

The SMA Trust Newsletter



UK Researchers' Conference

October 2009, Edinburgh

The Work of the SMA Trust

The sponsorship of research has been our raison d'être since the Trust's inception in 2003. A major research project being led by Dame Professor Kay Davies and Dr Kevin Talbot at Oxford University is the largest project we have undertaken, while other research interests have complemented this and helped young researchers to contribute to the important work being undertaken in SMA (see **Research Funding** below).

SMA Europe

Arguably the most important recent development for the Trust has been our contribution to SMA Europe, which was formed in 2006 to bring together patient groups from across the continent.

SMA Europe Call for Projects

The first SMA Europe Call for Projects, which took place in 2008, resulted in six new international SMA research projects being undertaken across Europe and the US this year, with total funding in excess of €750,000. The Trust provided over 40% of this funding.

SMA Europe membership

1. *Asociació Catalana de Enfermetats Neuromusculars* (ASEM Catalunya) and *Fundame* – **Spain**
2. *Association Française contre les Myopathies* (AFM) – **France**
3. *Deutsche Gesellschaft fuer Muskelkranke/Initiative SMA* (DGM) – **Germany**
4. *Famiglie SMA* – **Italy**
5. *Vereniging Spierziekten Nederland* (VSN) – The Netherlands
6. *The Jennifer Trust for SMA* – **UK**
6. *The SMA Trust* – **UK**

We are pleased to welcome two of the grant recipients, Dr Magarida Gama Carvalho from The University of Lisbon, and Professor Eugenio Mercuri from Università Cattolica, Rome to talk about their projects at this Conference.

The success of the first Call for Projects has been quickly followed by a second. The 2009 European Call is currently under way with an increased European contribution leveraged by our Trust's leading input.

The added value that the European Call process brings to the SMA research effort is significant, and includes:

- *a structured route to funding is now available to the research community;*
- *financial efficiency is achieved through pooled funds and administration;*
- *selection and monitoring of projects is administered by a Scientific Advisory Board, which includes some of the best international experts on neuromuscular diseases. No single institution can provide a service at this level;*
- *the applications provide valuable information to the SMA community on what areas of are being undertaken by each research team or centre.*
- *SMA Europe facilitates and encourages research institutions to collaborate internationally.*

Other News from the SMA Trust

European Medicines Evaluation Agency (EMA) London Meeting

An important event for all involved in SMA took place on October 13th 2008. Over a hundred members of the SMA community in Europe and the US came to London for the "Workshop on Clinical Outcome Measures and endpoints for efficacy assessment in SMA". This gathering was hosted with the EMA. It was a milestone meeting – the first time SMA had engaged with the European authorities with a view to

running important clinical trials. The EMA was complimentary about the co-ordination of the SMA community.




The SMA Trust hosted a dinner that evening to gather together many of the international representatives to review the meeting, with Cynthia Joyce of the New York based SMA Foundation, as key guest.

Working with the Research Community

Over the past two years, promoting good connections between research institutions involved with SMA and related diseases has been an important part of our activities. We also wanted to have a presence at some of the most important conferences on SMA to keep in touch with current ideas. Thirdly we wanted to get closer to the research community in the UK, and learn from it how best to promote and support meaningful research. Many of you will have met Jess O'Hagen, a young SMA physio from Columbia University who undertook visits to UK institutions on our behalf. Everyone was welcoming and informative, and the result has been increased awareness of the work being undertaken and better communication over all.

The Trustees would like to take this opportunity to thank all those who spent time with Jess on her visits, which are listed below.

SMA Trust visits to research institutions and companies 2008

Institute or Company	To meet:	Date:	Primary Visit Subject	Current Funding
Trophos SA Biotech company specialising in the development of drugs for neurological disorders	Stephen Harris	25 th April 2008	TRO19622: investigating safety, dosing parameters and proof of concept	AFM <i>(French SMA organization)</i>
Exeter University	Debra Shaw and Dr Phil Young	7 th May 2008	Investigation into SMN 2,3,6 proteins	
King's College London	Professor Stephen Minger	22 nd May 2008	Stem cells to create model of SMA-study of pathogenesis	Seeking MRC Funds
Sheffield University	Professor Mimoun Azzouz	11 th June 2008	Viral Vectoring for gene therapy	JT SMA and 
Harvard Stem Cell Institute	Professor Lee Rubin	19 th June 2008	Stem cells for therapeutic testing	<i>(HSCI)</i>
Oxford University	Sarah Boddy Professor David Sattelle	25 th June 2008	RNAi model of SMA	
Royal Holloway	Dr Rafael Yáñez	26 th June 2008	Integration deficient lentivirus for SMA	Genoma España
Imperial College	Professor Mazarakis	11 th July 2008	Viral vector gene Therapy	Seeking major funding
Newcastle University and Treat- NMD	Professor Bushby Treat- NMD Team Anna Mayhew Michelle Eagle	29 th July- 1 st August 2008	Clinical "centre of excellence" Neuromuscular network: SmartNet	EU funding Treat-NMD
Summit Plc	John Tinsley	16 th Feb 2009	Current work in the neurological arena	UK biotech company
Edinburgh University	Dr Tom Gillingwater	9 th March 2009	Aims to establish a motor neuron centre to foster collaboration across disciplines.	Neurological research centre

The SMA Trust Research Funding

Current and recent projects

Oxford University

1. Professor Dame Kay Davies, FRS, and Dr Kevin Talbot

“Motor neuron disorders research into SMA”

This is the largest of the Trust’s commitments: £437,000 over three years (2007-2009).

A concept guiding the team is that SMA is a developmental disease, implying that the abnormalities to the nervous system start to develop in very early life. This means that the earlier a diagnosis can be made the greater the chances of success for the treatments we all hope will soon become available.

In a collaboration with workers in Edinburgh the Oxford team has shown, in an animal model of SMA, that very early lesions occur at the point where the motor nerve joins the muscle. Some groups of muscles appear to be more vulnerable to this disruption at the motor end plate than others. The study also raises the possibility that SMN (the gene product that is lacking in the disease) may have a muscle-specific role as well as its well established neuron-specific activity.

SMA is a disease of motor neurons in the spinal cord; motor neuron disease (also called ALS: amyotrophic lateral sclerosis) is a

disease of motor neurons in both the cord and the brain. However, they are both diseases of motor neurons and there may be common pathological mechanisms at work. The Oxford team has shown for the first time that there may be an interaction between the SMN gene and the gene (SOD1) that causes one form of inherited ALS. Reducing the level of SMN in mice carrying a mutation of the SOD1 gene leads to a more rapid degeneration of their motor neurons and to reduced survival. Work supported by the Motor Neuron Disease Association (MNDA) is now underway to see if increasing SMN levels in these mice will slow disease progression. A positive result in this experiment could have the important consequence that increasing SMN levels may be a potential treatment for ALS, a much commoner disease, as well as for SMA.

Further studies have identified proteins in nerve cells which interact specifically with SMN. This is likely to help our understanding of the specific requirement of motor neurons for SMN which is not shared by other cells.

The aim of this wide-ranging programme is to help develop treatments for SMA and to solve a remaining mystery – the precise function of the “survival motor neuron” (SMN) protein.

2. A further grant will be made to support research supervised by Kay Davies and Kevin Talbot in autumn 2009

"Identification of the critical time point for SMN replacement therapy using a tetracycline repressible SMN transgenic mouse model."

3. Dr Sarah Boddy

A grant of £21,625 for six months was made in 2008, to support Sarah Boddy to extend her research after studies for a D.Phil. The research was carried out in the Department of Physiology, Anatomy and Genetics (alongside our major project at Oxford). The research work was supervised by Dr Kevin Talbot, Professor David B Sattelle, and Dr Matthew Wood.

"Development and application of an RNA interference-based system for modelling Spinal Muscular Atrophy in mouse cells"

Normal cells have been found that contain short RNA molecules which will combine with long RNAs and target them for destruction. The normal function of these small interfering RNAs (siRNA) is not altogether clear but they may provide a defence against invading viruses. A gene instructs the synthesis of a particular protein by first making a messenger RNA which is then translated into the protein. The phenomenon of RNA interference has been exploited experimentally to disrupt the synthesis of proteins by targeting

messenger RNAs before they can be translated.

Sarah Boddy has made a series of siRNAs which have enabled her to disrupt the production of SMN to varying degrees in cultures of cells *in vitro*. This has provided a cellular model of SMA in which the precise consequences of SMN knockdown can be observed. Different degrees of knockdown, unexpectedly, did not always lead to the same pattern of biochemical changes. This is interesting because such biochemical variations may possibly be mirrored in the varying severity of the human disease which, in turn, is already known to be due to variations in the amount of SMN produced. Importantly, it is planned to repeat this work in a cell line of nerve cells in which the consequences of knockdown and of overexpression of SMN will be observed.

Again, these experiments aim to illuminate the function of SMN and to reveal, in detail, the precise biochemical consequences of its loss from the cell.

Exeter University

Dr Debra Shaw, supervised by Dr Philip Young. A one year grant (2008/09) of £47,984 was made to enable Dr Shaw to complete her study at the Peninsula Medical School.

"Characterisation of the SMN_{2,3,6} protein: is a minimal SMN protein functionally possible?"

A complex structure called the "spliceosome" edits the primary RNA transcript produced from a gene by cutting it at defined sites. This allows unwanted fragments (derived from DNA sequences called "introns" to be discarded while the remaining fragments (derived from DNA sequences called "exons") combine to form the messenger RNA which is translated into protein. The SMN gene consists of 9 exons.

SMN is one component of the spliceosome and binds to another of its components in the early stages of its assembly in the cell. Debra Shaw set out to determine whether all nine exons of SMN were necessary for this crucial, early binding step. She found that only exons 2,3 and 6 appeared to be necessary, implying that this small construct may be functionally equivalent to the complete SMN molecule. The definitive functional test will be to determine whether this minimal SMN protein will, in fact, rescue an animal lacking the SMN gene. This test in an animal model of SMA is now being carried out.

Further funding was granted in summer 2009 for Debra to follow up on findings resulting from this project.

A second project at Exeter, with the same team, started in August 2009 entitled **"Identification of RNA cargo transported by SMN in neuronal cells"**

Sheffield University

A grant of £18,194 was made to the Jennifer Trust to support Professor Mimoun Azzouz in the second year of this two year project.

"Viral vector-mediated SMN replacement in SMA"

SMA is due to the loss of function, by mutation or deletion, of the SMN1 gene. An obvious strategy would be to make good this loss by gene therapy. Inserting a normal SMN gene into the DNA of a patient or an experimental animal requires attaching a "vector" to the replacement gene. Certain viruses will enter the nucleus of a cell and integrate with its DNA. This property is exploited in the use of virus-SMN complexes to carry the SMN gene into the defective DNA.

Professor Azzouz has already had a small but encouraging therapeutic success by injecting a virus-SMN complex into an animal model of SMA and plans to study other viral vectors in the hope of significantly improving the effectiveness of the treatment.

Gene therapy has been shown to be a potentially hazardous procedure in human patients but it holds promise for the future in the treatment of single gene defects, of which SMA is an example.

Grants made as part of SMA Europe

In 2008-09, the SMA Trust gave approximately €330,700 to SMA Europe to support research at the centres described below. A further €300,000 is pledged for 2009-10.

1. University of Lisbon:

Fundação da Faculdade de Ciências de Lisboa

SMA Trust in partnership with Deutsche Gesellschaft fuer Muskelranke (DGM)

Grant totalling €85,760, made to Dr Margarida Gama Carvalho for her research project "*Characterisation of post-transcriptional control mechanisms regulating SMN2 gene expression.*"

The work started on 01.03.2009 and is due for completion on 30.04.2011.

2. University of Missouri:

Research Laboratory Christopher S. Bond Life Sciences

SMA Trust scholarship grant of \$100,000 made to Dr Monir Shababi for her research project: "*A Two-Pronged Approach to Develop a Treatment for Spinal Muscular Atrophy.*"

The work started on 01.04.2009 and is due for completion on 31.03.2011.

3. University of Milan:

Department of Neurological Sciences SMA Trust in partnership with Families of SMA (USA) and Fundame (Spain)

Grant of €120,000 made to Dr Giacomo Comi for his research project, "*Development of therapeutic strategies based on stem cell transplantation for Spinal Muscular Atrophy*"

4. Università Cattolica Roma,

Paediatric Neurology Unit

SMA Trust in partnership with Famiglie SMA (Italy)

Grant of €276,000 made to Professor Eugenio Mercuri for his research project "*Outcome measures in SMA type II and III.*"

5. Paratek Pharmaceuticals

SMA Trust in partnership with FSMA (USA)

Grant of \$100,000 made to Dr Paul Higgins for his research project "*Tetracycline Compounds as SMN2 Splicing Modifiers for the Treatment of SMA*"

Support grant history

Jennifer Trust at Hammersmith Hospital, London

In 2007 a grant was made in support of the JTSMA for Professor Francesco Muntoni's drugs protocol research, entitled "*Establishing a UK Clinical Network to Monitor Strength and Functional Measurements in Spinal Muscular Atrophy*".

Jennifer Trust at Oxford University

Grants were made between 2004 and 2006 in support of The JTSMA's sponsorship of a Research Fellowship at Oxford: "*Molecular Analysis of Families with Spinal Muscular Atrophy*". The research work was carried out under the supervision of Professor Kay Davies and Dr Kevin Talbot.

Families of SMA and deCODE Genetics

A grant was made in 2005 to Families of SMA in the USA to support its sponsorship of a project in association with deCODE Genetics. *The deCode Project's* primary aim was to develop a drug for clinical trials.

The SMA Foundation and the Medical Research Council

A contribution was made in 2006 towards an MRC study in association with the SMA Foundation (USA)

The SMA Trust, Compton Scorpion, Shipston on Stour, Warwickshire

Charity No: 1097765

Tel: 07794 012344

www.smatrust.org

info@smatrust.org

Trustees: Sir James Gowans CBE FRS, Andrew Knight, Casimir Knight,
Marita Crawley, Hugo Pickering

General Manager: Karen Elder

Tel 01608 661180