ANNUAL CONFERENCE

2023

Friedreich's Ataxia Research Update

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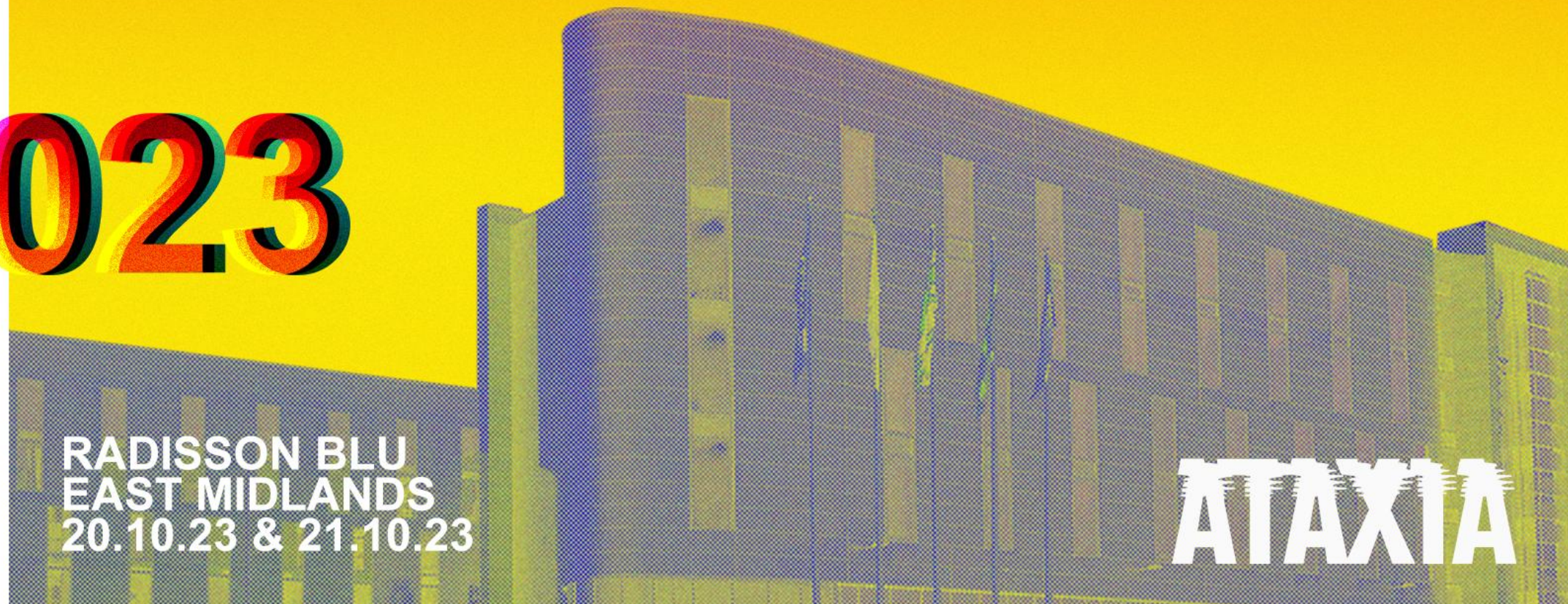
Research Officer



RADISSON BLU
EAST MIDLANDS
20.10.23 & 21.10.23

ATAXIA

Overview

Ataxia UK research activities and the process of research

Developments in new treatments

Opportunities to take part in research in the UK

Ataxia UK research activities and the process of research

Ataxia UK research activities

Fund research projects
Mostly small grants to get initial results

Organise research conferences

2023 Impact Report
Every £1 Ataxia UK spent on research projects raised £5 in further funding for ataxia research

First event for UK-based researchers
Sep 2023

International Congress for Ataxia Research

ATAXIA · ATAXIA GLOBAL INITIATIVE · FARA · NAF National Ataxia Foundation

SAVE THE DATE: ICAR 2024
November 12-15, 2024 • London, UK

Process of clinical trials

Preclinical several years

- Test drug in cells and/or animal models
- Dosing and safety before giving to humans

Phase 1 Several months

- Safety of drug
- How the body processes drug and its effect on body
- Information on dosing

Phase II Several months to 2 years

- Potential risks and benefits
- Does drug work in people who have the condition?
- Continues to study safety

Phase III 1 to 4 years

- Potential risk and benefits compared to no treatment or existing treatment
- Typically, people are given the drug or placebo
- Continues to study safety and whether drug works in more people

*for rare diseases such as ataxia, the numbers of people in trials are much smaller and the different phases of trial might be combined

Next step after a successful clinical trial

Step 1: a treatment needs to get a **licence** from a **regulatory agency** before it can be made available

Step 2: In the UK, **different bodies** decide whether the **NHS will provide** the treatment

UK: MHRA
Europe: EMA
US: FDA

England: NICE
Wales: NICE/ AWMSG
Scotland: SMC
Northern Ireland: DoH

Collaboration is key to advancing research

Ataxia UK links researchers and ataxia community for:

- Recruitment to studies
- Patient engagement in research

Work with pharma and biotech companies:

- Encourage involvement in ataxia research
- Assist with programmes
- Collect useful information

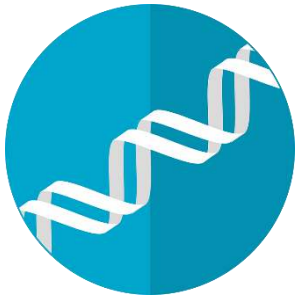
Pre-clinical → Clinical → Drug approval → Treatment available on NHS

Ataxia UK engagement at all stages of research

Developments in new treatments

The aim of FA research

A mistake in the frataxin gene



Genetic approaches to correct or replace frataxin gene

A reduction in the amount of frataxin protein

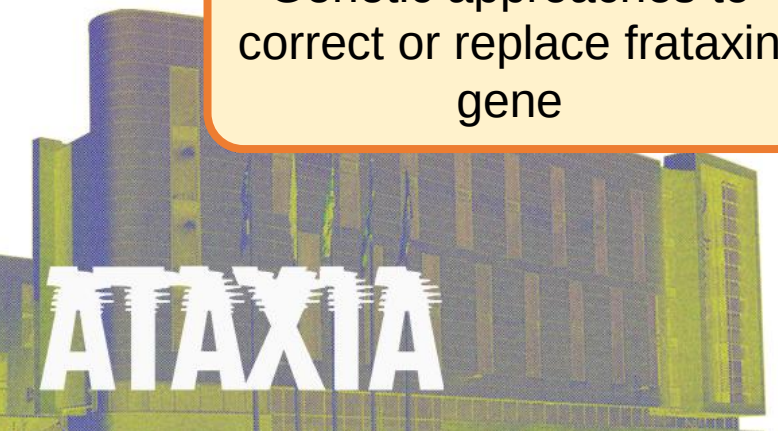
Frataxin protein

Increase the amount of the frataxin protein

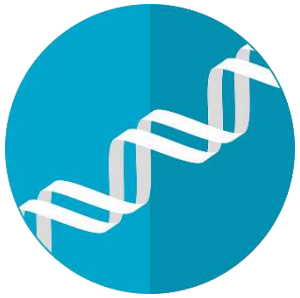
Disrupted processes within cells

- **Oxidative stress**
- **↑ iron in mitochondria**
- **Cell damage**
- **Disrupted mitochondrial function and ↓ energy production**

Target the disrupted cellular processes



A mistake in the frataxin gene



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Developments in new treatments

Genetic approaches

Genetic approaches in FA

LEXEO Therapeutics

- Treatment for cardiomyopathy in FA
- Gene therapy **LX2006** designed to transfer frataxin gene to heart cells

- **Phase I/II clinical trial** (SUNRISE-FA)
- August 2022 to 2029
- 3 ascending dose cohorts
- June 2023: 1st cohort **tolerated dose well** and 2nd cohort are receiving dose
- Expect results in the **first half of 2024**

Design Therapeutics

- **DT-216** designed to target the mutation in the frataxin gene

- Phase I clinical trial
- **Promising initial results** published in December 2022 and August 2023
- Now conducting nonclinical studies to **improve formulation**
- Next **phase I trial** expected in **2024,** with results in the first half of 2025.

Genetic approaches in FA

Many research groups and companies are conducting preclinical research for gene therapies for FA.

- Takeda - StrideBio
- **Solid Biosciences**
- **Lacerta Therapeutics**
- Neurocrine Biosciences + Voyager Therapeutics
- Pfizer + Voyager Therapeutics

- **Prime medicine**
- **CRISPR Therapeutics +** Capsida biotherapeutics

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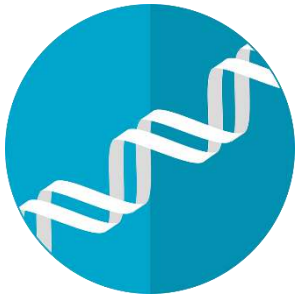

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↓ **Frataxin protein**

Disrupted processes within cells

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Developments in new treatments

Increase frataxin protein

Increase frataxin protein

Larimar Therapeutics

- Protein replacement therapy
- **CTI-1601** delivers frataxin to the mitochondria

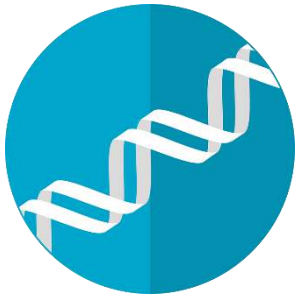
- **Phase II - ascending dose trial**
- May 2023: promising preliminary **results** from 1st stage
- July 2023: announced they will start second stage dosing and **open-label study**

Stealth Biotherapeutics

- **Elamipretide** targets the mitochondria
- A potential treatment for **vision loss** in FA

- **Phase I/II trial started in US**
- 18 participants
- Mar 2022 to Dec 2024

A mistake in the frataxin gene



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Frataxin protein

Disrupted processes within cells

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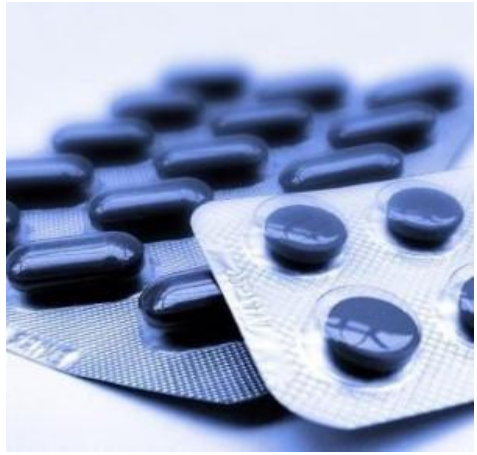
Developments in new treatments
Target disrupted processes

A disease-modifying treatment available for FA in the US

Omaveloxolone
The basics



Generic name: **Omaveloxolone -> 'Omav'**

Brand name in the US: **SYKCLARYS ®**

- **US licence**: Adults with FA **aged 16 years and over.**
- FDA approval February 2023
- Developed by **Reata Pharmaceuticals**
- Now owned by **Biogen (September 2023)**

What does Omaveloxolone do?

Reduces the damage caused by low frataxin levels

In FA, reduced frataxin leads to:

- Oxidative stress
- Disrupted mitochondria function
- Reduced energy production

Omaveloxolone

Nrf2 transcription factor activator

In preclinical models of FA:

- **Nrf2 detoxifying/ anti-oxidant**
  - **↑ mitochondrial function**
    - **↑ energy production**

The MOXIe trial

A multicentre trial. The London Ataxia Centre was the UK trial site.

Part I: Good safety and **best dose** for part II, Improvement in mFARS

69 participants
3:1 Omav: placebo
12 weeks
Results 2018

Part II: Single dose of 150mg: confirmed safety and **significant improvement** in **mFARS**

103 participants
1:1 Omav: Placebo
48 weeks
Results 2019

Open-label extension: Further evidence of **positive effect**

92 participants
All on Omav
Eligible from Part I and II
Results 2021

ICAR 2022 – positive comparison to natural history data

Updates on regulatory approval of Omav

- **FDA approved** Omaveloxolone to treat adults with FA aged 16 and over in the **US** in February 2023
- Reata **applied to the EMA** for approval of Omaveloxolone in **Europe** at the end of 2022

- Reata was acquired by Biogen in September 2023
- **For Omaveloxolone to be approved in the UK, Biogen needs to apply to the UK regulators (MHRA).** Ataxia UK will make every effort to encourage and support Biogen to seek UK regulatory approval, as we did with Reata.

Keep updated with Omav news at https://www.ataxia.org.uk/omav-updates/

Will Omav be approved in children?

Trials are needed to see if **Omav is safe** in children under 16

Biogen

Phase I Study
Children's Hospital of Philadelphia – US single centre
Start date November 2023
Single dose
To assess **safety and tolerability**
Estimated 20 participants
3-15 years – 3 cohorts
Estimated completion date: November 2024

PTC Therapeutics - Vatiquinone trial

Phase III trial MOVE-FA
Vatiquinone ~ antioxidant drug

May 2023 initial results:
No significant change in overall mFARS score (4 components)
But did see **meaningful clinical** benefit in:
1. Upright stability - ability to stand and walk
2. Bulbar function (speech)

Measured in 146 adults and children at 72 weeks

Next steps: **PTC Therapeutics will discuss a plan to try and get the drug approved by regulators in the US and EU**

Minoryx Therapeutics – Leriglitazone (MIN-102) trial

MIN-102 = PPAR gamma activator

PPAR gamma is a protein found in cells. In FA, PPAR gamma cannot function properly.

Results from Phase I clinical trial: well tolerated, and able to reach the brain

Phase II trial (FRAMES) in Europe

- Results from 32 participants. 12-60 years of age
- Promising results for **safety and upper limb ataxia**
- Data has been used to design a Phase III confirmatory study that is under discussion with the EMA and FDA

Developments in new treatments
Symptomatic relief

Non-invasive brain stimulation

Applying **a low electrical current** to the scalp may alleviate symptoms of ataxia.

Ataxia UK funded 2 trials, led by **Dr Borroni** in Italy, in a range of ataxias (FA, SCA, MSA)

- **Trial 1: Transcranial Direct Current Stimulation (tDCS)**
- Results in 2021 showed improvements in clinical rating scores of ataxia
- **Trial 2: Transcranial Alternating Current Stimulation (tACS) v tDCS**
- Received tACS, tDCS and placebo, in a random order (blinded)
- Results 2023:

1. **tDCS performed significantly better** than tACS in some measures
2. **Both tACS and tDCS significantly improved all measures, compared to placebo**

Opportunities to take part in research in the UK

FA Global Patient Registry

Many FA charities, including Ataxia UK, have patient registries - used to recruit for clinical trials and research studies.

These groups have come together to build a ***new*** **international registry - the FA Global Patient Registry (FAGPR).** A global effort to pool information in one place making it a more powerful resource for research (helps understand the condition and patient experiences).

Friedreich's Ataxia Global Patient Registry

How do I register?

FARA Friedreich's Ataxia Research Alliance

Friedreich's Ataxia Global Patient Registry

1000+
People with FA have registered since November 2019

51+
Countries represented in the FA Global Patient Registry

Visit : https://www.fapatientregistry.org/

FA App – research tool

- **The charity End-FA set up an App for people with FA to facilitate research**
- **Their aims are:**
  - Connects FAers with researchers running clinical and virtual research trials
  - Empowers FAers with useful tools for managing their life and treatment
  - Educates people about symptoms, diagnosis and treatments, sharing the latest FA news
- **https://www.thefaapp.org/** or download from **Apple store or Googleplay**

FA Global Clinical Consortium

- **New consortium – 33 clinical sites, 18 countries**
- **The UNIFAI Study** – harmonised study protocol
- **Multi-site global natural history study**
- **EFACTS incorporated** into this global study
- European Friedreich's Ataxia Consortium for Translational Studies
- **London Ataxia Centre** (and other global sites)
- Data being used to design trials

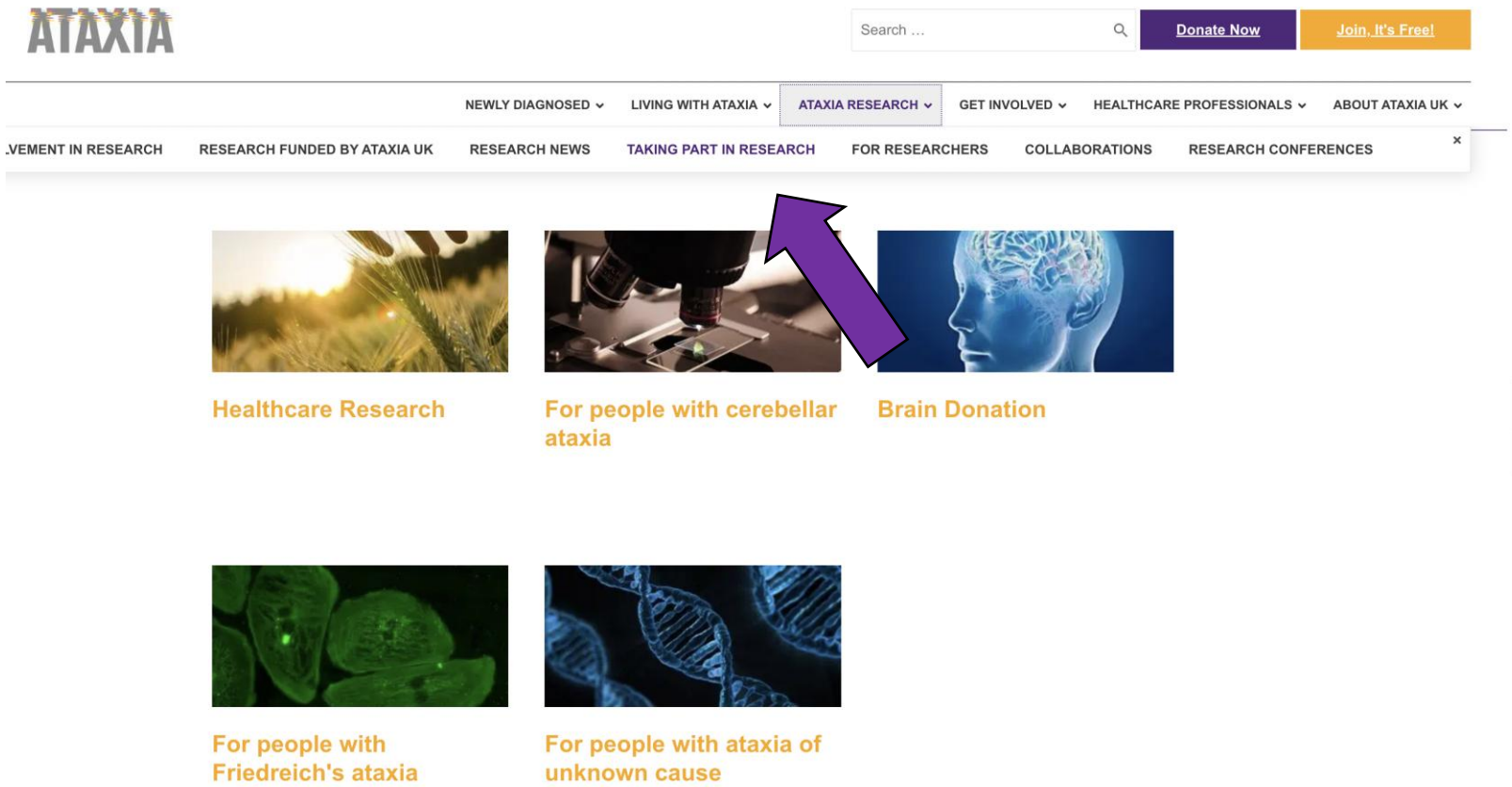
Healthcare research

Google's AI for Social Good programme

Project Euphonia

Collecting speech samples from people with speech difficulties in order to improve voice recognition technology – for example to improve Google Assistant.

All studies can be found on our website ataxia.org.uk



Thank you for listening!

www.ataxia.org.uk

Please contact mbarron@ataxia.org.uk or research@ataxia.org.uk for information and resources on FA research!