19. Drug Treatment Trials

The science behind the Progeria clinical drug trials

There are three drugs currently being studied in treatment trials for Progeria:

1) Farnesyltransferase Inhibitor (FTI)

2) A statin called Pravastatin

3) A bisphosphonate called Zoledronic Acid

All of these drugs work in different places along a common pathway that we hope will improve disease symptoms in Progeria.

The Progeria gene discovery opened the floodgates for research into Progeria that has led to clinical drug trials.

> How did we get from gene discovery to drug therapy for children with Progeria?

Finding the gene for Progeria was the key element to this entire avenue of exploration. This gene is called LMNA, and it normally encodes a protein called prelamin A (this protein is further processed and becomes lamin A). Children with Progeria have a mutation in LMNA which leads to the production of an abnormal form of prelamin A called "progerin." Many years' worth of basic research on prelamin A and lamin A gave us the ability to understand that the drugs administered in this trial may prevent progerin from damaging cells and thus reduce the severity of the disease Progeria. Since 2003, research has focused on systematically examining this possibility, first testing these drugs on Progeria cells and then on Progeria mice.

> How will the drugs work in Progeria?

The protein that we believe is responsible for Progeria is called progerin. In order to block normal cell function and cause Progeria, a molecule called a "farnesyl group" must be attached to the progerin protein. There are a series of steps necessary for a cell to make the farnesyl group, and place it onto the progerin protein. Each of the three drugs in this protocol target a different step in that process. Pravastatin, Zoledronic Acid, and Lonafarnib act by blocking (inhibiting) the production or the attachment of the farnesyl group onto progerin (see figure 1). The current clinical trial will evaluate whether the three drugs administered in this trial can effectively block this farnesyl group attachment to progerin with a resulting reduction in disease severity. Since all three drugs work at a different point in the pathway that leads to the production of the protein that is believed to cause the disease, their combination provides the opportunity to amplify the efficacy over the drugs used individually.

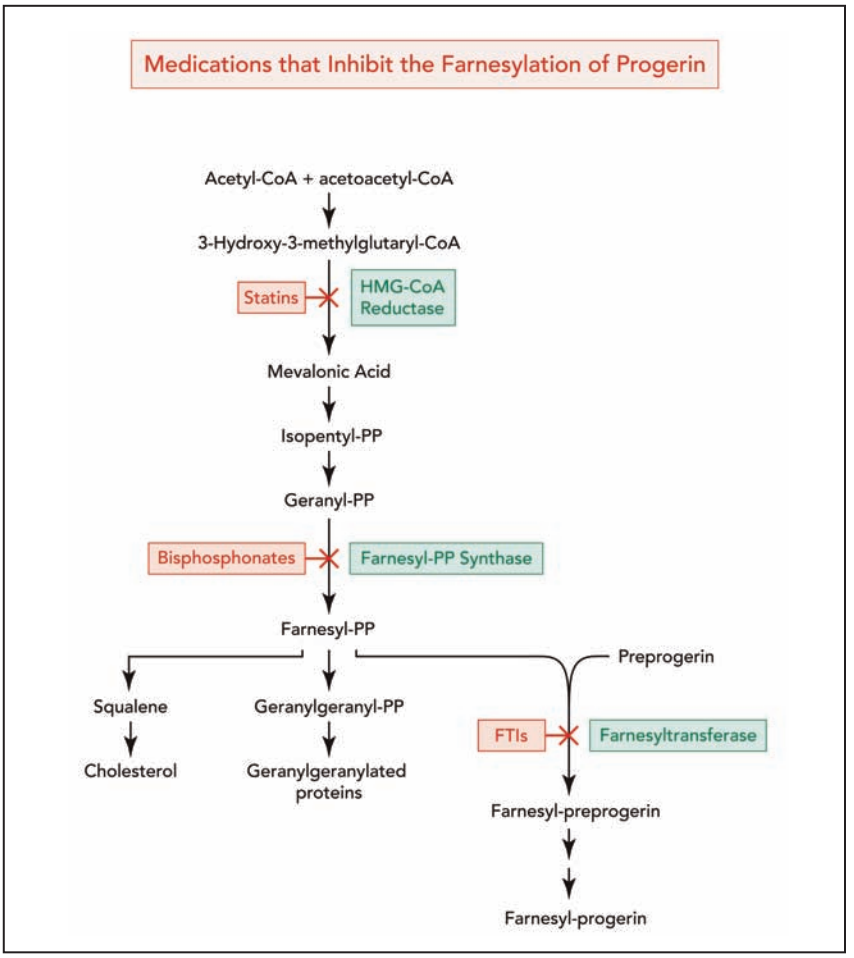


Figure 1

Trial medications at a glance

> What is Lonafarnib?

Lonafarnib is a Farnesyltransferase Inhibitor (FTI). FTIs are a class of drugs that inhibit an enzyme that is required to attach the farnesyl group to proteins. Because many proteins that regulate cancer cell growth require farnesylation, drug companies have been developing and testing these drugs to evaluate their effect on cancer cells. Progeria cells are not cancer cells, but progerin is a protein that shares this need to be farnesylated in order to fully function. The farnesylated form of progerin leads to some of the cellular damage observed in Progeria. FTIs prevent this farnesyl group attachment, and were therefore evaluated as a possible therapy for Progeria. Lonafarnib is not approved by the U.S. Food & Drug Administration, and can only be given through approved clinical trials.

All three drugs affect progerin protein in a similar manner. The hope is that they will make the progerin less toxic to cells.

> What is Pravastatin?

Pravastatin (marketed as Pravachol or Selektine) is a member of the drug class of statins. It is usually used for lowering cholesterol and preventing cardiovascular disease. Children with Progeria do not usually have high cholesterol. Pravastatin is being used for Progeria because it also has an effect on blocking the production of the farnesyl molecule that is needed for progerin to create disease in progeria. The U.S. Food & Drug Administration approved Pravastatin for sale in the United States for the first time on April 2006. It comes as a tablet that can be crushed into food for administration. It is usually given once daily.

> What is Zoledronic Acid?

Zoledronic Acid or Zoledronate (marketed under the trade names Zometa and Reclast) is a bisphosphonate. This agent is used to improve bone density in women with osteoporosis, and to prevent skeletal fractures in people suffering from some forms of cancer. It has been used in children with a bone disease called osteogenesis imperfecta, and for other bone problems. Children with Progeria can have low bone density and Zoledronic Acid may, over time, help with that problem. It also has an effect on blocking the production of the farnesyl molecule that is needed for progerin to create disease in Progeria. The U.S. Food & Drug Administration approved Zoledronic Acid for sale in the United States for the first time on August 2001 for the treatment of hypercalcemia of malignancy. It is administered intravenously several times per year.

> Treating cells in the laboratory: FTI improves Progeria in cell cultures

The nucleus (plural nuclei) is the structure at the center of each cell that contains DNA (the genes). Unlike the round nuclei from normal cells, Progeria cells have abnormally shaped nuclei. These abnormally shaped nuclei with multiple "lobes" can look like a cluster of grapes or bubbles (see figure 2).

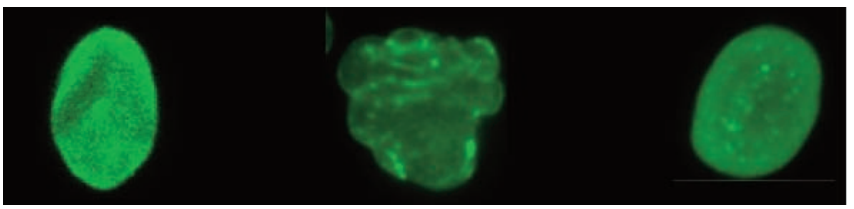
The gene LMNA normally produces a protein called prelamin A. When this gene is mutated, as occurs in Progeria, it causes abnormal cell shape and function that results in the clinical problems that are characteristic of this disease. Prelamin A requires a molecule attached to the end of it called a farnesyl group. It needs this farnesyl molecule to anchor the protein to the nuclear membrane. In normal cells, this farnesyl group is removed, but this step does not take place in Progeria because of the mutation and the progerin protein therefore remains stuck in the membrane, where it does its damage. FTIs function by not allowing the farnesyl molecule to attach onto progerin in the first place. In the laboratory, treating Progeria cells with FTIs restored their nuclei to a normal appearance (see figure 2).

> Training mouse models of Progeria: FTI, statins, and bisphosphonates improve Progeria in mouse models of disease

Whenever possible, new medications are given to mice before they are considered for humans. These mice are observed for side effects and toxicity effects, as well as for changes that may indicate the medicines would improve disease in people.

PRF-funded researchers at the University of California in Los Angeles developed two separate mouse models of Progeria that mimic many aspects of the human disease. They treated these mice with FTIs at a young age

Figure 2



Capell et al., PNAS, 2005

Normal Skin Cell | Progeria Skin Cell | Progeria Skin Cell Treated with FTI

before the onset of symptoms. Both types of Progeria mice received FTIs in their water and were followed for several months. FTI treatment dramatically prevented the development of disease characteristics. FTI reduced bone fractures, delayed the onset of the disease, helped with weight gain, and increased life spans. There were minimal side effects at the dose of drug that was given. It is not clear whether these two UCLA Progeria mice develop heart (vascular) disease. In a separate study, researchers at the National Institutes of Health created a mouse model of Progeria that does develop cardiovascular disease. They began daily treatments with FTIs at a young age before the onset of symptoms, and found that the heart disease was improved in treated mice when compared to untreated mice. Based on these studies, a first-ever clinical trial was undertaken in which a single FTI was given to children with Progeria.

Subsequently, researchers in Spain also treated a Progeria-like mouse model with Pravastatin and Zoledronic Acid. The mice experienced longer, healthier lives with more body fat and improved hair and bones. This experiment provided the scientific evidence needed for the development of clinical trials using these drugs in children with Progeria, either alone or in combination with an FTI.

> Reliable measures of disease improvement are essential for the clinical trials

Although studies with cells and mice are extremely encouraging, as with any experimental treatment, we must have measures of disease improvement that we can rely on to tell us whether the drugs are helping the children, within the two-year time frame of the trials. This means that careful off-drug measures need to be taken prior to the start of drug treatment, so that we will be able to measure changes while on this drug. To this end, careful analysis of baseline clinical status of children with Progeria is performed, using their medical charts, the weighing-in program, and data from pre-drug studies performed at the trial site. The baseline measurements can then be compared to measurements taken periodically while on the treatment drug, so that we can determine as precisely as possible the exact impact of the treatment on the children.

Progeria clinical drug trials

Over the past 10 years, Progeria has gone from obscurity, to gene finding, to first-ever treatment trials. There are currently two clinical drug trials ongoing for Progeria. This section will provide information on clinical trials in general, and where the Progeria clinical trials stand today. Websites where you can find more detailed information are provided.

Thanks to the 2003 Progeria gene discovery, studies in the years that followed paved the way for The Progeria Research Foundation to fund and co-coordinate a first-ever clinical trial for children with Progeria at Children's Hospital Boston, USA. Twenty-eight children from 15 different countries, speaking 9 different languages, flew to Boston every 4 months for a period of 2.5 years, from May 2007 through December 2009. The trial drug was an FTI. FTIs have shown great promise in the laboratory and in animal models of Progeria. Results will be announced in 2010.

Since 2007, two additional treatment trials for Progeria have begun. A trial in France was initiated in 2008 and is treating children with the drugs Pravastatin and Zoledronic Acid.

The third trial, which began in 2009 and is taking place at Children's Hospital Boston, is treating children with all three drugs: FTI, Pravastatin, and Zoledronic Acid. Forty-five children from 24 different countries, speaking 17 different languages, fly to Boston every 6 months for testing and treatment, for a period of 2 years.

> Clinical Trials 101

There is a vast amount of information about clinical trials available to you through the world wide web. Learning about clinical trials is very important, so that each family can decide whether to participate in any given study.

All clinical trials are considered research and are completely voluntary. The basic information for this section is derived from www.clinicaltrials.gov and modified for the Progeria clinical trials.

> What is a clinical trial?

Broadly defined, a clinical trial is a health-related research study in which either or both health observation or intervention may be applied. For Progeria, we have embarked on research studies with both goals in mind. We study as many things as possible before, during, and after children are taking trial medications. Studying the "natural history" of Progeria helps

us to define what is happening to the children, and develop treatment strategies for them in our efforts towards improving quality and longevity of their lives.

> Why participate in a clinical trial?

Participants in clinical trials can play a more active role in their own health care, gain access to new research treatments before they are widely available, and help others by contributing to medical research.

> Who can participate in a clinical trial?

All clinical trials have guidelines about who can participate. Using inclusion/exclusion criteria is an important principle of medical research that helps to produce reliable results. The factors that allow someone to participate in a clinical trial are called "inclusion criteria" and those that disallow someone from participating are called "exclusion criteria". For some of the Progeria trials, these criteria have included genetic confirmation of Progeria, age, record of weight gain over time, liver and kidney health status, previous treatment history, and other medical conditions. Before joining a clinical trial, a participant must qualify for the study. Inclusion and exclusion criteria are never used to reject people personally. Instead, the criteria are used to identify appropriate participants and keep them safe, since there is always a risk/benefit ratio to think about in research. The criteria help ensure that researchers will be able to answer the questions they plan to study.

> What happens during a clinical trial?

The clinical trial team includes many types of researchers, such as doctors, nurses, therapists, statisticians, coordinators, laboratory technicians, and other health care professionals. They check the health of the participant at the beginning of the trial, give specific instructions for participating in the trial, monitor the participant carefully during the trial, and stay in touch after the trial is completed.

For the Progeria trials, each patient family periodically flies to the trial site for testing and drug supply. There is also some monitoring at home, so that any toxicities can be addressed immediately.

> What is informed consent?

Informed consent is the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is also a continuing process throughout the study to provide information for participants.

To help someone decide whether or not to participate, the investigators involved in the trial explain the details of the study. The information is provided in the primary language of each family to ensure clear communication. Translation assistance is provided. Then the research team provides an informed consent document that includes details about the study, such as its purpose, duration, required procedures, and key contacts. Risks and potential benefits are explained in the informed consent document. The participant, or parents or legal guardians, then decide whether or not to sign the document. Children able to understand the major issues are usually asked to sign a form after the trial is explained to them in age-appropriate terms. For a child under age 18, this is called assent. Informed consent is not a contract, and the participant may withdraw from the trial at any time.

> What are the benefits and risks of participating in a clinical trial?

Benefits: Clinical trials that are well-designed and well-executed are the best approach for eligible participants to:

- Play an active role in their own health care
- Gain access to new research treatments before they are widely available
- Obtain expert medical care at leading health care facilities during the trial
- Help others by contributing to medical research

Risks: There are always risks to clinical trials:

- There are almost always side effects to experimental treatment. These are carefully monitored, but since the treatment drug has either never been given to children with Progeria, or the drug has not been given to many people in the world, we don't know all of the side effects that may occur. Side effects, especially newly identified side effects, are reported to participant families during the trial, whereas trial results about benefits cannot be reported until the trial has ended.
- The experimental treatment may not be effective for the participant. It is the clinical trial itself that asks whether the treatments are beneficial to children with Progeria. We do not know the answer until we finish the trial and analyze all of the data.
- The trial requires time and effort on the part of each family, including trips to the study site, more treatments, hospital stays or complex dosage requirements. Each family is a partner in the trial process.

It takes tremendous courage to travel far from home, to meet with people who often do not speak your language, and to entrust the care of your child to them.

> Does a participant continue to work with a home primary health care provider while in a trial?

Yes. The clinical trials provide short-term treatments related to a designated illness or condition, but do not provide extended or complete primary health care. Testing is focused on changes that may occur on drug. Home health care is focused on general health of the child. In addition, by having the health care provider work with the research team, the participant can ensure that other medications or treatments will not conflict with the trial medications.

> Can a participant leave a clinical trial after it has begun?

Yes. A participant can leave a clinical trial at any time. When deciding whether to withdraw from the trial, the participant should discuss it with the research team, to ensure that stopping the drugs is done safely. The drugs will usually need to be returned; the cost will be paid by the people running the trial, not the family.

> Where did the ideas for the trials come from?

Ideas for clinical trials came from researchers. (See *The science behind the Progeria clinical drug trials* on page 19.1 of this section.) After researchers test new therapies in the laboratory and in animal studies (called preclinical studies), the experimental treatments with the most promising laboratory results move into clinical trials. It is important to remember that, although treatments can look great in the laboratory, we will only know if and how well they work in patients by giving the treatments and then looking carefully at the results from the clinical trials.

> Who sponsors clinical trials?

Clinical trials can be sponsored or funded by a variety of organizations or individuals. In the United States, Progeria treatment trials have been funded by The Progeria Research Foundation, by the National Institutes of Health (NIH), Children's Hospital Boston, and Dana-Farber Cancer Institute. There is also a treatment trial ongoing in France for which European resources are used.

> What is a protocol?

A protocol is a study plan on which all clinical trials are based. The plan is carefully designed to safeguard the health of the participants as well as answer specific research questions. A protocol describes what types of people may participate in the trial; the schedule of tests, procedures, medications, and dosages; and the length of the study. While in a clinical trial, participants following a protocol are seen regularly by the research staff to monitor their health and to determine the safety and effectiveness of their treatment.

> What types of clinical trials are the Progeria trials?

Phase I trials determine drug dosage and toxicity in a small number of people.

Phase II trials determine both drug toxicity and the effectiveness of drugs on a disease in a small population.

Phase III trials determine the activity of a treatment by giving the real drugs to half the patients and placebo (sugar pills) or other therapy to the other half. These trials usually include a large number of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the experimental drug or treatment to be used safely.

Phase IV trials are post-marketing studies that delineate additional information including the drug's risks, benefits, and optimal use.

To date, all of the Progeria trials are Phase II trials, where both toxicity and effect on disease progression are studied. They are also "open label" trials, in which all of the children receive the same drug treatment (none of the participants receive placebo).