

Select 74 May 2014

Finding treatments for neurodegenerative diseases



Cardiff Huntington's
Disease Centre

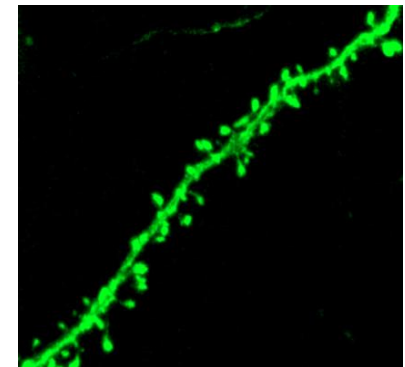
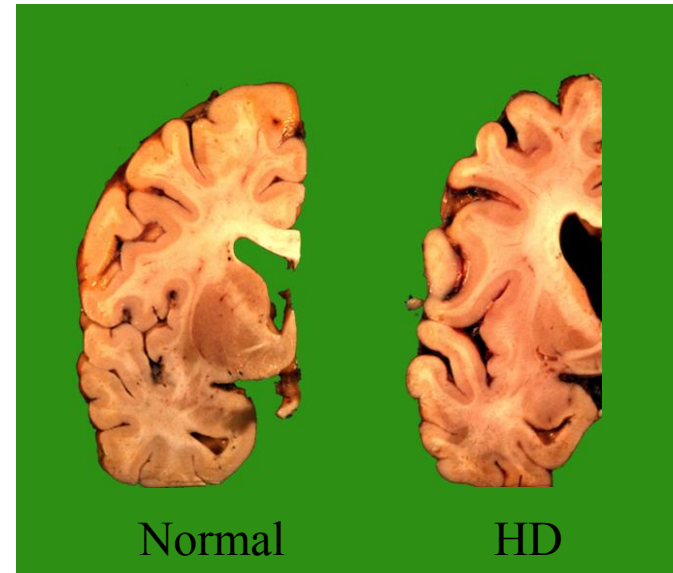
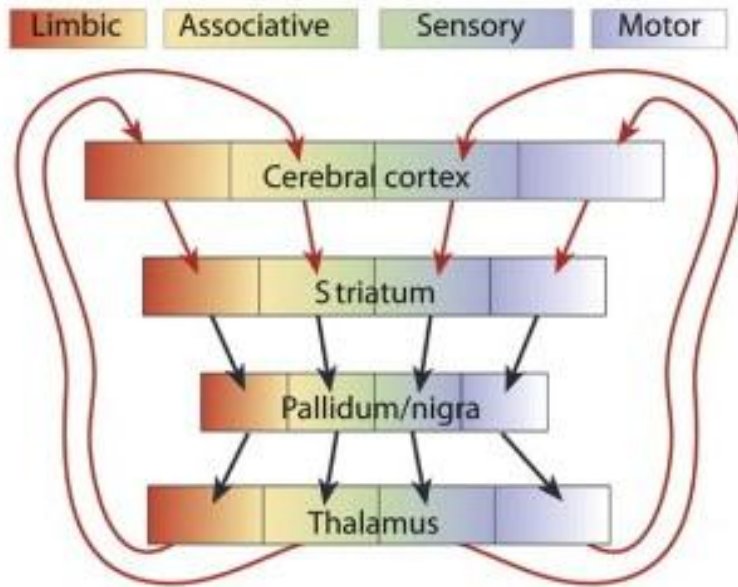


Neuroscience & Mental Health
Research Institute



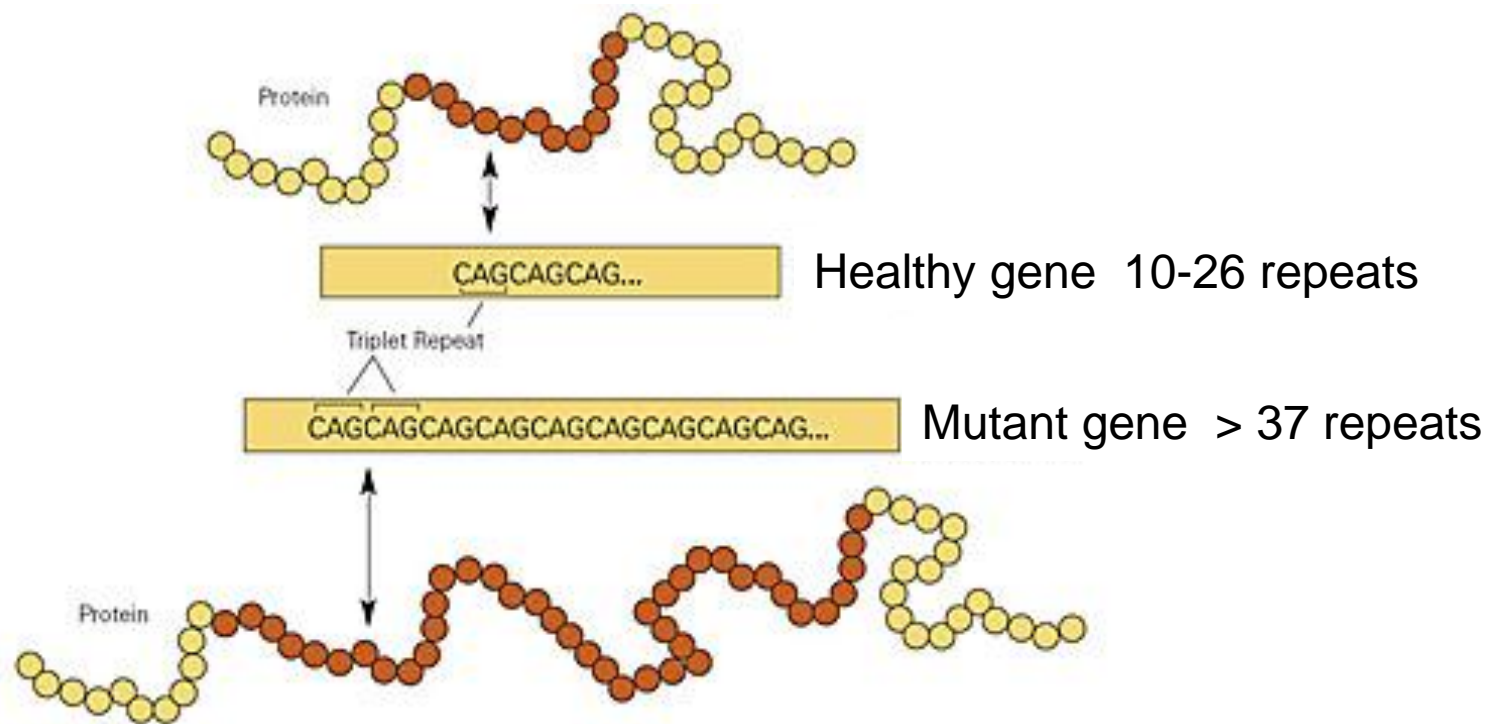
Anne Rosser
Cardiff University Brain Repair Group
Cardiff Neurosciences and Mental Health Institute

HD as a model disorder for identifying new treatments



Loss of medium spiny neurons

Genetics of Huntington's disease



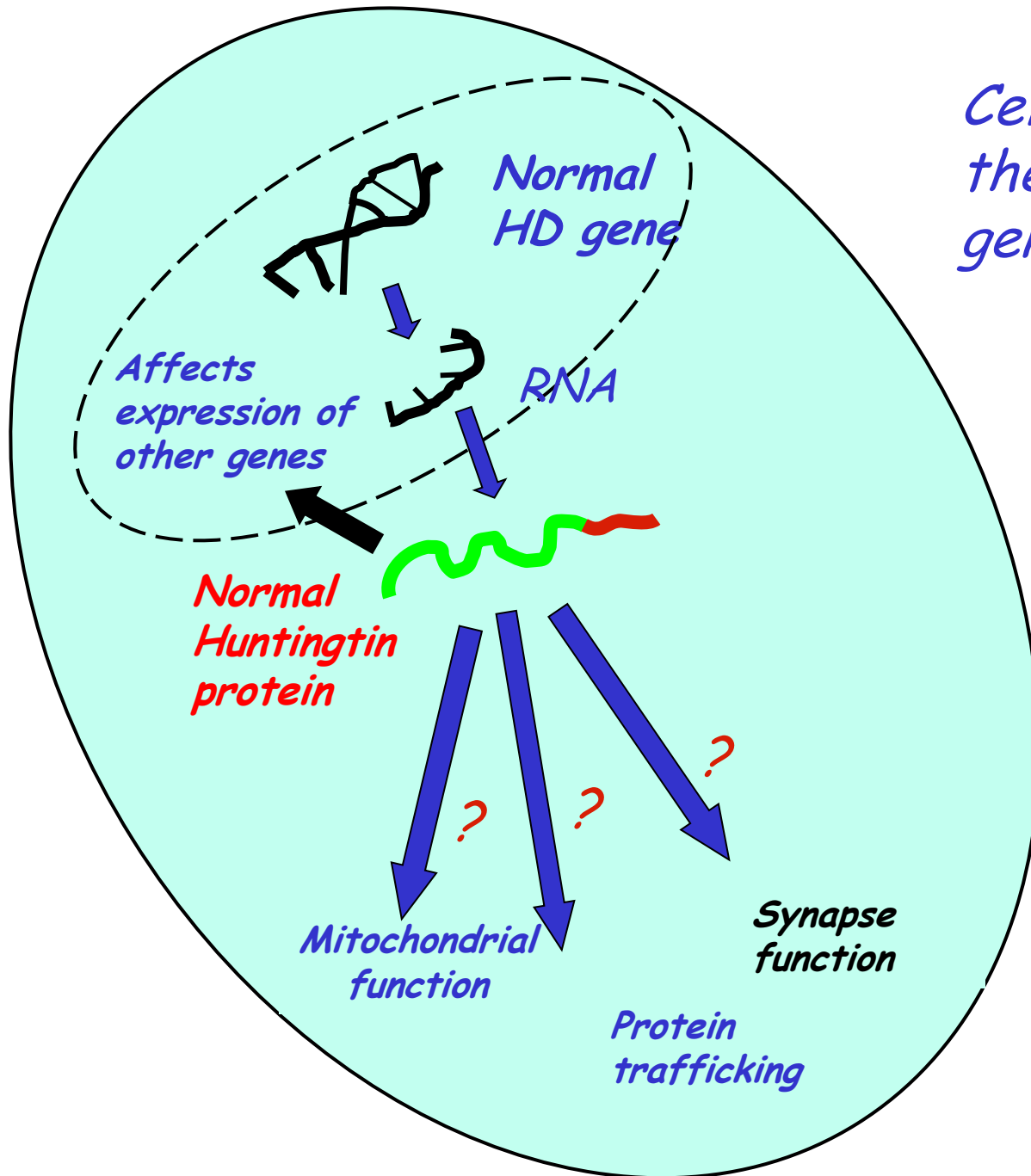
- *Normal population 17-26*
- ≥ 40 - *disease range*
- $\geq 36 \leq 39$ - *reduced penetrance*
- $\geq 27 \leq 35$ - *intermediate allele*

Toxic gain of function

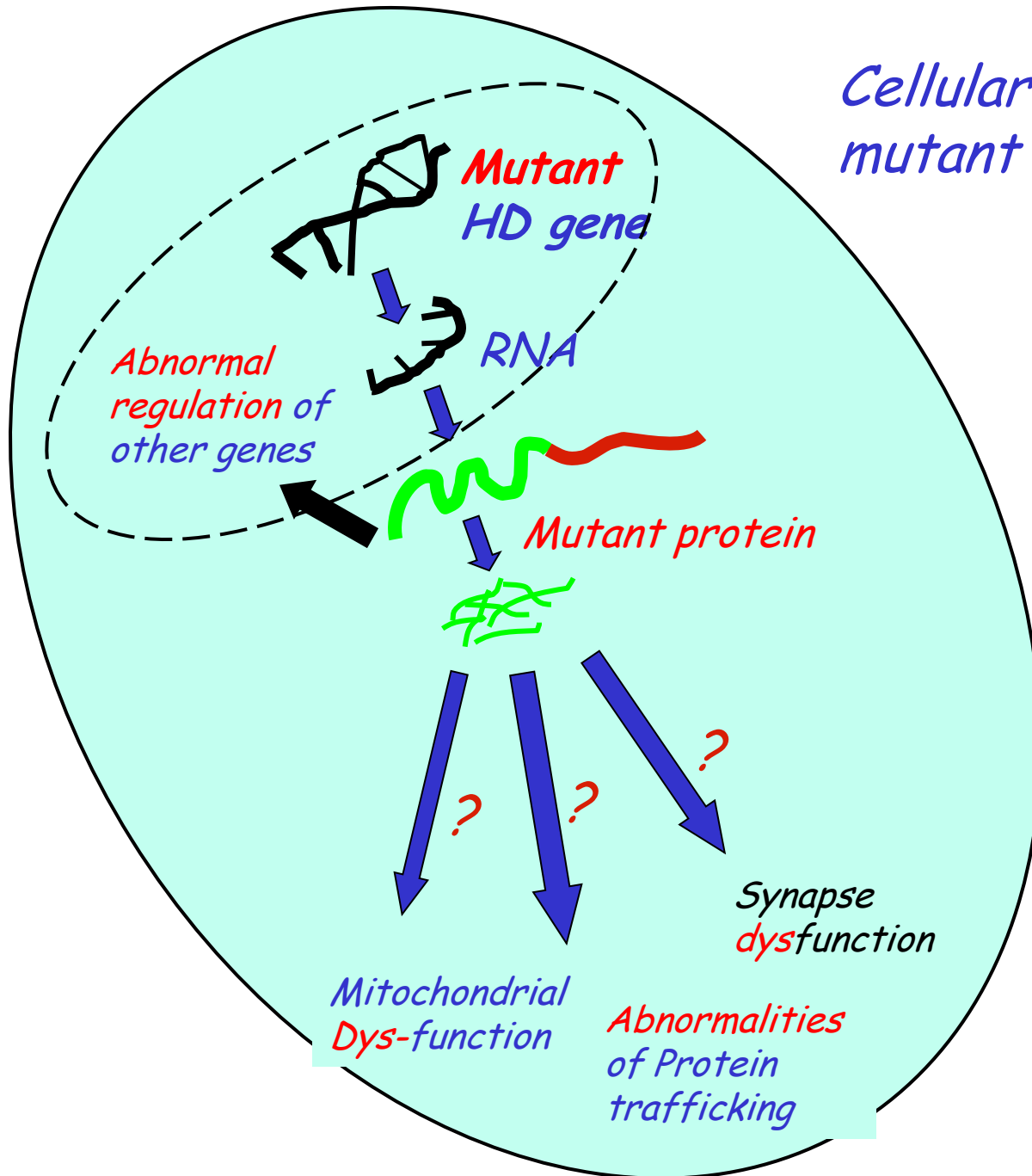
Targeted therapies - based on knowledge of specific underlying pathophysiology

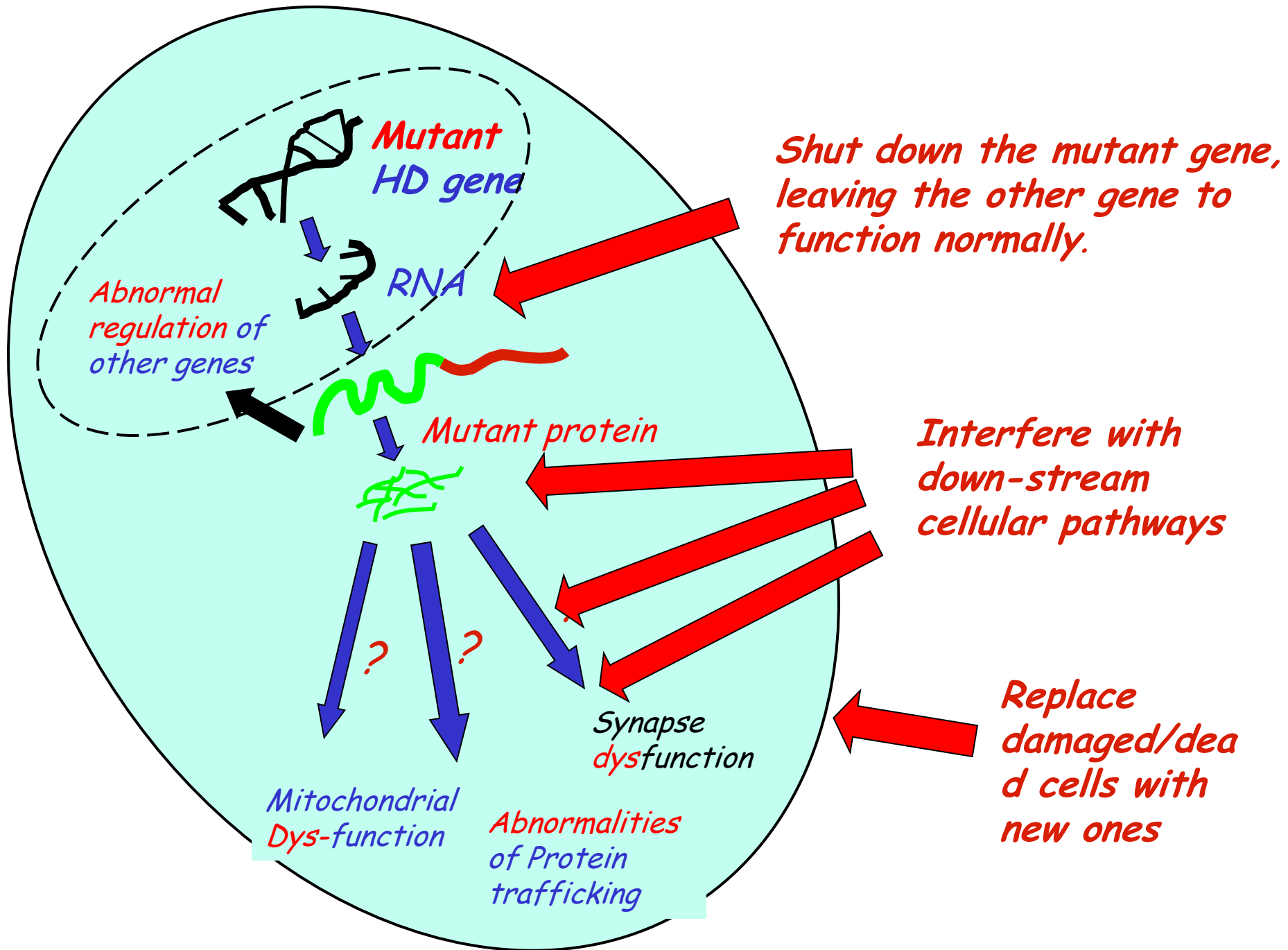
Non-targeted therapies - may be based on reasoning, but not necessarily specific to the disease

*Cellular functions of
the normal Huntingtin
gene*

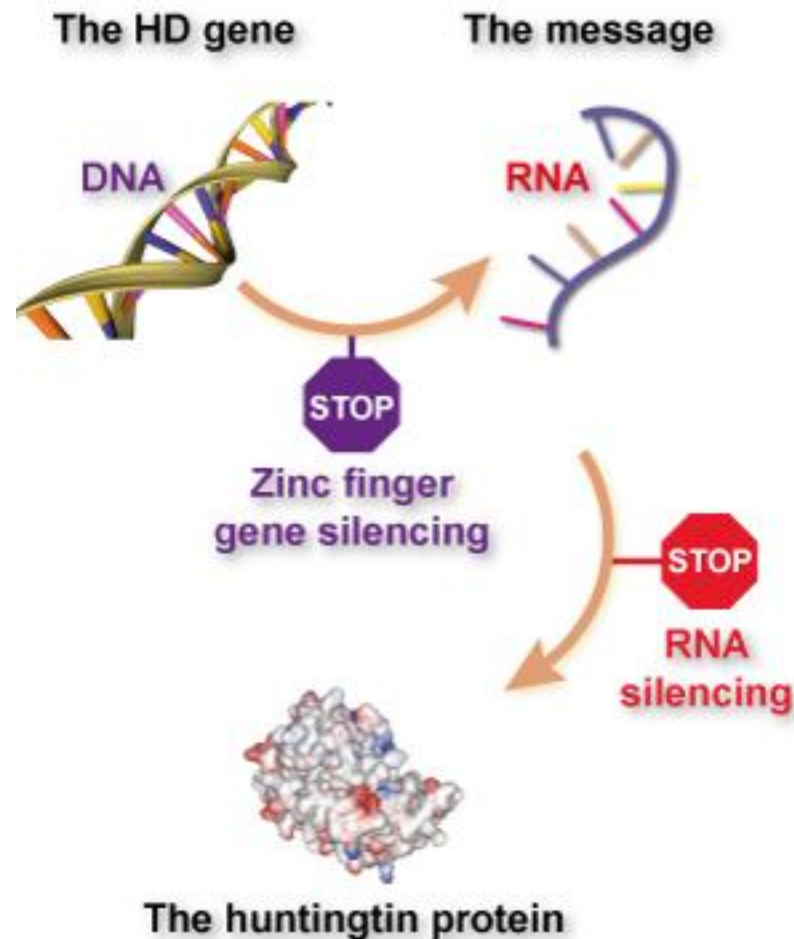


Cellular functions of the mutant Huntingtin gene





Targeted therapy: silencing the mutant allele



From HD Buzz (en.hdbuzz.net)

From: **Progress and Challenges in RNA Interference Therapy for Huntington Disease**

Scott Harper, *Arch Neurol.* 2009;66(8):933-938. doi:10.1001/archneurol.2009.180

Table. Preclinical Huntington Disease RNA Interference Therapy Studies in Rodent Models

Source	Animal Model	Inhibitory RNA Used	Delivery Method	Species Specificity	Correction	
					Histological	Motor
Harper et al, ¹⁰ 2005	N171-82Q	shRNA	AAV1	Human	Yes	Rotarod, gait
Rodriguez-Lebron et al, ¹¹ 2005	R6/1	shRNA	AAV5	Human	Yes	Clasping
Wang et al, ¹² 2005	R6/2	siRNA	Liposome	Human	Yes	Rotarod, clasping ^a
Machida et al, ¹³ 2006	HD190QG ^b	shRNA	AAV5	Human ^c	Yes	ND
DiFiglia et al, ¹⁴ 2007	AAV-Htt100Q ^d	siRNA	Cholesterol ^c	Human	Yes	Clasping, beam
Huang et al, ¹⁵ 2007	R6/2 and Ad-HttQ103GFP ^d	shRNA	Adenovirus	Human	Yes	ND
Franich et al, ¹⁶ 2008	Rat AAV-HD70 ^d	shRNA	AAV1	Human	Yes	Forepaw use
McBride et al, ¹⁷ 2008	CAG140	shRNA, miRNA	AAV1	Human, mouse	Safety study	Safety study
Drouet et al, ¹⁸ 2009	Mouse and rat lenti-htt171-82Q and lenti-htt853-82Q ^d	shRNA	Lentivirus	Human, mouse, rat	Yes	ND
Boudreau et al, ¹⁹ 2009	N171-82Q	miRNA	AAV1	Human, mouse	Yes	Rotarod

Abbreviations: AAV, adeno-associated virus; miRNA, microRNA shuttle; ND, not determined; shRNA, short hairpin RNA; siRNA, small interfering RNA.

^aThis study also demonstrated improved lifespan.

^bThe HD190QG model produces a truncated mutant human *HTT*-enhanced green fluorescent protein fusion protein. The shRNAs in this study targeted the enhanced green fluorescent protein portion of the transcript, resulting in coincident *HTT* knockdown.

^cThe siRNAs were cholesterol conjugated and codelivered with AAV1/8 vectors expressing mutant human huntingtin fragments.

^dIndicates nontransgenic animals in which viral vectors were used to deliver mutant human *HTT* to rodent brains.

Preclinical Huntington Disease RNA Interference Therapy Studies in Rodent Models

Challenges associated with gene knock-down

Indiscriminate knock down of mutant and normal allele:

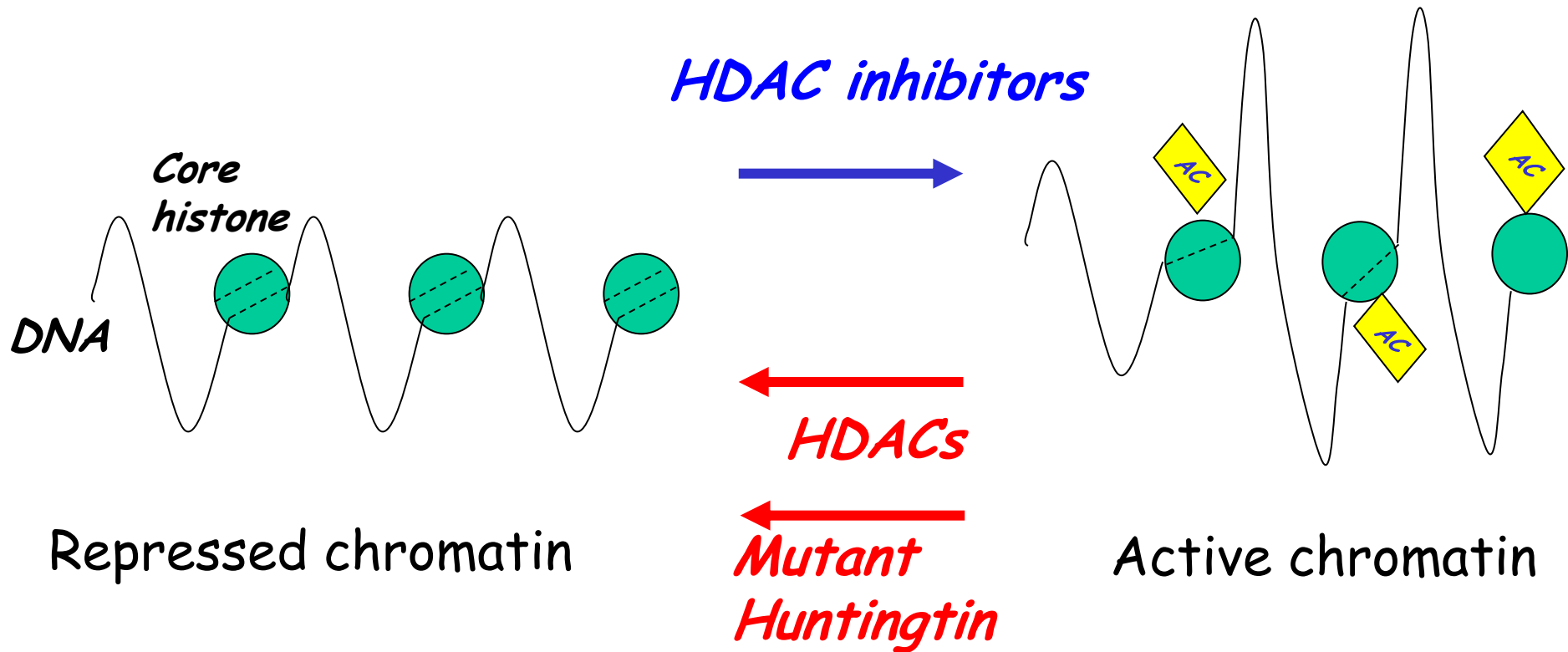
- Evidence of tolerance to general lowering huntingtin
- Allele-specific strategies

Delivery:

- Intracerebral
- Repeated injections - development of indwelling delivery systems
- Potential of delivery through transplantation of modified stem cells

Long term side effects not determined

Targeted therapy: Histone deacetylase (HDAC) inhibitors

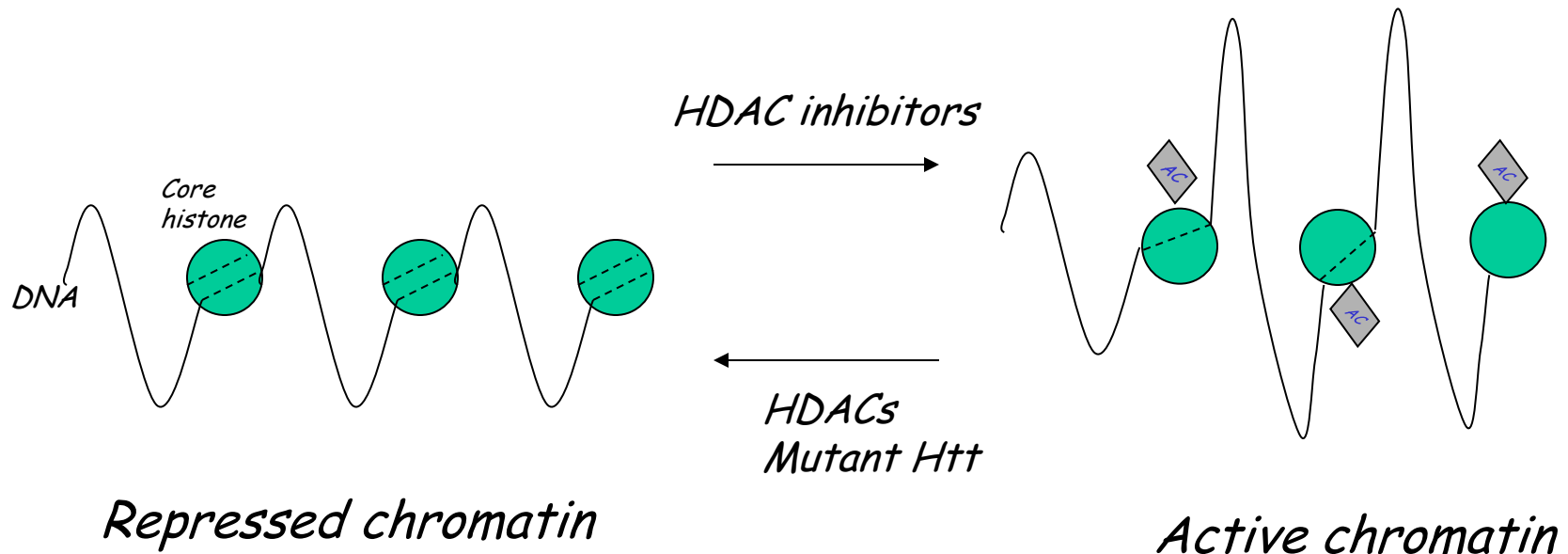


Evidence that histone acetylation important in HD

In the test tube, the presence of Htt decreases histone acetylation - effect is reversed by HDAC inhibitors

In animal models (fruit fly and mice) HDAC inhibitors reversed histone deacetylation and improved motor function and survival

Many HDACs already approved for clinical use



Sienna Biotech trial

The agent - SIRT1 inhibitor

Sirt1 is a deacetylase

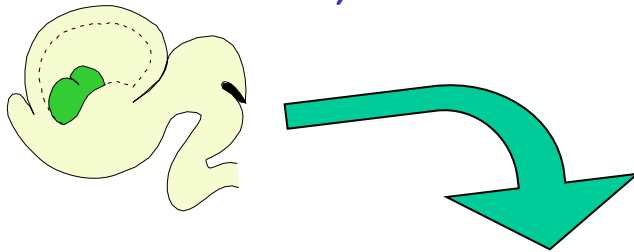
Inhibiting Sirt1 seems to modify acetylation of Htt causing it to be cleared more rapidly than the normal protein.

Transgenic mice- associated with reduced symptoms and longer lifespan.

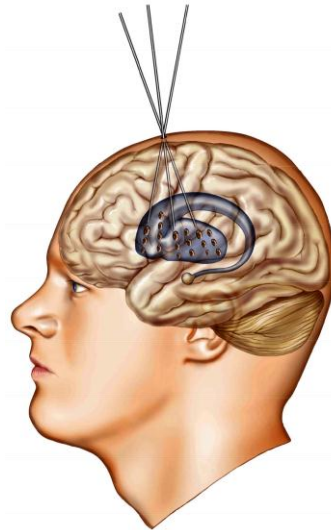
Phase II trial - Awaiting results

Targeted therapy: cell replacement

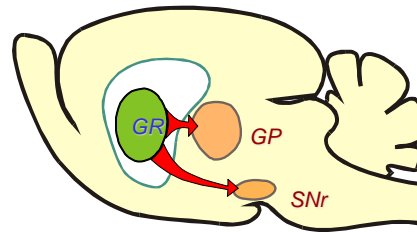
Developing neurons in the embryonic brain



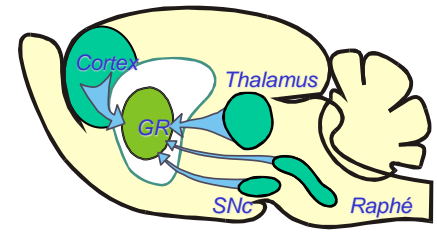
*Stereotaxic
implantation
Under
anaesthetic*



Efferents



Afferents

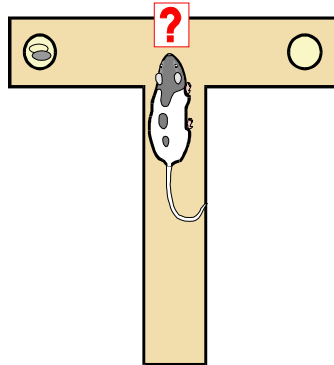
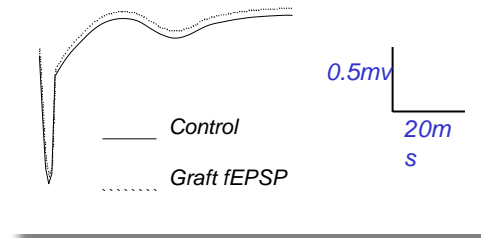
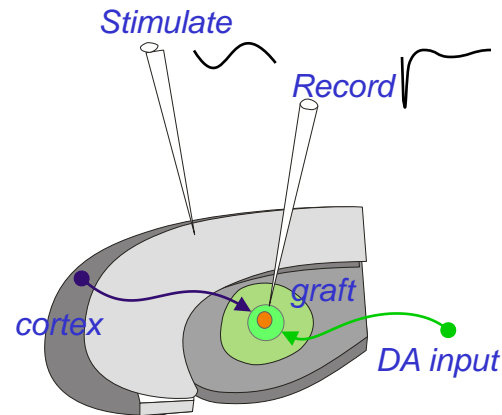
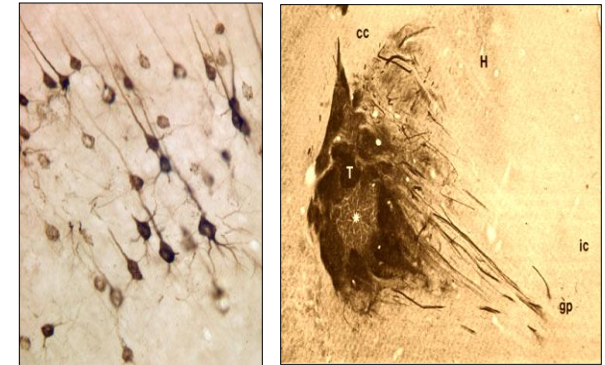
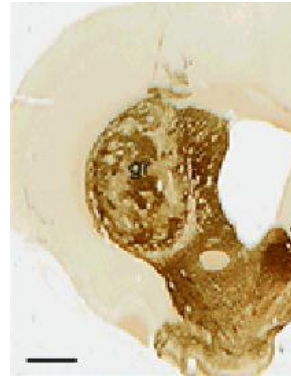
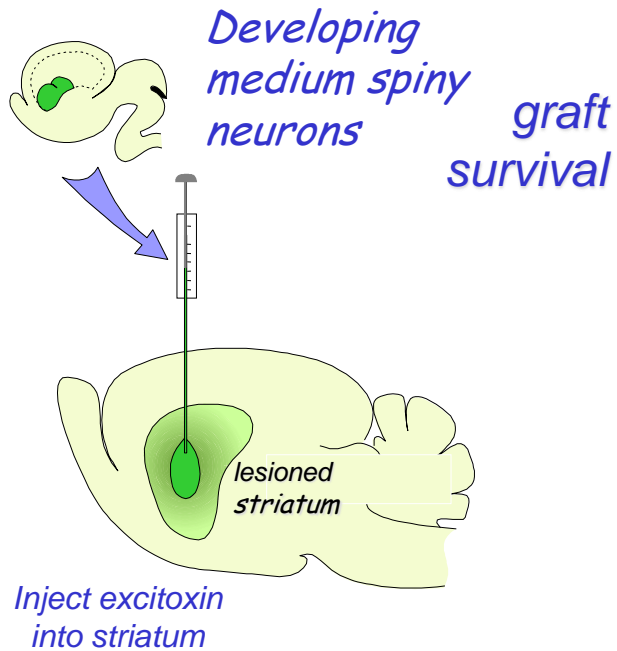


Cell survival

Degree of circuit reconstruction

Functional improvement

Does it work in animal models?

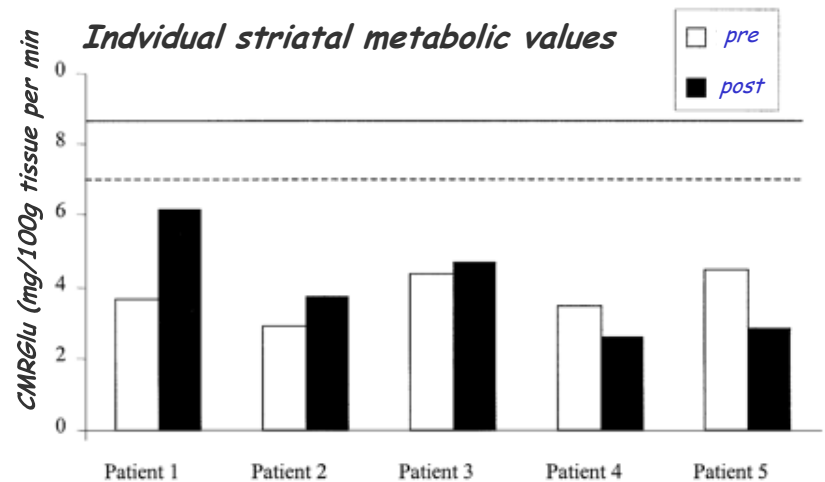
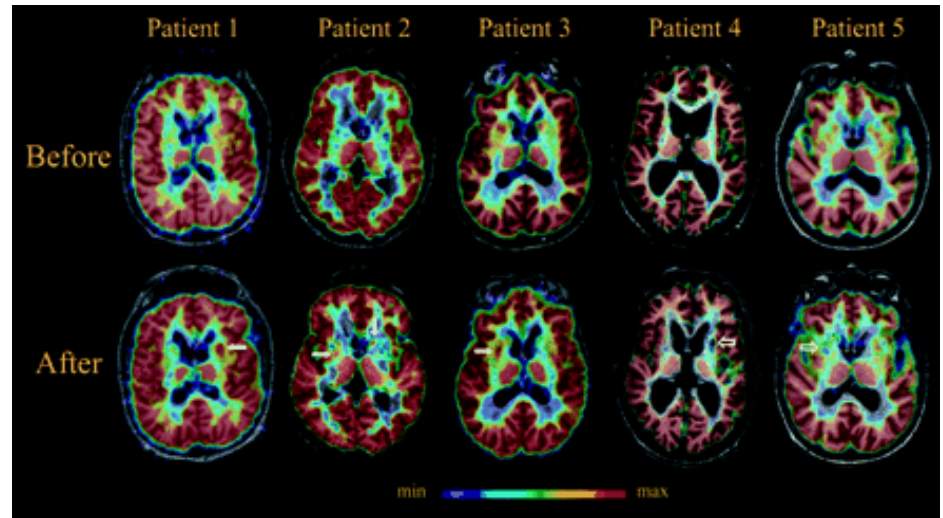
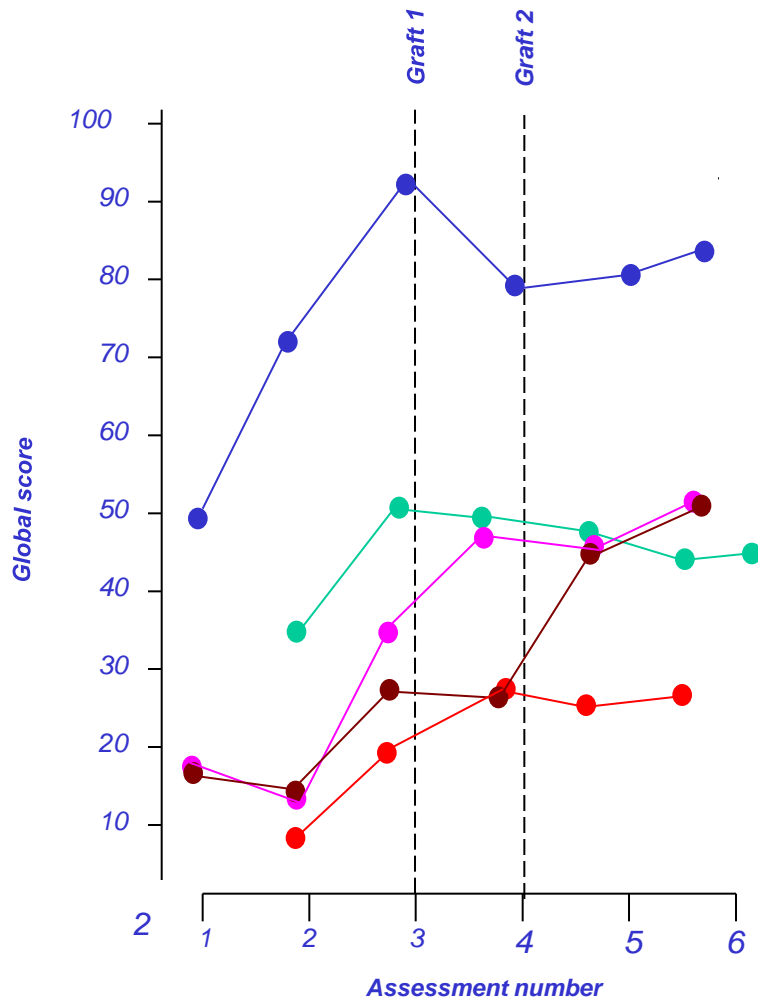


Behavioural recovery

SB Dunnett et al

Graft Function

Bachoud-Lévi et al 2000 Lancet





Repair-HD

*Repair-HD funded by the European
Commission within its FP7 Programme
Contract number HEALTH-F4-2013-
602245*



- EU funded series of work packages
- 4 year program
- Coordinated - Rosser and Dunnett
- Partners in Cardiff, Manchester, Edinburgh, ` , Milan and Münster

To establish all the components necessary to take human pluripotent stem cell derived neuronal cells through to the point of 'first-in-man' clinical trial in Huntington's disease (HD).



*Repair-HD funded by the European
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EuroStemCell

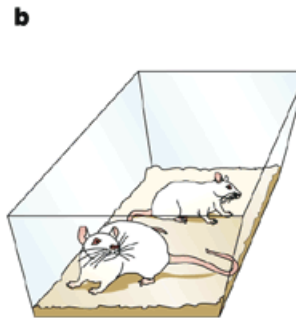
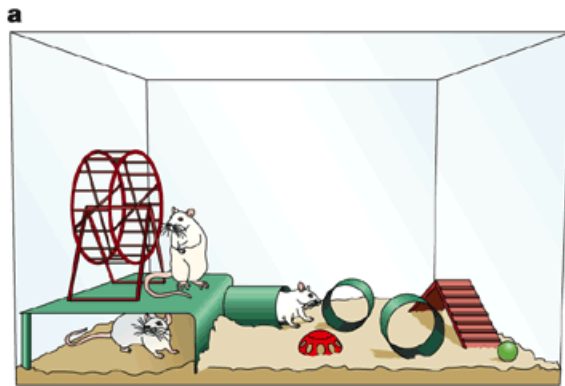


"Overall, the collective collaborative activities of the consortium are laying the groundwork for taking stem cell technology to the clinic - in the form of well characterised cell lines and a solid pre-clinical skills and knowledge base."



Elena Cattaneo

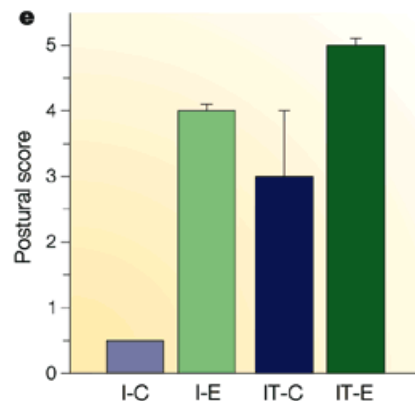
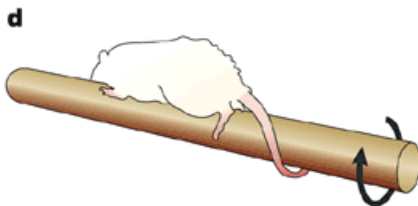
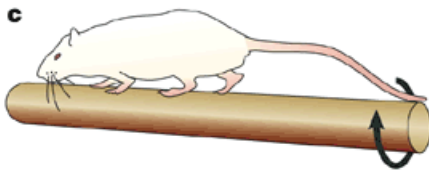
Non-targeted therapy: Exercise



*Animal studies -
environmental enrichment*

*Retrospective study of
lifestyle*

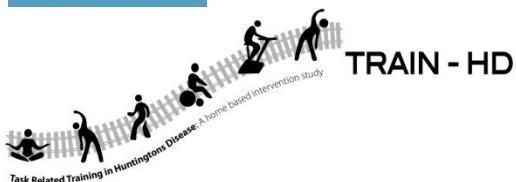
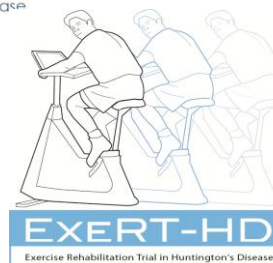
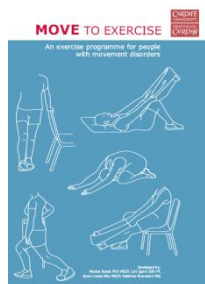
*Aerobic exercise in PD
and DAT*



Active-HD



Supporting Engagement in Activities
in people with Huntington's Disease



www.activehd.co.uk



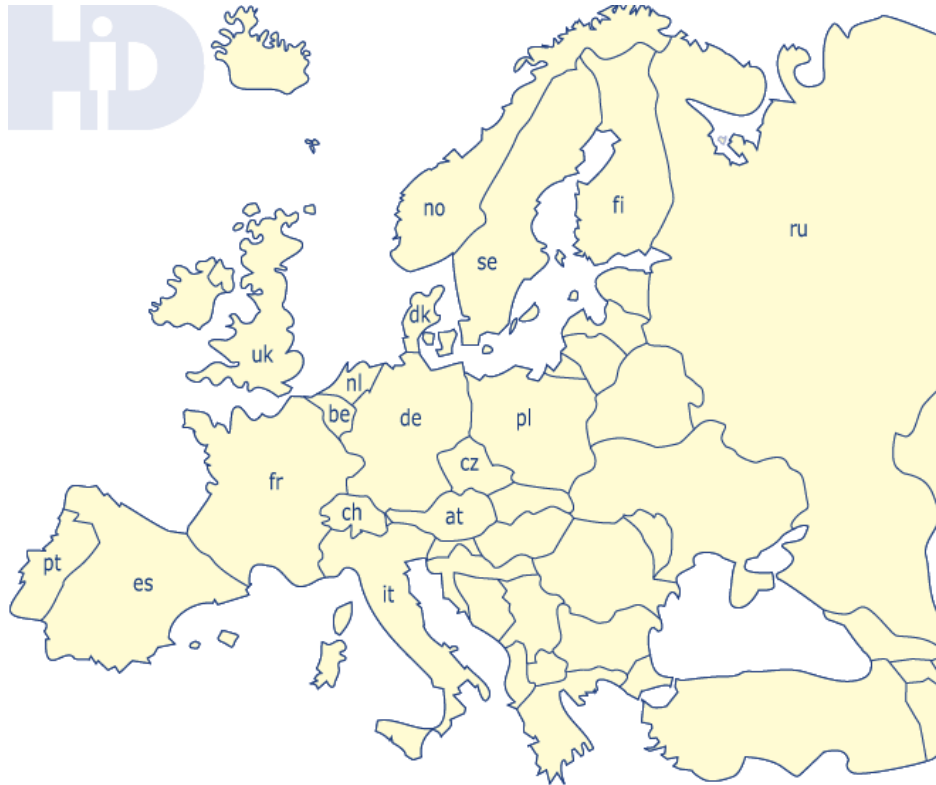
South East Wales
Trials Unit

Uned Ymchwil
De-ddwyrain Cymru



Patient video - effect of rehabilitation in HD patients

The importance of collaboration



Network of clinicians and scientists

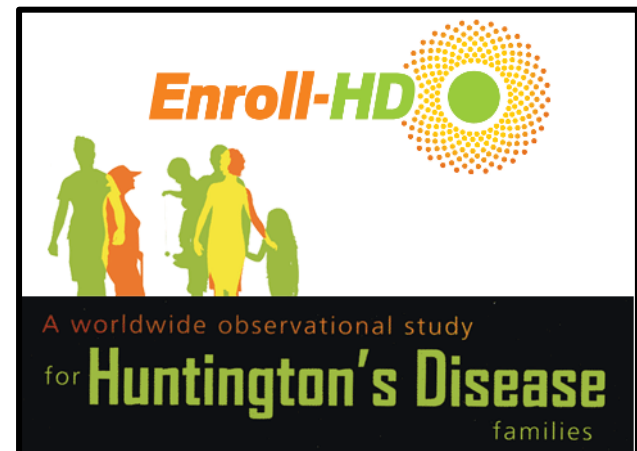
Information sharing and collaboration

Platform for clinical trials

REGISTRY - web based longitudinal database and biobank

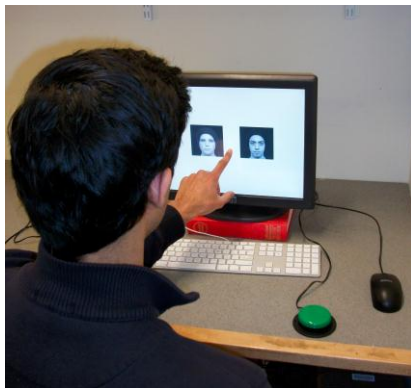
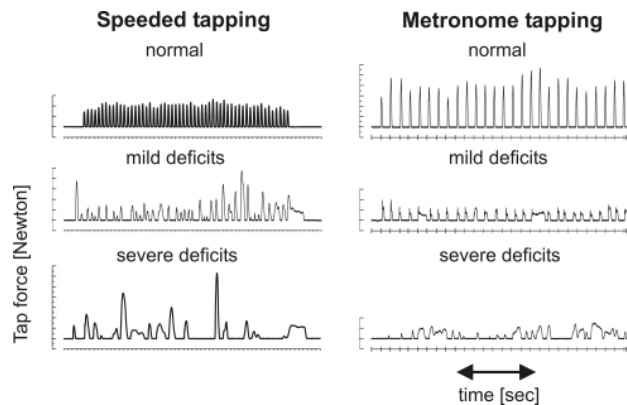
Working groups

EHDN: www.euro-hd.net



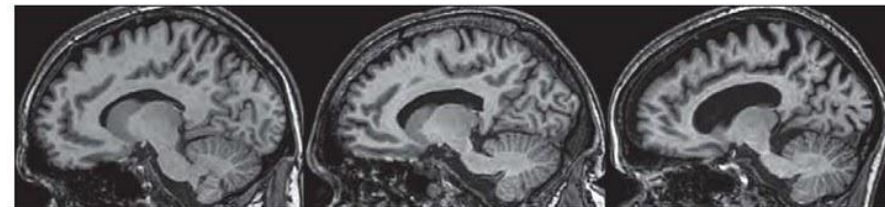
Discovery of the gene is the starting point

Improved assessment tools



Objective
cognitive and
behavioural
testing

Biomarkers



Sarah Tabrizi