Gene Therapy for MND: “Motor Neurons are getting the Message”

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The spectrum of motor neuron disorders
ALS & FTD form a clinical genetic pathological spectrum

TDP-43 inclusions occur in 95% of ALS and 60% of FTD cases

**Signature of pathological TDP-43**

1. Mislocalises to the cytoplasm
2. Cleaved into 25/35 kDa fragments
3. Forms insoluble aggregates
4. Post-translational modifications
   - Poly Ubiquitinated, Hyperphosphorylated
Genetic research will provide the strongest clues to the causes of MND and give us powerful tools to model it. Only when we understand the mechanisms of disease will we find drugs capable of curing MND.
MND gene discovery is increasing exponentially

The genes for 60% of familial and 10% of sporadic MND are known and can be offered for diagnostic and predictive testing in patients.
How does gene testing directly help MND patients?

Gene testing can go some way to answering why the disease occurred.

Excluding the presence of gene mutations can be greatly reassuring.

Pre-implantation Genetic Diagnosis IVF and gene testing.

Defective genes can be prevented from recurring in future generations.
Mutant or damaged proteins accumulate inside motor neurons initiating their degeneration.
Genes contributing to TDP-43 aggregation

- **Nuclear Transport**
  - C9orf72
  - MATR3
  - TARDBP

- **Accumulation**
  - OPTN
  - TBK1

- **Aggregation**
  - PGRN
  - VCP
  - UBQLN2
  - SQSTM1

- **Mislocalisation**
  - CHCHD10

- **Protein Recycling**
  - TUBA4A
  - ANXA11
  - PFN1

Adapted from Shaw Neuron 2011
From molecules to mechanisms to small molecule medicines.

Human Genetics

Proof of pathogenicity

Cell lines

IPS lines

Understanding Disease processes

Measuring Drug Target Effects

Axonal Transport

Energy Supply

Nuclear Transport

Preclinical trials

Clinical trials

In-house drug discovery

Lead compounds

Industrial drug discovery
Genetic discoveries are leading directly to gene therapies that will make the most dramatic impact on disease progression.

Gene therapies will eventually be given to those at greatest genetic risk to prevent them from ever developing MND.
Mutant or damaged proteins accumulate inside motor neurons initiating their degeneration.
Antisense drugs licensed in UK

Spinraza™ in Spinal Muscular Atrophy

Currently Active ASO trials in UK

SOD1 in MND

Huntingtin in HD

Tau in Alzheimer’s

ASO trials on the horizon

C9orf72
Gene therapy for sporadic motor neuron disease

Therapeutic reduction of ataxin-2 extends lifespan and reduces pathology in TDP-43 mice

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WT TDP-43 overexpressing mice survive no more than 30 days
Remarkable increase in survival up to 300 days when ATXN2 was knocked down and TDP-43 protein cleared in a model of sporadic MND
Gene therapy for type 1 spinal muscular atrophy

Spinal Muscular Atrophy Type 1
Inheritance of defective survival motor neuron gene from both parents
Presents as a “floppy baby” that rapidly gets weaker
Motor neurons degenerate causing progressive muscle paralysis

In Type 1 SMA the diagnosis is made before 6 months
Infants never sit unaided, never crawl and never walk

75% mortality after 1 year without ventilation
95% are ventilator dependent by 2 years of age
The genetic basis for Spinal Muscular Atrophy

Deletion mutant genes are unable to make a full length protein initiating motor neuron degeneration

SMA with RNPs missing

Control with RNPs present
Exon-skipping ASO-SMN2 in spinal muscular atrophy

SMA Type 1 (60%): Diagnosis <6 months
Never sit unaided, roll, crawl or walk
75% mortality by 13 months
92% ventilated by 20 months

Neurological Score

Overall Survival

Lumbar Puncture every 3 months, Costs: $750K year 1, $350K p.a. thereafter
Viruses can deliver missing genes or knock down a toxic genes.

The virus enters the cell it is **transported to the nucleus** where it delivers the target gene. This will either **replace a missing gene** or **knock down a toxic gene**. The gene is expressed for the lifetime of the cell, in neurons that is the **lifetime of the person**!
Viral gene delivery: “Replace the messenger”

Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy


Type 1 SMA ventilation status at 20 months
Historical controls: 8% are ventilator free
AAV-SMN treated: 100% are ventilator free

Type 1 SMA motor function scores (0-64)
Historical controls: None reach 40 points
All rapidly decline
AAV-SMN treated: All above 40
Some achieve max score

AAV9-SMN
Disease prediction leads to disease prevention: Getting from Guthrie Test to Whole Genome Test
Thank you