

**OVERVIEW**

This update details how The Stop ALD Foundation (The Foundation) continues to take a successful, entrepreneurial approach to Adrenoleukodystrophy (ALD) and Adrenomyeloneuropathy (AMN).

*We continue to make progress and leverage our funding and resources to amplify and magnify dramatically the donations from the generous people and organizations that have funded the Foundation to date. We continue to need your financial support to drive forward our efforts to save the children and adults devastated by this horrific and rare disease.*

The Foundation continues to oversee and participate in advancing five primary projects:

1. **Gene Therapy:** Since stem cell transplants (e.g., cord blood transplantation and bone marrow transplantation) are the only known therapy for treating ALD, gene therapy is designed to take a stem cell transplant a step further by finding a safer and universally available transplant for all ALD patients.
2. **ALDR Up-Regulation:** Aims to find a drug compound (medication) that will provide a therapy.
3. **Predicting ALD onset and finding new pharmaceutical compounds using Transcriptomics:** Transcriptomics is the description and study of gene expression patterns. This work is aimed at learning more about the disease to open additional avenues of treatment and be able to predict the expected impact of ALD on a particular child.
4. **Mesenchymal Stem Cells (MSCs):** Currently transplants are only effective if done early enough in the disease progression. MSCs may be used to provide a treatment for later stage patients.
5. **Awareness and Prevention:** We have directly influenced 15,000 US physicians with a world-class professional information pamphlet on ALD in order to increase the early diagnosis of ALD.

Please feel free to contact us if you have any questions. You can email [info@stopald.org](mailto:info@stopald.org) or call 713.756.3232

**DEDICATION**



**In Honor of Oliver Lapin (1992-2004)**

The Stop ALD Foundation was started immediately following the year 2000 ALD diagnosis of Oliver Abraham Lapin - at the time a sweet, caring, and extremely intelligent eight-year-old boy from Houston, Texas. Oliver was misdiagnosed for years and, by the time an accurate diagnosis was made, he was already severely affected with no treatment available to help him. The correct diagnosis did provide early warning for the two other affected boys in the family who could be "saved." The expression "it takes a village" was taken to heart when Oliver's extended family started The Stop ALD Foundation in early 2001.

On Thursday, August 12, 2004, the day before Oliver's 12th birthday, Oliver passed away from complications related to ALD. He was at home lovingly surrounded by his family.

The Stop ALD Foundation wishes to thank the outpouring of support and donations that we have received in memory of Oliver. We will continue with our mission to make sure more children are diagnosed earlier, and to facilitate the availability of better, more effective, and safer treatments.

We'll so deeply miss you Oliver. We'll never, ever forget you.

## THERAPY DEVELOPMENT

### Gene Therapy

Gene therapy research and implementation as a treatment for ALD has been the highest priority since the inception of The Stop ALD Foundation. In the early days of The Stop ALD Foundation, a thorough review by ALD experts, along with an international multi-disciplinary team, concluded that gene therapy applied to the patient's own stem cells was the best approach to pursue.

The following steps have been completed:

- ☑ Comprehensive preclinical lab experiments have yielded encouraging results, which have allowed the approach to continue moving forward. This includes work in tissue/cell cultures and in rodents.
- ☑ The design of the gene therapy vector itself (the product which will enter an ALD patient's stem cells and insert the corrected sequence of genetic material (DNA) that codes for a proper ALD gene) has been through numerous modifications, enhancements and follow-up experimentation. Because these are new biological agents, each of the reconfigurations is a result of new ideas and research applications that have never been attempted before.
- ☑ The actual gene therapy vector has recently been manufactured by a California-based biotech company. It is the very first time this particular vector will be used in humans. This process has been both expensive and time consuming given the stringent regulations in place in both the US and Europe that must be applied to novel biologicals such as this custom vector. There has been a high degree of expertise, resources, time, and funding (approximately \$1 million) that have been expended on the vector itself.

- ☑ The French equivalent of the US's FDA is known as AFSSAPS. Gene therapy clinical trials must be approved by AFSSAPS prior to opening for enrollment. A comprehensive application (consisting of hundreds of pages - many of which were translated into French) was submitted to this regulatory agency several months ago. The feedback was quite encouraging and only a few small details remain to be resolved between the agency and the research team.

Given that most of the preclinical work has been performed in France, the principal investigator, Dr. Patrick Aubourg and his team (all based in Paris) will be evaluating the clinical trial participants on a regular basis. Given the high expense involved in enrolling, treating, and closely monitoring patients, we are pleased that the French INSERM (similar to the NIH in the United States) will be financing this portion of the trial (approximately \$1 million).

We are very pleased to announce that we fully expect this gene therapy protocol to be approved and open for patient enrollment in France in early 2005.

The objective of this initial trial will be to test both the *safety* of this new approach, as well its *effectiveness*. Usually, in an initial trial such as this, the regulatory bodies such as the US FDA or France's AFSSAPS will only allow initial testing of *safety* (to make sure the therapy does no harm). However, *since ALD is a rare disease*, the trial will most likely be allowed to study how *effective* the treatment is as well. This is both unusual and wonderful news since the research team can learn more from the initial trial.

The initial trial will consist of only 6 patients. Most likely these boys will reside close to Paris. From a disease perspective these will be children who are considered good candidates for stem cell transplant (relatively earlier stages of cerebral ALD), but do not have good matches available. These boys would otherwise have to wait for a match to become available - all the time getting sicker and sicker, or they might possibly be transplanted with a significantly mismatched donor and need to face the sometimes fatal results of this type of procedure. The ALD gene therapy project is a multimillion dollar protocol. The Foundation was successful in spending only a fraction of this amount in order to marshal these resources on behalf of ALD research.

With direct Foundation expenditures of less than \$200,000 we have received capital and other investments of greater than \$2 million (a 10x boost to our seed investment).

### **ALDR Up-Regulation: A Gene Very Similar to The ALD Gene**

The second project is to pursue ALD homologue up-regulation. "ALD homologue up-regulation" is a way to encourage a gene that already exists (in design and function), but that exists in its *normal* form in all ALD patients. The desired effect would be for this normal gene to "over-express" so that it could *compensate* for the initial ALD defect. Work in the mouse model has led us to believe this could have actual impact on disease progression in ALD patients.

The Stop ALD Foundation has arranged for GlaxoSmithKline (GSK), the world's second largest pharmaceutical company, to share a small part of their library of compounds with the Austrian lab that is the leader in this category of ALD research. A series of experiments have been designed and promising results have begun to emerge.

Data was presented at a recent ALD conference in Paris. The systematic, small molecule approach that has been taken in this latest research has generated interest and optimism from several professional groups. The Foundation is now in discussions to transfer this European project over to a German group who are looking into gaining the participation of a reputable and well-established Swiss biotech.

Again, as a result of The Foundation "seeding" this work by investing a relatively small amount of resources, we are hopeful this project will now be pursued more aggressively. We will monitor progress in Europe, and we intend to participate as further needs may arise.

### **Transcriptomics: Predicting an ALD Child's Fate and Finding New Pharmaceutical Compounds to Help**

The third project, *Transcriptomics*, is aimed toward learning more about the various forms of ALD. This may offer two broad categories of opportunities. First, once pathways and mechanisms are better described and understood, specific targets can then be identified where pharmaceutical intervention may prevent or ameliorate clinical signs.

Another area of interest is prediction of disease phenotype (how the disease "presents itself" in a particular child). Given today's therapies, there would be tremendous value in predicting whether a particular young boy was facing cerebral involvement in the near future, or whether he was destined to suffer from AMN as an adult.

Current stem cell therapies (both bone marrow and cord blood transplantation) are very risky procedures and often, the outcome is better if performed when the patient is younger. If the family and their doctors could have a definitive technique to predict whether a young child was going to have a deadly cerebral onset as a child, that technique would be an extremely useful tool when making the decision if and/or when to transplant a particular patient.

We must remind ourselves that we still do not fully understand the pathology of this dreadful disease. Many questions still exist: *What role (if any) is played by the elevated long chain fatty acids? Why do males who carry identical gene mutations have different forms of ALD? Why do some female carriers show AMN symptoms (e.g., walking and bladder control problems) and others don't? Can the form of disease presentation be predicted?* The answer to all these questions, and many more, is, unfortunately, at the present time, "we don't know."

In an effort to better understand the mechanism of the disease, The Foundation has arranged for an interactive and cooperative *Transcriptomics* project between GlaxoSmithKline (GSK) and Dr. Patrick Aubourg (INSERM, Paris, France). Transcriptomics is the description and study of gene expression patterns.

Most fortunately, we have been able to utilize hundreds of thousands of dollars worth of equipment and expertise in order to better describe and understand the complex protein production and interactions that occur in the various human ALD pathological states.

Furthermore some of this data is being analyzed via very sophisticated proprietary techniques so that useful interpretations can be made. The next steps with this technology will be to try to develop a better prediction technique for patients.

### Mesenchymal Stem Cell (MSC) Therapy

The Mesenchymal Stem Cell (MSC) Therapy project involves scientists and physicians from St Jude's Hospital (Memphis, Tennessee), Children's Hospital of Philadelphia, Tulane University School of Medicine (New Orleans, Louisiana), and leading researchers and physicians in Germany. This experimental therapy involves the use of MSCs taken from the *bone marrow of adult donors*. The MSCs would be delivered into the blood and brains of ALD patients who are at an *advanced* ALD stage. In the first phase trial of MSCs, these stem cells would be used *in conjunction with* conventional bone marrow transplants.

This work will be ongoing in 2005 and we look forward to reporting on the early research results.

### AWARENESS & PREVENTION

#### ALD MediView Report Sent To 15,000+ US Physicians: Don't Misdiagnose an ALD Child as Having Attention Deficit Disorder (ADD)

Our fourth area of focus relates to prevention. This past spring The Foundation secured the cooperation and participation of a medical information company, Rogers Medical Intelligence Services, which distributes continuing education to physicians. On the Foundation's behalf, Rogers engaged a professional medical technical writer to research and write a comprehensive report detailing the medical presentation of ALD along with information regarding diagnosis, common misdiagnosis, treatment and prognosis.

Unfortunately, every year young boys die from ALD merely because it took too long for them to be diagnosed accurately. Typically these children are misdiagnosed as having attention deficit disorder (ADD) or attention-deficit/hyperactivity disorder (AD/HD). Thus, we targeted 15,000 US physicians who have the highest likelihood of seeing these boys in their practices. It is essential that we heighten awareness among doctors so they will be aware of ALD and help to diagnose ALD accurately while there is still time to help the children.

To read this very thorough report, please go to [StopALD.org](http://StopALD.org) and look for the *MediView Report* link on the home page.

We strongly urge you to share this article with your pediatrician or any other appropriate pediatric health care professional.

### CHANGES TO THE STOPALD WEB SITE

#### New Tools to Help Families Desperately Seeking Accurate Information, Direction, and Answers

In early 2005 on [StopALD.org](http://StopALD.org) there will be a new and very comprehensive Frequently Asked Questions (FAQs) section. In this section we'll include the answers to the most commonly asked questions that we receive. *Monthly, we receive and quickly respond to hundreds of emails from families, researchers, and patients all over the world.* Many of them have the same questions. We have been compiling our responses and plan to post them to this new Frequently Asked Questions (FAQs) section of the web site.

Another change coming to the site is a section entitled *"I just received a diagnosis of ALD. What do I do?"* Many inquiries we receive are from families who have just received the absolutely horrifying and devastating news that a loved one has been diagnosed with ALD. *They are scared, confused, and lack accurate, credible, and timely information about what they need to do immediately.* ALD can move extremely fast along its destructive path. Sometimes, when the diagnosis is received, it's an early diagnosis of a younger sibling to a related older child who has been diagnosed with ALD, and

now the younger child is found to have the disease as well, but is not yet symptomatic. More often than not, unfortunately, the diagnosis is received and the child is already affected. At this point, sometimes, *an emergency intervention can save the child's life*. Time is of the essence. Sometimes, it's too late and there is nothing that can be done to save the child. But, sometimes there is a very short "therapeutic window" measured in days or weeks where parents must move extremely fast in order to even have a chance at saving a child's life.

In the "I just received a diagnosis of ALD. What do I do?" section of the web site, we'll include:

- ✓ *A check list of detailed questions to ask medical professionals* (along with a brief explanation as to the meaning and importance of the questions). We have found that most people don't know the critically important questions they need to start asking immediately to ensure they are getting the best possible advice and care.
- ✓ *Steps that must be taken immediately for children/adults with ALD/AMN and family members* (e.g., having other children and family members tested).
- ✓ *Common ALD-related terms* as there is a whole new set of words parents and care givers will need to understand.

## HOW YOU CAN HELP

### We Need Your Help

The Stop ALD Foundation's work is time consuming and takes funding to keep driving it forward. Many of us volunteer our time as we have a deep and personal passion for saving ALD patient's lives since we have family members that have or had ALD. While we are a small Foundation, we carry a big, powerful, and highly leveraged "research punch." *Researchers around the world continue to be impressed with our impact and how we "move the ball forward" in finding better and more effective therapies for ALD and AMN.*

*But, we can't do it without continued funding.*

We ask you to make your financial contribution to The Stop ALD Foundation today, and to *ask family members, friends, and co-workers to contribute as well. Donors can be assured that their funds will have a large impact and that they will be making a material difference in many children's lives.*

Financial contributions should be sent to:

The Stop ALD Foundation  
500 Jefferson St., Suite 2000  
Houston, Texas 77002-7371

For more information on how to make a donation online (including via credit card) and how *your company may be able to double your donation with company matching funds*, please click on *Make a Donation* on our web site [www.stopald.org](http://www.stopald.org). You may also call 713.756.3232.

As always, please feel free to contact us at the number listed above at any time and let us know how we may be of assistance. More contact information is available at *Contact Us* at [www.stopald.org](http://www.stopald.org).

*Thank you for your continued support.*