Research progress in spinal muscular atrophy

Spinal muscular atrophy (SMA) is a genetic condition and the leading genetic cause of death in children. There are three main types of SMA defined by symptom severity and the age that first symptoms can be observed. In its most severe form (SMA type 1), symptoms occur before six months of age. Children with SMA type 1 develop (or are sometimes born with) muscle weakness and hypotonia (something also described as floppy baby syndrome). As the condition progresses they develop difficulties with swallowing (including feeding) and breathing. Children with SMA type 1 often do not survive beyond their first year due to recurrent respiratory infections, although, with improved respiratory support many do now live longer. SMA types 2 and 3 are less severe. In SMA type 2, symptoms develop from six to 18 months and in SMA type 3, from two to 17 years. Children with SMA type 2 may be able to sit independently but require support to walk or stand. The symptoms in children with SMA type 3 can be quite variable; some might be able to walk independently while others require support.

Every year between 70 and 120 children are born with the condition. There is currently no effective treatment or cure available for any type of SMA.

The genetic cause of SMA

SMA is caused by mutations in a gene called SMN1. This results in the lack of SMN protein and leads to the selective wasting of nerve cells that connect the spinal cord to the muscles. The connection between the nerve cells and the muscles is lost and electrical signals cannot be transmitted any more. This in turn results in the wasting of muscles.

In addition to the SMN1 gene, there is a second gene called SMN2. This gene is almost identical to SMN1 with the exception of one letter in the DNA code. This results in a truncated protein being made from this gene and is rapidly degraded in the cell. About ten percent of functional protein is made from the SMN2 gene. The different severities of SMA are due to different copy numbers of the SMN2 gene.
The discovery of the *SMN1* gene in 1995 has led to the development of animal models of SMA. In 2007 the first clinical trials using small molecules to treat SMA have started.

**The development of treatments for SMA**

Currently there are five main approaches to treat SMA that are being explored and taken forward into clinical trials. Three of these are based on targeting the *SMN2* gene and increasing SMN protein levels. They have shown substantial promise in the mouse model demonstrating improvements such as an increased life span and amelioration of the symptoms associated with the condition.

**Compounds that increase production of SMN protein from the *SMN2* gene.**

This approach explores small molecules that increase the production of SMN protein form the *SMN2* gene.

- **Valproate, Levocarnitine (AIIMS)**

  In preclinical studies valproate or valproic acid (VPA) has been shown to increase the levels of SMN in cell culture. Previous clinical trials have also shown that VPA might have a possible benefit for increasing muscle strength and/or motor function. Currently VPA is being tested in a phase III clinical trial in 60 children with SMA aged two to 15. The trial is currently recruiting participants in India.

- **LMI070 (Novartis)**

  In a phase II clinical trial, the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of the compound LMI070 is being tested in
participants aged one to seven months with SMA type 1. The trial is currently recruiting participants in Belgium, Denmark, Germany, Italy and Netherlands.

• RO6885247 (Roche/PTC/SMAF)

Pre-clinical studies have shown that this compound increases the levels of functional SMN protein, improves motor neuron function and increases the life span of the animals. Its safety and tolerability was being tested in a phase I clinical trial on participants aged two to 55 with SMA types 1, 2 and 3. However this trial has suspended participant recruitment.

• RG3039 (Pfizer)

RG3039 is a drug that was shown to increase the activity of SMN2 gene and result in the production of functional SMN protein. This would improve survival and motor function in mice and people with SMA. RG3039 was being tested in a phase I clinical trial however this has been terminated possibly due to the lack of efficacy results obtained.

• PTK-SMA1 (Paratek)

This is a derivative of the antibiotic tetracycline. Preclinical studies have shown that it can increase the production of SMN protein from the SMN2 gene. The molecular targets of PTK-SMA1 are not yet known.

Molecular patches that specifically increase levels of SMN protein

In this case, molecular patches or antisense oligonucleotides that increase the production of SMN protein from the SMN2 gene are being investigated.

• ISIS-SMNRx (ISIS/Biogen)

This is a molecular patch that masks the region of the DNA that differs between SMN1 and SMN2 genes. It is hoped that this way fully functional SMN protein can be produced from the SMN2 gene.

There are three clinical trials that test the safety and efficacy of the drug in children of different age groups. These trials are currently recruiting participants to test this drug. ISIS Pharmaceuticals recently gave an update on its clinical trial testing ISIS-SMNRx on infants with SMA type 1. Read our news story.

• Antisense oligonucleotides (RaNA)

A second company, RaNA has also developed molecular patches for SMA. Current studies are focusing on the effect of these molecular patches on survival in animal models.

Gene therapy using harmless viruses
Gene therapy approaches offer the possibility of delivering a functional copy of a gene to the body where it could restore production of functional protein. The most promising approach is based on the use of a harmless virus called Adeno-associated virus (AAV) that has been shown to effectively deliver genes to a range of different types of cells and tissues including muscle.

- scAAV9.CB.SMN (AveXis)

This is a phase I clinical trial evaluating the safety and efficacy of gene transfer as a treatment for SMA type 1. The study is currently recruiting infants between zero and nine months of age with SMA type 1 at Nationwide Children’s Hospital in Columbus, Ohio, USA.

- AAV mediated gene therapy (Genethon/INSERM)

The team of Dr Martine Barkats (Institut de Myologie – INSERM UMR 974, Paris) showed the efficiency of gene therapy based on AAV vectors using a mouse model of SMA type 1. Preclinical studies are currently ongoing to define the strategy for a future clinical trial.

Molecules that have neuroprotective properties

This approach aims to protect motor neurons, nerve cells that control muscle movement, by restoring their function and preventing their death. It does not tackle the underlying genetic cause of SMA but it could be used in combination with such therapeutic approaches. There are currently two clinical trials that are testing two such compounds:

- Olesoxime (Trophos now Roche)

A phase II clinical trial was conducted in 165 people with SMA type 2 and type 3 to test the safety and efficacy of olesoxime. In 2014, Trophos presented the results of the clinical trial at the American Academy of Neurology meeting. The results showed that the loss of motor function was prevented for two years in people treated with olesoxime. A New Drug Application for olesoxime to the US Food and Drug Administration (FDA) and the European Medicine Agency (EMA) are now planned.

- Pyridostigmine Bromide (CHRC)

This phase II clinical trial evaluates the safety and efficacy of Pyridostigmine Bromide on the motor function of people affected by SMA type 3. Pyridostigmine Bromide is an inhibitor of the enzyme acetylcholinesterase. This enzyme breaks down the neurotransmitter acetylcholine. Therefore it is hoped that by inhibiting this enzyme the duration and the action of the neurotransmitter can be increased. This trial is currently recruiting participants in Belgium aged six years and older and who have SMA type 3.
Stem cell therapy

Work by California Stem Cell Inc (now acquired my NeoStem), has shown that transplanting stem cells to mouse models of SMA had moderate beneficial effects. They proposed a clinical trial where stem cells would be injected in the spine of participants with SMA. However this clinical study was put on hold by the FDA. SMA Europe, a body representing the SMA organisations of seven European countries published a letter in April 2013 stating that they do not support stem cell treatment for SMA because the culture conditions and the handling of the cells to be transplanted did not meet the highest standards for therapeutic applications in humans and the treatments did not result in conclusively proven benefits.

The impact of MDUK on SMA research

In the last three years the charity has supported SMA research in the group of Professor Thomas Gillingwater at Edinburgh University. The results obtained from this group are focusing on understanding why some motor neurons are lost in SMA while some others are not. This will provide fundamental biological insights into the mechanisms of SMA as well as identifying critical features that protect some types of neurons from degeneration. Pharmacological or genetic techniques can then be used to reproduce this protective effect in vulnerable motor neurones in people with SMA.

In a second project, Professor Thomas Gillingwater tested whether a very important, but often overlooked, type of cell that supports motor neurons (known as glial cells) contribute to the onset and severity of SMA. This project has improved our understanding of what cell types need to be targeted in order for a new treatment, such as gene therapy approaches currently being developed, to be successful.

Another project we fund is in Professor Matthew Wood’s laboratory at Oxford University where the team are working on an adapted form of exon skipping technology to treat SMA. They are developing short protein fragments, called peptides, to help deliver molecular patches to the brain and spinal cord, eliminating the need for invasive spinal cord injections that are used in current clinical trials. The project will test this potential therapeutic approach in mice with SMA and establish a safe, therapeutic dose. This is necessary before the potential therapy could be tested in clinical trials.

Working with The SMA Trust and SMA Support UK, we helped to establish the SMA Research and Clinical Hub UK (SMA REACH UK). This aims to combine the Patient Registry and SMArtNet Clinical Network UK to establish the first national clinical and research network to promote a national agreement on clinical and physiotherapy assessment and standards of care. The project will design, pilot and expand an electronic database created to streamline the collection of data for patients with SMA. Starting at GOSH and Newcastle, this UK SMA database will be a unique infrastructure which would then be accessible to specialist centres across the UK who treat people with SMA. The database will also be used as a longitudinal data store where information can be audited and reviewed. This will provide clinicians and researchers a rich resource of available information on a large collection of SMA patients.
Summary figure of ongoing clinical trials for SMA

- Olasoxime (Trochos now Roche)
- Valproate, Levocarnitine (AIIMS)
- ISIS-SMNRx (ISIS/Biogen)
- Pyridostigmine Bromide (CHRC)
- LMI070 (Novartis)
- RO6885247 (Roche/PTC/SMAF)
- scAAV9.CD.SMN (AveXis)
- RG3039 (Pfizer)
- AAV mediated gene therapy (Genethon/INSERM)
- Stem cell therapy (CSC now NeoStem)
- Antisense oligonucleotides (RaNA)
- PTK-SMA1 (Paratek)

AIIMS: All India Institute of Medical Sciences; CHRC: Centre Hospitalier Regional de la Citadelle; CSC: California Stem Cells

Clinical Trials:
- Phase I
- Phase II
- Phase III

Early drug development → Lead optimisation → Pre-clinical → Phase I → Phase II → Phase III

- SUSPENDED
- TERMINATED
- ON HOLD