Friedreich's Ataxia Research Update

Dr Ruby Wallis

Senior Research Officer

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Friday 7th & Saturday 8th October 2022

Sponsored by

PTC THERAPEUTICS measured by moments

IONIS

Biogen

ATAXIA

Overview

Ataxia UK research activities and the process of research

Developments in new treatments

Opportunities to take part in research in the UK

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Ataxia UK research activities and the process of research

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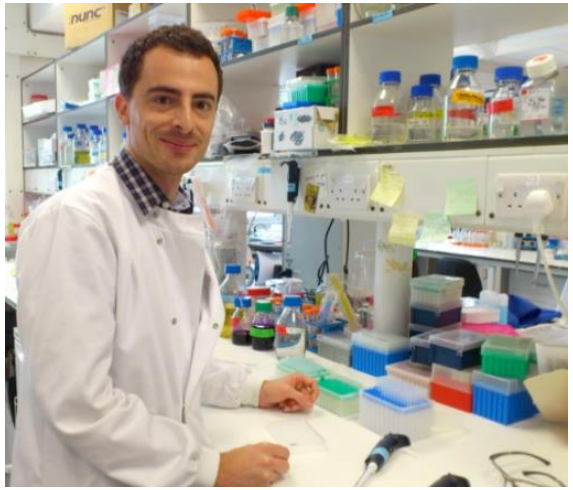
Ataxia UK research activities

Fund research projects mostly small grants to get initial results



2022 Impact Report

Every £1 Ataxia UK spent on research projects raised almost £5 in further funding of ataxia research

Organise research conferences

International Congress for Ataxia Research

ICAR 2022

ATAXIA Ataxia UK

FARA Friedreich's Ataxia Research Alliance

NAF National Ataxia Foundation www.ataxia.org

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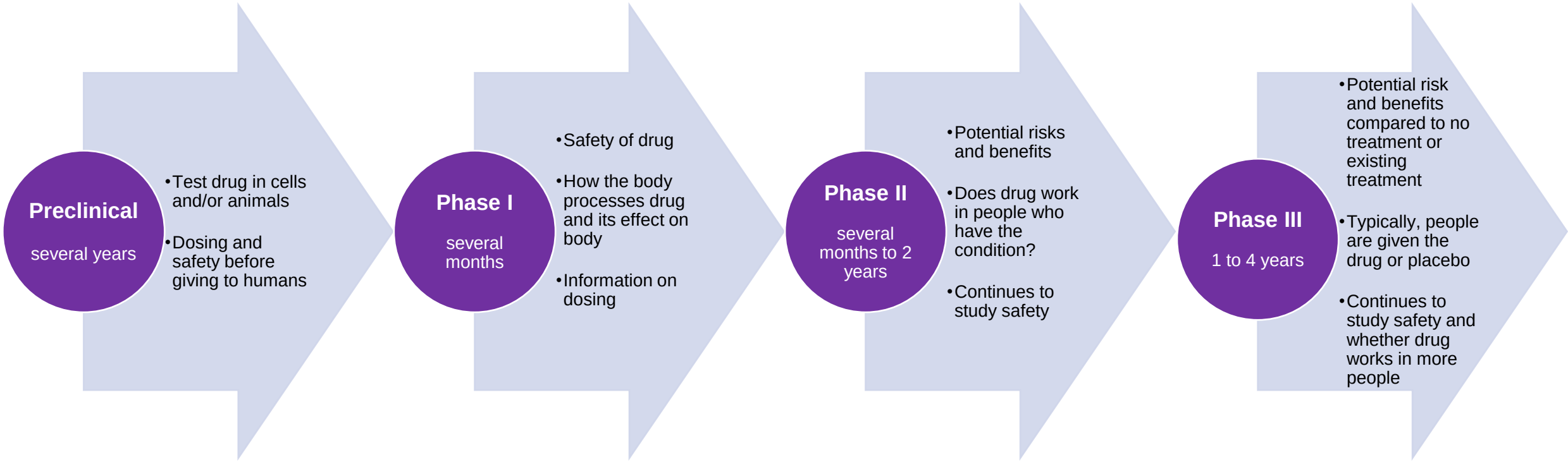
Process of clinical trials



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

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What happens next after a successful clinical trial?

- Treatment needs to get a license from a regulatory agency before being made available
  - UK= Medicines and Healthcare products Regulatory Agency (MHRA)
  - Europe = European Medicines Agency (EMA)
  - US = Food and Drug Administration (FDA)

- If the regulatory agency approves the treatment, different bodies decide whether it can be provided by the NHS

Collaboration is key to advancing research

Ataxia UK links researchers and ataxia community:

- 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

Engagement at all stages of research

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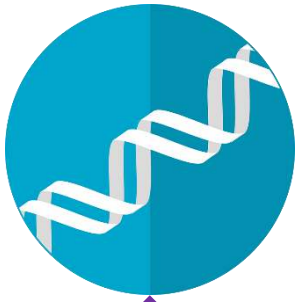
Developments in new treatments

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

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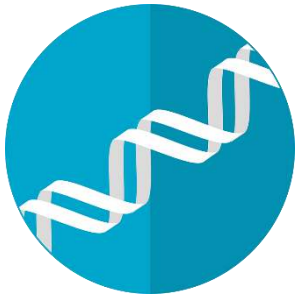
A mistake in the frataxin gene



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Developments in new treatments
Genetic approaches

Genetic approaches in FA

Lexeo Therapeutics

- Treatment for cardiomyopathy associated with FA
- Gene therapy LX2006 designed to transfer frataxin gene to heart cells
- Reversed cardiac symptoms of FA in animal models
- Started Phase I/II clinical trial in 10 people with FA in the US in August

Design Therapeutics

- DT-216 is designed to target the genetic mutation found in people with FA
- Positive results from cell and animal studies
- Started Phase I trial in US and dosed first cohort of patients
- Expect initial results in by end of 2022

Genetic approaches in FA

- A number of research groups and companies are developing **gene therapies** for FA
- Replace or edit frataxin gene

PTC Therapeutics
Takeda - StrideBio
Solid Biosciences
Lacerta Therapeutics
Lexeo Therapeutics
Neurocrine - Voyager Therapeutics
Pfizer - Voyager

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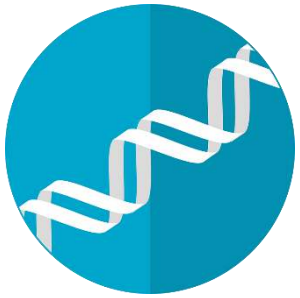

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↓ **Frataxin protein**

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Developments in new treatments
Increase frataxin protein

Increase frataxin protein

Larimar Therapeutics

- CTI-1601 delivers frataxin to the mitochondria
- Phase I trials in the US showed increase in frataxin
- May 2021, FDA announced clinical hold due to question around safety of higher drug dose in animal study
- September 2022, full clinical hold lifted, and partial hold imposed
- Phase II trial expected to start by end of the year

Stealth Biotherapeutics

- Elamipretide targets the mitochondria and has shown positive results in cell and animal studies
- Phase IIa in US to assess safety, visual function, and cardiac function

Drug repurposing approaches

Calcitriol

- Calcitriol (Active form of Vitamin D)
- Ataxia UK funded preclinical study in Spain
- Cell studies in animal cell models: improved mitochondrial function, cell survival and increased frataxin
- Trial started (September 2021) in Spain in 20 people for one year, safety and effect on quality of life

Drug repurposing approaches

Etravirine

- Etravirine, an antiviral, used to treat HIV, increases frataxin in cells derived from patients
- Being tested in a Phase 2 clinical trial in Italy to study its safety and efficacy in people with FA
- Ataxia UK funded a project to test drugs that have a similar structure or function to etravirine

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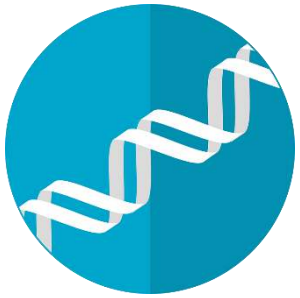

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Developments in new treatments
Target disrupted processes

Reata Pharmaceuticals – Omaveloxolone trial (MOXIe)

Rationale for Omav

- In FA have dysfunction of mitochondria and decrease energy
- Omav restores mitochondrial function in FA cell models by activating Nrf2 (transcription factor) that is reduced in FA

Multi-centre trial

- London Ataxia centre was UK trial site
- Trial had Part 1, Part 2 and Open label extension in adults (over 16)

Details of trials

Part I:
69 participants
3:1 Omav: placebo
12 weeks
To determine safety and dose for Part II

Part II:
103 adults
1:1 Omav: Placebo
To determine safety and efficacy of one dose
48 weeks

Open-label extension:
All on Omav
Eligible from Part I and II

Trial results

- Results of Part I (published: Lynch et al, Ann Clin Transl Neurol (2018)
  - Found best dose
  - Good safety
  - Improvement in mFARS (measurement of disease progression in FA)

- Results of Part 2 (announced Oct 2019, published: Lynch et al, Annals of Neurology (2020)
  - Patients taking Omav for 48 weeks had a statistically significant improvement in their symptoms associated with FA than those on the placebo trial (measured by mFARS)

- Results of extension (Announced in May 2021)
  - Further evidence for positive effect of Omav

Reata discussions with regulators to seek drug approval

- **November 2020:** FDA did initial review of data of Part II and part of extension and asked for additional analyses and may need another trial
- **January 2021:** Ataxia UK supported FARA's campaign to ask FDA and Reata to consider approval of the drug based on existing data
- **May 2021:** Positive results of extension phase announced
- **March 2022**: Reata completed submission of New Drug Application (NDA) to the FDA. The next step in this process is for the FDA to use this NDA to decide whether to approve the treatment.

Reata discussions with regulators to seek drug approval

- **May 2022:** The FDA granted Omav Priority Review designation, which means they will review Reata's application for approval in 8 months rather than the usual 12 months. Reata announce that they hope to complete European regulatory submission at the end of the year (this does not include the UK).

- **August 2022:** Reata met with the FDA and submitted further evidence to support Omav. We hope to hear a response regarding the FDA's decision on approving Omav in the US by 28 February 2023

- For Omav to be approved in the UK, Reata need to submit an application to the UK regulators (MHRA). Ataxia UK have been working with and meeting with Reata to encourage and support them in seeking UK regulatory approval.

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

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PTC Therapeutics – Vatiquinone (PTC743) trial

- Vatiquinone antioxidant, has shown positive results in small Phase II trials
- Phase III trial ongoing MOVE-FA
- Placebo controlled, 146 adults and children, 18 months
- mFARS (measurement of disease progression in FA)
- Started Dec 2020
- Anticipate results in second quarter of 2023

Minoryx Therapeutics – Leriglitazone (MIN-102) trial

- PPAR gamma is a protein found in cells. In FA, PPAR gamma cannot function properly
- MIN-102 is a PPAR gamma activator
- A Phase I clinical trial showed that MIN-102 is well tolerated, and able to reach the brain
- Phase II trial in Europe, 39 people – promising results for safety and upper limb ataxia. Changes in spinal cord inconclusive
- Data has been used to design a Phase III confirmatory study that is under discussion with the EMA and FDA.

Further trials

Resveratrol

- A naturally occurring compound found in the skin of red grapes. Potentially improves mitochondrial function.
- Micronised resveratrol Phase II trial in Australia (40 people, placebo controlled)

Nicotinamide adenine dinucleotide (NAD+) precursor (MIB-626,Metro International Biotech, LLC)

- Primarily safety trial in US
- 10 adults

Artesunate trial

- Phase I-II Efficacy-Toxicity study in France
- 20 people open label

Developments in new treatments
Symptomatic relief

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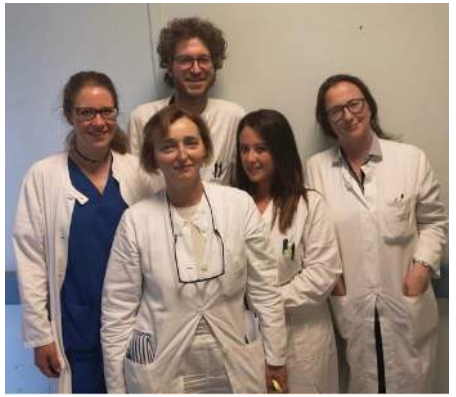
Current clinical trial

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

- Cerebellar transcranial Direct Current Stimulation (tDCS)
  - Ataxia UK funded a tDCS trial in Italy
  - Range of ataxias (FA, SCAs, MSA)
  - Results in 2021 showed improvements in SARA, ICARS, cognition and quality-of-life scores
  - Results in other studies in SCA have shown mixed results

- Transcranial Alternating Current Stimulation (tACS)
  - Ataxia UK are funding tACS trial by same group
  - tACs could potentially be more effective that tDCS



Opportunities to take part in research in the UK

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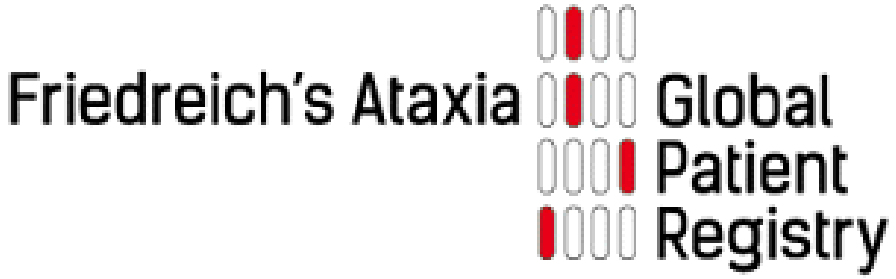
FA Global Patient Registry

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).



How do I register?

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

Friedreich's Ataxia Global Patient Registry

1000+
People with FA have registered since November 2019

51+
Countries represented in the FA Global Patient Registry

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FARA Friedreich's Ataxia Research Alliance

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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

EFACTS – European FA Consortium

- Multi-site European natural history study
  - London (and other European sites)
  - Still recruiting
  - Data being used to design trials
- Funding: EU, patient groups via Euro-ataxia and pharma partners

- London Ataxia Centre is recruiting: If you have been diagnosed with FA and are interested in taking part, please contact Prof Paola Giunti at p.giunti@ucl.ac.uk

EFACTS
Research For a Better Future

EUROPEAN FRIEDREICH'S ATAXIA
CONSORTIUM FOR TRANSLATIONAL STUDIES

Speech Therapy Study

- **Research question : Can intensive practice of articulation exercises improve speech in people with progressive ataxia?**
- Study will provide intensive one to one input with a speech and language therapist working on articulation in an online format
- Your involvement would last around 4 months in total including assessments and treatment, 4 weeks of these involve therapy input consisting of four 1 hour sessions per week
- Study is jointly funded by Ataxia UK and LSVT Global and carried out by researchers at Strathclyde University

If you are interested in taking part and would like more information, please email Prof. Anja Lowit a.lowit@strath.ac.uk

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Healthcare research

On our website:

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.

Moving from child to adult healthcare services

NCEPOD

The aim of this study is to produce a report for clinicians and other professionals about how to improve the care they deliver, and guidance for young people and families on what care you should expect to receive

Google

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Upcoming trials and opportunities

The European FA nicotinamide trial has been delayed.
Aim to recruit up to 90 people to the Nicotinamide trial in London when recruitment starts. Aim to start in 2023.

Join Ataxia UK to be kept informed of new research opportunities!

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

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Thank you for listening!

www.ataxia.org.uk

Please contact rwallis@ataxia.org.uk or research@ataxia.org.uk if you have any further questions!

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