24 years of research on leukodystrophies

ELA's contribution

ELA International - GEIE

Annual call for projects

Since 1992, 482 programmes have been funded for €41.4 million.

ELA is the leading funder of leukodystrophy research.

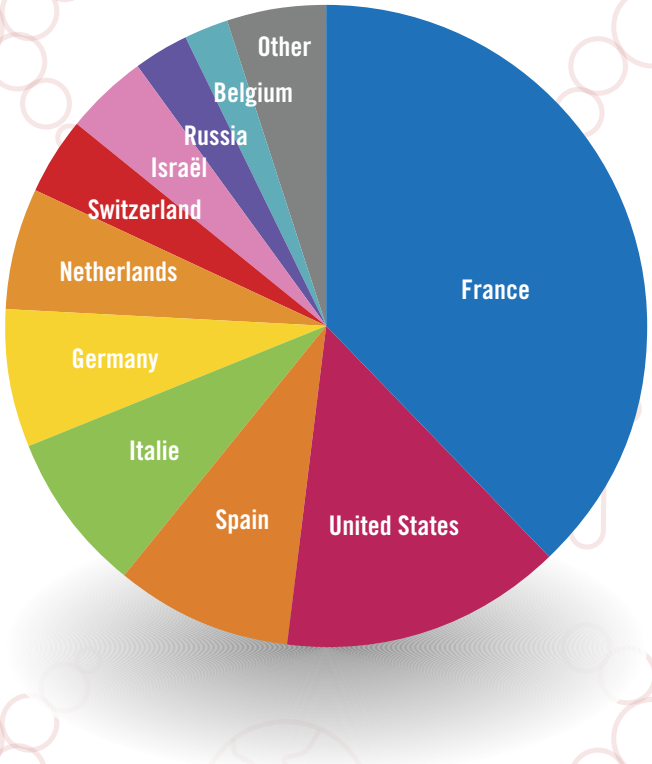
Each year, ELA invites the international scientific community to submit innovative research projects in the field of leukodystrophies and myelin repair, as a way to promote better knowledge of leukodystrophies worldwide and the development of promising therapies. These projects are selected by ELA's scientific board of world experts.

The majority of countries that receive funding are European (80%): France, Spain, Italy, Germany, the Netherlands, Switzerland, and the United Kingdom (UK); the United States and Israel account for just under 20% (Figure 1).

ELA has invested in the global development of research in France, Europe, and the world.

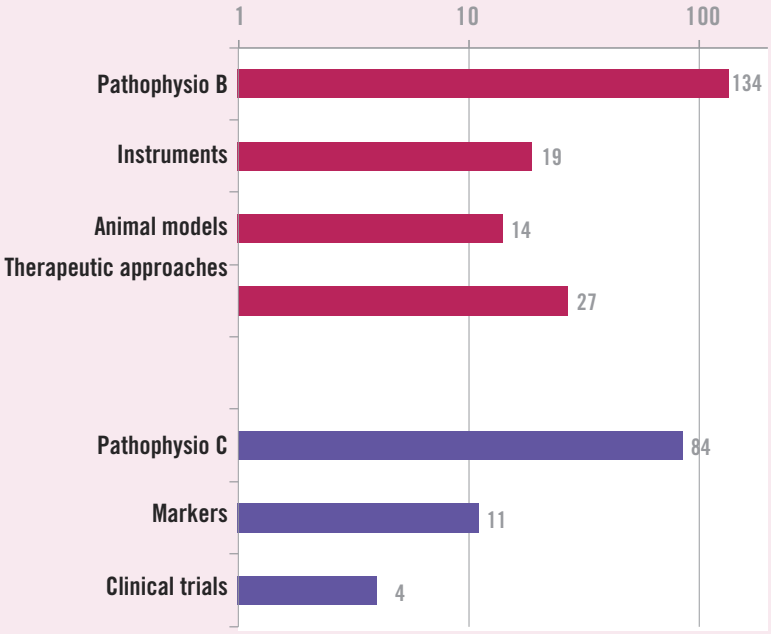
Distribution of funding by country of origin of researchers

Figure 1.



Important dates in the organisation of research

- **1992:** Implementation of the ELA's call for projects
- **2004:** Creation of the Foundation
- **2009:** Research strategy plan
- **2015:** Creation of ELA International and dissolution of the Foundation



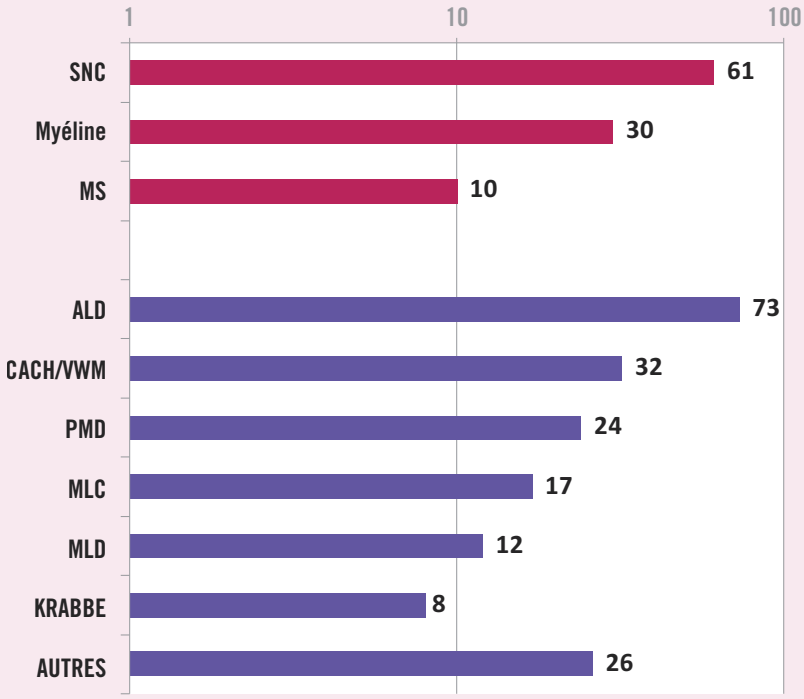
In terms of the orientation of the various research projects, understanding the biological mechanisms is by far the dominant objective.

This shows that the first step towards treatment continues to be the accumulation of knowledge.

Figure 2. Research project guidelines
Abbreviations:
Pathophysio B: pathophysiology of cellular abnormalities; Pathophysio C: pathophysiology of clinical manifestations

Publications:

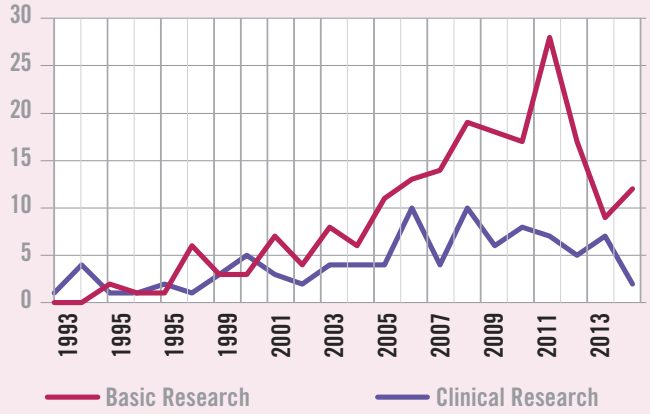
- **293** expert-reviewed articles were published
- Basic research: **199**
- Clinical research: **94**



The research work

Apart from the study of the functioning of the central nervous system (CNS), the production of myelin (MYELINE) and multiple sclerosis (MS), the research work concerns all leukodystrophies (see right side of figure 3) , with a predominance for the most frequent one, adrenoleukodystrophy (ALD).

Figure 3. Distribution of research work according to the types of leukodystrophies.
Abbreviations:
CNS: central nervous system; MS: multiple sclerosis; ALD: adrenoleukodystrophy; CACH/VWM: childhood ataxia with diffuse CNS hypomyelination / leukoencephalopathy with vanishing white matter; PMD: Pelizaeus-Merzbacher disease; MLC : megalencephalic leukoencephalopathy with subcortical cysts; MLD: metachromatic leukodystrophy.



Between 2006 and 2009, the significant increase in the budget for the call for projects mainly benefited so-called basic research
(Figure 4), which aims to improve general scientific knowledge. Clinical research, which aims to discover how to treat patients, continues to be ELA's principal goal.

Figure 4. Evolution of the number of publications over time:
clinical research publications in black and basic research publications in green.

Articles published in high-impact international journals

- Hematopoietic stem cell gene therapy with a lentiviral vector in X-linked adrenoleukodystrophy. Cartier N. et al. **Science 2009**
- HIV-1 restriction factor SAMHD1 is a deoxynucleide triphosphate triphosphohydrolase. Goldstone DC et al. **Nature 2011**
- Glycolytic oligodentrocytes maintain myelin and long term axonal integrity. Fünfschilling U. et al **Nature 2012**
- Megalencephalicleukoencephalopathy with subcortical cysts: chronic white matter edema due to a defect in brain ion and water homeostasis. Van der Knaap et al Lancet **Neurol 2012**
- Lentiviral hematopoietic stem cell gene therapy benefits metachromatic leukodystrophy. Biffi A. et al **Science 2013**

Projects supported by ELA apart from the call for projects

To accelerate research against leukodystrophies, other projects have been initiated and supported by ELA under the supervision of a steering committee.

- The D3BLeuko biobank (a biobank associated with a clinical database).
- The Leuconnect web platform dedicated to leukodystrophy patients and their relatives, with the aim of bringing together people likely to participate in clinical studies in this therapeutic area.
- Gene therapy in adrenoleukodystrophy (ALD) and metachromatic leukodystrophy (MLD).
- Biotin in AMN adrenomyeloneuropathy (MD1003, a therapeutic trial with an agent that promotes myelin repair).

The key milestones of the research

- **1995:** Gene transfer assay in patient cells. In vitro manipulation of fibroblasts from ALD patients (Cartier et al.)
- **1998:** Genetic correction of bone marrow cells. Correction of the gene responsible for ALD (Doerflinger et al.)
- **2004:** Creation of the Foundation
- **2005:** Successful grafting trial in macaques. Induction of repair of damaged myelin in mice by transplantation of myelin-producing cells into macaques. (Bachelin et al.)
- **2006:** Gene therapy trial in mice. Injection of a corrective gene into the brain of MLD mice inducing improvement. (Sevin et al.)
- **2009:** A world first: gene therapy to combat ALD. Team of Dr Patrick Aubourg (Cartier et al.)
- **2011:** Identification of the POLR3A gene. Evidence of the responsibility of this mutated gene in several leukodystrophies (Bernard et al.)
- **2013:** Ex vivo gene therapy to combat MLD. Initiation of a trial in Italy (Milan) in 3 children with MLD, but without disease symptoms (Biffi et al.) In vivo gene therapy to combat MLD. Initiation of a trial in Paris, France, in 5 children with MLD aged 6 months to 5 years (Aubourg et al.)
- **2015:** Creation of ELA International and dissolution of the Foundation.

Scientific conferences

- **2006 Paris**
- **2009 Luxembourg**
- **2015 Paris**

ELA has enabled researchers to meet at scientific conferences focused exclusively on leukodystrophies in 2006, 2009, and recently in June 2015. Another congress was organised in 2011 to target new drugs potentially active in leukodystrophies.

The dual objective of these meetings is to exchange knowledge and to encourage interaction between the various players in therapeutic development: scientists, clinicians and industrialists, as well as patients.

ELA works to ensure that research is conducted for the benefit of patients, always with a view to treatment. The annual family researcher conference contributes to this objective by bringing together patients, their families, and researchers.