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Progranulin Clinical Trials:

Studies Targeting the GRN gene are at the Forefront of Researching a Treatment for FTD

It is an extraordinary time in the research arena for frontotemporal degeneration (FTD). Research has reached the point where new **clinical trials** are specifically targeting certain types of these disorders caused by a mutation, or variant, in a gene. At the forefront are studies related to **progranulin**.

Progranulin is a protein that plays an important role in maintaining normal functions in the central nervous system. People with a *GRN* variant have lower than normal progranulin levels.

During the past two years, four studies targeting the *GRN* gene have advanced to the clinical trial stage and are recruiting volunteers. Each study has its own guidelines on who is eligible, what the procedures are, how long the study will last, and what the anticipated outcomes may be.

"All the people who participated in research over the years, all the clinicians who so diligently cared for individuals and worked to understand the disease, and all of the companies that devoted enormous efforts to developing therapeutics, it's all coming together now with these progranulin trials," said Laura Mitic, Ph.D., Chief Scientific Officer for Bluefield Project to Cure Frontotemporal Degeneration.

"This is an incredible achievement for the community, and we are so grateful to see these promising approaches now being tested in the clinic," she noted.

These clinical trials seek to determine the safety and effectiveness of a potential new medical treatment in humans who have tested positive for mutations in the *GRN* gene. The trials come after **pre-clinical** studies have tested the experimental drugs in the test tube or in animals.

Researchers follow specific protocols when designing and administering the studies. Their work is overseen by **institutional review boards** (IRB), which are independent committees that review the methods proposed for research that involves humans to ensure that they are ethical. The IRB protects the rights and welfare of the people recruited to participate, and it has the authority to approve, disapprove, monitor, and require modifications.

TYPES of TRIALS

Current clinical trials targeting the *GRN* gene focus on two therapeutic approaches: replacing the defective

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*Please note that this glossary is available to help you understand the scientific terms used in this article. Glossary terms are shown in **bold** the first time they appear.*

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progranulin gene by gene therapy or replacing the missing progranulin protein by injecting an engineered progranulin molecule. Additionally, other companies are advancing therapeutic approaches that use small molecules or antisense oligonucleotides.

According to a report by McKinsey & Company, there is the potential for gene therapy to cure diseases associated with faulty or missing genes. Clinical use of gene therapies to treat diseases, such as FTD, is increasing. Based on the number of gene therapy treatments in early development and success of these products, the U.S. Food and Drug Administration (FDA) estimates that by 2025 it will be approving between 10 and 20 gene therapies each year.

Currently, for FTD, there are two gene therapy clinical trials that focus on the progranulin gene (*GRN*) and several others in the preclinical stage. These are the PROCLAIM study, sponsored by Prevail Therapeutics Inc., and the up-liFT-D study, sponsored by Passage Bio Inc. Both are in **Phase** 1/2.

Phase 1 and Phase 2 are often combined to accelerate the time of drug development, reduce costs, and in the case of a rare disease like FTD, recruit enough volunteers. Phases 1 and 2 involve fewer participants, while Phase 3 studies require a larger group of people and last longer.

Gene therapy is a single dose of the *GRN* replacement material. Follow-up visits with tests are needed to monitor participants and track efficacy.

Large molecule, or biologics, are medications that target specific genotypes or protein receptors. They may use antibodies and have to be injected.

For FTD there are two studies of the large molecule type. INFRONT-3, sponsored by Alector Inc., is a Phase 3 clinical trial to see if increasing progranulin levels

after treatment with AL001 will delay the onset of symptoms or slow disease progression when compared to a placebo. AL001 is an antibody that increases circulating progranulin. The intervention is given by intravenous (IV) infusion every four weeks.

Also working in the area of large molecule treatments is Denali Therapeutics Inc., in collaboration with Takeda. They are testing an engineered transport vehicle for the progranulin molecule that is delivered intravenously (IV) and carried into the brain via Denali's Protein Transport Vehicle (PTV) technology. Denali recently dosed its first volunteer in a Phase 1/2 trial.

A handful of companies are working on small molecule or antisense oligonucleotide treatments, but there are no clinical trials ready to recruit volunteers to test these in humans yet.

"Small molecule treatments are generally orally available. The hope is that you could take a pill," Dr. Mitic said. Antisense oligonucleotide approaches are interesting from a regulatory perspective because there is the potential to get to human trials quickly.

"As far as what's in human trials for progranulin-FTD, it's large molecule and gene therapy right now. But we hope that soon we'll see the small molecule and antisense oligonucleotide options reach clinical trials, as well," Dr. Mitic said.

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TRIAL CONSIDERATIONS

Individuals seeking to participate in therapeutic clinical trials should talk with their physician and think carefully about every aspect of a clinical trial they are considering. Each trial is designed differently with its own protocols. Information is presented in the study materials and during the informed consent process when researchers provide the details.

For studies involving gene therapy, once you participate in one study you may not be eligible for any future studies. Be sure to learn about all of your options before making a decision.

Here are some questions to ask when you are considering participating in a therapeutic clinical trial:

- What is the purpose of the study?
- What are the potential risks of participating?
- What are the potential benefits of participating?
- How will my identifying information and privacy be protected?
- What kinds of treatment, procedures, or tests are involved?
- Will I receive the active treatment?
- How long will the study last?
- Will I find out the results of the study?
- Do I need a care partner to assist me if I participate?
- Will I need to travel?
- Are there any costs associated with participating?
- Will I be compensated for the study?
- If I experience a problem in the trial, what support will I receive?
- Can I drop out of the study?
- Will participating in this study affect whether I can participate in future studies?
- Is there a different trial that may be a better fit for me?

There are reasons one person may select to enroll in one study and another person would choose differently. These reasons are as different as the people.

Considerations include:

- Eligibility
- Site location and ability to travel
- Risk tolerance
- Durability

Eligibility Requirements

Clinical trials have inclusion criteria and exclusion criteria. These are guidelines for who can and cannot participate. They differ from study to study and may cover factors such as age and diagnosis as well as existing and past medical conditions and drugs.

Even though you are on medications, you may still be able to enroll as long as you have been stable for a set timeframe.

Ultimately, the **principal investigator** determines whether someone can enroll.

Ability to Travel

Logistics of traveling are important to consider when choosing whether to participate in a clinical trial. All of these progranulin studies require in-person visits for treatments and tests. For trials that require infusions, this means traveling to receive the intervention at a regular interval. If you don't live near a study site, that can be challenging for multiple reasons, noted Dr. Mitic.

"Unlike large molecule treatments that require repeated infusions, for gene therapy, since it's just a single dose, you go to the site once to have it administered and that's it," she said. "For either type [gene therapy or large molecule], however, you still have to return to a

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study site regularly to be evaluated and see whether the investigational drug is having an impact."

Evaluations may include a blood draw, a lumbar puncture, an MRI, cognitive testing, or neuropsychiatric testing. It depends on what the trial requires. They may also take several days to complete.

Additionally, many FTD studies require a study partner to accompany the participant. Depending on the stage of the disease, a caregiver may be necessary.

"The field is working hard to make remote aspects of trials more feasible," Dr. Mitic said. "But the reality is that most aspects of clinical trials are linked to being physically able to be at the site for all of the tests that need to be done and for the administration of the investigational agent."

Many studies offer a travel allowance to cover these expenses.

Risk tolerance

Risk tolerance is important to consider based on the phase of the trial, Dr. Mitic said. Those risks change depending on whether it is in Phase 1, 2, or 3. In a Phase 3 trial, people have already received the treatment so more is known about any potential risks.

Progranulin "gene therapy trials are first-in-human studies, although the concept is not new, and these viruses have been tested extensively in animal models" Dr. Mitic explained.

More needs to be done to understand the long-term risks associated with gene therapy in many diseases. Even as fast as progress is being made, much is still unknown about this type of treatment.

Durability

There is something called durability in the gene therapy field, in particular, she said. It's the durability of response that is not known yet. In other types of gene therapy, it has been observed for more than a decade, and in some cases up to two decades. So these can be very long-lasting interventions.

"People who are interested in a particular study can discuss it with their doctor, who should really be able to advise them as to whether it's a good fit," Dr. Mitic said.

GENETIC TESTING

To be eligible for the progranulin studies, as well as clinical trials for other FTD-causing genes, such as *MAPT*, *C9orf72*, and *FUS*, interested individuals need to know their genetic status. To help identify patients for these trials, drug companies have **sponsored genetic testing programs** (SGTPs).

SGTPs offer genetic testing at no charge to those who meet certain criteria. This enables them to be tested — and possibly understand the genetic cause of their FTD if there is one — no matter their economic status. Sponsors provide financial support for the testing and often receive de-identified variant and clinical information.

For persons diagnosed with FTD, learning if your disease is caused by a mutation in a specific gene has benefits for you, your family, and science. This is true whether your test results are positive or negative and whether you choose to participate in research.

Some people choose to undergo genetic testing because they want to contribute to something bigger.

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Many who have a dominantly inherited disease say that part of the reason they participate in clinical trials is for the benefit of younger people in their family — their kids, grandkids, nieces, and nephews.

Additional reasons people say they have genetic testing done include:

- to make informed decisions related to their medical care
- to know if they qualify for a clinical trial or therapy
- to understand any genetic risks for their family
- to contribute to research and leave this world better
- their physician suggested genetic testing

Knowing your genetic status now may be beneficial in the future for clinical trials or treatments. For example, someone who tests positive for the progranulin variant may decide not to participate in a study now because the nearest site is far away, thus requiring a lot of travel which would be a burden to them and their family. However, a year or two later there could be a new phase for the trial with a nearby location. The person's physician, also knowing their genetic status, could then contact them with the information to reassess whether they are interested in participating.

In addition, people who are members of the FTD Disorders Registry can note their genetic status in their accounts. This will provide scientists with more information about these diseases and allow the Registry to send emails specifically related to their disease type.

Last year the FTD Disorders Registry provided an in-depth look at SGTPs, discussing what they are and how the available FTD programs differ. *Read the NEWS article with an updated chart for 2022 here.*

FUTURE

Getting an investigational drug approved is very complicated. It is extra challenging for neurodegeneration treatments because they must show a change in brain function via a rating scale, which can be difficult, Dr. Mitic said.

The first trials help to provide a roadmap for regulatory approval, she explained. Once the door is opened and trials are enrolling, an infrastructure is created to support these kinds of trials. Procedures are established for working with the FDA and other regulatory bodies, which makes it easier for the next ones.

"We are looking at genetic forms of FTD right now, and progranulin is early out of the gate. But C9 [*C9orf72*] and tau trials are enrolling now as well," she noted. "I know it is really frustrating for the FTD community because obviously there are more people who are diagnosed with **sporadic FTD** [non-genetic] than have the **familial** [genetic] forms of FTD. The trials in these more tractable groups — the genetic forms — are leading the way. But there are other drugs that researchers are trying in sporadic populations, so those will come."

For a rare disease, there is a great amount of commercial interest in the FTD space, which gives hope to all who are affected by this rare disease that currently has no treatments or cure. However, all of these therapies are still experimental. Only after the trials are completed will the results determine whether the FDA will approve a treatment.

Meanwhile, the opportunities to participate in research are constantly changing, and clinical trials need volunteers. If these trials do not meet their

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enrollment numbers, it could not only prevent them from succeeding but could hinder the development of additional studies in the future.

"The more we can encourage people to consider participating in any aspect of research, the more we should because in a rare disease we all have to come together to work on these problems," Dr. Mitic said.

"In just the 13 years that I've been involved in this field, it is extraordinary the speed at which we've made progress, and that's due to the community working together," she said. "We are getting there. That is the exciting part."

RESOURCES

Learn More About Genetics in FTD (webpage)

Understand the Genetics of FTD (pdf)

Who Should Get Genetic Testing & Why? (pdf)

Understand Genetic Testing (pdf)

Understand Genetic Counseling (pdf)

Learn More About Sponsored Genetic Testing (article)

View Sponsored Genetic Testing Chart 2022

Watch Perspectives in Research Webinar Series

View Recruiting Progranulin Studies Chart

Join the Registry.
Tell Your Story.
Advance the Science.

"Together, we can make a difference!"

CURRENT PROGRANULIN STUDIES

While the progranulin trials are leading investigating treatment options, they all are struggling to find and enroll volunteers. All of them have been given orphan and fast-track designations by the FDA.

The first three interventional clinical trials summarized below are recruiting persons who have tested positive for a *GRN* variant. The fourth one is testing healthy volunteers before enrolling those with a *GRN* mutation. Click on the text links to read more about each trial on ClinicalTrials.gov.

INFRONT-3 (Alector)

INFRONT-3 is studying whether increasing progranulin levels after treatment with AL001 will delay the onset of symptoms or slow disease progression when compared to a **placebo** (a solution that contains no active AL001 drug).

This Phase 3 trial is seeking 180 volunteers between the ages of 25 and 85. Participants need to have a confirmed progranulin gene mutation, and either be diagnosed with FTD or at risk of developing FTD symptoms as evidenced by a biomarker.

The study drug (AL001 or placebo) will be administered every four weeks by an intravenous (IV) infusion. Time of commitment is 48 weeks or 96 weeks. Assessments include regular medical examinations, blood tests, brain imaging, and the completion of questionnaires.

There are 46 study sites located in the United States, Australia, Canada, and Europe.

LEARN MORE ABOUT INFRONT-3

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PROCLAIM
(Prevail, a subsidiary of Eli Lilly)

PROCLAIM is a Phase 1/2 study that is researching the safety and effectiveness of an investigational one-time gene therapy that is designed to treat FTD caused by a mutation, or change, in the progranulin gene.

This study will enroll 15 volunteers. To be eligible, you must be between 30 and 80 years of age, have a confirmed progranulin gene mutation, and be experiencing symptoms.

Participants receive a one-time injection of PR006 according to an escalating dose (low dose, medium dose, and high dose) cohort design. There is no placebo.

The duration of the study is five years. During the first year, patients are evaluated for the effect of PR006 on safety, tolerability, immune reactions, biomarkers, and efficacy. There is an additional four years of follow-up to monitor safety, biomarkers, and clinical outcomes.

There are two study sites in the United States, one in Australia, and one in Spain.

LEARN MORE ABOUT PROCLAIM

VIEW CHART of 3 STUDIES that are RECRUITING

upliFT-D
(Passage Bio)

The upliFT-D Study is investigating the safety and tolerability of a gene therapy (PBFT02) for persons with FTD who have a mutation in the progranulin gene.

This Phase 1/2 study is seeking six volunteers. Eligible participants are diagnosed with FTD-*GRN*, are between 35 and 75 years old, experience FTD symptoms, have a reliable study partner, and live in the community.

Participants will receive one dose of PBFT02. Additional assessments include blood tests, medical exams, questionnaires, brain imaging, and lumbar punctures. There is a two-year main commitment with an optional three-year safety extension for a total of 16 visits over five years.

There are nine study sites in the United States, Brazil, Canada, and Europe. Only the University of Pennsylvania and the University of Texas at Houston are currently recruiting.

LEARN MORE ABOUT upliFT-D

DNL593 (PTV:PGRN)
(Denali Therapeutics Inc.)

This randomized, double-blind, placebo-controlled study is testing for the safety, tolerability, pharmacokinetics, and pharmacodynamics of single and multiple doses of DNL593. Currently, it is only testing in healthy volunteers (Part A) with plans to test in persons with FTD symptoms who are *GRN* mutation carriers in Part B.

This Phase 1/2 clinical trial will enroll approximately 106 participants. In addition to having a granulin mutation, eligibility for Part B includes being between 18 and 80 years old, having a BMI of between 18 and 32 kg/m2, and having a CDR plus NACC FTLD global score greater or equal to 0.5.

This trial is recruiting in the United Kingdom now, but has plans to add sites in the United States and other countries.

LEARN MORE ABOUT DNL593 (PTV:PGRN) STUDY

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