

EDITOR'S CHOICE

Stem cells become front page news again! Why?

One of the most sought after solutions in medicine is the development of an ethically neutral, readily available and reliable source of cells by which repair could be effected by their use, and disease pathogenesis possibly studied by growing them in the lab. To date, the big problems have either been difficult ethical and theological issues associated with pluripotential embryonic stem (ES) cells derived from blastocysts from IVF programmes or the limited capacity to generate sufficient numbers of appropriate cells with other ethically more acceptable cells such as adult stem cells from bone marrow or brain. It is therefore of great interest that two groups have independently generated embryonic stem like cells with all their attendant pluripotentiality using reprogrammed skin fibroblasts – papers that have spurred numerous reports in the newspaper and scientific journals alike. These two papers in *Cell* and *Science* have both shown that adult human fibroblasts can be transduced with four factors to make pluripotent stem cells. Takahashi et al found that Oct4, Sox2, Klf4 and c-Myc were needed to produce pluripotential ES like cells which show all the characteristics of true embryonic stem cells in terms of their behaviour in culture, profile of molecular markers using gene arrays and behaviour in vivo. In contrast Yu et al used Oct4, Sox2, Nanog and Lin28 to produce similar results. These are exciting findings because if they can be refined to avoid the need for viral vectors (and especially the risk of tumours with the c-myc transfection), then one truly has the potential to repair damaged systems, including brains, in patients using their own cells. In addition, one could start to study disease pathogenesis in these individuals using these very same cells to model disease. Of course this work is predicated on the grounds that:

1. Cell repair therapies work and that any such human induced pluripotential stem cells (iPS) are not going to be affected by the same disease process in the short term whilst also allowing
2. The cells to accurately reflect disease states which have wider relevance to the modelling of disease beyond that of the individual affected by it.

Nevertheless the capacity to generate iPS cells using human fibroblasts is a tour de force although what the moral status of such a cell is in terms of its potentiality for human life is still debatable. Indeed the ethics of embryonic stem cell research will continue to vex many working in the field at the same time as the scientific advances take us into the realm of therapeutic reality. – **RAB**

Yu J, Vodyanik MA, Smuga-Otto K et al.

Induced pluripotent stem cell lines derived from human somatic cells.

SCIENCE

2007;318:1917-20.

Takahashi K, Tanabe K, Ohnuki M et al.

Induction of pluripotent stem cells from adult human fibroblasts by defined factors.

CELL

2007 131(5):861-72.

BRAIN REPAIR

The relationship between injury and repair in the brain is complicated. Take, for example, the bizarre observation that regeneration of retinal ganglion cells following an optic nerve crush injury can be improved by injuring the lens of the eye. (Who said two wrongs don't make a right?) The standard thinking had been that the lens injury attracted macrophages into the eye, which went on to secrete neurotrophic factors, specifically the rather grandly-named oncomodulin. In the latest issue of *Brain*, a team from Ulm, Germany, show otherwise. They injured the optic nerve and lenses of rats and then, five days later, dissected out the retina to study retinal cell behaviour in culture. Their first discovery was that lens injury upregulated the neurotrophin CNTF in the retina; and, secondly, that this was not in macrophages but in retinal astrocytes. They went on to show that the same CNTF secretion could be induced in uninjured retinas by

the application of lens proteins; in other words, that CNTF release was not just due to injury or an inflammatory response. This is intriguing: perhaps astrocytes recognise lens proteins through Toll-like receptors, or other innate immunity mechanisms? Antibodies to CNTF (but not anti-oncomodulin) blocked the regeneration of retinal ganglion cells induced by lens injury. And, crucially, dibutyryl-cAMP (which raises intraocular cAMP) amplified this regeneration. So, is the implication that everyone with an optic nerve injury should have a scalpel through their lens? Perhaps not. But there are real implications for treatment: the CNTF-production facility of astrocytes could be exploited to promote optic nerve repair by applying non-toxic lens proteins and drugs to boost cAMP. Given that this might be the difference between useful sight and not, this is no small discovery. – **AJC**

Müller A, Hauk TG, Fischer D.

Astrocyte-derived CNTF switches mature RGCs to a regenerative state following inflammatory stimulation.

BRAIN

2007 Dec;130(Pt 12):3308-20.

NEUROLOGY JOURNALS: Oooops!

It is rare to get frank self-criticism in the editorial of a journal. But Stephen Hauser has gone out of his way to apologise for a press-release from the *Annals of Neurology*. This all arose because of a growing feeling that epidemiological research gets too much, or inappropriate, press attention. So Hauser set up a little internal research to decide how the *Annals* promoted such research. In 2006, 84 of the 280 published manuscripts were epidemiological. Five of the 20 top-cited publications were epidemiological. And, of the 7 press releases for 2006, six were epidemiological. So, it does seem they are giving disproportionate attention to this sort of research. And, when they reviewed their press release for one of these studies [Scarmeas N et al *Mediterranean diet and risk for Alzheimer's disease Ann Neurol* 2006 Jun;59(6):912-21], they felt the journal had to take some of the blame for media distortions of the investigators' careful conclusions. Surely, never a problem for *ACNR*! – **AJC**

Johnston SC, Hauser SL.

Epidemiology in the Annals: part of the problem or the solution?

ANNALS OF NEUROLOGY

2007;62(4):A8-9.

EPILEPSY: Moving from epilepsy treatment to prevention

There are certain lesions which we know have a high risk of being complicated by epilepsy: major cerebral trauma, parenchymal CNS infection and intracerebral haemorrhage. So far all we can do is to wait and see if seizures occur and then treat them as best we can. How much better to identify those patients in whom epileptogenesis is taking place and treating them with drugs to abort the process. In this study, rats were given a lateral fluid-percussion brain injury, the laboratory rodent equivalent of assault with a baseball bat. They then had repeated MRI scans from hours after injury up to one year. All animals, whether having suffered traumatic brain injury or not, were exposed for just one hour to the epileptogenic agent pentylenetetrazole (PTZ) at one year after injury, using previously recognised subconvulsant doses and then underwent video-EEG-telemetry. At the end of this process, their brains were examined for mossy fibre reorganisation in the hippocampus, a common marker of epileptogenesis. The injury on its own was not enough to produce epileptic activity in any of the control animals but subconvulsant doses of PTZ caused electrographic abnormalities in all animals, controls and injured. There was no association between MRI evidence of cortical damage and the increased seizure susceptibility. The latency to onset of spikes was significantly shorter, and the number of spikes and epileptiform discharges significantly greater, in animals with traumatic brain injury. MRI showed an early (hours) fall in diffusion tensor signal from the ipsilateral hippocampus of injured animals and which then rose progressively compared to control animals, peaking at three months. T2 weighted signal in the ipsilateral hippocampus rose compared to controls progressively from about 3 months. Injured animals had mossy fibre sprouting into the inner molecular layer of the hippocampus and this was positively correlated with EEG measures of seizure susceptibility. This study identifies changes which may be markers of evolving seizure susceptibility. The questions to be addressed include their applicability to humans and whether any treat-

ments can influence this development and help to prevent late post-traumatic seizures, rather than simply trying to treat them (regrettably often unsuccessfully) after they have started. – *MRAM*

Kharatishvili, Immonen R, Grohn O, Pitkanen A.

Quantitative diffusion MRI of hippocampus as a surrogate marker for post-traumatic epileptogenesis.

BRAIN

2007;130:3155-68.

BRAIN INJURY: Trauma, drugs and alcohol

Because of the circumstances in which traumatic brain injuries are sustained, issues around drugs and alcohol often emerge during a patient's rehabilitation. This study looks at drug and alcohol use pre- and post-traumatic brain injury in an attempt to establish factors associated with heavy post-injury substance abuse. The basic method involved patients recalling (which is surely a problem in the brain-injured population) their pre-morbid levels of usage, and then re-assessing them at 1 and 2 years post-injury. There are no differences in baseline (pre-morbid) levels of substance use between patients and demographically matched controls. Perhaps, not surprisingly, the authors show that young, male, heavy drinkers are most likely to return to alcohol. Drug and alcohol use tends to diminish at 1 year but rises to levels approaching pre-morbid use at 2 years. What was encouraging, but somewhat understated in the discussion, was that very few people actually increased their drug and alcohol consumption following a brain injury. From this the authors conclude that there is a need for more active intervention to reduce alcohol and drug use following brain injury. While, as a principle, this would seem admirable, it would be interesting to see research demonstrating the effectiveness of such an intervention in this population. It is also, perhaps, worth considering if it is not overly paternalistic to try and modify peoples' lifetime basic behaviours and attitudes just because they happen to have had a brain injury. The social environment is a strong factor in guiding attitudes to recreational substances, generally, and it is interesting that the authors highlight the advice given in the States to completely abstain from alcohol permanently following a head injury conflicts with that given in Australia, where patients are advised that a return to drinking after a year has passed is permissible. – *LB*

Ponsford J, Whelan-Goodinson R, Bahar-Fuchs A.

Alcohol and drug use following traumatic brain injury – a prospective study.

BRAIN INJURY

2007;21:1385-92.

HEADACHE: Migraine and sinuses

*** RECOMMENDED

We all meet patients who vehemently deny migraine but have regular "sinus" headaches. Sometimes these even get worse perimenstrually, and often have other migrainous features. So this article is interesting. It examined the rate of radiological sinus disease in migraineurs and those with "sinus headache". It is a step in untangling the knot of people with migraine and sinus changes, a step towards getting them onto the right treatment. The impetus for the study is that previous work suggests that most patients with "sinus headache" fulfil the International Headache Society (IHS) criteria for migraine. This makes it difficult to know what is causing their symptoms. There are few studies on this question, and on whether CT scan findings distinguish the groups. Thirty-five patients presenting with sinus headache were prospectively scanned for sinus disease. Using validated methodology (Lund-Mackay score, [L-M score]), these scans were assessed for sinus abnormalities. A control group of migraineurs had their scans analysed in the same way. Of the sinus headache group, 74 % had migraine by IHS criteria. There was no difference in CT scan L-M scores between the two groups (2.07 in the migraine group and 2.66 in the "sinus" cohort). Five of the migraine group had significant sinus disease radiologically. The authors conclude that the majority of "sinus headache" patients satisfy IHS criteria for migraine, and are surprised that many of these have sinus disease radiologically. Because a number of migraine patients also have sinus disease they suggest we should be looking harder for sinus disease in migraineurs. I would view the situation somewhat differently. This small but useful study shows that radiological findings don't correlate well with the clinical diagnosis. There are false positives and negatives, and further it's hard to estimate the level of incidental sinus disease in the background population. This adds to the need for caution in interpretation of radiological changes of sinus disease. The

distinction between migraine and sinus headache is sometimes opaque, and radiological disease is not enough to diagnose causality. As its not always the cause of the symptoms, we need to remain careful to avoid sending the wrong patients down medical and surgical sinus treatment paths, when what they need is good migraine prophylaxis. – *HAL*

Mehle ME, Kremer PS.

Sinus CT findings in "sinus headache" migraineurs.

HEADACHE

2008;48:67-71.

HEADACHE: Migraine incidence

There is little definitive data on the incidence of migraine in the community. This study quantified incidence and comorbidity in a large cohort using the General Practice Research Database. 51,688 patients with a first time diagnosis of migraine were found, between 1994 and 2001. The migraine incidence rate was 3.69% cases per 1000 person-years and was 2.5 times more common in women. Compared to age-matched controls, most common chronic diseases were slightly more prevalent in migraineurs. Patients using triptans had higher health care utilization than other migraineurs. Possibly these patients were those who developed chronic daily and analgesia overuse headaches. However, this finding is open to so many interpretations that it is hard to draw any definite conclusions from it. The study provides solid incidence data on the most common neurological ailment we see. – *HAL*

Becker C, Brobert GP, Almqvist PM, Johansson S, Jick SS, Meier CR.

Migraine incidence, comorbidity and health resource utilization in the UK.

CEPHALGIA

2008;28:57-64.

EPILEPSY: Does your mother's epilepsy or education matter most?

The authors assessed 71 children of mothers with epilepsy (CME), identified prospectively from an epilepsy and pregnancy register. The children underwent an Indian adaptation of the Wechsler IQ test and a specially designed language test in the local Malayalam language at around the age of six and were compared to controls, matched for age and educational status. They developed a score for AED exposure, comprising tenths of a standard daily dose (each tenth scored ten points) of each drug and this allowed them to have a measure of total drug load, independent of which drug was being taken, as well as looking at different AED and monotherapy versus polytherapy. Their mothers had mild epilepsy compared to a standard neurology outpatient cohort, with over half having either no seizures or just one seizure during their pregnancy.

The mean FSIQ of CME was 87.7 compared to 93 (P=0.02) for controls. There was an especially dramatic difference in language function between the two groups. In a multiple regression analysis, the strongest predictor of IQ was maternal education, with medication having a weaker association and seizure type or severity no association at all. There was no difference between monotherapy and polytherapy, but numbers were small. For 50 CME exposed to an AED score <90, mean FSIQ was 94.6 (SD 13.4) and mean language score 77.3 (SD 13.9) compared to FSIQ 71.3 (SD 30.8) and language score 64.1 (SD 21.3) for children exposed to an AED score >90.

If maternal education is the key determinant, the study begs the question of what factors underlie this? Is it their epilepsy, their drugs or other factors? The study does raise the optimistic possibility that poorly educated mothers with epilepsy could be identified and they and their children targeted for educational support. – *MRAM*

Thomas SV, Sukumaran S, Lukose N, Geore A, Sarma P.

Intellectual function and language functions in children of mothers with epilepsy.

EPILEPSIA

2007;48:2234-40.

BRAIN INJURY: Calling time on prognosis

*** RECOMMENDED

One of the most challenging elements to dealing with the families and friends of those who have suffered severe brain injury is being able to have a sensible discussion about the longer term prognosis without either being too vague or too definitive (and, inevitably being proved wrong). There are many indicators, in the acute stage, which have varying degrees of usefulness. Glasgow coma scale on admission, duration of post-traumatic amnesia and initial brain scan findings can all provide clues as to what the longer term outlook

is likely to be for an individual being admitted to the neuro-intensive care unit. Uncertainty, however, is accepted in this environment. Six months later, in an outpatients' clinic, the situation has changed, somewhat. "Will he get any better?" The authors of this study have used the Glasgow Outcome Scale Extended (GOSE) to track the outcomes for 214 brain-injured patients admitted to an intensive care unit with a GCS of <9 over a year in order to assess improvements between 6 months and 1 year. The GOSE is a rather crude measure with eight categories ranging from death to 'upper good recovery'. Although there are many studies looking at outcomes of head injury with this broad categorical approach, the paper in question provides new information in terms of the specific changes occurring after 6 months, a point at which many would consider further functional recovery unlikely.

Perhaps unsurprisingly, patients admitted with more severe brain injuries (GCS <5) showed little change between 6 months and a year, whereas the less severe group (GCS >6) showed a number of improvements. None of the patients recruited deteriorated, in terms of this scale, between 6 months and a year. Although very small in number, half of the patients in a "persistent vegetative state" at 6 months had moved into improved functional categories at 1 year, which does somewhat question the validity of this element in the GOSE. Although this study supports the notion that recovery from brain injury is an ongoing process, it would have been more revealing to look at meaningful outcome measures, rather than broad categories. – **LB**

Corral L, Ventura JL, Herrero JI, Monfort JL, Juncadella M, Gabarrós A, Bartolomé C, Javierre CF, García-Huete L.

Improvement in GOS and GOSE scores 6 and 12 months after severe traumatic brain injury.

BRAIN INJURY

2007;21:1225-31.

EPILEPSY: How much does it cost?

This study reviews all those which estimate the costs of epilepsy. Whether you feel this kind of data should be in a journal which, for any clinical or basic science paper, would apply quite rigorous scientific standards, is an interesting question. But fortunately those who hold the purse strings do not apply scientific rigour and so these data are useful to anyone putting a case forward for service development. So long as you see it as game and are happy to play quasi-scientific numbers with the powers that be, then you can enjoy the process and not get too frustrated at its stupidity. So to help you bend the rules in your favour here are some figures for epilepsy. The authors divided the studies into three groups. The first were epidemiological, from which they concluded that in the EU the prevalence of epilepsy is 5.8-7.4/1,000 in men and 4.0-5.3/1,000 in women. Highest prevalences were in children and adults and lower in the elderly but this group is susceptible to poor case ascertainment. The second type of study was a cost-of-illness study. There was a very wide variation from €2,000 per case per year in Estonia to €11,500 per year in Switzerland, the UK coming in at around €9,000 per year. These figures mostly reflect the cost of living in these countries. This amounted to a total cost of €15.5bn across the EU in 2004. Indirect costs were 55% and direct health care costs €2.8bn (18%) half of which was outpatient care. Drug costs were €400m (only 3% of total costs). The remaining costs were social services costs. The breakdown of total costs was sick leave 51%, adaptations 14%, social services 13%, outpatient care 8%, hospitalisation 6%, premature mortality 4%, drugs 3%, devices and procedures 0.3%. As always the financial arguments used in health care do not take account of the massive social costs of the condition and until the NHS talks to the DSS all the financial arguments we use to make a case for improved medical care are only taking account of 18% of the financial cost, let alone the personal and social burden of this illness. – **MRAM**

Pugliatti M, Beghi E, Forsgren L, Ekman M, Sobocki P.

Estimating the cost of epilepsy in Europe: A review with economic modelling.

EPILEPSIA

2007;48:2224-333.

Dopamine, the basal ganglia and cognition

There is a long history of studies involving cognition and the role of dopamine on this and its differential effects in the basal ganglia and cortex. In a series of papers this has been further explored in an attempt to define more explicitly how the system works and what are the major determinants of any variability within it. Our own work in Parkinson's disease has clearly shown that a functional polymorphism in the COMT gene can influence working memory through an alteration in the fronto parietal cortical system linked to the striatum. Whilst the exact focus of action for the effect of the polymorphism is unknown (ie striatum or cortex) the latter seems more likely given the major effect COMT activity has on synaptic dopamine levels in the cortex compared to the striatum. We have recently extended these studies to show that this polymorphism in COMT not only influences performance in Tower of London in early Parkinson's disease and activation of the above network but also impacts on the ability to form an attentional set. These studies though have only looked at PD and COMT polymorphisms using specific tasks and functional MRI. Others have now directly looked at other aspects of this relationship and shown:

- Cortical dopamine release during task specific actions. Mark Hallett and his team have shown that they can measure dopamine release in the pre SMA and globus pallidum internal segment in healthy controls and that there is a motor learning related interaction between dopamine release in the left globus pallidum and pre SMA.
- Others have now shown that functional polymorphisms in dopamine receptors have an impact on cognitive performance especially D2 and D4 receptors and
- Finally that the basal ganglia seem to be responsible for allowing only relevant information into working memory and as such act as some form of selective filter.

Therefore we start to see emerging a tightly coupled cortical basal ganglia network where dopamine acts as the key determinant such that variations in it (through functional polymorphisms in genes known to impact on dopamine function) can influence our capacity to perform motor and cognitive tasks such as attentional sets and working memory. It is now necessary to dissect out exactly how this process occurs and what impact this has, if any, on our ability to perform everyday actions and functions. – **RAB**

Williams-Gray CH, Hampshire A, Barker RA, Owen AM.

Attentional control in Parkinson's disease is dependent on COMT val158met genotype.

BRAIN

2008, Epub Jan 4th

McNab F, Klingberg T.

Prefrontal cortex and basal ganglia control access to working memory.

NATURE NEUROSCIENCE

2008;11:103-7.

Garraux G, Peigneux P, Carson RE, Hallett M.

Task-related interaction between basal ganglia and cortical dopamine release.

JOURNAL OF NEUROSCIENCE

2007;27:14434-41.

Kramer UM, Cunillera T, Camara E et al.

The impact of Catechol-O-Methyltransferase and dopamine D4 receptor genotypes on neurophysiological markers of performance monitoring.

JOURNAL OF NEUROSCIENCE

2007;27:14190-8.

Cohen MX, Krohn-Grimberge A, Elger CE, Weber B.

Dopamine gene predicts the brain's response to dopaminergic drug.

EUROPEAN JOURNAL OF NEUROSCIENCE

2007; 26:3652-60.

Journal reviewers

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