Clinical Management Guidelines for Friedreich Ataxia

Chapter 2. Potential disease modifying therapies for Friedreich ataxia

Contents

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2. Potential disease modifying therapies for Friedreich ataxia

George Wilmot, Caterina Mariotti, David Lynch, Geneieve Tai and Massimo Pandolfo

2.1 History of examining modifying therapies

Since 1996, the year of the discovery of the genetic cause of Friedreich ataxia (FRDA), many pharmacological clinical trials have been conducted to explore potential medications and different strategies aimed at ameliorating or preventing cell damage due to reduced frataxin.

The first compounds tested in individuals with FRDA were medications that were already available – either supplements or drugs approved for other indications. Initially, medications used in clinical trials were compounds with antioxidant properties, including vitamin E, co-enzyme Q10 and idebenone. In particular, idebenone was the most tested drug, with numerous clinical trials conducted from 1998 to 2012. Administration of different dosages of idebenone was shown to be safe. However, the results of the most recent Phase III study did not confirm the efficacy of idebenone on neurological symptoms and it is still unclear whether idebenone provides any cardiac benefit (1).

Other compounds tested for their antioxidant and neuroprotective properties are EGb761, an extract of Ginkgo biloba leaves (EGb 761®, Tanaken, Ipsen, France), OX1 (indole-3-propionic acid, IPA) a naturally occurring small molecule, and A0001 or alpha-tocopherol quinone (Penwest-Edison Pharmaceuticals), a co-enzyme Q10 analogue (2, 3). Although these molecules have been demonstrated to improve mitochondrial function *in vitro*, their efficacy in ameliorating or stabilizing disease progression in individuals with FRDA has not been confirmed.

Pioglitazone hydrochloride (ACTOS®, Takeda Pharmaceuticals) has also been proposed as a potential treatment for FRDA because it was postulated to induce the expression of many enzymes involved in mitochondrial metabolism, including the superoxide dismutases. Pioglitazone is a thiazolidinedione oral antidiabetic agent, which may cause or worsen congestive heart failure and other cardiovascular problems in FRDA (4). Its efficacy in the treatment of FRDA has not been demonstrated (5).

A different therapeutic strategy came from the observation of iron overload in mitochondria of individuals with FRDA (6). The commercially available iron chelator deferiprone (Ferriprox®, Apopharma, Canada) has been tested in a double-blind placebo-controlled trial (sponsored by Apopharma) of 72 individuals with FRDA aged 7 to 35 years (7). The participants assigned to the high-dose arm (60 mg/kg/day) were prematurely discontinued due to worsening of ataxia. Participants receiving 40 mg/kg/day also had worsening Friedreich Ataxia Rating Scale (FARS) and the International Cooperative Ataxia Rating Scale (ICARS) scores, whereas participants receiving 20 mg/kg/day of deferiprone had no significant change in FARS, similar to the placebo-treated individuals. The lack of deterioration in the placebo arm impaired the ability to detect any potential protective effect of deferiprone. However, subgroup analyses in participants with less severe disease suggest a benefit of deferiprone at 20 mg/kg/day on ICARS, FARS, kinetic function, and 9-hole peg test (9HPT). Deferiprone-treated participants receiving 20 or 40 mg/kg/day showed a significant decline in the left ventricular mass index. Higher doses of deferiprone caused systemic iron depletion and anemia; however, only one participant treated with 20 mg/kg/day had to discontinue treatment because of this complication (7). The major risk with deferiprone is the sudden, idiosyncratic development of agranulocytosis, which may occur at any time, even after a few years of treatment. No cases of agranulocytosis occurred during this study, but one participant experienced neutropenia, which resolved upon discontinuation of deferiprone (7). This study

suggests that systemic iron depletion is deleterious in people with FRDA, possibly further impairing iron sulfur cluster biogenesis, but a low dose of a membrane penetrant chelator such as deferiprone may be beneficial by removing excess redox-active iron.

An anecdotal observation of an improvement in balance and coordination in patients treated with varenicline (Champix®, Pfizer), an agonist of nicotine receptors, to help quit smoking suggested the potential use of this drug for individuals with FRDA. However, a Phase II pilot study was stopped before completion due to concerns on safety and observations of worsening gait and imbalance. There was also insufficient evidence of efficacy. A complete report detailing study data will be issued shortly.

Other compounds have been tested for their *in vitro* property of increasing frataxin protein or enhancing frataxin gene transcription in cells from individuals with FRDA. Among these drugs, erythropoietin (EPO) and carbamylated EPO (C-EPO) were also tested in double-blind controlled studies, but neither neuro- nor cardio-protective properties were demonstrated *in vivo* (8-11).

Another drug tested for its property of increasing both frataxin messenger RNA (mRNA) and protein levels in a variety of cell types, including cells from individuals with FRDA, is the exogenous interferon gamma-1b (ACTIMMUNE). This drug was administered at different dosages via subcutaneous injection in an open-label study design. The twelve children with FRDA who received the treatment for 12 weeks improved in FARS scores without a clear relationship to changes in frataxin levels (12). The following double-blind placebo-controlled study performed in a much larger series of individuals with FRDA (n = 92) did not demonstrate significant differences between interferon-treated and placebo-control groups after 6 months of treatment. No change was noted in buccal cell or whole blood frataxin levels (13).

Although a great scientific effort has been dedicated to selecting these drugs and testing their efficacy in clinical trials, most of these compounds have been removed from the list of potential therapeutic candidates for FRDA. While there is currently no approved pharmacological treatment for FRDA, research into potential therapeutic agents has nevertheless advanced considerably in the past two decades. There are many other potential therapeutic candidates that have been proposed in the treatment of FRDA that have undergone or are in the process of undergoing clinical trial evaluation.

2.2 Potential targets for therapies

The research of therapies that could have clinically meaningful results leading to a cure for the disease is continuing, with new compounds and new clinical trials being designed, commenced and currently ongoing. The research of new strategies is still based on the evaluation of potential therapeutic effects of drugs that are already commercially available and approved for other diseases, as well as new compounds specifically intended for the cure of FRDA and not available for other indications.

2.2.1 Therapies that decrease oxidative stress and enhance mitochondrial function

The pathology of FRDA is characterized by mitochondrial dysfunction and oxidative stress, demonstrated in both cell and animal models of FRDA (6, 14). Respiratory chain dysfunction, accumulation of iron in the mitochondria and impaired antioxidant responses lead to increased production of reactive oxygen species (15). The use of antioxidants has therefore been investigated as a potential therapy for FRDA.

2.2.2 Anti-inflammatory therapy

Inflammation contributes to the pathology of FRDA and has been detected in animal models as well as in tissues of people with FRDA (16, 17). The anti-inflammatory properties of steroids may play a role in altering oxidative damage caused by frataxin deficiency. This hypothesis arose after an improvement in neurological symptoms was reported in an individual with FRDA following corticosteroid treatment (18). Methylprednisolone has thus been explored as a treatment in FRDA (19).

2.2.3 Modulators of frataxin-controlled metabolic pathways

FRDA is caused by the reduced expression of frataxin, a protein found mostly in the mitochondria (20, 21), where it acts as an activator of iron-sulfur (Fe-S) cluster biosynthesis. The resulting Fe-S deficiency impairs the activity of many cellular proteins, including respiratory chain subunits and Krebs cycle enzymes in the mitochondria, and triggers a homeostatic response that increases cellular and mitochondrial iron uptake (22). However, as the Fe-S cluster biosynthetic pathway is impaired, iron eventually accumulates in mitochondria where it may engage in redox reactions generating toxic free radicals, activate signaling pathways leading to neurodegeneration (23), and trigger cell death, in particular by ferroptosis (24).

It has been proposed that frataxin is also involved in various other pathways, including iron metabolism, transport and storage (25), as well as regulation of apoptosis (26). Furthermore, several metabolic pathways are perturbed because of frataxin deficiency, in particular those that control antioxidant responses and mitochondrial biogenesis. Therapies that modulate such pathways include nuclear factor erythroid-derived 2-related factor 2 (Nrf2) activators and peroxisome proliferator activated receptor (PPAR)-γ agonists.

2.2.4 Therapies that increase FRDA gene expression

Approximately 96% of individuals with FRDA have a homozygous mutation consisting of the expansion of GAA trinucleotide repeats within the first intron of the *FXN* gene (20), leading to the formation of heterochromatin (27). As a result, transcription of *FXN* mRNA is reduced (28, 29). Agents that counter heterochromatin formation can upregulate *FXN* mRNA, including histone deacetylase (HDAC) inhibitors (30, 31). Other agents directly boost *FXN* expression regardless of the presence of expanded GAA repeats. Those clinically tested include erythropoietin and derivatives, Interferon gamma (12, 32).

2.2.5 Frataxin replacement, stabilizers or enhancers

Frataxin replacement therapy has been proposed by pairing synthetic frataxin protein with a delivery system using a protein fragment called a trans-activator of transcription (TAT) to enable frataxin delivery into the mitochondria (33, 34). Another method of frataxin supplementation is through delivery of a normal copy of the *FXN* gene via gene replacement therapy (35-37).

Gene replacement and editing

Gene replacement therapy is perhaps the most promising in terms of correcting frataxin loss in FRDA, with numerous strategies currently being explored (https://curefa.org/pipeline). FRDA presents as a favorable candidate for gene replacement therapy due to several factors. About 96% of individuals with FRDA have the same single gene mutation which leads to gene silencing and a reduction of the frataxin protein levels. Because individuals with FRDA already produce frataxin, it is

less likely that an immune response will be produced. Furthermore, while carriers for FRDA possess one faulty copy of the gene and produce half the normal frataxin levels, these individuals do not exhibit any symptoms, indicating that even a small increase of frataxin has the likelihood to be beneficial.

There are several approaches to gene therapy (38). Adeno-associated viruses (AAV) are viral vectors that do not integrate into the host genome, avoiding genotoxicity. Their DNA persists for a long time in transfected cells as an episome, potentially lifelong. This makes AAV a vector of choice for perennial tissues such as the brain, spinal cord, and heart, which are most affected in FRDA. The potential efficacy of AAV-based gene therapy for FRDA was first demonstrated in a conditional cardiac and skeletal muscle *FXN* knockout mouse model (Mck-Cre-Fxn$^{L3/L}$ mice) that was treated intravenously with adeno-associated virus rh10 vector expressing human FXN, leading to prevention of cardiac disease onset if given early, as well as a complete reversal of cardiomyopathy when given after the development of symptoms (36). In a separate study, a parvalbumin-conditional *FXN* knockout mouse model (Pvalb cKO) with *FXN* delivered through an AAV9 vector resulted in a complete reversal of sensory ataxia but not of manifestations of central nervous system (CNS) disease (37).

There are, however, several issues that need to be resolved before AAV-based gene therapy becomes a reality in FRDA. Some naturally occurring AAVs, such as AAV9, can effectively cross the blood-brain barrier (BBB) after systemic administration, but only for a limited time after birth. For this reason, while AAV9-based gene therapy has been effective in treating diseases such as spinal muscular atrophy (SMA), that affects babies, there are ongoing efforts to generate new capsids that can penetrate the CNS in older children and adults after systemic administration (39). However, this may require very high intravenous doses of the vector, which, at least in the case of AAV9 and related capsids, may trigger a severe reaction with liver toxicity and cytokine release. While this reaction could be potentially lethal, it is at least partially preventable with immune suppressive treatment with steroids (40). Furthermore, an inflammatory reaction with neuron loss in the dorsal root ganglia (DRG) has been observed in some animal models (40). This is a particularly worrisome complication in FRDA, where DRG pathology is already present. Acquired immunity to AAVs, a common occurrence in the general population, is another problem, as neutralizing antibodies may inactivate the gene therapy vector and T cells may attack transfected cells presenting capsid fragments on their surface. This is also a major obstacle to re-administer AAV to patients who have previously received it. Overall, these difficulties impose the development of new capsids with improved biodistribution and ability to cross the BBB, as well as of strategies to control innate and acquired immune responses, allowing administration to individuals carrying anti-AAV antibodies and re-administration of a therapeutic vector if needed (41).

Proper control of transgene expression is also necessary. Frataxin expression must reach heterozygous carrier levels at least, but cannot be excessive, as it has demonstrated that very high levels are toxic, causing mitochondrial dysfunction and cardiac toxicity in mouse models (42). This requires a combination of appropriate vector biodistribution and promoter choice.

The possibility of dual routes of administration is an emerging option for what we may consider the first-generation gene therapy for FRDA, while “optimal” vectors are being developed. This approach aims at reaching peripheral organs (heart, pancreas, DRG, peripheral nerves, muscle) via a relatively low dose systemic administration, and the CNS via intrathecal or intraparenchymal administration, targeting key affected structures as the dentate nuclei in the cerebellum.

Other approaches may involve different viral vectors, such as Herpes virus-based, or non-viral vectors such as lipid nanoparticles. These are still in an early-preclinical phase.

Delivery of brain-derived neurotrophic factor (BDNF) is another approach to gene therapy in FRDA (43). BDNF has numerous neuroprotective properties including anti-apoptosis, antioxidation and autophagy suppression (44). The *stargazer* mouse model with severe cerebellar ataxia exhibited improved ataxia and motor impairment when crossed with mice overexpressing transgenic BDNF (45). In another study, a gene encoding BDNF was delivered via a herpesviral amplicon vector to a knockout mouse model which prevented the onset of cerebellar neuropathology and ataxia (46). Overexpression is an issue with BDNF as well, having been shown to cause learning and short-term memory impairment (47).

A lack of animal models that accurately depict FRDA is another barrier in the development of gene therapy in FRDA. Conditional knockout mouse models are useful in providing proof-of-concept, but models with a pathologically low systemic frataxin expression, as is the case in the human disease, are still unsatisfactory. A YG8JR mouse model carrying a human *FXN* gene with 800 GAA repeats has recently been developed and is the most genetically alike to individuals with FRDA. However, the phenotype of this model, as of other GAA repeat expansion-carrying mouse models, appears to be late disease onset and mild disease presentation. There is also a lack of models in larger animals which may be more useful with respect to translation to humans.

2.3 Therapies under investigation

2.3.1 Drugs available off-label

The current state of research into drugs available off-label as possible therapies for FRDA is summarized in Table 2.1 and details are given below.

Resveratrol

Resveratrol is a naturally occurring antioxidant commonly found in many plants, particularly in the skin of red grapes. Resveratrol has been postulated to have antioxidant and neuroprotective benefits and was found to increase frataxin expression in cell and mouse models of FRDA (48). An open-label, proof-of-principle study of 24 individuals over 12 weeks demonstrated improvement in the FARS, the ICARS, hearing and speech outcome measures, and an oxidative stress marker, plasma F2-isoprostanes, in participants on a high dose of resveratrol (5 g) compared to those on a lower dose (1 g) (49). There was no change in lymphocyte frataxin levels (the primary outcome measure) in either treatment group. Significant gastrointestinal adverse events were reported in the high dose treatment group (49). In light of these findings, a randomized blinded, placebo-controlled crossover study assessing the efficacy and safety of a micronized form of resveratrol is underway (https://clinicaltrials.gov/ct2/show/NCT03933163). This formulation of resveratrol has been shown to be safe and have superior bioavailability with a good adverse event profile (50). The primary objective of this study is to compare the change in the modified FARS (mFARS) score from baseline to 24 weeks following treatment with 2 g/day of micronized resveratrol, to treatment with placebo.

Etravirine

Etravirine is an antiviral drug approved in 2008 by the US Food and Drug Administration (FDA) and is currently in use for the treatment of HIV. Alfedi and colleagues (51) have shown that etravirine increased frataxin protein levels in fibroblasts and lymphoblasts derived from individuals with FRDA by increasing frataxin mRNA translation and restoring the activity of aconitase, the enzyme containing an Fe-S cluster that is decreased from frataxin deficiency and provides some resistance to oxidative stress in these tissues. The levels of frataxin in these cell lines were also found to be comparable to frataxin levels in unaffected carrier cells (51). The team are planning to conduct a

small study in individuals in FRDA to explore safety and tolerability, and changes in frataxin levels and other FRDA-specific biomarkers.

Dimethyl fumarate

Dimethyl fumarate (DMF) was identified through a drug discovery program by Cortopassi and colleagues who demonstrated this compound's ability to induce mitochondrial biogenesis through activation of the Nrf2 pathway in individuals with multiple sclerosis (52, 53). DMF was also found to increase mitochondrial gene expression and function in mice models of FRDA (54). A clinical trial of DMF in individuals with FRDA is planned to investigate safety, tolerability and other outcome measures.

Methylprednisolone

An exploratory study was conducted to determine the safety, tolerability and efficacy of pulse methylprednisolone in 11 individuals with FRDA (19). The 26-week open label study found that methylprednisolone was well tolerated; however, there was no change in the timed 25-foot walk (T25FW) which was the primary outcome measure. The 1-minute walk (1MW) in the pediatric participants demonstrated a modest improvement ($p < 0.05$). It is suggested that methylprednisolone may be useful in children who are ambulant; however, there are no plans for further studies at this stage (19).

Table 2.1 Summary of possible therapies: drugs available off-label

Therapy	Proposed mechanism	Stage of development	Study outcomes
Resveratrol	Natural phenol and antioxidant, increases *FXN* gene expression.	Randomized double-blind crossover placebo-controlled study.	Improvement found in oxidative stress marker, FARS, ICARS, hearing and speech outcome measures; little change in primary endpoint (lymphocyte frataxin levels). Randomized placebo-controlled study is underway.
Etravirine	Antiviral drug currently in use for HIV treatment. Appears to increase frataxin protein levels in fibroblasts and lymphoblasts derived from FRDA patients.	Safety and tolerability study planned.	Not available.
Dimethyl fumarate	Approved for treatment of multiple sclerosis and psoriasis. Has been shown to induce mitochondrial biogenesis in multiple sclerosis via activation of Nrf2 pathway which could be beneficial in FRDA.	Safety and tolerability study planned (anticipated to commence in 2021).	Not available.

Therapy	Proposed mechanism	Stage of development	Study outcomes
Methyl-prednisolone	Steroid: has anti-inflammatory properties; may alter oxidative damage caused by frataxin deficiency.	Open-label study.	No change in primary outcome measure (timed 25-foot walk) but modest improvement in 1-minute walk in pediatric participants.

2.3.2 Drugs not available for other indications

The current state of research into drugs that are not available for other indications as possible therapies for FRDA is summarized in Table 2.2 and details are given below.

Vatiquinone (PTC-743)

PTC-743 (previously EPI-743), or vatiquinone, is a follow-on compound to EPI-A0001. Vatiquinone is an orally absorbed small molecule that readily crosses into the CNS. It works by targeting NADPH quinone oxidoreductase 1 (NQO1). Its mode of action is to synchronize energy generation in mitochondria with the need to counter cellular redox stress (55). Vatiquinone seems to be 1000- to 10,000-fold more potent than co-enzyme Q10 or idebenone in protecting cells subjected to oxidative stress in patient fibroblast assays modelling the effects of mitochondrial disease.

A randomized parallel-arm, double-blind, placebo-controlled study evaluating vatiquinone is currently underway. The study aims to recruit approximately 110 children and young adults with FRDA. The 72-week placebo-controlled phase will be followed by a 24-week open-label extension phase. The primary endpoint is the change from baseline in mFARS, with key secondary endpoints assessing ambulation and activities of daily living (https://clinicaltrials.gov/ct2/show/NCT04577352).

A six-month placebo-controlled study of EPI-743 in 63 adults with FRDA has been conducted (56), with participants receiving placebo, 600 mg/day EPI-743 or 1200 mg/day EPI-743. This was followed by an 18-month open-label extension study where all participants were treated with EPI-743. While the primary endpoint of low contrast visual acuity assessment was not met, an improvement in the neurological examination subscale of the FARS was found in participants administered low-dose EPI-743 when compared to the placebo group ($p = 0.047$) at 6 months. There were significant improvements in neurological outcomes and treatment was well tolerated (57).

EPI-743 at 1200 mg/day has also been tested in people with FRDA who are compound heterozygous for a *FXN* GAA repeat expansion and a point mutation in an 18-month open-label study (58). There were significant improvements in neurological function as assessed by the FARS indicating potential benefit in this subgroup of individuals (58).

Omaveloxolone

Omaveloxolone was developed by Reata Pharmaceuticals to target activation of Nrf2, which is decreased in cells in individuals with FRDA. In a double-blind, randomized, placebo-controlled, multicenter study of 103 individuals with FRDA, participants aged 16 to 40 years received either placebo or omaveloxolone at 150 mg per day (59). Individuals treated with omaveloxolone experienced a statistically significant, placebo-corrected mean improvement in mFARS, the primary outcome measure, of 2.4 points after 48 weeks of treatment ($p = 0.014$). This benefit was mostly recorded in patients without pes cavus, a common feature of FRDA associated with more severe disease, suggesting that patients with milder disease benefited the most. Omaveloxolone was reported to be safe and well tolerated (59).

Additional analysis has been conducted on the open-label extension data. Similar slopes in the mFARS were found for the placebo to omaveloxolone group (0.59 points per year) and the omaveloxolone to omaveloxolone group (0.41 points per year). There was no significant difference in the rates of change between groups, demonstrating the disease modifying activity of omaveloxolone (59). The open-label extension study is ongoing with additional data collection and safety monitoring (https://www.clinicaltrials.gov/ct2/show/study/NCT02255435). As of May 2021, Reata has been asked to request a pre-NDA FDA meeting for omaveloxolone for the treatment of FRDA (60).

RT001 (dPUFAs)

RT001 is a deuterated polyunsaturated fatty acid (dPUFA). PUFAs are fatty acids that are essential to the structure and function of lipid membranes. As PUFAs are prone to oxidative damage and can therefore lead to mitochondrial dysfunction, a strategy for strengthening these compounds is to replace hydrogen molecules with deuterium, a hydrogen isotope, creating dPUFAs. This process protects cells from oxidative damage (61).

A Phase I/II randomized, double-blind, comparator-controlled study was conducted by Retrotope in 18 individuals with FRDA (62). Participants were administered either 1.8 or 9.0 g/day of RT001, or an RT001 comparator over 28 days. RT001 was safe and well tolerated over the duration of the study and an improvement in peak workload was found (62).

A subsequent Phase II/III study was launched in 2019. The randomized, double-blind, placebo-controlled trial enrolled 65 individuals aged 12 to 50 years, with peak workload change from baseline to 11 months as the primary outcome measure. Results are anticipated at the end of 2021. (see: https://www.clinicaltrials.gov/ct2/show/NCT04102501)

MIN-102

MIN-102, or leriglitazone, is a metabolite of pioglitazone, which has previously been trialed in FRDA. Like pioglitazone, leriglitazone is a potent agonist of peroxisome proliferator-activated receptor-gamma (PPARγ). MIN-102 has been developed by Minoryx Therapeutics. Pre-clinical studies showed that leriglitazone increased frataxin protein levels in DRG neurons that were frataxin deficient (63). An improvement in motor function deficits in FRDA mouse models was also demonstrated. A Phase 1 clinical study demonstrated that MIN-102 was well tolerated and was able to cross the BBB and engage PPARγ within the CNS much more efficiently that pioglitazone (64).

The Phase 2 FRAMES clinical trial enrolled 39 individuals with FRDA and examined the effects of leriglitazone on biochemical, imaging, neurophysiological, and clinical outcome measures. Topline results were announced in December 2020 (65). PPARγ engagement was demonstrated in all participants, as assessed by the biomarker adiponectin. Furthermore, leriglitazone significantly prevented iron accumulation in the dentate nucleus of individuals receiving treatment compared to placebo (ANCOVA $p = 0.05$). Numerical differences in favor of leriglitazone were also seen in magnetic resonance spectroscopic analysis of cervical spinal cord and in an upper-limb coordination measure. Leriglitazone was also well tolerated, with peripheral edema the most frequent adverse event. Full results are pending and a further confirmatory study is planned.

CTI-1601 (TAT-frataxin)

CTI-1601 is a delivery system whereby a TAT protein fragment is used to transport synthetic frataxin directly into the mitochondria (33). When tested in mouse models, cardiac function (increased heart rate and improved diastolic function) was improved and mean lifespan in the mice was increased.

The first in-human study of CTI-1601 commenced in November 2019, exploring safety and dosage compared to placebo in individuals with FRDA. Following the completion of the single ascending dose study (https://clinicaltrials.gov/ct2/show/NCT04176991), a multiple ascending dose study began in late 2020 (https://www.clinicaltrials.gov/ct2/show/NCT04519567). Individuals received subcutaneous injections of either CTI-1601 or placebo at increasing dose levels and frequencies over 13 days. Dose-dependent increases in frataxin levels from baseline were demonstrated in buccal cells, skin biopsies and platelets of participants receiving CTI-1601 compared to those receiving placebo. CTI-1601 was generally well tolerated at doses of up to 100 mg/day for 13 days (66). An open label extension study had been planned for commencement in mid-2021. However, as of May 2021, the FDA has placed a hold on the CTI-1601 clinical program due to deaths at the highest dose levels in an ongoing 180-day non-human primate toxicology study. At this stage, additional studies are not permitted to commence until a full report has been submitted to the FDA who will determine when this will be able to occur.

XCUR-FXN

XCUR-FXN is a form of antisense oligonucleotide spherical nucleic acid (SNA) therapy developed by Exicure and is designed to increase the production of frataxin. XCUR-FXN will be delivered through intrathecal injection into the spinal canal to enter the CNS. An investigational new drug (IND) application to the FDA is planned with the first in-human study planned for 2022 (67).

Gene-Tac (Syn-TEFS)

Synthetic transcription elongation factors (Syn-TEFs) are a novel class of compounds comprising programmable DNA binders that target desired genomic loci and ligands that engage transcription elongation machinery. Ansari and colleagues (68) have demonstrated that Syn-TEF was able to restore frataxin levels in cell lines from individuals with FRDA to the levels in control cell lines. The company Design Therapeutics has developed derivatives of the initial molecule with greatly improved pharmacological properties and is planning a first in-human study.

Granulocyte colony stimulating factor (GCSF)

Granulocyte colony stimulating factor (GCSF) is a cytokine which has been tested in humanized mouse models of FRDA together with stem cell factor (SCF) (69). Mice received monthly subcutaneous infusions of both compounds and were assessed with a range of behavioral motor performance tests. Frataxin levels increased after six months of treatment with monthly subcutaneous infusions of GCSF. Improvements in motor coordination and locomotor activity were also demonstrated, as well as an increase in neural stem cell numbers and reduced inflammation, indicating its potential as a possible therapy for FRDA. This research is planned to extend to human cell lines (69).

SHP622 (formerly VP20629 or OX1)

Indole-3-propionic acid (IPA), also called OX1 (and now called SHP622), is a naturally occurring, small molecule that has potent anti-oxidant properties that can protect against neurodegenerative disease. In contrast to the vast majority of antioxidants, OX1 has a rare advantage in that it cannot be metabolized through a pro-oxidant pathway. For these reasons, scientists identified the potential of OX1 for treatment of FRDA. In a recent Phase 1 safety and tolerability study conducted in the Netherlands, OX1 was demonstrated to be safe and well tolerated at all dose levels tested (http://www.clinicaltrials.gov/ct2/show/NCT01898884). There are currently no plans to pursue clinical development.

RG2833

HDAC inhibitors, of which RG2833 is one, are compounds that interfere with histone deacetylases, enzymes that remove a key post-translational modification of histones associated with active transcription. After observing excess deacetylation of histones in the *FXN* gene of cells from FRDA patients, Joel Gottesfeld of The Scripps Research Institute in La Jolla, California identified a family of benzamide HDAC inhibitors able to overcome the gene silencing effect of the GAA expansion in cellular (70) and animal (31) models of FRDA. These compounds specifically target the class I HDACs, HDAC1 and HDAC3, and have a particular slow ON-slow OFF kinetic that differentiates them from other HDAC inhibitors that are unable to upregulate *FXN* expression. The company Repligen sponsored a phase I study of RG2833 involving 20 adults with FRDA (71). The study comprised four cohorts: two were open-label in design with single 30 to 120 mg doses, while the other two were randomized, double-blind, placebo-controlled crossover studies. In the latter two cohorts, participants received either a single 180 mg dose or placebo or two 120 mg doses, or a placebo. RG2833 was well tolerated and was found to increase *FXN* gene expression in peripheral blood mononuclear cells. Despite being well tolerated, potentially toxic metabolites of the compound were detected. Together with poor BBB penetration, this made it unsuitable for further testing. Additional compounds with improved characteristics, developed by Repligen and then by BioMarin, are currently being studied as potential candidates for clinical trials (72, 73).

Nicotinamide

Nicotinamide is a class III HDAC and in high concentrations can cause product inhibition of enzymes that generate it by cleaving NAD (74). Nicotinamide has good bioavailability and has been shown to pass through the BBB (75). In an open-label dose-escalation study, 10 individuals with FRDA were treated with doses of up to 8 g/day of oral nicotinamide. While generally well tolerated, three participants demonstrated abnormal liver function test results after taking high doses of nicotinamide, but this resolved after the dose was reduced. Daily dosing at 3.5 to 6 g demonstrated a significant upregulation of frataxin expression in peripheral blood mononuclear cells ($p < 0.0001$). However, there were no significant improvements in clinical measures. A randomized, placebo-controlled, double-blinded study investigating the efficacy of high dose nicotinamide in FRDA (NICOFA) over two years is planned (76). It is important to note, however, that high-dose nicotinamide (exceeding 3 gm/day) is considered potentially toxic and should not be used without medical supervision (77).

Table 2.2 Summary of possible therapies: drugs not available for other indications

Therapy	Proposed mechanism	Stage of development	Study outcomes
Vatiquinone (PTC-743)	Previously EPI-743. Similar to A0001 – improves mitochondrial function and prevents oxidative stress.	Randomized double-blind placebo-controlled study followed by open label extension phase.	Study is currently underway.
Omaveloxolone (RTA 408)	Nrf2 activator – reduces intracellular oxidative stress and mitochondrial damage, increases mitochondrial respiration and biogenesis.	Randomized double-blind placebo-controlled study	Improvement in primary outcome measure (mFARS) of 2.40 points after 48 weeks of treatment ($p = 0.014$). Reported to be safe and well tolerated.

Therapy	Proposed mechanism	Stage of development	Study outcomes
RT001	Deuterised polyunsaturated fatty acid (dPUFA) – reduces oxidative stress in mitochondria therefore increasing ATP production.	Randomized double-blind placebo-controlled study.	Recruitment completed. Results anticipated at the end of 2021.
MIN-102	Metabolite of pioglitazone, potent agonist of peroxisome proliferator-activated receptor-gamma (PPARγ).	Randomized, double-blind, placebo-controlled study.	Found to modulate the frataxin pathway and restore bioenergetics deficits. Confirmatory study planned.
CTI-1601	Delivery system (trans-activator transcription, TAT) that transports synthetic frataxin directly into mitochondria.	Single ascending dose study followed by multiple ascending dose study. Open label extension study to commence in mid-2021. Pediatric multiple ascending dose study also planned for mid-2021. Currently on FDA hold.	Dose-dependent increases in frataxin levels from baseline demonstrated in buccal cells, skin biopsies and platelets of participants receiving CTI-1601 compared to placebo.
XCUR-FXN	Form of antisense oligonucleotide spherical nucleic acid (SNA) therapy, designed to increase frataxin production.	Investigational new drug (IND) application to the FDA is planned.	First in-human study planned for 2022.
Gene-Tac (Syn-TEFS)	A novel class of compounds called synthetic transcription elongation factors. Able to restore frataxin levels in cell lines in FRDA.	Investigational new drug (IND) application to the FDA.	No study outcomes as yet.
Granulocyte-colony stimulating factor and stem cell factor	Cytokines with neuroprotective effects; increases frataxin levels and reduces inflammation.	Animal studies.	Improvement shown in motor coordination and locomotor activity in mouse models.
SHP622 (formerly VP20629 or OX1)	Naturally occurring small molecular weight drug compound that prevents oxidative stress.	Phase 1 safety and tolerability study.	Safe and well tolerated. No further plans for clinical development.
RG2833	An HDAC inhibitor; increases histone	Randomized double-blind placebo-controlled study.	Increased *FXN* gene expression found; however,

Therapy	Proposed mechanism	Stage of development	Study outcomes
	acetylation resulting in increased frataxin levels.		toxic metabolites found indicating safety concerns.
Nicotinamide	An HDAC inhibitor; increases histone acetylation resulting in increased frataxin levels.	Open-label dose-escalation study.	Upregulation in frataxin expression found; however, no improvements in clinical measures. Randomized, double-blind placebo-controlled study is planned.

Author details

David Lynch, MD, PhD
Professor of Neurology and Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA
Email: lynchd@mail.med.upenn.edu

Caterina Mariotti, MD
Neurologist, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy
Email: caterina.mariotti@istituto-besta.it

Massimo Pandolfo, MD
Professor (Clinical), McGill University, Montreal, Quebec, Canada
Email: massimo.pandolfo@mcgill.ca

Geneieve Tai, BBiomedSc(Hons)
Research Assistant, Murdoch Children's Research Institute, Parkville, Victoria, Australia.
Email: geneieve.tai@mcri.edu.au

George Wilmot, MD, PhD
Associate Professor, Department of Neurology, Emory University, Atlanta, Georgia, USA
Email: gwilmot@emory.edu

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