



## Committed to Defeating Motor Neurone Disease through Innovative Fundamental Research

NEWSLETTER no. 1, SUMMER 2011

### A WORD FROM THE DIRECTOR

Professor Siddharthan Chandran

The Euan MacDonald Centre for Motor Neurone Disease Research was officially opened in June 2007. The Centre has made significant progress over the past four years. There are many examples of success particularly around adding important new areas of research to complement established and thriving activities in basic motor nerve - muscle laboratory research.

Three examples of new research programmes include:

- (1) Studies on human stem cells including from patients with rare inherited causes of MND, supported by the MNDA;
- (2) Re-establishment of the National MND Register, supported by MND Scotland;
- (3) Voice project where we are trying to improve speech communication devices to deliver speech output that is far closer to that of the patients' own.

The Centre now also has a critical mass of clinical and laboratory research sufficient to support clinical trials based in the new Anne Rowling clinic that we expect to be open in the second half of 2012. All of these different projects ranging from basic to clinical are united in a common purpose around the core mission of the Centre to undertake research to make a difference to patients living with MND.

### BASH AT THE BREWERY 2

The second EMC "Bash at the Brewery" was held on 12th May 2011, to celebrate the recent successes of the Centre. Over 70 guests attended, including the MacDonald family, researchers and staff, and donors and supporters.

This enjoyable event provided an opportunity to hear Siddharthan Chandran and Donald MacDonald speak eloquently about the achievements of the Centre and future aims and challenges, and for the researchers and supporters to mingle and share ideas.



Above, Siddharthan gets the party started. Above right, The Princess Royal listens to presentations from Sharon Abrahams, and Catherina Becker and Tatyana Dias (far right).



### ROYAL VISIT TO THE EMC

HRH The Princess Royal visited the EMC on April 19th 2011, in her capacity as the Royal Patron of the Motor Neurone Disease Association.

The Princess Royal toured the EMC labs and met researchers who are funded by the MND Association, Euan MacDonald and a number of other people living with MND.



The MND Association has funded an international MND stem cell research programme. This collaboration between the EMC, King's College, London and Columbia University, New York aims to manipulate stem cells to provide a unique tool to study MND, with the aim of developing new drugs.

Images courtesy of the MNDA and Douglas Robertson photography.



## RESEARCH NEWS

Below are a few of the highlights among the many papers published recently by EMC Principal Investigators.

The response of neuromuscular junctions to injury is developmentally regulated. Murray LM, Comley LH, Gillingwater TH, Parson SH. FASEB J. 2011 Apr;25(4):1306-13. Epub Jan 12.

Here, Simon Parson, Tom Gillingwater and colleagues studied the role of development in regulating the vulnerability of mouse neuromuscular junctions to two degenerative insults: hypoxia and peripheral nerve injury. They demonstrated that neuromuscular junctions in neonatal mice were significantly more resistant to injury than those in adult mice, in terms of retaining their structural and functional integrity. Interestingly, newly formed synapses in adult mice did not show this resistance, indicating that the resistance is not determined by the maturity of the synapse per se, but by the neonatal environment and/or the age of the neuron.

This work was supported in part by a seedcorn grant generously funded by the RS Macdonald Charitable Trust.

Activation of group I metabotropic glutamate receptors modulates locomotor-related motoneuron output in mice. Iwagaki N, Miles GB. J Neurophysiol. 2011 May;105(5):2108-20. Epub Feb 23.

Gareth Miles is a partner PI of the EMC from the University of St Andrews. In this paper, he and a co-worker investigated the effect of metabotropic glutamate receptors (mGluRs) on the locomotor-related output of motor neurons in isolated mouse spinal cord preparations.

They found that activating type I mGluRs inhibited motor neuron output, possibly providing negative feedback control to modulate the intensity of motor neuron output during locomotion.

### FEATURED RESEARCHER

Catherina Becker



Mammals, including humans, cannot replace motor neurons lost through injury or disease. The laboratory led by Catherina and Thomas Becker has found that adult zebrafish can regenerate motor neurons from progenitor cells that reside in their spinal cords. Catherina and Thomas are now using the fish for compound screens to find drugs that can stimulate such progenitor cells to produce more motor neurons. In collaboration with Siddharthan Chandran, they are then testing these drugs in human embryonic stem cell-derived neural stem cell cultures for their potential to promote generation of human motor neurons. They are continuing to investigate the molecular and cellular mechanisms of successful spinal cord repair.

*Catherina is a Reader in Neurobiology at the Chancellor's Building, Little France.*

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The ALS8-associated mutant VAPB(P56S) is resistant to proteolysis in neurons. Gkogkas C, Wardrop C, Hannah M, Skehel P. J Neurochem. 2011 Apr; 117 (2):286-94. Epub Feb 24.

The VAPB protein is mutated in a rare, dominantly inherited form of MND, ALS8. Here, Paul Skehel and colleagues demonstrated that proteolytic cleavage of VAPB occurs only in neurons and that the C-terminal cleaved fragment displays a subcellular distribution different from that of the full-length protein, implying that it may have a distinct function. The ALS8-mutated form of VAPB is resistant to this proteolysis; therefore, reduced levels of the cleaved fragment of VAPB may be involved in neurodegeneration in ALS8.

Retinoid-independent motor neurogenesis from human embryonic stem cells reveals a medial columnar ground state. Patani R, Hollins AJ, Wishart TM, Puddifoot CA, Alvarez S, de Lera AR, Wyllie DJ, Compston DA, Pedersen RA, Gillingwater TH, Hardingham GE, Allen ND, Chandran S. Nat Commun. 2011;2:214.

Siddharthan Chandran, along with Giles Hardingham and Tom Gillingwater and their colleagues, demonstrated that functional motor neurons could be generated from human embryonic stem cells, independently of retinoic acid signalling. This paper describes a small molecule "recipe" for the accelerated specification of motor neurons biased towards a caudal, medial subtype. The derived motor neurons could fire action potentials, established synaptic connectivity and expressed an array of neurotransmitter receptors. This ability provides a significant step towards the generation of accurate, clinically-relevant disease models.

Deficits in emotional and social cognition in amyotrophic lateral sclerosis. Girardi A, Macpherson SE, Abrahams S. *Neuropsychology*. 2011 Jan;25(1):53-65.

In this paper, Sharon Abrahams and co-workers tested volunteers with a battery of cognitive tasks to investigate whether ALS patients display deficits in emotional decision-making and social cognition. They found significant deficits in social, emotional and

cognitive functions that were independent of executive functions and were indicative of subclinical frontal variant frontotemporal dementia.

Pituitary adenylate cyclase-activating peptide (PACAP) induces long-lasting neuro-protection through the induction of activity-dependent signaling via the cAMP response element-binding protein (CREB) -regulated transcription coactivator 1 (CRTC1). Baxter PS, Martel MA, McMahon A, Kind PC,

Hardingham GE. *J Neurochem*. 2011 May 28. [Epub ahead of print].

Giles Hardingham and colleagues investigated the mechanism of neuroprotection by the peptide PACAP. Treating cortical neurons with PACAP increased action potential firing and protected the cells from apoptosis. Increased action potential firing induced calcineurin signalling, which in turn induced nuclear import of CRTC1 and the activation of CREB-mediated gene expression.

## A NEW MEMBER OF THE TEAM



Shuna Colville

Shuna Colville, a research nurse and clinical specialist, joined the EMC as the MND research nurse last year.

Shuna is the co-ordinator of the Scottish Motor Neurone Disease Audit, Research and Trials (SMART) project. SMART aims to audit the service provision for all people with MND in Scotland, providing a baseline against which to measure the recently published standards of care. This should improve the standards of care for people with MND and provide a more uniform service throughout Scotland.

The Audit will enable us to capture the geographic spread and the number of people with MND, all of which is essential in planning future service provision.

Supported by MND Scotland, the team is also re-establishing the Scottish MND Register; this valuable database will keep people informed of new research projects and clinical trials as they come along. Current research projects include the MND DNA Bank and the Lothian-based Neurological Voice Bank (more about this soon!).

[www.smart-mnd.org](http://www.smart-mnd.org)

## THE NEW-LOOK EMC WEBSITE

[www.euanmacdonaldcentre.com](http://www.euanmacdonaldcentre.com)

The EMC website was brought in-house and revamped at the end of 2010, and has since been regularly updated with news and featured publications.

Since Jan 1<sup>st</sup> 2011, we have had 6236 visits from 3867 unique visitors viewing 21260 pages. Unsurprisingly the Home page was visited the most frequently, followed by the News & Events, Siddharthan Chandran's profile, Research and About Us.

The 6236 visits came from 76 countries. After the UK, most of the



visitors came from the USA, Germany, India, Italy and Canada. On average, each visitor looked at 3.5 pages, spending almost three minutes on the site.

*Above, Number of visitors to the EMC website since Jan 1<sup>st</sup> 2011. Each peak and trough represents one week. Could the peak in mid-May be due to the Royal visit?*

*Below left, geographic spread of visitors to the EMC website since Jan 1<sup>st</sup> 2011.*



We hope that you have enjoyed this new newsletter. We will aim to publish this quarterly; if you have anything you would like to be included in the next issue please contact [Rebecca.Devon@ed.ac.uk](mailto:Rebecca.Devon@ed.ac.uk) before the end of August.

For general enquiries: [EMC\\_admin@ed.ac.uk](mailto:EMC_admin@ed.ac.uk). For information on giving and press enquiries: [edinburghcampaign@ed.ac.uk](mailto:edinburghcampaign@ed.ac.uk)

All charitable activities for the Centre are administered by The University Development Trust, registered charity no. SC004307.

## SUPPORTERS' NEWS

### THREE PEAKS CHALLENGE

Saturday 21st & Sunday 22nd May

Huge congratulations to Calley Kempson, Drew Craig, Emma Dresner, Kiki MacDonald and Paul Main for taking on the Three Peaks 24-hour mountain challenge. Widely regarded as one of the UK's most challenging events, it provides participants with the ultimate test of physical and mental stamina.



The team started their gruelling challenge on Saturday at 0846 at the foot of Ben Nevis, braving the wind and rain to reach the summit at 1200 noon. The journey down was also tough due to the terrible weather conditions, but happily everyone was safely off the mountain by 1446 on Saturday afternoon.

A thoroughly wet team then headed south to tackle Scafell Pike. Arriving at 2100 on Saturday evening to yet more driving rain and wind they started their ascent in horrible weather. As the weather conditions at Scafell deteriorated enough to threaten the health and safety of the team, the climb was abandoned only 250m short of the summit. More importantly though, the five participants got safely off the mountain at 0130 on Sunday morning, albeit soaked to the skin and with morale at a bit of a low!

Only Drew, Paul and Kiki felt they could take on the final leg of the challenge, with the three taking on Snowdon at 0630 on Sunday morning. Setting off into more high winds and rain Drew, Paul and Kiki reached the summit of Snowdon at 0900.



At 1131 on Sunday morning three exhausted and weather beaten climbers arrived at the bottom of their final mountain in an overall time of 26 hours and 45 minutes.



The team hoped to summit the three peaks in 24 hours; however given the horrendous weather conditions this was an exceptional team performance. Calley Kempson, Drew Craig, Emma Dresner, Kiki MacDonald and Paul Main all deserve huge congratulations for taking part in this incredible challenge.

Thank you so much to everyone who has already donated. To date the team has raised nearly £9,000.

<https://edinburghuni.workwithus.org/fundraising/Donate.aspx?page=6451>

*Far left, The starting line-up: Drew, Emma, Calley, Kiki and Paul; left, Drew, Emma and Paul at the top of Ben Nevis; above, Kiki and Paul at the summit of Snowdon.*

### BALLATER CHIELS TEXAS SCRAMBLE

Friday 10th June

This year's Ballater Texas Scramble Golf Charity Day will see approximately 70 teams competing for the Sandy Barclay Memorial Jug. This year marks the 10th anniversary of fundraising the local community and generously contributing to the EMC.

The day starts bright and early with the first players teeing off at 7am and the last revellers seeing in the wee small hours of Saturday morning! As well as golf, there's also lots of fun, food and fundraising. Players returning to the clubhouse will be refreshed by a wee dram before enjoying a buffet followed by a raffle and auction.

We hope that the sun shines for this wonderful event and look forward to reporting on how the day goes.

visit <https://edinburghuni.workwithus.org/Fundraising/Donate.aspx?page=6466> or email Paul Main at [thestroober@yahoo.co.uk](mailto:thestroober@yahoo.co.uk)

For general enquiries: [EMC\\_admin@ed.ac.uk](mailto:EMC_admin@ed.ac.uk). For information on giving and press enquiries: [edinburghcampaign@ed.ac.uk](mailto:edinburghcampaign@ed.ac.uk)

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