Friedreich's Ataxia Research

Newsletter, October 2007

Latest news on Friedreich's Ataxia therapeutic approaches

Without a doubt, 2007 has been marked by important progress made in breakthroughs towards possible therapeutic approaches for a cure to Friedreich's Ataxia FRDA.
To have a better understanding of the nature regarding the therapeutic approaches of international scientific interest, a brief introduction on the molecular basis of the disease is bellow illustrated.

FRDA is caused by deficiency of the mitocondrial protein frataxin. Frataxin insufficiency leads to progressive spinocerebellar neurodegeneration, causing symptoms of the disease. Numerous data indicates that a reduced level of frataxin induces an accumulation of iron in mitochondria and show increased sensitivity to oxidative stress. This suggests that FRDA is caused by mitochondrial dysfunction and free radical toxicity, with consequent mitochondrial damage, axonal degeneration, and cell death. For this FRDA patients have abnormal myocardial iron deposits.
Based on these findings, antioxidant (1) and iron chelation (2) based strategies appear promising in counteracting the course of the disease. However, these strategies only treat the symptoms of the disease and not its cause; thus, pursuit of other approaches that address the cause of the disease are worthwhile. Thus, pharmacological reactivation of the silenced *FXN* gene (3) has received considerable attention over the past few years. (*)

(1) Antioxidant
Santhera Pharmaceuticals announced that it has reached an agreement with the US Food and Drug Administration (FDA) under the Special Protocol Assessment (SPA) procedure relating to the Phase III clinical trial to evaluate SNT-MC17 (INN: idebenone) for the treatment of Friedreich's Ataxia (FRDA). The protocol incorporates advice provided by the FDA on the design of the study, its endpoints, statistical analysis and conduct.
The FDA granted a fast track designation to Santhera's compound in FRDA.

The positive clinical results from a recently reported study conducted in collaboration with the US National Institutes of Health (NIH) formed the basis for the design of the phase III trial. The trial with SNT-MC17, named IONIA (Idebenone effects On Neurological ICARS Assessments), is a double-blind, randomized, placebo-controlled study of six months duration investigating the efficacy of two doses of SNT-MC17 compared to placebo. The primary endpoint of IONIA will be a neurological endpoint, measured by the International Cooperative Ataxia Rating Scale (ICARS), comparing the change in the ICARS for each of the treatment groups with placebo over the 24 week study period.
The study will also investigate additional neurological endpoints as well as activities of daily living parameters and cardiac measures.

Based on the efficacy data obtained in the NIH study, particularly for the neurological outcome measures, Santhera's first dose group in the IONIA trial will be 450 mg/day for patients below 45 kg body weight and a corresponding dose of 900 mg/day for patients above 45 kg body weight. The second dose group will be 1350 mg/day for patients below 45 kg of body weight and 2250 mg/day

for patients above 45 kg. Using Santhera's 150 mg tablet, the daily dose of SNT-MC17 will be divided into three equal doses to be taken with a meal.

The IONIA study will recruit a minimum of 51 ambulatory FRDA patients between the ages of 8 and 17 years and will be conducted at two clinical centers in the US - the Children's Hospital of Philadelphia and the School of Medicine of the University of California, Los Angeles.

Patient recruitment is expected to start soon. (**)

(2) Iron-chelation

ApoPharma Pharmaceuticals sponsored a study investigating the Safety and Tolerability of Deferiprone in patients with Friedreich's ataxia.

This will be a multi-centre, double-blind, randomized, placebo-controlled clinical trial. A total of 80 patients (Ages eligible for study: 7 years to 35 years) with Friedreich's ataxia will be enrolled. Eligible patients will receive deferiprone oral solution or placebo at a total daily dose of 20 mg/kg/day, 40 mg/kg/day or 60 mg/kg/day, divided into two-daily doses for 6 months.

The primary objective of this study is to demonstrate the safety and tolerability of deferiprone in subjects with Friedreich's ataxia (FRDA).
The secondary objective is to evaluate the efficacy of deferiprone for the treatment of FRDA, as assessed by:

- 9-Hole Peg Test (9HPT)
- Timed 25-Foot Walk (T25FW)
- Low-Contrast Letter Acuity test (LCLA)
- International Cooperative Ataxia Rating Scale (ICARS)
- Friedreich's Ataxia Rating Scale (FARS).

The tertiary objectives are to evaluate the effect of deferiprone on:

1. cardiac function as measured by changes in Left Ventricular Shortening Fraction (LVSF), Left Ventricular Ejection Fraction (LVEF) and Left Ventricular (LV) mass using echocardiogram (ECHO),
2. functional status using Activities of Daily Living (ADL).

Principal Investigators:
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Anthony Schapira, M.D. *Royal Free Hospital, London, England*

This study is not yet open for recruiting participants. (***)

The results, if yet only slightly encouraging, of the pilot trial obtained by Prof Munich of Necker-Enfants Malades Hospital of Paris, France (*Blood, pre-published online March 22,2007*) have led us to not await the necessary time-frame of the multi-centric trials' attivavation, as stated above. To rapidly answer the call of need in verifying the eventual suitability of deferiprone in contrasting disease progression, during the past January we have contacted Prof. Piga, due to his vast experience in the field of iron chelators in hematology and in particular on the oral chelator deferiprone produced by ApoPharma. Following this fact, having taken into account the progressive and impairing traits of the FRDA pathology, since last March Prof. Antonio Piga, Microcytosis Center, Squid, O.I.R.M. S.Anna Hospital, Turin, Italy and his team (Dr. Filomena Longo) have

received the necessary authorization and now treat FRDA patients with deferiprone on individual and compassionate basis. (****)
For more information at this regard please contact GoFAR at *minagofar@yahoo.com*

3) The histone deacetylase inhibitors (HDACi)
The HDACs play critical roles in regulating gene expression. The genetic change in Friedreich's ataxia recruits excessive deacetylase activity to the frataxin gene silencing expression. Thus HDAC inhibitors may revert silent heterochromatin to an active chromatin conformation and restore the normal function of the frataxin gene. Studies carried out with patients' cells and mouse models indicate that a specific class of compounds known as histone deacetylase inhibitors (HDACi) can increase the production of the frataxin protein in human and mouse cells containing the silenced frataxin gene. This suggests that treatment may result in slowing-down or stopping disease progression. The compounds were first identified by Dr. Gottesfeld professor of molecular biology at the Scripps Research Institute (La Jolla, CA).

Last spring, Repligen Corporation (RGEN) purchased the exclusive commercial license from Scripps Research Institute for the compounds that could prove efficient for treating Freidreich's Ataxia (FRDA).

The development of HDAC inhibitors for treating Friedreich's ataxia can be summed up in the following way:

1) Clinical candidate selection and characterization
This involves identifying a compound with adequate potency and low toxicity as well as acceptable pharmacology. Potency must be determined in FRDA cell based assays and animal models that include the ability to define the genes altered in disease and the ability of the drug to restore aspects of normal gene expression. Toxicity must be determined in both cell and animal studies including detailed, well-controlled studies acceptable to the FDA and EMEA for qualifying a compound to be used in man. Adequate pharmacology means the compound must have suitable oral bioavailability and metabolism so as to be delivered in an acceptable way to patients.

The core collaborators include:
Dr. Joel Gottesfeld, *Scripps Research Institute, La Jolla, CA-US*
Dr. Massimo Pandolfo, *Hospital Erasme Brussels, Belgium*
Dr. Mark Pook, *School of Health Sciences & Social Care, Brunel University, Uxbridge, UK*
Drs. Dan Geschwind and Giovanni Coppola, *Neuroscience and Genetics Research Center, UCLA, Los Angeles,US*

2) Clinical evaluation of safety and biochemical evidence of efficacy
This involves the initial stage of research in patients in which it is essential to have biochemical and molecular biological measures to document the effect of drug treatment in short term dosing, too short to show functional improvements in patients.

3) Clinical demonstration of functional improvements in patients
These efficacy studies would be necessary to achieve drug approval. They would be designed to demonstrate drug safety as delivered to achieve a therapeutic benefit to the patient.

Considerations

The ethical issues regarding the relative difficulties of enrolling patients for clinical trials versus placebo are always at hand. Patients afflicted by progressive pathologies will not be very willing to

be treated by placebo, especially when the expected results are of modest entity. Negative bent spirits regarding the possibility of not even receiving the drug might very well interfere with all obtainable results either conditioning them. It is also true that a placebo-free treatment can on the contrary lead to a sort of initial euphoria, thus providing slight improvement, independently from actual drug efficiency. However, the ongoing timeframe of treatment should cancel out the positive "placebo effect" and, if indeed efficient, highlight any concrete variations.

The pharmaceuticals that are today available indicate the considerable progress achieved; nonetheless, it remains clear that we are still speaking about meager interventions that alone cannot satisfy the FRDA patient communities. It is dearly important to underline anew the necessity of committing everybody's' energies towards a more radical approaches in which the effects result indisputably positive in order to surpass the dragged-out issue of double-blind experimentation.

GoFAR announces that it intends by actively collaborating for the development of HDACi that which we hope will be able to reveal itself an efficient therapy for Friedreich's ataxia, potentially capable of modifying the course of this devastating and serious disease.

GoFAR will continue to carry out network actions among FA patient associations with the aim of reaching an effective therapy against this crippling disease in the shortest time possible.
In light of this goal it is today more necessary than ever that we have the availability of a unique European patient register, of which GoFAR will act as promoter. The aim of this action is to obtain the opportunity for HDACi clinical trials on patients even in Europe, when medical and scientific conditions have matured, from the onset of experimentation. Therefore, we ask that patients contact the local associations of reference or GoFAR directly, which is committed to the coordination of this crucial initiative.

At this end, the last 8th of October, Bernardo Ruggeri (GoFAR), in view of his role as representative of the european network of patients, participated in an encounter organized by Repligen in Washington D.C. along with the researchers involved in the drug's development phase. GoFAR has committed itself to the effort of providing incentive and financing the necessary studies conducted at research labs and universities dealing with HDACi development in order to ensure a rapid advance towards patient clinical trials as well as the facilitation and partial financing of R&D (research and development) even in Europe; while Repligen will be performing parts of medicinal chemistry, pharmacology, toxicology and clinical trials

This is the direction that GoFAR has chosen to follow; that of remaining alert and ready to support any therapeutic approach of scientific validity, though orientating the major part of its efforts towards HDACi development.

About GoFAR: www.fagofar.org

(*) Gottesfeld,J.M. "*Small molecules affecting transcription in Friedreich ataxia"*, Pharm.& Therap. (2007)
(**)*PipelineReview.com; September 28,2007*
(***)*Last Updated: September 28, 2007 from ClinicalTrials.gov (service of the U.S. National Institutes of Health), processed on October 19, 2007*
(****) *Information divulgated by GoFAR in occasion of the Patient Association Workshop , 30-31, March 2007,Torino, Italy; immediately after to all non-participant European associations and at GoFAR-AGM, 26 May 2007, Bologna, Italy)*

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