Overview of ataxia research
Dr Julie Vallortigara

Ataxia training day
Exeter, 07 July 2017

Presentation

- Developments in
  - Diagnosis
  - Identifying potential targets
  - Clinical research/trials
  - Alleviating symptoms

- Recruitment to research studies

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Development in the diagnosis of the ataxias

New technologies in diagnosis

- Next generation sequencing (NGS) successful in identifying new genes:

- NGS used in Oxford Ataxia Specialist Clinic for screening for around 100 genes involved in the ataxias

Service available through NHS with a referral

- Exome sequencing used Newcastle and London Ataxia Specialist clinics

ATAXIA

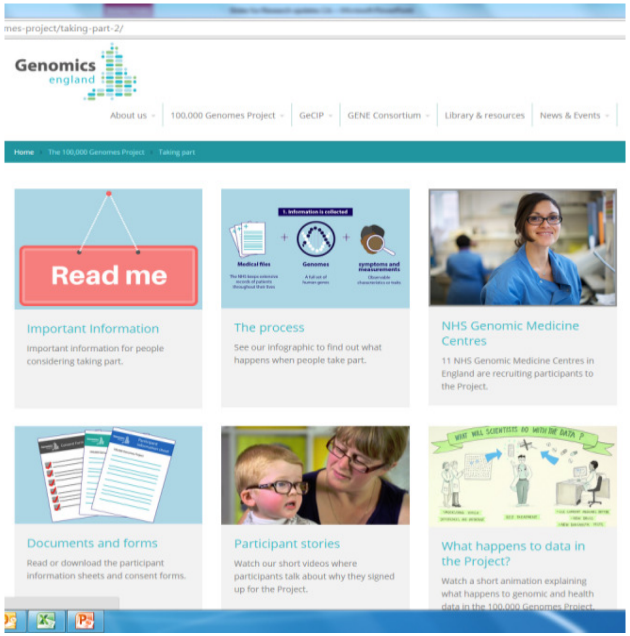
100,000 genome study

- Global studies such as *100,000 genome project* needed to discover new “ataxia” genes and new mechanisms responsible for the development of the disease
- National initiative in England to sequence 100,000 genomes in rare diseases
- Ataxias are included: 337 families with hereditary ataxia (~540 participants/genomes)- data Oct 2016
- Pilot study completed – second phase has started
- The study is bringing results, with 31,730 whole genomes sequenced

How to take part

- 13 Centres across UK taking part
- Scotland and NI have now joined
- Contact GP or neurologist
- Sample collected locally
- Ataxia expert group

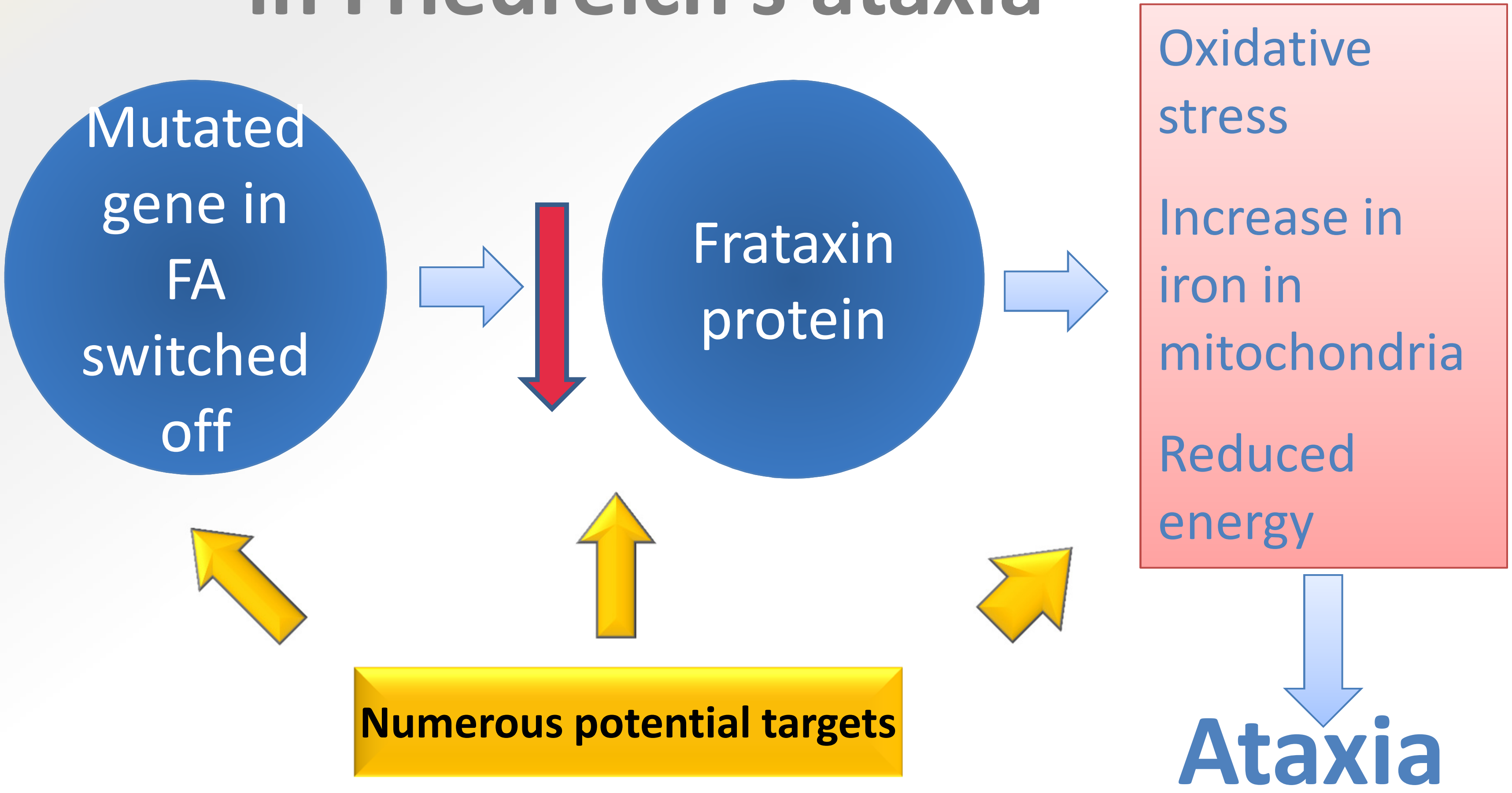
You can find more information on their website:
http://www.genomicsengland.co.uk/the-100000-genomes-project/



www.genomicsengland.co.uk

Identifying new targets

Numerous potential drug targets in Friedreich's ataxia



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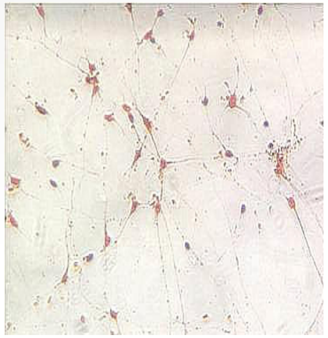
Strategies to treat Friedreich's ataxia: Gene therapy

- Renewed interest
- Vectors to deliver 'healthy' FA gene into cells
- Mostly inactivated viruses



Human neurons expressing the healthy frataxin gene (Dr Lim, Spain)

Universities
UK
Spain

Pharmaceutical companies
Agilis
AAV Life
Voyageur

ATAXIA

Delivering frataxin protein to mitochondria

- Using a carrier protein to deliver frataxin to mitochondria
- Commercial interest: Chondrial therapeutics and Bioblast

Chondrial Therapeutics Secures Up to $22.6 Million in Series A Financing and Licenses Novel Technology for the Treatment of Friedreich's Ataxia

Company Plans to Advance Pipeline of Product Candidates Focused on the Treatment of Rare Mitochondrial Diseases

Carole Ben-Maimon, MD, Named President & CEO

NEWS PROVIDED BY
Chondrial Therapeutics, Inc. →
Feb 06, 2017, 08:02 ET

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BALA CYNWYD, Pa., Feb. 6, 2017 /PRNewswire/ -- Chondrial Therapeutics, Inc., an emerging biotechnology company focused on the treatment of rare mitochondrial diseases, announced today that it has secured up to $22.6 million in Series A financing led by Deerfield Management and has appointed Carole Ben-Maimon, MD, as the company's president and chief executive officer. Concurrently, Chondrial announced the licensing of a novel investigational technology, CTI-1601, for the treatment of Friedreich's Ataxia from Indiana University Research and Technology Corp. (IURTC) and Wake Forest University Health Sciences. CTI-1601 was invented by R. Mark Payne, MD, professor of Pediatric Cardiology at Indiana University School of Medicine and director of the Translational Research Training Program of Indiana Clinical Translational Sciences Institute.

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Clinical studies

- Natural history studies
- Biomarkers and measures of ataxia
- Creation of European networks

Friedreich’s ataxia natural history study

- Multi-site European study:

- London, Dublin (and other European sites)
- 750 participants (still recruiting)
- Data for baseline, year 1 and 2 published
- Rating scales

EFACTS Research For a Better Future

EUROPEAN FRIEDREICH'S ATAXIA CONSORTIUM FOR TRANSLATIONAL STUDIES

- Funded EU initially, now by patient groups via Euroataxia and pharma

euro ataxia

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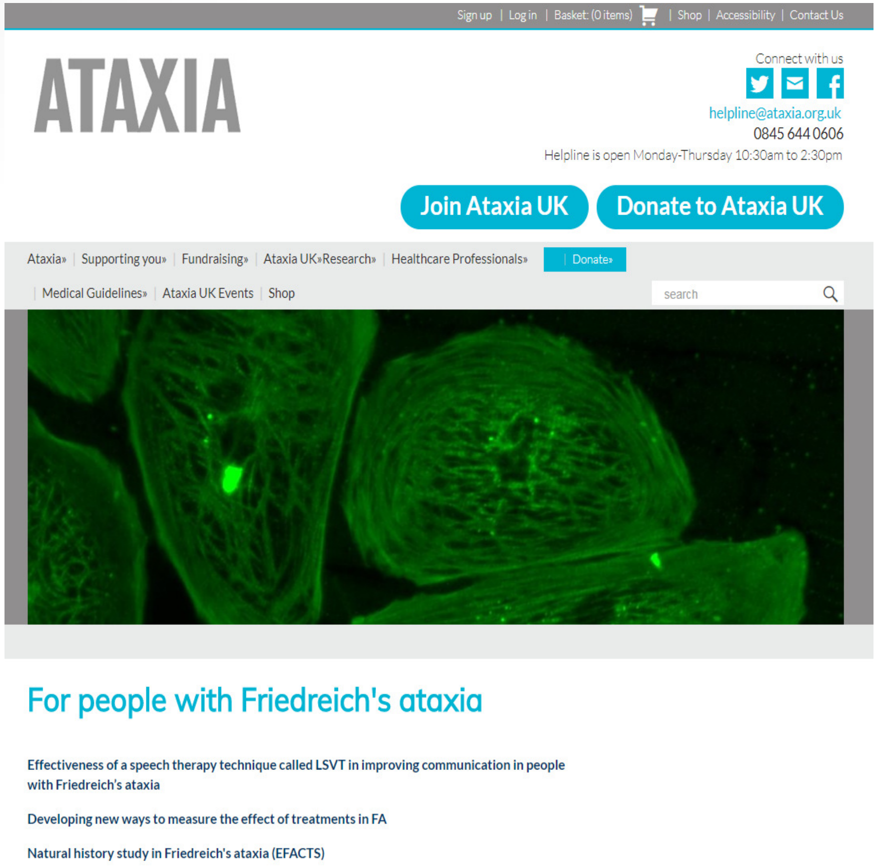
FA Clinical studies recruiting participants

- Tracking progression in FA to establish biomarkers
  - London
  - Oxford
  - Newcastle

- EFACTS (London, Dublin)

- Speech therapy LSVT effectiveness in improving communication



SCA3 natural history study

- Multi-centre European project coordinated at the German Centre for neurodegenerative diseases in Bonn (ESMI)
- Create a database with brain-imaging scans, standardised clinical assessments and blood samples from the patients, and will carry out a natural history study to assess how the participants' conditions progress over the years.
- In the UK the London Ataxia Centre is recruiting

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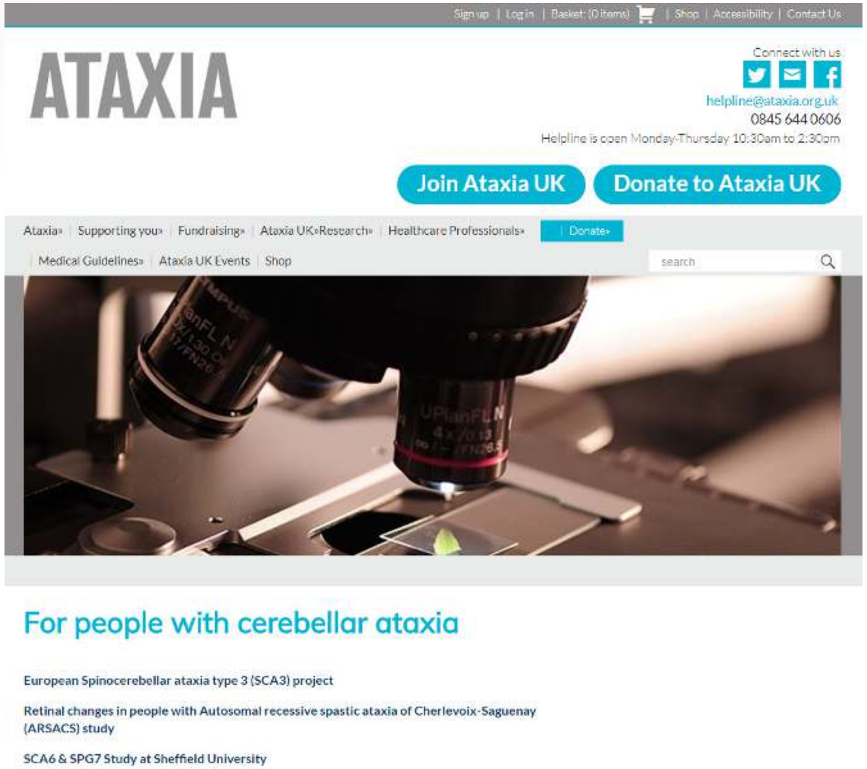
CA Clinical studies recruiting participants

- Balance and gait study in SCA6 and SPG7
  - Sheffield
- SCA3 project
  - London
- ARSACS study (London)



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Recent Clinical trials in the ataxias

- Academic-led trials
- Pharma trials
- Many drug repurposing

Nicotinamide trial in FA

- Switches gene on and increases frataxin in cells
- Positive results of pilot trial
- 10 people for 2 months, high dose
- Increased frataxin in blood cells
- Generally well tolerated (nausea)

Epigenetic and neurological effects and safety of high-dose nicotinamide in patients with Friedreich's ataxia: an exploratory, open-label, dose-escalation study

Vincenzo Libri, Cihangir Yandim*, Stavros Athanasopoulos, Naomi Loyse, Theona Natisvili, Pui Pik Law, Ping Kei Chan, Tariq Mohammad, Marta Mauri, Kin Tung Tam, James Leiper, Sophie Piper, Aravind Ramesh, Michael H Parkinson, Les Huson, Paola Giunti, Richard Festenstein*

Summary

Background Friedreich's ataxia is a progressive degenerative disorder caused by deficiency of the frataxin protein. Expanded GAA repeats within intron 1 of the *frataxin* (*FXN*) gene lead to its heterochromatinisation and transcriptional silencing. Preclinical studies have shown that the histone deacetylase inhibitor nicotinamide (vitamin B3) can remodel the pathological heterochromatin and upregulate expression of *FXN*. We aimed to assess the epigenetic and neurological effects and safety of high-dose nicotinamide in patients with Friedreich's ataxia.

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See Online/Comment
http://dx.doi.org/10.1016/S0140-6736(14)60573-0

Placebo controlled trial of nicotinamide

- Seeking funds to do large multi-centre placebo controlled trial
- Natural history data informing trial design (approx 200 people)
- Good news: EU grant (UK not included)
- Findacure model for funding trials
- Workshops for patient input

Ongoing and recent trials in FA

- **PUFAs** (polyunsaturated fatty acids) as *RT001* produced by Retrotope – Phase I extended, USA
- **Nrf2** (transcription factor) activator as *RTA 408* produced by REATA – Phase II, USA + <u>one site in the UK (start recruiting very soon)</u>
- **Interferon gamma** (produced by ACTIMMUNE) sponsored by Horizon Pharma – Phase III, USA
- **EPI-743** (antioxidant) produced by Edison Pharmaceuticals – Phase II, USA
- **Riluzole** (approved for ALS) – one year PCT shown positive results in both FA and SCAs

Episodic ataxia

- Ongoing Natural History study on various forms (US)

- Trial Phase 2 placebo controlled – episodic ataxia type 2

  testing 4-aminopyridine (US)

  awaiting results

Cabaletta trial in SCA3

- The drug is a high dose of the sugar trehalose that would be administered intravenously. The drug reduced the toxic protein aggregates, which are thought to cause the condition, and improve symptoms in animal models of SCA3.
- Bioblast Pharma has the patent
- Also patent Oculopharyngeal Muscular Dystrophy

Cabaletta trial results

- Results of phase IIa trial in US announced
- Six month open label trial in 14 people (plus 6 months follow-up)
- Results
  - Weekly infusions well tolerated
  - No change in SARA scale over 6 months (and stable for 12)
- Safety data on 57 people so far
- Need placebo controlled trial
- Could be a treatment for other SCAs caused by protein aggregates

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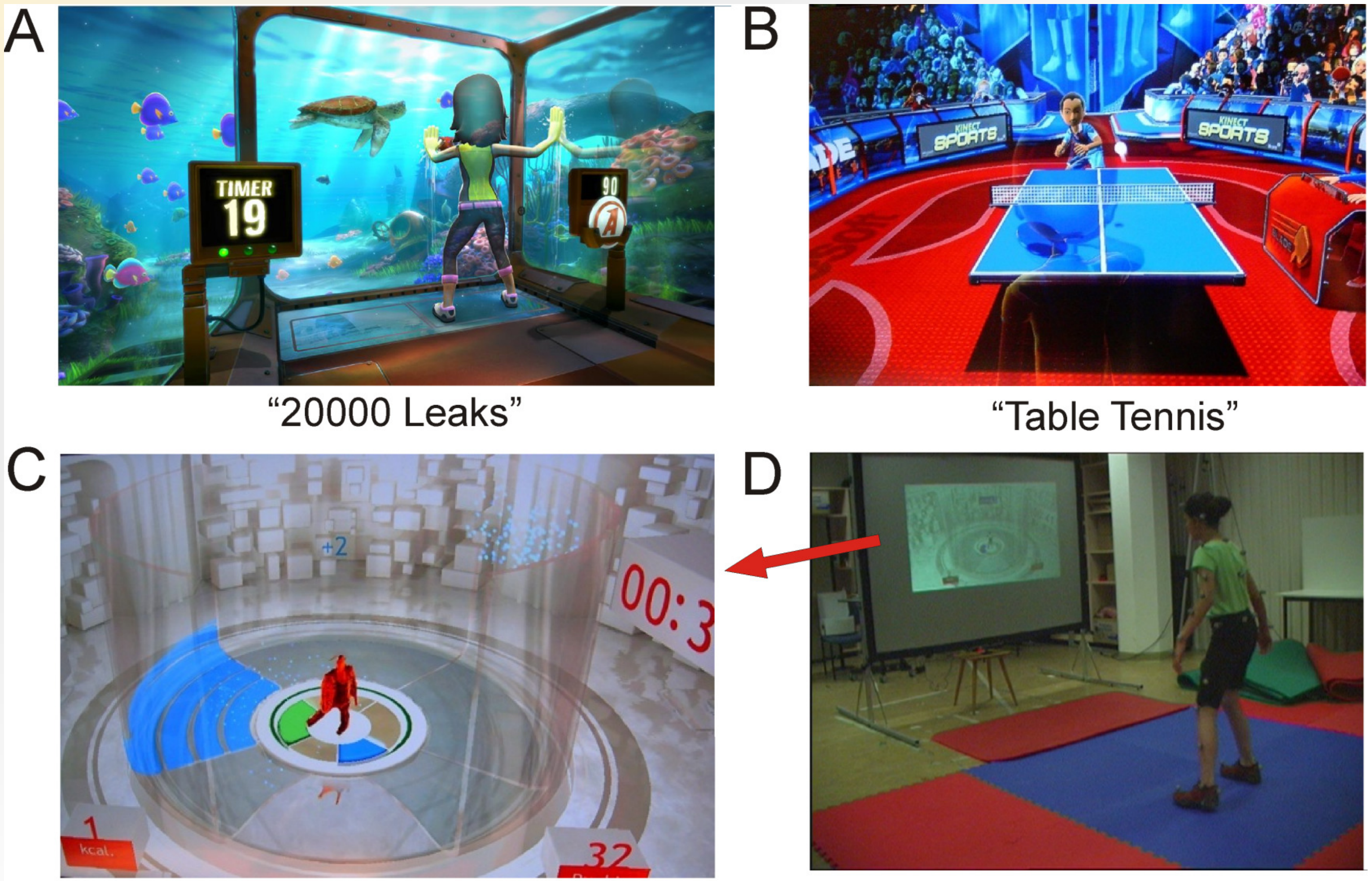
Alleviating symptoms

Move'n'fun project

- Aim: to assess the use of videogames controlled by full body movements on ataxia in children
- is based on findings that coordinative physiotherapy based training can be beneficial in adults with ataxia

Children were trained in the games in a motion lab and then continued training at home for a period of weeks



"20000 Leaks" "Table Tennis"

"Light Race" Playing "Light Race"

- The videogames are controlled by **full-body** movements and will use a **Microsoft Xbox kinect®**
- Training using videogames and can be done at home is expected to increase motivation in the children.

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Move’n’fun project: promising results

- Tested 10 children with progressive ataxias
- 8 week programme
- Assessed before and after treatment
- Found improvements in ataxia
  - ataxia rating scale (SARA – especially posture)
  - Quantitative movement analysis (decrease in step variability, lateral sway and errors in goal directed leg placements)

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Future plans for videogame project

- Test in children with more advanced ataxia
- Conduct larger trial
- Ataxia UK produced leaflet with advice based on current information
  - Protocol of current study
  - Important to be supervised by physiotherapist

New study using speech therapy in FA

- Majority of people with FA have dysarthria
- Gap in research studies to test SLT interventions
- Project to test the Lee Silverman Voice Treatment (LSVT)
- This treatment has shown some improvement in PD and some other conditions.
- Effectiveness measure by a range of outcomes measures

LSVT study recruiting participants

- 20 patients diagnosed with mild to moderate slurred speech due to FA
- Assessment before and after the treatment
- Treatment delivered via skype
- Feedback on the therapy process
- This project has started and now recruiting

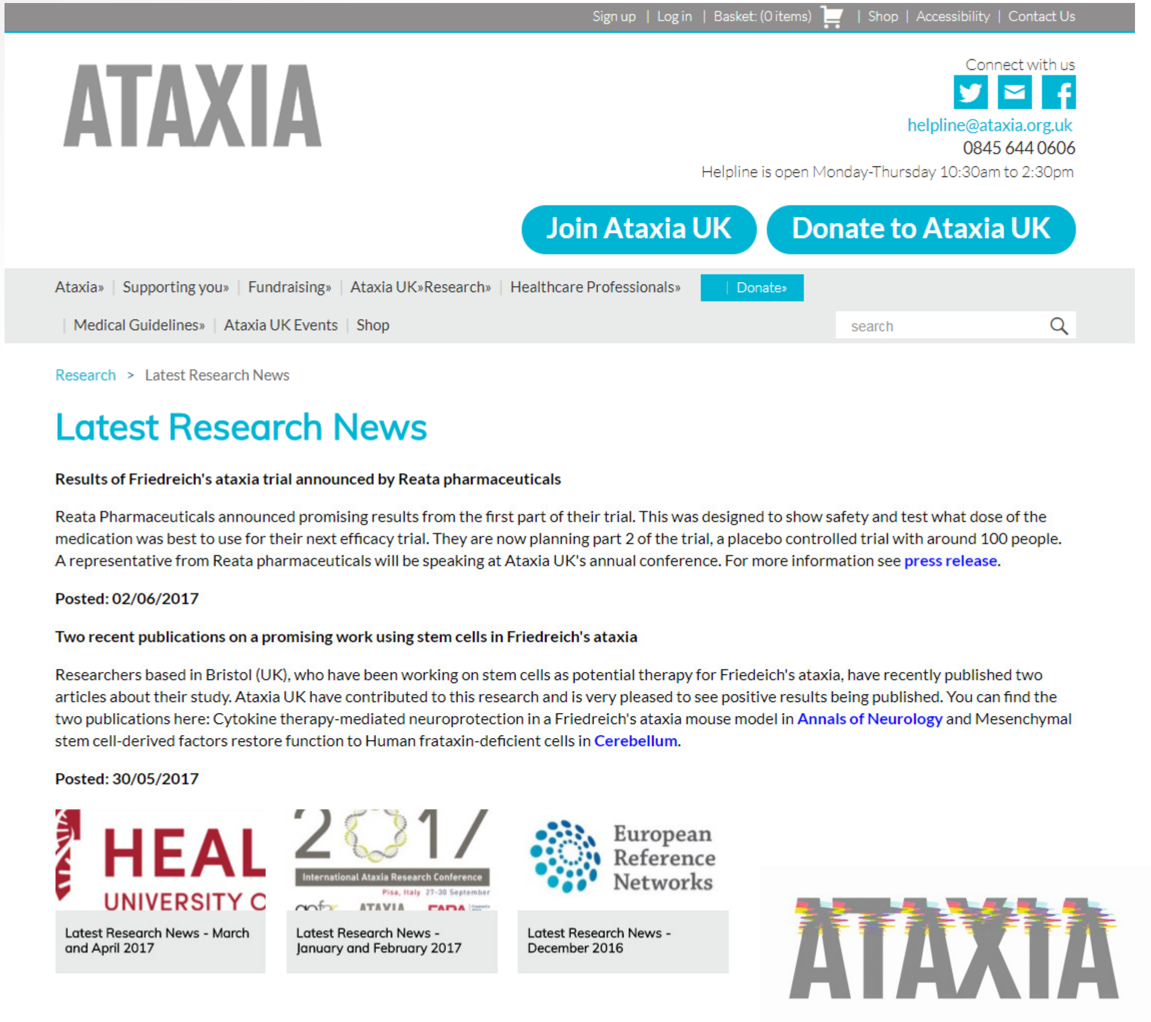
Opportunities to take part in research

Ongoing studies recruiting participants

- Genomics England project - UK
- ARSACS study – London
- SCA3 ESMI study - London
- SCA6 and SPG7 gait study - Sheffield
- Friedreich's ataxia natural history study – London, Dublin
- Friedreich's ataxia biomarker study – London, Newcastle, Oxford
- SLT study FA - UK

More information on research

- Website (Research news, taking part, conference)
- Join our Healthcare professionals' registry or researchers' registry



International ataxia research conference

Call for abstracts closed

registration still open

Late breaking news – by 17th July

2017
International Ataxia Research Conference
Pisa, Italy 27-30 September
gofar
ATAXIA
Ataxia UK
FARA Friedreich's Ataxia Research Alliance

THANK YOU!

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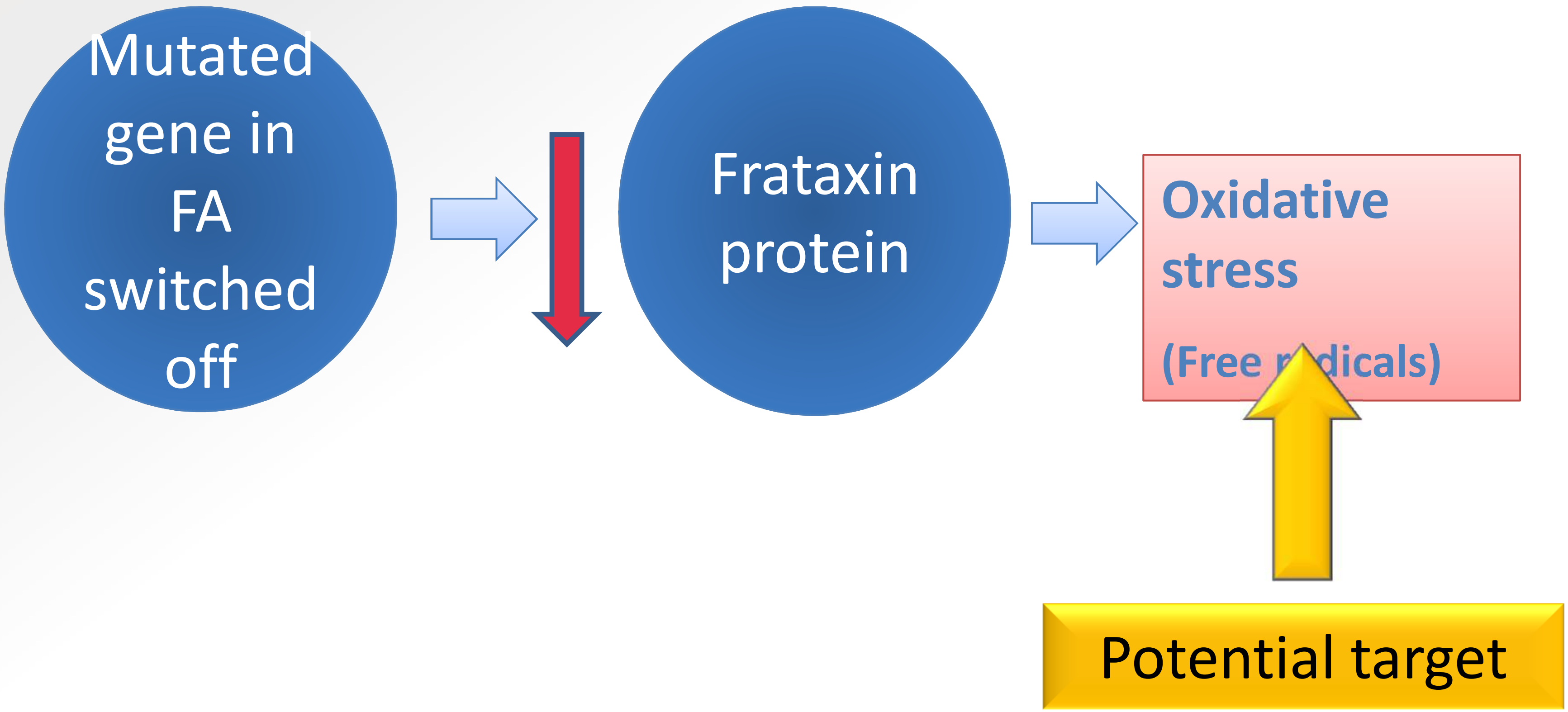
Strategies to treat Friedreich's ataxia: Tackling oxidative stress and cell damage



PUFAs (polyunsaturated fatty acids) - Retrotope

- Reactive oxygen species can cause lipid peroxidation (**oxidative degradation** of lipids)
- Lipid peroxidation is a **self-propagating chain-reaction**, the initial oxidation of only a few lipid molecules can result in significant tissue damage
- It is found to occur in FA and other neurodegenerative diseases

PUFAs (polyunsaturated fatty acids) - Retrotope

- RT1001 is deuterated linoleic acid
- Replaces naturally occurring linoleic acid in cell membranes and improves resistance to free radical damage
- Has an effect in FA animal studies
- Animal studies shown good safety
- Absorbed, metabolized, distributed and excreted similar to dietary linoleic acid

PUFAs (polyunsaturated fatty acids) trial -Retrotope

Study 1

- Phase I trial of RT0001 in US
- 18 participants with FA
- Randomised double blind
- Two doses for one month

Results

- Safe and well tolerated
- Found maximum tolerated dose
- Some signs of ‘drug effect’

Study 2 and beyond

- 6 month extension refine dose with a more relaxed diet
- Other trials

Sep 2016 press release

RTA 408 trial - Reata

- Nrf2 (transcription factor) activator with antioxidant properties
- Multi-centre phase 2 trial ongoing (MOXIe study)
- About 108 people (US sites ongoing)
- Two parts:
  – dose escalation placebo
  – two doses vs placebo
- Ataxia UK discussed trial with Reata

REATA PHARMACEUTICALS

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RTA 408 trial - Reata

New trial at London Ataxia Centre – recruiting soon (Dec 2016?)

Inclusion criteria

People with FA 16-40 years of age

Ability to do a bicycle exercise test

12 weeks treatment

5-7 visits

Information on Ataxia UK website soon

Contact Cathleen.Chabo@uclh.nhs.uk

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Interferon gamma 1b trial in FA

- Naturally occurring molecule; involved in the body's immune response
- Licensed for two other rare conditions
- Increases frataxin in cells and mice
- Two phase II human clinical trials positive results:
    - Italy – safety of 3 escalating doses (adults)
    - USA – identifying safe dose for children

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Interferon gamma 1b trial

- Phase III placebo controlled trial in the US
- 92 participants for 26 weeks
- Horizon pharma has marketing rights in US, with Europe to follow shortly
- Top line results announced in Dec
  - Did not meet primary endpoint (sig diff baseline and placebo in neuro-FARS)
  - Analysing data further

ACTIMMUNE®
(Interferon gamma-1b)

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Riluzole trials

- Approved treatment for amyotrophic lateral sclerosis
- Rationale: mechanism of action unknown but thought riluzole regulates nerve impulses and acts as a neuroprotectant
- Thought could have a generic effect on ataxias

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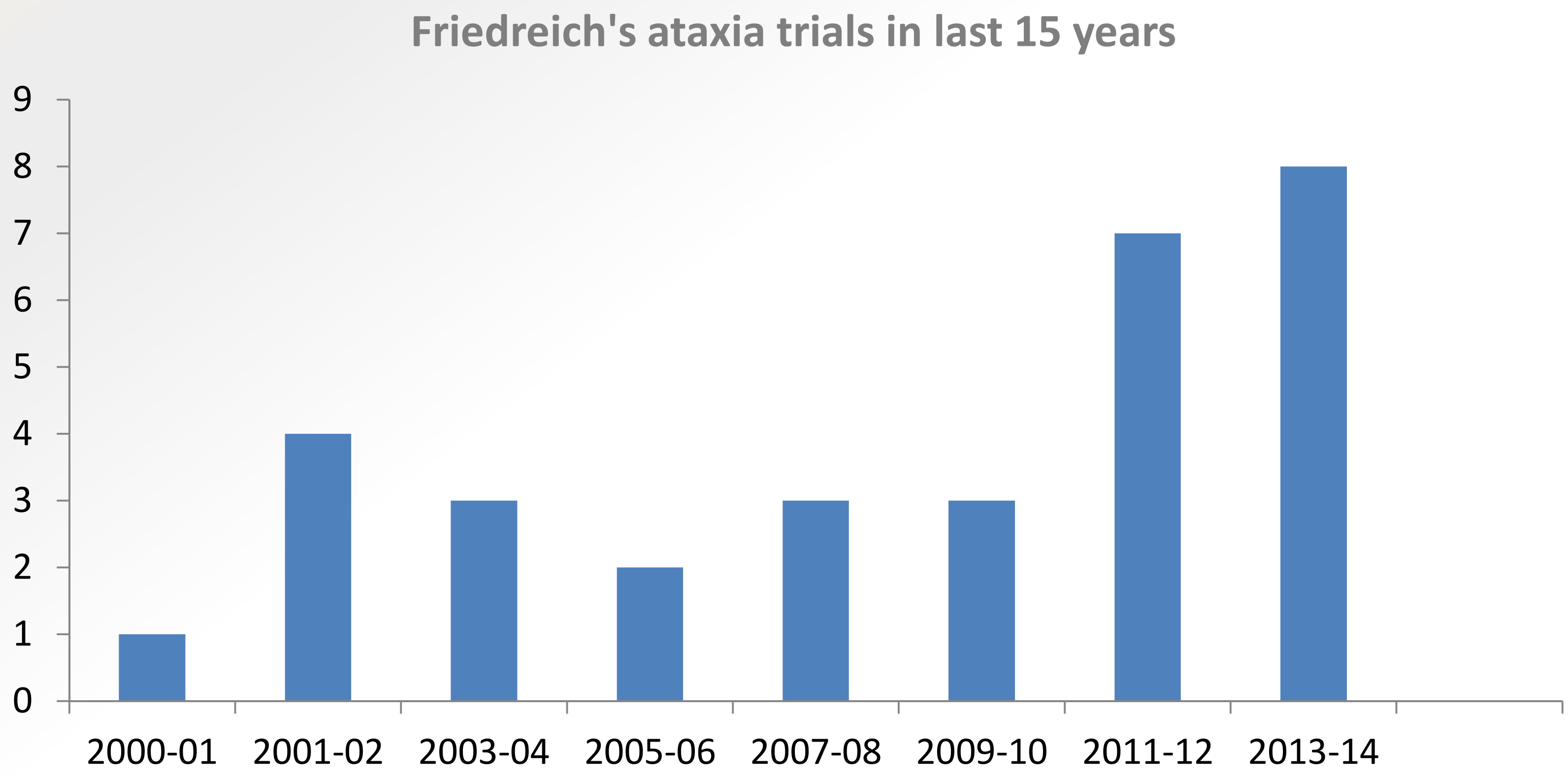
Riluzole trial results

- One year double blind placebo controlled trial
- Participants: final analysis 25 vs 25
- SCAs and FA
- SARA score improved in treatment group compared to placebo at 3 and 12 months

Authors say: 'Riluzole could eventually be used in clinical practice but confirmatory studies on larger and disease-specific populations, for a longer observation period (to reduce the effects of fluctuations in slowly evolving diseases) are needed'

Lance 1

Trials on ataxia



Pubmed search ‘Friedreich* AND trial in 2 year periods

Interest from industry

- Pharmaceutical companies increased interest in ataxia
  - Legislation: incentives for rare diseases
  - Making use of basic research developments
  - Ataxia Centres
- Ataxia UK engaging with companies
  - eg: Pfizer partnership

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Advances in research and future prospects

- New technologies emerging being exploited for ataxias
  - Sequencing whole genomes
  - Gene therapy
  - Stem cell therapy
- More animal and cell models available and drug targets identified
- Companies increased interest