WELCOME FROM THE CO-CHAIRS

On behalf of the International Society for Cellular Therapy, we are honoured to welcome you to the ISCT Europe 2015 Regional Meeting, hosted in Seville, Spain. Located in the South of Spain, Seville is the capital of Andalucía. It is situated on the plain of the river Guadalquivir. Its old town, the third largest in Europe with an area of 4 square kilometres, contains three UNESCO World Heritage Sites: the Alcázar palace complex, the Cathedral and the General Archive of the Indies. It is the birthplace of Velázquez and Murillo, the city of Carmen and Don Juan and the inspiration for many composers: Rossini (The Barber of Seville), Verdi (La Forza del Destino), Beethoven (Fidelio), and Mozart (Don Giovanni and The Marriage of Figaro).

Seville is a prominent business centre, well connected by its international airport and the Spanish high speed train AVE. Famous worldwide for its culture, monuments, traditions and artistic heritage, Seville is a city full of life and possibilities.

The meeting program will highlight the close working relationships between clinicians and scientists, laboratory professionals involved in cell-processing programs/facilities, industry personnel from cell therapy or enabling technology companies, as well as regulatory experts including strong representation from local competent authorities as well as EMA/CAT.

The central theme for this Regional Meeting is best described with a question: What can and should we do to make cellular therapies that bring value to patients available to these patients as soon as possible? Even though several cellular therapies have been granted marketing authorization in the last 5 years, it has become clear that this is not the only requirement for success. To make cellular therapies on a large(r) scale available for patients much more work is needed.

During the meeting we will for example focus on (1) how to drive the translation of cellular therapies for the benefit of patients and discuss the challenges and critical success factors, (2) new frontiers in the treatment of ophthalmological disorders, (3) the use of adoptive T-cell therapies/genetically engineered T-cells (T-cell receptors (TCRs), chimeric antigen receptors (CARs), and tumour infiltrating lymphocytes (TILs)) against tumour antigens, and (4) tissue engineering. A corporate symposium providing a hands-on tour of functionally closed, scalable solutions for clinical production and a floor of exhibits will also be part of this exciting event. The program will also include a joint ECA, AGORA, ISCT training session for QPs regarding the release of advanced therapy medicinal products (ATMPs), a training session on sterile manufacturing of ATMPs organized by AIAT-CTP-ISCT, and a CAT-ISCT joint workshop on the challenges and opportunities for the successful development and approval of ATMPs.

Seville is the largest city in Andalusia, the biggest region of Spain. The regional government is fostering research, development and innovation in the fields of cell therapy and regenerative medicine, clinical genetics and genomic medicine and nanomedicine by sponsoring research projects, implementing training programmes, recruiting research groups, creating a network of research facilities and establishing collaboration with some biotechnological and pharmaceutical companies through the Andalusian Initiative for Advanced Therapies (AIAT), part of the Andalusian Public Healthcare System. What better place therefore than Seville as host for this year’s Regional Meeting?

We must express our gratitude to the exhibitors, non-profit organizations and industry supporters who have contributed greatly to the overall success of this ISCT Europe 2015 Regional Meeting. Please be sure to take time to visit the vendors in the exhibit hall this year.

Lastly, thanks to the Regional Meeting Organizing Committee for sharing their expertise and for the significant time invested to make this a truly unique event.

We welcome you to Seville!
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GENERAL CONFERENCE INFORMATION

REGISTRATION HOURS

The conference registration desk is located in the Galeria outside of Seville II. Registration hours are as follows:

- Wednesday September 23rd: 1630 – 1930
- Thursday September 24th: 0700 – 1900
- Friday September 25th: 0730 – 1700
- Saturday September 26th: 0730 – 1530

INCLUDED IN YOUR REGIONAL MEETING REGISTRATION FEE:

- Access to the Welcome Address and Networking Reception
- Access to all Technical Sessions, Workshops, Plenary Sessions, Corporate Symposium and Tutorials, Oral Abstract Sessions, and Poster Session
- Lunch, all coffee breaks and refreshments served from September 24th-26th
- Program Book
- Delegate Bag
- Access to presentations online (post-event)

EXHIBIT HOURS

The exhibit hall is located in the Foyer and Galeria of the Barceló Convention Center.

Exhibit hours are as follows:

- Thursday, September 24: 1900 – 2100 (Networking Reception)
- Friday, September 25: 0900 – 1945
- Saturday, September 26: 0900 – 1230

EXHIBIT-ONLY ATTENDEES RECEIVE:

- Access to the Exhibit Area including the Welcome Address and Networking Reception on September 24th
- Conference meals and refreshments served in the exhibit hall
- Program Book
- Delegate Bag

ADDITIONAL REGISTRATION FEE REQUIRED FOR:

- Pre-Conference Workshop: MSC & Cancer: Trojan Horses For Novel Cancer Therapeutics or Fast Food for Tumors (September 23rd)

WIFI

Network: ISCT 2015
Password: Sevilla

SOCIAL EVENT

THURSDAY SEPTEMBER 24TH – WELCOME ADDRESS AND NETWORKING RECEPTION

Admission:
- Free for all conference delegates

Where & When:
- 1835 – 1900: Welcome Address in Seville I, II
- 1900 – 2100: Networking Reception in the Exhibit Hall; Wine and hors d’oeuvres will be served
ORGANIZING COMMITTEE

CO-CHAIRS

Edwin Wagena, PhD
Netherlands
ISCT Europe Regional Vice-President

Natividad Cuende, MD, MPH, PhD
Andalusian Initiative for Advanced Therapies
Spain
ISCT Europe Legal and Regulatory Affairs Committee Chair

COMMITTEE MEMBERS

Giuseppe Astori, PhD
San Bortolo Hospital
Italy

Katarina Le Blanc, MD, PhD
Karolinska University Hospital Huddinge
Sweden

Miguel Forte, MD, PhD
TxCell S.A.
France

Bruce Levine, PhD
University of Pennsylvania
USA

Martin Hildebrandt, MD
Technische Universität München
Germany

Katy Newton, PhD
Cell Medica Ltd.
United Kingdom

Mauro Krampera, MD
University of Verona
Italy

Robert Preti, PhD
PCT, a Caladrius Company
USA

Gunnar Kvalheim, MD, PhD
Oslo University Hospital
Norway

Ineke Slaper-Cortenbach, PhD
University Medical Center Utrecht
Netherlands

The International Society for Cellular Therapy would like to acknowledge and thank the Andalusian Initiative for Advanced Therapies for their support and contribution to the ISCT Europe 2015 Regional Meeting.
INVITED CHAIRS AND SPEAKERS

Miguel Alamínos, MD, PhD, University of Granada – Granada, Spain
Eddy Anglate, MD, Ocata Therapeutics, Inc. – Marlborough, United States
Diego Argidó, MD, PhD, Chiesi Pharmaceutical SpA – Parma, Italy
Giuseppe Astori, PhD, San Bartolo Hospital – Vicenza, Italy
Simona Badoi, MD, National Agency for Medicines and Medical Devices – Bucharest, Romania
Shirley Battido, PhD, Charité–Universitätsmedizin – Berlin, Germany
Giulio Bassi, MSc, PhD, University of Verona – Verona, Italy
Shomi Bhattacharya, PhD, Andalusian Center for Molecular Biology and Regenerative Medicine (CABIMER) – Seville, Spain
Karen Bieback, PhD, Institute of Transfusion Medicine and Immunology – Mannheim, Germany
Xenia Boergen, PhD, Simmons & Simmons LLP – Düsseldorf, Germany
Christelle Boniface, MSc, TaCell S.A. – Valbonne, France
Tomáš Boráň, MD, State Institute for Drug Control – Prague, Czech Republic
Eduardo Bravo, MBA, Tigenix NV – Leuven, Belgium
Gloria Carmona, MPPharm, Andalusian Initiative for Advanced Therapies – Seville, Spain
Patrick Celis, PhD, European Medicines Agency – London, United Kingdom
Natividad Cuende, MD, MPh, PhD, Andalusian Initiative for Advanced Therapies – Seville, Spain
Massimo Dominici, MD, University of Modena and Reggio Emilia – Modena, Italy
J. H. Frederik Falkenburg, MD, PhD, Leiden University Medical Center – Leiden, Netherlands
Margarida Menezes Ferreira, PhD, National Authority of Medicines and Health Products, IP – Lisboa, Portugal
Alicia El Haj, PhD, FRSB, FEAMBES, Kelee University – Staffordshire, United Kingdom
Óscar Fernández, MD, PhD, Regional University Hospital of Málaga – Málaga, Spain
Beatriz Fernandez-Munoz, PhD, Andalusian Initiative for Advanced Therapies – Seville, Spain
Miguel Forte, MD, PhD, TxCell S.A. – Valbonne, France
Arnaud Foussat, PhD, TxCell S.A. – Valbonne, France
Maria Luisa García-Martín, PhD, Andalusian Center for Nanomedicine and Biotechnology (BIONAND) – Málaga, Spain
Helmut Gehart, PhD, Hubrecht Institute – Utrecht, Netherlands
Simona Giudì, MD, CTP – Florence, Italy
Christine Guenther, MD, apceth GmbH Co. KG – Munich, Germany
Kurt Gunter, MD, FASCP, Cell Medica Ltd. – Houston, United States
Andrea Hauser, University Hospital Regensburg – Regenburg, Germany
Martin Hildebrandt, MD, TUM School of Medicine – Munich, Germany
Karín Hoogendoorn, PharmD, Quality RA – Leiden, Netherlands
Panos Kefalas, PhD, MBA, Cell Therapy Catapult – London, United Kingdom
Sven Kili, MD, GSK – Brentford, United Kingdom
Kenneth Kleinhenz, MSc, Cytomod Therapeutics, Inc. – San Diego, United States
Mauro Kramerpa, MD, PhD, University of Verona – Verona, Italy
Leopoldo Laricchia–Robbio, PhD, Andalusian Initiative for Advanced Therapies – Seville, Spain
Bruce Levine, PhD, University of Pennsylvania – Philadelphia, United States
Laura Leyva, MD, PhD, Regional University Hospital of Málaga – Málaga, Spain
Mark W. Lowdell, BSc, MSc, PhD, FRCPath, FBS, Royal Free Hospital & University College London – London, United Kingdom
Salvador Martínez, MD, PhD, Institute of Biomedicine of Murcia – Murcia, Spain
Marco Matteucci, PhD, Sant’Anna School of Advanced Studies – Pisa, Italy
Giovanni Milazzo, MD, Chiesi Pharmaceutical SpA – Parma, Italy
Francisco Moniche, MD, PhD, Virgen del Rocio University Hospital – Seville, Spain
Holger Müller, CFA, PhD, Cell Medica Ltd. – London, United Kingdom
Katy Newton, MD, Cell Medica Ltd. – London, United Kingdom
Tiina Palomäki, PhD, Finnish Medicines Agency (FIMEA) – Helsinki, Finland
Guido Pantè, PhD, Italian Medicines Agency – Rome, Italy
Christoph Peter, apceth GmbH Co. KG – Munich, Germany
Robert Preti, PhD, PCT, a Caladrius Company – Hackenack, United States
Martin Pule, MB, BCH, University College London – London, United Kingdom
Annigje Rietveld, PhD, The Health Inspectorate – Amsterdam, Netherlands
Sol Ruiz, PhD, Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) – Madrid, Spain
Paula Salmikangas, PhD, Finnish Medicines Agency (FIMEA) – Helsinki, Finland
Ralf Sanzenbacher, PhD, Paul–Ehrlich–Institut Federal Institute for Vaccines and Biomedicines – Langen, Germany
Daniel Saris, MD, PhD, University Medical Center – Utrecht, Netherlands
Richard Schäfer, MD, German Red Cross Blood Donor Service – Frankfurt am Main, Germany
Martina Schüller-Lenz, MD, Paul–Ehrlich–Institute – Langen Hesse, Germany
Luc Sensebé, PhD, Établissement Français Du Sang EFS – Toulouse, France
Armin Sepp, PhD, GSK – Stevenage, United Kingdom
Warren Sherman, MD, Celyad – Mont-Saint-Guibert, Belgium
Dariusz Sładowski, MD, PhD, Medical University of Warsaw – Warsaw, Poland
Imke Slaper-Cortenbach, PhD, University Medical Center – Utrecht, Netherlands
Jeske Smink, PhD, co don AG – Teltow, Germany
José Suárez de Lezo, MD, PhD, Reina Sofia University Hospital – Córdoba, Spain
Daniel Sünder, MD, Cardiocentro Ticino Foundation – Lugano, Switzerland
Ciro Tetta, MD, University of Torino, School of Biotechnology – Turin, Italy
Keith Thompson, MD, MBA, Cell Therapy Catapult – London, United Kingdom
Juan José Toledo-Aral, MD, PhD, Institute of Biomedicine of Seville – Seville, Spain
Edwin Wagena, PhD, – Voorburg, Netherlands

ORAL ABSTRACT PRESENTERS

Iris Bigalke, MD, Oslo University Hospital – Oslo, Norway
Sofieke de Wilde, MSc, Leiden University Medical Center – Leiden, Netherlands
Juan Domínguez-Bendala, PhD, Diabetes Research Institute, University of Miami – Miami, Florida
Óscar Fernández, MD, PhD, Regional University Hospital of Málaga – Málaga, Spain
Carmen González Gallardo, PhD, San Cecilio University Hospital – Granada Spain

Christine Guenther, MD, apceth GmbH & Co. KG – Ottobrunn, Germany
Else Marit Inderberg-Suso, PhD, Norwegian Radium Hospital – Oslo, Norway
Gunnar Kvalheim, MD, PhD, Oslo University Hospital – Oslo, Norway
Imke Slaper-Cortenbach, PhD, University Medical Center – Utrecht, Netherlands
Stephen Strom, PhD, Karolinska Institute – Stockholm, Sweden
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<td>SEVILLE I, II</td>
<td>J. H. Frederik Falkenburg – How to Bring Cellular Therapy From Science To and Through the Clinic</td>
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<td>FOR THE BENEFIT OF PATIENTS: CHALLENGES AND CRITICAL SUCCESS FACTORS</td>
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<td>Eduardo Bravo – Challenges and Opportunities in Commercializing Cellular Therapies</td>
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<td>Paula Salmikangas – Regulatory Insights into the Development of Authorized Products</td>
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<tr>
<td>0800 – 0930</td>
<td>PLENUMARY SESSION 2 – NEW FRONTIERS IN THE TREATMENT OF OPHTHALMOLOGICAL DISORDERS WITH CELL-BASED THERAPIES</td>
<td>SEVILLE I, II</td>
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<td>Chair: Shomi Bhattacharya</td>
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<td>Co-Chairs: Mauro Krampera and Beatriz Fernandez-Munoz</td>
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<td>Eddy Anglade – Human Embryonic Stem Cell-Derived Retinal Pigment Epithelium for the Treatment of Stargardt’s Macular Dystrophy and Atrophic Age-Related Macular Degeneration</td>
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<td>Miguel Alaminos – Feasibility and Preliminary Results of Allogeneic Tissue Engineered Nanostructured Human Corneas in Patients with Corneal Ulcers in Advanced Stages</td>
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<td>TECHNICAL SESSION 1 – HUMAN PLATELET LYSATE AS AN ALTERNATIVE TO THE USE OF FBS IN TISSUE CULTURES: PRODUCTION, CHARACTERIZATION, AND REGULATION</td>
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<td>Giuseppe Astori – Platelet Lysate: Are They All The Same?</td>
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<td>Richard Schäfer – Human Platelet Lysate: Ready to Replace FBS for Cell Therapies Manufacturing?</td>
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<td>Chair: Natividad Cuende</td>
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<td>Annigje Rietveld – Application of the Hospital Exemption in the Netherlands</td>
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<td>Sol Ruiz – Hospital Exemptions in Spain</td>
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<td>Ralf Sanzenbacher – Implementation of the ‘Hospital Exemption’ Clause for ATMP in Germany</td>
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<td>Guido Pantè – Implementing reg.1394/2007 art.28: the Italian Hospital Exemption Requirement</td>
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<td>NEXT GENERATION CELL THERAPY: MSC AS BIOLOGICAL DRUG FOR TARGETING CANCER - STATE OF THE ART: TECHNOLOGY, TRANSLATION INTO THE CLINIC AND LESSONS LEARNED</td>
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<td>CLINICAL GRADE HUMAN PLATELET LYSATE: AN EFFICIENT AND STANDARDIZED CELL CULTURE SUPPLEMENT TO EXPAND CELL THERAPY PRODUCTS</td>
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<td>Chair: Katy Newton</td>
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<td>1. BMP–7 INDUCES ADULT HUMAN PANCREATIC EXOCRINE–TO–ENDOCRINE CONVERSION</td>
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<td>Presenter: Juan Dominguez–Bendala, Diabetes Research Institute, University of Miami, Miami, USA</td>
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<td>2. ANTERIOR LAMELLAR CORNEAL SUBSTITUTE GENERATED BY TISSUE ENGINEERING FOR TREATMENT OF TROPHIC ULCERS. PRELIMINARY DATA</td>
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<td>Presenter: Carmen González Gallardo, Ophthalmology, San Cecilio Hospital, Granada, Spain</td>
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<td>3. VACCINATION WITH A NEW GENERATION OF TUMOR SPECIFIC MRNA LOADED DENDRITIC CELLS PROLONG PROGRESSION FREE SURVIVAL IN PATIENTS WITH DIFFERENT TYPES OF MALIGNANCES</td>
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<td>Presenter: Iris Bigalke, Department of Cellular Therapy, Oslo University Hospital, Oslo, Norway</td>
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<td>4. CLINICAL APPLICATION OF HUMAN ADIPOSE DERIVED REGENERATIVE CELLS (ADRCs) IN TISSUE REPAIR OF SEVERE SIDE EFFECTS FOLLOWING CURATIVE RADIOTHERAPY TREATMENT</td>
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<td>Presenter: Gunnar Kvalheim, Department of Cellular Therapy, Oslo University Hospital, Oslo, Norway</td>
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<td>5. AGORA SURVEY: ATMP REGULATORY DIFFERENCES IDENTIFIED IN EUROPE</td>
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<td>Presenter: Ineke Slaper–Cortenbach, Cell Therapy Facility, Department of Clinical Pharmacy, UMC Utrecht, Utrecht, The Netherlands</td>
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Friday, September 25, 2015

1415 – 1845

CAT-ISCT WORKSHOP: CHALLENGES AND OPPORTUNITIES FOR THE SUCCESSFUL DEVELOPMENT AND APPROVAL OF ADVANCED THERAPY MEDICINAL PRODUCTS

WELCOME FROM WORKSHOP CO-CHAIRS

Paula Salmikangas, Finnish Medicines Agency (FIMEA) – CAT Chair, Finland
Natividad Cuende, Executive Director, Andalusian Initiative for Advanced Therapies, Spain

1. INTRODUCTION

Moderator: Natividad Cuende, Executive Director, Andalusian Initiative for Advanced Therapies, Spain

Intelligent ATMP Development: Flexibilities and Pitfalls
Speaker: Paula Salmikangas, Finnish Medicines Agency (FIMEA) – CAT Chair, Finland

2. QUALITY DEVELOPMENT/MANUFACTURING ISSUES AND NON–CLINICAL TESTING

Moderator: Dariusz Śladowski, Medical University of Warsaw – CAT member, Poland

Experience from CAT on Quality Development/Manufacturing/GMP
Speaker: Margarida Menezes Ferreira, Autoridade Nacional do Medicamento e Produtos de Saúde, I.P. (INFARMED) – Alternate CAT member, Portugal

Experience from CAT on Non–Clinical Development
Speaker: Tiina Palomäki, Finnish Medicines Agency (FIMEA) – CAT member, Finland

Views from ATMP Developer from Academia on Quality/Manufacturing Issues Encountered During the Manufacture of ATMPs for Clinical Trials
Speaker: Laura Leyva, Technical Director of the Cell Therapy GMP Facility, University Regional Hospital in Málaga, Spain

Q&A

1550 – 1610  COFFEE BREAK WITH EXHIBITS

3. CLINICAL DEVELOPMENT

Moderator: Edwin Wagena, Netherlands

Clinical Trials with ATMPs: Experience from CAT
Speaker: Tomáš Boráň, Státní ústav pro kontrolu léčiv – CAT member, Czech Republic

Specificities of Clinical Development of ATMPs: Considerations Regarding Exploratory and Confirmatory Trials
Speaker: Martina Schüßler–Lenz, Paul–Ehrlich–Institute, Germany – CAT member and Vice–Chair, Germany

Use of Retrospective Studies for Marketing Authorization
Speaker: Giovanni Milazzo, Head Regulatory Affairs Advanced Medicines, Chiesi Farmaceutici, Italy

The New Clinical Trial Regulation: What Will Change for ATMP Developers
Speaker: Simona Badoi, Agentia Națională a Medicamentului și a Dispozitivelor Medicale – CAT member, Romania

Q&A

4. SUPPORT FROM EMA/CAT TO ATMP DEVELOPERS

Moderator: Paula Salmikangas, Finnish Medicines Agency (FIMEA) – CAT Chair, Finland

Presentation on Support Available to ATMP Developers and Approval Mechanism (Adaptive Pathways, Conditional Approval, Approval Under Exceptional Circumstances)
Speaker: Patrick Celis, European Medicines Agency, CAT Scientific Secretariat, UK

5. OPEN FORUM/PANEL DISCUSSION

Closing Remarks

1845 – 1945  POSTER SESSION WITH EXHIBITS
## Saturday, September 26, 2015

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### Saturday, September 26, 2015

**ORAL ABSTRACT SESSION 2**

**Chair:** Giuseppe Astori

1. **MESEMS: A RANDOMIZED, DOUBLE BLIND PLACEBO–CONTROLLED CROSS–OVER STUDY TO EVALUATE SAFETY AND EFFICACY OF INTRAVENOUS ADMINISTRATION OF AUTOLOGOUS MESENCHYMAL STEM CELLS IN PATIENTS WITH MULTIPLE SCLEROSIS**
   
   **Presenter:** Óscar Fernández, Regional University Hospital of Málaga – Málaga, Spain

2. **TREATMENT OF ADVANCED GASTROINTESTINAL (GI) CANCER IN A CLINICAL PHASE I/II TRIAL WITH GENETICALLY MODIFIED MESENCHYMAL STEM CELLS (gmMSC): A PHASE I CLINICAL STUDY**
   
   **Presenter:** Christine Guenther, apceth GmbH & Co. KG, Munich, Germany

3. **T CELL THERAPY TARGETING A NEOANTIGEN REDUCES IN VIVO TUMOUR GROWTH**
   
   **Presenter:** Else Marit Inderberg–Suso, Department of Cellular Therapy, Oslo University Hospital–Radiumhospitalet, Oslo, Norway

4. **TRANSLANTATION OF HUMAN AMNION EPITHELIAL CELL TO CORRECT ACUTE LIVER FAILURE AND METABOLIC LIVER DISEASE**
   
   **Presenter:** Stephen Strom, Karolinska Institute, Stockholm, Sweden

5. **REACHING REGULAR CLINICAL CARE WITH ACADEMIC ADVANCED THERAPY MEDICINAL PRODUCTS IN THE NETHERLANDS**
   
   **Presenter:** Sofieke de Wilde, Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, The Netherlands

**1335 – 1505**

**COFFEE BREAK**

**1505 – 1700**

**WORKSHOP 6 – CHALLENGES IN THE CLINICAL DEVELOPMENT OF CELL–BASED (ORPHAN) MEDICINAL PRODUCTS: TRIAL DESIGN, SAMPLE SIZE, AND PRIMARY ENDPOINTS**

**Chair:** Edwin Wagena

**Speakers:**

- Holger Müller – Introducing a Cellular Therapy into the Market: Opportunities and Hurdles
- Warren Sherman – The CHART-1 Study for Heart Failure: Design, Process, and Status

**WORKSHOP 7 – JOINT ISCT/RED TERCEL SESSION: CRITICAL FACTORS FOR CELL THERAPY SUCCESS IN NEURODEGENERATIVE DISORDERS**

**Co–Chairs:** Massimo Dominici and Salvador Martinez

**Speakers:**

- Juan José Toledo-Aral – Cellular Therapy With Carotid Body for Parkinson’s Disease
- Salvador Martinez – Autologous Bone Marrow Intra-Spinal Grafts Develop a Neurotrophic Activity in CNS Motor Areas of ALS Patients
- Óscar Fernández – Stem cell Therapy in Multiple Sclerosis: A Phase I/II DBPC Trial with 2 Doses of Mesenchymal Adipose SCT in Non-Responsive Secondary Progressive MS
TRAINING SESSIONS DESCRIPTIONS

A JOINT TRAINING SESSION (ECA – AGORA – ISCT EU) FOR QPS ON ATMPS: QP TRAINING SESSION ON ATMPS

Thursday, September 24th, 2015
Time: 0800 – 1045

Speakers: Mark W. Lowdell, Ineke Slaper-Cortenbach, Andrea Hauser, Christine Guenther, Christoph Peter, Martin Hildebrandt

Learning objectives:
Caught between a rock and a hard place, Qualified Persons and future QPs in charge of cell-based medicines and ATMPs face the need of finding training opportunities, but these are difficult to find in the traditional GMP training incentives. The European Compliance Association (ECA) pioneered in this field, and AGORA, an FP7-funded initiative, has similar goals in advancing the field of ATMPs. Together with ISCT, ECA and AGORA have joined to offer a QP training session in ATMPs.

In this interactive workshop, both basic and specific topics of importance in the field of ATMPs will be addressed. The topics will include APIs, investigational medicinal products, conditional release, multicenter trials, and others. In three sessions, we shall discuss:

• Basic requirements to become a QP, regulatory issues and obligations in everyday’s work as a QP;
• Import of APIs, starting materials and vendor qualification;
• Pitfalls when moving from non-GMP to the GMP world;
• Plenty of examples from the organizers and the audience.

A THEORETICAL AND PRACTICAL BASIC TRAINING SESSION FOR PEOPLE WORKING ON STERILE MANUFACTURING OF ATMPS ORGANIZED BY AIAT-CTP-ISCT

Thursday, September 24th, 2015
Time: 0800 – 1045

Teachers:
Simona Giudi and Gloria Carmona

Learning objectives:
This workshop is designed for quality assurance, quality control, and production personnel presently working (or intending to do so) on sterile manufacturing of ATMPs who have a limited knowledge of Good Manufacturing Practice (GMP).

In the theoretical part, participants will be provided with some tips and tricks to reach compliance to the cGMP rules. The practical aspects will address how to manage deviations on Quality Management Systems. The participants, supported by the presenters, will work in groups with different deviations and out of specification (OOS) in order to define corrective and preventive actions (CAPA).

The number of participants is limited, and early registration recommended. The workshop will be recognized with a certificate and 0.39 CME credits.
PLENARY SESSION SUMMARIES

PLENARY SESSION 1 – HOW TO DRIVE THE TRANSLATION OF CELLULAR THERAPIES FOR THE BENEFIT OF PATIENTS: CHALLENGES AND CRITICAL SUCCESS FACTORS

Thursday, September 24th, 2015  Time: 1100 – 1230

Chair: Robert Preti

HOW TO BRING CELLULAR THERAPY FROM SCIENCE TO AND THROUGH THE CLINIC

J. H. Frederik Falkenburg

- Although not all biological and biochemical features of cellular products need to be identified prior to potential development into clinical application, clear potential mechanisms of action should be identified and tested before entering the translational development. Especially when heterogeneous cell products are being developed, lack of product information in relation to the potential clinical application often severely hampers clinical development and interpretation of trials.
- To illustrate potential clinical benefit of cellular products, seeking marketing authorization is not necessary. Proof of concept clinical studies with cellular products are not extraordinary expensive and can be performed in investigator initiated clinical trials with mainly non-for-profit funding.
- Inadequate monitoring of non-classical end points following cellular therapy is a major cause of failure of development of cellular products. Preclinical monitoring is frequently far better developed than clinical and post-clinical monitoring resulting in misinterpretation of clinical studies. Bedside to bench clinical monitoring is a major source of new developments for future clinical applications.

CHALLENGES AND OPPORTUNITIES IN COMMERCIALIZING CELLULAR THERAPIES

Eduardo Bravo

- Challenges to get a cell therapy product approved and reimbursed.
- What is required to successfully commercialize a cell therapy product? Is this different to any other type of bio-pharma product?
- What needs to happen to make cell therapy products successful in the bio-pharmaceutical market?

REGULATORY INSIGHTS INTO THE DEVELOPMENT OF AUTHORIZED PRODUCTS

Paula Salmikangas

- This presentation will give insight into the EU regulatory framework of ATMPs and provides information on the available guidance.
- Information will be provided on licensed ATMPs, as well as on products in clinical trials.
- Latest regulatory changes will be addressed, as well as challenges identified by the CAT.

PLENARY SESSION 2 – NEW FRONTIERS IN THE TREATMENT OF OPHTHALMOLOGICAL DISORDERS WITH CELL-BASED THERAPIES

Friday, September 25th, 2015  Time: 0800 – 0930

Chair: Shomi Bhattacharya

Cell therapies are being extensively investigated as treatments for degenerative eye diseases, either for replacing lost cells, restoring injured corneas or, based on more recent evidence, as paracrine-mediated therapies to protect compromised endogenous cells from death and induce the growth of new connections. Eye injury or degeneration occurs in a number of blinding diseases. Conventional therapy consisted of preventing the initial injury or increasing the resistance of cells to injury. Recently, it has even become possible to repopulate tissue compartments with stem cells. There are currently many clinical trials ongoing which aim to test the safety and efficacy of cell-based therapies in the eye. This session focuses on the potential of different cell therapy approaches based on the use of human embryonic stem cell-derived retinal pigment epithelium, tissue engineered human corneas and Treg cells for the treatment of degenerative, traumatic and immunological eye diseases.

HUMAN EMBRYONIC STEM CELL-DERIVED RETINAL PIGMENT EPITHELIUM FOR THE TREATMENT OF STARGARDT’S MACULAR DYSTROPHY AND ATROPHIC AGE-RELATED MACULAR DEGENERATION

Eddy Anglade

- To examine the role of the retinal pigment epithelium (RPE) in the homeostasis of photoreceptor function.
- To examine the pathogenesis of atrophic age-related macular degeneration and Stargardt macular dystrophy.
- To examine the potential for RPE cellular replacement therapy for the treatment of degenerative diseases of the macula.
FEASIBILITY AND PRELIMINARY RESULTS OF ALLOGENEIC TISSUE ENGINEERED NANOSTRUCTURED HUMAN CORNEAS IN PATIENTS WITH CORNEAL ULCERS IN ADVANCED STAGES

Miguel Alaminos
- To recognize the importance and usefulness of tissue engineering for the treatment of ocular surface disorders.
- To learn the different steps involved in the basic design and preclinical evaluation of a cornea tissue substitute.
- To generate the cornea tissue substitute for clinical use by implementing current regulatory requirements in the context of a clinical trial.

AUTOLOGOUS TREG CELL THERAPY FOR NON-INFECTIOUS UVEITIS

Arnaud Foussat
- Regulatory T (Treg) cells are playing an important role in the maintenance of eye immune privilege. Treg functions are impaired in patients with eye inflammatory diseases.
- Autologous antigen-specific Treg (Ag-Treg) cells can be isolated and expanded from the peripheral blood of human donors under GMP conditions and displayed multiple mechanisms of action in vitro. The non-clinical development of Ag-Treg cells requires the production of highly comparable Ag-Treg cells from mice showing the same phenotype and in vitro functions.
- Intravenous administration of Treg cells specific for Collagen-II (Col-Treg cells), a protein found in the vitrous body of the eye, inhibits experimental autoimmune uveitis in mice. Col-Treg cells inhibits disease symptoms as well as histological features of uveitis by impacting ocular infiltration by pro-inflammatory cells as well as pro-inflammatory cytokines production.

CHIMERIC ANTIGEN RECEPTOR T-CELLS: FROM SUSTAINED REMISSIONS IN LEUKEMIAS TO NEW TRIALS IN SOLID TUMORS: WHAT ARE THE OPPORTUNITIES AND POTENTIAL PITFALLS?

Bruce Levine
- Understand the science and technology underpinning Chimeric Antigen Receptor (CAR) T cells.
- Understand the results from recent clinical trials of CAR T cells in hematologic malignancies.
- Understand the challenges of CAR T cell therapy in solid tumors and potent methods for assessing and enhancing potency.

SUICIDE-GENE STRATEGIES FOR GENETICALLY MODIFIED T CELLS

Martin Pule

PLENARY SESSION 3 – ADOPTIVE T-CELL THERAPIES/GENETICALLY ENGINEERED T-CELLS: T-CELL RECEPTORS (TCRS), CHIMERIC ANTIGEN RECEPTORS (CAR), AND TUMOR INFILTRATING LYMPHOCYTES (TILS) AGAINST TUMOR ANTIGENS

Saturday, September 26th, 2015  Time: 0800 – 0930

Chair: Kurt Gunter

Thanks to advances in our understanding of immunology and advances in manufacturing technology, adoptive immune cell therapy is now a reality. T cells can be genetically modified, activated and expanded in vitro and in large scale, GMP manufacturing suites. Unlike standard drugs and biologics, following in vivo administration, T cells can multiply, as well as persist long term, which enables durable efficacy with a single dose, but also raises questions about safety. As this field has progressed, we have learned much about the safety, efficacy and challenges to development of adoptive immune cell therapies. Multiple groups have reported exciting data with chimeric antigen receptor (CAR) T cells in liquid tumors, but progress in solid tumors has been more challenging. Infusions of genetically modified T cells may be accompanied by toxicities related to disease burden or off target effects and novel approaches for the engineering of in vivo “off switches” may serve to mitigate such toxicity. The discovery and initial development of immune cellular therapy has generally occurred in academic laboratories, but there has recently been significant industry interest. The translation of cellular therapies from academic laboratories to larger scale, GMP compliant manufacturing heralds a new era in the engineering of cellular therapies. In this session, we will review general progress in the field of adoptive T cell therapies, discuss current challenges and propose solutions in this rapidly evolving and exciting area of medicine.

PLENARY SESSION 4 – TISSUE ENGINEERING AND REGENERATIVE MEDICINE

Saturday, September 26th, 2015  Time: 1000 – 1130

Co-Chairs: Ineke Slaper-Cortenbach and Bruce Levine

The field of regenerative medicine is rapidly moving
forward aiming at replacing, engineering or regenerating human tissues or organs. This session is focused on the efforts to restore cartilage, intestine and liver. Prof. El Haj is a renowned researcher with expertise in the field of stem cell therapy for orthopaedic applications. She will present her research focused on innovative ways in which cells and tissues can be manufactured, which will lead to new orthopaedic repair strategies. Prof. Saris is a distinguished orthopaedic surgeon in the field of knee reconstruction and researcher in the field of cartilage repair. He was involved in the establishment of the first two registered cartilage cell therapy products in Europe. He will present the results of clinical trials using cell-based therapies and his perspective on the use of stem cells for cartilage repair in the future. Dr Gehart will present the research that has been done in the field of regeneration of liver and intestine. The underlying repair processes in combination with the development of culture systems for the expansion of tissue-derived stem cells paves the way for using stem cells for organ repair in medical practice.

TRANSLATING STEM CELL CONTROL AND DELIVERY PLATFORMS TO THE CLINIC
Alicia El Haj

- During this presentation, I will introduce the use of tissue engineering approaches to control and define stem cells for use in clinical therapy.
- I will outline two case studies of T.E. platforms which are being progressed to the clinic, 1) for MSC delivery and control for cell therapy and 2) for tissue engineering the stem cell niche.
- Both approaches form part of work being carried out through a new multidisciplinary initiative in the UK, the UK Regenerative Medicine Hubs.

CARTILAGE REGENERATION, THE IMPACT TRIAL (CHONDROMES MIXED WITH MSC) AND THE FUTURE
Daniel Saris

- How to efficiently get from bench to bedside.
- Learning from design and execution of an ATMP first in man knee reconstruction trial.
- Ensuring serendipity and open mindedness allow for unique scientific findings while maintaining patient safety.

ADULT STEM CELLS, ORGANOIDS AND REGENERATIVE MEDICINE
Helmuth Gehart

- The regenerative potential of adult tissues rests within adult stem cells. While the regenerative processes in different organs such as intestine and liver are highly dissimilar, the underlying mechanisms are shared.
- Adult stem cells can be expanded in vitro as organoids. Organoids are epithelial structures grown in a 3D matrix that are able to perform organ function in a culture dish.
- Due to their fast expansion rate, high genetic stability and ability to differentiate to hepatocytes and biliary cells, human liver organoids are a promising tool for research, drug development and regenerative medicine.

CAT-ISCT WORKSHOP

CHALLENGES AND OPPORTUNITIES FOR THE SUCCESSFUL DEVELOPMENT AND APPROVAL OF ADVANCED THERAPY MEDICINAL PRODUCTS

Friday, September 25th, 2015 Time: 1415 – 1845

Co-Chairs: Paula Salmikangas and Natividad Cuende
The workshop will allow the attendees of the ISCT meeting and the developers of ATMPs from academia and industry to learn about the development and authorisation of cell-based ATMPs in the EU, to understand the expectations of the CAT for the quality development, manufacturing, non-clinical testing and clinical trials and to hear about the support from EMA and CAT to ATMP developers. The workshop will also give the opportunity for direct interactions with the EU Regulators.

WORKSHOP SESSION SUMMARIES

WORKSHOP 1 – CLINICAL TO COMMERCIAL TRANSITION OF CELLULAR THERAPIES FOR THE BENEFIT OF PATIENTS

Thursday, September 24th, 2015 Time: 1415 – 1545

Chair: Miguel Forte
Cellular therapy products represent the next wave of therapeutic opportunities for patients with unmet medical needs. The session will discuss the challenges and opportunities in the translation process starting from the Target Product Profile all the way through to reimbursement. There will be a particular focus on market access and reimbursement in Europe.

WHAT COMPANIES NEED TO DO TO NAVIGATE THE TRANSLATION PROCESS

Miguel Forte
- The challenges and opportunities in the translation process for cellular therapy products. The first objective will focus on the setting of the TPP (Target Product Profile) in the early stages of the translation process, paving the way to the entire process to market launch.
The second objective will deal with the key elements of the translation process regarding product process development and generation of clinical evidence towards regulatory requirements for market authorization.

The third objective will discuss aspects pertaining to market access regarding patients, physicians and payers, setting the stage for the focused reimbursement discussion in the other two presentations in the workshop.

**REIMBURSEMENT MECHANISMS FOR ATMPs ACROSS THE BIG5EU**

Panos Kefalas
- The variation in pricing and reimbursement frameworks for ATMPs across France, Germany, Italy, Spain and the UK.
- The mechanisms that individual markets employ to translate incremental benefit claims to reimbursed price potential.
- The impact of the size of target population on market access processes and willingness-to-pay and adopt.

**REIMBURSEMENT OF ATMPs IN GERMANY**

Xenia Boergen
- Different reimbursement systems in Germany in hospitals and for outpatients in the statutory health insurance system:
  - AMNOG (=Arzneimittelmarktneuordnungsge- setz, reimbursement for novel medicinal products) vs. DRG (Diagnosis-Related Groups).
- The way to reimbursement and examples of reimbursed ATMPs in Germany.

**WORKSHOP 2 – LIGHT AND SHADOWS OF CELL THERAPY IN VASCULAR DISEASES**

Thursday, September 24th, 2015  
Time: 1415 – 1545

Chair: José Suárez de Lezo

Different studies have shown the feasibility and safety of several types of cell therapy on a wide spectrum of pathologies. Today, we have significant information on the clinical effects of such therapies. However, many shadows still obscure the real role they will have in the future. This session will discuss on the effects of cell therapy on acute myocardial infarction, neurological disorders and limb ischaemia. The mechanism of action, the potential benefits and the type of cell therapy still remain uncertain.

**BM-MNC TREATMENT AFTER ACUTE MYOCARDIAL INFARCTION - LESSONS FROM THE SWISS AMI STUDY WHILE WAITING FOR BAM!**

Daniel Sürder
- What do we know deriving from the different phase II trials and what do the results of the different meta-analyses add.
- The difference between cell therapy strategies after acute myocardial infarction and in the stable phase of chronic ischemic heart disease.
- The role of the different cell types.

**CELL THERAPY FOR STROKE: IS IT A FEASIBLE AND SAFE APPROACH?**

Francisco Moniche
- Stroke is the leading cause of long-term disability in the world. No neuroprotective or neurorestorative therapy has been approved for stroke. Cell therapy has demonstrated efficacy for regaining neurological function after stroke in animal models and could be a potential new treatment in stroke patients.
- Previous clinical trials have demonstrated safety of intravenous and intra-arterial administration of different type of stem cells in stroke, mainly bone marrow-derived population such as MSC or mononuclear cells. However, best delivery route, optimal time window and doses are still debated. Several clinical trials are ongoing to evaluate mechanisms of action in stroke patients and to test efficacy.
- Stroke damage is not limited to neurons but involve all brain cell types. Cell therapy targets a range of host brain cells and can promote neuroprotection and neural repair. Stem cells can provide paracrine support enhancing synaptogenesis, angiogenesis and axonal growth and modulate inflammatory response after stroke.

**CELL THERAPY FOR CRITICAL LIMB ISCHEMIA: EVIDENCE ON SAFETY AND EFFICACY**

Leopoldo Laricchia-Robbio
- The Andalusian Initiative for Advanced Therapies (AIAT) is a publicly funded organization created by the Regional Government of Andalusia to promote translational research in cell therapy field. The AIAT is part of the Public Healthcare System which comprises, 47 hospitals, a network of 10 GMP facilities, and it acts as promoter of several cell therapy clinical trials. Among them, a few are investigating the role of cell therapy to treat Critical Limb Ischemia.
- An overview of the cell therapy clinical trials sponsored by the AIAT will be presented. The first results obtained from the trials will be described with particular attention to the safety and some preliminary indications on the efficacy of this treatment.
• The efficacy results obtained from these clinical trials will be discussed in a critical way and correlated to the specific design adopted. It will be discussed how different aspects of the trial, including the dose and the way of administration, can affect the final outcome by comparing results of similar cell therapy clinical trials to treat Critical Limb Ischemia.

WORKSHOP 3 – ON DOSE FINDING, FREQUENCY, AND ROUTE OF ADMINISTRATION: WHAT IS THE CELL THERAPY EQUIVALENT TO PK/PD STUDIES?

Thursday, September 24th, 2015  Time: 1600 – 1730

Chair: Robert Preti
As practitioners in the development of the regenerative medicine industry, we are often compared to those that came before us in the biologics industry. In fact, whilst the challenges to commercial success in this industry are real, just as in the industries that we are being compared to, solutions are forming along the lines of the unique challenges presented. That being said, are we really that different than our biologics industry predecessors? What lessons can we learn from how they solved the challenges of developing novel and game changing therapeutics that didn’t quite fit their predecessors in the small molecule drug development industry? As we contend with the key issues including dose finding, optimal route of administration and frequency of administration for our therapeutics, it is often said that, in regenerative medicine, traditional drug and then biologic paradigms of pharmacokinetic (PK) and pharmacodynamics (PD) modelling are difficult, if at all possible to directly apply. This session is intended to bring experts on the topic of how PK/PD models have been adapted to biologics to describe the relation between dosing, concentration and efficacy, in an attempt to inform the practices and approaches of today’s regenerative medicine development professionals.

HOW DO TRADITIONAL CONCEPTS OF DEVELOPMENTAL PHARMACOLOGY APPLY TO LIVING MEDICINES?

Sven Kili
• Explore the traditional development activities of small molecule and how they differ from cell and gene therapy models.
• How might Pk and Pd data be gained in cell and gene therapies to guide dosage

ANIMAL MODELS OF STEM CELL THERAPY OF MYOCARDIAL INFARCTION

Marco Matteucci
• The Design of the Experimental Protocol.

Outcome of the cellular therapy in different animal models of myocardial infarction.
• Multimodal platform to assess cardiac cell therapy.

IMAGING (IMAGINING) CELL FATE
Maria Luisa Garcia-Martin
Presentation by Armin Sepp

WORKSHOP 4 – POTENCY TESTING FOR CELLULAR PRODUCTS + EXOSOMES

Thursday, September 24th, 2015  Time: 1600 – 1730

Chair: Mauro Krampera
The clinical use of stem cells in regenerative and immune regulatory medicine implies the need for standardized functional assays characterizing stem cell properties, foreseeing their clinical efficacy and acting as release criteria. Immunological assays in 2D- and 3D-culture conditions, mesenchymal stromal cell potency assays and experimental characterization of extracellular vesicle functions represent crucial tools to this aim and will be discussed in this workshop.

IMMUNOLOGICAL ASSAYS IN 2D- AND 3D- CULTURE CONDITIONS
Giulio Bassi
• The importance of standardized immunological assay.
• Quality control on MSC – biomaterials interaction.
• Long term effects of MSC – biomaterials culture.

THE CHALLENGE OF DEFINING MESenchymAL STROMAL CELL POTENCY ASSAYS AND THEIR POTENTIAL USE AS RELEASE CRITERIA
Luc Sensebé
• One of the main concerns in the field of MSCs is the lack of relevant controls and release criteria for safety and efficacy. A first aim will be how to define potency assays for immunomodulation and anti-inflammatory purposes, describing methods to reach this target.
• The second aim concerns the release criteria that can be used for MSCs in different fields. Particularly, how to go from potency assays to release criteria that should be fast and relevant.
• The third aim will concern the use of potency assays for comparing different sources of MScs (e.g MSCs/ASCs), productions and uses.
MINIMAL EXPERIMENTAL REQUIREMENTS FOR DEFINITION OF EXTRACELLULAR VESICLES AND THEIR FUNCTIONS: A POSITION STATEMENT FROM THE INTERNATIONAL SOCIETY FOR EXTRACELLULAR VESICLES

Ciro Tetta

- Understanding extracellular vesicles as the new paradigm shift in stem cell mediated regenerative effect;
- The relevance of miRNAs as genetic material concentrated in extracellular vesicles and horizontally transferred to target cells;
- Major relevant issues that need to solved in order to fulfill regulatory compliance and to bring vesicles to clinical application.

WORKSHOP 5 – MAKING CELLULAR THERAPIES AVAILABLE TO PATIENTS: THE PURPOSE OF HOSPITAL EXEMPTION

Friday, September 25th, 2015 Time: 1105 – 1235

Chair: Natividad Cuende

In Europe, advanced therapy medicinal products (ATMPs) are mainly governed by Directive 2001/83/EC amended by Regulation 1394/2007 which sets specific rules concerning their centralized marketing authorization, supervision and pharmacovigilance. Nevertheless, ATMPs not intended to be marketed and not industrially prepared are beyond the scope of Directive 2001/83/EC. This is commonly called hospital exemption (HE). In this workshop we will show how some European countries have transposed HE into their national laws and their experience so far. However, the main focus of the session is not the requirements every country has set to grant hospital exemption but the purpose of HE in the different countries: Is it an alternative to Marketing Authorization for products intended to be placed in local markets? Is it to allow hospitals to offer ATMPs once the quality, safety and efficacy have been demonstrated? Is it to allow a first in human proof of concept under less stringent rules? Is it only to allow off-label treatments or situations similar to compassionate use?...

APPLICATION OF THE HOSPITAL EXEMPTION IN THE NETHERLANDS

Annigje Rietveld

- Have an open ear for the field.
- Good collaboration with assessors.
- Keep it simple.

HOSPITAL EXEMPTION IN SPAIN

Sol Ruiz

- What is the objective of hospital exemption in the context of the regulation on advanced therapy medicinal products

- How hospital exemption has been interpreted in Spain. Requirements and procedure.
- Update on the current situation of hospital exemption in Spain.

IMPLEMENTATION OF THE ‘HOSPITAL EXEMPTION’ CLAUSE FOR ATMP IN GERMANY

Ralf Sanzenbacher

- This presentation aims to provide an overview on the implementation on the ‘Hospital Exemption clause’ for Advanced Therapy Medicinal Products (ATMP) in Germany.
- The pros and cons -as learned by the application procedures conducted so far- will be highlighted.
- Furthermore, the ‘Hospital Exception’ will be discussed in comparison to ATMP requiring a centralised ‘European’ marketing authorization.

IMPLEMENTING REG.1394/2007 ART.28: THE ITALIAN HOSPITAL EXEMPTION REQUIREMENT

Guido Pantè

- Key features and requirements of the Hospital exemption in Italy.
- Existing differences and purposes between HE, compassionate and off-label use.
- Examples of features of HE approved products.

WORKSHOP 6 – CHALLENGES IN THE CLINICAL DEVELOPMENT OF CELL-BASED (ORPHAN) MEDICINAL PRODUCTS: TRIAL DESIGN, SAMPLE SIZE, AND PRIMARY ENDPOINTS

Saturday, September 26th, 2015 Time: 1530 – 1700

Chair: Edwin Wagena

Advanced therapy medicinal products (ATMPs) constitute a major class of innovative therapeutics that are being investigated as treatments for several diseases. Despite the success of many such products in animal studies, few have been granted marketing authorization by the EMA. Only four ATMPs have a valid (centralized) marketing authorization in Europe: Glybera (gene therapy), ChondroCelect (tissue-engineered product), Holoclar (tissue-engineered product) and MACI (tissue-engineered product). While regulatory requirements for quality, safety and efficacy apply to advanced cellular therapies as for all other medicinal products, their demonstration is associated with very specific challenges related to the manufacture, nonclinical and clinical testing, as well as administration of the products. In order to increase the success of moving these innovative therapies down the development pipeline, there is a need to identify...
and overcome the challenges. In this session we focus on specific challenges and opportunities in the clinical development of cell-based (orphan) medicinal products.

**EX-VIVO EXPANDED AUTOLOGOUS HUMAN CORNEAL EPITHELIAL CELLS FOR THE TREATMENT OF LIMBAL STEM CELL DEFICIENCY: A CASE STUDY FOR THE USE OF RETROSPECTIVE CLINICAL STUDIES IN THE CONTEXT OF A MARKETING AUTHORIZATION APPLICATION FOR AN ATMP**

Diego Ardigò
- The presentation will provide a review of the history and clinical data of the first tissue engineered medicinal product containing stem cells conditionally approved in Europe. The historical perspective will be integrated with the evolution of the relevant regulations in the EU and the key clinical data of the product.
- The presentation will provide a review of the clinical backstage of the marketing authorization procedure, which was based on retrospective clinical data collected from the health records of patients treated with the product in clinical practice (“consolidated treatment”), outside a “traditional” development pathway. An analysis of the issues and challenges faced in the industrial use of these clinical data in the purview of a regulatory submission will be provided.
- A more general framework for value and reliability of retrospective data in the assessment of risk-benefit for Advanced Therapy Medicinal products will be discussed, analyzing potential biases and gaps generated by such type of data. The interplay between the degree of evidence provided at the Marketing Authorization Application and the content of the product’s Risk Management Plan (including post-approval commitments) will also be touched.

**INTRODUCING A CELLULAR THERAPY INTO THE MARKET: OPPORTUNITIES AND HURDLES**

Holger Müller
- Inform about challenges in designing clinical trials. Provide a rationale for the clinical trial design chosen.
- Regulatory complications for cellular therapies, specifically for non-ATMP products.
- Market uptake hurdles when introducing a cellular therapy into the market. Overcoming logistical and administrative challenges.

**THE CHART-1 STUDY FOR HEART FAILURE: DESIGN, PROCESS AND STATUS**

Warren Sherman
- To understand key elements in the formulation of Phase 3 Trials in patients with chronic heart failure.
- To identify ways of accelerating enrollment in heart failure trials.

**WORKSHOP 7 – JOINT ISCT/RED TERCEL SESSION: CRITICAL FACTORS FOR CELL THERAPY SUCCESS IN NEURODEGENERATIVE DISORDERS**

Saturday, September 26th, 2015 Time: 1530 – 1700

Co-Chairs: Massimo Dominici and Salvador Martinez

The brain has a much lower regenerative capacity if compared with other organs, such as skin, marrow and gut. Moreover, several of the neurological disorders are the most complex to be understood, and tissue accessibility represents a limitation for either local or systemic transplantations. Nevertheless, the advent of novel technologies for cellular therapeutics is progressively making them solid experimental realities for brain repair, with several groups worldwide involved in pioneeristic laboratory studies and early clinical trials. This session brings together ISCT and a Spanish network of cellular therapy (Red TerCel) to share novel findings from basic science to clinical translation in cellular therapies for neurological disorders. Juan José Toledo-Aral will present novel approach for Parkinson’s disease and Salvador Martinez will explain how clinical research may be benefiting a still lethal condition, such as the Amyotrophic Lateral Sclerosis. Finally, Óscar Fernandez will share novel data on how mesenchymal progenitors can be utilized for Multiple Sclerosis. Together these papers will present critical aspects during the development of projects for brain repair simultaneously showing a model of performing challenging researches in a national network, the Red TerCel. ISCT is sharing this vision and is embracing these efforts further calling for extra-national collaborations that may be starting from this interesting session.

**CELLULAR THERAPY WITH CAROTID BODY FOR PARKINSON’S DISEASE**

Juan José Toledo-Aral
- To introduce the cell therapy in Parkinson’s disease
- To explain the physiological bases of the use of carotid body cells in antiparkinsonian cell therapy
- To understand different factors that can affect the clinical use of carotid body cell therapy in Parkinson’s disease
AUTOLOGOUS BONE MARROW INTRA-SPINAL GRAFTS DEVELOP A NEUROTROPHIC ACTIVITY IN CNS MOTOR AREAS OF ALS PATIENTS

Salvador Martinez
• Design experimental approaches in translational research of cellular therapy.
• Investigate mechanisms of neurotrophic activity in models and translate into human clinical trials.
• Describe molecular and cellular effects of clinical experiments in human samples. Requirement of good basic research training to develop adequate analysis of patients’ biological materials.

STEM CELL THERAPY IN MULTIPLE SCLEROSIS: A PHASE I/II DBPC TRIAL WITH 2 DOSES OF MESENCHYMAL ADIPOSE SCT IN NON-RESPONSIVE SECONDARY PROGRESSIVE MS

Óscar Fernández
• In this presentation the basic knowledge on Multiple Sclerosis (MS) – Ethiology, Pathology, Epidemiology, Pathogenesis, Clinic – will be presented.
• All the information published on SCT in MS will be briefly presented.
• We will present the preliminary results of a DBPC phase I/II trial on efficacy and feasibility, in non-responsive to treatment patients with secondary progressive MS, treated with 2 doses of SC obtained from adipose tissue. Some clues to responsiveness analyzed.

TECHNICAL SESSION SUMMARIES

TECHNICAL SESSION 1 – HUMAN PLATELET LYSATE AS AN ALTERNATIVE TO THE USE OF FBS IN TISSUE CULTURES: PRODUCTION, CHARACTERIZATION, AND REGULATION

Friday, September 25th, 2015
Time: 1000 – 1100

Co-Chairs: Mauro Krampera and Beatriz Fernandez-Munoz
Human Platelet Lysate (hPL) is a xeno-free alternative to FBS for cell culture in a clinical and research context. In this session we will give an overview of different methods for hPL production and we will discuss several safety concerns such as the relevance of Donor Blood group/Rhesus factor or the need of agreed release criteria for GMP hPL.

This networking session will explore several questions, such as: what is the best protocol for hPL production? Which tests should we use for hPL characterization? What would be the release criteria? To what extent are we ready to replace FBS for cell therapies manufacturing? What will be the role of transfusion centres and private companies? etc.”. To this aim, Dr. Karen Bieback will present the experience of an academic facility on PL production and characterization under GMP conditions; Dr. Giuseppe Astori will discuss different methods of PL preparation and the problem of safety; Dr. Richard Schäfer will critically analyze pros and cons of FBS replacement with hPL.

PLATELET LYSATE PRODUCTION AND CHARACTERIZATION UNDER GMP CONDITIONS: THE EXPERIENCE OF AN ACADEMIC FACILITY

Karen Bieback
• To understand the advantages/disadvantages of using human platelet lysate as alternative to fetal bovine serum in tissue cultures, using human mesenchymal stromal cells as example.
• To compare the lab-scale and GMP-scale manufacturing and characterization process of PL.
• To propose improvements for GMPL-compliant production and characterization of platelet lysate.

PLATELET LYSATE: ARE THEY ALL THE SAME?

Giuseppe Astori
• Platelet lysate can be produced using different methods.
• The functionality of platelet lysate, intended as the ability to expand a culture of mesenchymal stromal cell is dependent by the platelet lysate production method.
• An original method for the platelet lysate production and safety assessment will be presented.

HUMAN PLATELET LYSATE: READY TO REPLACE FBS FOR CELL THERAPIES MANUFACTURING?

Richard Schäfer
• Introduce a new HPL joint project team between AABB and ISCT that is composed of blood suppliers, HPL manufacturers, basic and clinical science researchers, transfusion medicine professionals, quality and regulatory specialists.
• Discuss whether HPL is an adequate/superior replacement for FBS, including questions of HPL production requirements and capacities.

TECHNICAL SESSION 2 – AUTOLOGOUS CELLS AND THE USE OF POINT OF CARE DEVICES: AN OPPORTUNITY TO GET A SPECIFIC TYPE OF CELL THERAPY TO PATIENTS EARLY? PROS AND CONS OF POINT OF CARE TREATMENTS

Friday, September 25th, 2015
Time: 1000 – 1100

Co-Chairs: Martin Hildebrandt and Shirley Bartido
Point of Care (PoC) treatments in cell therapy challenge the borders of clinical procedure vs medicinal product
manufacturing, in a setting often claimed to be of reduced risk because of the autologous nature of the cell products. Is an autologous tissue simply “processed”, or does the process yield a distinct product? And, if so, is this product as simple and safe as the processing at the “point of care” would suggest? How should these be controlled?

The issue may be complicated by the fact that non-homologous use, scientifically verifiable or not, may turn the product into an ATMP from a regulatory perspective, resulting in a requirement to comply with pharmaceutical provisions, i.e. the necessity of a GMP-compliant environment for preparation. On the other hand, PoC treatments could change the manufacturing landscape dramatically, by a reduction of process- and user-inherent variations, a less stringent need for a controlled environment, and reduced overall costs, resulting in a broader access to cell-based treatment options. Will quality by design offer a solution for a controlled PoC product?

Point of care treatments offer novel, interesting therapeutic concepts, but may not be misunderstood to pave a way for the clinical application of cell preparations in an unregulated manner, blurring the lines between regulated clinical research and practice on the one hand, and unproven treatments on the other, with outreach into medical tourism and alchemy. With these spices at hand, we hope to witness a provocative and challenging session worthwhile attending. The speakers, Kenneth Kleinhenz (Cytori Therapeutics, San Diego, USA) and Ralf Sanzenbacher (Paul Ehrlich Institut, Langen, Germany), will lend us their expertise in the field to initiate a discussion of pros and cons, concepts and country-specific approaches, with the audience invited to contribute their opinions and experience.

PROS - POINT OF CARE TREATMENTS REGULATORY PERSPECTIVE
Kenneth Kleinhenz
- Cells and tissues derived from point-of-care devices and delivered back to the same patient in the same surgical procedure are part of the practice of medicine and are not clearly captured by centralized regulatory schemes. ATMP regulations were implemented to capture cells, tissues, and gene therapies that were not clearly captured by the Medicinal Products Directive 2001/83/EC or any of its amendments. However, the ATMP regulations assumed a centralized manufacturing process for the cells and tissues and did not contemplate a decentralized manufacturing process utilizing point-of-care devices. Moreover, the ATMP regulations’ focus on centralized manufacturing processes are incompatible with point-of-care cells and tissues delivered back to the same patient in the same surgical procedure as many of the labeling and quality requirements can not be fulfilled in the operating room suite; making these products derived from point-of-care devices unapprovable in a centralized marketing authorization application. Given the fact that there is no clear, centralized, regulatory pathway for point-of-care cells and tissues delivered back to the patient in the same surgical procedure, a decentralized regulatory pathway should be considered at the national level.

CONS - POINT OF CARE TREATMENTS: REGULATORY PERSPECTIVE
Ralf Sanzenbacher
- Over the past years we face an increasing number of bedside-manufactured human cell- and tissue-derived cell therapy products in a variety of therapeutic indications. Beside PRP and bone-marrow-derived progenitor cell preparations as well as fat tissue-derived SVF-fractions or cells derived thereof (e.g. ADSC) have become very attractive. Beyond, point-of-care concepts are also on the way for other cell- and tissue types like cartilage, skin (epidermis/dermis) and others. From a regulatory perspective it appears that there is a need for a harmonized course of action within EU member states on how point-of-care manufactured cell preparations could be adequately regulated and supervised.
- Give regulatory rationale for why cells and tissues derived from point-of-care devices are not captured by current legislation
- Give an overview on conflict between centralized procedures and point-of-care devices
- Provide ideas for potential regulatory pathways at the national level

TECHNICAL SESSION 3 – PATIENT MATERIALS TO BE USED FOR THE PHARMACEUTICAL DEVELOPMENT OF AUTOLOGOUS ATMPS – ETHICAL AND OTHER IMPLICATIONS

Saturday, September 26th, 2015  Time: 1230 – 1330
Chair: Karin Hoogendoorn
This session aims to get an understanding of the scientific and ethical challenges to develop ATMPs using patients’ own materials. After a brief introduction to the topic, two case studies will be presented.
MATERIALS FROM BOTH PATIENTS AND HEALTHY DONORS ARE REQUIRED TO VALIDATE MANUFACTURING PROCESS OF AUTOLOGOUS CELL THERAPIES IN INFLAMMATORY DISEASES: CHALLENGES AND REGULATORY PATHWAY

Christelle Boniface
- Why materials from patients and healthy donors are both needed for the pharmaceutical development of autologous cell therapies in inflammatory diseases?
- What are the challenges and the regulatory pathway to obtain such human materials in France?
- The procurement of patient materials and related logistic remain a challenge, even once clinical trials are authorised: some suggestions to overcome it.

THE LIMITATION OF DONOR MATERIAL TO ADDRESS QUALITY ASPECTS OF A CARTILAGE CELL TRANSPLANT

Jeske Smink
- What to consider when designing non-clinical assays for addressing quality aspects of cell therapies
- How to overcome the limited availability of donor material to perform non-clinical assays
- Limitations of non-clinical assays for addressing quality aspects of cell therapies

TECHNICAL SESSION 4 – ORGANIZATIONS SUPPORTING TRANSLATIONAL RESEARCH ON CELLULAR THERAPY

Saturday, September 26th, 2015
Time: 1230 – 1330

Chair: Edwin Wagena
Despite the tremendous potential of (innovative) cellular therapies, few innovative findings have been translated from the concept or discovery phase into proof-of-concept clinical trials. Research opportunities that are being translated may require 7 to 10 years from the initial preclinical discovery before advancing to a human trial. Progress in the application of cellular therapies for specific disease indications has been delayed along the entire development spectrum from discovery to preclinical studies and animal models, validation of product manufacture, and finally to implementation of the therapy in clinical trials. In this session we will have the opportunity to learn about the challenges and possible solutions from several organizations supporting translational research of cellular therapies and focusing on different aspects to increase translational success; the example of Catapult fostering commercialization, the model of the Andalusian Initiative for Advanced Therapies (AIAT) to drive clinical use of cellular therapies and the experience from ISCT in bringing together academia and the industry to overcome the scientific challenges, the technical difficulties in manufacturing, the regulatory issues and commercialization barriers.

BUILDING A CELL AND GENE THERAPY INDUSTRY IN THE UK

Keith Thompson
- Understand how the Cell Therapy Catapult has built assets and resources to address key barriers to the growth of the industry.
- Gain insights into how the Cell Therapy Catapult works in an ecosystem of research, translation and industry to accelerate innovation in cell and gene therapy in the UK.
- Understand how both pathfinder clinical projects and technical platform projects contribute to the development of companies with investable assets.

A REGIONAL INITIATIVE EXPLOITING THE CELL THERAPY POTENTIAL FOR CLINICAL USE: THE CASE OF THE ANDALUSIAN INITIATIVE FOR ADVANCED THERAPIES

Natividad Cuende
- Offer an overview of the support provided by the Andalusian Initiative for Advanced Therapies (AIAT) to researchers and companies for development of clinical research with cell-based medicinal products.
- Allow companies to know the technology maturation platform and the innovative model of funding under a risk-benefit sharing model offered by the AIAT.
- Share the strategy of the Andalusian Health Ministry to prepare the Regional Health Service for the provision of these regenerative treatments.

ISCT AS A GLOBAL PARTNER FOR RESEARCH & DEVELOPMENT ON THERAPEUTIC CELLS

Massimo Dominici
- To share basic questions that may be rising during research on therapeutic cells (TC).
- To present how a scientific society, like ISCT, can serve academic investigators and industries to provide support from early studies to clinical translation in the respect of regulatory and technological regional diversities.
- To inform on available ISCT resources for this dedicated partnership proving a vision on the role of global networking capable to propel the field with the ultimate goal to facilitate TC translation for the benefit of patients world-wide.
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CORPORATE SYMPOSIUM AND TUTORIAL PROGRAM AT A GLANCE

SYMPOSIUM

**Thursday September 24, 1730 – 1830, Seville III/IV**

**TERUMO BCT**

MANUFACTURING SOLUTIONS: A HANDS-ON TOUR OF FUNCTIONALLY CLOSED, SCALABLE SOLUTIONS FOR CLINICAL PRODUCTION

TUTORIALS

**Thursday September 24, 1300 – 1400, Seville I**

**PALL LIFE SCIENCES**

DESIGNING THE MOST COST-EFFECTIVE MANUFACTURING STRATEGY FOR ALLOGENEIC CELL-BASED THERAPIES

Presenter: Thierry Bovy, MSc, Global Product Manager, Xpansion® Bioreactors

**Friday September 25, 1245 – 1345, Seville I**

**APCETH GMBH**

NEXT GENERATION CELL THERAPY: MSC AS BIOLOGICAL DRUG FOR TARGETING CANCER - STATE OF THE ART: TECHNOLOGY, TRANSLATION INTO THE CLINIC AND LESSONS LEARNED

Chair: Christine Guenther, MD, CEO & CMO, apceth Munich
Presenters: Felix Hermann, PhD, Head of Preclinical Development, apceth
Ulrike Verzetnitsch, Graduate Engineer, CTO, apceth

**Friday, September 25, 1245 – 1345, Seville II**

**MACOPHARMA**

CLINICAL GRADE HUMAN PLATELET LYSATE: AN EFFICIENT AND STANDARDIZED CELL CULTURE SUPPLEMENT TO EXPAND CELL THERAPY PRODUCTS

Dr. Bruno Delorme, PhD, Scientific and R&D Director, Macopharma, Mouvaux, France
Dr. Sandy Eap, PhD, R&D Engineer, Macopharma, Mouvaux, France
CORPORATE SYMPOSIUM AND TUTORIAL
FULL DESCRIPTIONS

SYMPOSIUM

Thursday September 24, 1730 – 1830, Seville III/IV

TERUMO BCT

Manufacturing Solutions: A Hands-On Tour of Functionally Closed, Scalable Solutions for Clinical Production

EXPLORE TWO HANDS-ON STATIONS: STRATEGIES FOR END-TO-END MANUFACTURING OF CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPY AND A NEW APPROACH TO SCALING UP MANUFACTURING, ENABLING OVER 9 BILLION MULTIPOTENT ADULT PROGENITOR CELLS IN A CLINICAL PRODUCTION RUN.

Experience a hands-on tour of two distinct manufacturing solutions; see how one commercial manufacturing organization (CMO) is scaling up allogeneic manufacturing of MAPCs for clinical production, and how Terumo BCT is enabling an end-to-end solution for CAR T-cell therapy manufacturing. This interactive session provides attendees an exclusive opportunity to understand how different technologies may be applied to successfully execute critical steps in the manufacturing process, from collection to production to patient, for a range of cell therapy products.

TUTORIALS

Thursday September 24, 1300 – 1400, Seville I

PALL LIFE SCIENCES

Designing the Most Cost-effective Manufacturing Strategy for Allogeneic Cell-based Therapies

Presenter: Thierry Bovy, Global Product Manager, Xpansion® Bioreactors

This presentation will cover the key bioprocess economic parameters to be considered when designing the manufacturing process for an adherent cell-based allogeneic product, and how to determine the required manufacturing scale and select the most cost-effective technologies for the manufacture of allogeneic cell-based therapies.
APCETH GMBH

Next Generation Cell Therapy: MSC as biological drug for targeting cancer – State of the art: technology, translation into the clinic and lessons learned

Chair: Christine Guenther, MD, CEO & CMO, apceth Munich

BIOLOGY AND REGULATORY ASPECTS OF GENETIC MODIFICATION OF MSC: STATE OF THE ART AND PRECLINICAL DEVELOPMENT

Felix Hermann, PhD, Head of Preclinical Development, apceth

TRANSITION FROM IN-HOUSE DEVELOPMENT TO IN-HOUSE PHASE I/II TRIAL SUPPLY

Ulrike Verzetnitsch, Graduate Engineer, CTO, apceth

apceth is developing cell-based gene therapies for the treatment of cancer and other non-malignant diseases by exploiting the proprietary platform technology for cell engineering and cell-based drug delivery. Additional approaches by introducing genes into MSC coding for immune-regulating and other therapeutic agents may add further modalities for combined immune-therapy approaches.

As the first company worldwide apceth is running a phase II clinical study with genetically modified Mesenchymal Stem Cells (MSC) for solid tumors. In parallel the expansion to allogeneic, “off-the-shelf” products is ready for entering into the clinical application for advanced cancer. Pharmaceutical development, upscaling and manufacturing for advanced clinical development of complex cell therapies is established and successfully implemented also for partners in academia and industry.

The presentations will provide an overview with special focus on challenges and give an outlook to future development and perspectives.

MACOPHARMA

Clinical Grade Human Platelet Lysate: an efficient and standardized cell culture supplement to expand cell therapy products

- Development, standardization and validation of a clinical grade human platelet lysate on several types of cells.
- Preservation of optimal quality and efficacy of human platelet lysate pathogen reduced with photosensitizing additive-free THERAFLEX UV-Platelets technology.
- Standardized and clinical grade human platelet lysate hydrogel (HPLG) for large-scale expansion of human mesenchymal stem cells.

Speakers:
Dr. Bruno Delorme, PhD, Scientific and R&D Director, Macopharma, Mouvaux, France
Dr. Sandy Eap, PhD, R&D Engineer, Macopharma, Mouvaux, France
The main parts of the MC3 system are registered as Class IIa Medical Devices (MDD 93/42/EEC modified). Human Platelet Lysate contains human source material and must be treated as potentially infectious. Despite all testing, proper safety precautions for potentially infectious agents must be taken. This document is for the exclusive use of the healthcare and cell culture professionals.

For more information, see our dedicated website: www.platelet-lysate.macopharma.com
SUPPORTING ORGANIZATION

ANDALUSIAN INITIATIVE FOR ADVANCED THERAPIES  BOOTH #9

The Andalusian Initiative for Advanced Therapies is a publicly funded organization, created by the Regional Government of Andalusia, specialized in supporting activities of R&D in the regenerative medicine field with experience in promoting 24 clinical trials with different gene and cell-based therapies. We are part of the Andalusian Public Healthcare System which offers complete health services to 8.5 million people and comprises, among other infrastructures, 47 hospitals, a network of 10 GMP facilities (manufacturing 12 different ATMPs), research centres and a Biobank storing over 850,000 samples from patients and normal controls, including hiPS and hES cell lines. Being part of such a multidisciplinary system, and experts on Regulatory affairs, we offer advisory support, specialised training programmes (we organize a unique European Master Degree in Manufacturing of ATMPs) and collaborations with academic institutions and companies based in creating partnerships within a risk-benefit sharing model to accelerate the development of new products.

EXHIBITORS

ANTIBODY PRODUCTION SERVICES LIMITED  BOOTH # 5

APS Ltd is an independent UK company providing custom biological and in vitro products and services to Pharma, Biotech, CRO and Universities worldwide.

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APS also offers Custom Polyclonal and Monoclonal antibody development plus bulk production from customers’ own hybridoma to Research Grade, Clinical Diagnostic Grade or cGMP production standards. We also offer custom peptide and antigen design services, conjugation and purification, specialist QA services and Regulatory advice.

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BIOINVISION  BOOTH #16

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CELLGENIX GMBH  BOOTH #21

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CHEMOMETEC  BOOTH #28

CHEMOMETEC

ChemoMetec develops, manufactures and sell high quality automated Image Cytometers within cell counters and advanced cell analyzers to streamline processes for maximum efficiency. Our instruments are widely used in fields such as cancer research, stem cell research, production and quality control of a number of products such as pharmaceuticals, beer, animal semen and milk. 21 CFR Part 11 is also valued highly to have the highest standards. Our products are held in high regard because of their high quality and precision as well as the “ease of use” advanced cell analysis. We value our customers; Therefore our policy is “no hidden costs” - no service agreements, high level of support and free software updates.

CRYO BIO SYSTEM  BOOTH #13

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**IRVINE SCIENTIFIC**

Mature Scientific, a member of JX Group, is a worldwide leader in the innovation and manufacture of cell culture media, reagents, and medical devices for researchers and clinicians. The company provides unrivaled service and quality to scientists working in cell therapy and regenerative medicine, assisted reproductive technology and cytogenetics, and industrial cell culture for the large-scale production of biotherapeutics and vaccines. Irvine Scientific adheres to both ISO and FDA regulations and operates dual cGMP manufacturing facilities in California, USA and Tokyo, Japan. The company’s consultative philosophy combined with expertise in cell culture and compliance provides customers with unique capabilities and support. For over 40 years Irvine Scientific has remained uniquely flexible and focused on media while becoming a strategic global leader in media products and services.

**KANEKA PHARMA EUROPE N.V.**

Kaneka Corporation is a producer of chemical products including resins, pharmaceutical intermediaries, food supplements, synthetic fibres, fine chemicals and medical devices. Kaneka Pharma Europe N.V. is an independent subsidiary active in the European market. Our new products in the cell therapy and regenerative medicine field provide you with innovative device solutions for multiple stage of cell processing. CellEffic BM and CellEffic CB are CE-marked medical devices for separation and harvesting of mesenchymal stem cells from human bone marrow fluid and for processing of cord blood, respectively.

**MACOPHARMA**

Macopharma is a leading worldwide manufacturer of medical devices for transfusion, infusion and biotherapy. Investments in research and development as well as partnerships enable Macopharma Biotherapy to provide in the fields of cell and tissue therapy, regenerative medicine and transplantation worldwide high quality, GMP, single use, sterile, closed systems to collect, treat, expand and preserve human regenerative cells, tissues and organs that consistently improve and secure cellular therapy practices and clinical protocols.

**MASTHERCELL**

MaSTherCell, incorporated in Brussels in 2011, is a dynamic and global Contract Development and Manufacturing Organization (CDMO) whose mission is to provide cGMP manufacturing capacities for Phase I, II, III clinical trials, as well as commercialization to cell therapy developers, by striving to reduce their time to market. The heart of MaSTherCell is a team of 40 highly dedicated experts combining strong experience in cGMP cell therapy manufacturing with a technology-focused approach and an in-depth knowledge of the ATMPs industry.

From technology selection to business modelling, process development, quality management and assay development, MaSTherCell’s teams are fully committed to helping their clients fulfill their objective of providing sustainable and affordable therapies to their patients. The
company operates in a validated and flexible 600sqm GMP facility located in the strategic center of Europe within the Biopark, Immunology R&D center, surrounded by 6 cell therapy companies and Biologistics providers. Worldwide renowned, the center hosts key players from the bio industry and offers a central, highly connected location.

**MIL TEN Y I BIOTEC**

Milenyi Biotec is a global provider of products and services that advance biomedical research and cellular therapy. Our innovative portfolio supports scientists and clinicians at every level, from basic research to translational research to clinical application. Our technologies cover techniques of sample preparation, cell isolation, cell sorting, flow cytometry, cell culture, molecular analysis, and preclinical imaging. Our more than 25 years of expertise spans research areas including immunology, stem cell biology, neuroscience, and cancer, and clinical research areas like hematology, graft engineering, and apheresis. In our commitment to the scientific community, we also offer comprehensive scientific support, consultation, and expert training. Today, Miltenyi Biotec has more than 1,400 employees in 25 countries “all dedicated to helping researchers and clinicians around the world make a greater impact on science and health.

**NEWCASTLE CELLULAR THERAPIES FACILITY**

The Newcastle Cellular Therapies Facility is an MHRA-licensed clean room complex designed specifically for the production of cellular therapies, and is run as a partnership between Newcastle University and The Newcastle upon Tyne Hospitals NHS Foundation Trust.

We offer a flexible, bespoke service for the development and manufacture of Advanced Therapy Medicinal Products, as either Unlicensed Specials or Investigational Medicinal Products: both Somatic Cell Therapies and Tissue Engineered Products.

We are experienced in ATIMP manufacture for non-commercial and commercially sponsored trials, as well as the preparation of ATIMPs for patient administration, and the facilitation and oversight of commercial ATIMP trials.

For more information visit www.ncl.ac.uk/ctf or follow us on Twitter: @CellTherapyNewc

**NHS BLOOD AND TRANSPLANT**

NHS Blood and Transplant (NHSBT) is a national organisation within the NHS dedicated to saving and improving lives through the wide range of services we provide to the healthcare community. The Cellular and Molecular Therapy (CMT) function of NHSBT offers broad experience and expertise in novel stem cell therapies, processing technologies and gene therapy based treatments and research. Our Stem Cell and Immunotherapy (SCI) laboratories support about 50% of stem cell transplants in the UK through the collection, processing and cryopreservation of stem cells, including cord blood. The Clinical Biotechnology Centre specialises in the manufacture of plasmid DNA and novel recombinant proteins. MHRA licensed and fully GMP compliant, CBC operates from a production suite comprising multiple segregated rooms for processing and final fill. CBC is dedicated to supporting gene therapy-based clinical trials and research.

NHSBT is uniquely positioned to provide donor stems cells and we bring strength in specialist manufacturing, scientific skills, translational experience, regulatory expertise and distribution in support of this developing industry.

We welcome partnerships with clinical, academic and commercial organisations for the development and provision of cellular and molecular therapies.
PALL LIFE SCIENCES

Pall Life Sciences provides cutting-edge products and services to meet the demanding needs of customers discovering, developing and producing biologics and classic pharmaceuticals. The company’s membranes and membrane devices optimize detection and sample preparation in the drug research, clinical diagnostics, genomics, and proteomics markets. Pall is a leading provider of automated systems and single-use solutions to pharmaceutical and biotechnology companies - from upstream, through downstream, to formulation and filling - and maintains certified ISO9001 manufacturing facilities worldwide. The company’s Scientific and Laboratory Services (SLS), Technical Services and Validation Laboratories have been a cornerstone of customer support for more than 30 years providing compatibility studies, extractable/leachable studies, particulate validation and more.

PEPROTECH

Established in 1988 by a group of scientists, PeproTech is a privately owned biotechnology company focusing on the development and manufacture of high quality cytokine products for the life-science and cell therapy market. Over the past 25 years the company has grown into a global enterprise with state-of-the-art manufacturing facilities in the US, and offices around the world.

With over 2,000 products PeproTech has developed and refined innovative protocols to ensure quality, reliability and consistency.

Our mission is to provide the highest quality products to support the needs of today’s scientists and researchers.

TERUMO BCT

Terumo BCT, a global leader in blood component, therapeutic apheresis and cellular technologies, is the only company with the unique combination of apheresis collections, manual and automated whole blood processing, and pathogen reduction. We believe in the potential of blood to do even more for patients than it does today. This belief inspires our innovation and strengthens our collaboration with customers.

TRAKCEL

TrakCel is a technology platform to safeguard patients being treated with regenerative therapies. The platform ensures that the right patient receives the right therapy at the right time and location. Efficiently tracking, tracing and documenting the movement and handling of multiple regenerative therapies with minimal resources required. TrakCel is a comprehensive solution that covers all aspects of patient registration, sample collection, logistics, manufacturing, quality control; ensuring the right treatment is matched with the right patient. For autologous therapies TrakCel coordinates each patient’s cellular starting material collection, manufacture and engraftment. Real time data is generated and automatically monitored recording the location and the temperature of material in transit, issuing warnings and alarms if pre-defined limits are breached.
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ABSTRACTS

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BMP-7 INDUCES ADULT HUMAN PANCREATIC EXOCRINE-TO-ENDOCRINE CONVERSION  
University of Miami, Miami, United States  

The conversion of pancreatic non-endocrine tissue along the β-cell lineage is one of the proposed solutions to the scarcity of islets for transplantation in type 1 diabetes. Proof of concept has been generated using genetic manipulation (reprogramming) approaches. However, clinical translation is difficult owing to regulatory hurdles. On the other hand, the exocrine (acinar and ductal) compartment of the pancreas has been hypothesized to harbor progenitor cells with the ability to give rise to new β-cells. The activation of such progenitors may potentially result in new β-cell formation through differentiation, rather than reprogramming. Stimulation of progenitor pools has been shown to be dependent on the simultaneous inhibition of TGF-β signaling and the activation of the BMP pathway. BMP-7 is an FDA-approved ligand with dual TGF-β inhibition/BMP activation abilities. We thus reasoned that treating cultured human non-endocrine pancreatic tissue (hNEPT) with BMP-7 might induce the conversion of putative pancreatic progenitors into endocrine cells. Indeed, exposure of hNEPT to BMP-7 led to the generation of cell clusters with high insulin content (right within the range of that reported for research-grade human isolated islets) and glucose responsiveness in vitro and in vivo. These effects were mimicked by THR-123, a specific agonist of the BMP-7 receptor Activin-like kinase 3 (ALK3) and abrogated by dorsomorphin, a BMP/SMAD signaling inhibitor. BMP-7 was hypothesized to stimulate heretofore-unreported progenitor-like cells within the exocrine compartment characterized by PDX1 and ALK3 co-expression. In vitro lineage tracing additionally suggested that BMP-7-induced insulin+ cells arise mainly from extrainsular cells that express PDX1 and ALK3, but not CAA (mature ductal marker) or elastase 3α (acinar marker). The non-genetic conversion of human pancreatic exocrine to endocrine cells is novel and represents a safer and simpler alternative to genetic reprogramming.

2  
ANTERIOR LAMELLAR CORNEAL SUBSTITUTE GENERATED BY TISSUE ENGINEERING FOR TREATMENT OF TROPHIC ULCERS. PRELIMINARY DATA  

A new model of artificial cornea. This clinical trial is sponsored by the Andalucian Initiative for Advanced Therapies. The conversion of corneal non-endocrine tissue along the β-cell lineage is one of the proposed solutions to the scarcity of islets for transplantation in type 1 diabetes. Proof of concept has been generated using genetic manipulation (reprogramming) approaches. However, clinical translation is difficult owing to regulatory hurdles. On the other hand, the exocrine (acinar and ductal) compartment of the pancreas has been hypothesized to harbor progenitor cells with the ability to give rise to new β-cells. The activation of such progenitors may potentially result in new β-cell formation through differentiation, rather than reprogramming. Stimulation of progenitor pools has been shown to be dependent on the simultaneous inhibition of TGF-β signaling and the activation of the BMP pathway. BMP-7 is an FDA-approved ligand with dual TGF-β inhibition/BMP activation abilities. We thus reasoned that treating cultured human non-endocrine pancreatic tissue (hNEPT) with BMP-7 might induce the conversion of putative pancreatic progenitors into endocrine cells. Indeed, exposure of hNEPT to BMP-7 led to the generation of cell clusters with high insulin content (right within the range of that reported for research-grade human isolated islets) and glucose responsiveness in vitro and in vivo. These effects were mimicked by THR-123, a specific agonist of the BMP-7 receptor Activin-like kinase 3 (ALK3) and abrogated by dorsomorphin, a BMP/SMAD signaling inhibitor. BMP-7 was hypothesized to stimulate heretofore-unreported progenitor-like cells within the exocrine compartment characterized by PDX1 and ALK3 co-expression. In vitro lineage tracing additionally suggested that BMP-7-induced insulin+ cells arise mainly from extrainsular cells that express PDX1 and ALK3, but not CAA (mature ductal marker) or elastase 3α (acinar marker). The non-genetic conversion of human pancreatic exocrine to endocrine cells is novel and represents a safer and simpler alternative to genetic reprogramming.

3  
VACCINATION WITH A NEW GENERATION OF TUMOR SPECIFIC MRNA LOADED DENDRITIC CELLS PROLONG PROGRESSION FREE SURVIVAL IN PATIENTS WITH DIFFERENT TYPES OF MALIGNANCIES  
I. Bigalke1, K. Hannåshagen1, M. Lundby1, G. Solum1, L. Skog1, S. Saboe-Larsen1, J. Kaster1, D. J. Schendel3, G. Kvalheim1  
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Monocyte derived mature dendritic cells (DCs) loaded with antigen specific mRNA have previously been tested by us in clinical trials to treat different malignant diseases. Immune responses correlated with clinical responses but were only observed in about 50% of the treated patients. A new generation of IL-12p70 producing fast DCs showed superior results in pre-clinical models. Here we investigate the feasibility to produce this new generation of DCs for patients with different types of malignancies in advanced stage and show the clinical effect of the DC-vaccines. Autologous new generation mRNA loaded DCs were successfully produced for 1 lung cancer patient, 2 prostate cancer patients, 4 glioblastoma patients, 1 ovarian cancer patient and 4 AML (acute myeloid
leukemia) patients, showing the same phenotype and functionality as healthy donor derived new generation mDCs. Patients were treated according to a previously established vaccination protocol.

The lung cancer patient suffering from stage IV disease with lung and brain metastases has now been vaccinated since 12/2011 and remained in stable disease. One prostate cancer patient progressed before an immune response to the DC therapy could be expected, the second patient has been progression free under treatment now for 12 months. Three glioblastoma patients are in complete remission (CR) since 18 to 22 months, one patient died after 12 months. The AML patients have been treated now for 13, 10, 7 and 2 months. Clinical responses and immune responses are followed in all patients.

We observed strong DTH responses in all patients, some patients developed flu-like symptoms on the day of vaccination and up to three days after vaccination. In some patients progression free survival is superior to what we have observed previously.

Based on the extremely promising clinical results with the new generation of DCs we have started phase I/II trials in AML and prostate cancer and a phase III trial in glioblastoma is in preparation.

4

CLINICAL APPLICATION OF HUMAN ADIPOSE DERIVED REGENERATIVE CELLS (ADRCS) IN TISSUE REPAIR OF SEVERE SIDE EFFECTS FOLLOWING CURATIVE RADIOTHERAPY TREATMENT

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Our hospital has the regional responsibility for treating patients with chronic wounds following radiotherapy. The current therapy consists of plastic surgery and wound treatment. This is often combined with hyperbaric oxygen. Recently, it has been shown that injection of ADRCs directly into the chronic wound facilitates tissue healing. The ADRCs, also called the stromal vascular fraction (SVF) from the adipose tissue contains endothelial precursor cells, smooth muscle cells, and adipose derived cells. Although a limited number of patients have been offered this therapy, the results obtained are promising and might be an alternative to the current therapy.

ADSCs are easily accessible in large quantities with a minimal invasive, safe and well-established surgical procedure. Normally, we obtain more than 300-500 times stem cells in 1 gram of fat compared to 1 gram of aspirated bone marrow. ADSCs are therefore an attractive cell source for tissue repair. Recently, we have started to inject adipose stem cells into the wound area of patients with chronic wounds following curative radiotherapy. Stromal Vascular Fraction (SVF) was isolated from liposuction cells during surgery using the CelutionTM system, and administered freshly back to the patient. Normally, 200ml adipose tissue is harvested from the patient prior to SVF isolation.

So far, we have treated 3 patients with chronic wounds (two with perineal ulceration, and one with intestinal fistulas to the abdominal wall) following curative cancer treatment, including radiotherapy. In the first two patients we observed complete healing of the wounds within 8 weeks after injection of the cells, whereas in the third patient the fistula was almost completely healed with a minor secretion 6 weeks after injection.

In conclusion, our findings show that preparation and injection of SVF cells is feasible resulting in successful healing of chronic wounds.

5

AGORA SURVEY: ATMP REGULATORY DIFFERENCES IDENTIFIED IN EUROPE

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Academic GMP facilities play a pivotal role in the development of advanced therapy medicinal products (ATMPs). Until now, only a few ATMPs have received marketing authorization. Many are currently tested in clinical trials (CT) or are administered under the hospital exemption clause (HE) of the ATMP-regulation. AGORA (ATMP-GMP-Open-Access-Research-Alliance), a FP-7 supported project, performed a survey among European facilities on the impact of the ATMP Regulation (EC) 1394/2007.

Using an electronic questionnaire, we gathered information on the activities in 2013 of 55 responding CMP manufacturing facilities from 13 countries (type and number of products regulated in CT or HE, number of patients treated, the requirements and timelines set by regulating bodies). This survey showed that the number of patients treated outside the regulatory boundaries of a CT was high (45% of 1174 patients treated). In fact, a third of facilities indicated that, they only produced ATMPs for non-clinical trials (compassionate use, named patient use and HE).

Furthermore, the opinion of the responding facilities was solicited on certain issues raised by the European Commission in the open consultation on the ATMP Regulation. The responding facilities didn’t have a strong opinion on a mandatory central classification of ATMPs, but 75% were in favour of harmonisation of ATMP classification. Most of the facilities (non-industrial) are not pursuing marketing authorization for their products and prefer a different approach on the requirements set for HE, depending on the availability of clinical trial data (Fig 1).

The creation of data registries for ATMP’s supplied under the HE was supported by 80% of respondents. This remains a challenge, given the individual nature of the specific products and the fact that the ATMP classification is not harmonised. This survey also provided evidence of significant variation in Europe, highlighting the need for HE harmonisation between competent authorities.
MESEMS: A RANDOMIZED, DOUBLE BLIND PLACEBO-CONTROLLED CROSS-OVER STUDY TO EVALUATE SAFETY AND EFFICACY OF INTRAVENOUS ADMINISTRATION OF AUTOLOGOUS MESENCHYMAL STEM CELLS IN PATIENTS WITH MULTIPLE SCLEROSIS

O. Fernando1, U. A. B. U.1, M. Claveti1, A. Larani1, P. Murano1, R. Oliveri1, E. Radue1, P. Soelberg Sorensen2, M. Sormani1, M. Freedman4
1Hospital Regional Universitario de Málaga, Málaga, Spain, 2University of Genova, Genova, Italy, 3Karolinska Institute, Stockholm, Sweden, 4University of Toulouse, Toulouse, France, 5Imperial College London, London, United Kingdom, 6University of Copenhagen, Copenhagen, Denmark, 7Universitätsklinik Basel, Basel, Switzerland, 8Ottawa Hospital, Ottawa, Canada

Aims: To describe the protocol for a phase II trial assessing safety and efficacy of MSC for the treatment of Multiple Sclerosis (MESEMS).

Methods: The MESEMS network is a group of independent clinical trials, following the same protocol and sharing key centralized procedures: analysis of MRI data (Basel, Switzerland); central randomization and collection of safety and clinical data (Genoa, Italy).

Results: MESEMS is being investigated in 8 countries, with an anticipated enrollment of 160 MS patients. The MESEMS protocol is a double-blind, randomized, sham-controlled cross-over trial. The main inclusion criteria are: relapsing-remitting, primary progressive or primary progressive MS displaying disease activity by clinical and MRI parameters, age 18-50, EDSS 3.0-6.5 and disease duration 2-10 years. The primary endpoints are safety and efficacy of autologous MSC in MS patients by measuring the total number of gadolinium enhancing lesions on MRI at week 4, 12 and 24 in the MSC vs. sham treatment groups. Secondary outcomes aim to gather preliminary information of the efficacy on other MRI metrics, clinical, immunological, neuropsychological and neuro-ophthalmological parameters. Two treatments, one with 1-2 millions of autologous bone marrow-derived MSC/kg body weight and one with sham (media), are administered at week 0 and week 4-24 according to randomization. The total follow up is 48 weeks.

Conclusion: A novel network approach has permitted us to overcome financial and logistic issues and to start an International academic trial with stem cells for MS. Results of the MESEMS trial will permit the rationale for designing a Phase III program.

TREATMENT OF ADVANCED GASTROINTESTINAL (GI) CANCER IN A CLINICAL PHASE I/II TRIAL WITH GENETICALLY MODIFIED MESENCHYMAL STEM CELLS (GMMSC): A PHASE I CLINICAL STUDY

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We describe here an autologous gmMSC product Agenmesencel-T with the inborn ability to target tumors and express the therapeutic transgene HSV-TK under RANTES promoter in situ. Administered i.v., the cells home to tumors where the promoter is switched on, driving the expression of HSV-TK. After its i.v. administration, Ganciclovir (GCV) is activated in tumors by HSV-TK, killing surrounding cells (bystander killing).

A Phase I/II clinical trial TREAT-ME 1 was designed based on in vivo efficacy data and proof of concept (POC) in mice. In the completed Phase I part 6 advanced-stage GI adenocarcinoma patients were treated: 3 CRC, 2 pancreatic, 1 CCC. gmMSC were administered in a low (3 patients; 0.5x106 cells/kg BW/week) or a high (3 patients; 106cells/kg BW/week) dose per week for 3 weeks each followed by GCV administration on the day 3, 4 and 5.

The treatment was safe and tolerable in all patients. No related Serious Adverse Events or other Adverse Events with CTCAE Grade 3-5 toxicity and no signs of clinically significant negative changes and trends were recorded. Preliminary results indicate that elevated liver enzymes and cholestasis parameters due to the liver involvement declined significantly in chronological correlation to the therapy. The effect was not sustained after end of the treatment and might require repeated doses. According to RECIST (1.1) 4/6 patients showed stable disease at 3 months follow-up, 2/6 progressive disease. 1/6 was in sustained SD (>5 months). 2/6 patients had stable clinical condition.

This is the first reported clinical trial with gmMSC and the first report of MSC being used in oncology. It shows that gmMSC are a viable, safe and promising therapeutic modality. The trial has now entered the Phase II part to evaluate the safety, tolerability and efficacy of Agenmesencel-T and establish POC in 10 patients. Also, a new Phase I trial will start in 2015 to evaluate the use of donor-derived allogeneic gmMSC for solid tumor therapy.

T CELL THERAPY TARGETING A NEOANTIGEN REDUCES IN VIVO TUMOUR GROWTH

E. Inderberg-Suso1, s. wallchli1, 2, M. R. Myhre1, S. Trachsel1, K. Liserud1, H. Almåsbak1, G. Kvalheim1, G. Gaudernack1
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T-cell receptor (TCR) transfer is an attractive strategy to increase the number of cancer-specific T cells in adoptive cell therapy. However, recent clinical and pre-clinical findings indicate that careful consideration of the target antigen is required to avoid off-tumour/on-target toxicity. Targeting mutated proteins such as frequently occurring frameshift mutations may thus be a safer alternative than directing T cells against tumour-associated self-antigens. Furthermore, such frameshift mutations result in novel polypeptides allowing selection of TCRs from the non-tolerant T-cell repertoire circumventing the problem of low affinity TCRs due to central tolerance. The transforming growth factor β Receptor II frameshift mutation (TGFBRIImut) is found in Lynch syndrome cancer patients and in approximately 15% of sporadic colorectal and gastric cancers displaying microsatellite instability (MSI). The -1A mutation in the TGFBRII gene gives rise to immunogenic peptides previously used for vaccination of MSI+ colon cancer patients in a Phase I clinical trial.

From a clinically responding patient we isolated a CTL clone from which we cloned an HLA-A2-restricted TGFBRIImut-specific TCR. We showed that both CD8+ and CD4+ T cells transiently redirected with this TGFBRIImut-TCR recognised colon cancer cell lines harbouring the frameshift mutation, indicating CD8 co-receptor independence. From two other vaccinated patients we isolated and cloned HLA-DR restricted TGFBRIImut-specific TCRs from CD4+ T helper clones. These HLA-DR restricted TCRs were shown to be functional in both CD8+ and CD4+ T cells upon transient redirection. The redirected T cells specifically recognised antigen presenting cells loaded with exogenous peptide or transfected with mRNA encoding the epitope.
Finally, T cells transduced with the HLA-A2-restricted TGFβRII-specific TCR significantly reduced the growth of colorectal cancer and enhance survival in a NOD/SCID xenograft mouse model.

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TRANSPANTATION OF HUMAN AMNION EPITHELIAL CELL TO CORRECT ACUTE LIVER FAILURE AND METABOLIC LIVER DISEASE

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Our group has been treating patients with liver disease with hepatocyte transplants for more than 10 years. A severe shortage of useful liver tissues limits a wider application of this cellular therapy. Stem cell sources for hepatocyte transplants would be useful, and placenta may represent a non-controversial and readily available source of stem cells that can be used in regenerative medicine. We previously reported that amnion epithelial cells (hAEc) from term human placenta express surface markers and genes characteristic of pluripotent stem cells. Importantly, they do not express telomerase, are not immortal and are not tumorigenic. Encouraged by the lack of tumorigenicity and hepatic differentiation in vitro, and in vivo we examined the efficacy of hAEc transplants in mouse models of acute liver failure and metabolic liver disease. We report that hAEc transplants completely reverse acute liver failure induced by d-galactosamine and significantly improve the branched chain amino acid and phenylalanine levels in mouse models of Maple Syrup Urine Disease and Phenylketonuria respectively, even though animals were not provided immunosuppressive drugs. hAEcs have reported tolerogenic, anti-inflammatory and immunomodulatory properties, and HLA-A expression in the human hAEc transplanted may be the reason the human xeno-transplants were tolerated without added immunosuppression, and for this reason is under further investigation.

Based on this strong preclinical data, we have received ethical approval to treat patients with liver disease with hAEc cellular therapy.

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REACHING REGULAR CLINICAL CARE WITH ACADEMIC ADVANCED THERAPY MEDICINAL PRODUCTS IN THE NETHERLANDS

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The European legislation permits application of Advanced Therapy Medicinal Products (ATMPs) via (1) a clinical study protocol, (2) the hospital exemption (HE) clause or (3) under a marketing authorization (MA). Until now only five ATMPs succeeded to achieve MA in the EU, despite that hundreds of clinical trials with ATMPs are conducted. Many academic developed ATMPs seem to remain in clinical development, while they appear to be safe and effective.

This project aims to identify whether there is a problem in development of ATMPs towards regular clinical care. There is a problem in the development route of academic ATMPs towards regular clinical care. 53% of the research groups plans to use the current regulatory routes, HE and MA, to reach regular clinical care, which is encouraged by the stakeholders. However, 25% of the research groups want the products in regular clinical care monitored by authorities in ongoing patient registries. And 19% even only aimed to establish human proof of concept, without ambition for further development. One main reason not to register is the perception that owning relevant intellectual property is essential. Main hurdles were the rapid evolving field and insufficient financial support for clinical development. Furthermore lacking specific knowledge is restrictive towards ATMP implementation.

Based on the results, optimal routes for academic development and implementation of ATMPs will be designed and communicated to the academic field.

*This project and the selected ATMPs are supported by Dutch Cancer Society (DCS) and Netherlands Research Organisation of Health Research and Development (ZonMw).

11

EPITHELIAL STEM CELLS FOR THE TREATMENT OF SKIN WOUNDS IN HORSES: THE HONEY OR THE BEE?

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Bees are famous for their skills to produce honey, which is being used as a wound dressing since ancient times. However, these small and invertebrate animals are also associated with a painful sting that can cause a pronounced inflammation and create discomfort for a long time. In allergic people, hypersensitivity reactions can occur and result in a life-threatening situation without treatment. Comparable to working bees, stem cells are currently being considered as a promising regenerative therapy, however, a certain caution exist for their clinical use in patients. In recent years, different classes of stem cells have been investigated for their safety and ability to regenerate organs and tissues following injury. Since ongoing regeneration of the skin is achieved through somatic stem cell differentiation within the epidermis and hair follicle, skin may serve as an excellent source of epithelial stem cells (EpSCs) which could prove itself useful in skin reconstitution after injury.

Following skin peeling, equine EpSCs were purified by means of sphere formation at a critical clonal density. Isolated EpSCs were positive for CD29, CD44, CD49f, K67, expressed low amounts of cytokeratin (CK) 14 and were negative for CD105, CK18, Wide CK and Pan CK. However, EpSC harvesting and culturing were time consuming processes, resulting in a delayed treatment (after the acute inflammatory peak). Therefore, allogeneic EpSC treatment using cells obtained from a fully characterized cell bank could substantially standardize and enhance the treatment modality. To assess the regenerative capacities of EpSCs, skin wounds of 6 cm² were experimentally induced in 6 horses (12 wounds/horse). Following treatments were applied in triplicate per horse: autologous EpSCs (a), allogeneic EpSCs (b), vehicle treatment (c) or untreated control (d). Wound evaluation was performed until five weeks after treatment through laser camera evaluation, wound fluid analyses and histology at different time points.
In comparison to control groups, wound closure (circumference and surface reduction to zero) appeared approximately one week earlier in autologous (P < 0.0001) and four days earlier in allogeneic EpSC-treated wounds (P = 0.0549). Significantly less granulation tissue (+25%) and more vascularization were observed after both EpSC treatments. MHC II and CD20 positive cells were significantly increased in EpSC-treated wounds at week two. The integrated number of autologous and allogeneic EpSCs was 11.7% and 6.1% at week one, respectively. This decreased to 7.6% and 1.7% at week two and became undetectable at week five. In conclusion, both autologous and allogeneic EpSC treatment significantly improved different wound healing parameters in an equine model without generating any adverse events.

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AN IN SILICO PREDICTED AND COMPUTER-AIDED MOLECULAR DESIGNED CTLA-4 BLOCKADOR FOR THE INCREASEMENT OF THE ANTIGEN-SPECIFIC CD8+ T-CELLS THE IN PRE- VACCINATED PATIENTS WITH MELANOMA USING THE BIOGENETOLIGANDOROLTM NEW CLUSTER OF ALGORITHMS AND THE ISTAR THROUGH A WEB PLATFORM FOR LARGE-SCALE PROTEIN-LIGAND DOCKING EXPERIMENTS.
I. G. Grigoriadis
Biogenea Pharmaceuticals Ltd, Thessaloniki, Greece

BACKGROUND: Anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) antibodies, such as ipilimumab, have generated measurable immune responses to Melan-A, NY-ESO-1, and gp100 antigens in metastatic melanoma. Vaccination against such targets has potential for immunogenicity and may produce an effector memory T-cell response. It has been previously determined the effect of CTLA-4 blockador on antigen-specific responses following vaccination. In-depth immune monitoring was performed on three ipilimumab-treated patients prevaccinated with gp100 DNA (IMF-24), gp100b209–217 and tyrosinase peptides plus GM-CSF DNA (IMF-32), or NY-ESO-1 protein plus imiquimod (IMF-11). In previous studies it was shown that peripheral blood mononuclear cells were analyzed by tetramer and/or or intracellular cytokine staining following 10-day culture with HLA-A*0201-restricted gp100b209–217 (ITDQVPFSV), tyrosinase369–377 (YMDGTMQV), or 20-mer NY-ESO-1 overlapping peptides, respectively. It has also been evaluated on the PDBind v2012 core set where istar platform combining with RF-Score manages to reproduce Pearson’s correlation coefficient and Spearman’s correlation coefficient of as high as 0.855 and 0.859 respectively between the experimental binding affinity and the predicted binding affinity of the docked conformation. Here, we have discovered for the first time an in silico predicted and computer-aided molecular designed CTLA-4 blockador for the increasement of the antigen-specific CD8+ T-cells to the in prevaccinated patients with melanoma using the istar. A Web Platform for Large-Scale Protein-Ligand Docking.

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A COMPUTER SIMULATED GP100 PEPTIDE MIMIC DESIGNED PHARMACOPHORE AS A VACCINELIKE AND INTERLEUKIN-2 IN SILICO GENERATED SUPERAGONIST WITH POTENTIAL CLINICAL EFFECT IN PATIENTS WITH ADVANCED MELANOMA USING AN IMPROVED ALGORITHM FOR CHEMICALLY TRACTABLE, SEMI-AUTOMATED PROTEIN INHIBITOR DESIGN.
I. G. Grigoriadis
Biogenea Pharmaceuticals Ltd, Thessaloniki, Greece

Stimulating an immune response against cancer with the use of vaccines remains a challenge. We hypothesized that combining a melanoma vaccine with interleukin-2, an immune-activating agent, could improve outcomes. In a previous phase 2 Research Scientific Project, patients with metastatic melanoma receiving high-dose interleukin-2 plus the gp100b209–217(210M) peptide vaccine had a higher rate of response than the rate that is expected among patients who are treated with interleukin-2 alone. We here, present an evolutionary algorithm that works in conjunction with existing open-source software to automatically optimize candidate ligands for predicted binding affinity and other drug-like properties. We used the rules of click chemistry to guide optimization, greatly enhancing synthesizability. Here, we have for the first time discovered a computer simulated gp100 Peptide mimic designed pharmacophore as a Vaccine-like and Interleukin-2 superagonist in Patients with Advanced Melanoma using an Improved Algorithm for Chemically Tractable, Semi-Automated Protein Inhibitor Design.

14

COMPUTER DESIGNED OF A SAFE AND IMMUNOGENIC PHARMACOPHORIC ACTIVATOR MIMICKING PHYSICOCHEMICAL PROPERTIES OF THE MART-1 (26-35,27L), GP100 (209-217, 210M), AND TYROSINASE (368-376, 370D) IN ADJUVANT WITH PF-3512676 AND GM-CSF WITH PROMISING CLINICAL OUTCOME IN METASTATIC MELANOMA USING A NEW CLUSTER OF ALGORITHMS AND A LIGANDBASED VIRTUAL SCREENING APPROACH THROUGH A SUPPORT VECTOR AND INFORMATION FUSION BAYESIAN MACHINE.
I. G. Grigoriadis
Biogenea Pharmaceuticals Ltd, Thessaloniki, Greece

The effectiveness of cancer vaccines in inducing CD8+-Tcell responses remains a challenge, resulting in a need for testing more potent adjuvants. In previous clinical trials it has been determined the safety and immunogenicity of vaccination against melanoma-related antigens employing MART-1, gp100, and tyrosinase peptides combined with the TLR-9 agonist PF-3512676 and local GM-CSF in-oil emulsion. Using continuous monitoring of safety and a two-stage design for immunological efficacy, More than 20 immune-response evaluable patients were targeted. Vaccinations were given subcutaneously on days 1 and 15 per cycle (1 cycle=28 days) for up to 13 cycles. Structure-based virtual screening of molecular compound libraries is a potentially powerful and inexpensive method for the discovery of novel lead compounds for drug development. That said, virtual screening is heavily dependent on detailed understanding of
the tertiary or quaternary structure of the protein target of interest, including knowledge of the relevant binding pocket. Here, in Biogenea we have for the first time discovered a Safe and immunogenic pharmacophore activator mimic physicochemical properties of the MART-I (26-35,27L), gp100 (209-217, 210M), and tyrosinase (368-376, 370D) in adjuvant with PF-3512676 and GM-CSF as a future anti-cancer agent in metastatic melanoma conditions introducing a novel multi-parametric algorithm drug discovery approach using a Ligand-Based Virtual Screening approach through a Support Vector Machine and Information Fusion attempt.

15

ALGEBRAICALLY IN SILICO DISCOVERED OF A MULTI-EPI TOPE MIMIC POLY-PHARMACOPHORE TO MULTIPLE PEPTIDES DERIVED FROM CANCER-TESTIS ANTIGENS AS A PROMISING Anti-TUMOR PHARMACO-AGENT FOR THE MAINTANCE OF A SPECIFIC T-CELL RESPONSE IN LONG-TERM VACCINATED PATIENTS ADVANCED BILIARY TRACT CANCER USING A PARALLEL WEB SERVICE FOR STRUCTURAL PROTEOME-WIDE LIGAND-BINDING SITE COMPARISON.

I. G. Grigoriadis
Biogenea Pharmaceuticals Ltd, Thessaloniki, Greece

The prognosis of patients with advanced biliary tract cancer (BTC) is extremely poor and there are only a few standard treatments. We conducted a phase I trial to investigate the safety, immune response, and antitumor effect of vaccination with four peptides derived from cancer-testis antigens, with a focus on their fluctuations during long-term vaccination until the disease had progressed. A unified statistical model to support local sequence order independent similarity searching for ligand-binding sites and its application to genome-based drug discovery. Bioinformatics, 25, 1305–1312). These algorithms have been extensively benchmarked and shown to outperform most existing algorithms. Moreover, several predictions resulting from SMAP-WS have been validated experimentally. Thus far, SMAP-WS has been applied to predict drug side effects, and to repurpose existing drugs for new indications. SMAP-WS provides both a user-friendly web interface and programming API for scientists to address a wide range of compute intense questions in biology and drug discovery. Here, we have for the first time discovered a multi-epitope mimicking pharmacophore to Multiple Peptides Derived from Cancer-Testis Antigens for the maintenance of a Specific T-cell Response in Long-term Vaccinated patients with Advanced Biliary Tract Cancer using the BiogenetoligandorolTM based SMAP-WS chemical informatic parallel web service for structural proteome-wide ligand-binding site comparison.

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A COMPUTER-ASSISTED IDENTIFIED II-KEY/HER-2/ NEU(776-790) HYBRID POLY-MIMIC PEPTIDE MIMOTOPIC VACCINE-LIKE CHEMO-STRUCTURE WITH ACTIVE PHARMACOPHORE SITES AS A FUTURE IN SILICO PROMISING NOVEL INHIBITOR TRANS-ACTIVATOR IN PROSTATE CANCER PATIENTS GENERATED BY THE BIOGENETOLIGANDOROLTM AND CHEMMINE TOOLS.

I. G. Grigoriadis
Biogenea Pharmaceuticals Ltd, Thessaloniki, Greece

Active immunotherapy is emerging as a potential therapeutic approach for prostate cancer. First phase I trials of an II-Key/HER-2/neu (776–790) hybrid peptide vaccine (AE37) with recombinant granulocyte macrophage colony-stimulating factor as adjuvant in patients with HER-2/neu+ prostate cancer have shown positive results. The primary functionalities of ChemMine Tools fall into five major application areas: data visualization, structure comparisons, similarity searching, compound clustering and prediction of chemical properties. First, users can upload compound data sets to the online Compound Workbench. Numerous utilities are provided for compound viewing, structure drawing and format interconversion. Second, pairwise structural similarities among compounds can be quantified. Third, interfaces to ultra-fast structure similarity search algorithms are available to efficiently mine the chemical space in the public domain. These include fingerprint and embedding/indexing algorithms. Fourth, the service includes a Clustering Toolbox that integrates cheminformatic algorithms with data mining utilities to enable systematic structure and activity based analyses of custom compound sets. Fifth, physicochemical property descriptors of custom compound sets can be calculated. These descriptors are important for assessing the bioactivity profile of compounds in silico and quantitative structure-activity relationship (QSAR) analyses. ChemMine Tools is available at: http://chemmine.ucr.edu. Here, in Biogenea we for the first time discovered a COMPUTER-assisted Identified II-Key/HER-2/neu (776–790) Hybrid Peptide-mimotopic poly-mimic chemostructure with vaccine-like active pharmacophore sites as a novel inhibitor trans-activator in Prostate Cancer Patients using the ChemMine tools. An online service for analyzing and clustering small molecules.

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AN IN SILICO DESIGNED FUSION INHIBITOR CONSISTING OF FIVE CANCER FILTERED CONSERVED PHARMACOPHORIC CHEMICAL FRAGMENTS WITH GREATLY PROMISING PHARMACO-MIMIC PROPERTIES TO A RATIONALLY ENGINEERED WILMS’ TUMOR PEPTIDE AS A FUTURE COMPUTER GENERATED HYPER-MOLECULE FOR THE POTENTIAL TREATMENT OF THE ACUTE MYELOID LEUKEMIA.

I. G. Grigoriadis
Biogenea Pharmaceuticals Ltd, Thessaloniki, Greece

Wilms’ Tumour 1 (WT1) is a zinc finger transcription factor that is overexpressed in acute myeloid leukaemia (AML). Its restricted expression in normal tissues makes it a promising target for novel immunotherapies aiming to accentuate the cytotoxic T lymphocyte (CTL) response against AML. It has been previously reported a phase I/II clinical trial of subcutaneous peptide vaccination with
two separate HLA-A2-binding peptide epitopes derived from WTI, together with a pan-DR binding peptide epitope (PADRE), in Montanide adjuvant. Here, in Biogenea we have for the first time discovered an in silico designed Fusion Inhibitor consisting of five conserved cancer-related pharmacophores with Greatly Promising PharmacoMimic Properties to a Rationally Engineered Anti-Wilms’ Tumour Peptide.

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AN IN SILICO DESIGNED CONSERVED TETRAPEPTIDE MOTIF-MIMETIC PHARMACOSTRUCTURE FOR THE POTENTIATING THE APOPTOSIS THROUGH IAP-BINDING AS A PROMISING NEO-AGONISTIC CHEMO-ACTIVATOR IN CANCER AND THE NEURODEGENERATIVE DISORDERS.
I. G. Grigoriadis
Biogenea Pharmaceuticals Ltd, Thessaloniki, Greece
Alterations in apoptotic pathways have been implicated in many debilitating diseases such as cancer and neurodegenerative disorders.1,2 Thus, targeting cell death pathways has always been therapeutically attractive. In particular, as it is conceptually easier to kill than to sustain cells, abundant attention has been focused on anti-cancer therapies using pro-apoptotic agents such as conventional radiation and chemo-therapy. These treatments are generally believed to trigger activation of the mitochondria-mediated apoptotic pathways. However, these therapies lack molecular specificity. Over the last year or so, the discovery and structural characterization of an IAP-binding peptide motif have generated much enthusiasm in screening for an anti-cancer drug tailored for the caspase pathways.3 Apoptosis is primarily executed by activated caspases, a family of cysteine proteases with aspartate specificity in their substrates. Caspases are produced in cells as catalytically inactive zymogens and must be proteolytically processed to become active proteases during apoptosis. In normal surviving cells that have not received an apoptotic stimulus, most caspases remain inactive. Our method employs a grid-based algorithm and a knowledge-based potential derived from ligand-binding sites in the experimentally solved RNA-ligand complexes. The predictive power of LigandRNA favorably compares to five other publicly available methods. Here, in Biogenea we have for the first time discovered an in silico designed conserved motif-like tetrapeptide consisting of high free and total binding energy mimetic pharmacostructures for the potentiating apoptosis through IAP-binding as a possible future therapeutic compound using the BiogenetoligandorolTM and the LigandRNA.

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IN SILICO FRAGMENT BASED STRUCTURAL DESIGN OF AN APELIN-ANALOGUE PHARMACOPHORIC AGENT AS A POTENTIAL HYPER-SENSITIVE DRUGGABLE CHEMO-MODULATOR FOR THE MITOCHONDRIAL ROS INHIBITION AND CARDIOMETABOLIC PROTECTION IN MYOCARDIAL ISCHEMIA-REPERFUSION INJURIES.
I. G. Grigoriadis
Biogenea Pharmaceuticals Ltd, Thessaloniki, Greece
Mitochondria-derived oxidative stress is believed to be centrally involved in cardiac ischemia-reperfusion (I/R) injury, although currently no therapies exist that specifically target mitochondrial reactive oxygen species (ROS) production. The potential effects of the structural analogues of apelin-12, an adipocyte-derived peptide, on mitochondrial ROS generation, cardiomyocyte apoptosis, metabolic and functional recovery to myocardial I/R injury have successfully previously been reported. Treatment of cardiomyocytes with AI and AII significantly decreased cell apoptosis in a dose-dependent manner. In the chemical informinic field, ALOHA is demonstrated to discriminate between members of the same chemical series with strong statistical significance, suggesting that ALOHA can be used effectively to select compound candidates for synthesis and progression at the lead optimization stage of drug discovery. Here, in Biogenea Pharmaceuticals Ltd we discovered for the first time the GE-NEA-Sapemitor-45345. An In silico Structure-based designed of an apelin-analogue pharmacophoric agent for the mitochondrial ROS inhibition and cardiometabolic protection in myocardial ischemia-reperfusion injury using the BiogenetoligandorolTM and the ALOHA: a novel probability fusion approach for scoring multi-parameter drug-likeness during the lead optimization stage of drug discovery.

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TECHNICAL LIMITATIONS IN BIODISTRIBUTION STUDIES USING MESENCHYMAL STROMAL CELLS
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Biodistribution must be addressed in the development programme of any cell-based medicine. To date, however, there is no single satisfactory method of tracking cell fate and developers have to choose from a plethora of methodologies of labelling and detection, each of them having its own particular sensitivity, specificity, and standardization issues. In the present work, we analysed four methodologies of biodistribution assessment using MSC in preclinical animal models (Table). Real time cell tracking was achieved by molecular imaging methodologies using MPIO and by genetic engineering with reporter genes. It was possible to track single MPIO-labelled ovine MSC by MRI, at a very much more resolution than eGFP-labelled oMSC in ex vivo organ imaging. MRI showed better sensitivity and tissue penetration, with the disadvantage that the signal was detected only transitory because of dilution upon cell division. Alternatively, ex vivo fluorescence imaging showed less sensitivity, but durable signal. End-point PCR were performed by amplification of either reporter gene fragments or specific genomic sequences resulting in the detection of above 100 human cells in animal tissue samples. However, the quality of genomic DNA had an impact on the success of the PCR, being genomic extracts from spleen, gonads and kidney those with the highest quality when using standard commercial DNA extraction kits, as opposed to DNA extracts from lungs and liver. Human cells were detected individually by immunohistochemistry. However, this methodology is laborious, expensive and requires individualised processing of each specific tissue (i.e. decalcification of bone).
We conclude that PCR is the most convenient technique for assessing biodistribution of MSC in preclinical studies (because of cost, throughput, speed, sensitivity and specificity), and that best results were obtained by combining more than one technique in the same study (i.e. screening by PCR, and confirmation by IHC) (Figure).
Decision tree. Methodologies for cell tracking in biodistribution studies are organised according to the origin of the cells (homologous or heterologous) and the experimental system (immunocompetent or immunocompromised). Lu= Luciferase; PCR= Polymerase Chain Reaction; eGFP= enhanced Green Fluorescent Protein; IHC= Immunohistochemistry; MPIO= Magnetic Particle Iron Oxide; SPIO= Superparamagnetic Iron Oxide.

Summary of biodistribution studies performed by our group

<table>
<thead>
<tr>
<th>Study description</th>
<th>Experimental system</th>
<th>Dose/Route of administration</th>
<th>Detection</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell fate tracking of eGFP-labelled hMSC administered to osteoarthritic femoral head</td>
<td>Ovis aries (Ripollesa breed, ♂ and ♀), surgically-induced ONTH</td>
<td>6x10^6 hMSC, transplantation</td>
<td>IHC</td>
<td>Time-consuming, low-throughput</td>
</tr>
<tr>
<td>Biodistribution of systematically infused GFP-labelled hMSC in immunodepressed mice</td>
<td>Mus musculus (NRG, ♀ and ♂)</td>
<td>4x10^5 hMSC, tail-vein injection</td>
<td>PCR, Biomaging, IHC</td>
<td>Robust by combining results from the three assays</td>
</tr>
<tr>
<td>Biodistribution of intra-articularly infused hMSC in athymic rats</td>
<td>Rattus norvegicus (RNU, ♀)</td>
<td>Up to 6x10^5 hMSC, intra-articular</td>
<td>PCR</td>
<td>High sensitivity, specificity and throughput, but results dependant on the quality of genomic DNA extracts</td>
</tr>
<tr>
<td>Biodistribution of hMSC administered subdermally in athymic mice</td>
<td>Mus musculus (NIH nude, ♂)</td>
<td>6x10^4 hMSC, subdermal transplantation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell fate tracking of MPIO-labelled AF-UCMSC administered to MMC footuses</td>
<td>Ovis aries (Ripollesa breed, ♂ and ♀), surgically-induced MMC</td>
<td>Up to 4x10^5 AF-UCMSC, transplantation</td>
<td>MRI, Prussian blue staining</td>
<td>Offtarget labelling of hemosiderin-laden macrophages after phagocytosis of labelled MSC, signal interference from blood cells</td>
</tr>
</tbody>
</table>

Summary of biodistribution studies. Biodistribution studies performed by our group are listed, including the experimental system, type of cells and methodology used for their labelling and detection. AF= Amniotic Fluid; eGFP= enhanced Green Fluorescent Protein; IHC= Immunohistochemistry; MNC= Mielomeningocele; MSC= Mesenchymal Stromal Cell; MPIO= Magnetic Particle Iron Oxide; OA= osteoarthritis; oMSC= ovine MSC; hMSC= human MSC; N/A= Not Applicable; NIH=National Institutes of Health; NRG= NOD.Cg-Rag1tm1Mom Il2rgtm1Wjl/SzJ; PCR= Polymerase Chain Reaction.

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This abstract will not be presented.

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EFFECTS OF FREEZE-THAWING AND THE LUNG MICROENVIRONMENT ON MESENCHYMAL STROMAL CELLS

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We investigated the effect of freeze-thawing and of the in vivo microenvironment on culture-expanded human adipose tissue-derived mesenchymal stromal cells (MSC). Typically, MSC are isolated from bone marrow or adipose tissue, expanded in culture and cryopreserved until usage for treatment of immune or degenerative disease. The efficacy of MSC treatment will at least in part depend on the phenotypical and functional characteristics of MSC. The freeze-thawing procedure may change these characteristics. Furthermore, it has become clear that MSC localize to the lungs after intravenous infusion and the lung microenvironment may affect the properties of MSC. In the present study we demonstrate that freeze-thawing affects the MSC-induced inflammatory response in blood and the activation of complement. The effect of freeze-thawing on the whole genome expression profile of MSC was, however, small and did not exceed inter-donor differences. In contrast, expression analysis of human MSC that were infused in mice and localised to the lungs revealed that exposure to the lung microenvironment for 2h had a major effect on MSC gene expression and affected metabolic pathways. In addition, the MSC gene expression profile reflected a response to an immune activated environment. This indicates that MSC undergo functional changes after infusion, which may affect the efficacy of MSC to modulate inflammatory responses.

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This abstract will not be presented.

THE OPERATIONAL TRANSPLANT TOLERANCE AXIS. MSC – MDSC – TREG/TH17

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The immunomodulatory capacities of mesenchymal stem cells (MSCs) and multipotent adult progenitor cells (MAPCs) are undergoing preclinical and clinical assessment in solid-organ transplantation. We have demonstrated that in a fully allogenic, rat heterotopic heart transplantation model, 3rd party MAPCs treatment (drug-free immunosuppression) can induce long-term, transferable acceptance and that tolerance was dependent on myeloid-derived immunosuppressive cells (MDSC). Recently we have shown that
MSC induced long-term acceptance of allogeneic heart grafts in mice acts via MDSC-mediated conversion of Th17 cells into T(reg) cells. This is consistent with the observation that liver transplant patients enrolled in our current phase-I clinical trial (MiSOT-I) have an increased T(reg) frequency following intraoperative exposure to low-dose third-party MAPCs.

CHALLENGES FOR PUBLIC INSTITUTIONS IMPLEMENTING QUALITY STANDARDS IN THE DEVELOPMENT OF CELL-BASED MEDICINES

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New therapies involving the use of cell-based products are emerging in the regenerative medicine field. That is the case of advanced therapy (cell, gene and tissue engineered) medicinal products that have a complex and rapidly evolving regulatory framework in Europe. Academic institutions, charities and transfusion centres are best positioned to lead the development of such therapies up to early-stage clinical trials. Besides the scientific component, this endeavour requires compliance with Good Scientific Practice (GxP) regulations. This may represent a major difficulty for non-commercial institutions, which are not familiar with regulatory and quality issues already in place in the biopharmaceutical industry. Here we describe the main challenges for institutions aiming at developing cell-based therapeutics and discuss how current quality management structures already in use can facilitate the translation of cell-based products into the clinics and future marketing authorisation or, alternatively, its use under the hospital exemption clause. The generic quality assurance system ISO9001, and specific quality assurance systems for blood and bone marrow-related (such as JACIE, NetCord, FACT, and AABB) were analysed and compared to GxP standards.

Developers of cell-based medicines must guarantee the fulfilment of quality requirements that ensure their safety and efficacy following current regulations. A number of tools are currently available for Quality Risk management. In this work we used an Ishikawa diagram for the identification of main risks in the development of any cell-based medicine (Figure 1) and describe them in Table 1.

A CASE STUDY REVIEW ON LARGE SCALE MANUFACTURING OF STEM CELL THERAPIES

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MaSTherCell rapidly moved to a scaled production process with the Quantum system, a hollow fiber bioreactor. Training and technology transfer were completed within four weeks. Process optimization then provided more efficient use of both seed stock (~20% reduction) and media (~10% reduction) in the context of a new cell bank and new reagent batches. Finally, in the three weeks following process optimization, two sequential batches of 9-10 billion cells were produced using 10 Quantum systems. Variability in yield between all individual Quantum runs was limited to 12%, and viability was maintained above 95%. Additionally, each batch maintained the quality standards that were previously demonstrated for the one billion cell batches, while meeting all safety requirements (i.e., sterility, mycoplasma, and endotoxin). The cells quality profile was also consistent between the single and the 10 Quantum runs.

The breadth of this work was easily accomplished within a small, non-classified production space, including a single biosafety cabinet and two 3-m-long benches to support the 10 Quantum systems. Moreover, the 900% increase in process capacity (i.e., from one Quantum to 10 Quamums) was easily maintained by two operators.

A HUMAN PLATELET LYSATE-BASED CULTURE SUPPLEMENT FOR THE SUCCESSFUL ISOLATION AND SCALABLE EXPANSION OF UMBILICAL CORD MATRIX-DERIVED MESENCHYAL STEM/STROMAL CELLS

C. L. da Silva1, A. M. Soure1, A. Fernandes-Platzgummer1, F. Moreira1, S. Lui2, C. Ku2, Y. Huang2, W. Milligan2, J. M. Cabral1
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Umbilical cord matrix (UCM)-derived mesenchymal stem/stromal cells (MSC) are considered promising therapeutic agents. However, low cell yields per UC unit and high cell doses required in clinical settings emphasize the need for ex vivo expansion. We recently demonstrated the ability to isolate and ex vivo expand UCM MSC under serum-/xeno-free culture conditions using static systems.1 Also, we have previously established a xeno-free microcarrier-based system for the scalable expansion of human MSC from bone marrow and adipose tissue, using plastic microcarriers and a commercially available xeno-free medium formulation.2-3 However, the scalable expansion of UCM MSC under dynamic conditions using plastic microcarriers combined with different commercially available serum-/xeno-free media remains challenging. Here, we demonstrate the use of a human platelet lysate (HPL)-based culture supplement (UltraGROTM, HELIOS BioScience Inc.) for the successful isolation and scalable expansion of UCM MSC. MSC-like cells were isolated from UCM explant cultures after 11±2 days and after 5 passages cells retained their immunophenotype and multilineage differentiation potential. In addition, UCM MSC expanded using UltraGROTM-supplemented medium
expanded faster compared to the previously established protocol (1.0 vs. 0.54 day-1, respectively). Importantly, UCM MSC were successfully expanded on plastic microcarriers using UltraGROTM-supplemented medium in spinner flasks. Upon an initial 42-60% cell adhesion to the beads, UCM MSC were able to expand by >12 fold after 4-6 days, maintaining their immunophenotype and multilineage differentiation ability, as well as the capacity to support the ex-vivo expansion of hematopoietic progenitors. To our knowledge, this is the first study reporting the successful expansion of UCM MSC in a fully scalable xeno-free microcarrier-based system, representing an important advance in obtaining safer and clinically meaningful MSC numbers for Cell Therapy.

References:

This abstract will not be presented.

IDENTIFYING OPTIMAL DONOR CHARACTERISTICS FOR INCREASED MESENCHYMAL STEM CELLS RECOVERIES FROM ADULT HUMAN BONE MARROW.

O. Malik, K. Valasaki, A. Khan, J. Hare, B. Longsomboon

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Adult Human Mesenchymal Stem Cells (MSC) derived from healthy young adult donor’s bone marrow can verily be cultured and expanded in vitro, when provided with all suitable environments of growth and cell reproduction. The ultimate aim of cellular expansion is to develop stem cell based therapies for the cure of cardiovascular diseases mainly at our site, and multiple other possible utilities yet to discover. Cultured and expanded stem cell isolated from donor marrow exhibit very stable phenotype and maintains their cellular integrity even after multiple passages of expansion. Culture and expanded cell yield is always dependent on donor selection, and skilled handling of cells during each expansion passage. Key factor as always is a healthy donor with adequate body mass index, along with cell harvesting techniques at desired cellular confluence and all under standard-GMP guidelines. Stem cells requires long term cultures which requires monitoring of culture parameters and intermittent / periodic nutrient rich media replenishment before these stem get confluent enough to harvest. A shortage of healthy donors is a major limitation we face for MSC cell cultures. Identifying optimal donor characteristics can greatly increase the MSC cell recovery from bone marrow and reduce the cost of patient treatment. Currently, there is a gap in the literature on the optimal characteristics of bone marrow donors for MSC cell proliferation. This study will identify optimal donor characteristics from donor data gathered during the last five years at the Interdisciplinary Stem Cell Institute. Donor selection criteria including age, gender, body mass index for 25 donated bone marrow donors will be analyzed. Bone marrow that recovered 800million MSCs will be compared to those generating less than 800million MSCs to analyze the factors affecting cell yield during cell culture and expansion procedures.

This abstract will not be presented.

LABORATORY PRACTICE MODEL: R&D TRANSITION TO GMP AND BEYOND

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Background: In the field of regenerative medicine, bringing a novel product from research and development (R&D) to the clinical applications (“bench to bedside”) is always costly, time consuming and overwhelming for most scientists, laboratories, and principal investigators. Proving the validity of the scientific data to obtain approval for the IND can be challenging. A questionable data can cause a major setback on the process. A well-structured and well-designed product development process will provide smooth transitions for each phase of the study, reduce cost, optimize available resources, ensure integrity of the scientific data and fulfill regulatory requirements.

Model: Guided by applicable law, regulations, the model is structured and designed to integrate Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP) for the laboratory operations. Included in the model are the product development structures, facility requirements, laboratory management structures, critical control points, personnel, and quality management. Special considerations on current industry standards, when applicable, are also incorporated into the model. Recognizing the critical requirements of each stage of research development, the model is designed to introduce level of operational control step by step as the transition progress from R&D to GMP and beyond. Some requirements that are unnecessary at certain stage of development will be initiated at the later stage.

Conclusion: With the attempt to captures all the critical areas of R&D and laboratory operations, the model will enable the scientists to achieve the goal of bringing their novel product from bench to bedside without encountering unexpected draw back, wasting of funding, and other critical resources. Most importantly, the model also helps ease the burden of proving the validity of the scientific data and being in compliance.

This abstract will not be presented.

INTRAPERICARDIAL ADMINISTRATION OF CARDIOSPHERE-DERIVED STEM CELLS IN A CLINICALLY RELEVANT ANIMAL MODEL OF MYOCARDIAL INFARCTION

V. Álvarez Pérez, R. Blázquez Durán, V. Cristóstomo Ayala, C. Bézó Díaz, J. Maestre Antequera, F. Sánchez-Margallo, J. García Casado

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The intrapericardial delivery has been defined as an efficient method in compliance. With the attempt to captures all the critical areas of R&D and laboratory operations, the model will enable the scientists to achieve the goal of bringing their novel product from bench to bedside without encountering unexpected draw back, wasting of funding, and other critical resources. Most importantly, the model also helps ease the burden of proving the validity of the scientific data and being in compliance.

The intrapericardial delivery has been defined as an efficient method for pharmaceutical agent delivery, as the pericardial fluid has a low turnover rate and provides a long term effect to achieve the desired therapeutic effect. Here we hypothesize that the proinflammatory environment of pericardial fluid following myocardial infarction may induce the release of paracrine factors from intrapericardially-administered resident stem cells. In this study, we have selected porcine Cardiosphere-Derived stem Cells (also called CDCs) because of...
their promising results reported from current clinical trials. To our knowledge, this is the first report studying the effects of CDCs for myocardial repair using the intrapericardial delivery route.

CDCs lines were isolated, expanded and characterized by flow cytometry and PCR. Their differentiation ability was determined using specific culture media and differential staining. 300x10^6 CDCs/kg were injected into the pericardial space of pigs five weeks after the myocardial infarction model creation. Previously to cell administration and 30 days post-administration, magnetic resonance imaging, biochemical analysis of pericardial fluid and plasma, cytokine measurements and flow cytometry analyses were performed.

Our results showed that phenotype and differentiation behaviour of these cells were equivalent to previously described CDCs by other groups. Moreover, the intrapericardial administration of CDCs fulfilled the safety aspects as non-adverse effects were reported. Finally, the phenotype of resident lymphocytes and TH1 cytokines in the pericardial fluid was significantly altered after CDCs administration.

In conclusion, the pericardial fluid could be considered as a safe and optimal vehicle for CDCs administration. The intrapericardial administration of CDCs could be considered as an efficient strategy to modulate the inflammatory environment of infarcted hearts.

**HUMAN WHARTON’S JELLY MESENCHYMAL STEM CELLS SEEDED ON SILK FIBROIN SCAFFOLDS IMPROVE EFFECTIVENESS OF MURINE CUTANEOUS WOUND HEALING.**

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**INTRODUCTION:** Mesenchymal Stem Cells (MSCs) have been proposed as a potential therapeutic tool for inducing wound healing in some clinical settings. Also, several biosynthetic scaffolds have been used alone or in combination with cells to treat wounds. Silk fibroin (SF) seeded with MSCs has been shown to possess some efficacy in repairing experimental wounds of the skin. The aim of this study was to investigate the wound healing and cutaneous regeneration effects after implantation of SF scaffolds cellularized with human Wharton’s jelly MSCs (hWJ-MSCs-SF) using a murine excisional wound splinting model.

**METHODS:** Conformational and structural analysis of hWJ-MSCs-SF was performed by Scanning Electron Microscopy (SEM). Wounds were made by using the mouse excisional wound splinting model, and hWJ-MSCs-SF scaffolds were grafted onto the wound on the back of SKH-1 mice. Lintif® gauzes were used to treat the control group. Moreover, hWJ-MSCs were injected into the dermis around the wound. The efficacy of each treatment was assessed by immuno-histopathological analysis.

**RESULTS:** SEM analysis revealed optimal adhesion and spreading of hWJ-MSCs on the SF scaffold. Flow cytometry analyses showed no significant changes in the mesenchymal immunophenotype or cell viability of hWJ-MSCs after culturing on SF scaffolds. Also, immunohistopathological examination at day +15 confirmed the presence of infiltrated human fibroblast-like CD90+ cells in the dermis of the hWJ-MSCs-SF scaffolds treated group. Furthermore, hWJ-MSCs-SF grafts showed a well-vascularized granulation tissue in the dermis with less collagen matrix production and macrophage infiltration and a complete epidermal regeneration compared to the control group.

**CONCLUSIONS:** hWJ-MSCs in the wound bed might contribute to the generation of well-vascularized granulation tissue, enhanced epithelialization of the wound and reduced formation of fibrotic scar tissue and inflammation.

**MECHANISMS INVOLVED IN THE REDUCTION OF INFLAMMATION AND IMPROVEMENT OF CARTILAGE CHARACTERISTICS IN OSTEOARTHRITIS BY MESENCHYMAL STROMAL CELLS**

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Cell-based therapeutics differ from small molecule or biological drugs in that living medicines are delivered to patients with the aim of repairing damaged tissue, reduce inflammation and restore organ functionality. In the present study, clinical-grade human mesenchymal stromal cells (MSC) were tested at three doses (high: 6x10^5 MSC, medium: 6-8x10^4 MSC, and low: 8x10^3 MSC) for the treatment of monoidoacetate-induced osteoarthritis in athymic rats by intra-articular injection in the femorotibial joints. At 4 weeks post-treatment, no toxicity was reported even at high cell dose, and persistence of injected MSC was primarily found in the infrapatellar fat pad. Interestingly, a reduction of the inflammation of synovial membrane and local joint pain relief (measured by response to pressure, flexion and extension of the limb) was observed in treated animals rather than significant improvement of cartilage characteristics, which only showed higher scores for cell viability in MSC-treated OA-induced knees according to the ICRS histological grading scale (p=0.0742, n=3). In vivo co-culture experiments of MSC with peripheral blood mononuclear cells evidenced a reduction of the secretion of IL-6 and an increase of PGE2 levels. MSC also inhibited the proliferation of activated lymphocytes, unveiling the importance of paracrine properties of MSC in OA treatment rather than their chondrogenic progenitor capacity.

**ORTHOTOPIC IMPLANTATION OF HUMAN MESENCHYMAL Stromal CELLS FOR CRITICAL SIZE BONE DEFECTS IN IMMUNODEFICIENT RATS: SAFE, POSSIBLY EFFECTIVE.**

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**Background.** The autologous and allogeneic mesenchymal stromal cells (MSC) were tested at three doses (high: 10^6 MSC) in critical size bone defects in immunodeficient rats. The persistence of injected MSC was primarily found in the infrapatellar fat pad. In the present study, clinical-grade human mesenchymal stromal cells (MSC) were tested at three doses (high: 6x10^5 MSC, medium: 6-8x10^4 MSC, and low: 8x10^3 MSC) for the treatment of monoidoacetate-induced osteoarthritis in athymic rats by intra-articular injection in the femorotibial joints. At 4 weeks post-treatment, no toxicity was reported even at high cell dose, and persistence of injected MSC was primarily found in the infrapatellar fat pad. Interestingly, a reduction of the inflammation of synovial membrane and local joint pain relief (measured by response to pressure, flexion and extension of the limb) was observed in treated animals rather than significant improvement of cartilage characteristics, which only showed higher scores for cell viability in MSC-treated OA-induced knees according to the ICRS histological grading scale (p=0.0742, n=3). In vivo co-culture experiments of MSC with peripheral blood mononuclear cells evidenced a reduction of the secretion of IL-6 and an increase of PGE2 levels. MSC also inhibited the proliferation of activated lymphocytes, unveiling the importance of paracrine properties of MSC in OA treatment rather than their chondrogenic progenitor capacity.

**Methods.** The xenogeneic transplantation of human MSC has been conducted on mnu-mnu rats. Created (drilled) 5 mm femoral defect was stabilized by metal plate. The defect was filled with either human plasma clot with hMSC (experimental groups) or with human plasma clot only (control groups). In experimental groups, median 10x10^6 (range, 7.5–10x10^6) cells were used for clot formation. Rats...
were sacrificed 8 or 16 weeks after transplantation. The distance of proximal and distal bone was measured by X-ray after explantation and the formation of new bone was studied by microCT scan and histologically. Human cells were detected with antibodies against human nestin, human cell nuclei and mitochondria.

Results. 42 rats were used and 38 of them (90%) were evaluable. On histological examination, human cells were present in all experimental samples both in 8 and 16 week group, both in newly formed bone and in connective tissues (fibrous or adipous tissue or disorganized cartilage) in the remaining defect. No inflammatory or other adverse host reaction was noted. Improved bone formation was found after 8 weeks in experimental than in control femurs on radiography (remaining defect, 1.7 v. 2.5 mm, p <0.05). After 16 weeks, however, there was no difference between remaining defect in experimental and control bones (2.0 and 2.2 mm, respectively). MicroCT scans confirmed these results.

Conclusion. The orthotopic implantation of human MSC in rat bone defects seemed to be safe and well tolerated. Human MSC survived at the place of implantation for the whole 16 weeks of experiment and seemed to contribute to the healing of defect during first eight weeks of experiment.

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**BIOCONTAMINATION CONTROL OF ADIPOSE TISSUE TO MANUFACTURING MESENCHIMAL STEM CELLS BASED MEDICINES**

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**Background:** One of the essential mechanisms to identify sources of microbial bioburden is the appropriate implementation of a Biocontamination Control Program based on Risk Analysis tools. Cell therapy based medicines manufacturing by Aseptic Processing, one of the main sources of contamination is the microorganism that accompanies the adipose tissue. The cell culture medium used in the cell expansion process is usually supplemented with antibiotics, such as gentamicin, used in our process. *Staphylococcus* genus is the more common microorganism in human skin and it shows a 40% gentamicin resistance. We analyze the microbial contamination from adipose tissue

**Methods:** Culture media: BD-BACTEC™ Plus Aerobic/F and BACTEC™ Lytic/10 Anaerobic/F culture vials. Detection system: BD-BACTEC, incubation time 7 days at 35ºC. Product/sample: 5 from the saline in which the adipose tissue obtained from surgery is embedded during transport. Microorganisms identification was carried out by MALDI-TOF Mass-Spectrometry.

**Results:** nine out of the eleven analyzed samples of adipose tissue in the last year were positive. Four positive samples were contaminated by at least two different microorganisms. Isolated microorganisms are depicted in the following table. In two cases, decontamination with gentamicin and vancomycin was not enough to eliminate contamination.

**Conclusions:** in our experience, we believe appropriate to perform microbiological culture from raw material, incubation with antibiotics solution for at least 1-2 hours and subsequent verification of the decontamination process.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Microorganisms</th>
<th>Vancomycin</th>
<th>Gentamicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><em>Staphylococcus</em> epidermidis</td>
<td>Sensitive</td>
<td>Sensitive</td>
</tr>
<tr>
<td>2</td>
<td><em>Corynebacterium</em> amycolatum</td>
<td>Sensitive</td>
<td>Sensitive</td>
</tr>
<tr>
<td>3</td>
<td><em>Staphylococcus</em> epidermidis</td>
<td>Sensitive</td>
<td>Resistant</td>
</tr>
<tr>
<td>4</td>
<td><em>Staphylococcus</em> capitis</td>
<td>Sensitive</td>
<td>Sensitive</td>
</tr>
<tr>
<td>5</td>
<td><em>Clostridium</em> perfringens</td>
<td>Sensitive</td>
<td>Resistant</td>
</tr>
<tr>
<td>6</td>
<td><em>Staphylococcus</em> epidermidis</td>
<td>Sensitive</td>
<td>Sensitive</td>
</tr>
<tr>
<td>7</td>
<td><em>Staphylococcus</em> oralis</td>
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<td>Sensitive</td>
</tr>
<tr>
<td>8</td>
<td><em>Negative</em></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td><em>Bacillus</em> cereus</td>
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35
This abstract will not be presented.

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EXOSOME-DERIVED MESENCHYAL STEM CELLS FOR THE TREATMENT OF SYNOVITIS: PROOF OF CONCEPT IN A LARGE ANIMAL MODEL
F. Vela González, F. Sánchez-Margallo, A. Tapia Aroya, R. Blázquez Durán, V. Álvarez Pérez, J. García Casado

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The general objective of this work is the development of a preclinical study to evaluate the efficacy of exosome-derived Mesenchymal Stem Cells (exo-MSCs) in the treatment of synovitis.

Three months old Large White female pigs were used in this study, with an initial weight of 25 Kg. They were previously immunized with an emulsion of Freund Complete Adjuvant (FCA) and Bovine Serum Albumin (BSA) at 20 mg/ml. Subcutaneous immunizations were performed using 0.4 ml/Kg. All procedures were done under proper anesthesia. The synovitis was induced by intra-articular injection of 0.5 ml of BSA at 20 mg/ml on the right wrist. Exosomes from porcine MSCs were isolated from cell culture supernatants and intra-articularly injected. For immune monitoring of BSA immunization, peripheral blood was weekly collected. Plasma was stored to quantify humoral response against BSA (IgG anti-BSA) by ELISA test. Peripheral blood and synovial fluid lymphocytes (PBLs and SFLs, respectively) were isolated by density gradient, and analyzed by flow cytometry to study the different leukocyte subsets. Finally, TH1/TH2 cytokines and chemokines were quantified in synovial fluid by Luminex using the ProcartaPlex Porcine kit.

Our results showed that BSA immunization protocol induced a humoral and cellular response with changes on PBLs and SFLs subsets, increasing an increase of CD4+ T cells. The intra-articular immunization of BSA reproduces, at least in part, the clinical features and inflammatory events that normally occur in synovitis. Finally, here we demonstrate that exo-MSCs had an immunomodulatory effect on the synovial T cells and may represent an alternative therapy to other conventional treatments of synovitis.

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RHEOLOGICAL QUALITY CONTROL OF BIOENGINEERED TISSUES. EVALUATION OF BIOMECHANICAL PROPERTIES IN A FIBRIN-AGAROSE TISSUE-LIKE MODEL
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1University of Granada, Granada, Spain, 2Instituto de Investigación Biomática ibs GRANADA, Granada, Spain

Introduction. Different artificial tissues have been developed by using fibrin-agarose biomaterials (FA), including cornea, oral mucosa and peripheral nerve. Although histological and genetic controls have been carried out, few studies focused on the determination of the rheological properties of these tissues. In the present study, we performed a rheological analysis of acellular tissue-like constructs to determine their putative usefulness as tissue substitutes.

Materials and Methods. FA tissue-like constructs were generated in the laboratory with increasing agarose concentrations (0, 0.1, 0.2, 0.3, 0.4 and 0.5%). Constructs were then subjected to nanostructure and evaluated at different development times by scanning electron microscopy (SEM) and rheological analysis under shear stress at 37°C.

Results. A regular and homogenous superficial structure was found in all tissue-like constructs at 0, 1, 2, 3 and 4 weeks. The fibrin-agarose mesh was stable along the time and no signs of degradation were detected. The rheological analysis showed that constructs were more elastic than viscous (G'>G''), and each specific agarose concentration was associated to definite biomechanical properties. The artificial tissues showing the highest G' and G'' moduli were those with 0.2% agarose concentration (G'>2000 Pa and G''>300 Pa). However, the compression tests revealed that the elastic modulus Ec tended to increase with the agarose concentration, reaching the maximum value for 0.5% agarose.

Conclusions. The results show that the biomechanical properties of the FA tissue-like constructs are tunable and may be modified in order to mimic the properties of the native tissue to be reproduced in the laboratory. Determining the rheological properties of the tissue-like constructs should be considered in the quality control protocol of these artificial tissues.

Supported by grants FIS PI14/0955, PI14/1343 and PI14/2110 from Instituto de Salud Carlos III, cofinanced by FEDER, EU.

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AUTOLOGOUS CHONDROCYTE IMPLANTATION TO TREATMENT OF ARTICULAR CARTILAGE LESIONS OF THE KNEE. FINDINGS AT 5 YEARS.
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Articular cartilage lesions are becoming increasingly common and it can progress to osteoarthritis, being among the leading causes of disability in the 21st century. Recently, are increasing the evidence of the successful treatment of these lesions by ACI, provided durable outcomes.

Patients undergoing ACI were selected by experienced traumatologists following standardized criteria including age, clinical symptoms, type and size of lesion. To date, 22 patients were treated in our centre, with an age range of 18–46 years and a lesion sizes ranging from 3 to 9 cm2. Cultures were successfully established in all patients. The initial chondrocyte yield was 0.3±0.29 x 106 cells. The time to primary confluence was 8 ± 2.6 days and after a maximum 4 subculture steps, 39±13.4 x 106 cells were obtained. The cellular duplications were 6.91±0.91 and a mean of 4.15±1.36 x106 cells/cm2 lesion were implanted.

In 15 patients with more than one years of follow-up we founded significant improvement (p<0.001), both daily activities (89,3% preop. limitation - 9% postop.), as in the sports (90,2% preop limitation - 38% postop.) and the exploration of the knee (67,7% pathological findings preop-13,3%postop). This improvement was maintained in the four patients with more than 5 years of follow-up (Fig1). The SF-36 score (Fig 2) improved in all categories, over all in mental health. The patient satisfaction was high or very high in 12 of the 15 patients (80%), and low in 3 patients.

ACI improve quality of life and knee function in femoral condyle chondral lesions. Our GMP facilities allow us to create care circuits.
for treatment of patients in the Public Sanitary Health System. It is necessary to increase the experience with this type of therapy, consolidating multicenter workgroups that provide strength to the conclusions.

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MURINE AMNIOTIC MEMBRANE: A RICH SOURCE OF STEM CELLS FOR REGENERATIVE CELL THERAPY STUDIES.

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Introduction: Recent studies have shown that human amniotic membrane is a rich source of stem cells with capacity for multipotent differentiation, reduced immunogenicity, and some immunomodulatory properties. The murine model is the most commonly animal model of choice for many areas of scientific research and because of that we consider the successful isolation, culture and characterization of murine amniotic membrane stem cells (AMSCs) as a first approach for subsequent studies of their biological properties and possible therapeutic potential in different murine models of disease.

Methods: Amniotic membranes from pregnant female C57Bl/6 mice were carefully separated from the yolk sacs and collected. After, phenotype and genotype of murine AMSCs were analyzed by immunofluorescence and RT-PCR techniques. For other experiments, AMSCs were isolated by collagenase digestion and characterized by flow cytometry. Furthermore, immunosuppressive capacity of murine AMSCs on T cell proliferation was studied by using mixed lymphocyte cultures (MLC) with allogeneic stimulator Balb/c and responder C57Bl/6 splenocytes, cultured in presence of different ratios of AMSCs.

Results: RT-PCR and immunofluorescence experiments showed a positive expression of E-Cadherin, Occludin, Nestin, Vimentin, Oct3/4, Sox2, Nanog and Slug in freshly isolated amniotic membranes. In addition, flow cytometry analysis determined that murine AMSCs was CD44+, CD90+, CD73+, CD105+ and Ki67+. Further, immunosuppressive capacity of murine AMSCs on T cell proliferation was studied by using mixed lymphocyte cultures (MLC) with allogeneic stimulator Balb/c and responder C57Bl/6 splenocytes, cultured in presence of different ratios of AMSCs.

Conclusions: Murine AMSCs may represent a rich source of pluripotent stem cells that could be useful for their use in murine preclinical studies in order to develop future human translational therapies.

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MESENCHYMAL STEM CELLS MODULATE THE IMMUNE SYSTEM VIA PASSIVE MECHANISMS

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Mesenchymal stem cells (MSC) are under investigation as immunosuppressive therapy for several immune disorders. It is, however, not clear how MSC distribute their immunomodulatory effect after infusion. In vitro immunomodulatory effects of MSC depend on soluble factors and membrane proteins induced on MSC under inflammatory conditions. However, recent data demonstrates that MSC have a short survival time after infusion. To investigate whether MSC actively contribute to the anti-inflammatory response or whether they merely trigger responses by host cells we compared disease-modulating activity of inactivated MSC with viable MSCs.

MSC were inactivated by heating at 50°C (HI) to suppress their ability to produce soluble factors while keeping the surface molecules intact. Immunomodulatory effects of HI and viable MSC on T cells were evaluated in vitro. Migration of HI and viable MSC was examined in a kidney ischemia-reperfusion injury model and immunomodulatory effects were examined in healthy and LPS induced septic mice.

In vitro, only viable MSC suppressed T cell proliferation. In vivo, tracking of HI and viable MSC showed similar distribution and survival time and a lack of active migration to the site of inflammation. However, both MSC induced a systemic increase in IL-6, MCP-1, CXCL1 and IL-10 after intravenous infusion in healthy mice indicating that MSC therapy induces a systemic immunomodulatory response. Moreover, in serum of sepsis mice viable and HI MSC significantly increased IL-10 and significantly reduced IFN-γ. While HI MSC lack many of the immunomodulatory properties of viable MSC in vitro, HI and viable MSC induce similar immunomodulatory responses in vivo. This suggests that the immune modulatory response induced by MSC is mediated by passive interactions with host cells. This has implications for the development of MSC immune therapy as not the secretome of MSC but their phenotype appears to be most determinative for their clinical effect.

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A SIMPLE METHOD FOR RISK ANALYSIS AND VALIDATION OF COMPUTERISED SYSTEMS IN ACADEMIC CELL THERAPY FACILITIES

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Hospitals, academic institutions, transfusion centers and small companies currently lead the development of novel advanced cell therapeutics (ATMP) for human use. Compliance with pharmaceutical quality standards is mandatory in the manufacture of this type of products, thus pushing academic developers to implement methods for control and monitoring of bioprocess parameters that, until present, were only found within large corporate environments. Here we present our approach for risk analysis and validation of a computerised system for monitoring environment parameters in incubators (that is: CO₂ levels and Temperature, T), fridges and freezers (T), and clean rooms (T and Relative Humidity, RH), used in bioprocesses.
designed for the production of ATMP under Good Manufacturing Practices (GMP). The implementation of computerised monitoring systems allow working under the latest concept of Quality By Design (or QbD) that it is key in products with very limited shelf-life, as is the case of ATMP. In the present study, the experimental system was composed of a total of 36 probes for T, 11 probes for CO₂ and 1 probe for RH connected to 34 data loggers that transferred measures to 4 modems and one single server. The initial Ishikawa risk analysis permitted to identify critical parameters qualitatively that were subsequently quantified using a Failure Modes and Effects Analysis (or FMEA), resulting in a list of tests that were included in the protocols for Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ). The approach presented here contributes to simplify and streamline the qualification of computerised monitoring systems in compliance with GMP standards.

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This abstract will not be presented.

GENERATION OF INDUCED PLURIPOTENT STEM CELLS (hiPSCs) AS CELLULAR MODEL TO STUDY THE PATHOGENESIS OF MYOTONIC DYSTROPHY TYPE 2 (DM2)
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Human induced pluripotent stem cells (hiPSCs) are an innovative tool to study multisystemic disorders because this cell type can be derived from patients as a renewable source for unlimited cells that are difficult to acquire. Myotonic dystrophy type 2 (DM2) is caused by an unstable (CCTG)n expansion in intron 1 of the CNBP gene leading to a progressive disease involving muscle, heart and brain. To date, no cellular or animal models fully recapitulate the complex molecular and clinical phenotype of DM2 patients. In this study, we generated two DM2 and one wild type hiPSC lines from dermal fibroblasts by lentiviral transduction using the hSTEMCCA-loxP polyicosatronic vector (containing hOct4, hSox2, hKlf4, and hc-Myc sequences). The successful reprogramming of DM2 and wild type-derived hiPSCs has been confirmed by specific morphological, molecular, immunocytochemical markers and by their teratogenic potential when inoculated in vivo. We further demonstrated the stability of reprogrammed cells over 10 and more passages and their ability to differentiate into the three embryonic germ layers. CCTG expansions and intranuclear CCUG-containing RNA foci, hallmarks of DM2 in patients-derived fibroblasts, were conserved in DM2-hiPSCs before and after their neural differentiation. Further expression studies are currently in progress to determine if the DM2-hiPSCs show the spliceopathy typical of DM2 adult cells and tissues. The development of an experimental system based on hiPSCs technology could aid in the identification of molecular pathogenic mechanisms and personalized therapeutic treatments for DM2.

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STANDARDIZED AND CLINICAL GRADE HUMAN PLATELET LYSATE HYDROGEL (HPLG) FOR THE OPTIMIZATION OF LARGE-SCALE EXPANSION OF HUMAN MESENCHYML STEM CELLS.
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The amplification of stem cells, such as human Bone-Marrow Mesenchymal Stem Cells (MSC), in standardized and xeno-free conditions represents a major challenge for the production of safe and reproducible cell therapy products in clinical applications. Recently, human platelet lysate has emerged as a safe and efficient substitute for Fetal Calf Serum (FCS), a traditionally-used animal product showing risks of pathogens transmission and xenogeneic immune reactions.

We evaluated the use of a standardized HPLG manufactured under GMP conditions as a 3D-supportive environment for large-scale expansion of MSC. In culture on HPLG, MSC were progressively degrading the gel, releasing the growth factors entrapped (VEGF, PDGF-AB, IGF-1, TGF-b1, bFGF) with specific kinetic profiles. These profiles were different in absence of cells. HPLG thickness studies (from 50 to 200µL/cm²) identified the 100µL/cm² condition as the more potent on MSC’s expansion. Fluorescently labeled MSC seeded on HPLG surface were shown to migrate inside the gel during culture. Cells harvesting from HPLG was quicker and easier than on plastic using a clinical grade enzymatic solution. Comparing MSC’s expansion on plastic with a 10%FCS-bFGF supplemented-medium to a 10% HPLG without any medium supplementation, we demonstrated 1) On HPLG, on 3 consecutive passages, the maintenance of MSC proliferation rate around 90% when a 60% decrease was observed at passage 3 on plastic; 2) no modification for CD13, CD29, CD44, CD45 and CD73 expression; 3) an increase expression of CD90 and CD105 on HPLG; 4) a similar osteogenic and adipogenic differentiation potential. Interestingly, without any medium change on a 10-days period, we observed that the total number of cells continued to efficiently increase on HPLG, while on plastic proliferation stopped after D5.

Taken together, the presented data clearly demonstrate that HPLG represents a new, secured and efficient way to amplify MSCs for cell therapy.

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PRESERVATION OF QUALITY AND EFFICACY OF HUMAN PLATELET LYSATE PATHOGEN REDUCED WITH PHOTOSENSITIZING ADDITIVE-FREE THERAFLEX UV-PLATELETS TECHNOLOGY
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We recently developed and characterised a standardised and clinical grade human Platelet Lysate (hPL) that constitutes an advantageous substitute for foetal bovine serum for human mesenchymal stem cell (hMSC) expansion required in cell therapy procedures, avoiding xenogenic risks (virological and immunological) and ethical issues. Because of the progressive use of pathogen reduced (PR) labile blood components, we evaluated the impact of the novel procedure THERAFLEX UV-Platelets for pathogen reduction on hPL quality (growth factors content) and efficacy (as a medium supplement for hMSC expansion). This technology is based on short-wave
ultraviolet light (UV-C) and has the main advantage to not need the addition of any photosensitizing additive compounds (that might secondary interfere with hMSCs). We performed UV-C treatment on fresh platelet concentrates (PCS) suspended in platelet additive solution (PAS) and prepared hPL from these treated PCS. We compared the quality and efficacy of PR hPL with the corresponding non-PR ones (n=12). We showed no impact on growth factor content for all the cytokines tested (EGF, bFGF, TGF-β1, PDGF-AB, VEGF and IGF). Large scale expanded hMSCs cultured in PR or non-PR hPL containing medium maintained their profile of hMSC membrane markers expression. The amplification yield, the clonogenic potential and the differentiation potential in adipogenic and osteogenic lineages of hMSCs cultivated in parallel in both conditions remained also identical. In conclusion, we demonstrated the feasibility to use UV-C treatment to subsequently obtain pathogen reduced hPL, while preserving its optimal quality and efficacy for hMSC expansion for cell therapy applications.

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**GMP COMPLIANT STEM CELL THERAPY FOR THE OCULAR SURFACE**

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The cornea is the clear front surface of the eye which acts as our window to the world. Corneal homeostasis is essential to maintenance of a normal vision. The cornea is separated from the conjunctiva by a thin band of tissue called the limbus which houses limbal stem cells (LSC); which are responsible for maintaining corneal transparency. Damage to LSC’s can be caused by Stevens Johnsons syndrome, chemical or thermal insults, microbial infection and leads to LSC defect (LSCD) leading to severe visual impairment or blindness. Conventionally, limbal epithelial cells (LEC) cultured on human amniotic membrane (HAM) have been used for ocular surface reconstruction following LSCD. In our experience, 30% of the grafts cultured using this technique failed to grow. This could be attributed to batch-to-batch variability between HAM. In addition, an autologous limbal biopsy risks LSCD in the healthy bilateral eye and transplantation using autologous tissue requires heavy immunosuppression. We have therefore developed a novel, GMP compliant fibrin substrate which supports the growth of human oral mucosal and conjunctival epithelial cells; as an alternative to LEC. Both cell types stratify to form multiple layers and exhibit positive staining for the putative stem cell marker, p63a. In addition, cultured oral mucosal epithelial cells express CK19, CK13 and the differentiation marker, CK3. Similarly, cultured conjunctival epithelial cells expressed CK19 and the putative stem cell marker, CK15.

Apart from offering a less invasive epithelial cell alternative to limbal tissue, this technique offers various advantages including a highly reproducible, CE marked substrate that is capable of achieving cell confluence within 12± 5 days without the support of murine 3T3 feeder cells; which whilst traditionally used for cell therapies can also cause xenogeneic contamination of the cell therapy product.

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THREE-DIMENSIONAL BIOACTIVE HUMAN LIVER ACCELLULAR SCAFFOLD WITH PRESERVED ARCHITECTURE AND BIOMECHANICAL PROPERTIES

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Background: The key challenge in tissue engineering is the development of biomaterials that mimic the complexity of human tissue. The aim of this study was to develop a rapid protocol for the decellularisation of small samples of healthy human liver, to demonstrate preservation of ECM composition, 3D-architecture, bioactivity and biomechanical properties. In addition, repopulation with cultured human liver cell lines, namely hepatoblastoma (HepG2), hepatic stellate (LX2) cells, and human umbilical vein endothelial cells (HUVEC).

Methods: Decellularisation was completed within 3 hours of agitation in solutions with detergents and enzymes. The decellularisation efficiency was determined by immunohistochemistry for ECM components and residual DNA, scanning electron and second harmonic generation microscopy, proteomic, raman spectroscopy, atomic force microscopy and chorio-allantoic membrane assay. The liver cube scaffolds were seeded and repopulated with HepG2, LX2 and HUVEC for up to 14 days.

RESULTS: This innovative protocol resulted in liver cube scaffolds with a preserved 3D structure and ECM composition, while DNA and cellular residues were successfully removed. Tissue stiffness was preserved and the acellular liver maintained the capability to induce neo-angiogenesis. Interestingly, HUVEC repopulated the decellularised vessels and expressed functional markers such as FVIII. Acellular human liver repopulated with LX2 and HepG2 cells showed remarkable difference in gene and protein expression when compared with 2D-system. Notably, HepG2 cells upregulated albumin gene expression after 14 days in 3D-culture.

CONCLUSION: This is the first report describing a protocol for fast human liver tissue cubes decellularization. The decellularization protocol maintained the natural 3D structure and ECM composition. This is a key advance in the development of 3D technologies for the study of liver disease and for the development of 3D-carrier for hepatocyte transplantation.

HEMATOPOIETIC PROGENITORS CRYOPRESERVATION

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Introduction: We have previously established the safety of the automated washing of cryopreserved hematopoietic progenitors (HP) with the Sepax device (Biosafe) using normal saline plus 2.5% albumin (NSA) (Sánchez-Salinas et al. 2012). We now compare NSA with a ready-to-use free of human derived components solution: Voluven. Methods: 411 (229 NSA, 182 Voluven) 9% DMSO HP cryopreserved units corresponding to 211 (130 NSA, 81 Voluven) apheresis and 158 (96 NSA, 62 Voluven) autologous HP transplants were studied. Total nucleated cells (TNC), CD34 cells, CFU-GM, BFU-E, cell viability, engraftment and infusion reactions were evaluated.

Results: At thawing we observed a significant loss of CD34 cells, BFU-E and viability (p<0.01), but not of TNC and CD34 cells. After washing we observed a significant loss of CD34 cells, which was higher with NSA (p<0.01). However CD34 cells, CFU-GM, BFU-E and cell viability values did not differ from the thawed ones with either washing solution. When analysing the data from the apheresis to the washing, a significant loss of TNC, CFU-GM, BFU-E and viability was observed (p<0.01), being the CD34 cell numbers stable. There were no significant differences between washing solutions. We observed three adverse events (mild nausea and hypotension, epileptic fit) with the Voluven washes (1.6%) and none with NSA. There were no differences in neutrophil engraftment or in platelet engraftment.

Conclusion: We observed a negative impact of the freezing-thawing procedure on CD34 cell numbers, CFU-GM, BFU-E and cell viability. Both NSA and Voluven are equally effective for washing cryopreserved HP, ensuring a good CD34 cell recovery and preserving their viability and engraftment potential. Both solutions avoid the DMSO infusion related adverse events. As so, Voluven constitutes an excellent alternative free of human-derived products and ready-to-use solution to our previous NSA standard washing solution.
advanced NKT lymphoma who have relapsed after asparaginase based treatments.

Results: We have transferred the process from an academic setting to an industry platform, and qualified the process, including starting material and final product shipping, to allow US-based manufacturing for clinical sites in France, Germany, Korea, UK, and US. We have received regulatory authorization to begin clinical testing in France, Germany and the UK (through the European Voluntary Harmonization Process), Korea and in the US. The first patient was treated on 11 Feb 2015 and the clinical trial is ongoing.

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THE EFFICACY OF SPHEROIDAL HEPATOCYTE ON HEPATOCYTE TRANSPLANTATION
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Background: Hepatocyte transplantation (HCTx) is an attractive and novel treatment option for patients with metabolic liver diseases or acute liver failure. The strategy requires transplant recipients to receive repeated infusions of viable hepatocytes over 1-2 days to achieve adequate liver functions. However, the disruption of cell-to-cell and cell-to-matrix contacts during the cell isolating process leads to subsequent hepatocyte dysfunction. The isolated hepatocytes lose their specific functions if the cells are not anchored and cultured under appropriate conditions. Herein, we evaluated the efficacy of spheroidal hepatocytes was evaluated by using mouse HCTx model. Materials and methods: Mouse hepatocytes were isolated from C57BL/6 mice. Isolated hepatocytes were seeded into the ultra-low attachment plates, and the spheroids of hepatocytes were harvested with a pipette at 5 days after seeding. Five hundred spheroidal hepatocytes (contains 3.5 x10³ hepatocytes) were transplanted into the liver of apolipoprotein E (ApoE) (also knockout mice (apoE-/-); B6.129P2-Apoetm1 Unc N11) via the portal vein. As a control, the same amount of hepatocytes (3.5 x10³ hepatocytes) was also transplanted in the same procedure. Blood samples were obtained after HCTx. To evaluate the function of transplanted hepatocytes, serum ApoE and hepatic ApoE mRNA expression were evaluated by ELISA and PCR analysis.

Results: Serum ApoE was under the detection level before HCTx. After the spheroidal hepatocyte transplantation, serum ApoE appeared in the circulation, and the concentration increased to 0.195% of the concentration in wild type mice at 4 weeks after HCTx. In the control animal, serum ApoE concentration increased to 0.134%. The hepatic ApoE mRNA was also detected in the spheroidal hepatocytes transplanted mouse. Transplanted spheroidal hepatocytes were detected pathologically, remaining spheroidal formation.

Conclusion: Spheroidal hepatocytes is a promising strategy for HCTx.

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MSCTRAIL AS A CELLULAR THERAPY FOR METASTATIC LUNG CANCER
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Lung cancer kills >34,000/yr in the UK alone and is the leading cause of cancer death worldwide. Over 70% of patients present with metastatic disease and cannot be cured by surgery or radiotherapy. One year survival is approximately 15%. Current treatment options involve palliative chemotherapy and radiotherapy which improve life expectancy by a few months despite severe toxicity. Around 8% of patients can be treated with molecular targeted therapies and gain an average of 9 months before relapse. Novel therapies are desperately needed.

Bone marrow-derived MSCs home to tumours after systemic delivery, are readily modified with viral vectors to carry anti-cancer therapies and are non-immunogenic allowing a tumour-targeted therapy. TRAIL is a pro-apoptotic molecule that kills cancer cells without affecting healthy. There is strong evidence that TRAIL is highly synergistic with other anti-cancer therapies. We have modified MSCs to carry TRAIL (MSCTRAIL), shown elimination of lung metastases in animal models and potent synergy with chemotherapy in vitro.

The MSCTRAIL trial is a Phase I/II safety and preliminary efficacy trial of MSCTRAIL with chemotherapy in lung cancer patients. We will undertake large scale manufacture of MSCTRAIL to GMP standard, deliver radiolabelled cells within the phase I safety component to allow determination of the biodistribution and biokinetics of MSCTRAIL, and then proceed to a phase II randomised trial to determine the efficacy of MSCTRAIL in combination with chemotherapy compared to chemotherapy alone. If successful this could lead to testing of MSCTRAIL in other tumour types and cellular delivery of alternative anti-cancer agents.

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GENERATION OF TISSUE-LIKE MEMBRANES WITH CONTROLLED FIBER ORIENTATION USING MAGNETIC PARTICLES
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Introduction. Novel biomaterials containing magnetic particles are currently considered in tissue engineering due to their dynamic properties and the possibility of controlling the biomechanical behavior of the tissue-like membranes (TLM) generated with these biomaterials. The objective of this work is to analyze the capability of these magnetic particles to modify the biomechanical properties of TLM.

Materials and Methods. TLM were generated by using a biomaterial consisting on human plasma fibrin with 0.1% agarose and 2% magnetic particles (v/v) in which human fibroblasts were cultured. During the gelation process, TLM were exposed to 0, 16, 32, and 48 KA/m magnetic fields, and their rheological properties were
analyzed by using a shear-stress rheometer. Histology was analyzed in each group by H&E staining and SEM.

Results. Histological analysis revealed that cells were able to grow and spread in the biomaterial, and fibers were highly oriented in TLM generated under magnetic fields. The presence of magnetic particles was able to increase the elastic shear modulus of the TLM. The strength of the magnetic field applied to the construct (16, 32 and 48 KA/m) did not influence the histological and rheological results.

Conclusions. These results show that TLM generated with magnetic particles are biocompatible ex vivo. The use of magnetic fields during the elaboration of the TLM regardless the intensity makes possible the construction of novel artificial membranes with highly-oriented fibers and increased mechanical properties, which could be used for tissue engineering applications requiring definite fiber orientation.

Supported by grants FIS P114/0955 and P114/1343 from Instituto de Salud Carlos III, co-financed by FEDER, EU.

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SEQUENTIAL CELL-BIOMATERIAL INTERACTION IN AN EX VIVO MODEL OF NEURAL TISSUE FOR NEURAL ENGINEERING APPLICATIONS

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Introduction. Different nerve substitutes consisting on cells and biomaterials have been used for peripheral nerve regeneration with promising results. However, the role of the cells used in these nerve substitutes has not been elucidated to the date. In the present work, we have elaborated a bioengineered nanostructured nerve substitute (BNNS) with human mesenchymal stem cells and biomaterials and we analyzed the cell-biomaterial interaction that takes place ex vivo to determine the influence of the cells on the BNNS.

Materials and Methods. BNNS were generated with human adipose stem cell cultures and nanostructured fibrin-agarose biomaterials and concentric tubular structures were engineered to mimic the structure of the peripheral nerve. BNNS were kept in culture for 16 days. BNNS and controls were evaluated at days 2, 8 and 16 by histological analysis with H&E, scanning electron microscopy (SEM), and laminin and collagen immunohistochemistry.

Results. Histological analysis of BNNS showed a highly-dense concentric pattern with cells initially allocated among the biomaterial layers that tended to form cell clusters with culture time. Cells in clusters progressively synthetized laminin and collagen and tended to remodel the surrounding biomaterial and to replace the fibrin-agarose by newly-synthetized extracellular matrix components.

Conclusions. These results demonstrate that cells are able to modify and remodel the biomaterial used for the construction of the BNNS and contribute to replace the scaffold by extracellular matrix components synthetized by the cell population. Future works should determine the most adequate development time when the interaction between cells and biomaterial allows obtaining a more biomimetic nerve substitute for use in nerve regeneration.

This study was supported by the Spanish Instituto de Salud Carlos III, grant FIS P114/1343 (co-financed by FEDER, EU).

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EVALUATION OF LIVING AND CADAVERIC DONORS AS SOURCES OF EPITHELIAL URETHRA CELLS FOR TISSUE ENGINEERING

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Introduction. Generation of artificial models of the human urethra by tissue engineering could contribute to the treatment of numerous diseases affecting the urinary tract. In this regard, the cell source is one of the most important factors influencing the success of the construction of artificial urethras. Cells obtained from living and cadaveric donors have been proposed for the generation of bioengineered urethras. In the present work we have evaluated the effectiveness of both types of tissues as epithelial cell sources for urethra tissue engineering protocols.

Materials and Methods. Urethra biopsies obtained from living donors subjected to urethral surgery and from cadaveric multiorganic donors were used to generate primary epithelial cell cultures for tissue engineering. In each case, tissues were washed in PBS, excised in small 2x2mm fragments and used as explants for cell culture in the presence of growth factor-rich cell culture medium. The number of cells grown from each explant was quantified at increasing periods of time and cell viability was determined.

Results. The results showed that cells were able to grow and expand from the explants corresponding to both types of donors from the first week of culture with no differences in the cell number or the growing pattern. Furthermore, cell viability was higher than 95% in both cell cultures, with no differences between living and cadaveric donors.

Conclusions. Our results show that both the cells obtained from cadaveric donors and the cells obtained from living donors are adequate for tissue engineering protocols according to the quality controls used on both cell cultures. Therefore, the use of cadaveric donors should be considered as a possible alternative to living donors due to the side effects and complications frequently associated to urethra biopsy.

Supported by grant FIS P112/2736 from Instituto de Salud Carlos III, co-financed by FEDER, EU.

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THE PRODUCTION OF A PATIENT-DERIVED IPS CELL BANK FACILITATES ACCURATE DISEASE MODELLING OF OPHTHALMIC DISORDERS THAT WILL AID IN DEVELOPMENT OF CURATIVE THERAPIES

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Ophthalmic disorders can severely compromise patients’ quality of life, whilst the economic burden on society is also substantial. Age-related macular degeneration (AMD), for example, is the leading cause of irreversible blindness and affects over 40 million sufferers worldwide. There are currently limited effective treatment options with patients facing a bleak prognosis. Whether genetic or acquired, diseases of the eye can be extremely...
complex. Contributing to limited progress in developing curative treatments for these disorders has been a lack of suitable animal models. That being said, results from animal studies can only be extrapolated so far, to establish truly effective treatments for humans these need to be developed and tested on humans, or indeed, human cells. Adding further complexity to the issue, disease phenotypes most often present themselves in a specific organ rather than every cell in the body. Genotyping a patients skin cells, for example, is unlikely to provide insight into the underlying pathology of an eye condition. To do that we require access to study the patient’s own affected eye cells.

In light of these challenges, we propose a fresh approach to studying the aetiology of eye disease and development of curative treatment options. Within The London Project we are compiling a patient-derived induced pluripotent stem cell (iPSC) bank that is providing researchers with access to a range of diseased human cell lines. Generation of iPSC-derived retinal cells and tissues from patients therefore provides an effective technology for use in accurate disease modelling of ophthalmic disorders.

This bank provides an invaluable, standardised source of diseased cell lines that will facilitate the elucidation of the genotype, mechanical pathways and pathology of these complex and debilitating disorders and aid in the development of new therapies.

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PHASE 1-2 CLINICAL TRIAL ON MED THERAPY FOR CHRONIC AND COMPLETE SCI PATIENTS

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Background: During ISCT 2014 (Paris) We reported the feasibility of using Autologous Adipose MSC instead of Autologous Bone Marrow MSC (Cytotherapy. 2006;8(3):202-209; J.SpinalCord. 2009;57:499-503) for treatment of Chronic Complete SCI patients. To confirm Safety and Efficacy of MED therapy we conducted this trial.

Material and Methods: This is a prospective study of 9 patients with chronic Frankel/ASIA A paralysis of between 2.5 to 12 years duration without a Control Group. We followed Simon’s design and the ISCoS 2007 guidelines. 3/9 patients were quadriplegic and 6/9 paraplegic. Patients underwent Intensive rehabilitation for 1.5 to 6 months before cellular intervention.

Each patients signed an informed consent approved by Ethics Research Committee of Maimonides University and registered by Ministry of Health of CABA. MED and Rehabilitation therapy programme were randomized in three groups: control group (placebo); experimental groups: (1 million MSC/Kg body weight; 4 millions MSC/Kg body weight). Safety parameters: occurrence of any adverse events (AA), intensity and relationship with the treatment and occurrence of any severe adverse event (SAE). Factibility parameters: clinical variables (relapses and progression) and paraclinical variables (MRI, evoked potentials, OCT, neuropsychological tests and quality of life scales) Results: 70 AA and 4 SAE: one case of choking, two urinary infections and one respiratory infection. In each case, the possibility of causal relationship with the treatments or with the way of administration was investigated, without finding any causal relationship in any case.

Conclusion: Safety of the treatment has been demonstrated for the 3 experimental groups: no SAA attributable to treatment or the way of administration, AA incidence wasn’t superior to the one founded in a MS cohort of patients out of a clinical trial. Feasibility has been demonstrated because we have been able to recruit 30 patients, extract their adipose tissue, isolate, expand and administer MSC intravenously and measure all the proposed clinical and paraclinical variables.

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AN INTERACTIVE TOOLBOX AS A PART OF THE ATMP GMP OPEN ACCESS RESEARCH ALLIANCE (AGORA)

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Among the bottlenecks in ATMP development are issues related to a) product classification, b) documentation, and c) contact points in the member states. Our objectives were: a) to create an on-line decisional chart to assist researchers in deciding the likelihood of their product to be an ATMP; b) to create an on-line tool box of proven
GMP-compliant documents to facilitate development of new ATMPs, and c) to provide contacts to the Competent Authorities (CA) and to fellow researchers in the EU member states via an interactive map.

Many researchers are unfamiliar with the ATMP regulations and either fail to realize that a product is an ATMP (so the clinical study is never formally monitored as a trial and the data are inadmissible for regulatory compliance later) or over interpret the regulations so that unnecessary barriers are created and trials delayed. In many cases the investigator may not know who to contact at their CA or refrains from doing so through lack of knowledge of the process.

To compensate for this, we have developed a decision tree to determine the likelihood that a given product will be classified as a medicine, and to assist end-users in their discussion with their internal R&D committee and their CA. The interactive map allows to approach the right contact at the CA and to find scientific contact partners who volunteered to give informal advice.

We had shown previously that experience in the manufacture of cell-based medicines is inextricably linked to success in ATMP development, making it difficult for new facilities to enter the field. To create a forthcoming and supportive environment for the development of ATMPs, we have established a depository of SOPs, technical and regulatory documents. Upon registration at our web site (www.agora-gmp.org), these documents are accessible at no charge. We invite others to benefit from - and contribute to - our interactive platform, and to ignite an open-minded, collaborative atmosphere in ATMP development.

TRUE-POSITIVE RATE IN MICROBIOLOGICAL CONTROL OF CELLULAR PRODUCTS

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Background: Sterility of cell based medicinal products has to be checked according European Pharmacopoeia 2.6.27 Microbiological control of cellular products prior to use in patients. An important limitation of the method is the proper choice of the sample in order to make profitable the assay’s sensitivity. In fact, the amount of contamination that may occur during packaging of a cell product in Grade A environment would be low (a few ufc). The sample volume that can be allocated for quality controls is scarce. Moreover, there are microorganisms difficult to grow. Therefore, the amount of microorganisms and the volume of sample are critical parameters for the sterility assay. In this study, the Most Probable Number (MPN) methodology has been used to calculate the number of true-positive tests that would result from a deliberately contaminated sample.

Methods: Bioball SingleShot 30 ufc and Bioball SingleShot 550 ufc of Staphylococcus aureus, each diluted in 110 ml of Bouillon Trypcase Soja (TSB) to simulate the final product. Sample: aliquots of 1.0 ml from previous dilution were inoculated in individual 9 ml TSB vials. Incubation time: 3 days at 30-35°C.

Results: of the 110 inoculums seeded in each case, 24.5% were positive when the sample was contaminated with 30 ufc and 98.2% when it was contaminated with 550 ufc.

Conclusions: as contamination occurring during packaging and conditioning of the final product would be by low bacterial load, it would be advisable to introduce an adjustment of the sample used in the sterility test in order to increase significantly the number of microorganisms present before testing. Depending on the manufacturing process, an option could be the pre-incubation of the sterility assay sample at 30-35°C before use an automated incubation methods and, wherever possible, an increase in the volume of sample.

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This abstract will not be presented.

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ADIPOSE MENCEHYMAL STEM CELLS AS ALTERNATIVE FEEDER LAYER FOR KERATINOCYTE CULTURE

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Introduction: In vitro keratocyte culture has applications in research such as the generation of skin substitutes using tissue engineering. These cells under somatic conditions have a high proliferation rate, however, in vitro rapidly lose their proliferative capacity. This problem has been solved using feeder layers, mainly irradiated 3T3 murine fibroblasts. Despite its wide use in research, using xenogenic feeders in products for human implant it is still debatable because of the risk of transmission of retroviruses and other pathogens to the receptor. The objective of this poster is to compare to types of feeders for keratocyte culture: 3T3 cells and Adipose Mesenchymal Stem Cells (AMSCs).

Methods: AMSCs were obtained from plastic surgery exceeding tissue, they were isolated using collagenase, expanded by three passages and characterized. They were irradiated at 50 Gy in a cell suspension with a concentration of 4 million cells per milliliter. 3T3 cells from the European collection of cell cultures followed the same irradiation process. Keratinocytes were isolated from tissue surplus circumcision surgeries by trypsin and seeded on culture flasks with feeder layer at different concentrations.

Results: We determined that a radiation dose of 50 Gy is optimal to stop the proliferation of AMSCs and 3T3. Keratinocytes from primary cultures seeded on AMSCs in proportions 1:1 and 2:1 are able to form colonies and preserve its morphology. Cultures of keratinocytes seeded on AMSCs in proportion 1:6, as reported in 3T3 coculture, are unable to form colonies. During its expansion, culture times are similar to those obtained using 3T3 cells preserving morphological characteristics, being capable of multiplying the initial population ten times over a period of 3 weeks.

Conclusion: The results demonstrate the feasibility of using AMSCs as feeder layers for the keratocytes culture in proportion 1:1 and 1:2, as an alternative to the use of 3T3 cells.

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A NEW MODEL FOR ADVANCED HEALTHCARE: THE ANDALUSIAN PUBLIC GMP NETWORK

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A logistic handicap arose together with the founding of the Andalusian Initiative for Advanced Therapies (AIAT) as public organization devoted to promote the development of new therapies in order
PORCINE BULBAR CONJUNCTIVA DECELLULARIZATION: CHARACTERIZATION OF ACELLULAR MATRIX AND REPOPULATION WITH PORCINE BULBAR CONJUNCTIVAL CELLS

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Decellularized tissues have been successfully used in tissue engineering/regenerative medicine applications. Our aim was to analyze the suitability of acellular matrix obtained after porcine bulbar conjunctiva (PBC) decellularization.

Porcine eyes were obtained from a local slaughterhouse. Bulbar conjunctiva (PBC) was decellularized using a decellularization protocol. The decellularization protocol was able to remove cellular components and to preserve 3D tissue structure. The acellular matrix obtained is suitable as a potential scaffold for culture of conjunctival cells. The generated tissue has similar structural characteristics to the native bulbar conjunctiva.

In the current study, we investigated the suitability of PBC for cell therapy applications. We characterized the acellular matrix and analyzed the repopulation of DPBCs with bulbar conjunctival cells.

Decellularized tissues were characterized by analyzing the structure of the extracellular matrix (ECM). Glycosaminoglycans, collagen and elastin of the ECM were quantitated. Assessment of ECM was performed by biomechanical analysis. Bulbar fibroblasts were injected into the DPBCs; bulbar epithelial cells were seeded onto the surface of the DPBCs. Evaluation was undertaken at 2 weeks. The phenotypical properties of the cultivated conjunctival cells were considered using immunolocalization of vimentin and pancytokeratin.

HE and AB showed efficient elimination of conjunctival cells. SEM showed the microstructure. MT confirmed high preservation of the ECM. Concentration of ECM components and biomechanical analysis showed no differences from the native conjunctiva. Porcine bulbar conjunctival cells were efficiently cultured and expanded on the DPBCs.

The decellularization protocol was able to remove cellular components and to preserve 3D tissue structure. The acellular matrix obtained is suitable as a potential scaffold for culture of conjunctival cells. The generated tissue has similar structural characteristics to the native bulbar conjunctiva.
abdominoplasty in relation to abdominoplasty with ventral hernia repair, showed higher nearly significant adjusted cell yield (5526 vs. 31968 p = 0.06). There were no significant differences regarding hypotension or OSAS.

Conclusion: In this study, type II diabetes and surgical procedure modified the results of MSCS cultures. More studies are necessary to define clinical parameters and comorbidities of potential donors to optimize the selection process.

MANUFACTURING OF A TISSUE ENGINEERING PRODUCT BASED ON AUTOLOGOUS MESENCHYMAL STROMAL CELLS FOR CLINICAL APPLICATION IN SPINAL FUSION

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XCEL-MT-OSTEO-ALPHA is a tissue engineering product based on autologous “ex-vivo” expanded mesenchymal stromal cells (MSCs) from bone marrow (BM) loaded onto allogeneic bone graft substitutes (Patent P201030238). The present work describes our experience on the GMP production of 16 consecutive batches of XCEL-MT-OSTEO-ALPHA which is being evaluated in the phase I-IIa clinical trial EudraCT 2010-023999-12 as an alternative of the gold standard treatment for Spinal Fusion. Manufacturing process included isolation and plating of Nucleated cells (NCs); MSCs expansion; Harvesting, washing and concentration of MSCs; Dynamic colonization of 10 cc bone graft substitutes and conditioning of the final product. Quality controls included: Cell counting, viability assessment and immunophenotyping of the MSCs; Endotoxin, Sterility Test and Mycoplasma detection (conducted according to Eu. Ph.) and Gram Staining (parametric release). BM samples from 16 patients with an initial volume of 147.8 (127.6-186.8) mL, a NC concentration of 2.37x10^6 (1.02x10^6 – 4.81x10^6) and a viability of 92.2% (71.2–95.8) were processed. After 20 (20-22) days of culture, when the MSCs expansion was concluded, we recovered 8.21x10^10 (2.20x10^10–14.7x10^10) cells with viability greater than 89.7% in all the cases. Antigen expression for CD105, CD45, CD31, CD90 and CD73 was consistent with MSCs with viability greater than 89.7% in all the cases. Antigen expression for CD105, CD45, CD31, CD90 and CD73 was consistent with MSCs.
The aim of this poster is to analyze the quality controls carried out in the manufacturing process of the HAC in the clinical trial CAH / ULC / 2010 (EudraCT: 2010-024290-40).

METHODS: Quality control assays performed in the manufacturing process, meet requirements of Good Manufacturing Practices (GMP) and European Pharmacopoeia. The absence of microorganisms is demonstrated by Microbiological Control of Cellular Products (EP 2.6.27) using the automated blood culture system “BactAlert” (Biomerieux) and by Gram and Calcofluor staining. The mycoplasma test is performed by conventional PCR (Eu.Ph. 2.6.27) in the culture supernatant. Genetic Fingerprint test is based on PCR amplification of microsatellite and subsequent nucleotide sequencing. The determination of adventitious virus is performed by co-culture over cell lines MRC-5, Vero and RD, and subsequent observation of cytopathic effect. Chromosomal stability is demonstrated by karyotyping with metaphase arrest with colcemide, and observation of Giemsa bands. The absence of endotoxins (2.6.14 Eu.Ph.) is demonstrated by chromogenic endpoint method. Table 1 shows a summary of quality controls assays and the process step where is performed.

RESULTS: All quality control results meet the acceptance criteria in the first 5 human artificial corneas manufactured for the clinical trial.

CONCLUSION: The correct design and planning of quality control of advanced therapies medicinal products is of great importance to compliance with the requirements of GMP and the European Pharmacopoeia.

Summary of QC

<table>
<thead>
<tr>
<th>ACCEPTANCE CRITERIA</th>
<th>STEP</th>
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<tbody>
<tr>
<td>Microbiological Control of Cellular products</td>
<td>Absence of microorganisms</td>
</tr>
<tr>
<td>Gram stain</td>
<td>Absence of microorganisms</td>
</tr>
<tr>
<td>Calcofluor stain</td>
<td>Absence of fungal structures</td>
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<tr>
<td>Mycoplasma assay</td>
<td>Absence of Mycoplasma</td>
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<tr>
<td>Genetic Fingerprint</td>
<td>Cell uniformity and absence of chimerism</td>
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<tr>
<td>Adventitious Virus</td>
<td>Absence of Virus</td>
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<tr>
<td>Karyotype</td>
<td>Absence of chromosomal alterations</td>
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<tr>
<td>Bacterial endotoxins</td>
<td>≤ 12.5 EU / mL</td>
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ST: Starting tissue
LSC: Limbal Stem Cell
K: Keratocytes
HAC: Human Artificial Cornea

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BIOCOMPATIBILITY OF MSCS-COATED SURGICAL MESHERS: AN IN VITRO AND IN VIVO EVALUATION

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Surgical meshes are widely used in clinics to reinforce soft tissue’s defects and to give support to prolapsed organs. The correlate has estimated that about one million of surgical meshes per year are worldwide used. However, their implantation often induces fibrosis and a strong foreign body reaction having a greater impact in pain and patient discomfort, being difficult to eradicate without removing the mesh. Here we hypothesize that Mesenchymal Stem Cells (MSCs) could be a useful tool to reduce the inflammatory reaction secondary to mesh implantation, favoring the biocompatibility of the material. The aims of this work were to optimize the coating of surgical meshes with MSCs, to analyze the in vitro immunomodulatory potential of MSCs-coated meshes and to determine their safety and feasibility in a murine model.

In vitro determinations of viability, metabolic activity and immunomodulation assays were performed on MSCs-coated meshes. Magnetic resonance imaging, laparoscopy and histology were performed for safety assessment. Finally, flow cytometry and qRT-PCR were used to elucidate the mechanism of action of MSCs-coated meshes.

Our results demonstrate the feasibility to obtain MSCs-coated surgical meshes and their cryopreservability to be used as an ‘off the shelf’ product. In vitro, MSCs-coated meshes exerted a regulatory effect on T cell proliferation and IFN-γ production. In vivo, these biological meshes fulfill the safety aspects as non-adverse effects were observed when compared to controls. Moreover, both in vitro and in vivo studies evidenced a local immunomodulation which is mediated by a macrophage polarization towards an anti-inflammatory phenotype.

In conclusion, the combined usage of surgical meshes with MSCs fulfills the safety requirements for a future clinical application, providing an anti-inflammatory environment that could reduce the inflammatory processes commonly observed after surgical mesh implantation.

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OPTIMIZATION OF A TISSUE ENGINEERING SKIN MODEL IN A GMP FACILITY

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PURPOSE: The manufacturing of an artificial human skin model under GMP conditions allow the treatment of cutaneous diseases (disorders): burns, cutaneous tumors and giant melanocytic nevus. Our aim was to analyze the histological and immunohistochemical characteristics of an artificial human nanostructured skin model.

We compared two cell culture medium with different fetal bovine serum (FBS) concentration during a four-week period (10% vs 0.2%).

METHODS: Human fibroblasts obtained from the human prepuce were seeded inside the fibrin-agarose scaffolds (n=8). The scaffolds were under culture conditions 2 weeks (DMEM, 10% FBS, Glutamine and Gentamicin vs Medium 106 Invitrogen).

Human keratinocytes obtained after 8-10 incubation cycles with TrypLE Select were seeded onto the surface of the fibrin-agarose scaffolds.

Standard cell culture medium (10% FBS) were used in 4 scaffolds with air-liquid interface. Low FBS concentration (0.2 %) culture medium (Medium 154CF Invitrogen) were used in 4 scaffolds with air-liquid interface. Every week, histological and immunohistochemical analysis were carried out after nanostructuration process.

RESULTS: The weekly histological analysis with H&E staining showed a normal dermis formation and an epidermis with a progressive stratification of epithelial tissue (high at 4 culture week). The specific epithelial markers (CK) were positive in all the scaffolds.

CONCLUSIONS: The histological analysis at 4 culture week showed an stratified epithelium and a normal dermis with a progressive expression of CK similar to native human skin. The histological and the immunohistochemical analysis showed no differences from the culture medium used.

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TECHNOLOGICAL TRENDS AND LIFE CYCLE STAGES IN STEM CELLS TECHNOLOGIES

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Pluripotent stem cells, including embryonic stem cells (hESCs), offer theoretically the potential of being differentiated in all cell types of the body and can be grown relatively easily in culture. On the other hand, adult stem cells are in principle limited to differentiating into different cell types of their tissue of origin, they are relatively difficult to isolate because are found in small quantities in mature tissues, and the methods to expand them in culture are not optimized, which involves a number of disadvantages for their use in therapy. But the use of hESC give rise to ethical dilemmas, have an increased likelihood of immune rejection, and in recent years other technologies have emerged as alternatives, such as induced pluripotent stem cells (iPScs), stem cells obtained by Somatic Cell Nuclear Transfer (SCNT), by parthenogenesis or by transdifferentiation.

The main approach to estimate the future development of one technology and to measure their technology life cycle stage is the use of the S-curve and the analysis of the number of patent applications over time. But patents numbers are an imperfect approach to overall innovation activity, because there are differences between the countries influenced by various factors, including cultural factors associated with the patent system, commercial interests that may make it prefer to keep the technology secret, and even the costs associated with the legal/administrative process of patenting. For this reason, it is necessary to use other additional information like the academic publications, the clinical trials and the commercial product information.

In order to identify the different developing patterns of the stem cells technologies and their evolutionary potential, we studied trends in related patent applications, information about clinical trials, and academic publications, and on the basis of this information we determine their life cycle stages.

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IMMUNOPHENOTYPIC CHARACTERIZATION OF MESENCHYMAL STEM CELLS FROM THE AMNIOTIC FLUID.

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Introduction: The amniotic fluid (AF) is an extraembryonic tissue described as a source for stem cells (SCs), with capacity for multipotent differentiation, reduced immunogenicity, and immunomodulatory properties. Our goal was to study the phenotypic features and differentiation potential of AFSCs as it can be considered a precursor of mesenchymal SCs. On the other hand, hemophilia A is a recessive genetic disease, in which blood cannot coagulate properly because of the deficiency of factor VIII. As FVIII can be released by hAFMSCs and be used for the treatment of hemophilia A, hAFMSCs were resuspended in low glucose DMEM supplemented with 20% FBS (culture medium) and cultured at 37°C and 5% CO2. Then, the expression of mesenchymal surface markers on hAFMSCs was analyzed by flow cytometry. Cultures of hAFMSCs at passage 4-5 and 80% confluence were subjected to osteogenic differentiation and MTT assays. Furthermore, the expression of factor VIII on hAFMSCs was analyzed by RT-PCR.

Results: hAFMSCs cells displayed the typical elongated morphology of MSCs. Flow cytometry analyses showed that hAFMSCs were homogenously positive for the mesenchymal SC markers CD90, CD73, CD105 and negative for the hematopoietic markers CD45 and CD34. Osteogenic differentiation assays showed that AFMSCs could readily differentiate into osteoblast. In addition, RT-PCR showed that hAFMSCs express factor VIII.

Conclusions: AF could be considered as a suitable source of MSCs, allowing its use for in vitro studies or future human cell therapies, such as graft versus host disease or osteoarticular diseases. Importantly, FVIII can be released by hAFMSCs and be used for the treatment of hemophilia A.
C-PEPTIDE SECRETION OF ENGINEERED HUMAN PANCREATIC LIKE ISLETS OBTAINED FROM ADIPOSE MSC CULTURED ON AN ACELLULAR MATRIX IN PRESENCE OF ACTIVATED EFFECTOR CELLS.

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Introduction: In ISCT meeting of 2012 (Netherland) was reported morphologic successful production of engineered pancreatic like islets. It was done using human adipose Mesenchymal Stroma Cells (MSC), growing on swine cell free pancreatic islet matrix (PIM) and co cultured with anti-pancreatic islet effector T cells (ETC). Peroxidase immune stains showed change in MSC phenotype that becomes Insulin and Glucagon producing cells. This reports study the functionality of these Pancreatic like Islets. Methods: Adipose MSC were obtained from healthy donors. Mononuclear cells (MNC) were isolated from peripheral blood and processed to obtain ETC against pancreatic islets [Cytotherapy. 2006; 8:196-201]. PIM was obtained from isolated islets of a pig gland. They were frozen-thawed and Tween 80 treated to destroy any rest of pig cells. Cultures were done in six well plate. 10 PIM + 1000 MSC were seeded in each well in DMEM + PRP for 24hr. Then, 10000 ETC were added to form three wells. At day 5 of culture, glucose was added to each well reaching a concentration of 25 mMol/L. Supernatant samples were taken at 0, 15, and 30 min as well as 24 and 48 hours to perform ELISA assay of C Peptide. Results: Basal C-peptide concentration in the supernatant of both type of Islets was 70 pMol/L. Supernatant from the PIM+MSC islets keep stable during the first 24 hr and suddenly rise up to 235 pMol/L at 48 hr post challenge. Opposite, the supernatant of PIM+MSC+ETC rise C-Peptide concentration up to 185 pMol/L at 15 min post challenge and up to 300 pMol/L at 30 min, keeping these values at 24 and 48 hr post challenge. Conclusion: Engineered islets have a physiologic behave in vitro. Animal experiments are under development to study the clinical potency of these engineered islets.

THE ROLE OF PHARMACY IN SUCCESSFUL DELIVERY OF CELL THERAPY CLINICAL TRIALS

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Hospitals wanting to participate in ATIMP (Advanced Therapy Investigational Medicinal Product) clinical trials require specialist infrastructure, staff expertise and processes to successfully deliver them. ATIMPs may require:

i) a final manufacturing step and release before delivery to the patient, which requires an appropriately licensed GMP facility to be located in close proximity to the clinical site, or

ii) a simple step classified as preparation for administration to be undertaken in an aseptic preparation facility for biological medicines.

In Newcastle, the University and NHS Hospitals Foundation Trust have been working together to provide the aseptic suites, staff, regulatory licences and specialist pharmacy support to provide a joined-up solution for delivery of these innovative medicines. Our Cellular Therapies Facility, a GMP-grade cleanroom complex, has been working closely with Pharmacy to overcome logistical, organisational and process barriers to provide a high quality regulatory-compliant service to trial PI’s and sponsors.

Part of their work has been to inform and educate staff from many disciplines including clinicians, research nurses, pharmacists and pharmacy technicians as to the additional considerations for cell therapy trials, to support them through the process and drive interest in recruiting to cell therapy clinical trials.

Pharmacy have a key role in the delivery of these trials and administer the MHRA authorisation for manufacturing IMPs on behalf of the Newcastle upon Tyne Hospitals NHS Foundation Trust. We have developed a process that ensures ATIMP clinical trials are overseen by both Pharmacy and the Cellular Therapies Facility, ensuring that only staff experienced in handling cellular products will undertake any of the final processing/handling/distribution required, but that Pharmacy retains responsibility for accountability and good clinical practices. Using anonymised case studies, we will illustrate how this process works in practice.

This abstract will not be presented.

A SAFE VALIDATION OF THERAPEUTIC T CELLS

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T cell-based therapies have become increasingly attractive during the past decades. One method consists in the isolation of the T-cell Receptor (TcR) from active tumour reactive lymphocytes and transfer of this TcR to patient T cells. A main concern is the safety of these TcRs. Indeed recent work has demonstrated that cross-reactivity or polyreactivity might be inherent to TcR, thus difficult to avoid. Pre-clinical testing of peptide libraries or humanized mouse systems will never predict hidden epitopes of a TcR, and poor evaluation can lead to fatal therapeutic outcomes. Another important issue is whether a given antigen of interest is only expressed in tumour tissue. Here one can question the use of tissue libraries to evaluate target restrictions since not all cells can be grown in Petri dishes.

We have developed a method that could be used to validate therapeutic TcRs and other antigen receptors in vivo. We reasoned that the validation of a redirected T cell should be performed using the same material as for the clinical settings; the patient T-cell expressing the therapeutic receptor. Furthermore, this receptor should bind the target with similar kinetics as the therapeutic one without activating the T cell. This “dummy T cell” could then be used as a tracer in patients to monitor the correct homing and potential off-target or off-tumour reactivity. By overexpressing a negative regulator, we were able to completely shut down the TcR distal signaling without affecting the binding property of the TcR. Accordingly dummy T cells could bind their targets, but were unable to kill them. The use of these cells therefore has the potential to validate the selectivity and the specificity of therapeutic antigen receptors expressing cells for ACT.
ABSTRACTS

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TRANSNATIONAL GOVERNANCE OF BIOMEDICAL INNOVATION AND HEALTH CHOICES: THE CASE OF STEM CELL THERAPIES.
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Healthcare seekers and patients frequently access both conventional and innovative therapies, like stem cell therapies, that are available across the globe. From a political perspective, governance of the global supply of innovative stem cell therapies is problematic as a majority of the therapies is supplied by providers utilizing practice-based models of biomedical innovation whilst very little is supplied by the orthodox science-based model of innovation. Interestingly, much of the analysis of the governance problem has adopted a supply-side perspective informed by the values of the orthodox model, arguing that (trans)national regulation has failed to impose appropriate standards on the ‘illicit’ supply of stem cell therapies. We offer a political-economic analysis with a strong demand side perspective, arguing that the supply of innovative stem cell therapies are embedded in the global demand-supply relationship increasingly shaped by the global health consumer and its mediation by different models of stem cell innovation. Furthermore, we argue that given the nature of this demand-supply dynamic, policy recommendations on stem cell innovation governance that neglect this perspective are unlikely to be productive. This paper draws from interviews conducted across India, China and UK UK, China to understand i) the nature and implications of the political and economic demands by health consumers on the global healthcare market, ii) the engagement between these demands and different models of stem cell innovation governance ie. how innovation models mediate between consumer demand and the emerging healthcare supply– and its implications for the global competitiveness of a particular model, and iii) the synergies and dissonances in the interaction between market dynamic and existing structures of (trans)national stem cell innovation governance.

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PRODUCTION OF A TISSUE ENGINEERED OESOPHAGEAL CONSTRUCT IN A GMP-COMPLIANT BIOREACTOR
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Tissue engineering offers a promising approach towards oesophageal tissue replacement or augmentation, for which traditional techniques are unsuitable. Synthetic scaffolds have proven largely unsuccessful in reproducing the complex structure and functionality of native oesophagus. In contrast, donor derived acellular matrices appear promising; particularly following demonstration of their clinical success in other hollow organs, e.g. trachea. We are funded to address the need for tissue engineered (TE) oesophageal constructs suitable for clinical application.

We have developed a detergent enzymatic decellularisation process established in our research laboratories into a GMP-compliant aseptic process within a bespoke closed bioreactor, to create a TE decellularised oesophagus with the potential for ex vivo celluarisation for in vivo application.

A novel, modular bioreactor was designed, manufactured, and validated to GMP-compliant specifications. Porcine oesophagi were decellularised using cyclical detergent-enzymatic perfusion. Accluarility, as well as structural and functional biomolecular maintenance, was established histologically and via biomolecular techniques. Scaffold biomechanical integrity was evaluated using a series of biodynamic tests, before in vitro repopulation with appropriate cell types, including mesoangioblasts.

Our process yielded acellular oesophageal scaffolds that maintained putative integral biomolecular composition and structural architecture. In addition, biomechanical characterisation suggested the production of a viable construct capable of extended patency during ex vivo repopulation. Repopulation of the acellular matrix confirmed the production of a biocompatible construct capable of supporting distinct cell types.

The successful production of a tissue engineered oesophageal construct within a GMP-compliant system realises not only the concept of complex organ regeneration, but also paves the way for scalable future clinical application.

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STEM CELL-BASED THERAPY AND TISSUE ENGINEERING FOR TRAUMATOLOGY AND ORTHOPEDICS: OUR EXPERIENCE IN CIVIL AND WAR TIME
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1State Institute of Genetic and Regenerative Medicine NAMS of Ukraine, Kiev, Ukraine; 2Medical company ilaya®, Kiev, Ukraine

The treatment of femoral head avascular necrosis (AVN), fracture nonunion and critical size bone defects is an actual problem in traumatology and orthopedics. Stem cell-based approaches seem to be perspective for the indicated pathologies.

Materials and methods: The technique of the transcervical intracapsular transplantation of 3D tissue-engineered bone equivalent (3D-TEBE) based on autologous cells was developed for the AVN therapy (26 patients, 14 – AVN I-II, 12 – AVN-II-III with subchondral fracture) For the fracture nonunion treatment (24 total) both injection cell therapy (5 patients) and 3D-TEBE transplantation (19 patients) were used. For critical size bone defects restoration the 3D-TEBE transplantation was performed for 12 civilian and 15 combat casualties. The following autologous cell types were used: BM-MSCs, peristeme progenitor cells (PPCs) and endothelial progenitor cells (EPCs). If the defect size would not exceed 3 cm we used MSCs alone; more than 5 cm - MSCs + PPCs (3:1); more than 7 cm – MSCs + PPCs + EPCs (3:1:1). Devascularized allogeneic bone as blocks or chips in fibrin hydrogel was used as a scaffold.

Results and conclusions: After AVN therapy we obtained bone structure recovery in 25 cases, 23 of them had the MRI signs of cartilage restoration. Twenty patients got the maximally possible joint function recovery. One patient needed total hip arthroplasty. Bone consolidation occurred in 24 fracture nonunion cases. One patient needed second cell transplantation. In 12 cases of the critical size bone defects the bone was restored over 4-8 months. The bone integrity was restored in all combat casualties. 3D-TEBE integration with host bone was observed 1.5 months after transplantation by X-ray examination. The full bone defect restoration occurred at the end of 5-6 months (two times faster comparing to the conventional
treatment). Our clinical results in stem cell-based bone therapy prove its high efficiency for traumatology and orthopedics.

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RANDOMIZED, OPEN-LABEL PHASE III STUDY TO EVALUATE THE ADJUVANT VACCINATION WITH TUMOR RNA-LOADED AUTOLOGOUS DENDRITIC CELLS VERSUS OBSERVATION OF PATIENTS WITH RESECTED MONOSOMY 3 UVEAL MELANOMA

B. Schuler-Thurner, J. Doerrie, N. Schaft, S. Gross, M. Erdmann, S. Schliep, A. Baur, G. Schuler

University of Erlangen-Nuremberg, Erlangen, Germany

Accumulating evidence suggests that T cells recognizing mutated cancer antigens are crucial for successful cancer immunotherapy. They seem to represent the common mechanistic pathway to control tumors and prolong overall survival in active antigen-specific (vaccination) as well as passive antigen-non-specific (checkpoint blockade) therapies. Dendritic Cells (DC) are besides mutated antigens the other key to develop better T-based vaccines. Following the discovery of DC maturation and the development of methods to generate mature human DC from monocytes, we have systematically developed the adoptive transfer of these monocyte-derived DC for cancer vaccination loaded with antigens in form of peptides or by RNA transfection. In lately secluded trials high immunogenicity and long-term clinical benefit correlating with certain biomarkers in blood (including simple ones such as eosinophilia) became evident.

Our recent work has focused on the induction of T cell responses against passenger and driver mutations. Following preclinical work and evidence for clinical efficacy in metastatic disease we have designed a randomized phase III (NCT01983748) trial in high risk (monosomy 3) uveal melanoma using RNA-transfected DC to vaccinate against the total antigenic repertoire of patient’s individual tumors to retard or prevent metastases after resection of the primary tumor in the eye. A total of 200 patients will be randomized into arm A (DC vaccination) or arm B (observation as standard of care). Twenty million mature, monocyte-derived DC loaded with autologous tumor RNA are administered respectively at 8 vaccination time points over two years. Objectives are 1) to prolong DFS, 2) to prolong OS and 3) to induce and measure immune responses. The trial has recently been started and is currently performed in cooperation with Departments of Ophthalmology at 8 University Hospitals in Germany (Erlangen, Essen, Hamburg-Eppendorf, Homburg/Saar, Köln, Lübeck, Tübingen, and Würzburg).

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INDUCIBLE CASPASE9-MEDIATED SUICIDE AS A SAFETY SWITCH FOR MSC-BASED CANCER THERAPY

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Cellular therapies are promising strategies in cancer treatment and regenerative medicine. We have recently developed anti-tumor approaches based on mesenchymal stromal/stem Cells (MSC) expressing the potent anti-cancer ligand TRAIL, demonstrating in vitro and in vivo efficacy against several cancers. Despite these encouraging results, there is still some level of concerns on inoculating progenitor cells in cancer patients. One possibility resides in engineering MSC by incorporating a suicide gene in order to control their fate once infused. To date, the most commonly used are the Herpes Simplex Virus Thymidine Kinase and the Cytosine Deaminase genes. In recent years alternative strategies have been developed to overcome these limitations. In particular, investigators described a novel suicide gene, namely iCasp9, based on the sequence of human Caspase9 whose product binds with high affinity to a synthetic, bioinert small molecule (AP20187) resulting in iCasp9 dimerization leading to cell death. Based on this background, we tested the suitability of iCasp9 suicide strategy in MSC to further increase the safety of our cell therapy approach. MSC have been transfected by a lentiviral vector carrying iCasp9 gene and then tested for viability after AP20187 treatment in comparison with mock-transfected cells. Moreover, we generated MSC co-expressing iCasp9 suicide gene together with a TRAIL variant, confirming that anti-cancer and suicide mechanisms can coexist without hampering the tumoricidal activity mediated by TRAIL. In conclusion, this study indicates the suitability of combining an anti-cancer gene therapy approach with iCasp9 suicide gene strategy demonstrating its efficiency and specificity.

This study was supported in parts by Associazione Italiana Ricerca Cancro (AIRC) and by Associazione a Sostegno Ematologia ed Oncologia Pediatrica (ASEOP).

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RELEASE CRITERIA OF HUMAN AMNION EPITHELIAL CELL FOR CLINICAL THERAPIES


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Placenta is a non-controversial and readily available source of stem cells that can be used in regenerative medicine. We previously reported that amnion epithelial cells (hAEC) from term human placenta express markers and genes characteristic of pluripotent stem cells, are not tumorigenic, have immunomodulatory and anti-inflammatory properties and once transplanted differentiate to hepatocyte-like cells resulting in correction of liver diseases. These results motivated banking of hAEC at our Institute for clinical therapies. As required by regulatory authorities, we standardized reagents and procedures in accordance with Good Manufacturing Practice (GMP), and established “release criteria” to insure cell quality prior to transplantation.

Flow cytometry analysis was performed using several antibodies, including pluripotency markers ( Nanog , Sox2, Oct4), embryonic stem cell markers ( SSEA-3, SSEA-4, TRA-60, TRA-81), adhesion molecules (integrin subunits and several CAMs), HLA (-ABC, -DR, -G), and cell lineages ( CD31, CD44, CD45, CD73, CD105, CD90).

All preparations were negative for hematopoietic markers, while stromal markers were observed in less than 5% of cells. Adhesion molecules such as integrin subunits (CD29 and CD49f) and EpCAM were highly expressed (above 85%). Stem cell markers, SSEA-3, TRA-60 and 1-81 positive cells comprised 12-15% of the population. We measured expression of immunomodulatory molecules such as HLA-G isoforms.

Based on our experience on quality assessment of liver cells, we propose FACS profiling for adhesion molecules as a quick and sensitive method to characterize hAEC suspension as quality control assays with which to accept or eliminate a particular cell batch for consideration for transplantation.
ASSSESSMENT OF THE ROLE OF NOGO RECEPTOR GENE BLOCK IN ENHANCING THE NEUROREGENERATIVE EFFECT OF MESENCHYMAL STEM CELLS

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Background: The membrane protein Nogo-A is a negative regulator of neuronal growth, leading to stabilization of the CNS connectivity at the expense of plastic rearrangements and regeneration after injury. Mesenchymal stem cells (MSCs) present a promising tool for cell therapy as they are easily isolated, expanded and have proven preliminary positive regenerative functions in a variety of disorders.

Objectives: To study the role of MSCs in neuro-regeneration and compare it to genetically modified MSCs with NOGO receptor gene block.

Study Design: Ethical committee approval: All procedures were approved by institutional review board.

Methods: I: MSC Isolation and Manipulation

MSCs were isolated from BM, propagated and transfected with a plasmid coding for silencing ribonucleic acid (SiRNA) to NOGO receptor with a green fluorescent protein (GFP) label and an antibiotic resistance gene. II: Animal Model

20 experimental mice were included, 5 used as a normal control group and motor neuron degeneration was induced in 15 mice using mercury intoxication, further divided into 3 groups: one serving as a positive control, one injected with unmanipulated MSCs and the third injected with gene-modified MSCs.

All groups were subjected to an assessment of neuronal regeneration after 4 weeks through clinical motor assessment using BBB score. Animals were sacrificed and histological evaluation of neuronal regeneration and cell tracking was done.

Results and Conclusion: Both gene-modified and unmodified MSC-treated mice models showed improvement in BBB score, with statistically significant difference from control group. Transplanted MSCs were found in autopsy sections of the brain and spinal cord. GFP-positive neurons were also found. MSCs represent a regenerative tool in motor neuron disease animal model. They also represent an efficient gene delivery tool.

Keywords: stem cell therapy, mesenchymal stem cells, motor neuron disease, neurodegenerative diseases

ADIPOSE DERIVED STEM CELLS APPLICATION FOR BURNS, SKIN WOUNDS, SCARS AND ULCERS CURE: PRECLINICAL AND PRELIMINARY CLINICAL RESULTS

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Adipose derived stem cells (ADSCs) are capable of multilineage differentiation and possess strong paracrine effect manifested in immunomodulation, neoangiogenesis and stimulation of reparative regeneration. ADSCs low immunogenicity allows their use in autologous and allogeneic manner. The aim of a study was to develop approaches to use of cultured ADSCs for burns, skin wounds and ulcers treatment.

Material and methods: Preclinical: full-thickness burn model in CBA group as control untreated burn; treated with dermal equivalent (DE) (FVB mice ADSCs in collagen hydrogel); treated with DE (FVB mice ADSCs in fibrin hydrogel). Rating: planimetry wound measurement, histology (H&E and Masson’s trichrome stains) and morphometry analysis.

DE has been used for complex cure of burned casualties, acute skin wounds and diabetic foot ulcers. DE fabrication - 80 cm², 10³ ADSCs in pooled fibrin hydrogel.

Results and conclusions: In preclinical studies, fibrin DE showed the highest efficiency in rate of wound closure with better wound vascularization, epithelialization and collagen fibers formation.

Clinical cases: A patient with diabetic foot ulcer of 10 cm² area, 2 years non-healing, single application of fibrin-based DE led to intensive granulation tissue formation after 10 days resulted in successful split thickness skin transplant engraftment.

A patient with a full-thickness extensive acute wound (230 cm²/690 cm²) was subjected to 4 fibrin-based DE applications. The latter application was combined with a suspension of primary isolated autologous keratinocytes resulted at Day 60 in full wound epithelialization.

One patient was treated with autologous ADSCs in combination with V.A.C. therapy without foam dressing for closure of 4 weeks lasting deep wound (3 cm depth) resulted in full wound closer in 10 days.

To Day 10 it was observed an engraftment of autologous perforated split thickness skin graft in 4 burned casualties with subsequent fast epithelialization of graft perforations.

SYSTEMS APPROACH TO DESIGN, IMPLEMENTATION AND EVALUATION OF MEDICINES ADAPTIVE PATHWAY TO PATIENTS (MAPPs) IN THE ERA OF PERSONALIZED MEDICINE: ENABLING SUSTAINABLE PATIENT ACCESS TO CELL THERAPIES

M. Amador
Técnico Lisboa, Setubal, Portugal

Cell Therapies (CT) are among the frontiers of personalized medicine. The uncertainty and complexity posed by these new healthcare paradigms are challenging the conventional pharmaceutical regulatory frameworks. To provide patients’ access to promising breakthrough CT, existing and new accelerated licensing pathways have been explored. However, early approval had not shown capable to provide a sustainable patient access, lacking in reimbursement and clinical adoption.

Medicine Adaptive Pathways to Patients (MAPPs) is being proposed as an alternative regulatory framework to the traditional binary process, introducing a drug life-cycle stepwise regulatory learning and evaluation. In 2014, the European Medicine Agency launched an MAPPs pilot project, relying on existing accelerated pathways and licensing mechanisms. However, different designs and scenarios are expected, under the general principle, for addressing the specificities and challenges of different drug classes. Understanding how MAPPs could improve CT innovation, diffusion and adoption towards sustainability motivates this research work.
Expert opinions have shown how these changes extend to reimbursement, clinical practice and regulatory science, include multiple stakeholders, and require enabling policies, surpassing national levels. However, risk governance revision, as an iterative process, is challenged by the lack of adequate criteria and tools for evaluation of proposed regulatory systems and strategies. For this purpose, is considered a system perspective of the process of decision-making and evidence generation. A retrospective case approach assesses gaps in existing approaches. Additionally, a prospective construction of MAPPs scenarios is considered, using simulation tools, and the capture of stakeholder risk perception and evidence requirements. Finally, a readiness assessment is used to guide policy and feasible implementation scenarios. These tools provide an impact of MAPPs on Cell Therapies.

**Adaptive Licensing Frameworks versus Traditional Licensing Framework**

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*Probable/final: Confirmation of efficacy within national population.

This poster will be presented by Anne Dupraz Poiseau.

**THE IMPORTANCE OF POTENCY ASSAYS FOR SUCCESSFUL DEVELOPMENT OF CELL BASED MEDICINAL PRODUCT**

V. Pimpaneau
Voisin Consulting Life Sciences, Saint Gregoire, France

Abstract: Integrating analytical development early on in the development of cell based medicinal product allows to provide the knowledge baseline necessary to strengthen the CMC elements of CTAs and INDs. Amongst other important quality attributes, Potency is considered critical for any biological product and the implementation of the relevant assays are often at the center of many challenges and discussions throughout product development amongst developers and regulators. Potency assessment is indeed important not only as a tool to assess product quality and consistency, but also as a link to product clinical efficacy and establishment of the dose.

Cell Therapy Products present additional challenges in terms of potency assay development due to the complexity of their mode of actions which may not always be fully understood and often involves multiple pathways. Status of knowledge of the mode of actions supported by literature, development data, and by risk assessment will constitute important elements to build and defend the potency assessment approach that will evolve and refine throughout the entire product development.

This presentation will provide a quick overview of the regulatory expectations in terms of quality and potency assessment for Cell Therapy Products throughout the different phases of development. Using case studies we will illustrate how defining an incremental strategy early on can help alleviate certain challenges and strengthen overall product development.

**Cryo-Imaging System and Software for Assessing MSC Biodistribution in a Preclinical Model of Liver Disease**

M. Gargesha1, D. L. Wilson1, P. N. Newsome1, G. Hirschfield1, C. Clissmann1, V. Macarthuri2, S. J. Elliman2, S. Watt2, D. Hollyman2, C. C. Boon2, M. J. Hoogduijn3, A. Viola3, D. Roy1

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Primary sclerosing cholangitis (PSC) is a type of liver disease that causes biliary inflammation, leading to liver damage. There is currently no curative treatment for PSC, and liver damage from the disease means that patients often require liver transplantation. Researchers from Europe and USA are collaborating in a EU FP7-funded
project ‘MERLIN’ (Mesenchymal stem cells to reduce liver inflammation) to develop anti-CD362 antibody selected MSC from umbilical cord tissue (Cynadel™, Orbsen Therapeutics) through a Phase 1/2 clinical safety trial in patients with PSC. Knowledge of stem cell homing, biodistribution, longevity, optimal dosing strategies and the mechanism of action is essential for lab-to-clinic translation of stem cell therapies. A cryo-imaging system CryoViz™ (BioInVision, USA), has been customized for MERLIN for high-throughput 3D visualization, analysis, and quantification, enabling the optimization of PSC cell therapy. CryoViz™ consists of a fully automated system for sectioning and tiled microscopic imaging of tissues, providing anatomical brightfield and molecular fluorescence with single cell sensitivity. BioInVision has developed a software suite for CryoViz™ for rapid, high-throughput 3D quantification of tagged MSCs in excised organs or whole mice. The software includes multi-fluorophore stem cell detection and quantification, 2D/3D image visualization/exploration, probabilistic image segmentation, and 3D co-registration of organ volumes. In a tail-vein-infused MSC retention study of MERLIN, a whole mouse was cryo-imaged to examine stem cell biodistribution (Figure 1). Organ-wise 3D visualization and cell quantification was also performed (not shown). The CryoViz™ cryo-imaging system and software suite is enabling MERLIN to (i) perform multi-sample, longitudinal studies and comparisons, and (ii) accelerate preclinical studies to understand MSC distribution and retention in mice, an important first step towards clinical translation.

Results: IDC-MSCs displayed a reduced proliferative capacity as compared to HD-MSCs whereas no differences were found in morphology, differentiation capacity and immunophenotype. IDC-MSCs inhibitory effect on T-cell proliferation was similar to HD-MSC effect, with a percentage of inhibition of 87% (SD ± 12) and 73% (SD ± 29) at MSCs:PBMCs ratios 1:2 and 1:10, respectively. IDC-MSCs ability to suppress B cell and plasma cell proliferation at MSCs:PBMC ratio 1:10 was maintained.

Conclusions: Our results show that IDC-MSCs maintain morphologic and functional properties similar to those of HD-MSCs, with the exception of proliferative capacity, which is reduced in IDC-MSCs.

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BIOLOGICAL AND FUNCTIONAL CHARACTERIZATION OF BONE-MARROW DERIVED MESENCHYMAL STROMAL CELLS ISOLATED FROM PEDIATRIC PATIENTS AFFECTED BY ACUTE MYELOID LEUKEMIA.

L. Tomao, M. Algeri, N. Starc, A. Pitisci, A. Conforti, M. Bernardo, F. Locatelli

Bambino Gesù Children’s Hospital, Rome, Italy

Objective. Mesenchymal stromal cells (MSCs) play a fundamental role in the bone marrow microenvironment, where they promote the formation of the hematopoietic niche, however abnormalities of these cells may contribute to acute myeloid leukemia (AML) pathogenesis.

In this study, we characterized MSCs isolated from pediatric patients with AML (AML-MSCs) at diagnosis and/or after remission or relapse.

Methods. Mesenchymal stromal cells were expanded ex vivo from bone marrow of 12 AML pediatric patients (mean age: 9 years; range: 1-15), at diagnosis and eventual further pathologic remission or relapse. Morphology, proliferative capacity, immunophenotype, differentiation potential and immunomodulatory properties of AML-MSCs, at any pathologic stage, were analysed and compared with those of MSCs isolated from 10 healthy donors (HD-MSCs; mean age: 21 years; 5-34).

Results. Morphology, proliferative capacity (in terms of population doublings), immunophenotype and in vitro life-span did not differ between AML-MSCs and HD-MSCs, while the AML-MSCs showed an increased adipogenic potential as compared with HD-MSCs (p=0.05). The immunomodulatory properties of MSCs (activated or not with INF-γ and TNF-α) were evaluated in an allogeneic setting (AML-MSCs/HD-PBMCs) by measuring PHA-induced T cell proliferation and CpG-induced B cell proliferation. Non-activated AML-MSCs were able to reduce T cell proliferation up to 85% (MSCs/PBMCs ratio 1:2) and 69% (MSCs/PBMCs ratio 1:10), whereas HD-MSCs reduced up to 90% (ratio 1:2) and 81% (ratio 1:10). After...
MSCs activation the inhibition rates were even more robust, being 88% and 77% for AML-MSCs (ratio 1:2 and 1:10 respectively), while 89% and 84% for HD-MSCs (ratio 1:2 and 1:10 respectively). The inhibition of B cell proliferation was obtained exclusively after MSCs activation, with an inhibition rate of the 87% for AML-MSCs and 90% for HD-MSCs.

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This abstract will not be presented.  
HIGHLY STANDARDIZED AND SENSITIVE DETECTION OF MINIMAL RESIDUAL DISEASE IN AUTOLOGOUS CELL PRODUCTS AND PERIPHERAL BLOOD OF MYELOMA PATIENTS BY FLOW CYTOMETRY: IMPLICATIONS FOR STEM CELL TRANSPLANTATION AND CELLULAR IMMUNOTHERAPY  
A. A. Wieczorek, M. Streitz, C. Tietze- Bürger, I. Blau, L. Uharek  
Charité, Berlin, Germany  

Introduction: Detection of minimal residual disease (MRD) at the time of stem cell collection prior to autologous stem cell transplantation as well as enumeration of malignant plasma cells in autologous stem cell transplants identifies patients with high risk of progression. There is a rising demand for highly standardized, rapid and sensitive assays for MRD testing to improve quality control of cellular products and patient monitoring.  

Methods: Following recent recommendations, a multiple myeloma MRD-panel including monoclonal antibodies directed against CD38, CD45, CD81, CD27, CD171, CD19, CD138, and CD56 was applied on peripheral blood of multiple myeloma patients. Data was analyzed using multivariate approaches including principal component analysis.  

Results: A total number of 33 samples ( peripheral blood and apheresis products) were assessed. Normal and aberrant plasma cells were assessed both in stem cell apheresis products as well as in peripheral blood (drawn at the day of apheresis) of multiple myeloma patients. Data was analyzed using multivariate analysis enabling a clear discrimination between aberrant and benign phenotypes, reaching to a detection limit in 6 of 17 cases. CD200 allowed for better discrimination of malignant cells in 42% of the cases as shown by expression overlap analysis. All in all, minimal residual disease was shown in 41% of the patients. Moreover, in 43% of the cases malignant plasma cell have been detected in stem cell products.  

Conclusions: Standardized flow cytometric analysis can serve as sensitive and rapid quality control method to detect residual malignant plasma cells in autologous stem cell transplants thus identifying biologically aggressive disease with a high risk of early relapse.

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COST MODELING FOR REGENVOX: A PHASE I/II CLINICAL TRIAL OF STEM CELL-BASED TISSUE-ENGINEERED LARYNGEAL IMPLANTS  
E. Culme-Seymour1, C. Carvalho2, O. Bain1, J. Round3, R. Sheridan1, R. Ezra1, J. Bakokbi1, K. Champion1, G. Ambler1, H. Herbert1, M. A. Birchall1, M. Lowndell1, C. Mason1  
1London Regenerative Medicine Network, London, United Kingdom, 2Royal Free Hospital, London, United Kingdom, 3University College London, London, United Kingdom  
The larynx (‘voicebox’) regulates breathing, voice and airway protection during swallowing - all critical human activities. For patients who lose laryngeal function due to trauma or cancer, there are no satisfactory long-term solutions, hence quality of life would be dramatically improved if a living, tissue-engineered laryngeal replacement could be transplanted. Based on prior experience from ‘first-in-man’ successes, a Phase I/II clinical trial of these autologous cell-based, tissue-engineered laryngeal implants is now underway for ten UK patients with severe irreversible structural disorders of the larynx, unresponsive to conventional treatment. Whilst primarily the outputs of the trial are to prove safety and efficacy for the patients, additional economic and business modelling of the manufacture and clinical delivery of the implants is being performed. Cost data has been collated for the individual elements involved with the GMP manufacture of the implants, such as consumables required or equipment costs anticipated, as well as for the individual clinical items planned for the patients according to the entire trial schedule. Further work is being performed on exploring the potential market for a RegenVOX technology, as well as understanding patient costs and implications for product uptake and delivery. This work will be discussed, as well as additional considerations for onward commercialisation and translation into routine healthcare.

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This abstract will not be presented.

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ACHIEVING COST EFFICIENCY WHILE SCALING-UP STEM CELL MANUFACTURING  
T. Boey  
Pall LifeSciences Brussels, Brussels, Belgium  
Over the past 15 years, cell therapies have begun to reach the market. Some companies have faced challenges to achieving scalable, cost-effective, and robust cell therapy manufacturing — leading to notable failures caused by manufacturing concerns, such as high CoG. Cell-based therapies are however gearing up to have extensive impact on the healthcare field in coming years. In order to capitalize on the potential of these therapies, there must be efficient methods for growing the adherent stem cells at larger scales. This has set the stage for high productivity manufacturing technology with an emphasis on safety, reproducibility and compliance to GMP standards while maintaining the comparability of the products released and keeping the cost of goods under tight control.
In this presentation, we will discuss the review the factors influencing your bioprocess scale, design optimized manufacturing strategies for allogeneic cell-based therapies, evaluate and select the most cost-effective technology according to lot size to align the process development and product roadmaps.

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TECHNOLOGY MATURATION PLATFORM FOR ADVANCED THERAPIES WITHIN THE ANDALUSIAN PUBLIC HEALTHCARE SYSTEM


1 Andalusian Initiative for Advanced Therapies, Junta de Andalucía, Sevilla, Spain; 2 Technology Transfer Office, Fundación Progreso y Salud, Consejería de Salud, Sevilla, Spain

The Andalusian Initiative for Advanced Therapies (AIAT) is a publicly funded entity, created in October 2008 by the Andalusian Government to promote R&D&I activities in the Cell Therapy and Regenerative Medicine field. AIAT is part of the Andalusian Public Healthcare System (APHS) comprising, among other infrastructures, 47 hospitals and a network of 10 GMP facilities, which allows AIAT to work as a technology maturation platform to generate added value by translating conceptual research to clinical practice.

By means of a close collaboration with the regulatory authorities (achieved with 15 Scientific Advices), a multidisciplinary team of professionals working for the AIAT coordination unit and the involvement of 300 doctors with different specializations, nearly 600 patients have either participated in one of the 24 clinical trials fostered by the AIAT so far or received treatment by means of compassionate use. Consequently, Andalusia has become the most active European Region in clinical research in the field of Regenerative Medicine driven by a Public Healthcare System, at present immersed in an authorization process for hospital use of 4 ATMPs.

In collaboration with other organizations, and with the support of the Technology Transfer Office of the APHS, a noteworthy portfolio of advanced therapies and related technologies patents (more than 100) has been generated. Moreover, a fruitful relationship with the biomedical industry has been achieved with more than 25 prominent alliances & agreements signed and more than 3 million Euros raised. Therefore the AIAT and the APHS, acting as a technology maturation platform, are in a position to offer collaboration with academic institutions and companies by creating partnerships within a risk-benefit sharing model to accelerate the development of new cell-based products.
NOTES:
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