



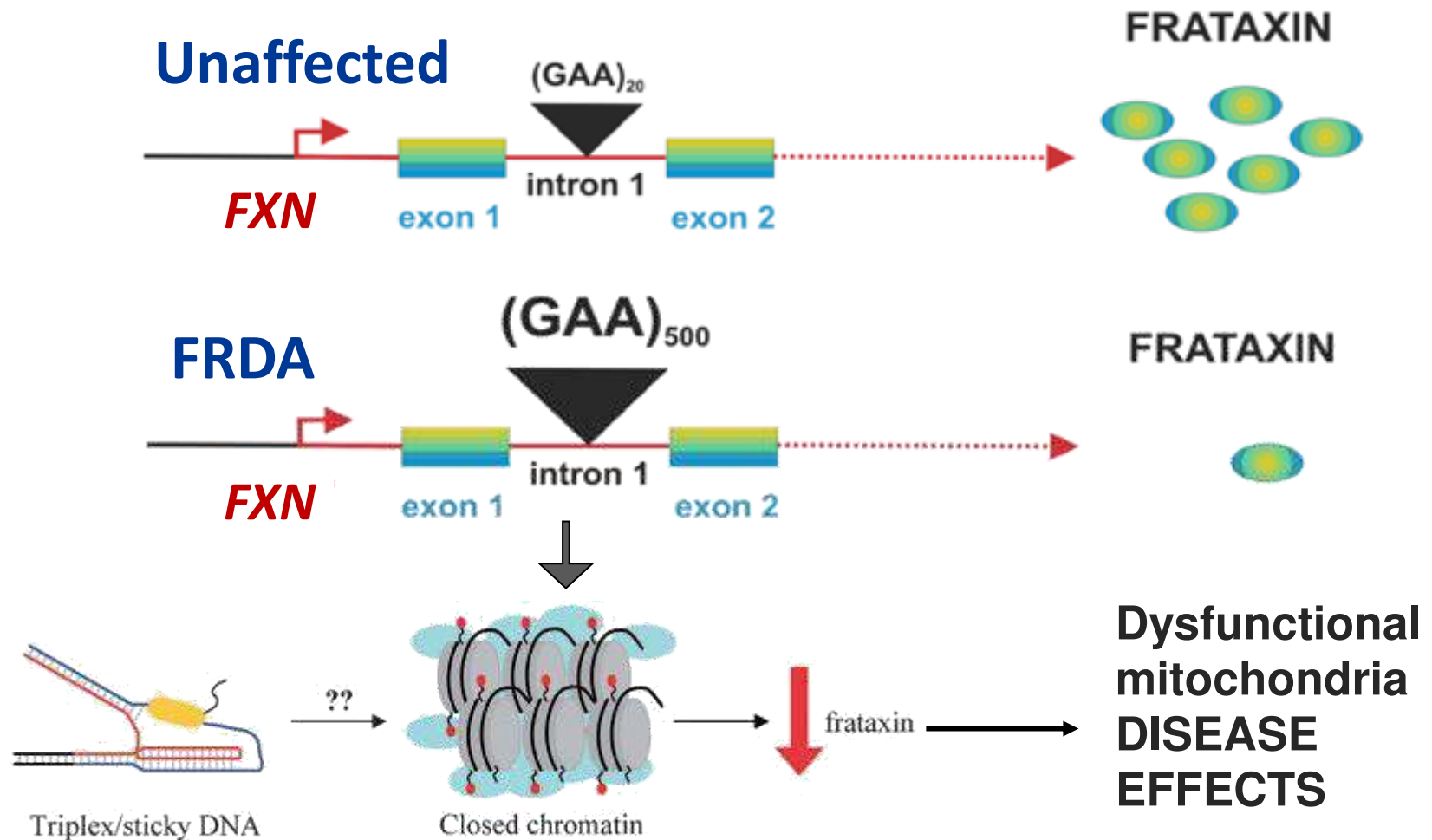
Brunel
University
London

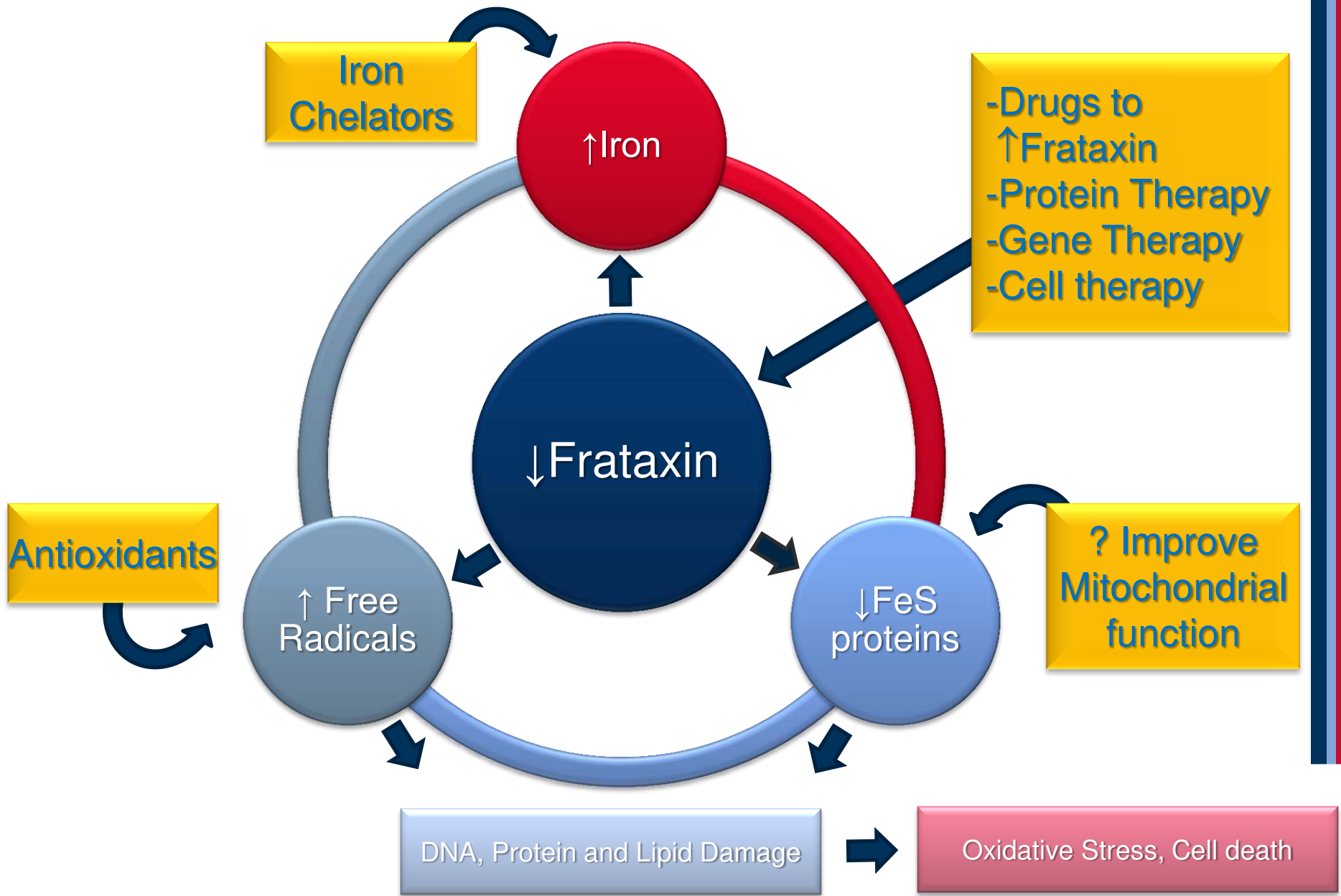
Current Research into Drug Treatments for Friedreich ataxia

Mark Pook

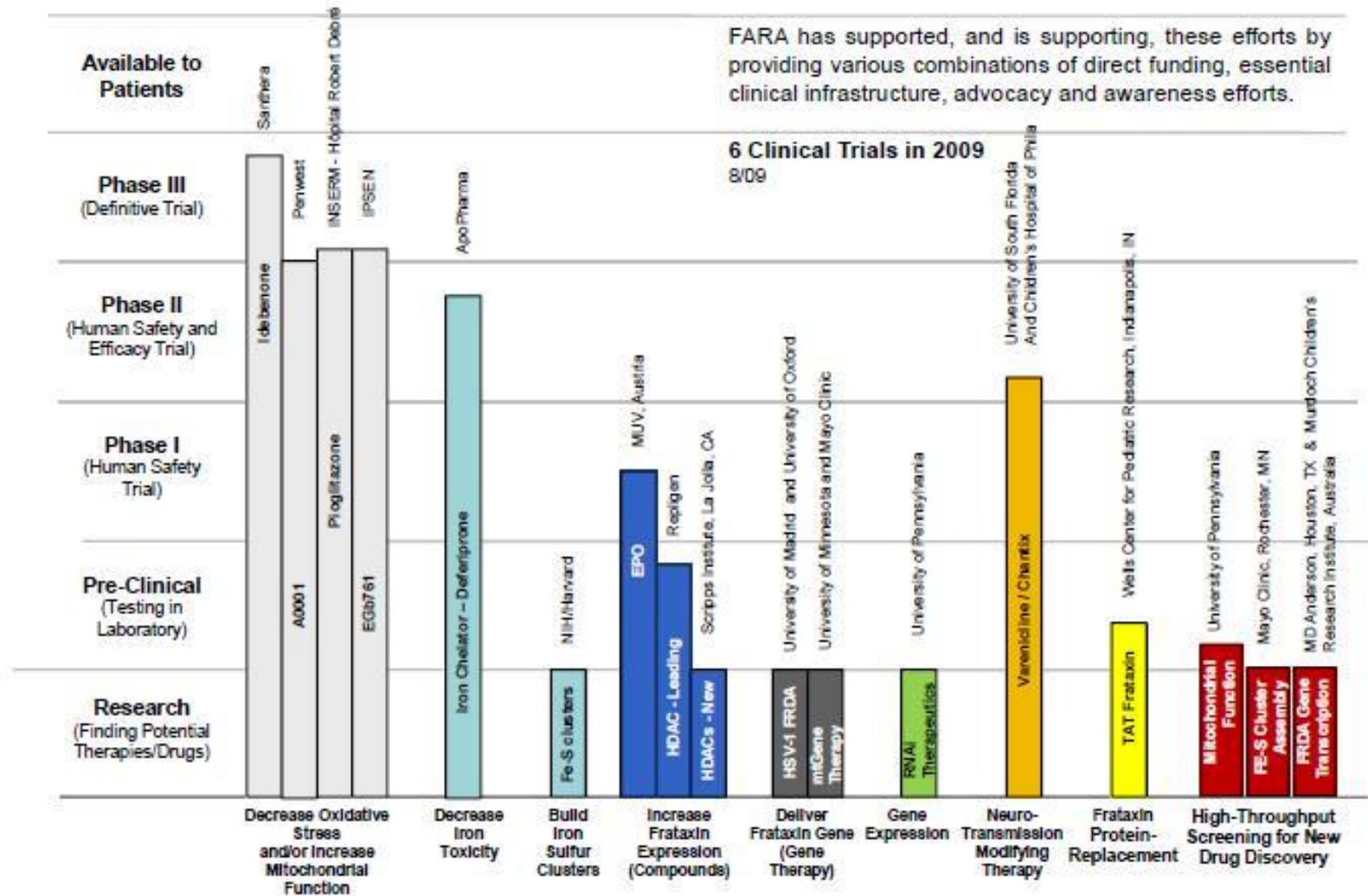
ARC – Windsor March 2015

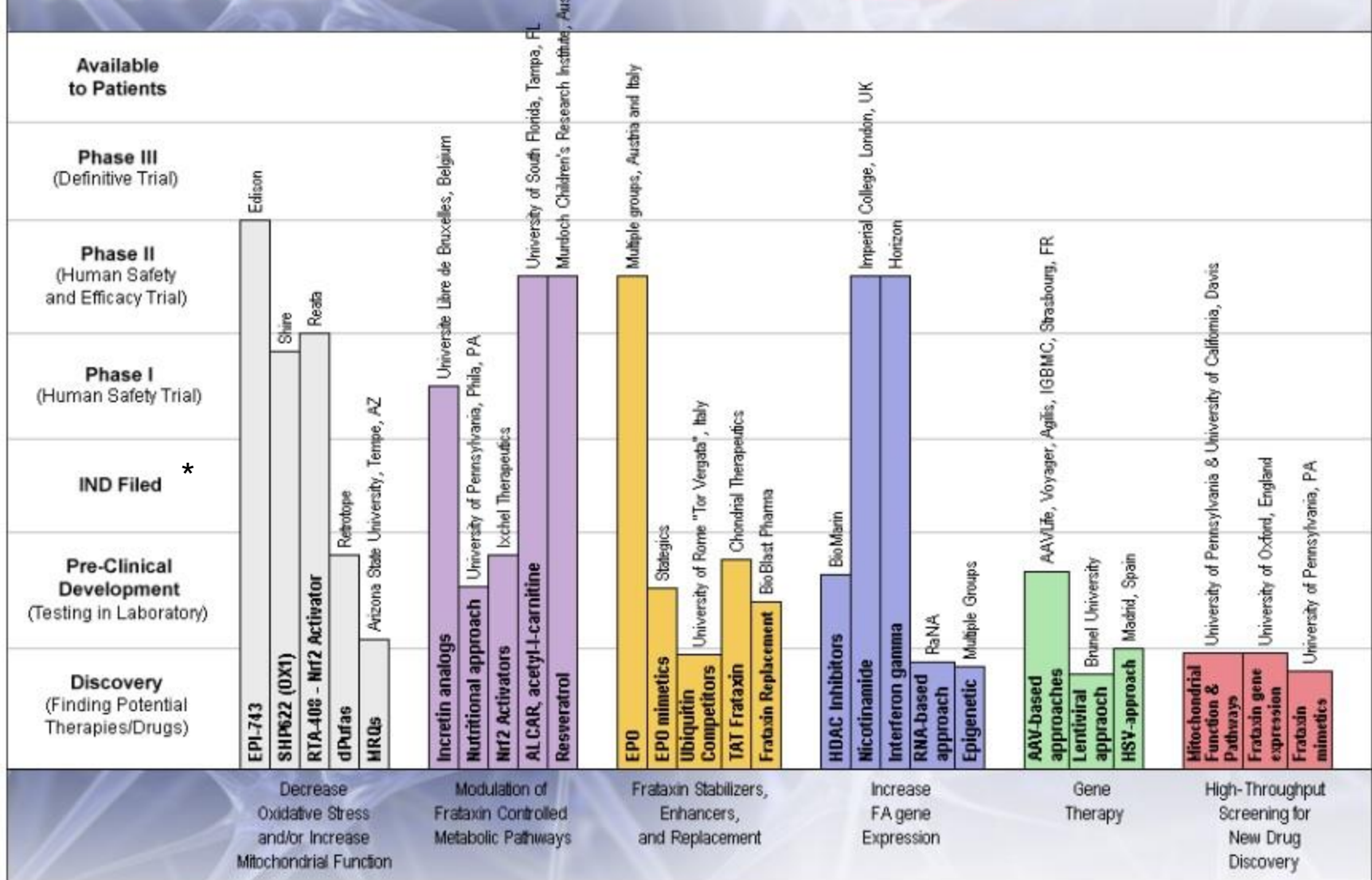
FRDA Molecular Disease Mechanism





Friedreich's ataxia treatment pipeline - 2010





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

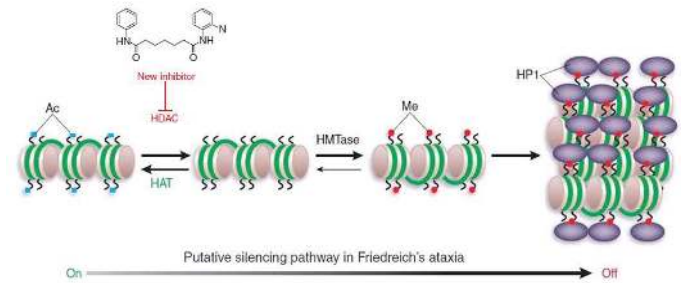
Modulation of frataxin-controlled metabolic pathways

- **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 PGC1 α , 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)

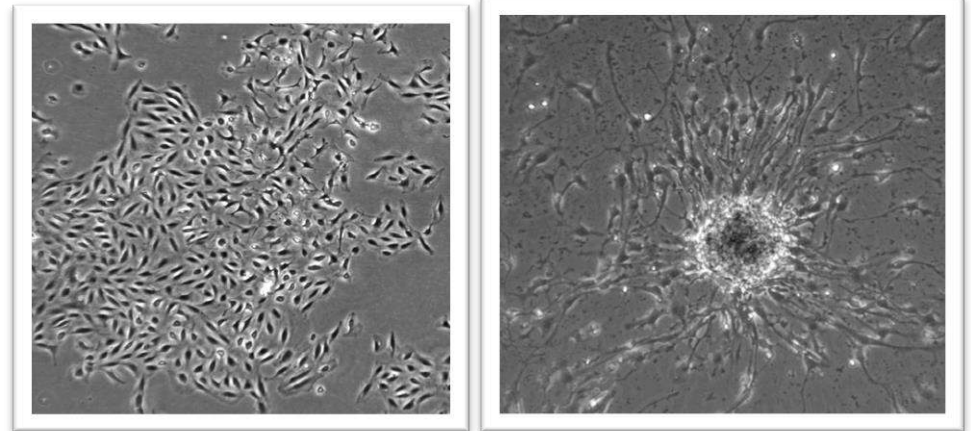
Research into potential new FRDA drug therapies

Resources

> Patient cells/tissues

> Cell cultures

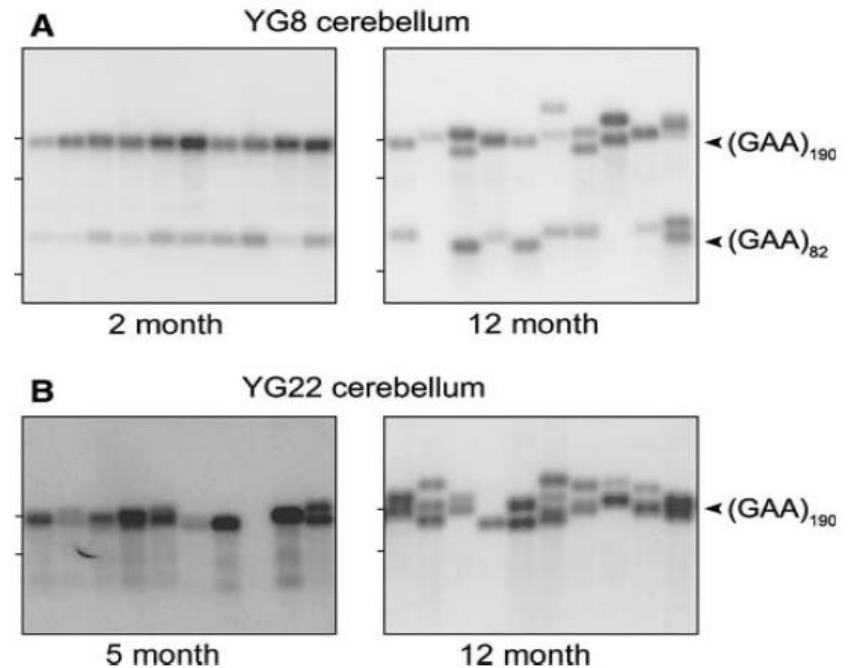
- > Blood cells
- > Skin cells
- > Olfactory nasal cells
- > Skin cells → (iPS cells) →
 - > Cultured neurons and heart cells



> 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?

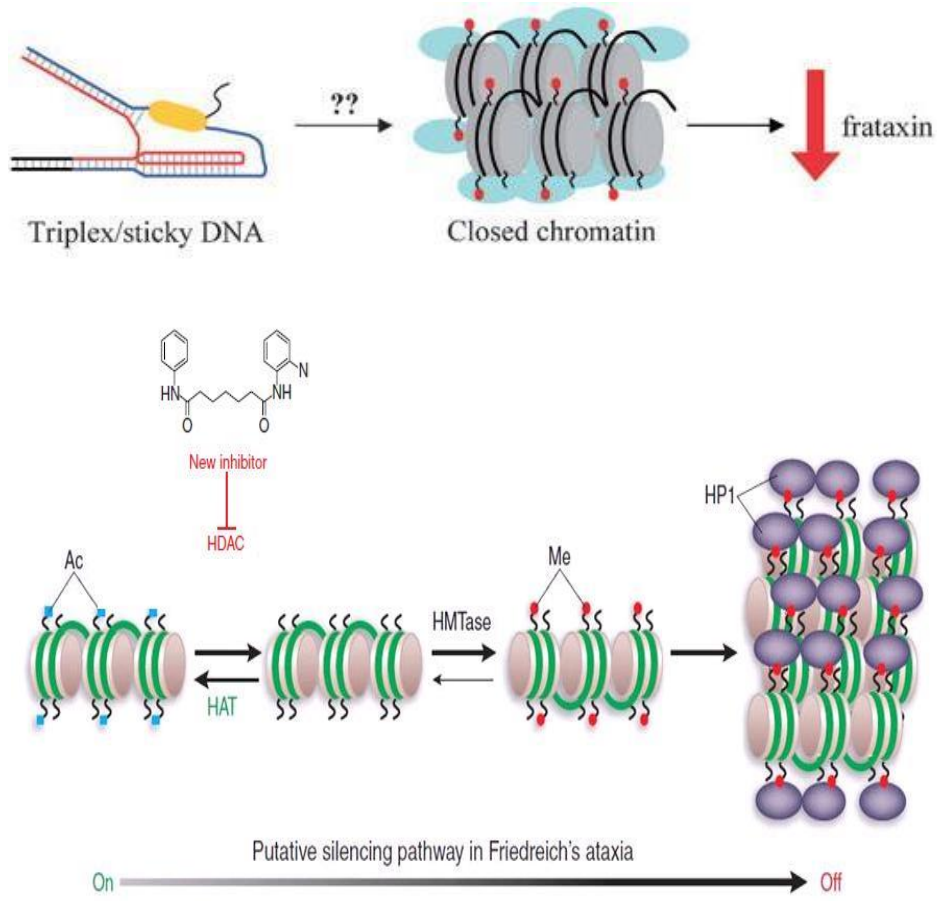


Effects of GAA Mutation

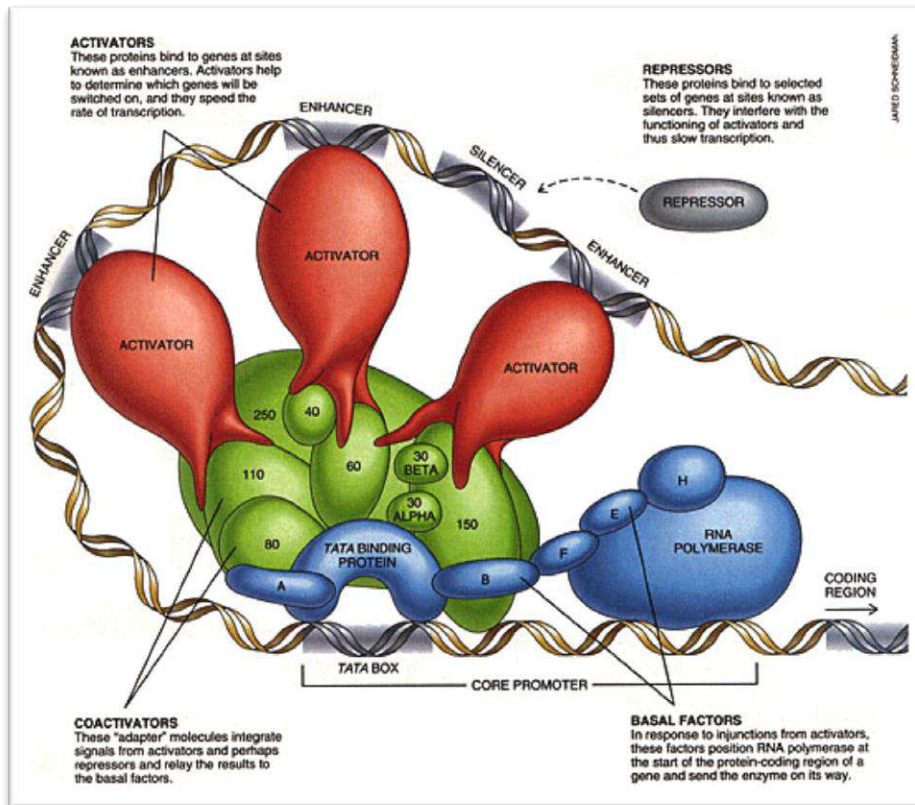
- How does the GAA mutation cause repression of the *FXN* gene?

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

→ New therapeutic targets?



Regulation of the *FXN* Gene

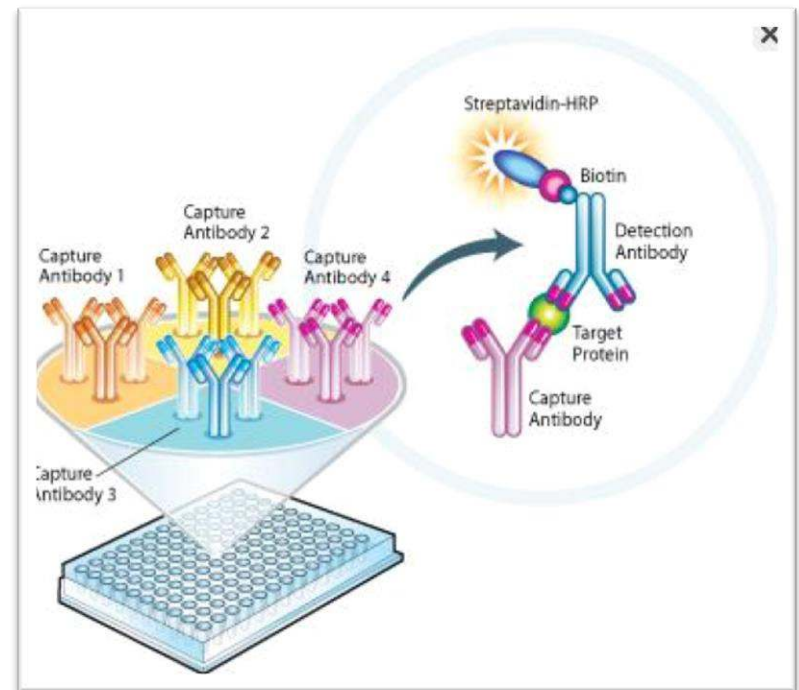


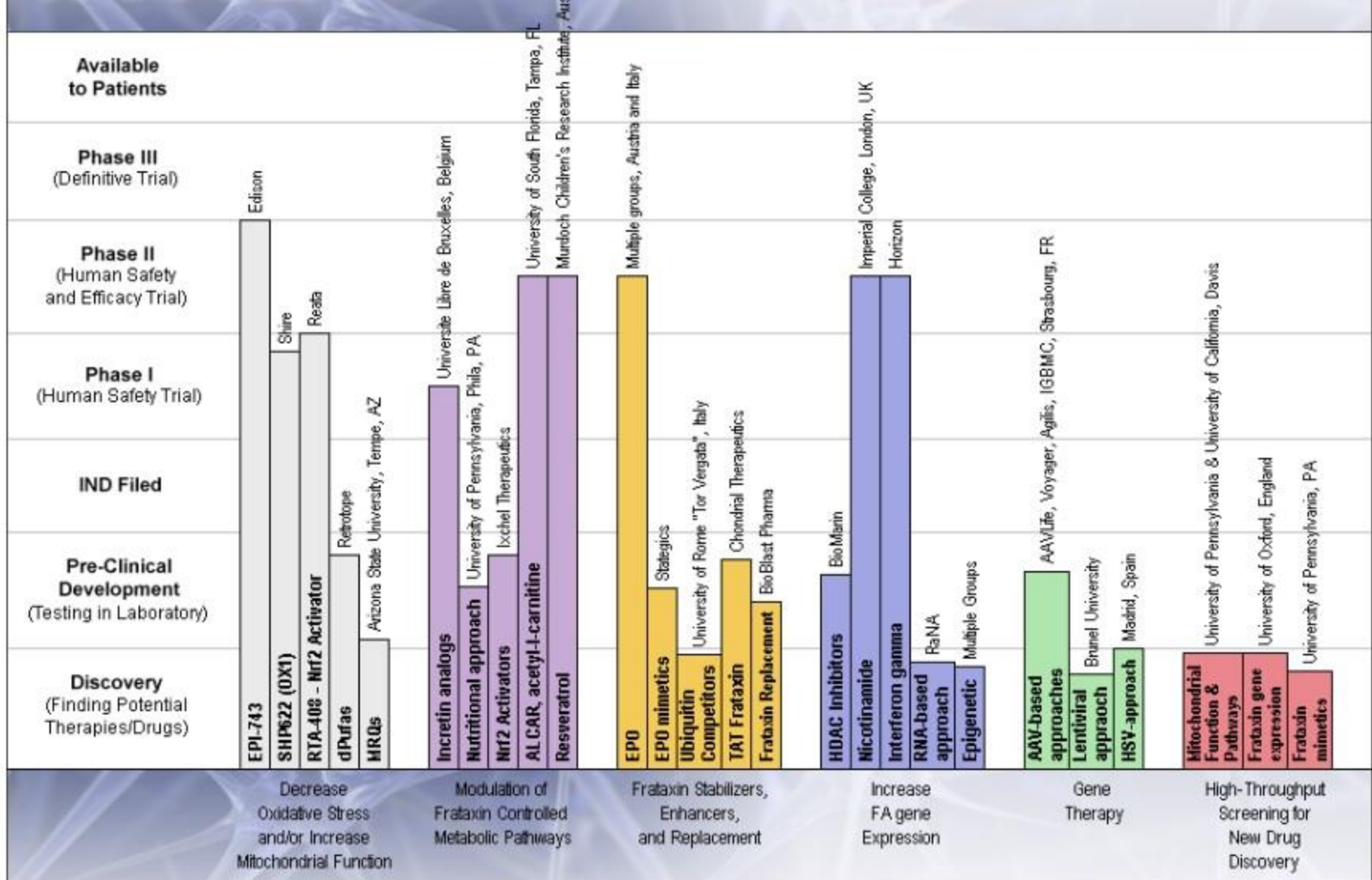
- What factors control the amount of *FXN* gene expression?
 - PPAR γ , PGC1 α , HIF1/2, SRF, TFAP2, p53, microRNAs?
- New therapeutic targets?

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?





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