



Restoration of *Frataxin* gene expression in Friedreich's ataxia -identification and characterisation of novel epigenetic therapies
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Scientific abstract

Friedreich's ataxia (FRDA), the most common autosomal recessive ataxia, is the result of a GAA repeat expansion in the *frataxin* gene which causes its repression. This repeat induces gene silencing which resembles the archetypal epigenetic phenomenon of Position Effect Variegation, caused by heterochromatin formation. Importantly, this silencing can be modulated *in vivo* by chromatin modifiers providing a potential radical therapeutic approach for this frequently devastating and largely untreatable condition (Saveliev *et al.*, 2003). We have now confirmed that a similar form of silencing occurs in cells from FRDA patients. As a result of our studies we and others have identified histone deacetylase (HDAC) inhibitors which can overcome such silencing and are potential therapeutic agents (Festenstein, 2006; Herman *et al.*, 2006). We will investigate the mode of action of these novel inhibitors and screen for additional HDAC inhibitors and other chromatin modifiers with therapeutic potential. We will analyse *frataxin* gene regulation in primary cells from normal controls and FRDA patients at the chromatin level. Potential therapeutic agents identified will be tested on a humanised mouse model for FRDA. It will be crucial to determine the specificity of effect in alleviating *frataxin* silencing and monitor any potential toxic and beneficial effects.

Lay summary

Friedreich's ataxia is caused by an abnormality in a gene called *frataxin* which inappropriately switches off the gene. We have examined the way this gene is switched off in blood cells obtained from patients. Our previous studies showed that the abnormal gene may be switched off in a way that is very similar to a gene switching defect which has been extensively studied in fruit flies. We have applied this knowledge to investigate whether this type of switching defect occurs in patients and whether we can use the knowledge obtained from fruit-fly studies to turn the gene back on again. Our initial results are promising as we and others have identified new drugs that can turn the *frataxin* gene back on again in cells from patients. This may provide a new way of treating the disease in patients in the future.

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