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FRDA is not a never-to-be-treated disease but is now a disease for which real treatments are slowly coming to fruition

Q1 Your career has spanned a period of major transformation in our understanding of Friedreich's ataxia (FRDA), from defining the underlying disease mechanisms to developing targeted therapies. What first drew you to this field, and which milestones have been most significant in changing how clinicians understand and manage this condition?

A series of coincidences led me to FRDA. Initially, Rob Wilson, University of Pennsylvania, USA, who had a small project on ferritin levels that he needed a clinician for and I was 'volunteered' to recruit 10 patients. Wilson also had another small study to assess mitochondrial disease in exercising patients that I became involved in, but what attached me to FRDA was the collaborative nature of the patient population and the presence of the strong advocacy group Friedreich's Ataxia Research Alliance (FARA), which was in its infancy then. I think through this collaboration and advocacy, the perspective has changed such that FRDA is not a never-to-be-treated disease but is now a disease for which real treatments are slowly coming to fruition.

Q2 FRDA is a rare, multi-system neurodegenerative disorder that can affect neurological, cardiac, metabolic, and other aspects of health. What are the key challenges in recognising and diagnosing FRDA, and how canclinicians improve earlier identification of affected individuals?

The biggest diagnostic challenges are those common to all slowly progressive disorders: separating an individual with a progressive disease from one whose difficulties represent variants of normal and are not destined to progress, an extremely difficult distinction. Earlier diagnosis (necessary because FRDA has now become a partially treatable disease) will require that clinicians err on the side of testing sooner and, thus, test more people who do not have the disease. This is counter to the way we are traditionally taught, particularly in paediatrics, in which progression over time is used to differentiate pathologic symptoms from benign ones.

Q3 Your research has contributed significantly to understanding the metabolic dysfunction caused by frataxin deficiency. How has our understanding of the molecular and cellular mechanisms underlying FRDA evolved over recent decades, and what important biological questions remain unanswered?

When the mutation was first identified, and the protein frataxin discovered, the emphasis was on FRDA as a form of mitochondrial disease and on frataxin as a regulator of mitochondrial function. Now, with the identification of the role of frataxin in iron-sulfur cluster synthesis in diverse proteins outside the traditional mitochondrial enzymes of energy production, FRDA must be viewed as a disease with many distinct features, though some are more important than others. The key question remaining is why some tissues are affected in FRDA and others are spared, even though the loss of frataxin and

iron-sulfur clusters is relatively ubiquitous. Within these cells, is the pathological process the same in all cells? This remains to be determined.

Q4 FRDA is a multi-system disorder, with neurological symptoms occurring alongside important cardiac and metabolic complications, including cardiomyopathy and diabetes. How has understanding and management of these non-neurological manifestations evolved, and what should clinicians be aware of when caring for patients with FRDA?

The non-neurological features of FRDA are complex, and one part has become clear: cardiomyopathy, diabetes, scoliosis, and vision loss are most severe in the earliest onset individuals. The risk is lower for people presenting as teenagers, and essentially non-existent for those presenting as adults. However, such non-neurological issues vary among those with early onset. Different people with FRDA all handle things differently within the high-risk group, and it is hard to differentiate what will become a problem from what will remain abnormal but not problematic. The diastolic dysfunction can become problematic anytime, and the unusual fatigue of FRDA makes many infections more sustained. Due to such variability, non-neurologist clinicians must become knowledgeable about all aspects of the disease.

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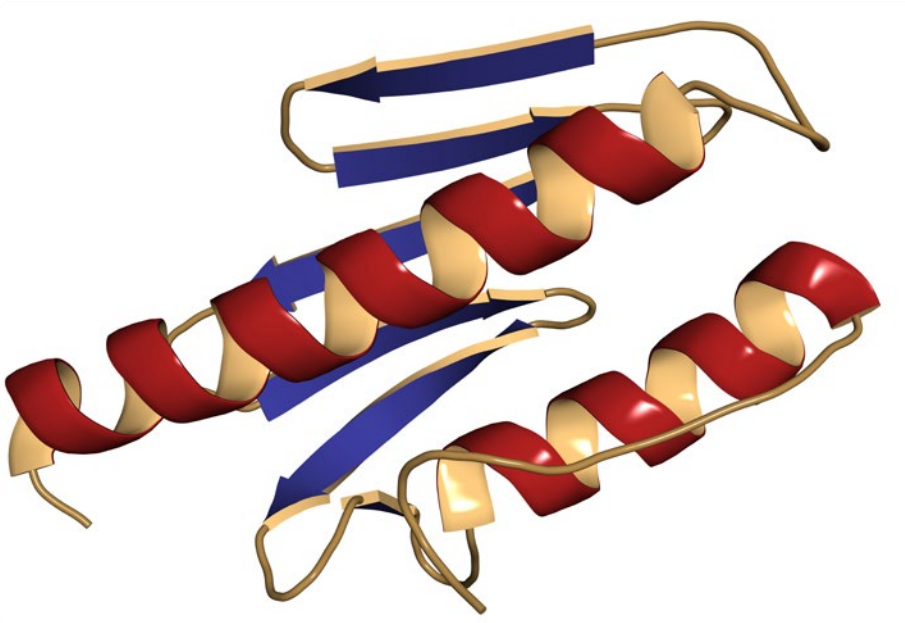
Q5 The approval of omaveloxolone represented a landmark moment for the FRDA community as the first approved therapy targeting disease progression. How has this changed the treatment landscape, and what have we learned from its introduction into clinical practice?

The most important aspect is hope, to some degree, in the identification of a helpful drug, but also simply in the realisation that new treatments can come. This makes people willing to work for further agents. Its value for slowing progression is modest and clearly will require other agents to create an ideal treatment. Still, it pushes people to seek better synergistic treatments.



Q6 Beyond currently available treatments, several therapeutic approaches are being explored, including metabolic therapies, novel small molecules, and gene-based strategies. Which emerging approaches do you believe hold the greatest promise for further transforming outcomes for people living with FRDA?

Ideal therapy goes to the root cause: loss of frataxin. The ideal therapy restores frataxin levels at all relevant sites to a sufficient degree without significant side effects. Many of the new agents satisfy some of these, but I'm not sure any meet them all. Some of them have severe side effects. Others fail to enter the brain, making their effects on ataxia very limited. Others are, at present, insufficiently tested. We have to find out systematically which ones work.

Q7 Clinical trials in rare neurological diseases face unique challenges, including small patient populations, variable disease progression, and the need for sensitive outcome measures. What lessons have been learned from FRDA trials, and how can these insights improve future studies in rare diseases more broadly?

The key aspect is collaboration at all levels: basic and clinical science, patients, investigators, and clinicians. Only by working together can things be sufficiently efficient to work in rare disease.

On these matters, patients become well informed more reliable subjects, trials recruit quickly, and results become consistent, ensuring the results of trials have applicability to the real world. The collaboration of all groups in FRDA has made this possible.

Q8 Biomarkers are increasingly important in rare disease research, both for understanding disease progression and evaluating treatment response. What progress has been made in identifying meaningful biomarkers for FRDA and how might these tools support future clinical trials and personalised treatment approaches?

More and more biomarkers are emerging, both imaging (e.g., optimal coherence tomographs of the retina and brain MRIs) and biochemical (e.g., frataxin and neurofilament light chain levels). It should be possible to design trials that look for alterations in biomarkers rather than less sensitive clinical measures. However, one has to remember that the results from biomarker studies require interpretation in the context of the meaning of benefit, as well as the safety of the intervention. Biomarkers can reflect cause of disease, but they can also reflect homeostatic responses. In other cases, they are epiphenomena whose relationship to disease is neither causal nor protective. Care must be used in future biomarker-based trials to ensure that results are meaningful.

Q9 Rare disease research increasingly depends on close collaboration between researchers, clinicians, patients, and advocacy organisations. How has engagement with the FRDA community shaped research priorities and accelerated progress towards new treatments?

For shaping priorities, regulatory authorities are constantly asking what is clinically important to patients. Thus, engagement with the patient community is essential for understanding this. In FRDA, the strong relationship with the patient community and advocacy organisations has directly aided FRDA research through recruitment and support. Trials in FRDA always recruit fast, and we always get enough samples for biomarkers studies. That wouldn't be possible without the support of FARA and other advocacy groups.

Q10 Despite recent advances, significant unmet needs remain for people living with FRDA. Beyond the development of new therapies, what areas of patient care, access, and support require greater attention?

While new pharmacology is important, does it improve people's lives? While we think so, it is difficult to measure. Individuals' lives differ greatly so the effects of biological advance in treatment will vary. If new therapies are indeed helpful, we will have more individuals going to college, developing new careers, and having a greater satisfaction with their lives. In particular, I think access in the workplace is a crucial aspect of the future improvement in the lives of people with FRDA. Adults, in some ways, are defined by their jobs, but many patients with FRDA cannot find jobs. Some of this reflects economic developments, but it is still hard to find jobs with appropriate accommodations. This needs to be addressed in the upcoming years.

Q11 Looking ahead, what developments in FRDA research and care are you most hopeful about, and what message would you give to clinicians and researchers entering the field?

The message is that this is a period of evolution and improvement, but also a period of hard work. There are many new developments right now in research but translating them into clinical care takes effort in the form of clinical trials, as well as studies, to understand the true benefit of new agents. A single treatment does not make a cure; optimum long-term treatment takes an iterative approach in which the goal of each new study is to improve on the previous. That takes time. The collaborative nature of the FRDA field should serve well during this period.

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