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30 years of research on leukodystrophy

Since 30 years, ELA accelerates research on Leukodystrophies. During thirty years, researchers first learned about these diseases in order to consider long-awaited therapeutic options. Today the research is in a clinical trials phase and the very first therapies have been authorized. There is great hope that treatments will finally be offered outside the experimental phases. But we must keep in mind that these new treatments will not be for all patients, and that their use is subject to strict conditions. Leukodystrophies have as many faces as there are patients, and much work remains to be done so that a solution can be proposed for each patient.

1. New therapies

Already experimented for other diseases, bone marrow transplant was the first treatment allowing, if not to cure, at least to interrupt the progression of certain forms of leukodystrophies. Without a clear understanding of the mechanisms, the researchers have been able to verify for many years the clinical benefits of hematopoietic stem cell transplant in pre-symptomatic patients with a compatible donor.

Technical and technological advances in this last 30 years have paved the way for gene therapy. The idea grew with the discovery of the genes and their mutations. Directly repairing the genetic anomaly responsible of the disease looked like science-fiction a few years ago, but successes show that it is now possible. Derived from marrow transplant, it is an alternative that does not require a compatible donor or long-term immunosuppressive treatment. Gene therapy as a treatment for leukodystrophies has been a major research focus for investigators supported by the association. From the beginning of the association, ELA has been involved in the development of gene therapy against leukodystrophies. Financing the very first work in the experimental models, ELA permited the first clinical trial in the world, carried out by the teams of Pr. Aubourg in Paris, for children with cerebral adrenoleukodystrophy. In 2009, first results were encouraging, and in 2017 an American study confirmed these results and paved the way of its authorization in Europe.

In less than one year, two gene therapies for the treatment of Leukodystrophies were authorized in Europe.

- ***Gene therapy for the treatment of early onset metachromatic leukodystrophy***

Authorized on December 21st, 2020 in Europe, this treatment (called Libmeldy) uses the patient's hematopoietic stem cells in which functional copies of the *ARSA* gene are inserted into the genome using a lentiviral vector.

Metachromatic leukodystrophy is characterized by bi-allellic mutations in the *ARSA* gene conducting to a reduction of the ARSA enzymatic activity. The treatment is for patients with either:

- a late infantile form without clinical manifestations of the disease
- an early juvenile form, without clinical manifestations of the disease
- an early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline.

In Europe, this treatment is today proposed for 2 forms of the disease, late infantile or early juvenile forms, without clinical manifestations of the disease, at the site of Robert Debré hospital in Paris.

- ***Gene therapy for the treatment of cerebral adrenoleukodystropy* for patients less than 18 years of age without matched sibling**

Autorized on Jully 21st, 2021 in Europe, this treatment uses hematopoietic stem cells (blood cells) of the patient. A one time therapy delivery (Skysona) demonstrated a sustainable effect on the survival of patients and the preservation of their neurological functions in the long term, with a follow-up period of up to almost seven years at the time of authorization. About 35 to 45% of the boys with genetic X-adrenoleukodystrophy develop inflammatory brain damage between the ages of 3 and 18 years. An allogeneic hematopoietic stem cell transplant (allo-HSC) can be considered as a first line of treatment, to stop the progression, often fatal, of cerebral demyelination, provided that the procedure be realized at a very early stage of the disease and that a compatible donor be identified. Bone marrow transplant and gene therapies are not without risks, but they are an option for patients who can benefit from them and offer hope for the search of other therapies. Let us keep in mind that they are efficient only in a short therapeutic window, often already pasted when the diagnosis is performed. The research must be continued to find alternative solutions for patients who are not eligible for this treatment.

- ***Others gene therapies developed for the treatment of leukodystrophies***

Still in experimental phase, gene therapy is also envisioned for the treatment of others forms of leukodystrophies, and clinical trials are multiplying.

Two clinical trials using gene therapy for the treatment of **Krabbe disease** have been opened in 2021 in United-States.

- GALax-C is a phase 1/2 trial of AAVhu68 gene therapy for the treatment of early infantile Krabbe disease by injection into the cisterna magma[1], initiated by Passage Bio, Inc. to establish safety, in 24 children aged from 1 to 9 months.
- RESKUE is a phase 1/2 trial of AAVrh10 gene therapy for the treatment of Krabbe disease by intravenous injection, opened by the company Forge Biologics, Inc. to establish safety, in 6 children under 12 months of age receiving a hematopoietic stem cell transplant.

Two clinical trials investigating gene therapy for the treatment of **Canavan disease** have been opened in 2021 in United-States.

- CANaspire is a phase 1/2 trial of AAV9 gene therapy for the treatment of Canavan disease by intravenous injection, opened by Aspa Therapeutics to establish safety, in 18 children under 30 months of age.
- CAN-GT is a phase 1/2 rAAV-Olig001 gene therapy trial for the treatment of Canavan disease by intraventricular cerebral injection, opened by Myrtelle Inc. to establish safety, in 24 children aged 3 to 60 months.

[1] Injection into the cisterna magma: injection into one of the cerebral cisterns, occasional widenings of the space that surround the central nervous system, called subarachnoid space.

These trials open new possibilities, and at the same time question the technical options to be prefered. Many questions are raised about the methods, the conditions of treatment, their safety and their efficacity. Many questions to which the clinical trials will have to provide elements of answer.

2. Drugs

Gene therapy may not be the solution for all forms of leukodystrophies, for all patients, especially since these treatments must be administered early, at the very beginning of the disease manifestation. There is a real need for drugs that can stop symptoms, or better yet, provide clinical improvement. Some symptomatic treatments already exist, others are expected.

With the support of ELA, some drug trials were conducted, like the one started in September 2015 and led in France by Pr. Crow, testing the effect of reverse transcriptase inhibitors[2] in patients with Aicardi-Goutières syndrome. This work will be continued with a phase 2 trial in preparation in Scotland.

It is in fact two clinical trials for the treatment of **Aicardi-Goutières syndrome** that are in preparation:

- AGS-RTI is a phase 2 trial testing oral triple therapy in Aicardi-Goutières syndrome, in preparation at the University of Edinburgh, to determine the effect of treatment on the level of type I interferon in 24 children, aged 3 months to 15 years.
- RTI in AGS is a phase 1/2 trial comparing oral dual therapy versus placebo in Aicardi-Goutières syndrome, in preparation at the Philadelphia Children's Hospital, to establish the effect of treatment on interferon activation in 34 children, aged 2 to 18 years.

ELA has also supported research on **CACH syndrome**, including projects led by Pr. van der Knaap and Dr. Wolf. This work allowed to open the first ever clinical trial for the treatment of CACH syndrome in Amsterdam on June 1rst, 2021, funded for 500,000 € by ELA International. The trial should establish the effect of guanabenz (a molecule used for many years in the United States and Europe for the treatment of hypertension in adults) on the signaling pathway defective in the disease. The goal is to test the safety and efficacy of the molecule as quickly as possible in 30 children up to 10 years old at the time of inclusion in the study. In 2014, ELA was the sponsor of a study testing the efficacity of the drug MD1003 for 60 men affected by **adrenomyeloneuropathy (AMN)** without cerebral form. We knew that similarities exist between adrenomyeloneuropathy and progressive multiple sclerosis (MS). The drug MD1003 developed by the startup MedDay Pharmaceuticals being able to stop the progression of the disease in patients with primary progressive or secondary progressive multiple sclerosis, a double-blind placebo randomized trial was developed to test its effect in adrenomyeloneuropathy.

This trial was funded by ELA for 800 000 €. The very slow evolution of adrenomyeloneuropathy makes it very difficult to measure the impact of drugs on the progression of the disease. After 2 years of treatment, it was not possible to conclude of a positive effect of the drug for this

[2] Reverse transcriptase: enzyme that transforms RNA into DNA. In Aicardi-Goutières syndrome, molecules produced by reverse transcriptase are in excess and are recognized by the immune system, triggering inflammation.

form of leukodystrophy. Thanks to the partnership established and following the marketing authorization of the treatment in other indications, the whole investment, returned to ELA, has been reinvested in other research projects.

Although trials of drugs for the treatment of adrenoleukodystrophy have not yet shown positive results, many clinical trials are now in progress or in preparation.

- VK0214-102 is a phase 1b trial of the treatment VK0214 versus placebo in adrenomyeloneupathy, initiated by Viking Therapeutics, Inc. to establish the safety and pharmacodynamics of treatment, in 36 men over the age of 18.
- MT-2-01 is a phase 2/3 trial of the treatment MIN-102 versus placebo in adrenomyeloneupathy, in the follow-up phase, by Minoryx Therapeutics, to establish the effects of treatment on disease progression, in 105 men aged 18 to 65 years.
- A phase 2/3 proof-of-concept trial is in the follow-up phase at the Hospitalet in Llobregat, Spain, to establish the effect of plasma exchange with albumin in 5 men aged 18 to 65 with adrenomyeloneupathy.
- PXL770-011 is a phase 2 trial on of the treatment PXL770 in adrenomyéloneuropathie, in preparation by Poxel SA, to establish the safety and pharmacodynamics of the treatment, in 24 men aged 18 to 65.

For the treatment of **cerebral adrenoleukodystrophie (cALD)**, a pediatric trial is in progress with the goal to improve the patient's condition before a marrow transplant.

- NEXUS is a Phase 2 trial on of MIN-102 treatment in cerebral adrenoleukodystrophy, initiated by Minoryx Therapeutics, to assess the effects of treatment on disease progression prior to human stem cell transplant, in 13 boys aged 2 to 12 years.

A clinical trial of antisense oligonucleotide therapy for the treatment of **Alexander's disease** was opened in 2021 in the United States and in the Netherlands.

- ION373-CS1 is a phase 1/3 trial of intrathecal injection on of antisense oligonucleotides versus placebo in Alexander's disease, initiated by Ionis Pharmaceuticals, Inc. to establish the safety and efficacy of the GFAP-ASO (ION373) treatment on motricity, in 58 patients aged 2 to 65 years.

Summary of ongoing and upcoming clinical trials:

Leukodystrophie	Compagny	Treatment	Year	Study
AGS	University of Edimbourg *Scotland*	Oral triple therapy	In preparation	Phase 2
	ChildrenHhospital of Philadelphia *USA*	Oral dual therapy versus placebo	In preparation	Phase 1/2
Alexander	Ionis Pharmaceuticals *USA*	Intrathecal therapy of antisense oligonucleotides versus placebo	2021	Phase 1/3
AMN	Minoryx *Sapin*	MIN102 versus placébo	2017	Phase 2/3
AMN	Hospitalet de Llobregat *Spain*	Plasma exchange with albumin	2020	Proof-of-concept
AMN	Viking Therapeutics *USA*	VK0214 versus placébo	2021	Phase 1b
AMN	Poxel *France*	PXL770	In preparation	Phase 2
ALDc	Minoryx *Spain*	MIN102	2019	Phase 2
CACH	Vumc *Netherlands*	Guanabenz	2021	Clinical trial
Canavan	ASPA Therapeutics *USA*	Gene therapy AAV9	2021	Phase 1/2
	Myrtelle *USA*	Gene therapy rAAV-Olig001	2021	Phase 1/2
Krabbe	Forge Biologics *USA*	Gene therapy AAVrh10	2021	Phase 1/2
	Passage Bio *USA*	Gene therapy AAVhu68	2021	Phase 1/2

3. The actions of ELA

- ***Calls for proposals***

For other forms of leukodystrophies, those identified more recently or for which the gene is not yet known, the way to treatments remains long. To prepare the clinical trials of tomorrow, ELA has supported and supports many fundamental research programs.

Experts try to understand those diseases, and ELA supports them with an annual scientific call for proposals. More than 550 programs since the beginning of the association:

- like the preparatory work to gene therapy for the treatment of megalencephalic leukoencephalopathy with subcortical cysts (MLC), conducted by researchers of the Autonomous University of Barcelona, supported by ELA for many years;
- or the project of a team at the Case Western Reserve University in United States, to test thousands of drugs for their ability to restore myelin, and to validate and advance one or more of these drugs able to improve cell differentiation (OPC) and survival of cells that make myelin, in a model of Pelizaeus Merzbacher disease (PMD);
- or a project on leukodystrophy linked to SLC44A1, recently discovered, and for which a team from the University of Porto in Portugal will work, to better understand the pathology and the mechanisms of the disease caused by an altered transport of choline.

To each leukodystrophy its teams and its research. Over the last 7 years, 16 leukodystrophies have been studied with the support of ELA.

- ***Events***

ELA has been looking to experts since its beginnings: to relay to them the expectations of families, to give them financial supports to work on leukodystrophies, but also having to hart to provide them with the space and the time to meet and reflect.

Every year, in person, ELA organized the meeting of families and researchers. More recently, this event has become international and has been organized online, in 5 languages. This is without a doubt a major event for the families. But it is also a privileged time for experts, an opportunity to exchange with families and with each other.

Conversation feeds minds and promotes progress. ELA has been the initiator of these conversations and has organized smaller conferences, symposium and meetings, where researchers talk about leukodystrophy.

- ***Leuconnect***

To help in the early diagnosis of the disease, the treatment of symptoms and the implementation of actions to improve the quality of life of patients and their families, clinicians are also interested in the natural history of these diseases and try to understand how and why the diseases appear, what are their first signs, how they evolve and at what rate. As leukodystrophy are rare diseases, each clinician has only few patients to follow.

Due the rarity of leukodystrophies and the isolation of patients, and to meet the needs of families, ELA created Leuconnect, an innovative tool able to bring together patients and

caregivers who want to meet, and those who want to concretely help research by participating on clinical studies. Developed over several years, Leuconnect.com is now a reality and a success. It is an online platform that brings together a community of patients concerned by leukodystrophies and their families in France and internationally. The aim is to favor links between families and accelerate clinical trials in the field of Leukodystrophies, including natural histories of the diseases.

This international platform opened in 2019 by ELA, to families and to the scientific community, exists in 5 languages (German, English, Spanish, French and Italian). It is hosted by an approved provider of health data and meets the European standards of the General Data Protection Regulation (GDPR) and the French National Commission for Data Protection (CNIL). Today two studies have already taken place on the platform.

- The first study was addressed to caregivers of patients with metachromatic leukodystrophy (MLD). In partnership with ELA, it was conducted by the pharmaceutical company Orchard Therapeutics with the independent study agency ARGO Santé, to better understand the evolution of the disease and measure its impact on the quality of life and the daily life of families.
- A second clinical study, conducted by the pharmaceutical company Bluebird Bio and ARGO Santé in partnership with ELA, reached out to caregivers of patients with cerebral adrenoleukodystrophy (cALD) to understand the impact of the disease on daily life.

Thanks to the involvement of families and the mobilization of the experts and of ELA teams, the platform has facilitated the recruitment of patients and allowed an easy and rapid implementation of these studies.

- A third study in progress, involving women with X-related adrenoleukodystrophy (X-ALD), is being conducted by the team of Pr.Wolfgang Koehler from the University of Leipzig in Germany. The aim is to characterize the expression of the disease in women, who do not present the same clinical picture as men. The study is currently being conducted in three languages (German, English and French) and the scientific teams are considering opening it up more widely.

Leuconnect has become a partner for families and is today an engaged community. It is also a valuable tool offered by ELA to health professionals. Desired by families, Leuconnect is an innovative tool, unique in its kind, resulting from an interdisciplinary work, and which continues to evolve to better meet needs and expectations.

Conclusion

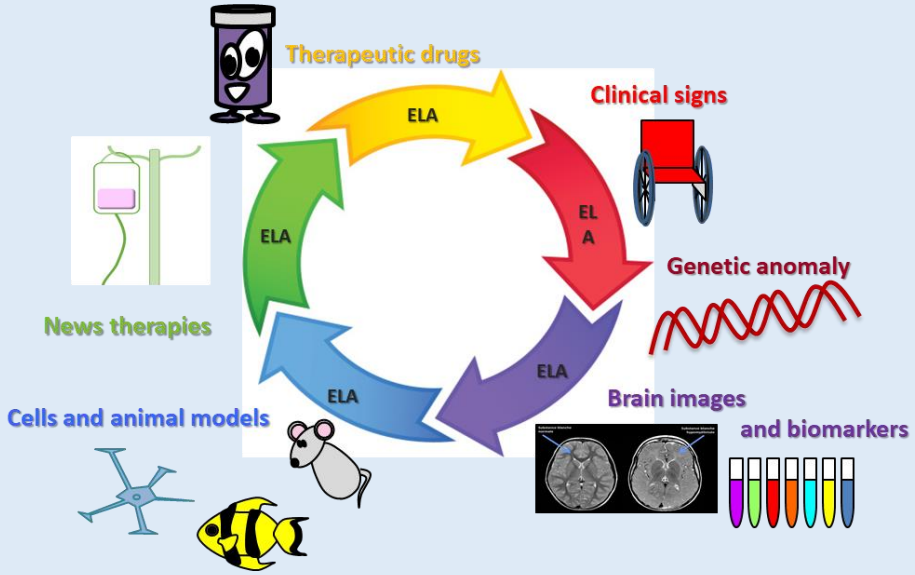
The ultimate goal is to find treatments to fight leukodystrophies. Whether in the form of transplants, gene or cell therapies, drugs, or physical therapies, we need to improve the quality of life of patients and increase their life expectancy.

After 30 years of research and therapeutic trials, the first two treatments are authorized in the form of gene therapy, for cerebral adrenoleukodystrophy and metachromatic leukodystrophy. These treatments are the tip of the iceberg. The individual diversity of patients and clinical cases indicates that much work remains to be done: the number of leukodystrophy types continuously increases and each can manifest itself in several forms.

For 30 years, ELA has been accelerating research on leukodystrophies and supporting numerous projects that have led to a better understanding of these diseases and the biological mechanisms involved.

Accelerate research

To meet the expectations of patients and their families and find treatments as quickly as possible, research must be conducted on all fronts. Since its creation, ELA has wanted to accelerate research on leukodystrophies, raising funds from the public and funding research and initiatives that address all aspects of the disease.



Through phenotypic (clinical signs) and genetic analysis, the study of markers, cell and animal models, the researchers have improved their knowledge of these diseases and are now developing treatments to win the fight against leukodystrophies.

But now, we must keep in mind that these new therapies are not for everyone. 5% of children with these leukodystrophies will be able to be considered for these treatments. For others, the therapeutic window will be past, and other solutions are to be found. Research and discovery of biomarkers could facilitate early diagnosis.

Neonatal screening allows to identify patients at birth. With the discovery of effective treatments, screening could be the opportunity to offer these treatments before the disease has progressed significantly, before irreparable damage has occurred.

Since its creation, ELA invested more than €46.7 million in more than 550 research programs around the world. Last year, 12 research projects on leukodystrophies were supported for €1,105,557 and a clinical trial for CACH syndrome will receive a total of €500,000. For 30 years, ELA has been fighting to break the isolation of patients and their families, and to maintain the research effort on these diseases, despite the high costs and the limited number of patients who would receive a treatment. Accelerating research and helping patients today, to win tomorrow the fight against leukodystrophies, remains ELA's top priority.