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Briefing Notes

Developing a Gene Therapy for Motor Neuron Disease

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Motor Neurone Disease (MND)

“There is no worse disease than MND.” - Dame Cicely Saunders OM DBE FRCP, founder of the modern hospice movement.

What is MND?

Motor neurone disease (MND) has first been described by the French neurologist Jean-Martin Charcot in 1869. MND is a term used for a group of diseases which are caused by the death of motor neurons in the brain and spinal cord leading to progressive muscle paralysis. MND is also known as Lou Gehrig's or Charcot's disease or Amyotrophic Lateral Sclerosis (ALS), the most common form of MND.

What happens when motor neurones die?

Motor neurones initiate and control our muscle movements. When motor neurones die, the muscles stop working and waste away. MND often starts with walking problems, followed by the loss of arm and hand movements, until swallowing, talking and finally breathing are affected. Patients die from weakness and paralysis of their breathing muscles on average 2 to 3 years after the onset of symptoms. MND is a progressively debilitating and fatal condition. Only 1 out of 10 diagnosed MND patients survives longer than five years. Many doctors regard MND as the worst disease in medicine.

Who has MND?

Any adult can get motor neurone disease at any age. In over 90% of cases the cause for the disease is unknown, only 5-10% of cases are inherited forms linked to certain genes, e.g. SOD1, C9orf72, TDP43, FUS. In the UK over 5,000 people suffer from MND, and 5 people die from MND every day. Worldwide over 750,000 people suffer from MND, men are more often affected than women. The longest known MND survivor is the eminent physicist Stephen Hawking. Other well-known MND patients include Mao Zedong, former England Manager Don Revie and the actor David Niven.

What are the treatment options?

As yet, there is no cure and no effective treatment for MND. Current treatment is based predominantly on symptom management and palliative care e.g. assisting breathing and nutrition and improving other disease related symptoms. At present, only one drug (riluzole) has been proven to slow the progression and modestly extend survival of MND patients by several months. Non-invasive ventilation (NIV) has also been shown to extend survival, as well as improving quality of life for some people with MND who experience problems with breathing.

What are the challenges to finding a treatment?

Due to its generally rapid course from diagnosis to death, the prevalence of MND in the population is only 6-8/100,000. MND is therefore regarded as a relatively rare “orphan disease” and as a consequence, there is limited interest in government or private sector funding for therapy development. This leaves academic institutions with a major role in developing new treatments for MND. Widely now regarded as a disease of ageing, it is expected that more cases of MND will be seen in our ageing population which further stresses the need for an effective treatment.

MND is a complex disease

Today, MND is regarded as a multisystem disorder not purely affecting motor neurones, although these specialised neurones tend to be affected earliest and most severely. At least 15 genes have so far been identified to be associated with MND and in up to 70% of inherited “familial” cases the gene causing the disease is known. What causes motor neurones to die in MND is not yet fully resolved and is best understood in the subtype of MND linked to a faulty SOD1 gene. A defective SOD1 gene is the known cause of 20% of inherited cases and approximately 2% of all MND cases.

For more information on MND visit: www.mndassociation.org or [NHS choices: MND](#).

Developing a Gene Therapy for Motor Neurone Disease caused by a faulty SOD1 gene

What is the potential? – As close as we might get to a cure!

As yet, there is no known cure and no effective treatment for any form of motor neurone disease. The gene therapy for SOD1 MND is expected at the very least to alleviate the symptoms and slow the progression of this severely debilitating disease. Hopes are that the gene therapy could even prevent the disease when a faulty SOD1 gene is diagnosed and treated at an early enough stage. Although SOD1 MND only accounts for 2% of all MND cases, once established as a gene therapy for use in humans, gene therapies against other subtypes of the disease linked to faulty genes, e.g. C9orf72, FUS, TARDP, can potentially be developed and fast-tracked for clinical trials.

Who is leading and funding this project?

Professor Dame Pamela Shaw and Professor Mimoun Azzouz at SITraN have been at the forefront of MND research and gene therapy for neurodegenerative diseases internationally over the last 20 years. A new gene therapy for spinal muscular atrophy (SMA), the childhood form of MND, has already been developed successfully at SITraN and is currently advancing to start a first trial in the UK in 2015. The team have now received a major donation (£2.2M) from an American philanthropist to develop a gene therapy for the inherited form of motor neurone disease (MND) linked to the faulty SOD1 gene. The gene encodes a protein called Cu/Zn superoxide dismutase 1 (SOD1).

Silencing the faulty SOD1 gene: What is the logic behind this approach?

The faulty SOD1 gene produces a protein that is believed to be toxic to motor neurones leading to cell death and motor neurone disease as a result. It has been observed, that the disease is more aggressive and severe, the more toxic SOD1 protein is present. The complete lack of SOD1 protein on the other hand appears to have no major detrimental effects. Therefore, silencing the faulty gene and reducing the levels of toxic SOD1 protein in patients is a logical approach to alleviate SOD1-linked ALS.

How exactly does this gene therapy work?

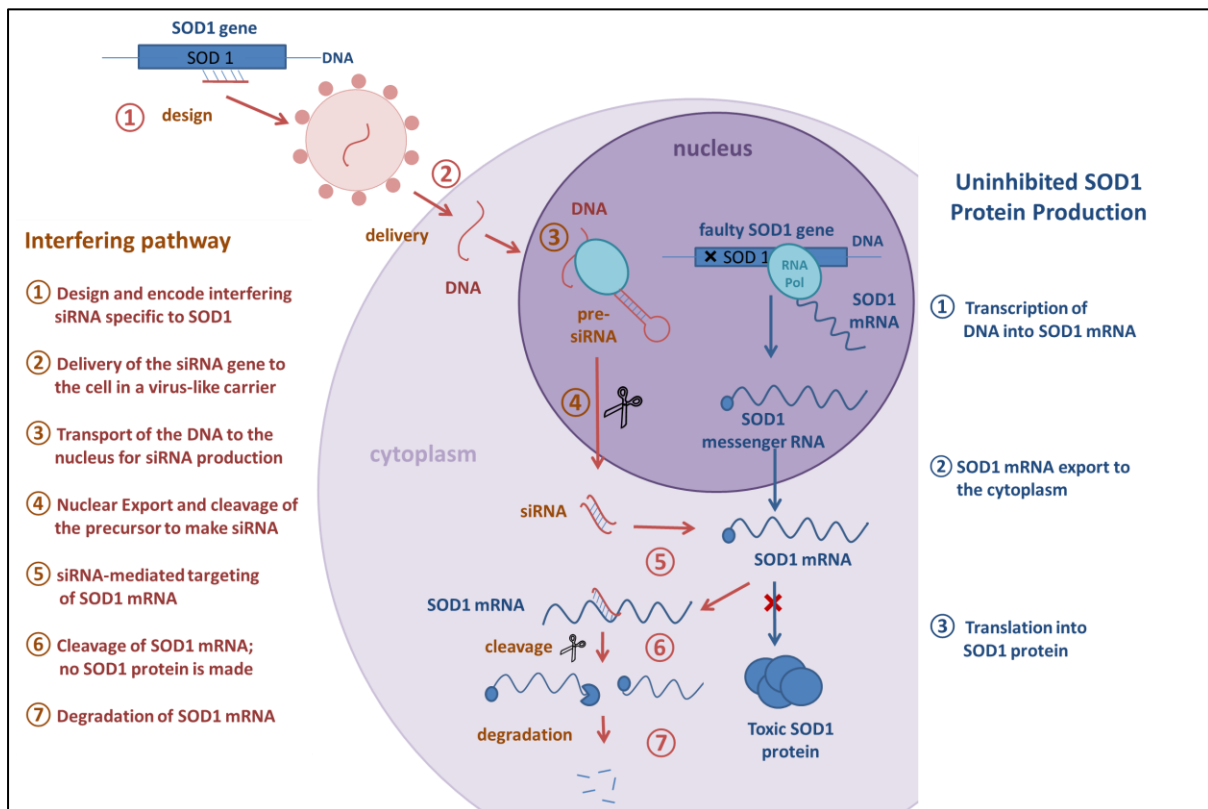
A technology called RNA interference (RNAi) provides us with a powerful tool to silence the faulty SOD1 gene. Short interfering RNAs (siRNAs) can be designed to specifically target the SOD1 gene and its copies used by the cell for protein production, so-called messenger RNAs (mRNAs). A gene is introduced into the cell to produce the designed therapeutic siRNAs. The siRNAs target and bind specifically to the SOD1 mRNA, rendering the messenger unusable for protein production. Once in the cell, the SOD1-specific siRNAs are continuously produced and recycled, thus effectively repressing SOD1 protein production. *See also schematic of SOD1 silencing on the next page.*

How do the genes for short interfering RNAs (siRNAs) get into the right cells?

In order to deliver our gene therapy to the right cells, we use virus-like carriers based on adenovirus. These so-called “vectors” have been modified to carry our designed DNA sequences and have been “disarmed” of all their harmful viral properties. These carriers, termed adeno-associated vectors (AAV), provide a safe and efficient method to deliver our short interfering RNAs across the blood brain barrier (BBB) to their target cells. They have proven safe and effective in gene therapy approaches for other diseases e.g. haemophilia and Parkinson’s disease.

Developing a Gene Therapy for Motor Neurone Disease caused by a faulty SOD gene (2)

Silencing the SOD1 gene



Simplified schematic of SOD1 silencing using short interfering RNAs (siRNA)

In untreated cells, SOD1 protein is made as shown on the right along the blue pathway: The SOD1 gene is copied into a messenger RNA which contains the instruction to make SOD1 protein. The SOD1 mRNA is exported to the cytoplasm and translated into SOD1 protein which is toxic in SOD1 MND. What happens when cells receive gene therapy is shown on the red pathway to the left: Using short interfering RNA (siRNA) the SOD1 protein production can be disrupted. A siRNA is designed to specifically target the SOD1 gene. The siRNA is encoded within DNA and encapsulated in a virus-like carrier that can target the affected motor neurons in SOD1 MND patients. The carrier delivers the DNA to the cell where it is transported to the nucleus and transcribed into precursor siRNAs. These precursors are exported to the cytoplasm and processed into functional siRNAs. The siRNAs target the SOD1 mRNA which is cleaved and degraded as a result and thus no SOD1 protein is made.

This image is available to download from:

<http://sitran.dept.shef.ac.uk/news/picture-archive/neuroscience>

Developing a Gene Therapy for Motor Neurone Disease caused by a faulty SOD1 gene (3)

From pre-clinical studies to clinical trials in patients

Our goal is to make our gene therapy safe and effective for human use and ultimately to offer an effective treatment to patients with MND linked to SOD1. Therefore, before entering clinical trials in humans, further pivotal pre-clinical studies are required to prove the safety of our therapy and obtain a license for human use (Biologic License Application (BLA)).

Our results so far: Reducing SOD1 protein levels in the central nervous system

We have been working on optimising dosage and route of delivery of our SOD1 gene therapy (scAAV9-hSOD1si) and have achieved a consistent reduction of SOD1 messenger RNA and protein levels at 2 weeks after treatment. It should be noted that a further reduction of the SOD1 protein would be predicted at later time points beyond 2 weeks.

The next steps in pre-clinical development

1. Evaluation of the effect of reduced SOD1 protein levels in mice following treatment before and at the onset of symptoms as a clinically relevant “proof of concept”.
2. Providing evidence that our RNAi molecules specifically target the SOD1 gene by screening for potential off-target effects both in vitro and in vivo;
3. Scaling up the production of our therapeutic scAAV9 vector according to guidelines and good manufacturing practice (GMP) for safe medicinal products;
4. Regulatory GLP Toxicology and Biodistribution studies in rodents which will be outsourced to an experienced Contract Research Organisation (CRO);
5. Dosing studies in large animals;
6. Obtaining a Biologic License Application (BLA) to initiate a phase I trial in ALS/MND patients.

How long will it take to start a Phase I trial in humans?

We are hoping to start a first human trial for the gene therapy for SOD1 MND within the next two years.

How will our expertise help to drive this forward?

Prof Azzouz has led the field internationally in developing and evaluating gene therapy approaches using viral vectors for neurodegenerative diseases. A gene therapy in models of Parkinson’s disease (PD) is currently trialled in humans and his new gene therapy for spinal muscular atrophy (SMA) has received “orphan drug designation” from the European Medicines Agency and is on its way to a first UK trial in humans in 2015. This therapy uses the same carrier system that will be used for the SOD1 gene therapy (self-complementary adeno-associated virus serotype 9, short scAAV9). With all the processes for safety, manufacturing and application already in place, the team will be able to fast-track a gene therapy for SOD1 MND and in succession other genetic disease variants.

How our gene therapy for SMA paves the way

We have already shown that the carrier system optimised for our gene therapy programme at SITraN crosses the blood-brain-barrier and delivers fast, robust, long-lasting gene transfer to the brain and spinal cord. Replacing the faulty *survival motor neuron* gene that causes SMA with a healthy copy in an SMA mouse model leads to a complete correction of the movement problems in the treated animals; their life span increases from an average of 15 days to more than 300 days. These data provide evidence for the most efficacious SMA therapy observed in this field to date.

[Link to summary for Gene therapy for SMA. \(website link\).](#)

SITraN

The Sheffield Institute for Translational Neuroscience

A Centre of Excellence for Research into MND & Neurodegenerative Diseases

SITraN is the first and only European Institute dedicated to and directly linking basic and clinical research into motor neurone disease (MND) and related neurodegenerative diseases. Our aim is to accelerate therapy development and offer new treatments to patients with neurological disorders.

A Unique Research Facility with a Unique History

SITraN is the result of an unprecedented fundraising initiative set in motion by patients and supporters of Professor Pam Shaw for a research institute dedicated to research into MND and related neurodegenerative disorders including Parkinson's and Alzheimer's disease. SITraN was officially opened in November 2010 by The Queen and Prince Philip.

Visionary Leadership, Wide-ranging Expertise and Collaborative Spirit

SITraN founder and director Professor Pamela Shaw has attracted and directs a multi-disciplinary team of eminent doctors and scientists working and collaborating in SITraN under one roof. SITraN scientists combine wide-ranging skills and expertise in clinical neurology, pathology, neuroscience, gene therapy, cell and molecular biology, genetics, biochemistry, bioinformatics, imaging including MRI, stem cell technology, disease modelling, pharmacology, drug screening and development, drug trialling, as well as clinical trials and applications.

Translating Research Discoveries into Benefits for Patients

SITraN is devoted to translational neuroscience – the rapid application of scientific research discoveries to the benefit and treatment of patients with neurological disorders. In order to accelerate the pace of therapy development, scientists and clinicians are working together closely with the added input and feedback from MND patients. Basic research is directed towards finding the disease causes and mechanisms, as well as testing the right targets to develop new and more effective treatments for patients.

Direct links to clinical research and patient care

The specialist MND Care and Research Centre for Motor Neurone Disorders established by Prof Shaw in 2003 in Sheffield serves as a focus of excellence for specialist patient care and clinical MND research, as well as a pivotal resource for the scientific research undertaken at SITraN.

Securing MND research excellence for the future

SITraN will provide a long-term international focus for research excellence in neurodegeneration by offering future clinicians and scientists highly specialised training. In addition to PhD training, two new Masters courses in Clinical Neurology and Translational Neuroscience have been established at SITraN with a combined intake of 40 students per year.

SITraN's success so far:

Since its opening in 2010, SITraN has grown immensely, now employing close to 100 staff, including 10 professors, and 90 postgraduate students. SITraN scientists have produced over 300 original peer-reviewed research publications and attracted over £15M in research funding for neurodegenerative diseases. The gene therapy for SMA and the drug S(+) apomorphine for MND have received "orphan drug designation" and are being further trialled, as is a promising drug for Parkinson's disease. While more potential therapies are being uncovered at SITraN, a range of assistive technologies are being developed and trialled to ensure better care and quality of life for MND patients. **For more information on SITraN visit our homepage: <http://sitran.dept.shef.ac.uk/>**

SITraN - Fast Facts

Name: Sheffield Institute for Translational Neuroscience, SITraN

Location: Sheffield, UK - within the central campus of The University of Sheffield

Opened: November 2010 by The Queen and Prince Philip

Founder and Director: Professor Dame Pamela Shaw DBE FRCP

Founding Patrons: Sheffield Institute Foundation and The University of Sheffield

Honorary Patron: The Duke of Devonshire KCVO CBE DL

USP: a dedicated centre of research into MND and related neurodegenerative diseases, purpose-built to allow unique collaboration of a multi-disciplinary team of clinicians and scientists under one roof to link pure science to clinical research and accelerate therapy development.

Purpose: Translation of scientific discoveries into new therapies for patients

Current Staff: >100 staff, including 30 faculty academic staff

Postgraduate Students: > 40 MSc students in 2013/14, > 50 PhD students since 2010

Research funding since 2010: > £15 mio

Publications of SITraN researchers since 2010: > 300 peer reviewed original research articles

SITraN pipeline: "Orphan drug designation" for ReSagen (SMA), and S(+) apomorphine (MND)

Scientific Disciplines: SITraN hosts 10 Professorships in

Neurology – Pamela J Shaw; Translational Neuroscience – Mimoun Azzouz;
Neuropathology – Paul Ince, Steve Wharton; Movement Disorders – Oliver Bandmann;
Clinical Neuropsychology – Annalena Venneri; Clinical Neurology – Markus Reuber;
Cerebrovascular Neurology – Arshad Majid; Machine learning and Computational Biology – Neil Lawrence; Bioinformatics and Computational Biology – Winston Hide;

Space: 2800m² of research laboratories, offices, conference and research training facilities.

Pivotal Resources:

- Sheffield Care and Research Centre for Motor Neurone Disorders established and directed by Prof Shaw with a clinical database of >1000 MND patients, and biobanks of human material and tissues donated for research.
- Host to Sheffield Brain Tissue Bank (SBTB) with material from > 1500 donors.
- Host to Public and Patient Research Advisory Groups for MND and dementia research
- Host Centre leading the UK Dementia (DeNDRoN) Clinical Studies Group for MND
- MRC Centre for Developmental and Biomedical Genetics with access to animal models e.g. zebrafish, drosophila (fruit fly)
- Access to facilities within University of Sheffield and Sheffield Teaching Hospitals
- National and international collaborations

Profile: Dame Pamela Shaw

Professor of Neurology, Director of SITraN, University of Sheffield

Dedicated to improving the lives of patients with motor neuron disease (MND)

Professor Pamela Shaw has a worldwide reputation as an acclaimed Clinical Neurologist and Neuroscientist who has dedicated her life's work to the exemplary care of MND patients and the understanding and development of treatments to combat the disease. She is one of the most renowned and experienced specialist consultants for motor neurone disease worldwide and has been at the forefront of MND scientific and clinical research for the last two decades. She has played a crucial role in influencing and implementing policies, guidelines and infrastructures in the UK to improve care for MND patients and put MND on the national healthcare agenda. In addition to numerous scientific awards and accolades, Pam Shaw's services to Neuroscience were acknowledged by HM The Queen in the New Year's Honours 2014 with a Damehood.

Promoting MND research and specialist care for MND patients

After her very successful medical and specialist training in neurology, Pam Shaw took up a post as Honorary Consultant Neurologist in 1991 and directed a specialist MND care and research centre in Newcastle. She embarked on a major clinical and laboratory programme of MND research funded by the Wellcome Trust which she transferred to the University of Sheffield in 2000 accepting a Chair in Neurology. In 2003, with support from the MND Association, she established and continues to direct one of the major national Care and Research Centres for Motor Neurone Disorders in Sheffield which serves as a focus of excellence for MND care and clinical research. She continues to lead the systematic development of clinical research nationwide to tackle major problems faced by MND patients where new approaches and new evidence-based guidelines are required.

Putting motor neuron disease (MND) on the agenda - nationwide

Prof Shaw's influence has ensured that neurodegenerative diseases are included in the NHS Clinical Research Networks Initiative and she has helped to implement MND care guidelines by providing the required evidence through clinical research. Prof Shaw has taken part in more than 15 MND clinical trials and played a key role in promoting into clinical practice the only known MND treatments to prolong survival, riluzole and non-invasive ventilation. For 8 years she has led the Clinical Studies Group for MND within the NIHR Dementia and Neurodegenerative Diseases (DeNDRoN) network and helped to develop a high quality UK clinical research network (UKCRN) linking 19 MND Care and Research Centres and establishing a network of 10 UK centres experienced in MND clinical trials.

SITraN, a research centre to reach the ultimate goal: Finding a cure for MND

The opening of SITraN by Her Majesty The Queen in 2010 was the culmination of over a decade's work, for which Pam Shaw provided both the overarching vision and the relentless practical driving force. The unique research institute is dedicated to accelerating the therapy development and improving care and quality of life for patients with MND and other neurological disorders. Scientific research undertaken at SITraN is firmly linked to the clinical research at the specialist MND Care and Research Centre in Sheffield which also serves as a pivotal resource.

Professor Shaw has authored more than 350 publications of original research (Google Scholar H-index 69), reviews and book chapters and has edited several books on MND. She has supervised the research training of more than 100 individuals from medicine and science including 30 PhD students and since 1983 has generated more than £50 million in research funding.

For more information on Professor Shaw, her research and biography,

visit: <http://sitran.dept.shef.ac.uk/people/shaw>

Profile: Mimoun Azzouz

Professor of Translational Neuroscience and Head of Gene Therapy, SITraN

Pioneering gene therapy for neurodegenerative diseases

Professor Mimoun Azzouz has led the field internationally in developing and evaluating gene therapy approaches using viral vectors for neurodegenerative diseases. He has received multiple awards for his pioneering work in gene therapy, most recently an MRC Translational Award for his SMA therapy and a €2.5 million award from the European Research Council (ERC) who also recognised his achievements with the prestigious ERC Advanced Investigator Award, a great distinction in European biomedical research. Prof Azzouz has now accumulated 17 years of experience and unrivalled expertise in gene therapy research and development for neurodegenerative diseases. He is leading an extensive gene therapy programme at SITraN including approaches for genetic variants of motor neurone disease (MND).

Successful translation of gene therapies into the clinic

Prof Azzouz has already been successful with a gene therapy for Parkinson's disease developed at Oxford BioMedica Ltd which is currently being trialled in humans. Azzouz' gene therapy for spinal muscular atrophy (SMA), the childhood form of MND, has received "orphan drug designation" from the European Medicines Agency, crucial to secure further funding and licensing for the European market. The team at SITraN are in preparations for a first clinical trial of the SMA therapy in humans.

Committed to find an effective therapy for motor neuron diseases

With an early commitment to Neuroscience, Mimoun Azzouz graduated in Biology and Neuroscience from the University of Rabat in 1993 and obtained a Masters in Neuroscience with 1st Class Honours from the University of Marseille in 1994. In 1997 he was awarded a PhD in Neuropharmacology at the University Louis Pasteur in Strasbourg for his work on a drug-based therapy for motor neuron disease (MND). His encounters with families affected by MND greatly motivated him to urgently develop a treatment or cure which led him to explore gene therapy approaches during his postdoctoral research at the Gene Therapy Center in Lausanne, Switzerland, from 1997 to 2000. His portfolio included motor neurone disease (MND), spinal muscular atrophy (SMA) and Parkinson's disease.

"Translating" gene therapy approaches at Oxford BioMedica Ltd

In order to advance gene therapy approaches to the clinic, Azzouz changed from academic science to industry in 2000 undertaking further gene therapy research as a visiting scientist at the University of Oxford between 2000 and 2005 for Oxford BioMedica Ltd. Azzouz' work in Oxford, first as a Senior Scientist and from 2003 as Director of Neurobiology, was very successful providing "proof-of-concept" for three gene therapy approaches for SMA, MND and Parkinson's disease. The dopamine replacement gene therapy for Parkinson's disease went into clinical trials in 2008.

Chair of Translational Neuroscience at SITraN, University of Sheffield

Mimoun Azzouz was approached by Pamela Shaw to develop a gene therapy programme for motor neuron diseases in Sheffield and in 2006 was appointed Professor of Translational Neuroscience at the University of Sheffield. His experience acquired in both academia and industry is pivotal in translating potential gene therapies into new treatments for patients and his gene therapy programme is one of the cornerstones for therapy development at SITraN.

For more information on Professor Azzouz, his research and biography, visit: <http://sitran.dept.shef.ac.uk/people/azzouz>

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Glossary and Abbreviations

MND – motor neuron disease

A fatal disease resulting from the death of motor neurons and loss of muscle control.

ALS – amyotrophic lateral sclerosis

The main form of MND.

SMA – spinal muscular atrophy

The childhood form of MND.

BBB – blood-brain-barrier

This barrier protects the brain from unwanted intrusions and is also a challenge to overcome for drug delivery to the brain in humans.

SOD1 – superoxide dismutase 1

A protein/enzyme that protects the batteries or energy producing compartments of the cell (mitochondria) from damage through free radicals (oxidative stress).

DNA – deoxyribonucleic acid.

DNA is the chemical term for the substance our genes and chromosomes are made of. It contains genetic information encoded in its sequence of bases A,C,G,T. DNA is generally made up of two complementary strands to safeguard the genetic information. It is wound into a double helix and further packaged into chromosomes.

Gene

A gene is a stretch of DNA which contains in its sequence all the information a cell needs to survive i.e. instructions to make functional RNAs and proteins (see below). Like a recipe book, the DNA contains all the instructions from our genetic master plan. A gene is like a chapter or page in this book containing a certain recipe or instruction.

RNA – ribonucleic acid – a copy of DNA

RNAs are generally single stranded copies made (“transcribed”) from DNA. RNA copies are chemically similar to DNA, but more flexible and more versatile than DNA. There are many types of RNAs with many different functions in living cells. The best known (but by far not the most common) type of RNA is messenger RNA, short mRNA.

messenger RNA (mRNA)

Messenger RNA is a transcript of a gene that contains the instructions to make a protein. The mRNA is copied from the DNA, packaged and transported to one of the cell’s protein factories, the ribosome. The ribosome reads the instructions contained within the mRNA and “translates” them into a chain of amino acids, the building blocks of proteins. The amino acid chain is folded into 2D and 3D or 4D structures to make the final protein. A short amino acid chain is often called a peptide.

Proteins

Proteins have many important structural and functional roles in our bodies. Our muscles are made up of proteins, as are our hairs and nails. Enzymes, e.g. digestive enzymes, and many hormones, e.g. insulin, are made up of protein and have very important functions. Proteins are made up of amino acids and the instructions for a certain protein are encoded within genes on DNA and their RNA copies which are “translated” into long amino acid chains and folded into the finished proteins.

Resources and References

Motor Neuron Disease (MND)

- MND Association - www.mndassociation.org, mndresearch.wordpress.com
- [NHS choices](#) - MND
- [Sheffield MND Care and Research Centre](#)

Gene therapy - Selected publications

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