Visiting the Labs of AFM-Telethon

The French Association against Myopathies, known as AFM-Telethon, was founded in 1958 by parents of children living with Duchenne muscular dystrophy. AFM-Telethon is an impactful patient-led organization for neuromuscular diseases based in Evry, France, about one hour south of Paris. Currently, 580 employees and 3118 volunteers work for the association. Thanks to generous donations from the annual Telethon TV show, AFM-Telethon has become a significant player in biomedical research for rare diseases. Its three major laboratories involved in developing biotherapies are Genethon, I-Stem, and the Institute for Myology.

Recently, Kathryn Bryant Knudson, founder of the Speak Foundation and editor-in-chief of the *LGMD News* Magazine, was invited to visit the AFM-Telethon headquarters with Mélanie Bordes, a patient advocate who leads AFM's LGMD Patient Interest Group. Together they toured the I-Stem lab with Xavier Nissan, and met with Stephane Degove, CEO of Atamyo Therapeutics, and Professor Isabelle Richard of Atamyo Therapeutics.

With the generous support of donors, AFM-Telethon raised over 92 million Euros (~100 million U.S. Dollars) in 2023 alone, with one main goal: to overcome neuromuscular diseases. The next Telethon will take place on November 29-30, 2024.

Bottom: The members of the LGMD Interest Group of AFM-Telethon, led by Mélanie Bordes (far right)

Right (Top): Kathryn Bryant Knudson, Xavier Nissan, and Mélanie Bordes at the I-Stem Lab

Right (Bottom): Xavier Nissan explains the recent developments and findings to Kathryn Bryant Knudson

The AFM-Telethon LGMD Interest Group

The French LGMD Interest Group was created in 2018 by AFM-Telethon to accompany and support patients and families affected by limb-girdle muscular dystrophies. Led by expert volunteers with different types of LGMDs, the group is a place for patients to be heard. Giving patients a voice is essential for future treatments and adequate medical and social care. The group also provides regular information on medical and scientific developments and advice specific to LGMDs. The creation of the group was based on the simple fact that, at the time, there was no patient advocacy group specifically for LGMDs in France.

The LGMD Interest Group regularly organizes national LGMD meetings to connect patients and families with doctors and researchers in France. The group also collaborates with departmental delegations to improve the quality of life of patients and their family caregivers. There are delegations of AFM-Telethon all over the different regions of France. Members of these delegations advocate for the rights of people with disabilities in various public councils and authorities.

The Mission of the LGMD Interest Group:

- Provide information about LGMDs
- Advocate for the needs of LGMD patients in France and abroad
- Organize regional meetings between patients, their families, doctors, and researchers
- Provide support and advice to patients
- Monitor and inform about scientific developments
- Visit scientific conferences in France and internationally
- Create lasting relationships with international LGMD patient associations

Since November 2023, the group has been led by Mélanie Bordes, a trained patient advocate living with LGMD R9/2i who has considerable experience in national and international advocacy.

Touring the I-Stem Laboratory

Kathryn's tour started at I-Stem, the Institute for Stem Cell Therapy and Exploration of Monogenic Diseases, established in 2005. There, she met Xavier Nissan, research director of the LGMD pharmacology program, and Noëlla Grossi, a pharmacist and PhD student living with LGMD R2/2B.

Xavier Nissan and his team use pluripotent stem cells to study and treat LGMDs by developing high-content/high-throughput screening strategies to identify possible drug candidates. The pharmacological approach consists of identifying drugs that can correct the functional consequences of the mutation to stop or slow down the disease progression. However, this approach does not correct the mutated gene, as in gene therapy. That is why it is essential to identify the specific disease pathways and mechanisms affected by the mutation for the pharmacological approach.

Understanding these pathways is the first step for researchers to develop targeted drugs that can more effectively mitigate the adverse effects caused by the mutation. Once identified, researchers test thousands of pre-existing drugs to avoid creating a new drug from scratch, which is extremely expensive, time-consuming, and restrictive in terms of regulations. This approach, called drug repurposing, is also being followed by other companies involved in LGMD research.

Currently, I-Stem's pharmacological LGMD research program mobilizes six researchers working mainly on:

- Preclinical evaluation (in vivo) of givinostat for LGMD R3/2D and LGMD R5/2C
- Preclinical evaluation (in vitro and in vivo) of a recently discovered molecule for LGMD R2/2B
- Understanding the mechanism of action (in vitro) of new drugs for improving membrane repair in LGMD R2/2B
- Understanding the role of immune cells in LGMD R2/2B pathophysiology
- Understanding dysregulation of pathways involved in LGMD R2/2B
- Identification of new phenotypes and biomarkers for LGMD R9/2i

Discovery of Givinostat for LGMD R3/2D

In 2022, Xavier Nissan's team, in collaboration with Isabelle Richard's team at Genethon, identified a combination of two approved drugs, bortezemib and givinostat, which can treat some mutations in alpha-sarcoglycanopathy (LGMD R3/2D). These findings were published in *Frontiers in Pharmacology*[1] in 2022. This discovery opens new possibilities for treatment of LGMD R3/2D and LGMD R5/2C. Currently, preclinical studies are evaluating the effects of givinostat in an animal model prior to a possible clinical trial in humans.

After the lab tour, Kathryn and Mélanie met Stephane Degove, CEO of Atamyo Therapeutics, and Professor Isabelle Richard, Chief Scientific Officer of Atamyo Therapeutics, at AFM's headquarters.

LGMD Pioneer Award

However, before embarking on the presentation of Atamyo Therapeutics, Kathryn had the great pleasure of awarding Professor Isabelle Richard with the *Fifth Annual LGMD Pioneer Award* for her leadership in the LGMD R9/2i community on behalf of the CureLGMD2i

Foundation. Professor Richard has always been very determined to find treatments for LGMD R9/2i and all of the most common LGMDs. Isabelle Richard was given this award in recognition for her outstanding work and engagement with the LGMD community.

Gene Therapy Approaches by Atamyo Therapeutics

Atamyo Therapeutics is a clinical-stage biopharmaceutical company focused on developing a new generation of effective and safe gene therapies for muscular dystrophies and cardiomyopathies that currently lack treatment options. Its most advanced programs currently target LGMDs, including LGMD R9/2i, LGMD R5/2C (gamma-sarcoglycanopathy), and LGMD R1/2A (calpainopathy).

The name of the company comes from two words: Celtic *atao*, which means "always" or "forever," and *myo*, the Greek root for muscle. Atamyo Therapeutics is fully committed to improving the lives of patients affected by neuromuscular diseases with life-long efficient treatments.

Located in Paris and Evry, Atamyo was founded in 2020 as a subsidiary of Genethon. It leverages unique expertise in AAV-based gene therapy and muscular dystrophies from the Progressive Muscular Dystrophies Laboratory at Genethon, led by Isabelle Richard. Professor Richard is co-founder and Chief Scientific Officer of Atamyo.

Isabelle Richard is an international expert in neuromuscular diseases and a pioneer in researching LGMDs and developing gene therapies targeting LGMDs. She

Opposite: Professor Isabelle Richard receiving the 5th Annual LGMD Pioneer Award from the CureLGMD2i Foundation

Above: Mélanie Bordes and Kathryn Bryant Knudson meeting with Atamyo Therapeutics in the headquarters of AFM-Telethon in Evry, France

Left: Professor Isabelle Richard, Chief Scientific Officer and Stephane Degove, Chief Executive Officer of Atamyo Therapeutics

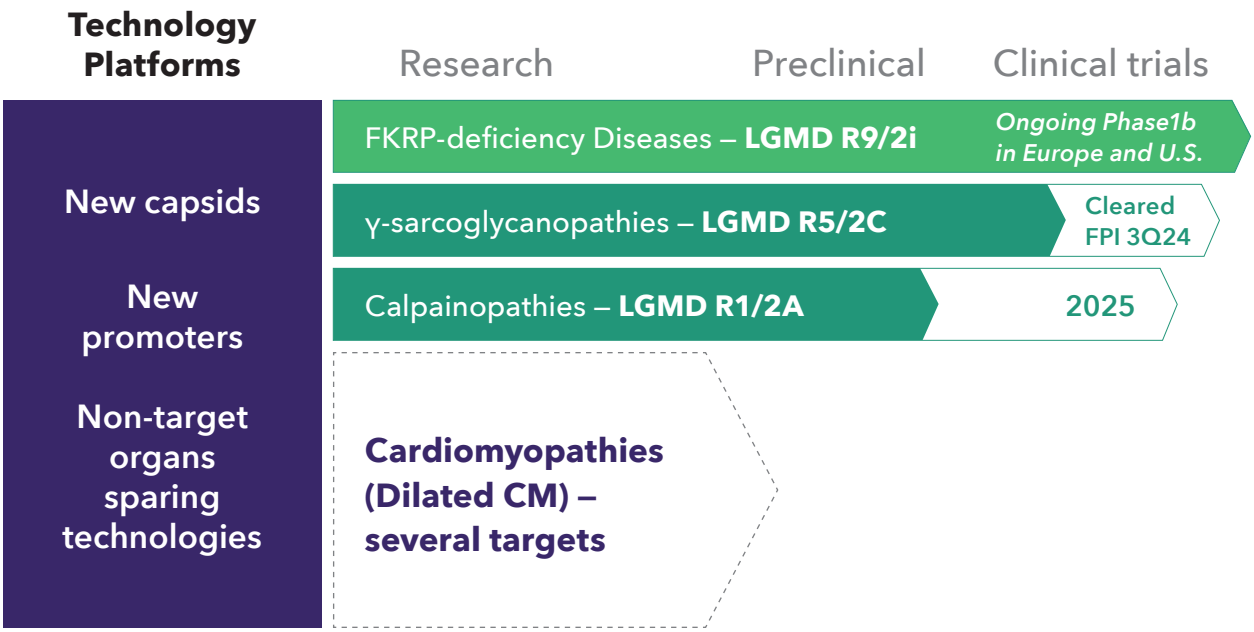

Figure 1: Atamyo Therapeutics pipeline for LGMDs

has published more than 160 scientific papers on muscular dystrophies. Noteworthy highlights of her work include identifying calpain-3 as the first gene implicated in an LGMD, demonstrating the heterogeneity of LGMDs, participating in the identification of the causative genes for all the frequent LGMDs, and proof-of-concept studies of the efficiency of gene therapy for all the most common LGMDs.

Gene therapies developed by Atamyo Therapeutics are single-injection treatments designed to replace the mutated genes that cause LGMDs with functional genes. Atamyo is introducing "first-in-class" technologies that improve the efficacy of gene therapies and prevent adverse effects, such as cardiac or liver toxicity.

ATA-100 for LGMD R9/2i

Atamyo's most advanced gene therapy program, ATA-100, is being developed to treat LGMD R9/2i patients (clinicaltrials.gov ID# NCT05224505). The first clinical results were presented at the Myology Congress in Paris in April 2024. Enrollment of the first low-dose cohort of the study in Europe has been completed with promising initial functional results, and two patients have already been treated in the high-dose cohort. Overall, ATA-100 has been well tolerated to date in all treated patients. In June, Atamyo obtained Fast Track Designation for ATA-100 by the FDA in the USA. Updated results will be presented at the 29th International Annual Congress of the World Muscle Society (WMS) in Prague, October 8-12, 2024.

ATA-200 for LGMD R5/2C

Atamyo's second gene therapy, ATA-200, is cleared to start clinical trials in Europe (France and Italy) for LGMD R5/2C patients (ID# NCT05973630). This phase 1b dose-escalation study will evaluate the safety and efficacy of ATA-200 in children aged 6-11 years at screening. Plans have been made to dose the first patients in the last quarter of 2024. Additionally, Atamyo Therapeutics is in IND-enabling studies (Investigational New Drug) for LGMD R1/2A related to deficiencies in the calpain-3 protein. ■

Written by Mélanie Bordes

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