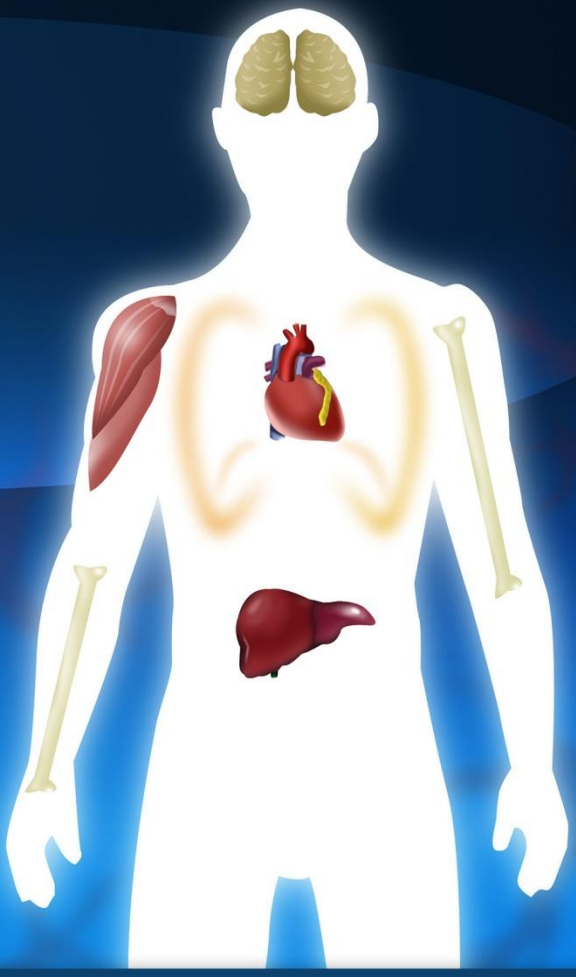
MOVING FORWARD WITH STEM CELL THERAPY



ABSTRACTS

6TH - 8TH SEPTEMBER 2016

Location: Online

EuroSciCon

From basic research to clinical practice, this multi-disciplinary event provides an opportunity to share and compare research progress and clinical experiences to establish reliable stem cell and other cellular therapies.

This event has CPD accreditation

www.lifescienceevents.com/stemtherapy2016

#StemTranspESC

Table of Contents

EuroSciCon Ltd. Registered in England and Wales, Company number: 4326921, Trading Address: Euroscicon Ltd, Highstone House, 165 High Street, Barnet, Herts. EN5 5SU, UK. Registered Office: 47 High Street, Barnet, Herts, EN5 5UW, UK

EuroSciCon Ltd. Registered in England and Wales, Company number: 4326921, Trading Address: Euroscicon Ltd, Highstone House, 165 High Street, Barnet, Herts. EN5 5SU, UK. Registered Office: 47 High Street, Barnet, Herts, EN5 5UW, UK

Invited Speakers Abstracts

Stem Cell Therapies: Regulatory Considerations for Successful Translation into the Clinic.

Dr Houria Bachtarzi, ERA Consulting (UK) Ltd., London, United Kingdom

Stem cell-based therapies have recently emerged as valuable tools for treating a number of pathological conditions including: metabolic, degenerative and inflammatory disorders.

The complexity of such cell-based medicinal products and the limited scientific knowledge and clinical experience available with some classes of stem cells such as: human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs) raise some challenges ahead.

Some of the regulatory barriers to successful clinical translation and approval of such advanced therapies will be highlighted and issues considered for the generation of safe (minimising risks of tumorigenesis and infections), clinically effective and GMP-compliant stem cell therapy medicines.

Adipose-derived stem cell seeded biominerizable nanocomposite for chest wall repair: suppression of inflammatory response in a murine model

Dr Johanna Buschmann, University Hospital Zurich, Plastic Surgery and Hand Surgery, Switzerland

Defects to the chest wall can occur after tumor resections or trauma caused by accidents, and appropriate chest wall reconstruction is therefore needed. Stability and integrity of the repaired chest wall should reach similarity to natural physiology. Here, we present the implantation of a biocompatible, biodegradable and easily vascularizable nanocomposite seeded with adipose-derived stem cells (ASCs) as a chest wall graft in a murine model. Inflammatory response towards the graft material was significantly reduced for macrophages, lymphocytes and foreign body giant cells in the presence of ASCs compared to cell-free scaffolds.

Using induced Pluripotent Stem Cell-derived Cardiomyocytes for cell therapy and tissue regeneration

Professor Ofer Binah, Technion, Israel Institute of Technology, Haifa, Israel

In view of the therapeutic potential of cardiomyocytes derived from human induced pluripotent stem cells (iPSC-CM), our overall goal is to investigate their molecular characteristics, functional properties related to the excitation-contraction coupling (e.g., [Ca2+]i handling), pacemaker function and underlying ion currents, the effects of □-adrenergic stimulation, and responsiveness to common modifiers of cardiac function (e.g., If blocker). The iPSC clones we investigate are derived from human dermal fibroblasts and hair keratinocytes. Reprogramming is accomplished by infecting the cells with retroviruses containing the four human genes: OCT4, Sox2, Klf4 and C-Myc. Our major findings show that iPSC-CM: (1) express cardiac specific RNA and proteins; (2) exhibit regular pacemaker activity; (3) exhibit key features of the excitation contraction coupling machinery; (3) respond to ryanodine and caffeine (albeit less than adult cardiomyocytes), and express the SR-Ca2+ handling proteins ryanodine receptor and calsequestrin; (4) respond to autonomic agonists and antagonists. (5) Demonstrate Beat Rate Variability. Hence, our work demonstrates that iPSC-CM exhibit features resembling the adult myocardium, and thus constitute a potential source for cardiac regeneration. Additionally, we are investigating iPSC-CM generated from skin biopsies/keratinocytes obtained from patients with the inherited cardiac diseases, such as Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT), laminopathies and dystrophynopathies. Our research demonstrates that the mutated iPSC-CM feature the clinical phenotype of the disease, thus establishing the foundation for personalized medicine.

A holistic approach to MSC culture process design

Dr. Karen Coopman, Loughborough University, Leicestershire, UK

With the growth of the cell-based therapy industry, one of the key challenges in the field is the successful preservation of these therapies in order to enable, for example, centralised manufacture of an 'off-the-shelf' allogeneic product. Here the concept of end-to-end process design will be discussed as data is emerging which shows the impact that changes in downstream processing (I.e. cell harvesting, washing and re-suspending cells in cryopreservation medium) can have on cell

recovery post-thaw despite a consist freezing process. The idea of optimising each unit operation in isolation will therefore be questioned

Restoring immune competence after allogeneic stem cell transplantation: A double edged sword

Dr Martin Guimond, University of Montreal, Maisonneuve-Rosemont Hospital, Montreal QC, Canada
Martin Guimond is an assistant professor at the University of Montreal. He received his PhD from the University of Montreal on stem cell transplantion and graft-versus-host disease. Since summer 2009, Dr. Guimond has directed an independent research program working on the biology of T cell depletion and the physiopathology of graft-versus-host disease.

Human amniocytes as a countermeasure to osteopenia in a mouse model of fragile bones.

Dr. Pascale V Guillot, University College London, London, United Kingdom
Transplantation of fetal mesenchymal stem cells has been proposed as skeletal anabolic therapy to enhance bone formation, but the mechanisms underlying the contribution of the donor cells to bone health are poorly understood and requires further elucidation. We showed that transplantation of amniotic fluid-derived mesenchymal stem cells (amniocytes) into mice with brittle bones reduced fracture susceptibility by strengthening the bones and improving their flexibility and structural quality. The beneficial effects of amniocytes were achieved by promoting the maturation of resident mesenchymal progenitor cells and endogenous collagen production. Together these findings identify amniocytes as countermeasure to bone fragility and reveal their trophic effect on resident osteoblasts.

The leukaemic stem cell niche and its possible therapeutic targeting

Professor Daniela Krause, Georg-Speyer-Haus, Frankfurt, Germany
Insight into the physiology of the normal haematopoietic stem cell niche, as well as the pathophysiology of the leukaemic stem cell niche is increasing. In this talk background information on the normal haematopoietic stem cell niche will be provided, before showing interactions of leukaemic cells with their bone marrow microenvironment and posisble strategies to target the leukaemic niche in the future.

Sex, stem cells and regenerative medicine

Dr Kirsten McEwen, Imperial College London, London, UK
Sex influences many factors including drug response, disease prevalence and cell differentiation. In vitro cultured cells originate from either male or female tissues and therefore have the potential to manifest sex differences. We demonstrate that male and female pluripotent stem cells differ in signalling, metabolism and epigenetic processes. The choice of culture condition can interact with these effects and can alter the male:female sex ratio during the derivation process. These results exemplify the importance of identifying sex differences in pluripotent reprogramming and differentiation for regenerative medicine.

ErbB retargeted CAR T-cell immunotherapy of head and neck cancer

Dr John Maher, King's College Hospital NHS Foundation Trust, Allergy and Immunology Service, London, United Kingdom
The most effective targeted immunotherapies developed against solid tumours to date recognize ErbB family members. We have developed a chimeric antigen receptor (CAR) named T1E28z that targets the extended ErbB network. Engineered T-cells are expanded and enriched using a co-expressed IL-4-responsive chimeric cytokine receptor. Efficacy of the resultant "T4 immunotherapy" has been demonstrated in tumour models of head & neck, breast and ovarian cancer in vivo, without significant accompanying toxicity. With excessive dosing however, human T4+ T-cells elicit macrophage-dependent cytokine release syndrome. To de-risk this approach in man, phase 1 testing has been initiated in patients with head & neck cancer, using intra-tumoral delivery to minimize risk of toxicity.

CXCR4 knockdown in hematopoietic stem cells as a cure strategy for WHIM syndrome immunodeficiency

Dr. Philip M. Murphy, National Institute of Allergy and Infectious Diseases, Bethesda, United States

We identified a patient with WHIM syndrome immunodeficiency whose disease causing mutation in the chemokine receptor CXCR4 was deleted by chromothripsis (chromosome shattering) in a single hematopoietic stem cell which then repopulated the bone marrow with a clone of CXCR4 haploinsufficient cells, curing her of the disease. We are therefore attempting to develop gene editing of the CXCR4 WHIM allele as a general cure strategy for WHIM syndrome, with potential application as a ge.neral adjuvant approach for other gene therapy target diseases of the blood.

Functionalized carbon nanotubes in the ex vivo expansion of hematopoietic stem & progenitor cells

Associate Professor and Assistant Head Gigi Chiu Ngar Chee, National University of Singapore, Singapore

This seminar examines the use of functionalized, single-walled carbon nanotubes (f-SWCNT) in mediating survival and ex vivo expansion of hematopoietic stem and progenitor cells (HSPC) from human umbilical cord blood (UCB). In comparison to amide and polyethylene-glycol functionalized SWCNT, carboxylic acid (-COOH) variants gave optimal viability support which correlated with maximal reduction of mitochondrial superoxides in HSPC. f-SWCNT-COOH could maintain higher proportion of HSPC-associated cytokines and minimal level of differentiation promoting factors. Transplantation of f-SWCNT-COOH expanded grafts in a murine model resulted in higher engraftment of HSPC in bone marrow compared to control when they were co-transplanted with non-expanded cells from the same UCB. Expanded grafts mediated higher survival rate of mice compared to non-expanded grafts, which could be a consequence of fewer immune cells in the grafts resulting in lower graft-versus-host-disease incidence.

Experimental and clinical airway resetoration by mesenchymal stromal cell transplantation

Dr Francesco Petrella, Istituto Europeo di Oncologia, Milano, Italy

Post-resectional bronchopleural fistula is a pathological connection between the airway and the pleural space that may develop after lung resection; it still represents a challenging life-threatening complication for thoracic surgeons.

Our project investigates the hypothesis of experimental bronchopleural fistula closure by bronchoscopic injection of autologous bone marrow-derived mesenchymal stem cells into the cavity of the fistula, evaluating its feasibility in a large animal model and in humans.

Following our previous preliminary experimental results, we suggest that mesenchymal stem cells targeted to broncho pleural fistula through submucosal bronchoscopic injection can promote tissue regeneration, thereby occluding bronchial stump dehiscence and preventing pleural empyema.

Why Cell Therapy Needs an Extracellular Matrix: Hydrogels for the Clinic

Professor Glenn D. Prestwich, The University of Utah, Salt Lake City, United States

We created a synthetic extracellular matrix (sECM) from hyaluronic acid (HA) that affords highly reproducible, manufacturable, approvable, and affordable biomaterials. These injectable clinical materials are used for delivery, retention of progenitor cells for cell therapy. These injectable clinical materials are now commercial products three fields of use: (i) human medical devices, (ii) cell therapy and research tools for 3-D cell culture, and (iii) veterinary wound care and adhesion prevention.

Towards optimising the use of umbilical cord blood for immunotherapy

Dr Aurore Saudemont, Anthony Nolan, London, United Kingdom

Umbilical cord blood (UCB) has been increasingly used as a source of hematopoietic stem cells (HSC) for transplantation, as it has some advantages such as less stringent HLA matching, fast availability of the graft and reduced incidence of graft versus host disease. However, it is also associated with a higher incidence of infections, graft failure, slow engraftment and immune reconstitution. UCB is mainly used as a source of HSC however it is rich in immune cells that could be used to treat the

main complications post-transplantation. Here, we aim to describe some of the immunotherapies currently developed that used UCB.

Immune-senescence and immune-exhaustion in hematopoietic stem cell transplantation and adoptive immunotherapy

Dr Federico Simonetta, Geneva University Hospitals, University of Geneva, Geneva, Switzerland

Allogeneic hematopoietic stem cell transplantation (HSCT) is a well-established therapeutic modality for a variety of hematological malignancies. Donor lymphocytes exert an essential role after allogeneic HSCT mediating a Graft-versus-Tumor (GvT) effect and protecting the recipient from infections. Unfortunately, several quantitative and qualitative abnormalities of donor derived lymphocytes limit their efficacy. In this talk we provide an overview of the contribution of immune-senescence and immune-exhaustion to effector cells impairment after HSCT. We will discuss how these processes can represent potential targets for immunotherapeutic approaches. Finally we will extend our discussion to the field of adoptive immunotherapies, including the recently developed chimeric antigen receptor (CAR) T cell therapy, where the negative impact of immune-senescence and exhaustion starts to be uncovered.

Finally, a method to determine stem cell dose for stem cell transplantation medicine

James Sherley, Asymmetrex, Boston, United States

A well known, but understated, challenge in stem cell medicine is determining the stem cell dose of transplantation treatments. Both approved stem cell transplantation therapies, like hematopoietic stem cell transplant for cancer treatments, and regenerative medicine clinical trials are undermined by this shortcoming. This limitation exists as well for basic tissue stem cell research, because of the lack of biomarkers that identify tissue stem cells specifically. Asymmetrex circumvented this problem by developing a technology for quantifying adult tissue stem cells based on their unique asymmetric self-renewal kinetics. The new “AlphaSTEM Test” technology is a major advance for stem cell therapeutics.

Impact of Deploying A Genetic Approach to Stem Cells Opens-Up New Facets in the “Blank Slates” of Our Body

*Jyoti Bhojwani**
School of Life Sciences, DAVV/Indore University, Indore (M.P.), India.

*Corresponding author: Dr. Jyoti Bhojwani (jbhojwani2005@gmail.com)

Since the dawn of the Post-Genomic era (25 years back), applying a genetic approach to solving various intricate problems/issues in research has taken-off even more swiftly than ever before. Spatio-temporal cues defined for certain critical components in a particular developmental pathway (involved in causing/progression of certain disease) provide a firm basis for detecting the order, hierarchy and “switching-off or on” of genes that regulate it. The various time-points, at which genes are switched on/off, clearly determines the fate of what a cell does in terms of being functional or non-functional, due to disruption of that specific pathway. Recent research-work in this area (Bhojwani, 2015) provides strong evidence, toward identifying such components (associated with Wnt-signaling involved in Colorectal Cancer-CRC disease). These crucial elements indeed determined the genetic transformation of a “blank-slate” (“cells of origin” and/or putative “cancer stem cells”) or “primitive-state” epithelial cells to an intermediate adenoma/polyp (dyspastic), and later to a proliferative (hyperplastic) or cancerous (neoplastic) state. The idea is to re-iterate the power of genetics, in solving and filling the missing links of any developmental pathway involved in progression of a disease (in this case, CRC). A critical temporal requirement of certain molecules [Caesin-Kinase I (CKI) and Human-Discs-large (hDlg)] was finally established and these proteins were identified as “early” and “late” acting molecules respectively, in a very crucial developmental event, that basically transforms “polyps” to full-fledged “carcinomas” (epithelial cancers) in COLORECTAL tumors. The detection of these genetic and developmental parameters, served as a focal-point and a prominent diagnostic feature, for detection of effects, ie. gain/ loss of other components involved

during progression of CRC disease. Coincidentally, the chromosomes on which these genes reside have been found to be dense and rich in SNPs (hot-spots), the details of which were published in a separate report (Patidar & Bhojwani, 2013). This work harnessed the potential of Genetics, Developmental Biology and Bio-Informatics tools to solve a long-standing puzzle in pin-pointing some genetic factors that were critically involved in the progression of CRC disease. The report has created enough impact, in terms of authentically suggesting, that it is only when we deploy a combinatorial approach towards certain complicated biological problems, can we successfully unveil the underlying mechanisms in greater details.

However, it is now conceived that, at the heart of every tumor lies a rare sub-population of cells (Cancer Stem Cells-CSCs),, which give rise to most of the Cancers and are now the targets of investigation. Since no definitive markers or efficient labeling tools are available, this population of cells still remains elusive in both cancer and stem cell biology. Therefore, it would be critical to understand molecular differences between stem cells and cancer cells, which might be helpful in providing novel insights into the mechanism of tumorigenesis as well as potential therapeutic targets, in foreseeable future. We have come a long way in the stem cell advances over time. Very recent breakthroughs include: (a) The tuning and genetic re-programming of stem cells (iPS cells) by a handful of genetic factors (Takahashi et al, 2006, 2007; discussed in Bhojwani, 2008) and; (b) The transformation of cancerous cells to normal cells by reversing the genetic changes involved and also restricting the awry cancerous cells by using microRNAs (http://yournewswire.com/breakthrough-scientists-find-way-to-change-cancer-cells-into-healthy-cells/). My talk would shed light on how we could intelligently utilize these efficient tools together, to attack the “Bad seeds” in ways to cure the myriad diseases, like Cancer.

Day 1:

Oral Presentation Abstracts

Oral presentations will be added after the submission deadline

FROM HUMAN MSCS TO IPCS

By
Sahar A. Rashed & Maha M. Azzam and Mohamed A. Ghoneim

We have succeeded in the production of insulin producing cells (IPCs) from human MSCs by a process of directed differentiation.

Although the yield following directed differentiation of adult human MSCs to form IPCs is modest, yet transplantation of these cells in diabetic mice resulted in their cure. We have tried to provide an explanation for this observation. Differentiated MSCs, were transplanted under the renal capsules of diabetic mice. The kidneys were harvested after 1, 2, 4 and 12 weeks. The insulin producing cells were counted and the relative expression of relevant endocrine genes determined. The proportion of IPCs increased to reach a maximum of ≈ 20% at 4 weeks. There was no change thereafter. There was a parallel increase in the relative expression of endocrine genes.

In order to study the efficiency of these cells in treatment of larger animals and identify their functional longevity, we have induced diabetes in 6 dogs (15-20 kg) by a mixture of alloxan and STZ 50-80 million differentiated human cells were encapsulated and transplanted beneath the rectums sheath. 6 dogs are currently under follow up. 3 had completed a 6 months follow up. 2 became euglycemic with normal glucose tolerance curve. The third is on the hyperglycemic side although the profile of its glucose tolerance resembles a normal one. A harvested capsule after 6 months from transplantation was histologically examined and the relative expression of pancreatic endocrine genes determind. By immunofluorescence, insulin +ve cells were seen, and co-expression with c-peptide was seen. The proportion of insulin +ve cells was again in the range of ≈ 20%.

EuroSciCon Ltd. Registered in England and Wales, Company number: 4326921, Trading Address: Euroscicon Ltd, Highstone House, 165 High Street, Barnet, Herts. EN5 5SU, UK. Registered Office: 47 High Street, Barnet, Herts, EN5 5UW, UK

In conclusion, insulin producing cells can be formed by directed differentiation from of MSCs. After their transplantation, these cells undergo further differentiation in vivo. Evidence was provided that these cells can cure chemically induced diabetes in small as well as large animals.

Day 2:

Oral Presentation Abstracts

Oral presentations will be added after the submission deadline.

Day 3:

Oral Presentation Abstracts

Oral presentations will be added after the submission deadline

CLINICAL PHASE II TRIAL EVALUATING THE EFFICACY OF SYSTEMIC MESENCHYMAL STROMAL CELL (MSC) INJECTIONS FOR THE TREATMENT OF SEVERE AND CHRONIC RADIOTHERAPY-INDUCED ABDOMINO-PELVIC COMPLICATIONS (PELVIC RADIATION DISEASE, PRD) REFRACTORY TO STANDARD THERAPY

A Chapel[1], A Semont[1], N Mathieu[1], C Linard[1], V Holler[1], C Strup[1], B Usunier[1],C Demarquay[1], B LHomme[1], C Squiban[1], L Douay[2], NC Gorin[2], M Mothy[2], JM Simmon[3], JJ Lataillade[4,6], J Voswinkel[3], H Rouard[5,6], R Tamarat[1] and M Benderitter[1]

1 Radiological Protection and Human Health Division, Institute of Radiological Protection and Nuclear Safety, Fontenay-aux-Roses, France

2 Department of Hematology, Saint Antoine Hospital APHP and UPMC University, UMRS 938, Paris, France;

3 Department of Radiation Oncology, Pitie-Salpetriere University Hospital, Paris, France;

4 Blood Transfusion Center of Army, Percy Military Hospital, Clamart, France;

5 Unit of Engineering and Cellular Therapy , French Establishment of the Blood, Créteil france

6 Ecell France , Montpellier France

Radiotherapy may induce irreversible damage on healthy tissues surrounding the tumour. The late adverse effects of pelvic radiotherapy concern 5 to 10% of them, which could be life threatening. A medical consensus concerning the clinical management of healthy tissue squeal does not exist. No pharmacologic interventions have yet been proven to efficiently mitigate radiotherapy severe side effects. Our group has demonstrated in preclinical animal models that systemic MSC injection is a promise approach for the medical management of gastrointestinal disorder after irradiation. Furthermore our network has confirmed in compassionate treatment that MSC injection improved the clinical status of four first patients suffering from severe pelvic side effects resulting from an over-dosage. Bone marrow-derived MSC from the patients´ children were injected to four patients. A quantity of 2x106 - 6x106 MSC /kg were infused intravenously to the patients. Pain, hemorrhage, frequency of diarrheas and fistulisation as well as the lymphocyte subsets in peripheral blood were

evaluated before MSC therapy and during the follow-up. Two patients revealed a substantiated clinical response for pain and hemorrhage after MSC therapy. In one patient pain reappeared after 6 months and again substantially responded on a second MSC infusion. A beginning fistulisation process could be stopped in one patient resulting in a stable remission for more than 3 years of follow-up. The frequency of painful diarrhea diminished from an average of 6/d to 3/d after the first and 2/d after the 2nd MSC injection in one patient. A decline of CD4+ and CD8+ T lymphocytes and an increase of regulatory CD25+ T cells accompanied the clinical response in this patient after the MSC injections. In all patients, prostate cancer remained in stable complete remission. A modulation of the lymphocyte subsets towards a regulatory pattern and diminution of activated T cells accompanies the clinical response in refractory irradiation-induced colitis. No toxicity occurred. MSC therapy was safe and effective on pain, diarrhea, hemorrhage, inflammation, fibrosis and limited fistulization.

A Clinical phase II trial evaluating the efficacy of intravenous MSC injections for the treatment of severe and chronic radiotherapy-induced abdomino-pelvic complications (pelvic radiation disease, PRD) refractory to standard therapy will start in 2016. Twelve Patients will receive 3 intravenous injections of MSCs. Efficiency will be evaluated by a decrease in rectorrhagia or hematuria and secondary in a decrease of frequency of diarrhea, frequency of drug consumption, quality of life.

Poster Presentation Abstracts

Poster abstracts will be finalised weeks before the event