: The Road to Treatment Timeline Cards for Wall (1 set for teacher use)
• Student worksheet: The Road to Treatment Timeline Cards (1 per student or student group)

Background Information:
Background information needed for this assignment is at the beginning of the guide and included on the information cards. Teachers should read the information cards prior to the start of the lesson.
Advance Preparation:

1. Prepare the student timeline cards for each student pair or group: Print one set single sided and write the corresponding letter on the back to spell POMPE DISEASE (see answer key and teacher timeline cards for order); copy and cut a set for each student pair or group. For extended use, consider cardstock and/or laminating.

2. Prepare the wall timeline cards. For extended use, consider cardstock and/or laminating.

3. Make copies of the student worksheet, one per student or student group.

4. Draw a timeline on the board or on the wall to affix the enlarged cards. Include 1930 – 2011.

Procedure and Discussion Questions with Time Estimates:

1. **(5 min)** Use the flipchart to restate what the students learned yesterday (or call on student volunteers to share.) Probe to see if anyone did research on Pompe last night. If so, what did they learn?

2. **(2 min)** Tell the students they will now look at historical and current (2011) events and place them in chronological order. Have the students work in groups of 2-4. If the home groups from the previous day worked well together, you may wish to use the same groupings.

3. **(3 min)** Once students are assembled in groups of 2-4 and settled, distribute one envelope of timeline cards to each group.

4. **(15 min)** Allow the students to order the cards and complete the worksheet. Move around the groups and alert them to clues in the cards if needed.

5. **(10 min)** Using the teacher timeline, place the first card on the timeline.

6. Call on a group to place the next as they give their one sentence summary. Ask the class if they agree with this choice.

7. Continue around the groups until all cards have been placed, addressing disagreements by asking questions to lead the students to the correct answer.

8. Once the timeline is complete, help lead students to the following conclusions:
   a. The disease was characterized rather recently.
   b. It has been a worldwide effort to understand and treat Pompe disease.
   c. The advances in the last 15 years have been quite incredible. Ask the students why? Awareness and technological advances have pushed the research. Biotechnology has provided the tools and techniques needed. Also, since Pompe is a rare disease, there are special incentives for research and clinical trials involving orphan drugs. Often, orphan drugs are pushed through faster since there is no alternative treatment, and lessons can be learned and applied to treatment for other less severe illnesses.

Assessment Suggestions:

- Student worksheet can be collected. If student timeline cards are sequenced correctly, they spell POMPE DISEASE.

**LITERATURE:**

- Therapeutic approaches in Glycogen Storage Disease type II (GSDII)/Pompe disease: [http://amdapompe.ehclients.com/downloads/publications/Therapeutic_Approaches.pdf](http://amdapompe.ehclients.com/downloads/publications/Therapeutic_Approaches.pdf)

**RESOURCES/REFERENCES:**

- How is Lumizyme made? (has a very informative biomanufacturing video): [http://www.lumizyme.com/patients/about_lumizyme/how_lumizyme_is_produced.aspx](http://www.lumizyme.com/patients/about_lumizyme/how_lumizyme_is_produced.aspx)

**EXTENSION ACTIVITIES:**

Have students investigate a stakeholder involved with the research and/or clinical aspects of Pompe disease.

Students may be curious about Genzyme’s role and business motives behind acquiring all competing labs. This can lead to a great discussion about the business of major pharmaceutical companies. The topic will come up again in the final lesson of a gene therapy role play.
1 Dr. Joannes Cassianus Pompe carried out a postmortem on a 7-month old girl who had died of pneumonia. He found the enlarged heart now known to be characteristic of the infantile form of the disease and had some microscope slides prepared. These showed that the muscle tissue was distorted into an oval mesh. Dr. Pompe later characterized the second glycogen storage disorder (GSD II) which now bares his namesake.

2 G T Cori described what are now known as glycogen storage disease types 1-4. Only in the case of Pompe disease (glycogen storage disease type 2) was the missing enzyme and its location unknown. The key to solving the puzzle of what caused Pompe disease lay in a seemingly unrelated discovery taking place elsewhere. Gerty and Carl Cori won a joint Nobel Prize for their work on glycogen metabolism.

3 Christian de Duve and co-workers were investigating the effect of insulin on the liver, when they discovered intra-cellular particles which seemed to have digestive properties. de Duve named these particles lysosomes. The idea that cells themselves had compartments (now known as organelles) with particular functions was now firmly established. Thus was the idea of the lysosome as the ‘recycling plant’ of the cell established. Prof de Duve was later awarded the Nobel Prize for his discoveries.

4 Henri-Gery Hers discovered a new enzyme, alpha-glucosidase, and knew it worked best at an acid pH. This set him thinking about his previous work with de Duve on lysosomes which had an acid environment. He further deduced that the normal function of this enzyme was to break down glycogen inside the lysosomes and that, in its absence, glycogen would accumulate. He established the concept of lysosomal storage diseases based on his Pompe disease research.

5 There were attempts at a treatment for Pompe disease. Soon after Hers characterized lysosomal storage diseases, it had been suggested that enzyme replacement therapy might be a potential treatment. This was tried for Pompe disease, first using enzyme prepared from the fungus Aspergillus niger and later with enzyme derived from human placenta. All attempts failed; the enzyme was simply soaked up by the liver and did not reach the muscles.

6 Arnold Reuser, a researcher at Erasmus University in Rotterdam, and his then PhD student, Ans van der Ploeg, looked again at enzyme replacement therapy. In particular, they made use of the recent discovery that enzymes made their way into the lysosome using a receptor for the sugar mannose-6-phosphate. Their first experiment was to take cell lines isolated from Pompe patients – human muscle cells grown in a dish in the laboratory. Reuser & Van der Ploeg added the phosphorylated enzyme – and the glycogen was degraded. Reuser cloned the gene and shared with YT Chen.
In 1996, the Rotterdam group joined with a biotech company called Pharming to produce the enzyme alpha glucosidase (acid maltase) in the milk of transgenic rabbits. Pharming got off to a quick start, announcing the start of Phase I clinical trials on April 15, 1998. This stage of clinical trials involves dosing healthy human volunteers to check for toxic effects. This was followed in July 1998 by the news that Pharming had entered into a partnership with Genzyme.

Duke University announced that YT Chen’s group would also be conducting clinical trials of ERT, in collaboration with a company called Synpac Pharmaceuticals. They would be using the more ‘traditional’ method of producing the GAA enzyme in Chinese hamster ovary (CHO) cells engineered to produce the human enzyme. This meant that there was now real competition, with a race to be first to announce results and to commercialize the product.

Genzyme entered into agreements or acquired all parties working on ERT including Pharming, Synpac, and Novazyme. Additionally, they were working on their own internal enzyme. Genzyme initiated a major effort to study and compare the four drugs to determine which candidates offered the best chance of success in treating Pompe disease. This effort involved extensive research and analysis – the undertaking so large and so important it was nicknamed “The Mother of All Experiments” by the research team leaders. The winner would later be named Myozyme.

After two global clinical research studies conducted at seven study sites, Myozyme was approved for the treatment of infant and juvenile forms of Pompe disease in the U.S. (April 28) and European Union (March 29) and it remains the only approved therapy for the treatment of Pompe disease in the world today. Additional clinical trials indicated ERT is effective in patients with late onset Pompe disease as well. Myozyme is repackaged as Lumizyme and approved for use in the US.

In 2010 enrollment in the first gene therapy clinical trial was initiated. This phase I/II study is designed to target respiratory insufficiency which is the most life-threatening manifestation of Pompe. The vector is directly administered to the diaphragm. The target population for this study is children aged 3 – 14 who are dependent on mechanical ventilation despite ERT. These children represent the more severely affected spectrum of Pompe patients and the population most in need of improved therapeutic strategies.

After previously halting clinical trials due to adverse effects, Amicus Therapeutics announced the initial infusion of the first subject in an open-label Phase 2 drug-drug interaction study of AT2220 (a pharmacological chaperone) co-administered with enzyme replacement therapy (ERT) in individuals with Pompe disease. The announcement was made in December, 2011.
Timeline Wall Cards (page 1)

Copy and cut to display on wall. (Laminate for repeated use.)

1930

DR. JOANNES CASSIANUS POMPE carried out a postmortem on a 7-month old girl who had died of pneumonia. He found the enlarged heart now known to be characteristic of the infantile form of the disease and had some microscope slides prepared. These showed that the muscle tissue was distorted into an oval mesh. Dr. Pompe later characterized the second glycogen storage disorder (GSD II) which now bares his namesake.

1947

GERTY CORI described what are now known as glycogen storage disease types 1-4. Only in the case of Pompe disease was the missing enzyme unknown. The key to solving the puzzle of what caused Pompe disease lay in a seemingly unrelated discovery taking place elsewhere. Gerty and Carl Cori won a joint Nobel Prize for their work on glycogen metabolism.

1955

CHRISTIAN DE DUVE and co-workers were investigating the effect of insulin on the liver, when they discovered intra-cellular particles which seemed to have digestive properties. de Duve named these particles lysosomes. The idea that cells themselves had compartments (now known as organelles) with particular functions was now firmly established. Thus the idea of the lysosome as the ‘recycling plant’ of the cell was established. Prof de Duve was later awarded the Nobel Prize for his discoveries.
HENA 1965-GY HER discovered a new enzyme, alpha-glucosidase, and knew it worked best at an acidic pH. This set him thinking about his previous work on lysosomes which had an acidic environment. He further deduced that the normal function of this enzyme was to break down glycogen inside the lysosomes and that, in its absence, glycogen would accumulate. He established the concept of lysosomal storage diseases based on his Pompe disease research.

1965-75

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1991

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Duke University announced that YT Chen’s group would also be conducting clinical trials of Enzyme Replacement Therapy (ERT), in collaboration with a company called Synpac Pharmaceuticals. They would be using the more ‘traditional’ method of producing the GAA enzyme in Chinese hamster ovary (CHO) cells engineered to produce the human enzyme. This meant that there was now real competition, with a race to be first to announce results and to commercialize the product.

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2006 & 2010

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2010

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2011

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The Road to Treatment

Directions: Complete the chart below based on the timeline cards.

<table>
<thead>
<tr>
<th>Date</th>
<th>ONE SENTENCE SUMMARY OF CARD</th>
<th>Letter on Card</th>
</tr>
</thead>
<tbody>
<tr>
<td>1930</td>
<td></td>
<td></td>
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<tr>
<td>1947</td>
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<tr>
<td>1955</td>
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<td>1965</td>
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<td>1965-1975</td>
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<td>1991</td>
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<td>1996-2000</td>
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<td>2002</td>
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<td>2006-2010</td>
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<td>2010</td>
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</tr>
<tr>
<td>2011</td>
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</tr>
</tbody>
</table>

NAME
DATE
### The Road to Treatment

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</thead>
<tbody>
<tr>
<td>1930</td>
<td>Dr. Pompe describes pathology of then unknown disease.</td>
<td>P</td>
</tr>
<tr>
<td>1947</td>
<td>Dr. Gerty Cory and husband describe glycogen storage diseases.</td>
<td>O</td>
</tr>
<tr>
<td>1955</td>
<td>De Duve discovers lysosomes.</td>
<td>M</td>
</tr>
<tr>
<td>1965</td>
<td>Hers discovers the enzyme alpha glucosidase, its optimal function at an acidic pH, and describes lysosomal storage diseases.</td>
<td>P</td>
</tr>
<tr>
<td>1965-1975</td>
<td>Attempts to extract enzyme from fungus and placenta and use enzyme replacement therapy unsuccessful. Enzyme absorbed by liver and did not reach the muscles.</td>
<td>E</td>
</tr>
<tr>
<td>1991</td>
<td>Modified enzyme for uptake by lysosome in human cell line.</td>
<td>D</td>
</tr>
<tr>
<td>1996-2000</td>
<td>Published use of transgenic rabbits in clinical trials to produce needed enzyme.</td>
<td>I</td>
</tr>
<tr>
<td>2001</td>
<td>Use of CHO cells to produce GAA enzyme and begin clinical trials.</td>
<td>S</td>
</tr>
<tr>
<td>2002</td>
<td>Genzyme acquires all groups working on various ERT.</td>
<td>E</td>
</tr>
<tr>
<td>2006-2010</td>
<td>First commercial ERT product available. Myozyme in 2006 for infant and juvenile forms; repackaged as Lumizyme in 2010 for late onset form.</td>
<td>A</td>
</tr>
<tr>
<td>2010</td>
<td>Enrollment begins for the first Pompe gene therapy trial.</td>
<td>S</td>
</tr>
<tr>
<td>2011</td>
<td>Clinical trials for chemical chaperone resume.</td>
<td>E</td>
</tr>
</tbody>
</table>