The 8th annual UK Spinal Muscular Atrophy (SMA) Research Conference was hosted by Prof. Kevin Talbot from the University of Oxford at the Oxford Belfry Hotel, just outside of the city centre. Over 40 researchers from laboratories across the UK and the rest of Europe were in attendance, along with representatives from both the Jennifer Trust for SMA and the SMA Trust, who jointly sponsored the meeting.

In total, 17 presentations were given focusing on two main themes – first, understanding the basic biology of the survival motor neuron (SMN) protein and the cause of tissue degeneration in SMA, and second, highlighting both the clinical side of SMA research and therapies at the cusp of potential translation to human clinical trials. Hence, the strapline of the conference, “SMA at the crossroads of basic science and therapy.”

As in previous years, the conference provided an excellent opportunity for SMA scientists to present unpublished work, interact and exchange ideas with other researchers and clinicians, and set up future collaborations. The conference dinner was opened with speeches from SMA Trust trustee Tessa Rice, and Jennifer Trust representative Srin Madipalli, who both gave personal accounts of living with SMA. Hearing experiences from our dinner guests provided extra encouragement and motivation to work towards a cure for SMA. In the tradition of recent conferences, the evening was closed with a barn dance, which was very much enjoyed by all.

In this report, the main findings and themes from the presentations will be summarised to provide an overview of some of the current work being conducted on SMA.
Day 1 (3rd October, 2011)

Session 1: Basic function of proteins involved in SMA

Does SMN have a neuronal-specific function?

Michael Sendtner from the University of Würzburg (Germany) opened proceedings with his talk asking the question of whether the SMN protein has a specific function within the nervous system. When SMN levels are reduced, the first cells/tissues that become affected are the lower motor neurons, which are the nerve cells that connect the spinal cord to skeletal muscles such as the biceps, allowing conscious contraction of the muscle and therefore movement. SMN is found in all cells of the body throughout life, so one of the major conundrums of the disease, and many other neurodegenerative disorders, is why should lowering the levels of a widely expressed protein cause such a specific detrimental effect on the health of the nervous system?

One potential explanation for this is that the SMN protein plays a specific and important role within lower motor neurons, not performed in other cell types and tissues, such that when less SMN is available, this function is disturbed causing the nerve cells to degenerate.

Prof. Sendtner presented work from his laboratory and others supporting the notion of a neuron-specific function of SMN. He showed that in motor neurons the SMN protein is able to bind and form complexes with a protein called hnRNP-R, which it does not normally do in other cell types. Cell culture experiments have shown that the hnRNP-R protein is also able to bind to specific messenger RNAs (which are the molecules copied from genes in our DNA and used as templates to produce proteins, see below) that are then transported to different regions of the nerve cell where they can be used to produce protein. It is thought that when SMN levels are reduced, this affects the transport of certain messenger RNA (mRNAs) to sites where they are needed, which in turn causes defects in the growth and function of the nerves, providing a potential explanation for the specificity of motor neuron loss seen in SMA.

Characterising SMN protein expression at the synapse

Tom Wishart from the University of Edinburgh (UK) presented some of his unpublished findings looking at the expression of the SMN protein at the synapse, which is the region between a nerve cell and another cell (this can be a nerve cell or a different type of cell, for example a muscle cell) that permits the passage of electrical or chemical signals (Figure 1).

Low levels of SMN protein lead to the breakdown of specialised synapses called neuromuscular junctions (NMJs), which are the connections between lower motor neurons and their target muscles. Dr. Wishart has shown that the SMN protein is expressed at the fruit fly (Drosophila) NMJ and synapses in the mouse brain. Interestingly, SMN was found in the mitochondria, the energy-producing powerhouses of the cell, at the mouse synapses, yet these cellular bodies were no more vulnerable in a severe mouse model of SMA.
Figure 1. Synapses allow the passage of electrical and chemical signals between nerve cells and other cells. Specialised synapses called neuromuscular junctions (NMJs) allow the passage of signals from lower motor neurons to their associated skeletal muscles, causing contraction of the muscle.

Dr. Wishart also showed data which revealed that reduced SMN levels result in alterations in the amounts of specific proteins and mRNAs at the mouse synapse.

This work suggests that SMN has an important role to play at the synapse, where it influences the expression of specific genes, the disturbance of which may contribute to the specific degeneration of lower motor neurons seen in SMA.

A novel pathway of neurodegeneration

Zameel Cader from the University of Oxford (UK) presented his recent work using both Drosophila and mice to study a neurological disease with similarities to SMA known as Charcot-Marie-Tooth type 2d (CMT2D). Like SMA, CMT2D is caused by mutations in a gene that produces a protein found in all cells of the body. The protein affected in CMT2D is called glycyl-tRNA synthetase (GlyRS) and it ensures the fidelity of protein production from our genes, a process vital for cell survival.

Dr. Cader highlighted recent experiments performed in his laboratory that indicate a potential cause of the motor neuron degeneration seen in CMT2D. He proposed that the toxic effects of mutant GlyRS arise from muscles, causing the disruption of normal signalling and growth of the associated nerves at their point of contact with the muscle (i.e. the NMJ). In contrast to SMA, which is caused by disturbed protein function, CMT2D-associated mutations cause GlyRS to gain a toxic function. Dr. Cader suggests that mutant GlyRS, with this new, detrimental capacity, leaks out from the muscle and causes damage to the nerves.
Although this work was on models of CMT2D, the genes and proteins highlighted as being involved in the degeneration of nerve cells may converge on the same process in SMA and could thus be potential targets for SMA therapy.

**A potential mechanism for splicing defects in SMA**

Judith Sleeman from the University of St. Andrews (UK) discussed work from her laboratory that points to a potential mechanism for the “splicing” defects seen in mouse models of SMA.

Proteins are made in the cell from genes (**Figure 2**). First, DNA must be copied into mRNA, which is then read by molecular machines called ribosomes and used as a template to produce proteins with specific amino acids corresponding to the genetic information encoded by the DNA. Before the mRNA, which at this point is called pre-mRNA, is converted to protein, there is a special process called “splicing” that must occur.

**Figure 2. From genes to protein.** Stretches of DNA known as genes are copied or “transcribed” into pre-mRNA with a corresponding sequence. Before pre-mRNA can be used as a template for protein production (i.e. “translated”), the exons, which encode important information about the protein, must be spliced together. Exons are interspersed by regions called introns that do not contain information necessary to build a protein. Introns are removed from pre-mRNA in the process of splicing to produce mature mRNA, which can then be translated into protein by molecular machines called ribosomes. All exons need not be included in the mature mRNA. For instance, in the example above, exons 1-5 are used to produce the first mRNA, while exon 3 is not included in the second mRNA. This “alternative splicing” allows a single gene to encode multiple distinct proteins.
The pre-mRNA includes important sections called exons, which contain the information to produce parts of a protein. These exons are interspersed by regions called introns that do not contain important information for the protein sequence. The SMN protein, as part of a multi-protein conglomerate called the SMN complex, is involved in the production of proteins that remove the introns from pre-mRNA and splice, or stick, together the remaining exons. Once this has occurred, the mRNA can be used as a template for protein production.

There is some evidence that when SMN levels are reduced, the process of splicing is affected. This has led to the hypothesis that SMA is potentially caused by this process going awry. Dr. Sleeman showed results from her laboratory suggesting that when SMN levels are reduced, the molecular machinery that participates in the splicing process is formed less efficiently. This may provide an explanation for the reported deficiency in splicing.

Session 2: SMA Pathogenesis

Lower motor neurons: the only vulnerable cell in SMA?

Tom Gillingwater from the University of Edinburgh (UK) posed the question, are motor neurons the only vulnerable cells in SMA? The answer to this question has implications for potential future SMA therapies, because if the answer is no, then treatments will have to be targeted to numerous, if not all, parts of the body for the best chances of success.

Prof. Gillingwater presented evidence from both his laboratory and others implicating a range of different cells and tissue in SMA pathology. Bone and heart complications have been reported in patients with more severe forms of SMA, and mouse models of the disease support these findings: SMN deficiency has recently been implicated in bone pathology as well as cardiac defects including arrhythmia. In addition to this, defects in the brain, nerve cells other than the lower motor neurons, and muscles have also been reported in the more severe SMA mouse model.

Prof. Gillingwater concluded his talk by presenting work from his most recently published study suggesting that SMA muscle pathology may be contributing to the course and severity of the disease, which has been recently reported on for the Jennifer Trust (http://www.jtsma.org.uk/igs/dbitemid.1073/sfa.view/latest_research_news.html).

The evidence emerging from patients and animal models of SMA suggests that lower motor neurons are not at all the only cell type affected by the disease. However, the observed pathology in non-motor nerve cells is predominantly seen in more severe cases, suggesting that there is a differential vulnerability to SMN depletion (Figure 3). The Threshold Hypothesis proposes that different cell types and tissues can be placed along a vulnerability-resistance spectrum. At one end lie lower motor neurons as they are the most sensitive to reduced SMN levels. As SMN levels are further reduced, the range of affected cell types becomes greater, to a point at which there is insufficient protein for the survival of any cell. In all, Prof. Gilingwater presented a compelling argument that SMA is a multi-system disorder.
Figure 3. Are motor neurons the only cells affected in SMA? Cell types and tissues appear to show different levels of susceptibility to SMN reduction. At one extreme of a vulnerability-resistance spectrum reside the lower motor neurons, which are the most severely affected cell type in SMA. As SMN levels are further diminished, tissues and organs such as the heart, bone and brain (hippocampus) become affected, while other areas remain relatively healthy. To illustrate this, at 10-20% of normal SMN levels (as seen in some type I SMA patients), lower motor neurons are severely affected, some cells/tissues/organs such as the heart are beginning to show signs of deterioration, while many other areas remain largely unaffected.

What can stem cell-based models tell us about SMA?

María Gabriela Boza-Morán from the University of London (UK) presented some of her preliminary experimental work using induced pluripotent stem cells (iPSCs). iPSCs are cells that have been altered or “reprogrammed” by the expression of specific genes to become able to potentially differentiate into a number of different cell types. For instance, skin cells can be taken from an adult and induced to become motor neurons. In a recent study, iPSCs were generated from skin cells taken from a child with SMA and used to generate motor neurons in culture. These cells possess the same genetic makeup and characteristics as those found within the patient and are therefore likely to more accurately model the disease than immortal cell lines in which SMN protein levels are artificially reduced.

Miss Boza-Morán has been involved in an effort to generate and characterise iPSCs from siblings differentially affected by SMA despite all having identical mutations in the SMN1 gene, possessing four copies of SMN2 and displaying no difference in the levels of a protein known to modulate disease severity (Plastin 3). The rationale behind choosing such a family is that the discordance in disease severity is unlikely to be directly due to SMN levels, but other modifying
genetic pathways. Therefore, identifying differences between the iPSC lines may help to elucidate important pathological mechanisms. Currently differentiating the iPSCs into motor neurons, in the future Miss Boza-Morán intends to study SMN-interacting proteins in the nerve cells and how disruption of these interactions may influence SMA pathology.

Reduced SMN levels affect blood vessel architecture in muscle

Simon Parson from the University of Edinburgh (UK) presented work from his laboratory looking at the microvasculature, which is the network of the smallest blood vessels such as capillaries, in skeletal muscles of severe SMA mice. As Prof. Gillingwater alluded to in his earlier talk, SMA is not simply a disease of lower motor neurons, especially in more severe cases. The vascular system (i.e. circulatory system) has recently been implicated in disease pathogenesis both directly, via heart defects, and indirectly through ear and tail necrosis (tissue death), in mouse models of SMA. Heart complications have also been reported in patients.

Dr. Parson set out to compare the capillaries, which are the blood vessels that are embedded within tissues and organs allowing the exchange of useful and waste products (Figure 4), of a number of different muscles between severe SMA mice and unaffected littermates. Five days after birth, there was a greater than 50% reduction in the density of capillaries in SMA mice, which was uniform across the length of the muscle. Furthermore, capillaries were not as well embedded into the muscle and displayed a significantly larger average diameter.

This disruption to the microvasculature was also seen in three day old pups but not one day old, suggesting that capillaries are normal at birth but become rapidly affected postnatally. Interestingly, the extent of vascular degeneration was similar in a range of muscles types, even those with no signs of lower motor neuron degeneration, which suggests that the pathology is independent of nerve cell loss. The identified defects are likely to impact blood flow to muscles and thus the delivery of oxygen, which in turn will affect muscle function. This work adds further weight to the assertion that SMA pathology is not exclusive to the lower motor neurons.

![Figure 4. The vasculature system.](image)

Figure 4. The vasculature system. Oxygenated blood travels away from the lungs down arteries and then arterioles, until it reaches the capillaries, which are the smallest blood vessels that allow the exchange of various useful (e.g. oxygen) and waste products (e.g. carbon dioxide) between blood and the cells. Once oxygen has been delivered to the cells, the deoxygenated blood can be carried back to the lungs via the heart along venules and then veins. The architecture of the capillaries appears to be quite severely affected at later stages of disease in SMA mice.
The effects of salbutamol, a potential treatment for SMA, on cellular proteins

Heidi Fuller from the University of Keele (UK) presented the work of Emma Humphrey on the effects of salbutamol on protein expression in skin cells derived from SMA type I patients. Salbutamol is commonly used for the treatment of respiratory conditions such as asthma, yet has been shown to cause a rapid and significant increase in the amount of SMN protein produced from the SMN2 gene.

Humans possess two genes that code for and make SMN protein: SMN1 and SMN2 (Figure 5). SMN1 produces fully functional, full-length SMN protein, and is the gene that when mutated leads to SMA. SMN2, however, due to a single difference in the DNA, only produces approximately 10-20% of the amount of SMN protein that is made from SMN1. Patients with SMA have at least one copy of the SMN2 gene, but usually more, and SMN2 copy number inversely correlates with disease severity. This means that the more SMN2 copies a patient with SMA has, the less severe the disease is likely to be.

![Diagram](image)

**Figure 5.** Salbutamol treatment can increase SMN expression levels in cellular models of SMA.

SMN2 has thus emerged as a potential therapeutic target, because if expression from this gene can be increased or the single mutation in the DNA corrected, more SMN protein can be produced, which has the potential to reduce disease severity.
The exact mechanism whereby salbutamol increases SMN levels and whether this effect is specific for just SMN2 are unclear. Consequently, Dr. Humphrey compared the expression of proteins found in SMA patient-derived skin cells with and without treatment with salbutamol. She found that the amounts of at least two proteins were altered by treatment with salbutamol. The largest increase was in a protein involved in the degradation of excess or damaged proteins. The SMN protein is known to be degraded via this pathway. Dr. Humphrey therefore hypothesised that the highlighted protein is important for the control of SMN stabilisation and/or degradation.

**NMJ defects in type I SMA**

Eduardo Tizzano from the Hospital de Sant Pau (Barcelona, Spain) concluded the first day with his talk on studies of the NMJ in pre- and postnatal type I SMA samples. Type I SMA symptoms become apparent very soon after birth, perhaps indicating that underlying defects are occurring prenatally. To test this hypothesis, Dr. Tizzano decided to look at the structure of the human neuromuscular junction at various time points.

In prenatal samples, he reported defects in the structure of NMJs in all the muscles he examined, including the diaphragm and intercostal muscles, which are involved in breathing, and muscles of the upper and lower limbs. This work confirms that neuromuscular pathology starts during development in the most severe form of the disease. This has relevance for potential future SMA therapies, as they will likely have to be delivered early on in the disease to most successfully counteract such pathology.

Dr. Tizzano also reported a delay in the maturation of the neuromuscular junctions in postnatal samples, adding to the debate as to whether SMA is either a neurodegenerative (i.e. caused by the progressive damage or loss of neurons) or neurodevelopmental (i.e. caused by disturbance of the growth and development of the nervous system) disease, or in fact a combination of the two.
Day 2 (4th October, 2011)

Session 3: Clinical Trials

Practical realities of clinical trials in SMA

Francesco Muntoni from the University of London (UK) kicked off the second day of the conference with his talk discussing some of the practical difficulties of performing clinical trials in SMA. This was followed by Volker Straub from the University of Newcastle (UK), who highlighted the importance of having a mobile SMA patient community.

As discussed above, SMN2 is an attractive therapeutic target for increasing SMN protein levels in SMA patients (Figure 5). A number of compounds have been identified over the last decade that can successfully increase SMN protein expression from SMN2 in cells (for example salbutamol), and that have been shown to improve muscle strength and lifespan of SMA mice. Groups from around the world are in the process of planning and carrying out clinical trials of some of these drugs. However, given the limited funding and small number of SMA patients eligible for trials, it is a major challenge to be able to translate potential pre-clinical research findings into clinical trials.

Prof. Muntoni stressed the importance of recognising some of the major hurdles that will need to be surpassed in order to successfully determine the efficacy of drugs with potential to treat SMA. For instance, for the compounds to be effective it is likely that they will need to be injected directly into the spine, as they are unlikely to target lower motor neurons when administered orally or intravenously (into a vein). Moreover, there is the issue of timing; studies in mice suggest that earlier SMN restoration is more successful at alleviating symptoms, leading to the question of whether treatments will be effective, and to what extent, once symptoms have already manifested. For the greatest chances of success it is therefore likely that clinical trials will need to be performed in young children, and perhaps even before disease onset.

For this to happen, a range of practical and ethical issues need to be discussed, for instance, whether neonatal screening for SMA should be commonplace when there is currently no available treatment. Prof. Muntoni concluded his talk by urging investigators, patients and families to maintain an informed dialogue in order to forge the best strategy for taking forward novel potential therapies.

Following on from this, Prof. Straub identified the key role of patient advocacy groups and suggested that the SMA community as a whole needs to come together and do the following in order to be “trial ready”:

1. Choose and evaluate without bias the most appropriate compounds for clinical trials
2. Locate the investigators and centres with the best expertise to successfully run the trials
3. Identify and enrol eligible patients
4. Develop standardised guidelines of patient care

5. Validate the methods used to measure the outcome of the trials (outcome measures)

TREAT-NMD, with the help of patient organisations, has begun to develop tools to address these specific challenges, and Prof. Straub stressed how important the contribution of patients to databases and biobanks has been to ongoing research. To conclude, Prof. Straub recognised how relatively well developed the infrastructure for SMA translational research is and acknowledged the value of patient involvement.

**Analysis of motor performance scales for SMA**

Anna Mayhew from the University of Newcastle (UK) talked about the necessity of having a set of outcome measures that are relevant to the SMA patient population. Outcome measures gauge physical ability along a numerical scale and can thus be used to determine patient improvement or decline. For instance, the ability to stand from a sitting position may be recorded as able to stand up with no problems (2), able to stand up with difficulty (1), or unable to stand up (0). A number of different physical abilities can be measured and an aggregate score recorded.

It is important that this overall score can be used to detect any changes in physical performance over time and that this potential is uniform across the scale. Ideally, an increase of two points should mean the same irrespective of the stage of disease. In the past, data relating to motor performance has been collected using at least ten different scales, which incorporate different physical tasks and scoring criteria.

Dr. Mayhew was involved in an in depth evaluation of the ability of nine different scales to assess motor performance in SMA patients. The scales were all found to have a number of issues. For example, measured categories being dependent on one another and thus duplicating information, and scores of particular abilities not reflecting the stage of disease progression (i.e. the disease has little effect on the measured ability, thus the ability is not likely to be the best indicator of disease state).

As a consequence of this analysis, Dr. Mayhew suggests that the currently available scales are not sufficiently robust for assessing motor function in SMA, and that the application of new methods will be critical to creating linearised and meaningful outcome measures for clinical trials in SMA. The next phase of this work is to determine how well the different scales measure the same outcome, for instance ability to stand, and then begin to incorporate them on a unified scale.
Phase II clinical trial of olesoxime

Rebecca Pruss from the pharmaceutical company Trophos (Marseille, France) concluded session 3 with her presentation on olesoxime, a drug found to increase nerve cell growth, improve nerve cell electrical signal conduction and prevent motor neuron death in culture when specific growth supplements are removed. These neuro-protective properties of olesoxime could potentially benefit SMA patients.

In Phase I clinical trials, olesoxime was shown to be safe and well tolerated in both healthy volunteers, and children and adults with SMA. Olesoxime is now being tested in a large-scale, Phase II clinical trial across 23 centres in seven European countries including the UK. To assess the effects of olesoxime in the broadest range of SMA patients, a once-a-day liquid formulation that can be taken orally by children as young as three years old was developed.

The primary outcome measure that will be used at the end of the two year study will be the rate of decline in motor function using the MFM (Motor Function Measure) scale. Respiratory function, quality of life, muscle excitability and motor function using a different scale will also be recorded as secondary measures. Enrollment is now complete, with over 160 type 2 and 3 SMA patients between 3-25 years of age.

Session 4: Pre-clinical Translational Research

Gene therapy for SMA

Martine Barkats from the Institute of Myologie (Paris, France) gave a talk on recent work from her laboratory on the delivery of SMN protein using viruses. The Barkats Laboratory was one of the first to show that single injections of harmless viruses into the blood of 1-2 day old mice and cats was able to target up to 60% of motor neurons. They then went on to show that SMN protein replacement in severe SMA mice using the viruses not only improves motor function, reduces weight loss, and prevents motor neuron loss, but also extends lifespan from two weeks to well over 300 days in some mice (median survival of 199 days). This is one of the most impressive improvements in SMA mice seen upon any type of treatment.

These results provide a proof-of-concept that defects caused by low levels of SMN protein can be rescued by virus-mediated SMN replacement.

In her talk, Dr. Barkats presented recent, unpublished work investigating the efficiency of alternative routes of viral injection in SMA mice, in particular the triceps and gastrocnemius muscle (commonly known as the calf muscle in the lower leg). Delivery of the viruses into these two muscles on both sides of the body resulted in an improvement not quite as impressive as intravenous delivery, but the enhancement in lifespan was still noteworthy (median survival of 163 days).
In the future, the efficacy of direct injections into the brain will be assessed and compared with alternative routes to identify the most efficient for SMN replacement. Work from the Barkats Laboratory highlights the considerable potential of viral-mediated SMN gene replacement as a viable option for the treatment of SMA.

A novel therapy delivery method

Matthew Wood from the University of Oxford (UK) discussed work from his laboratory on a novel method for delivering therapies to the central nervous system (i.e. the brain and spinal cord). This part of the nervous system is notoriously difficult to target due to the blood-brain barrier (BBB), which protects the brain and spinal cord from foreign substances in the blood such as drugs. Delivery of substances across the BBB is therefore a major challenge in the treatment of neurological diseases.

Exosomes are very small, natural structures found within mammalian cells that allow the exchange of molecules such as proteins between cells. The Wood Laboratory has managed to exploit these particles for targeted delivery of substances to the mouse brain after intravenous injection. Importantly, there appears to be no detectable immune response to the loaded exosomes.

As a proof of principle for the treatment of neurological disease, the exosomes were successfully used to target a molecule to the brain in mice that can specifically reduce the expression of genes associated with Alzheimer’s disease. The treatment appeared to have no ill-effects and was well tolerated by the mice.

These results suggest that exosomes may provide a novel, natural method of therapy delivery to the difficult to access central nervous system, and thereby possess great potential for the treatment of a range of neurological diseases including SMA.

PTEN protein depletion enhances motor neuron survival

Ke Ning from the University of Sheffield (UK) presented his work on a protein called PTEN, which is found in motor neurons and is involved in the regulation of protein production.

When PTEN protein levels are artificially reduced in cultured mouse spinal motor neurons, it promotes cell survival and growth. Consequently, Dr. Ning went on to show that PTEN reduction in a mouse model of SMA also results in increased motor nerve cell survival.

Dr. Ning then presented some unpublished results that suggest that PTEN reduction can also improve the neuromuscular junction defects of SMA mice and increase their lifespan. Through additional cell culture experiments on motor neurons, the enhanced nerve cell survival was suggested to be caused, at least in part, by inhibition of a particular receptor protein involved in neurotransmission in the brain and spinal cord.
SMN overexpression: a potential therapy for amyotrophic lateral sclerosis?

Kevin Talbot from the University of Oxford (UK) closed this year’s conference with work from his laboratory, which suggests that upregulation of the SMN gene may potentially also serve as a therapy for the adult-onset motor neuron disease amyotrophic lateral sclerosis (ALS). It has previously been identified that low levels of SMN protein (albeit, not sufficiently depleted to cause SMA) increase susceptibility to and the severity of ALS. Furthermore, the Talbot Laboratory has previously shown that halving the normal levels of SMN in a mouse model of ALS results in the exacerbation of disease symptoms and reduced lifespan.

This work has lead to the suggestion that SMN levels may be a general factor for motor neuron survival. In his presentation, Prof. Talbot showed unpublished results from a follow-up study in his laboratory, which indicate that increasing SMN levels after birth in the brain and spinal cord of ALS mice leads to a delay in weight loss and disease onset, and preservation of spinal motor neuron numbers. However, this did not translate into an increase in lifespan.

Interestingly, SMN levels remained elevated at 60 days, yet returned to normal after 120 days at the time of death. Prof. Talbot speculated that the mutant protein in ALS mice may cause degradation of the SMN protein leading to a reduction in SMN levels. Given the apparent protection against early stages of disease and neurodegeneration in the ALS mice, therapies developed to increase SMN levels for SMA patients may also provide benefit for ALS patients.
Poster Displays

In addition to the 17 platform talks, a number of poster presentations were given covering a range of topics. Each presenter was asked to give a two minute summary of their findings so as to breed later discussion throughout the conference. Titles, authors and institutions are included below.

Young Scientist Awards were presented to Benjamin Förthmann and Haiyan Zhou (in bold below) for the best presentations by PhD students or Post-Docs. The awards of £500 are to provide early career scientists with the opportunity to attend an upcoming SMA conference.

Conditional expression of SMN in the mouse.
Angie Biba, Ben Davies and Kevin Talbot.
University of Oxford, UK

SMN2 gene expression studies by using HDAC inhibitors.
Gamze Bora-Tatar and Hayat Erdem-Yurter
Hacettepe University, Turkey

The survival of motoneuron (SMN) protein dysregulates Rho-kinase (ROCK) downstream targets.
Peter Claus, Anna Nölle, Yvonne Schill et al.
Hannover Medical School, Germany

The C. elegans allele, smn-1(cb131), mimicking a human mutation, provides a platform for exploring drug re-use and novel chemistry for the treatment of spinal muscular atrophy.
Behrooz Esmaeili, James N. Sleigh, Frederick Partridge et al.
University of Manchester, UK

The intranuclear mobility and neuronal differentiation capacity of the survival of motoneuron protein is regulated by FGF-2.
Benjamin Förthmann, Yu-Wei Lee, Jeroen van Bergeijk et al.
Hannover Medical School, Germany

Evaluating human SMN overexpression phenotypes using a Drosophila model.
Marie L. Hannam, Helen E. Jarrett, Robert Morse et al.
University of Plymouth, UK

Analysis of the complete Fibroblast Growth Factor system in a mouse model of spinal muscular atrophy.
Niko Hensel, Andreas Ratzka, Claudia Grother and Peter Claus
Hannover Medical School, Germany

Gene expression in glycyl-tRNA synthetase (GARS) related neurodegeneration.
Jinghuan Li, Carmen Coxon, Sheena Lee et al.
University of Oxford, UK
Functional mammalian spliceosomal complex E contains proteins present in the SMN complex.
Olga Makarova, Paul Smith, Evgeny Makarov et al.
University of Leicester

A potential role for chondrolectin in the pathogenesis of spinal muscular atrophy.
James N. Sleigh & Kevin Talbot
University of Oxford

Drug treatment in spinal muscular atrophy types 1, 2, and 3: an update of the systematic Cochrane review.
Renske I. Wadman, W-Ludo van der Pol and Alexander F. Vrancken
University Medical Centre Utrecht, The Netherlands

Segmental distribution of muscle weakness in Dutch patients with SMA type 2, 3, and 4.
Renske I. Wadman, Leonard H. van den Berg and W-Ludo van der Pol
University Medical Centre Utrecht, The Netherlands

Evaluate therapeutic antisense oligonucleotides in transgenic mouse model of spinal muscular atrophy.
Haiyan Zhou, Jennifer Morgan and Francesco Muntoni
University College London, UK
Glossary

**Atrophy:** The wasting of a part of the body. SMA is called spinal muscular atrophy because the motor neurons within the spinal cord degenerate, which leads to the wasting of the muscles.

**Cell:** The basic building block of life. A group of cells can work together with a common function to form a tissue. Cells come in many different forms such as motor neurons (a type of nerve cell), keratinocytes (main cell type of the skin), or erythrocytes (red blood cells).

**Denervation:** The degeneration of nerve cells such that they no longer contact and excite their target muscle.

**Drosophila:** A type of fruit fly that is frequently used as a model organism to study biological processes. *Drosophila melanogaster* is the full Latin name of the most frequently used fly.

**Gene (replacement) therapy:** A method for altering, removing or adding genetic material (DNA) to correct particular defective genes that are responsible for the development of a genetic disorder.

**Induced pluripotent stem cell (iPSC):** A cell that has been altered or “reprogrammed” by the expression of specific genes to become able to potentially differentiate into a number of different cell types, for instance a motor neuron.

**Motor neurons:** The nerve cells that connect the brain and spinal cord to the muscles allowing conscious movement. They act as a message delivery system: electrical signals originating in the brain are fired down the spinal cord along ‘upper motor neurons’ and on to skeletal muscles via the ‘lower motor neurons’. Lower motor neurons are the main tissue affected by SMA.

**Messenger RNA (mRNA):** An intermediate molecule between DNA (genes) and proteins, serving as a template that can be read by the ribosomes to produce proteins.

**Mitochondria:** Distinct structures found within cells often referred to as the powerhouses as they generate most of the cell’s energy supply.

**Neuromuscular junction (NMJ):** Specialised synapses between lower motor neurons and skeletal muscles that allow the passage of signals from the nerves resulting in contraction of the muscle.
**Outcome measures:** A gauge of physical ability along a numerical scale that can be used to determine patient improvement or decline over time.

**Pathology:** The anatomical and/or functional consequences of a disease, i.e. the deviation from a healthy condition caused by disease.

**Ribosome:** Molecular machines that can read mRNA and use it as a template to produce protein with specific amino acids corresponding to the genetic information encoded by the DNA.

**Skeletal muscle:** Consciously controlled muscles that attach to bones allowing movement. Examples include the biceps, triceps, and thighs.

**Synapse:** The region between a nerve cell and another cell (this can be a nerve cell or a different type of cell, for example a muscle cell) that permits the passage of electrical or chemical signals.

**Tissue:** A collection of cells that work together to perform a common function. Organs are formed from multiple tissues working together with a common function.
Conference Photographs

Deep in concentration for the poster presentations

Having fun at the barn dance
Srin Madipalli’s pre-dinner speech

This report was written by the research correspondent of the Jennifer Trust for SMA, James Sleigh, who is currently in his final year of a PhD at the University of Oxford studying the underlying molecular causes of motor neuron degeneration seen in SMA.