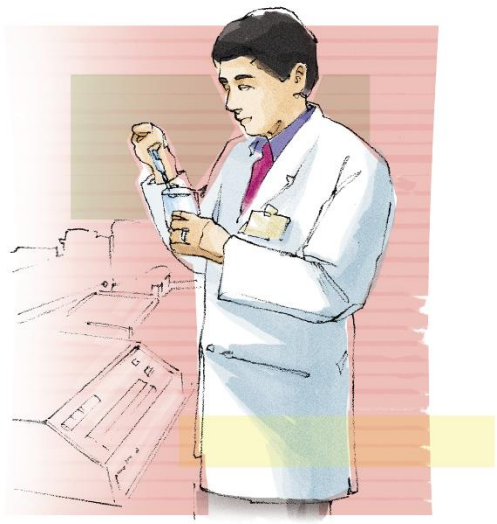
MEDICAL PROGRESS IN POMPE DISEASE



In 1932, JC Pompe, a Dutch pathologist, described a 7-month-old infant with a greatly enlarged heart who had died shortly after being admitted to the hospital. This was the first mention of the disorder that later became known as Pompe disease (more on the history of Dr. Pompe, refer to Attach 1). Thirty years later, a scientist in Belgium discovered that people with Pompe disease were missing an enzyme called **acid alpha-glucosidase,** or **acid maltase.** This enzyme is normally found inside a compartment of the cell called the **lysosome.** Like all enzymes, acid alpha-glucosidase has a specific job to do. It helps break down glycogen, a form of sugar that is stored in muscle cells and released when the body needs energy. Without the enzyme, glycogen builds up in the cells and weakens muscles throughout the body. Ever since the link between acid alpha -glucosidase and Pompe disease was discovered, researchers around the world have been searching for ways to replace the missing enzyme. Though we do not yet have a cure for Pompe disease, enzyme replacement therapy (ERT) provides patients with the enzyme (alpha-glucosidase) they are lacking. The replacement enzyme helps to break down glycogen and stops it building up abnormally in the cells.

ERT is a treatment intended to replace an enzyme that is missing or markedly deficient in people diagnosed with Pompe disease. Treatment with ERT is not a cure for Pompe disease; that is, it does not correct the underlying genetic defect.

Q: What is enzyme replacement therapy? How can it help people with Pompe disease?

A: People who have Pompe disease have little or none of a lysosomal enzyme known as acid alpha-glucosidase (GAA). Enzyme replacement therapy (ERT) works by replacing the missing or deficient GAA enzyme. Enzyme replacement has been a treatment approach used with other lysosomal storage disorders such as Type 1 Gaucher disease and Fabry disease

ERT is made using recombinant genetic technology, a process that allows scientists to alter the genetic make-up of an organism to produce human proteins, including enzymes. This process, occurs in three stages:

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Stage 1 - Growing Cells to Produce Human Enzyme:
Making ERT begins by inserting the human gene for the acid alpha-glucosidase (GAA) enzyme (the enzyme that is deficient in people with Pompe disease) into cell line.

Once the cells have the gene, they will begin to manufacture the human GAA enzyme. For this to happen, the cells are kept under special conditions in large tanks called bio-reactors. Each day, liquid is removed from the bioreactor, and the enzyme those cells have produced is collected for purification.

Stage 2- Enzyme Purification:
ERT must meet very high standards for purity and safety. The enzyme is purified using a process called column chromatography. Chromatography is a method of separating and isolating the parts of a mixture to remove the unwanted substances. As the enzyme moves through multiple chromatography columns, it becomes more purified.

Stage 3 - Filling and Finishing:
After purification, the enzyme is put into sterile glass vials. After the vials are filled, they are placed into a freeze dryer for about 48 hours. In the freeze dryer, water evaporates off the enzyme and leaves a cake-like dry substance. In this form, the enzyme is more stable. Multiple tests are conducted through the manufacturing process to help ensure - the treatment meets the highest standards. Each vial is inspected before it is released and made available to patients.

Making ERT is a complex process that takes several months and could only be accomplished after many years of development and testing.

ERT is given **intravenously** (injected directly into the bloodstream) so that it can reach the muscles and break down the glycogen that causes damage when it builds up in the cells. While ERT is not a cure for Pompe disease, it may slow the progression of muscle weakness and can help improve muscle function. ERT is a long-term treatment that is given at regular intervals. The dose is based on the patient's weight or age.

There are a number of next generation treatments available and under investigation. For more information, please refer to the Pompe Connections information section, the IPA website or contact your national patient organisations.

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Q: What is the process for developing new treatments?
A: The process of developing, testing and gaining approval for new treatments involves many critical steps and can take approximately ten years from pre-clinical development to drug approval. The following is a general description of the stages of drug development in the United States.

Pre-clinical Testing:
Pre-clinical testing is conducted to evaluate the safety of an investigational treatment before administration to humans and to assess the treatment's potential to impact a disease. In this stage, scientists test the treatment in a laboratory and through animal experiments in order to collect safety data and to evaluate biological activity against the targeted disease.

Clinical Trials:
Clinical trials are research studies that test how well new medical approaches work in people. Each study answers scientific questions and tries to find better ways to prevent, screen for, diagnose or treat a disease. Clinical trials may also compare a new treatment to a current treatment.

Every clinical trial has a protocol, or action plan, for conducting the trial. The plan describes what will be done in the study, how it will be conducted, and why each part of the study is necessary. Each study has its own rules about who can participate. Some studies need volunteers with a certain disease. Some need healthy people. Others want only men or only women.

In the United States, an independent committee of physicians, statisticians and members of the community must approve and monitor the protocol. They make sure that the risks are small and are worth the potential benefits.

Clinical trials have 4 phases:

Phase I Clinical Trial

Phase I clinical trials are done to test a new biomedical intervention for the first time in a small group of people (e.g. 20-80) to evaluate safety (e.g. to determine a safe dosage range and identify side effects). [2]

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Phase II Clinical Trial

Phase II clinical trials are done to study an intervention in a larger group of people (several hundred) to determine efficacy (that is, whether it works as intended) and to further evaluate its safety. [2]

Phase III Clinical Trial

Phase III studies are done to study the efficacy of an intervention in large groups of trial participants (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions (or to non-interventional standard care). Phase III studies are also used to monitor adverse effects and to collect information that will allow the intervention to be used safely. [2]

Phase IV Clinical Trial

Phase IV studies are done after an intervention has been marketed. These studies are designed to monitor the effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use over longer periods of time. [2]

Once the treatment is on the market, additional studies may be performed to evaluate treatment effectiveness and safety during routine use or to assess the treatment in new segments of the patient population.[1]

Q: What are the benefits and risks of participating in a clinical trial?
A: For rare disorders like Pompe disease, taking part in a research study may give patients access to experimental treatments that could improve, save, or extend their lives. Expanded access programs could provide treatment to patients with more severe disease who might not otherwise qualify for a clinical trial. Randomized studies that enroll larger numbers of patients (but assign them to different groups to compare treatments) could give people with less severe disease the chance to begin treatment before muscle weakness has progressed beyond mild disability. Because your health is closely monitored,

[1] Understanding Clinical Trials: http://clinicaltrials.gov/ct2/info/understand

[2] https://www.australianclinicaltrials.gov.au/what-clinical-trial/phases-clinical-trials

enrolling in a clinical trial also gives you access to medical care from experts in Pompe disease.

Before deciding to participate in a clinical trial, it is important to weigh the possible risks as well as the benefits. Read the protocol and talk with your healthcare provider (or your child's healthcare provider) to get a better idea of your chances for being accepted into the clinical trial and how long it might be before you could start treatment. Think about how taking part in the trial could affect your health, your family, your job, and anything else that may matter to you. Be sure to ask what kind of support would be available to you if you decide to enroll. Also be sure to ask if any of your expenses would be covered if you have to travel any distance to the study site.

Q: How can I find out about clinical trials that are going on in my area? Please see the More information section and the Gene Therapy Pompe Connections brochure.

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