

Future Advances in Regenerative Medicine

The BioPark Hertfordshire, Welwyn Garden City, AL7 3AX: 13th June 2008

- 9:15 – 10:00 **Registration**
- 10:00 – 10:15 **Introduction by the Chair:** *Dr Stephen Minger*, Kings College, UK- Director of the Stem Cell Biology Laboratory and a Senior Lecturer in the Wolfson Centre for Age Related Diseases at King's College London.
- 10:15 – 10:45 **Updates on Regenerative Medicine: Nanobiomaterials and Stem Cells**
Professor Nureddin Ashammakhi, Keele University, UK
Regenerative medicine techniques aim at helping body's own mechanisms to heal tissue by tissues which are similar in type to the ones lost and not by scar tissue. This may involve the use of cells, biomaterials, released factors or combinations. Recently, development of Nanofibre based matrices attracted attention as those matrices have some properties which are biomimetic to natural extracellular matrix, and thus may help to develop improved scaffolds for regeneration of various tissues. The use of stem cells is attractive as these cells can differentiate to various types of cells, such as bone, cartilage, tendon, muscle, etc. In combination, these approaches can improve our tools for helping patients.
- 10:45 – 11:15 **Limbal epithelial stem cell therapy for the treatment of blinding ocular surface disease.**
Dr Julie T Daniels, Director, Moorfields Eye Hospital Cells for Sight Tissue Bank, UK.
The transparency of the cornea, and therefore vision, is dependent upon the integrity of the corneal epithelium. A population of limbal epithelial stem cells (LESCs) which reside at the periphery of the cornea are responsible for maintaining the epithelium throughout life. If the LESCs become depleted as a result of disease or injury, blinding ocular surface failure occurs. Cultured LESC therapy has the potential to restore vision in patients with LESC failure, however, little is known about the characteristics and functionality of the LESC niche. The outcome of LESC therapy in patients at Moorfields Eye Hospital, London will be discussed.
- 11:15 – 11:25 **Speakers photo**
- 11:25 – 12:00 **Mid-morning break**
- 12:00 – 12:30 **Differentiation of embryonic stem cells towards germ cells**
Dr Lyle Armstrong, Centre For Stem Cell Biology & Developmental Genetics International Centre For Life, UK
Embryonic stem cells are able to differentiate into any cell type found in the adult and this seems to include the cells of the germline at least as far as the primordial germ cell stage. In this presentation, I will discuss our recent progress towards primordial germ cell isolation and characterisation.
- 12:30 – 13:00 **Stem Cell Transplantation Supports the Repair of Injured Olfactory Neuroepithelium after Permanent Damage**
Professor Roberto P. Revoltella, University of Pisa, Italy
Several environmental products cause necrosis of the olfactory neuroepithelium (NE) with permanent damage to the underlying mucosa. We investigated whether human umbilical cord blood CD133⁺ stem cells (HSC) injected i.v. to *nod-scid* mice pre-treated with a toxic herbicide, may engraft and contribute to the regeneration of the injured NE. I will provide evidence that transplanted HSC migrating to the damaged olfactory area may provide conditions piloting the resumption of the olfactory sensorineural cell loss
- 13:00 – 13:10 **BioPark Introduction**
- 13:10 – 14:00 **Lunch**

*This meeting was **organised by Euroscicon** (www.euroscicon.com), a team of dedicated professionals working for the continuous improvement of technical knowledge transfer to all scientists. Euroscicon believe that they can make a positive difference to the quality of science by providing cutting edge information on new technological advancements to the scientific community. This is provided via our exceptional services to individual scientists, research institutions and industry. The event was hosted by **'BioPark'** (www.biopark.co.uk), a research and development centre in Welwyn Garden City providing specialist facilities and support for bioscience and health technology businesses to grow, and to develop new products and technologies*

- 14:00 – 14:15 **Interaction of Grafted Neural Precursor Cells with Purkinje Cells in a SCA1 Mouse Model**
Satyan Chintawar, Laboratory of Experimental Neurology, Université Libre de Bruxelles, Brussels, Belgium
 Spinocerebellar ataxia type 1 is caused by the expansion of a polyglutamine repeat within the disease protein, ataxin-1. It is characterized by ataxia due to the loss of cerebellar Purkinje cells and neurons in the brainstem. Grafting Neural Precursor cells at the different stages of the disease, their migration towards pathological site and their neuroprotective effect in terms of behaviour, morphology and electrophysiology will be discussed with possible mechanism of action.
- 14:15– 14:45 **Building a Regenerative Medicine Company**
Dr Paul Kemp, Founder and Chief Scientific Officer, Intercytex, UK
 The various sciences that lie behind Regenerative Medicine are currently advancing at a staggering pace and the newly formed iPS cells raises a whole new series of strategies. The regulatory system around the world are similarly changing quickly as they attempt to regulate the area and bring new effective therapies to their citizens. Building and growing a viable Regenerative Medicine company in such a rapidly changing environment is an exciting challenge. Intercytex has now been operational for 8 years and in that time has brought products to the clinic and to market. But this is just the first step. The talk will be directed towards how future strategies will be adapted to the changing scientific and regulatory environment
- 14:45 – 15:15 **Afternoon Tea/Coffee and Last Poster Viewing**
- 15:15 – 15:45 **Neural transplantation for Parkinson's and Huntington's disease: stem cells and beyond**
Dr Rike Zietlow, Cardiff University, UK
 Stem cells hold great promise as a readily available, well characterised and standardised cell source for treating a variety of neurodegenerative diseases. Neural transplantation therapy for Parkinson's and Huntington's disease, using primary fetal cells, has been trialled in animals and patients for over two decades. The experience gained from this work is and will continue to be vital for the development of effective transplantation therapies and must be integrated into, rather than superseded by developments in stem cell biology.
- 15:45 – 16:15 **The Role of the UK Stem Cell Bank in Cellular Therapy**
Dr Glyn Stacey/ Dr Charles Hunt, UK Stem Cell Bank, National Institute for Biological Standards and Control
- 16:15 – 16:30 **A new IP landscape for stem cells?**
Julian Hitchcock, Life Science Group, Mills & Reeve LLP
 Times are changing on the IP front. The European Patent Office is due to hand down its decision on the WARF hESC patent application by the end of June. What might be the implications of the decision? What will be the impact of innovations in induced pluripotency?
- 16:30 – 17:00 **Discussion and Chairman's summing up**
- 17:30 **Soiree at *The Best Western Homestead Court Hotel for all the participants**

About the Chair

Dr Stephen Minger is the Director of the Stem Cell Biology Laboratory and a Senior Lecturer in the Wolfson Centre for Age Related Diseases at King's College London. Dr Minger received his PhD in Pathology (Neurosciences) in 1992 from the Albert Einstein College of Medicine. From 1992-1994, he was a post-doctoral fellow at the University of California, San Diego, where he first began to pursue research in neural stem cell biology. In 1995, Dr Minger was appointed an Assistant Professor in Neurology at The University of Kentucky Medical School. He moved his stem cell research programme to Guy's Hospital in 1996 and was appointed a Lecturer in Biomolecular Sciences at King's College London in 1998. Over the last 15 years, his research group has worked with a wide range of somatic stem cell populations, as well as mouse and human embryonic stem (ES) cells. In 2002, together with Dr Susan Pickering and Professor Peter Braude, Dr Minger was awarded one of the first two licenses granted by the UK Human Fertilisation and Embryology Authority for the derivation of human ES cells. His group subsequently generated the first human embryonic stem cell line in the UK and was one of the first groups to deposit this into the UK Stem Cell Bank. They have gone on to generate five new human ES cell lines, including one that encodes the most common genetic mutation resulting in Cystic Fibrosis and another one that contains the Huntington's disease mutation.

About the Speakers

Professor Nureddin Ashammakhi - Leading a multidisciplinary group towards developing regenerative medicine. Research area is mainly in biomaterials and their interaction with biological systems. This include also drug releasing devices and recently nanofibre based materials for tissue repair and regeneration. Biomaterials that were investigated so far include biodegradable polymers and their composites with ceramics. Results have been published in journals, conferences and patent applications. Transfer of knowledge to industry and applications takes place through collaborative projects with industry and clinics. The main area of applications is musculoskeletal system.

Dr Glyn Stacey is in charge of the UK Stem Cell Bank, which prepares stem cell lines for use worldwide in research and in the development of new therapies for human diseases.

Dr Charles Hunt's scientific background has been in the fields of cryobiology and tissue banking. In 1978, he joined the MRC Medical Cryobiology Group at the University of Cambridge where his research interests involved the cryopreservation of cornea, pancreatic islets, and arteries. In 1992, he and colleagues founded the East Anglia Tissue Bank, where he was responsible for setting up the heart valve and autologous stem cell programmes and developing skin and amniotic membrane banking. In 2003, took charge of the newly founded UK Stem Cell Bank at the National Institute for Biological Standards and Control, where he is currently the Operations Manager

Dr Lyle Armstrong is a lecturer in stem cell biology at Newcastle University. Interests in directed differentiation of embryonic stem cells and in reprogramming somatic cells back to pluripotency

Dr Paul Kemp founded Intercytex in 1999 and is its Chief Scientific Officer. He has over 17 years of experience in the commercial development of cell therapy. Prior to founding Intercytex, he was VP Research at Organogenesis Inc. He is a principal inventor on several patents related to regenerative medicines including the wound repair stimulant, Apligraf®

Dr Julie Daniels obtained her first degree in Microbiology and her PhD in tissue engineering from the University of Leeds. She has worked at the Yorkshire Regional Tissue Bank where she produced cultured keratinocytes for burns victims and leg ulcer patients. She joined the Institute of Ophthalmology, UCL in 1996 as a post-doc working on anti-scarring strategies. Julie is now a Lecturer at the Institute and her group is aiming to understand the biology and therapeutic potential of stem cells. She is also the Director of the Moorfields Eye Hospital Cells for Sight Tissue Bank which is delivering stem cell therapy to patients with blinding ocular surface disease.

Satyan Chintawar, obtained a Bachelor of Pharmacy (1997, India) and Master of Pharmacy, specialisation-Pharmacology (1999, India), Lecturer - University of Pune (1999-2000, India), Business officer - Cadila Pharmaceuticals (2000-2001, India), PhD student (2002-present) investigating the interaction of NSCs with Blood-brain barrier and grafting in animal models with cerebellar degeneration.

Dr Rike Zietlow. After graduating from the University of Aberdeen with a degree in Neuroscience in 1995, Dr Zietlow went on to complete her Ph.D. at the Brain Repair Centre at Cambridge University under the guidance of Steve Dunnett and James Fawcett. Since 2001, she has worked as a post-doc at the newly established Brain Repair Group at Cardiff University led by Prof Dunnett and Prof Anne Rosser. Her research is focused on the use of stem cells for neural transplantation into Huntington's and Parkinson's disease models.

Julian Hitchcock is an expert on cell and tissue law, whose involvement began in the 1980s, following an education in medicine. Having qualified as a solicitor at Wragge & Co. in 1998, Julian took the Bristol University IP Diploma in 2000 and practiced for Blake Dawson Waldron in Melbourne, where he conducted patent litigation on leading products. His clients include life science companies, research-orientated universities and health organisations such as NHSBT. An earnest advocate of stem cell research and translation, Julian is a founding director of the East of England Stem Cell Network. He joined **Mills & Reeve** in 2004.

FULL ABSTRACTS

Stem cells transplantation supports the repair of injured olfactory neuroepithelium after permanent lesion

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We investigated whether human cord blood-selected CD133⁺ stem cells (HSC) may engraft the olfactory mucosa and contribute to restoration of neurofactory epithelium (NE) in *nod-scid* mice damaged by an herbicide that selectively causes necrosis of the dorsomedial part of the NE and underlying mucosa, while the lateral part of the olfactory region remains undamaged. The aim of this research was to demonstrate that HSC stimulate self-renewal of neuronal stem cells and promote their differentiation into bipolar olfactory neurons to replace the injured NE. By PCR, we tested the presence of HLA-DQ α 1 and 3 human specific microsatellites (CODIS), used as DNA markers for traceability of the engrafted cells, demonstrating a long term chimerism in various tissues of the host, including the olfactory mucosa, after one month from transplantation. By immunohistochemistry and lectin staining, we demonstrated that, in injured mice, HSC contributed to stimulating residual endogenous olfactory neurons, promoting recovery of the original phenotype of the NE, in contrast to the lack of spontaneous regeneration in similar injured areas always seen in the non-transplanted control mice. Multiple color-FISH (M-FISH) analysis detecting 7 human genomic sequences present in different chromosomes provided further evidence of positive prolonged engraftment of chimeric cells in the olfactory mucosa. This study provides evidence that transplanted HSC migrating to the neurofactory mucosa may contribute to NE structure restoration with resumption of the sensorineural olfactory loss.

Interaction of Grafted Neural Precursor Cells with Purkinje Cells in a SCA1 Mouse Model

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Spinocerebellar ataxia type 1 (SCA1) is caused by the expansion of a polyglutamine repeat within the disease protein, ataxin-1. It is characterized by ataxia due to the loss of cerebellar Purkinje cells (PC) and neurons in the brainstem. In a transgenic mouse model, expression of mutated human ataxin-1 gene containing 82 CAG repeats was directed to PCs using the regulatory region of the PC specific gene *Pcp2*. These animals show PC dysfunction and ataxia as early as 5 weeks, abnormalities in the dendritic tree of PC cells can be seen at 12 weeks, PC loss is evident at 24 weeks, with severe reduction of the molecular layer thickness and ectopic location of the remaining PC bodies. We derived neural precursor cells (NPCs), cultured as neurospheres, from the subventricular zone of GFP expressing mouse of the same strain background. Three injections each of 100000 cells were made in the cerebellar white matter of 13 and 24 weeks old transgenic SCA1 and wild type mice. Accelerating rotarod and grip strength showed a significant amelioration in 24 weeks old SCA1 mice. Grafted NPCs migrated to all cerebellocortical layers and acquired neuronal or astrocytic markers, while they remained in the cerebellar white matter in wild type mice. No grafted cell expressed PC markers, indicating that the observed behavioral amelioration was not due to PC replacement but rather to a neuroprotective effect. Quantitative analysis of grafted 24 weeks old mice showed significant less shrinkage of the molecular layer, less ectopic and more surviving PCs. The electrophysiological properties of Purkinje cells in grafted vs. control animals are currently under study. In addition, some grafted cells in the molecular layer had processes wrapped around and getting in close contact with the host PCs. Immunofluorescence analysis showed the expression of connexins in these processes and in the host cells, suggesting the formation of gap junctions. We conclude that: 1. Significant cells loss in the cerebellar cortex is needed to attract grafted NPCs; 2. Grafted NPCs provide a neuroprotective effect in SCA1 transgenic mice that results in improvement in motor behavior; 3. This effect may be mediated in part by a direct contact between grafted cells and the host PCs with formation of gap junctions.