Current Research into Drug Treatments for Friedreich ataxia

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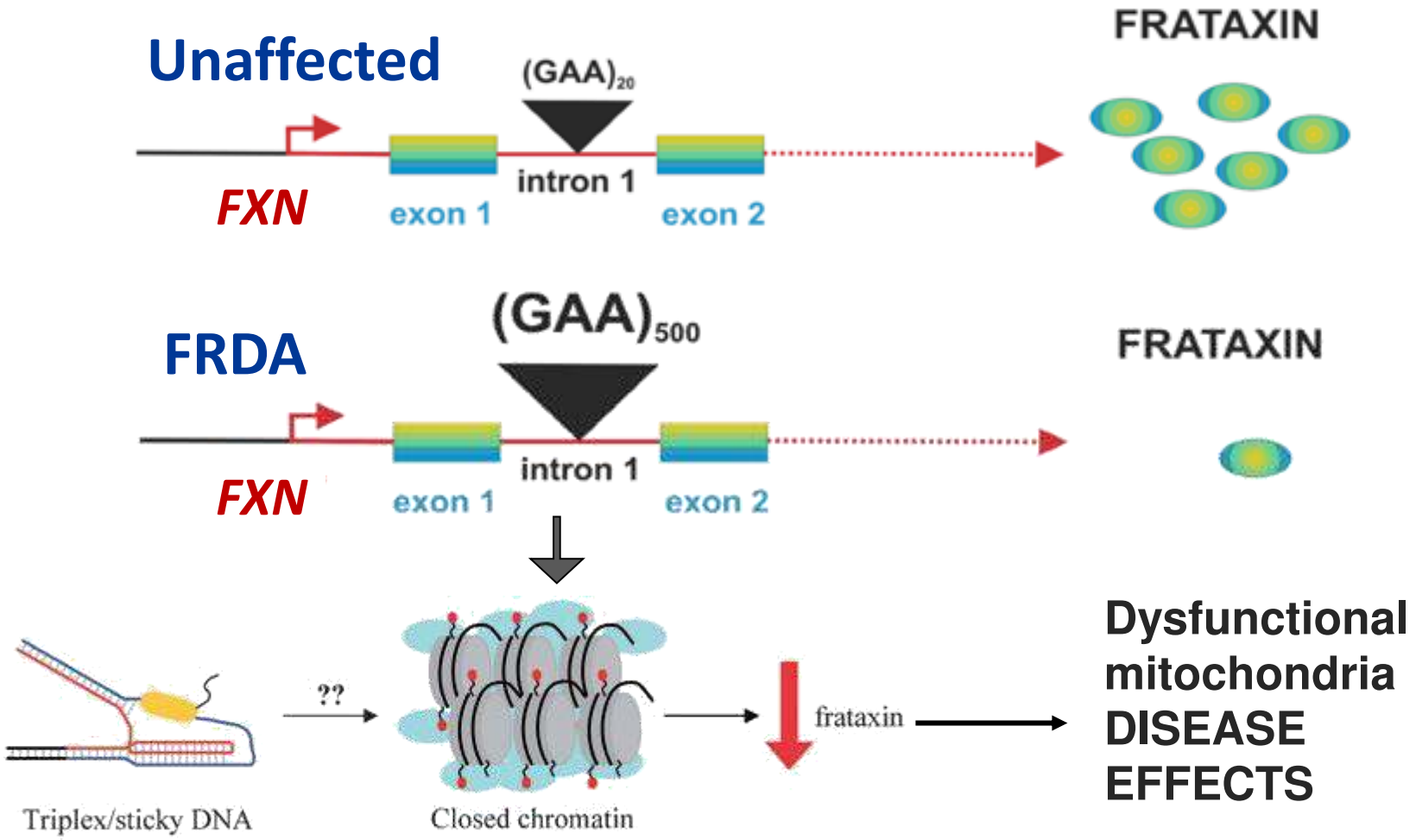
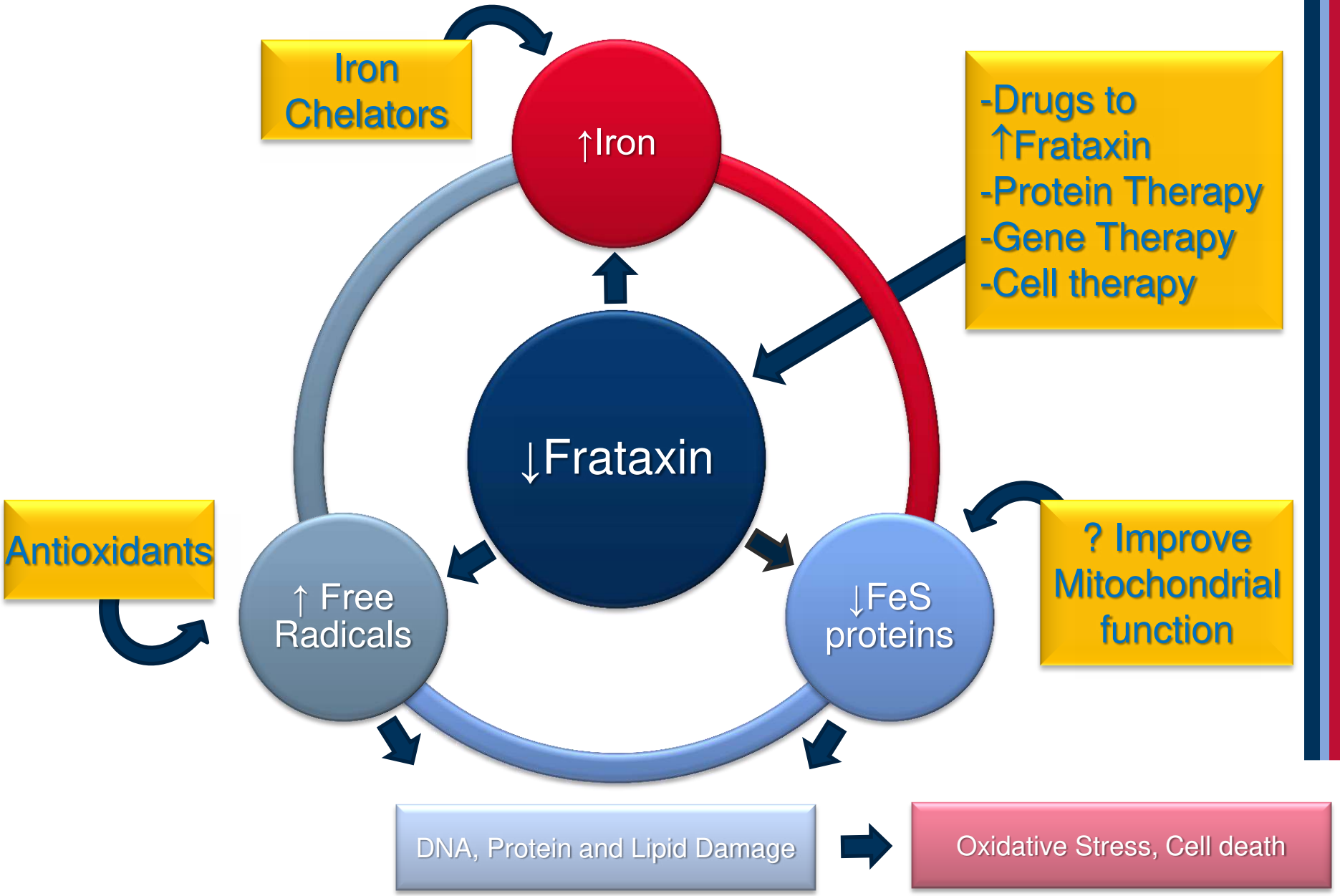
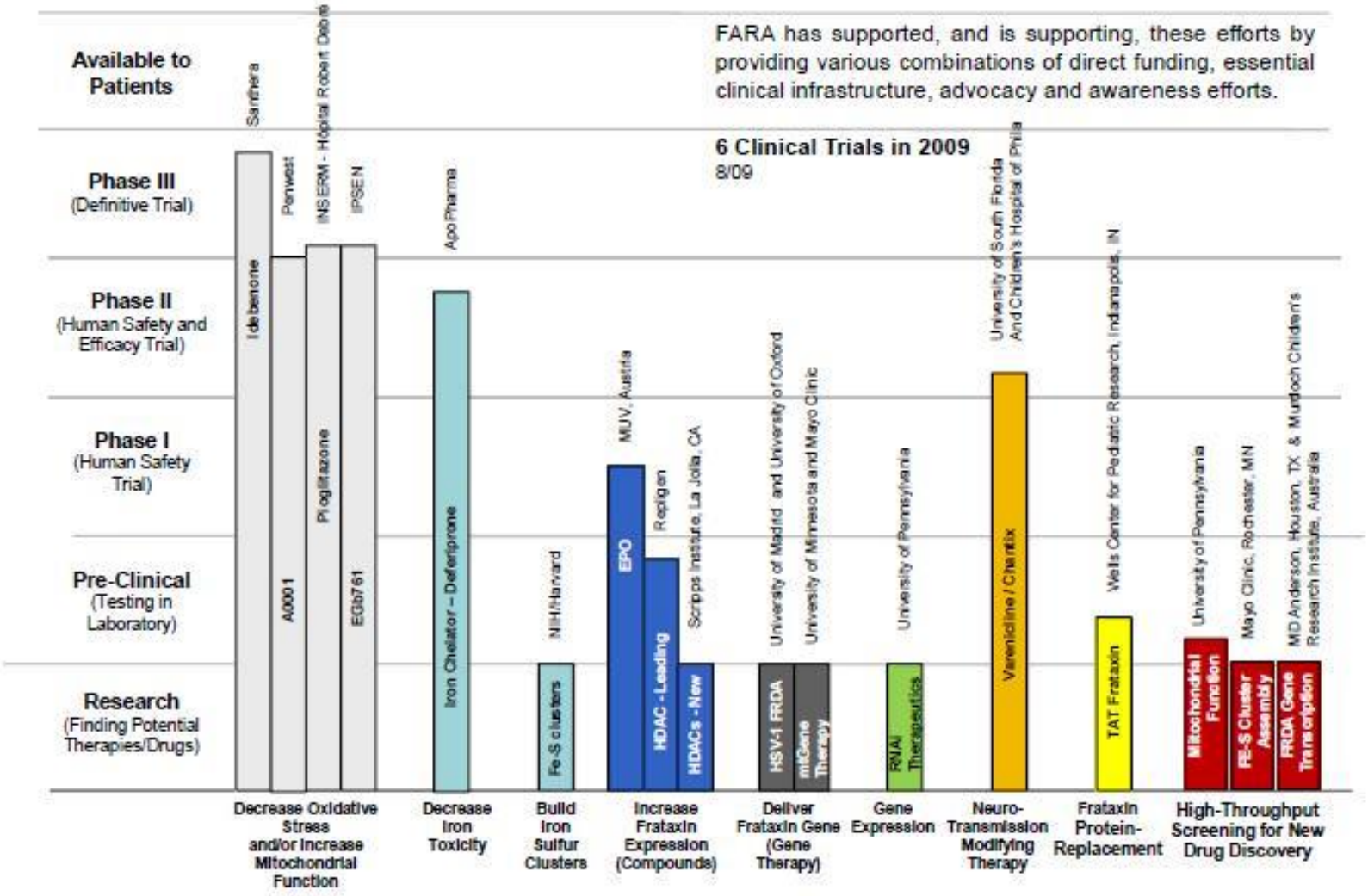
ARC – Windsor March 2015

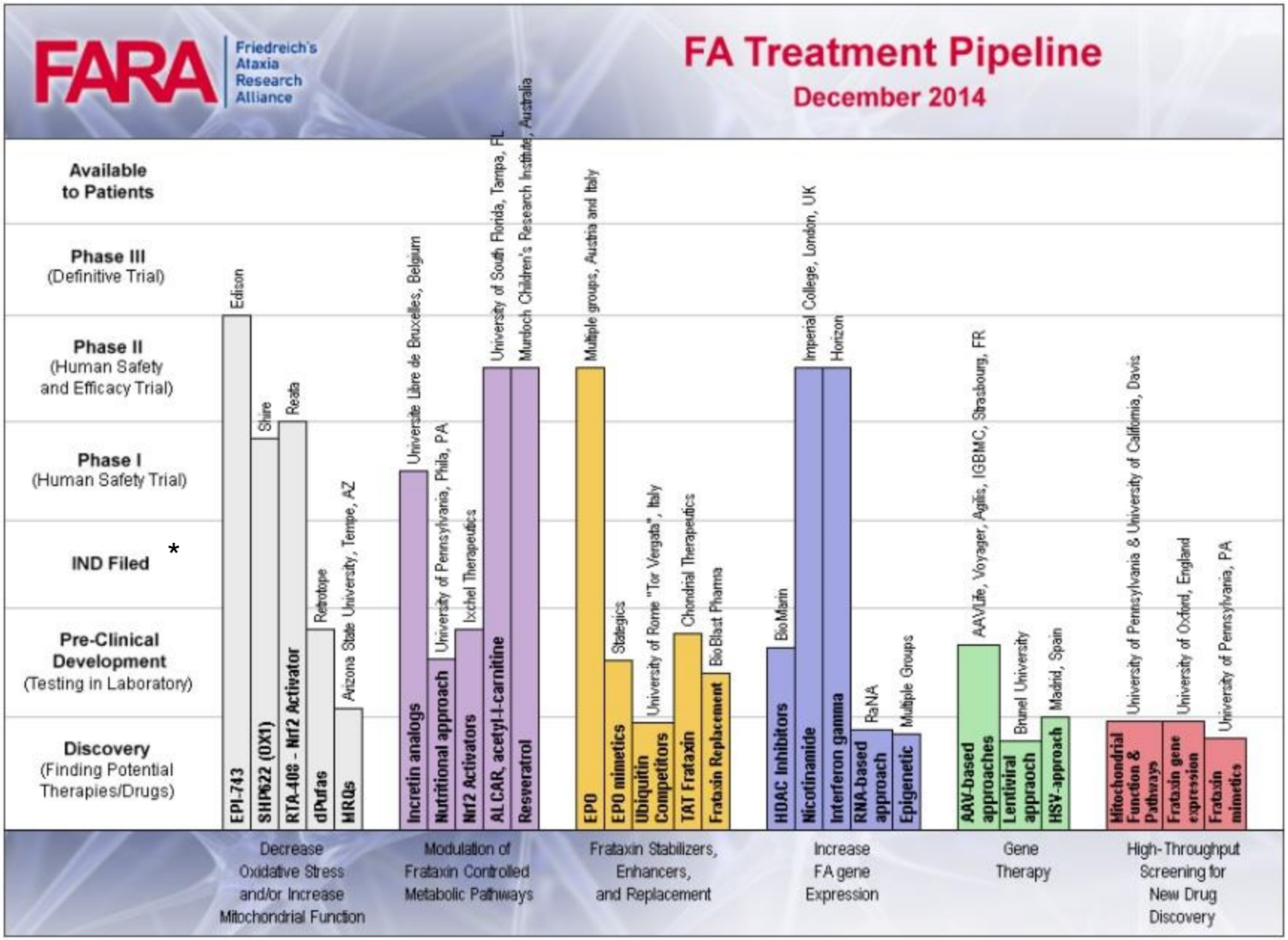
FRDA Molecular Disease Mechanism




Iron Chelators
↑Iron
-Drugs to ↑Frataxin
-Protein Therapy
-Gene Therapy
-Cell therapy
↓Frataxin
Antioxidants
↑ Free Radicals
↓FeS proteins
? Improve Mitochondrial function
DNA, Protein and Lipid Damage
Oxidative Stress, Cell death

Friedreich's ataxia treatment pipeline - 2010





* IND = Investigational new drug

Decrease oxidative stress and/or increase mitochondrial function

- EPI-743 (Edison)
  - Compound that aims to improve mitochondrial function by countering oxidative stress
  - Ongoing Phase 2 studies
- SHP622 (formerly VP20629 or OX1) (Shire)
  - Naturally occurring compound that prevents oxidative stress
  - Ongoing Phase 1 trial
- RTA-408 (Reata)
  - Antioxidant inflammation modulator (AIM) that acts by activating Nrf2, a transcription factor that regulates antioxidant responses
  - Phase 2/3 trial initiated in Jan 2015
- dPUFAs (Retrotope)
  - Deuterized polyunsaturated fatty acids that resist oxidative stress
- MRQs (Arizona State U.)
  - Multifunctional radical quenchers - Compounds that target mitochondrial dysfunction

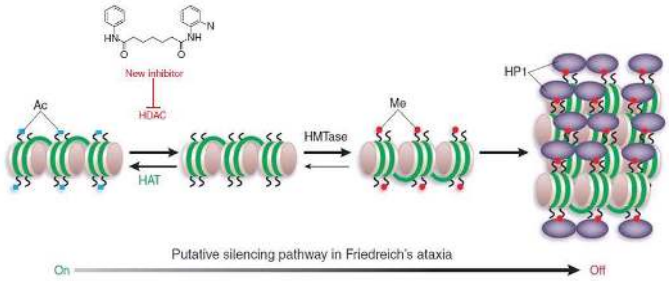
Modulation of frataxin-controlled metabolic pathways

- Incretin analogues (ULB, Brussels)
  - Incretins are gut hormones that control blood sugar levels
  - Analogues developed to treat diabetes have been shown to increase frataxin levels in the pancreas
  - ongoing small pilot trial
- Nutritional approach (Upenn)
  - Nutritional compounds to increase PGC1α, a controller of energy metabolism that is decreased in FRDA cells
- Nrf2 activators (UC Davis, Ixchel Therapeutics)
  - Dyclonine, dimethyl fumarate activate Nrf2 and increase frataxin expression
  - Small pilot study using dyclonine as a mouth rinse has reported increased frataxin levels in 6/8 FRDA patients
- ALCAR (Acetyl-l-carnitine) (U South Florida)
  - Naturally occurring compound involved in fatty acid breakdown and glucose metabolism
  - Ongoing Phase 2 trial
- Resveratrol (Murdoch Children's Research Institute)
  - A compound found in the skin of red grapes that increases frataxin expression and may improve mitochondrial function
  - A Phase 2 study has reported improved neurological rating scales and speech measures in a high dose group, but further studies using a placebo group are required

Frataxin stabilizers, enhancers and replacement

- EPO (Erythropoietin) (Multiple groups)
  - EPO is a natural hormone and an approved drug to increase red blood cells
  - EPO increases frataxin expression by as yet unknown mechanisms
  - Completed and ongoing Phase 2 studies – EPO is well tolerated, produces sustained increases in frataxin, but has no effect on cardiac function or neurological scales.
- EPO mimetics (STATegics)
  - Small molecule mimetics of EPO are being developed
- Ubiquitin competitors (U.Rome Tor Vergata)
  - Small molecules that inhibit degradation of frataxin protein
- Src tyrosine kinase inhibitors (U.Rome Tor Vergata)
  - Small molecules that inhibit degradation of frataxin protein
- TAT-Frataxin (Chondrial Therapeutics)
  - A method to deliver frataxin protein to the mitochondria using a protein fragment called ‘Trans-Activator of Transcription’ – or ‘TAT’ – ‘Rapidly advancing...’
- Frataxin replacement (BioBlast Pharma)
  - Development of other fusion proteins similar to TAT-Frataxin that target mitochondria- progression to Phase 1 trials

Increase frataxin gene expression

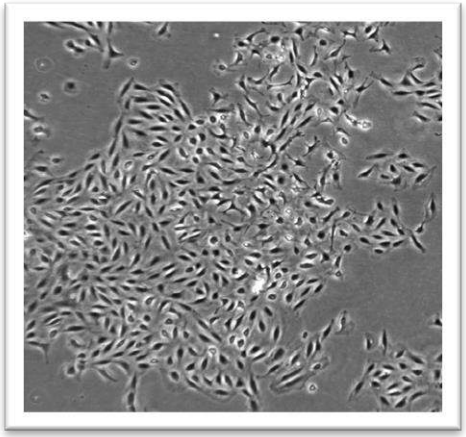


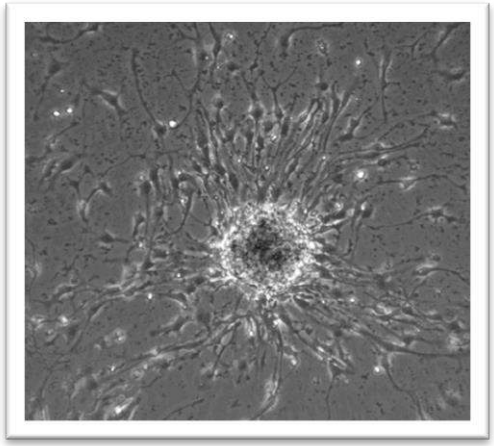
- HDAC inhibitors (BioMarin)
  - RG2833 (Repligen) completed a Phase 1 trial – treatment was well tolerated and there was increased frataxin expression.
  - Follow-on compounds are being developed that have better CNS delivery and better metabolic stability – e.g. *Click-1* (Soragni et al (2015) *Front. Neurol.* 6: 41)
- Nicotinamide (Imperial College London)
  - Nicotimanide (vitamin B3) is a class III HDAC inhibitor that increases frataxin expression
  - Phase 2 trial showed increased frataxin, but no clinical improvement
- Interferon Gamma (Horizon)
  - Interferon gamma (Actimmune) is an approved drug for other rare diseases that increases frataxin expression by an unknown mechanism
  - Completed and ongoing Phase 2 studies – no significant increases in frataxin expression, but indications of improved neurological function – Now starting placebo controlled Phase 3 studies
- RNA-based approaches (RaNA Therapeutics)
  - Oligonucleotide targeting of FXN mRNA to increase frataxin expression
- Other epigenetic and serendipitous frataxin-increasing approaches (multiple groups)
  - e.g. HMTase inhibitors, such as GSK126 or BIX-01294 (Brunel University London)
  - e.g. diazoxide, an approved drug for hypertension and diabetes (Brunel University London)

Research into potential new FRDA drug therapies

Resources

- Patient cells/tissues
- Cell cultures
  - Blood cells
  - Skin cells
  - Olefactory nasal cells
  - Skin cells → (iPS cells) →
    - Cultured neurons and heart cells
- Animal models

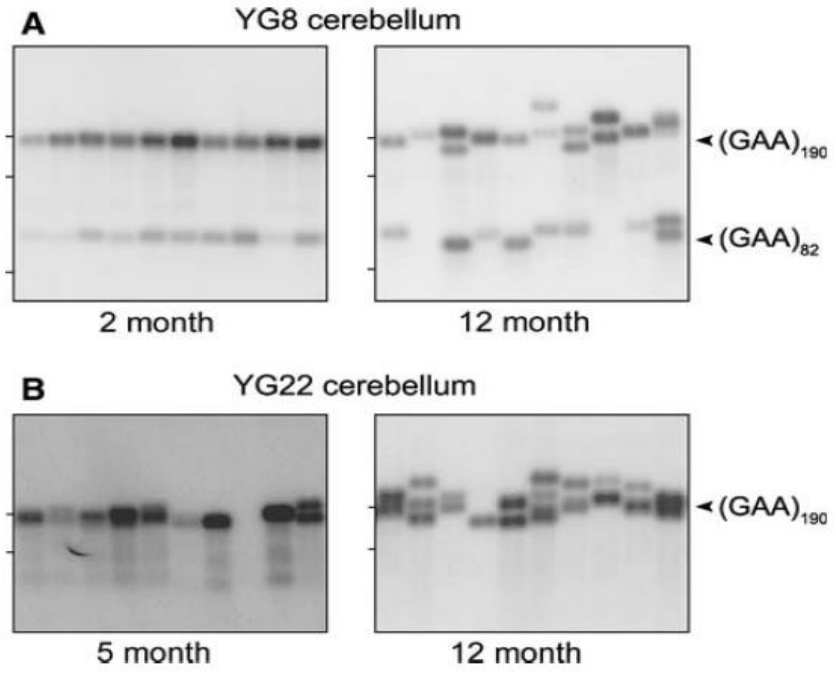




Basic Research - GAA Instability

- Why are the GAA repeat mutations larger in specific parts of the CNS?
- Does this cause pathology?
- What is the role of DNA repair proteins?

→New therapeutic targets?

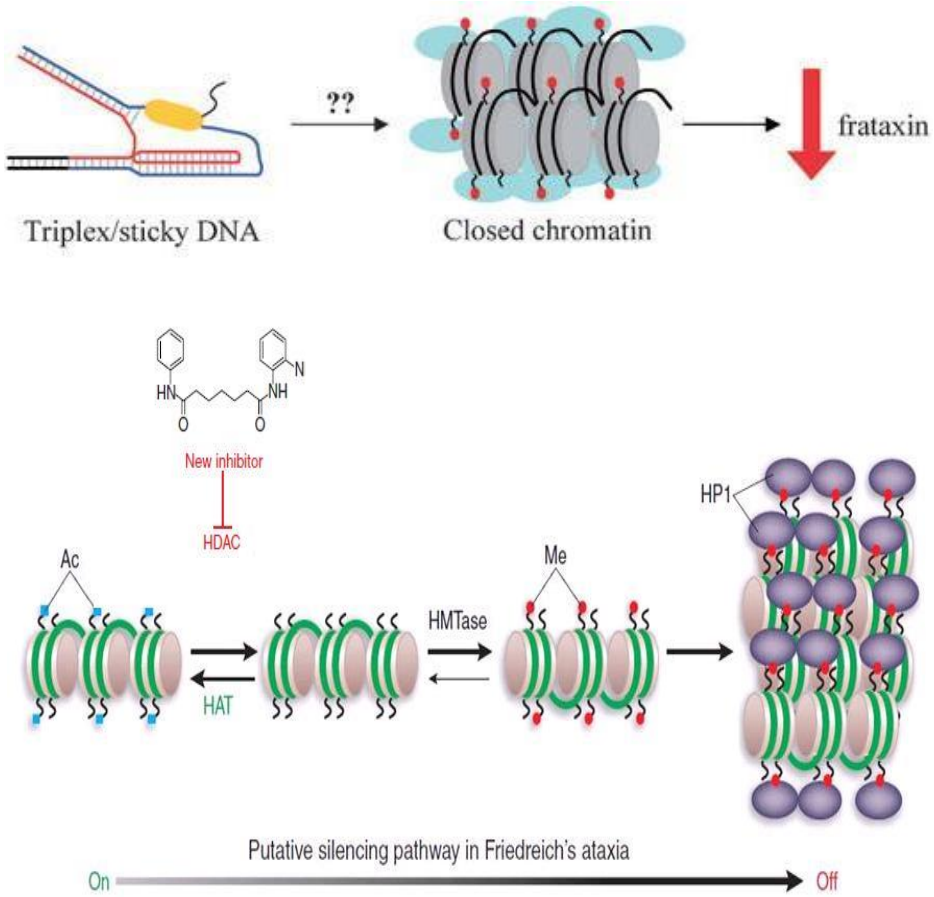


Effects of GAA Mutation

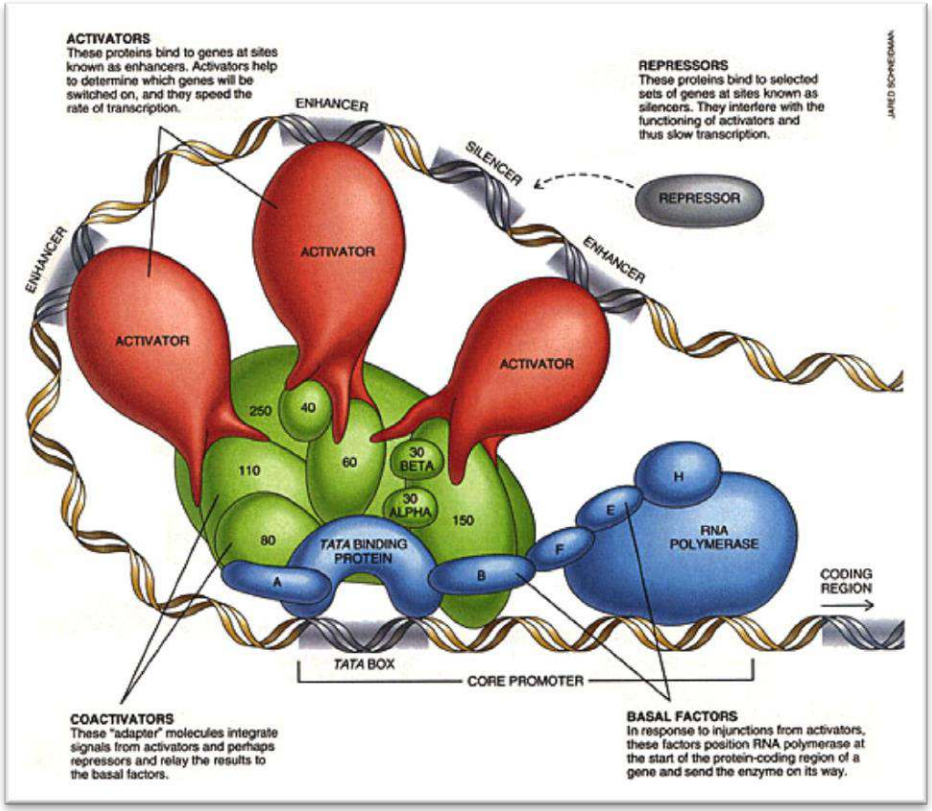
- How does the GAA mutation cause repression of the *FXN* gene?

- Abnormal DNA structures?
- DNA methylation changes?
- Histone modifications?
- Non-coding RNA changes?

→ New therapeutic targets?



Regulation of the *FXN* Gene



- What factors control the amount of *FXN* gene expression?
- PPARγ, PGC1α, HIF1/2, SRF, TFAP2, p53, microRNAs?

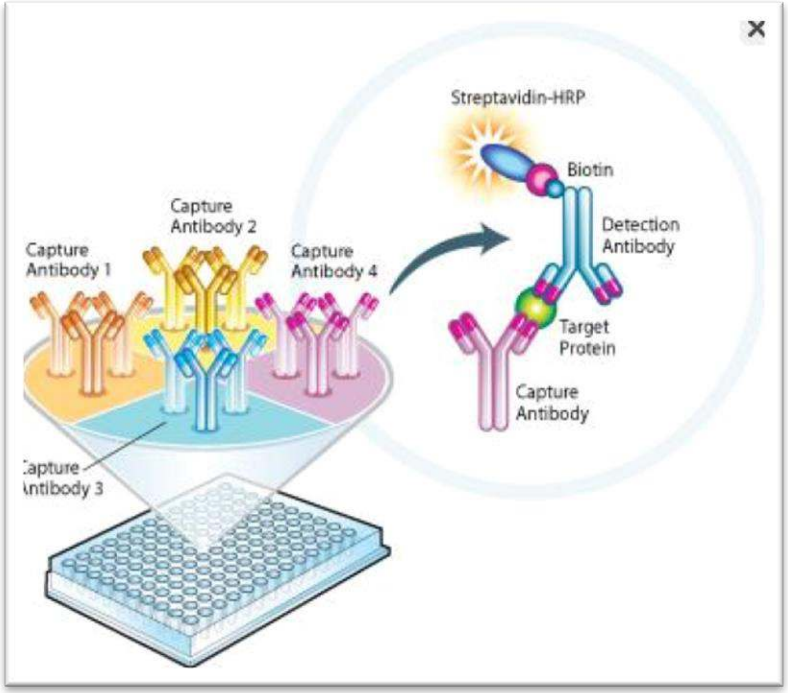
→ New therapeutic targets?

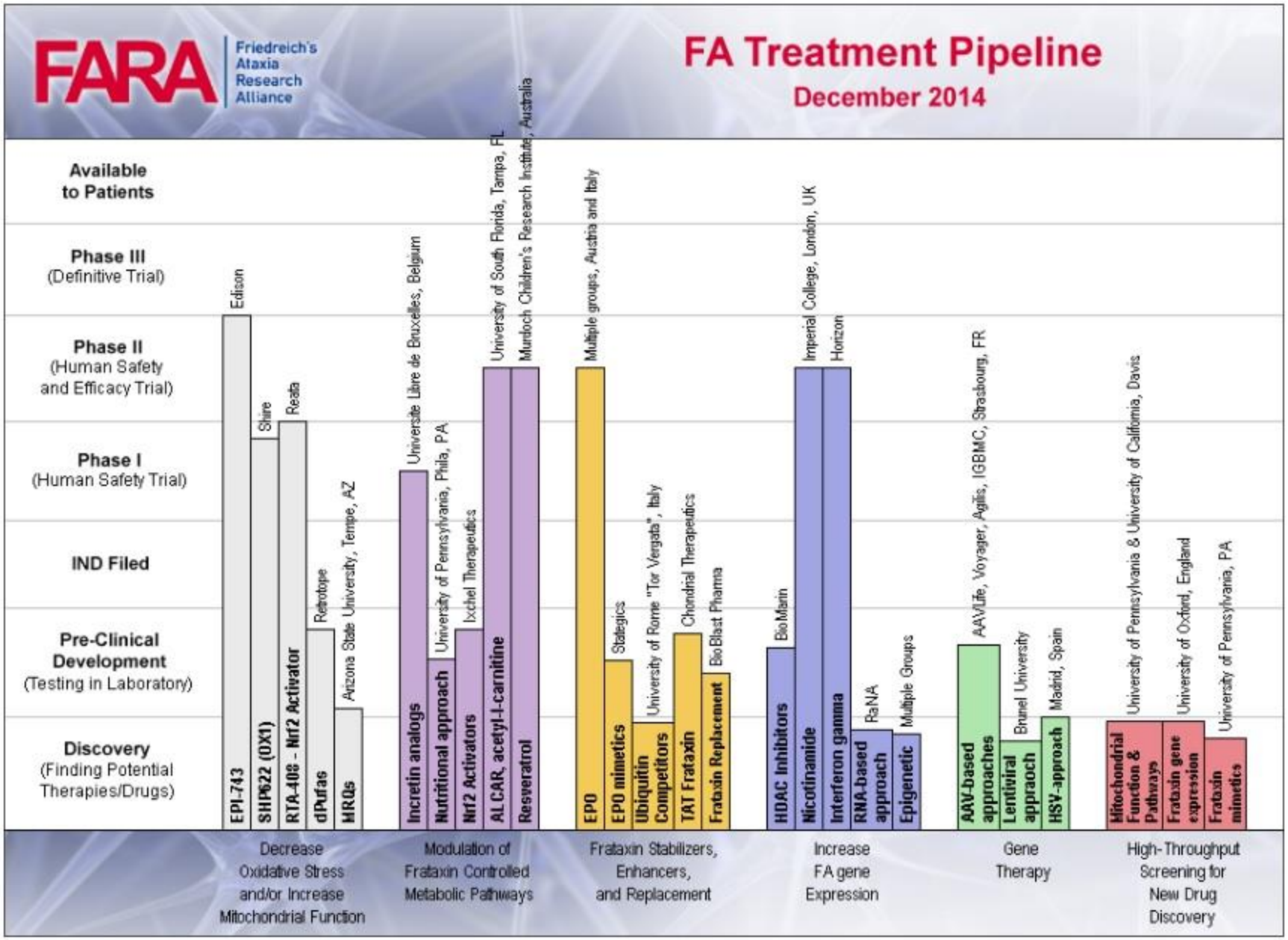
Regulation of Frataxin Protein Levels

- High throughput screening to identify novel compounds that increase frataxin by unknown mechanisms.

- e.g. Prevention of frataxin degradation
  - Identifying compounds that target the ubiquitin-proteasome system

→ New therapeutic targets?




FARA
Friedreich's Ataxia Research Alliance
FA Treatment Pipeline
December 2014
Available to Patients
Phase III (Definitive Trial)
Phase II (Human Safety and Efficacy Trial)
Phase I (Human Safety Trial)
IND Filed
Pre-Clinical Development (Testing in Laboratory)
Discovery (Finding Potential Therapies/Drugs)
Edison
EPI-743
Shire
SHP622 (DX1)
Reata
RTA-408 - Nrf2 Activator
Retrotope
dPufas
Arizona State University, Tempe, AZ
MRQs
Universite Libre de Bruxelles, Belgium
Incretin analogs
University of Pennsylvania, Phila, PA
Nutritional approach
Ixchel Therapeutics
Nrf2 Activators
University of South Florida, Tampa, FL
Murdoch Children's Research Institute, Australia
ALCAR, acetyl-l-carnitine
Resveratrol
Multiple groups, Austria and Italy
EPO
Stalegics
EPO mimetics
University of Rome "Tor Vergata", Italy
Ubiquitin Competitors
Chondrial Therapeutics
TAT Frataxin
BioBlast Pharma
Frataxin Replacement
BioMarin
HDAC Inhibitors
Imperial College, London, UK
Nicotinamide
Horizon
Interferon gamma
RaNA
RNA-based approach
Multiple Groups
Epigenetic
AAVLife, Voyager, Agilis, IGBMC, Strasbourg, FR
AAV-based approaches
Brunel University
Lentiviral appraoch
Madrid, Spain
HSV-approach
University of Pennsylvania & University of California, Davis
Mitochondrial Function & Pathways
University of Oxford, England
Frataxin gene expression
University of Pennsylvania, PA
Frataxin mimetics
Decrease Oxidative Stress and/or Increase Mitochondrial Function
Modulation of Frataxin Controlled Metabolic Pathways
Frataxin Stabilizers, Enhancers, and Replacement
Increase FA gene Expression
Gene Therapy
High-Throughput Screening for New Drug Discovery