



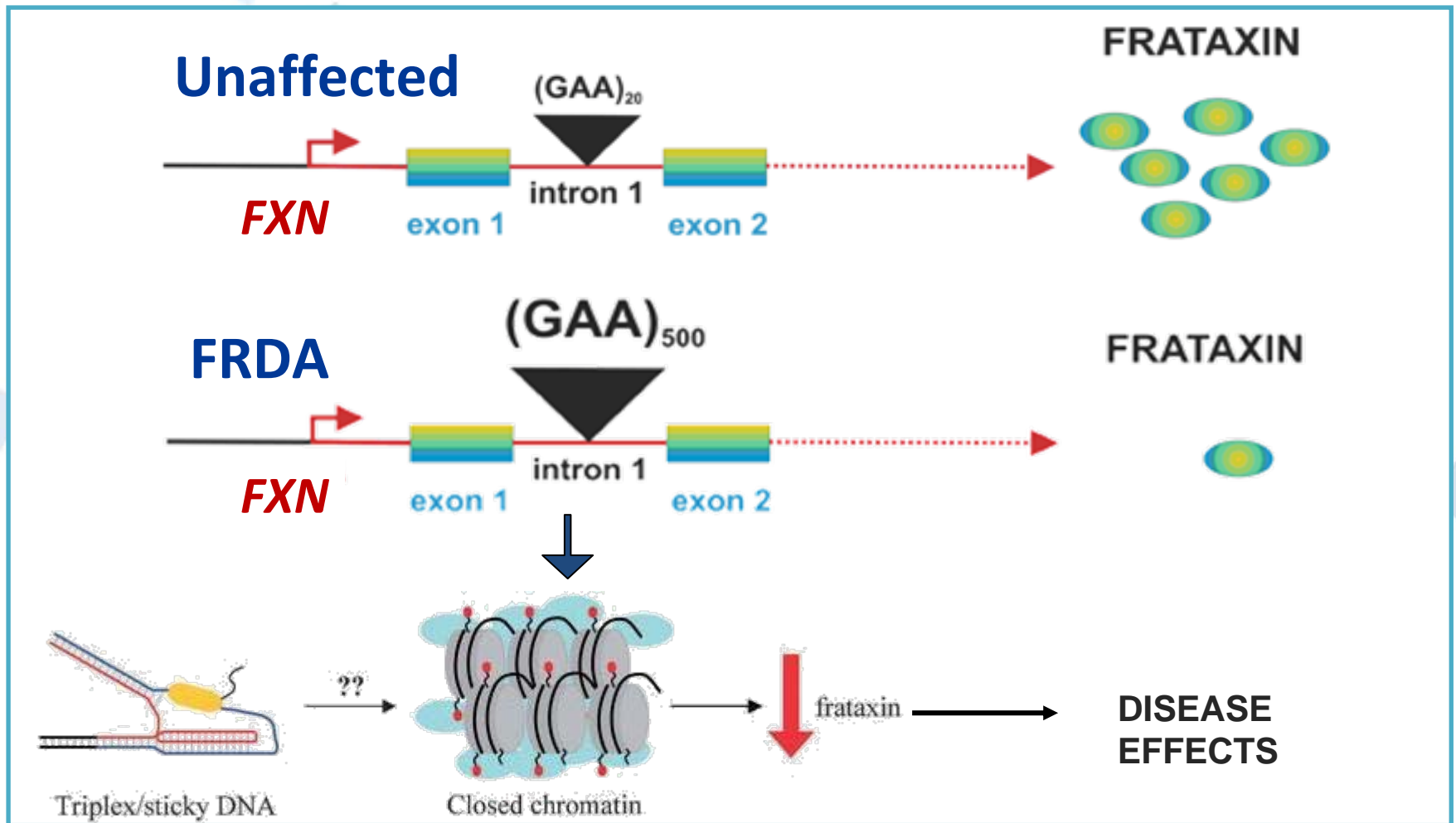
Friedreich's Ataxia (FRDA) Research Update

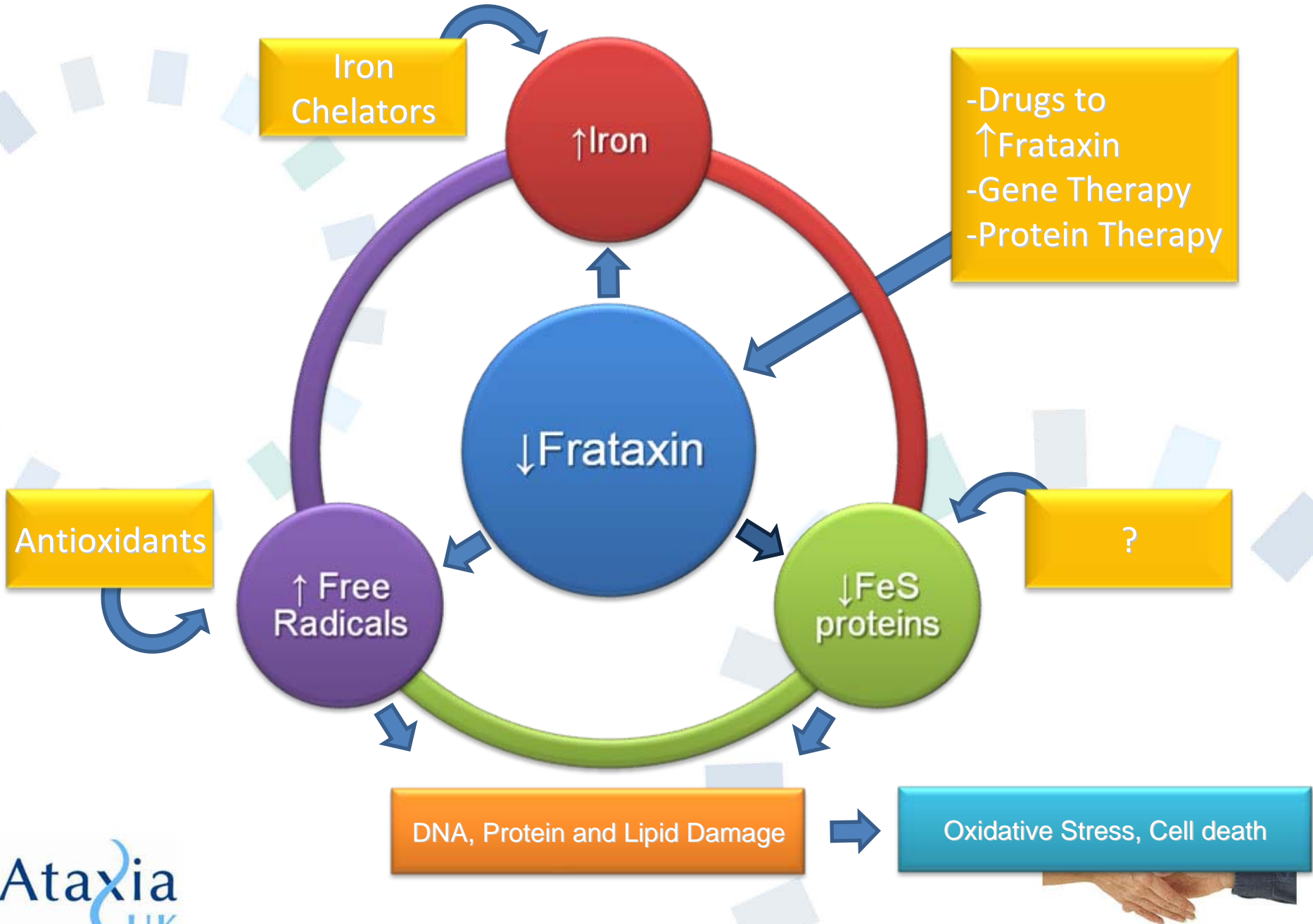
Mark Pook, Brunel University



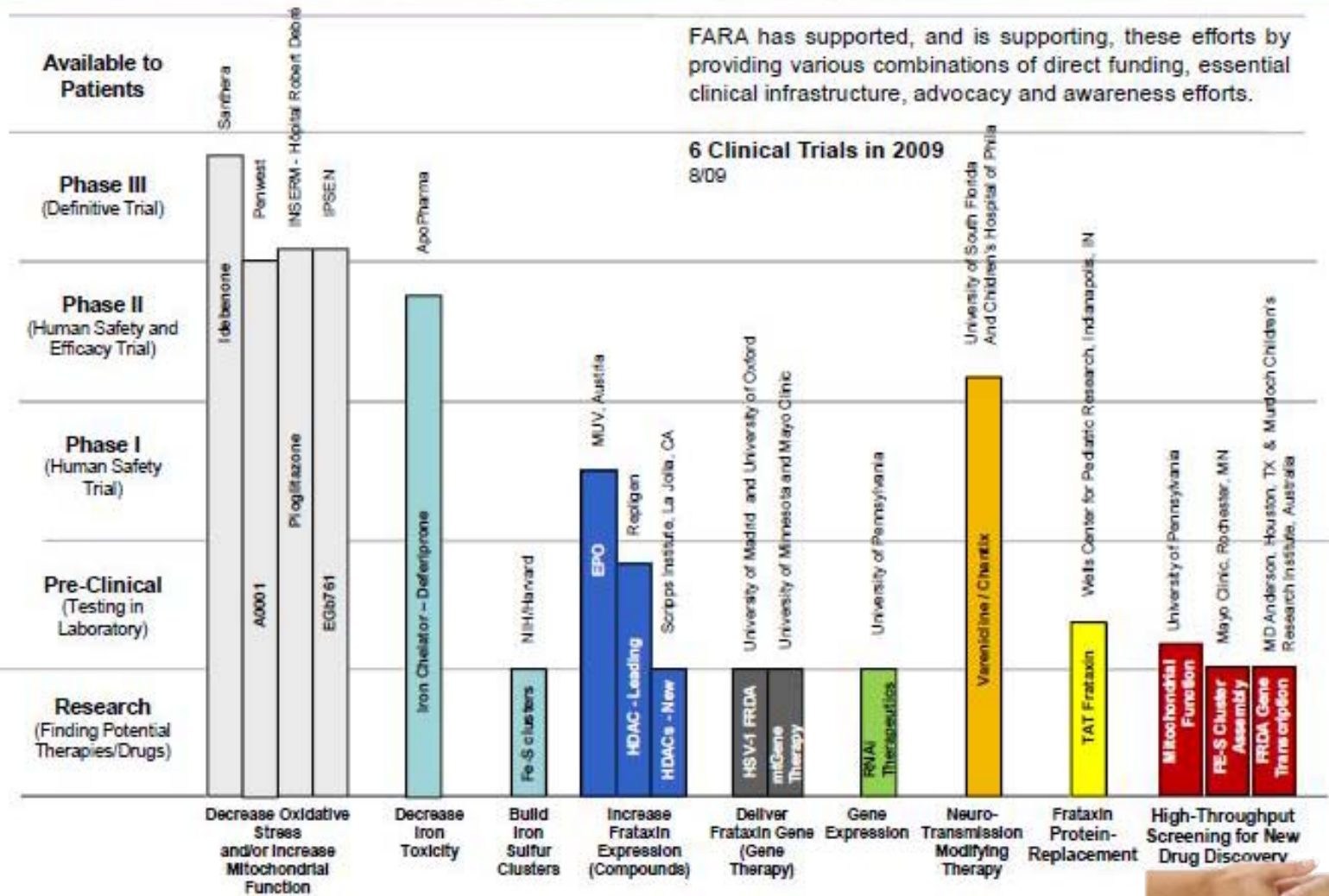
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FRDA Disease Mechanism





FARA Treatment Pipeline



Clinical Trials

- Idebenone - Phase III, **Santhera**
 - 6-month study in the USA and 1-year study in Europe. Both studies showed idebenone to be safe, but neither showed any statistically significant improvement in neurological function – combined analysis and extension studies now ongoing.
- Pioglitazone - Phase III, **INSERM, France**
 - Already licenced for type 2 diabetes
 - 2-year study of FRDA patients (7-24yrs)
- A0001 - Phase II, **Penwest, USA**
- EGb761 - Phase II, **Ipsen, France**



Clinical Trials

- Deferiprone and idebenone - Phase I/II, **France 2007**
 - 6-month study, 13 FRDA adolescents, revealed no major safety concerns and improvement of ataxia (ICARS).
- Deferiprone - Phase I/II, **Apopharma**
 - 6-month study, 80 FRDA patients (7-35yr) revealed no major safety concerns
- Deferiprone - Phase II, **Apopharma**
 - 1-year, 48 FRDA patients, Belgium, France, Italy, Spain



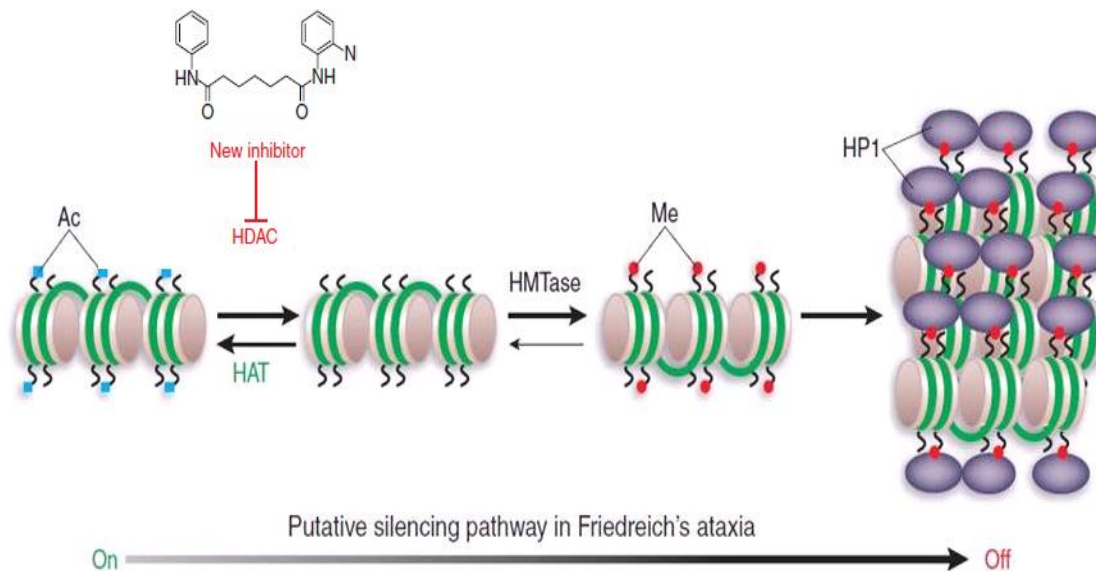
Clinical Trials

- Recombinant human erythropoietin (rhuEPO) - Phase II - **B. Scheiber-Mojdehkar and B. Sturm, Austria**
 - Pilot study (8 patients) resulted in increased frataxin levels and decreased oxidative stress
- Carbamylated EPO (CEPO) - Phase II, **Lundbeck**
 - 2 week treatment period, Austria, Germany, Italy.



Clinical Trials

- Histone deacetylase (HDAC) inhibitors
 - RG2833 - **Repligen** (USA) have approval from the FDA to start Phase I studies soon.
 - Class III HDAC inhibitor - **R. Festenstein** (Hammersmith Hospital) is undertaking a small pilot trial in the UK.

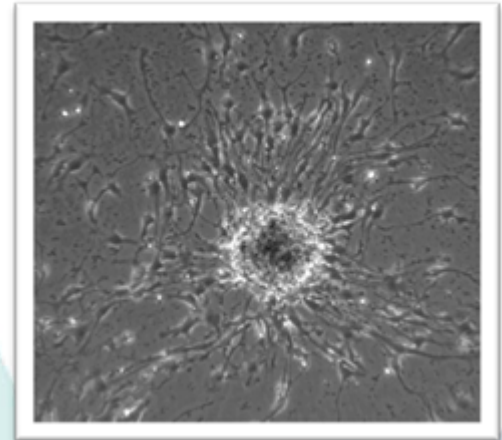
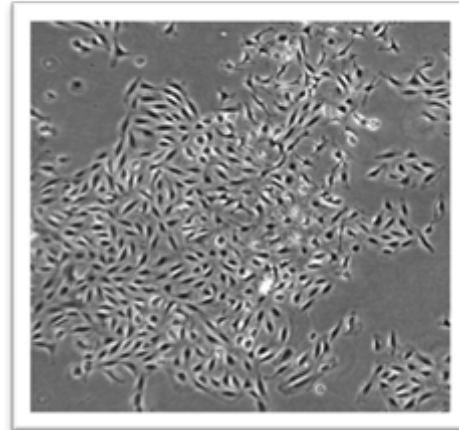


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Research – Finding Potential FRDA Therapies

- Resources

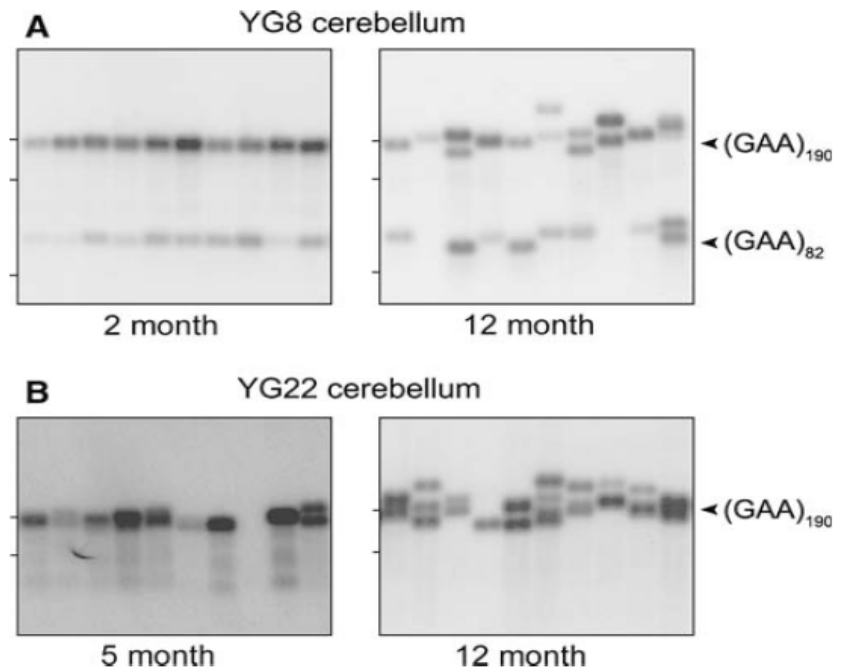
- Patient cells/tissues
- Cell cultures
 - Blood cells
 - Skin cells
 - Stem cells (iPS cells) →
 - Neurons and heart cells
- Animal models
- High throughput screening



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GAA Instability

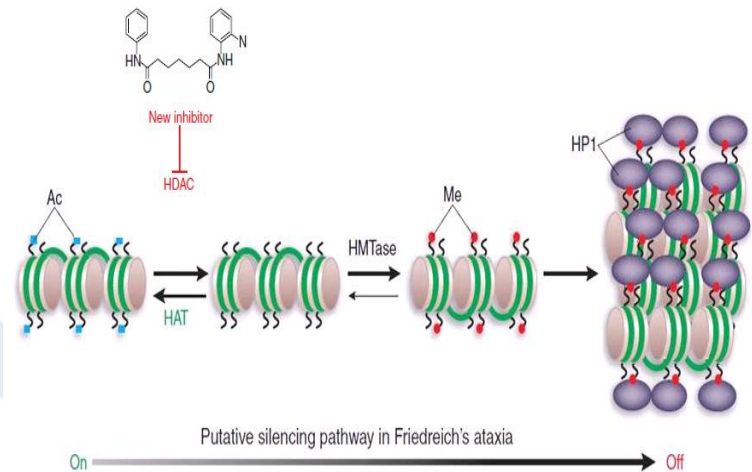
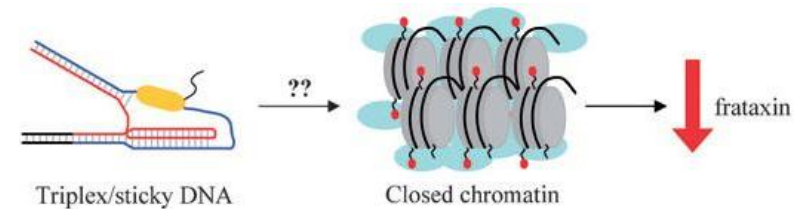
- Pook, Bidichandani and Grabczyk
- Why are the GAA repeat mutations larger in specific parts of the CNS?
- Does this cause pathology?
- What is the role of DNA repair proteins?
- New therapeutic targets?
 - Further research needed



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Effects of GAA Mutation

- Festenstein, Gottesfeld, Pandolfo, Pook, Usdin, Bidichandani, Grabczyk et al
- How does the GAA mutation cause repression of the *FXN* gene?
- Abnormal DNA structures, DNA methylation, histone modifications, HP1, CTCF binding, *FAST1* antisense?
- New therapeutic targets?

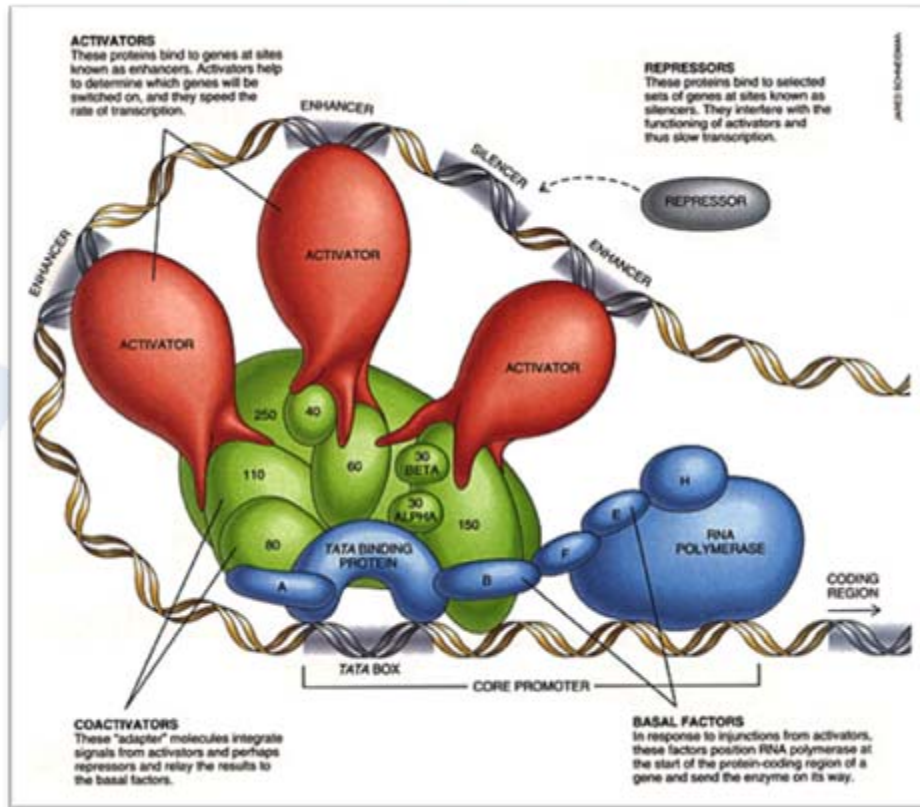


Yes, HDAC inhibitors



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Regulation of the *FXN* Gene



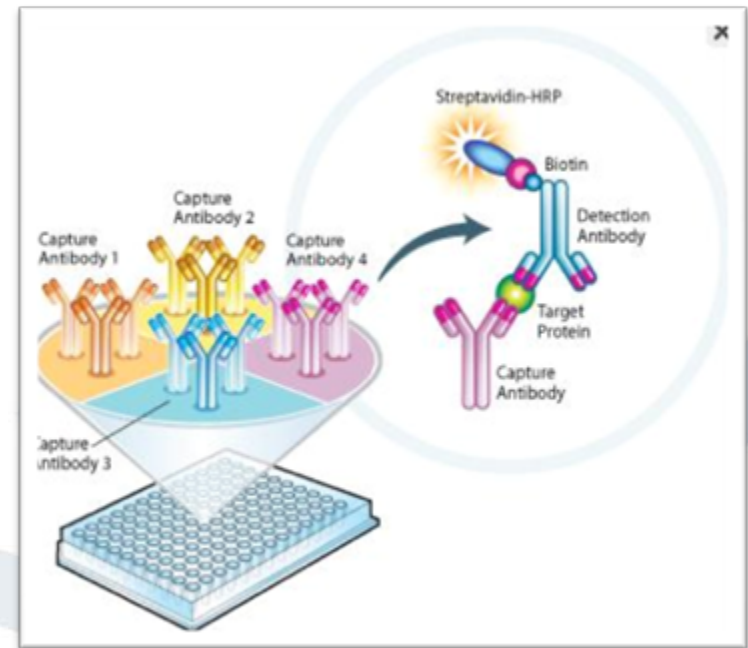
- Pandolfo, Rouault, Napierala, Mahishi et al.
- What factors control the amount of *FXN* gene expression?
- PPAR γ , PGC1 α , SRF, TFAP2, microRNAs?
- New therapeutic targets?
 - Yes, Pioglitazone



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Regulation of Frataxin Levels

- Puccio, Sarsero, Scheiber-Mojdehkar and Sturm, Testi et al
- High throughput screening to identify novel compounds that increase frataxin by unknown mechanisms.
- Prevention of frataxin degradation
 - Identifying compounds that target the ubiquitin-proteasome system
- New therapeutic targets?
 - Yes, CEPO



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Normal Frataxin Function and Disease Effects of Decreased Frataxin

- Pandolfo, Puccio, Pastore, Rustin, Isaya, Cortopassi, van Houten et al
- Frataxin is primarily a regulator of FeS cluster protein formation, with subsequent downstream effects:
 - Mitochondrial iron accumulation
 - Blunted antioxidant defences (abnormal Nrf2 signalling)
 - Mitochondrial dysfunction (decreased oxygen consumption)
 - DNA damage in the mitochondria and the nucleus
- Many potential therapeutic targets and biomarkers to identify



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Replacement Therapies

- TAT-frataxin protein - **M. Payne, Indiana**
 - Tested in mice and now moving into preclinical development
- *FXN* gene therapy - **F. Lim, Spain and R. Wade-Martins, Oxford**
 - “Frataxin gene supplementation”
 - Further research studies are still needed
- Stem cell therapy -
 - Bone marrow-derived stem cells - **A. Wilkins, N. Scolding, Bristol**
 - Cerebellar stem cells - **S. Marino, London**
 - iPS cells derived from FRDA patient skin cells - **H. Puccio (France), J. Gottesfeld (USA), M. Dottori (Australia)**
 - Further research studies are still needed



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EFACTS

- European Friedreich Ataxia Consortium for Translational Studies
 - EU funded (€6 million for 4 years)
 - 13 clinical, basic and computational research groups (5 UK) and Pharma (Repligen)



There is activity in all “Research” and “Pre-clinical” aspects of the “Treatment Pipeline” that aims to take new FRDA treatments through to clinical trials



FARA Treatment Pipeline

