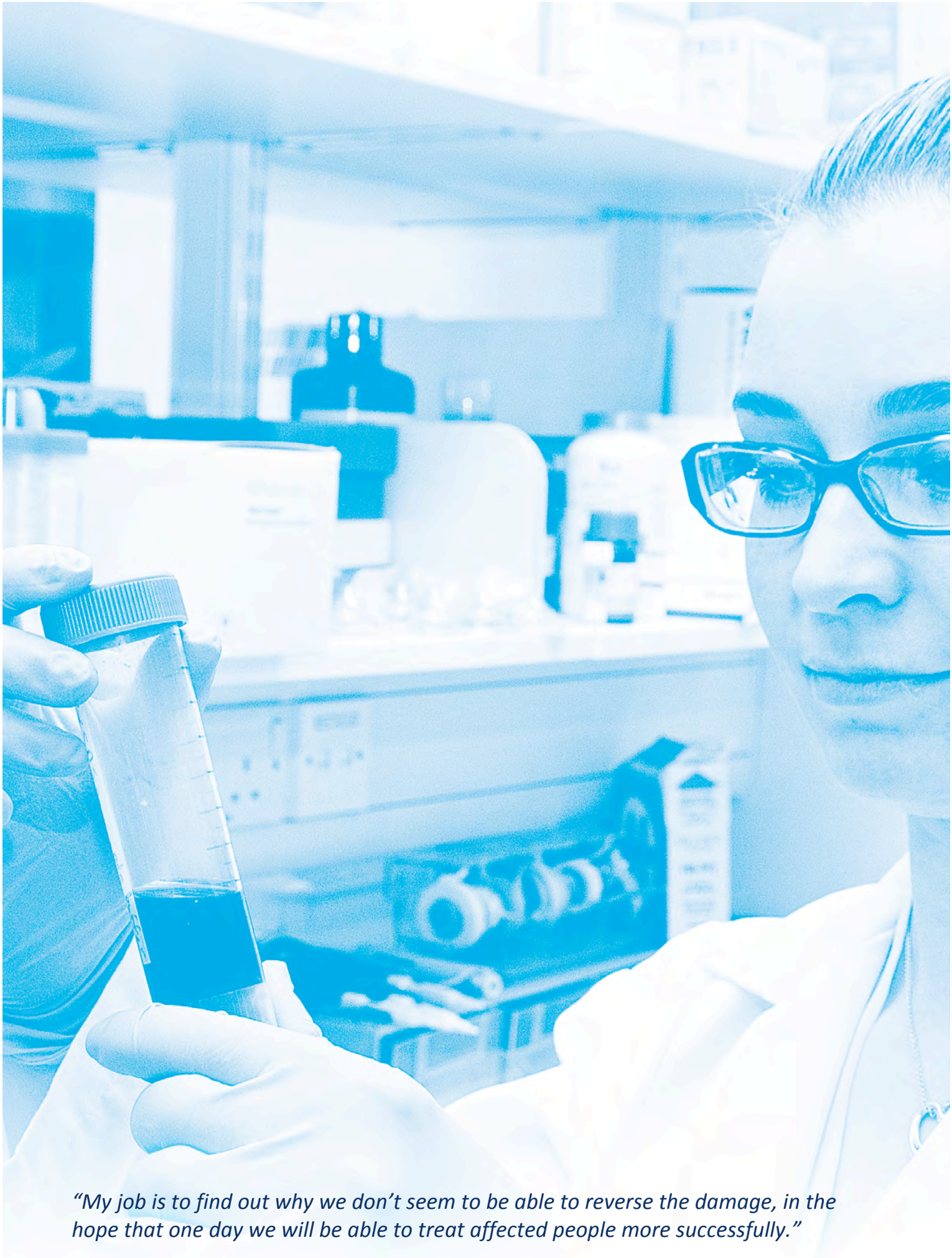
Ataxia UK

VISION 2020

aiming for a cure

Ataxia UK RESEARCH STRATEGY



"My job is to find out why we don't seem to be able to reverse the damage, in the hope that one day we will be able to treat affected people more successfully."

Kate Duberley, Ataxia UK-funded PhD student, is researching ataxia caused by low levels of a substance called Coenzyme Q_{10} (CoQ10) and the potential of CoQ_{10} to reverse the damage done to the brain.

Our 2020 Vision - aiming for a cure …

Foreword by Professor Barry Hunt

Ask any parent what their hope is for a child affected by ataxia and they will tell you that it is for a cure. Ask any adult with ataxia and they will tell you their hope is for a cure or at the very least a treatment that can arrest any further development of their ataxia.

At Ataxia UK we share their hopes for the future.

The prospects of finding a cure or an effective treatment for the ataxias are better today than they have ever been. This *could* be within reach for the current generation. But as with all neurological conditions, we must tread a fine line between promising something which may not be delivered, and giving genuine hope.

Nevertheless, it is our duty to offer that genuine hope today – and it is right and proper to do so. The advances made in genetics, molecular biology and stem cell research over recent years have been quite simply breath-taking. In today's world, advances in science are happening very quickly in many countries. Often, these advances are over-enthusiastically communicated by the media and we are ever mindful of the need not to offer a false dawn to those who are looking for a breakthrough every day of their lives.

We must do all we can as an organisation to ensure that cutting edge research is funded and that researchers communicate well, both with each other and with those affected by the ataxias. We are committed to making increased efforts to do exactly that; working with colleagues across the globe to pull in one common direction – a cure for *this* generation.

A great deal has already been done, but we must engage with the best research and drive it forward, wherever it may be. We must be even more active in seeking out the areas in which most progress is being made, and securing funding for that research. We must also remember that we do not know whence a cure will come, and so we will devote some of our resources to new lines of research.

Our ultimate goal will obviate the requirement for organisations such as ours. Until that is achieved, we must also do all we can to communicate the need for ataxia research and to be as clear as possible about where it is directed, and why, with those who fund that research (or are considering doing so). That is the aim of this document.

I ask that you take the time to read it and to consider joining us in our quest to find a cure for this generation.

Professor Barry Hunt
October 2012

Ataxia UK's Research Strategy

Ataxia UK is the country's leading charity providing vital support services for people with different forms of ataxia; a group of neurological conditions that affect people's ability to co-ordinate movements. Most types of ataxia are progressive, meaning that people's conditions gradually get worse over time. Many people lose their ability to walk, and need to use wheelchairs. Problems with hearing and speech can cause communication difficulties that make people feel isolated, and people with ataxia often become reliant on others for their everyday needs. Many types of ataxia are life-limiting, reducing people's quality of life and carrying the risk of an early death.

There are more than 10,000 people in the UK today with ataxia, and as yet, there is no cure or effective treatment. Ataxia UK supports people affected by ataxia in many different ways. Importantly, we fund world-class medical research that has great potential.

In recent years, we have been successful in raising money for important research, and much progress has been made. So now is the time to make sure that funders understand the possibilities of research, and to ensure that research is fully coordinated around the globe. This is what we have set out to achieve in cooperation with our international partners.

It is an absolute priority to find effective treatments that can stop ataxia from progressing, or cure it. In the meantime, we also aim to fund research into alleviating symptoms. Our research must reflect the wide spectrum of ataxias that affect the people we support.

Huge strides have been made in the last 20 years to identify genes that cause ataxias, leading to more people than ever getting a specific diagnosis. With recent developments in genetics, there are now opportunities for research to advance such that everyone with ataxia can be accurately diagnosed. We need to harness this potential and also ensure that research findings are translated into clinical practice. Ataxia UK has helped develop and accredit Specialist Ataxia Centres within the NHS, which play a fundamental role in the translation of research into benefits for patients.

Understanding of the causes and mechanisms involved in many different ataxias has improved, and this has lead to the identification of promising targets for therapy. The need for model systems to test these is paramount and Ataxia UK has played a major role in developing a number of cell and animal models that are now in use by scientists around the world. With increased understanding we are now at a point where we have promising therapies being tested in human trials that we hope will lead to treatments.

Lastly, the relative rarity of each form of ataxia means there has been limited interest from pharmaceutical companies, so our support for early-stage work is vital in keeping ataxia on their clinical development agenda. With changes in legislation to encourage companies to invest in clinical trials on orphan conditions and drugs, the developments being made in ataxia research will be an important way to drive their interest. We aim increasingly to engage with pharmaceutical companies as we believe that only through working in partnership can we achieve our vision – a world free of ataxia.

Research activities

Ataxia UK currently:

- Funds research in the UK and internationally
- Facilitates the recruitment of participants for research studies
- Disseminates research information
- Organises research conferences and workshops
- Fosters research collaborations
- Encourages researchers to work on ataxia

We now hope to go a lot further with a determined fundraising effort and awareness-raising campaign around the ataxias. This will accelerate progress and raise the prospects for a cure.

Funding research

Specifically, we will fund research that can be demonstrated to be of actual or potential benefit to finding a cure or effective treatment for one or all of the progressive ataxias.

There are many different types of ataxia, including conditions such as Friedreich's ataxia, and the spinocerebellar ataxias. Our research will reflect the wide spectrum of ataxias that affect the people we support.

We will aim to build up our research funds to ensure we are ready to direct them into research programmes in which there is a real prospect of genuine progress.

In doing so, we will always promote a balanced programme of:

- basic and applied research
- long and short-term projects to gather preliminary data
- projects that are speculative and ones with clear potential benefits
- research that could benefit people of different ages

We will continue to work with our colleagues making excellent progress in North America, Europe and Australasia, and will foster new relationships wherever there is great promise.

Strategic themes

Four key strategic themes for research funded by Ataxia UK have been identified as the main areas that require investment.

1. Improving diagnosis
2. Finding treatments
3. Moving from laboratory studies to human trials
4. Alleviating symptoms

1. Improving diagnosis

There have been huge advances in genetics and genomics worldwide. For single-gene ataxias, the effect could be dramatic, with diagnostic tests for all inherited ataxias becoming a reality. We are already beginning to see these developments having an impact in ataxia research, but there are still challenges ahead.

Despite these advances and the identification of many new genes causing a number of ataxias, there are still a large number of people with no specific diagnosis. We aim to increase the number of people with accurate diagnoses through supporting research into identifying previously unknown causes of ataxia and in translating research findings into clinical practice. The creation of Ataxia UK accredited Specialist Ataxia Centres in UK hospitals also helps us achieve this aim.

Next generation sequencing to improve diagnosis in ataxia

Ataxia UK's award to Dr Andrea Nemeth at the Oxford Specialist Ataxia Centre has been instrumental in testing next-generation sequencing in patients with ataxia of unknown cause. It has resulted in more patients gaining a specific diagnosis and plans are underway to establish this (initially research-based) service within the NHS.

Research into next generation sequencing is continuing in Dr Nemeth's lab

2. Finding treatments

It is paramount that we invest in research to find treatments which will stop ataxia from progressing and possibly to reverse the damage done.

We will invest in research that aims to identify pathological pathways and new drug targets, to screen for disease-modifying drugs and to test any promising therapies in cell and animal models.

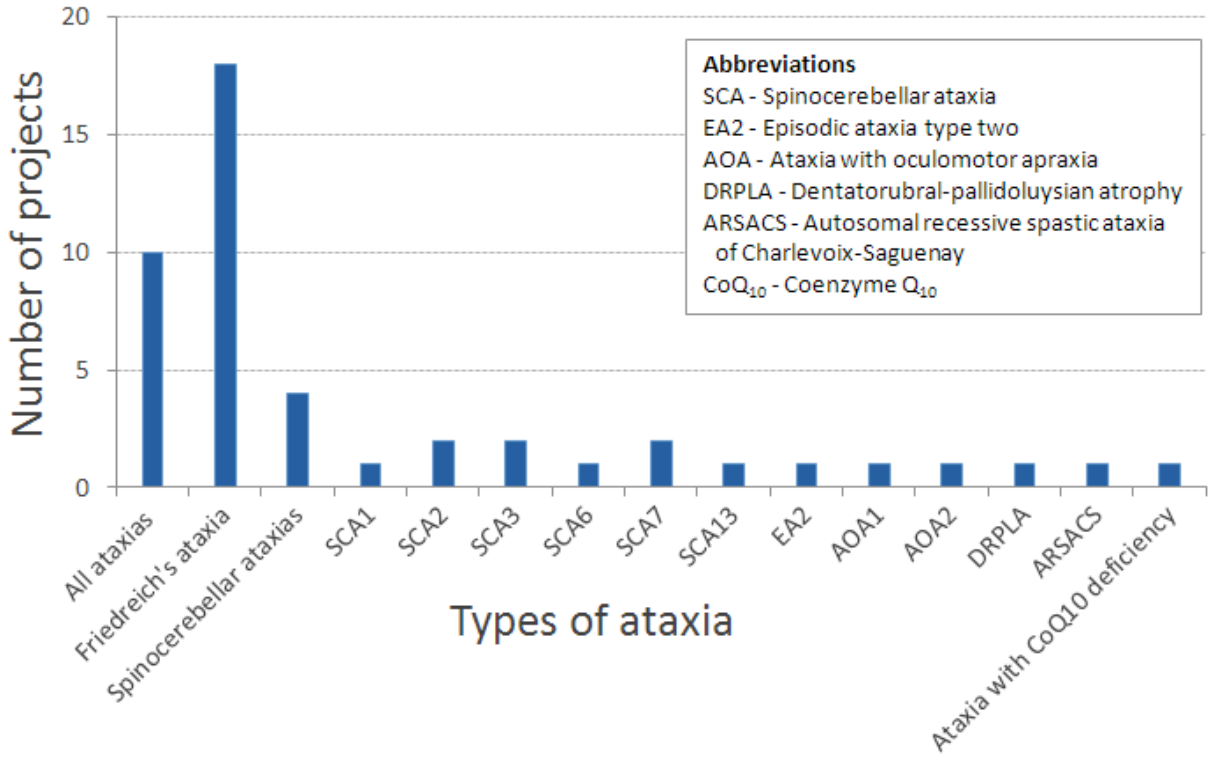
We also recognise the importance of developing model systems specific to ataxia and have supported the creation of cell and animal models that are being used extensively by ataxia researchers worldwide.

Advances in identifying the different genes that cause ataxia will also help us in finding treatments.

Detailed understanding of each condition will lead us to targeted therapies for each condition, as it is unlikely that there will be a single cure for all ataxias. On the other hand, common pathways have been identified in a number of ataxias that could lead us to a treatment that can be used for a related group of ataxia conditions.

Research funded by Ataxia UK

Ataxia UK believes it is important to fund research in a wide spectrum of ataxias.

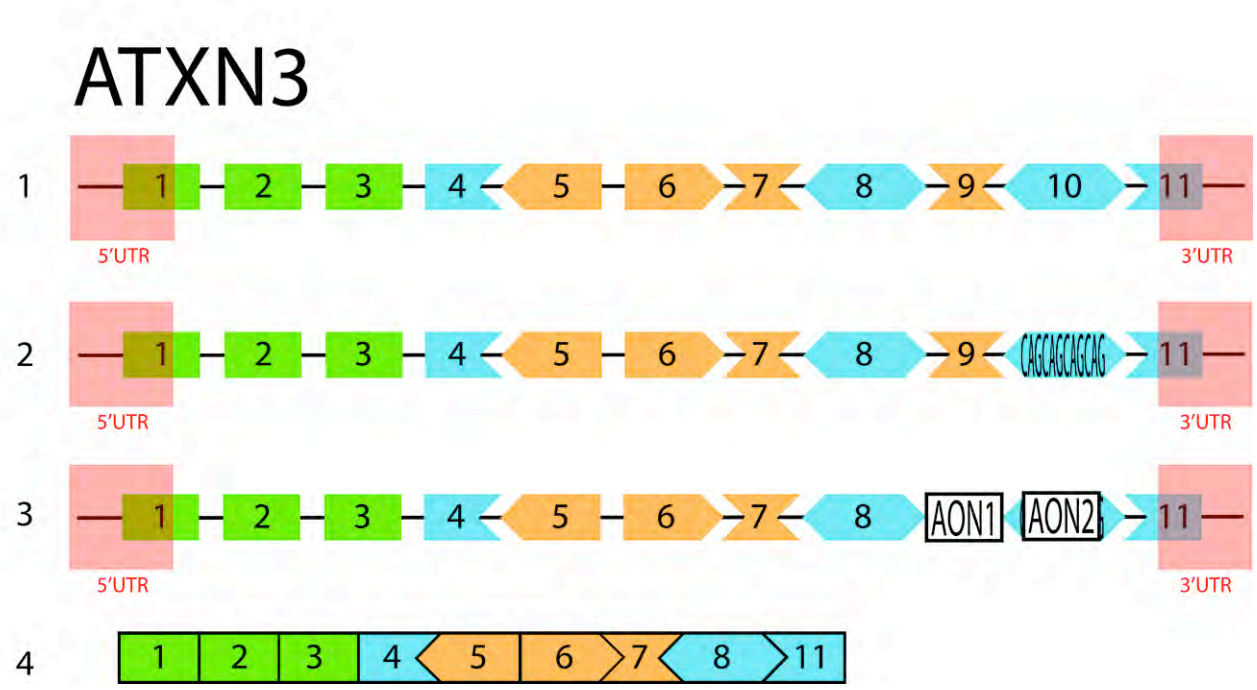


An overview of research funded beween 2007 and 2012.

Exon skipping and gene silencing as potential genetic therapies for spinocerebellar ataxias

Ataxia UK recently awarded a grant to Dr Willeke van Roon-Mom at Leiden University in the Netherlands to explore a new approach that could prove beneficial in a number of spinocerebellar ataxias. We also engaged with the ataxia charity in the Netherlands which was pleased to contribute to this research.

This project aims to test a genetic therapeutic approach known as exon skipping in cells derived from people with spinocerebellar ataxia (SCA) type 3, SCA7, SCA17 and DRPLA. These types of cerebellar ataxias are all caused by expansions of certain sections of genes (known as CAG repeat expansions) that lead to the production of toxic protein. The exon skipping technique would bypass the part of the gene that produces the toxic protein, thus producing non-toxic functional protein. This technique has already been shown to work in another neurological condition in laboratory experiments using cells and has also generated interest from industry, resulting in a step forward to the clinical trial stage. We are hopeful that if this technique is shown to work in these cells in ataxia there will be a direct route for translation into a therapy to be tested in human trials.



Schematic representation showing how single strands of DNA known as antisense oligonucleotides (AONs) can be used to skip exons containing CAG repeat expansions, by binding to, and thus inactivating the toxic repeat.

The ATXN3 gene is shown in (1), it is mutated in SCA3 by having CAG repeat expansions in exon 10 (2). AONs are used to skip the exon containing the CAG repeat expansions (3) and a new gene without the CAG repeats is created (4).

3. Moving from laboratory studies to human trials

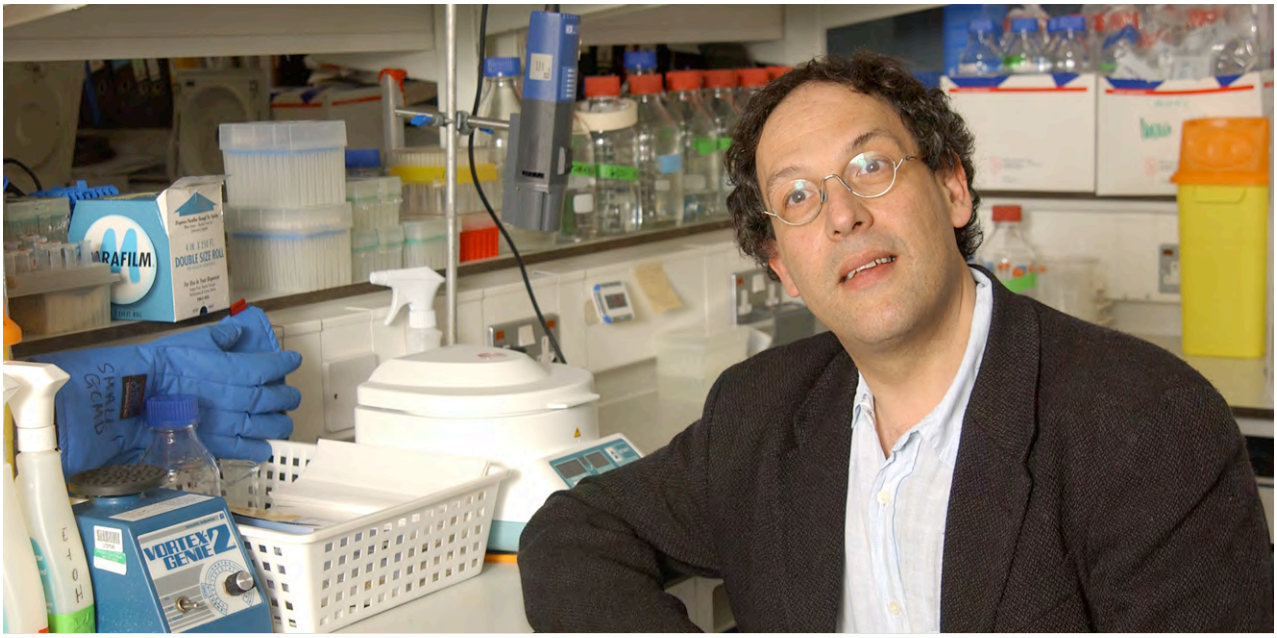
There has been great excitement over the last few years in the ataxia research community, about a number of potential treatments that showed promise in pre-clinical studies and have moved on to human trials. We are committed to funding pilot studies to test promising therapies. We also aim to support larger, multi-centre trials that need to be international due to the rarity of the ataxia, by assisting with recruitment of participants and engaging with pharmaceutical companies and ataxia-related charities worldwide.

A radical new therapy for Friedreich's ataxia?

Our funding enabled Professor Richard Festenstein and his team at Imperial College London to explore a potentially radical new therapy. Their research provided the first evidence that a type of drug, known as a histone deacetylase inhibitor, can jump-start the frataxin gene in cell samples from people with ataxia.

"These drugs are thought to work by 'opening up' the frataxin gene, making it accessible to the cellular machinery which switches it on," says Professor Festenstein. "This then leads to an increase in the levels of frataxin (the protein deficient in people with the condition) in cells taken from Friedreich's ataxia patients."

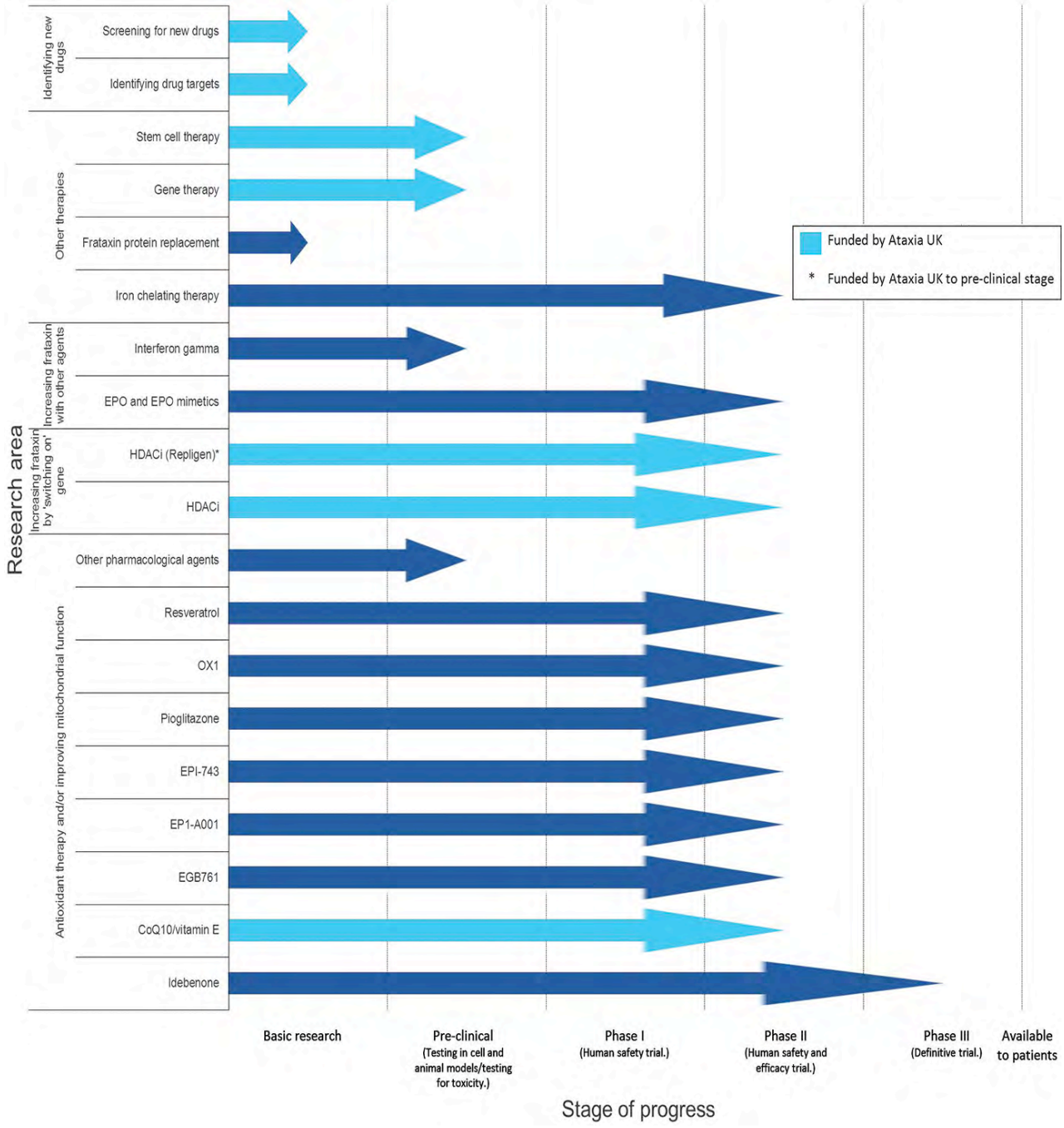
As a result of these exciting initial studies, a pilot clinical trial of one drug as a potential treatment for Friedreich's ataxia has been supported. We funded this exciting new development together with three other ataxia charities. The impact of our funding of the initial studies has been global, and a number of additional teams are studying various other histone deacetylase inhibitors as potential therapies for Friedreich's ataxia.



Professor Richard Festenstein is investigating a potential therapy for Friedreich's ataxia

International research in Friedreich's ataxia

Friedreich's ataxia – the most common inherited ataxia – has recently seen much progress in research, with many avenues being explored and some reaching the stage of human trials. The figure below illustrates the current status of research in Friedreich's ataxia and the contribution that Ataxia UK is making to help move things forward. The increased interest from pharmaceutical companies can also be seen with a few industry sponsored trials.



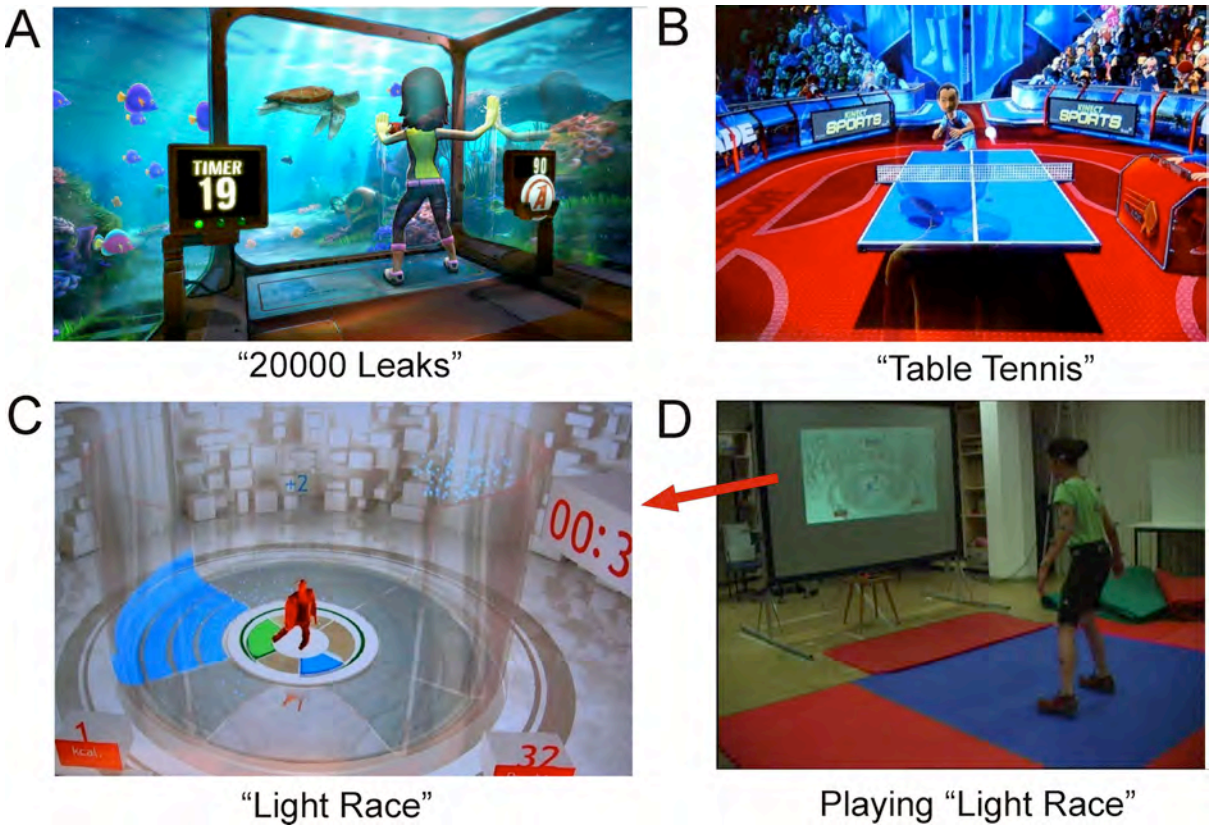
4. Alleviating symptoms

It is important to recognise that there are treatments that do not cure people with ataxia, but may help them in the short-term. Various treatments can alleviate some of the symptoms associated with having a type of ataxia, but to date no proven treatments have been found that improve balance and co-ordination. Much more can be done to improve people's quality of life. Ataxia UK believes it is important also to support research that may have more immediate impact on people with ataxia and thus funds research in areas such as physiotherapy, speech and language therapy and rehabilitation.

Videogame training for children with ataxia

Ataxia UK is funding a novel project that assesses the ability of videogames to improve co-ordination in children with ataxia. "We will conduct a systematic assessment of the risks and effectiveness of co-ordination-training controlled by full-body movements," said Dr Matthis Synofzik, one of the lead researchers. This exciting project is co-funded with Ataxia Ireland and Deutsche Heredo-Ataxie Gesellschaft e.V.

"Our assessments will use several clinical ataxia rating scales as well as quantitative movement analysis. And we should be able to compare the effects of training in a laboratory setting compared to home-based training."



Screenshots from the three games used in the study (A-C). (D) Snapshot from the "Light Race" game: a patient performs dynamic stepping movements in order to control the avatar's movement to the highlighted areas on the floor.

Facilitating recruitment of participants to research studies

Ataxia UK recognises the importance of patient databases for use in research. These are an essential tool in ensuring there are sufficient people coming forward to take part in clinical trials and other important research studies. As a membership organisation, we have a large database of people with different types of ataxia. Accurate records are kept about each individual's diagnosis and key demographic data is also recorded. This is an immensely useful resource that has been employed by researchers working both in academia and in industry and we are keen to continue providing this. With developments in research we anticipate that demand for this resource will increase. Ataxia UK assists the research process by acting as a link between researchers and people with ataxia who are particularly interested in taking part in research. Ataxia UK will always follow rigorous procedures to ensure high ethical standards are maintained and that no information is passed on to researchers without specific permission from potential participants.

Information sharing

Information exchange is imperative for progress in research. We are increasing our efforts with international colleagues to make sure that research findings are shared across international boundaries, so that resources can be directed in the most effective way possible.

Researchers funded by Ataxia UK are required to disseminate their results through peer-reviewed high-impact journals. In addition, any research outcome or product (eg animal models) should be made freely available to other researchers.

Information exchange and collaborations are also encouraged with researchers in other research areas, both in academia and industry (such as mitochondrial disorders, gene therapy, stem cell therapy and neural regeneration). Reports from Friends of Ataxia UK based upon their personal experience of living with ataxia and what benefits or worsens their symptoms are also encouraged, as we believe that their analysis may lead to new lines of research.

We believe it is vital to ensure that information on ataxia research is made available to people affected with ataxia in an easily comprehensible format. We therefore have regular articles in our quarterly magazine, *The Ataxian*, ensure the website has an extensive section on research for a lay audience and give presentations at conferences and meetings.

Ataxia UK also aims to disseminate information about research and about ataxia in general to healthcare professionals with interest in ataxia in order to increase awareness of the conditions and their understanding and result in better care for people with ataxia. Ataxia UK has held a number of well-attended ataxia training days for healthcare professionals that received very positive feedback.

"The event gave well-balanced and up-to-date information which will have a positive impact on future practice."

Feedback from a delegate attending the ataxia training day in Manchester

Organising and supporting conferences

Ataxia UK will encourage information exchange by supporting national and international links, for example, funding attendance at international meetings by ataxia researchers and Ataxia UK representatives.

Ataxia UK has organised its own international research conferences and has worked in partnership with other ataxia charities worldwide to ensure relevant, timely research conferences and meetings take place. International ataxia conferences have been organised by Ataxia UK in 2005/2006 and, together with Ataxia Ireland, in 2008 and 2012.

Fostering collaborations and working together

Ataxia UK is keen to promote research that is collaborative in nature and which promotes exchange of information between different research groups.

In addition, the charity has had a big drive to engage with ataxia charities worldwide, which is resulting in many beneficial partnerships. This has in part been due to playing a major role in coordinating activities of *euro*-ATAXIA, an umbrella organisation consisting of ataxia organisations around Europe. We have also partnered with ataxia charities in the USA and Australia, for example, in a stem cell initiative. There is now increased co-ordination of conferences worldwide, increased communication flow and many more jointly-funded research projects. We aim to engage further with pharmaceutical companies, as we believe that only through working in partnership can we achieve the best results.

In 2011 we partnered with the Motor Neurone Disease Association to jointly fund a project that is of relevance to both ataxia and motor neurone disease.

Encouraging researchers to focus on ataxia

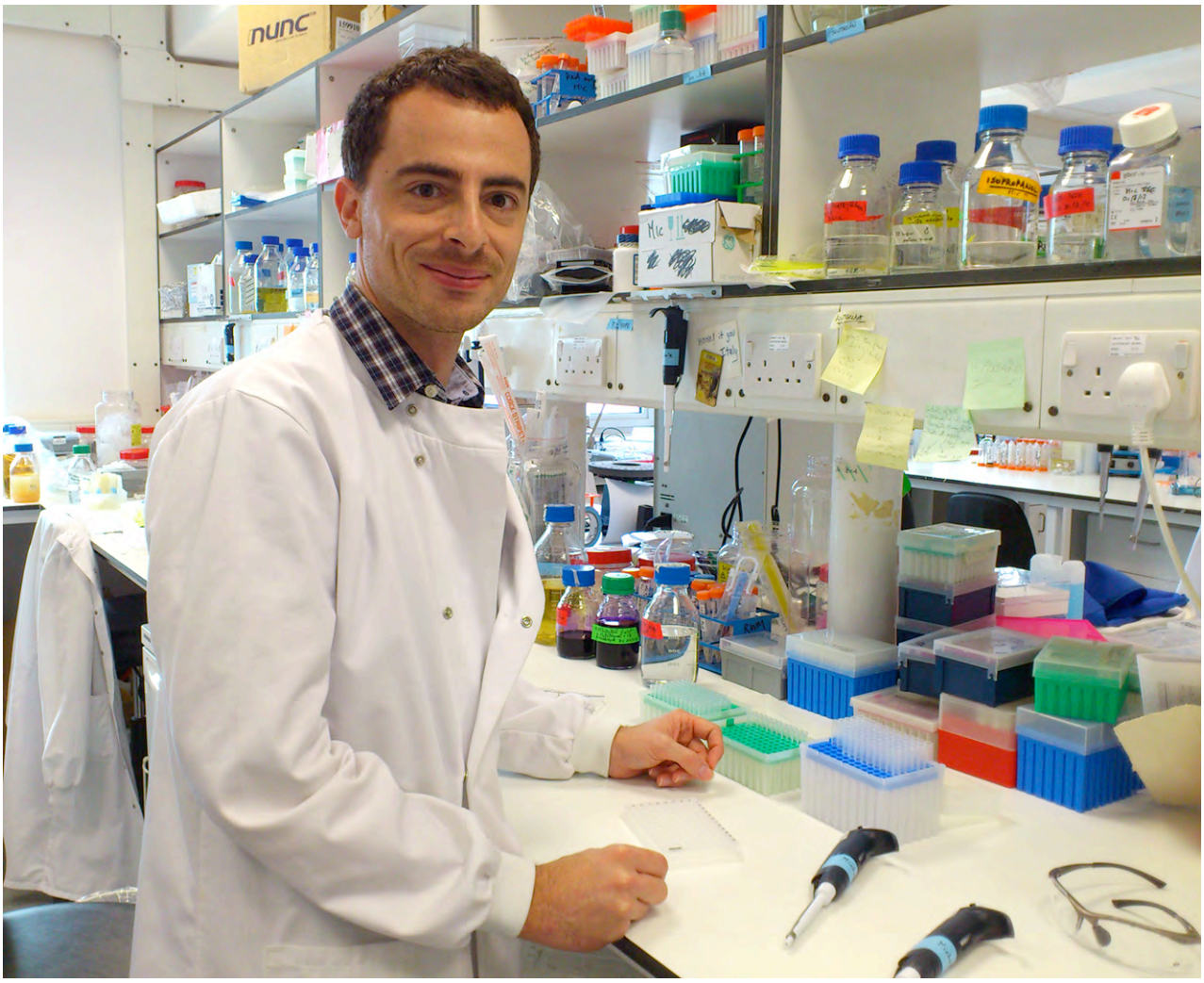
It is important to build capacity and ensure more researchers are attracted to working on ataxia. We welcome applications from people at an early stage of their career, as well as from established ataxia researchers.

Applications for PhD studentships are particularly welcomed as a means of bringing young researchers into ataxia research, eg eight studentships have been supported in 2012. We also aim to work with pharmaceutical companies and encourage their involvement in ataxia research.

Encouraging scientists in ataxia research

We awarded a fellowship to Dr Michele Lufino, a young researcher at the University of Oxford, who is keen to pursue his career in Friedreich's ataxia research. Dr Lufino said, "I am excited and thrilled to have been awarded a fellowship by Ataxia UK. This is a great opportunity to deepen our understanding of the causes of such a devastating condition."

The research generated much interest and we were pleased to collaborate with four other ataxia charities in funding this project.



Dr Lufino's Friedreich's ataxia research is funded by Ataxia UK

Our research funding programme: how it works

In order to deliver all the aims set out in this research strategy, Ataxia UK will utilise the robust framework we have developed over the last ten years, comprising a dedicated research staff and a Scientific Advisory Committee. In addition, Ataxia UK is a member of the Association of Medical Research Charities, the UK organisation that ensures its members follow good practice in research funding, including rigour, transparency and accountability in the selection process.

amrc PEER REVIEW AUDIT 2011

Ataxia UK's Scientific Advisory Committee provides advice to the Trustees on whether specific research proposals should be funded. This committee comprises independent experts from fields including molecular biology, biochemistry, clinical pharmacology, physiology, neuroscience, genetics and neurology together with lay representatives with an interest in research. In addition Ataxia UK employs research staff to manage our research grants programme. This involves ensuring research proposals are peer reviewed by experts in the field, that regular progress reports are made to the charity, that information is disseminated usefully and that appropriate interaction between Ataxia UK and its Friends, funded researchers, project applicants and the wider scientific community takes place.

Because Ataxia UK is a small charity with limited resources, grants will normally last for one to three years and we prefer to fund a variety of relatively short projects to the point where grant-holders have enough data to realistically seek funds from elsewhere. For more information on eligibility criteria and types of grants we award see our document 'Guidance for Researchers'. Funded projects are appraised through the critical evaluation of annual reports and occasional site visits by Ataxia UK's research team.

"Funding from Ataxia UK enabled us to start our research programme in Friedreich's ataxia and to gain useful data. This allowed us to be successful in getting funding from the Medical Research Council to take the research forward, hopefully eventually to clinical trials. We're very grateful to Ataxia UK for this initial support."

Dr Alastair Wilkins, whose research investigates the therapeutic benefit of stem cells in Friedreich's ataxia.

Ataxia UK 2020 VISION
aiming for a cure

Ataxia UK RESEARCH STRATEGY

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