The Progeria Research Foundation

Update: Farnesyltransferase Inhibitors (FTIs) as Potential Drug Therapy for Children with Progeria:

Recent Research Findings and Frequently Asked Questions

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From Leslie B. Gordon, MD, PhD, Medical Director

Several researchers have published studies that support the initiation of a first-ever drug treatment for children with Progeria. We're proud that PRF has funded or participated in many of these studies, and we are excited about the implications they may have for children with Progeria. Now PRF is preparing for a clinical trial using farnesyltransferase inhibitors (FTIs) to treat children with Progeria.

In this document, we have addressed many frequently asked questions that will help you to understand FTI treatment for Progeria and how the research community has taken steps to test its safety and potential beneficial effects for the children. This information sheet explains why FTIs are a promising treatment for Progeria.

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TOPICS

The FTI/Progeria Relationship

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 FTIs may be a viable treatment for Progeria. During the past three years, research has focused on systematically examining this possibility, first testing FTIs on Progeria cells and then on Progeria mice.

What are FTIs?
Farnesyltransferase inhibitors, or FTIs, are a class of drugs that can reverse an abnormality in Progeria cells in the laboratory. The nucleus (plural nuclei) is the structure at the center of each cell that contains DNA. Unlike the round nuclei from normal cells, Progeria cells have abnormally shaped nuclei. These abnormally shaped nuclei with multiple "lobes" can even look like a cluster of grapes or bubbles. In the laboratory, treating Progeria cells with FTIs restored their nuclei to a normal appearance, as recently reported in five journal articles (1-5) and reviewed in another (6). The finding that FTIs efficiently reverse this disease-related abnormal shape at the cellular level has provided compelling proof-of-principle that these drugs may be effective in improving disease in children with Progeria. Further optimism has come from recent studies with Progeria mice whose disease symptoms were prevented by FTI treatment (7,8).

How will they 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. FTIs act by blocking (inhibiting) the attachment of the farnesyl group onto progerin. We believe that if the FTI drug can effectively block this farnesyl group attachment in children with Progeria, then progerin may be "paralyzed" and Progeria may be improved.

What improvements will FTI treatment bring to the children?
Although FTI studies with cells and mice are extremely encouraging, as with any experimental treatment, we will not know how FTIs will affect disease in children with Progeria until we implement treatment. However, we are extremely hopeful about our upcoming clinical studies with FTIs and we are making sure that we recognize and can objectively measure the disease characteristics that may change with treatment. To this end, we have performed careful analysis on baseline clinical status of children with Progeria, using both their medical charts and data from the ongoing NIH natural history study program. We will compare these baseline measurements, obtained prior to drug treatment, to measurements made upon FTI treatment so that we determine as precisely as possible the exact impact of the treatment on the children.

How close are we to treating Progeria children with FTI?
We plan to have a clinical trial up and running in the near future, and are working every day towards that goal. There are the three important things that Progeria families should do now in order to optimize the chance of being included in the clinical trial:

- Genetic Diagnosis of Progeria: This test can be done at no cost to you through the Progeria Research Foundation Diagnostics Program, or we will accept a copy of the genetics report from another facility.

- Medical and Health Records: The PRF Medical and Research Database Program collects the medical records of the children from each of their health care providers. These records provide essential health information for us to evaluate data such as growth rates and cardiac status, so that we can best understand whether the clinical trial option is right for each child.

- The Weighing-In Program: We have discovered that each child with Progeria has a consistent and slow weight gain. We plan to use this data to track baseline weight gain, and potentially to track improvements with treatment in the future. We send families a scale, log book, and instructions so that they can report weekly weights directly to us.

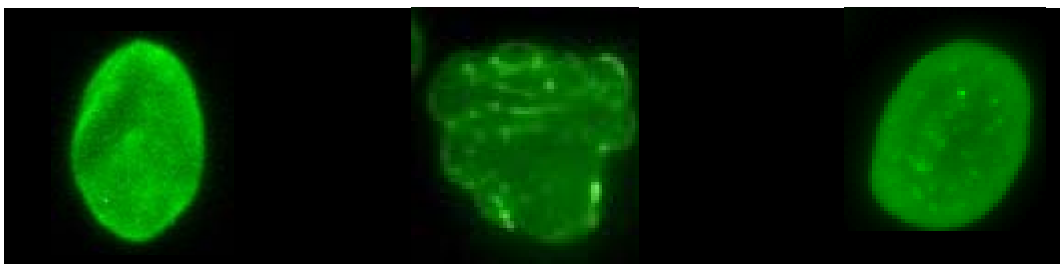
Basic Principles of FTIs

Can you explain the basic principle behind possible FTI treatment in Progeria?

- Treating Cells in the Laboratory; FTI Improves Progeria in Cell Cultures:

The gene *LMNA* normally produces a protein called prelamin A. When this gene mutates, it causes Progeria. Prelamin A has a molecule attached to the end of it called a farnesyl group. It needs this farnesyl molecule to anchor the protein to the nuclear rim. In normal cells, this farnesyl group is removed, but this step does not take place in Progeria and the progerin protein remains attached to the rim, where it appears the progerin does its damage. FTIs function by not allowing the farnesyl molecule to attach onto progerin in the first place, thus "neutralizing" the damaging properties of progerin and restoring the nucleus to a more normal state.

Capell et al., PNAS, 2005



Normal Skin Cell **Progeria Skin Cell** **Progeria Skin Cell Treated with FTI**

- Treating Mouse Models of Progeria; FTI Improves 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 have treated these mice with FTIs at a young age before the onset of symptoms. Both types of Progeria mice received FTIs in their water and followed for several months. FTI treatment dramatically prevented the development of disease characteristics (7,8). 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 will develop heart (vascular) disease. In a separate study, researchers at the National Institutes of Health are testing the effects of FTI on vascular disease in a different mouse model (9). We are looking forward to those results in the coming year.

FTIs are currently being used to treat some types of cancer. Is there a connection between Progeria and cancer?

No, Progeria is not cancer; it is an entirely distinct disease. However, there are hundreds of molecules, both in normal daily cellular functioning and in some forms of cancer that use the farnesyl group to do their jobs. Scientists developed the concept that we might be able to fight cancer by blocking the attachment of the farnesyl group to certain “cancer-causing” proteins (not progerin, but other proteins) with FTIs. This is why drug companies have spent the last 10 years and millions of dollars developing FTIs that they hope will be effective for cancer, bringing them through toxicity testing all the way to clinical trials in adults with various types of cancer and in children with brain tumors.

Is there risk that the child treated with FTI could develop cancer?

There is no evidence that cancer would be *caused* by this treatment. There has been some speculation that Progeria children may have a higher risk of cancer due to cellular damage. Therefore, if they live longer, cancer could come to clinical significance. However, this is extremely speculative and it should be stressed that there is no direct evidence for this.

How Will the Treatment Work?

How are FTIs given?
They are usually given to people in pill form, twice per day. Parents of young children will be able to open the pill and mix the treatment with food.

What are the side effects of FTI?
To date the only experience with the FTI proposed for the Progeria drug therapy trial is in a series of adults with a variety of tumors, and in children with terminal brain cancer. All of these patients had previously been treated with surgery, radiation therapy, and chemotherapy for their cancer. As such, it was difficult to know with certainty the cause of all side effects when experimental drugs were administered. The two most common side effects associated with the FTI in children taking the pills twice a day (as will be performed for children with Progeria) were diarrhea and changes in certain blood tests of liver function. The diarrhea was easily prevented by starting an anti-diarrhea medicine first, while the changes in the liver function tests never caused any problems and resolved. Like most drugs, there is also the possibility of rare or unknown side effects that have not yet been identified. For this reason, patients on this medicine will be followed very carefully and the dose of the medicine modified if any new or unexpected side effects arise.

Are there risks associated with FTI treatment?
Nothing will give us 100% assurance of safety, but the prior work done with these drugs in mouse models and in people (both adults and children) without Progeria makes this a great candidate treatment. Clinical testing in cancer studies has shown us that these drugs can be used in adults and children with tolerable side effects as noted above. The known side effects will be explained in detail to each family as they consider entering the clinical trial. However, while unlikely, there may be potentially new side effects with FTI treatment in Progeria. This is why the decision to move into treatment is so difficult for everyone, especially children with Progeria and their families, who ultimately make highly personal treatment decisions for themselves.

Our responsibility and that of the research community is to do everything we can to fully test the drugs in the laboratory, and fully inform parents before implementing an experimental treatment on any child with Progeria.

If you have questions, please contact The Progeria Research Foundation at info@progeriaresearch.org **or phone us at 978-535-2594.**

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