Workshop
Regenerative Medicine

NATO STO HFM-243

Berlin, Germany, May 19th - 21st 2014

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In cooperation with

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Charité - Universitätsmedizin Berlin, Germany

NATO OTAN

S&T organization Collaboration Support Office

BwK BERLIN

E.S.T.R.O.T. – European Society for Tissue Regeneration in Orthopaedics and Traumatology

Sanitätsdienst

Welcome!

Dear colleagues,

It is an honor to welcome you to Berlin. Thank you for joining our NATO workshop on Regenerative Medicine. It is a great pleasure to have so many experts and specialists from all over the world among the participants. We are very grateful that you have traveled so far to join us here in Berlin.

As a result of NATO´s and allied involvement in military operations a significant number of personnel have suffered debilitating injuries. Gunshot wounds, large soft tissue and bone defects due to explosive devices, nerve injuries, comminuted fractures, infections, especially with a different spectrum of bacteria, traumatic amputations, and (infected) non-unions are all injuries we have to deal with as consequences of military actions. To have detailed insights into best possible treatment and future treatment options, NATO and allied countries are very interested in using "Tools of modern Regenerative Medicine" for the treatment and rehabilitation of their wounded soldiers. This is the reason for our international workshop.

The main goal of the workshop will be:

- Creation of an overview about the most relevant initiatives and efforts on the field of Regenerative Medicine "Who is doing what in NATO / internationally in RM".
- Creation of an overview about the expanding network of specialists in the field of Regenerative Medicine.
- Definition of the most important needs (and possibilities) of scientific and clinical projects in the field of Regenerative Medicine.
- Develop the foundation of an international network of experts in the field of Regenerative Medicine to bring forward new therapies to enhance the recovery of those wounded in action.
- To establish common research projects and to prepare for further activities (e.g symposia, specialist meetings and workshops).

Never before has the scientific world been so "networked" and connected for combat injured as it is today. However, we still think that it is of exceptional value to get together regularly and have stimulating discussions in person.

We hope that this workshop in Berlin in May 2014 can be the cornerstone for further meetings of the same kind. Thank you for your cooperation during the organization phase, your participation in the questionnaire, your numerous ideas and your abstracts. With your input, we were able to establish a workshop program that combines all of your ideas and suggestions.

In cooperation with the Julius Wolff Institute and Berlin-Brandenburg-Center for Regenerative Therapies and our comrades of the Julius-Leber-Kaserne and our Bundeswehr hospital we were able to organize this workshop. This would not have been possible without the assistance of many colleagues. We are particularly indebted to Peter Mees, our NATO-Panel Mentor, as well as Joachim Kohn and Georg Duda for their many helpful discussions and constructive suggestions.

We would also like to express our sincerest gratitude to our organization team members David Back, Catharina Scheuermann-Poley, Marcus Storch and Juliane Ruft, the staff of our Bundeswehr hospital as well as the colleagues of the Department of Trauma & Orthopedic Surgery, Septic & Reconstructive Surgery, Bundeswehr Hospital Berlin.

Once again, it is a great pleasure to welcome you to Berlin. We wish you a very stimulating three days, many new insights and an expansion of your professional network. Hopefully we will see each other and many more new colleagues again – perhaps in Brussels in 2016.

Christian **Willy**
Berlin, May 2014

John **Scherer**
Fort Detrick, May 2014

Content

Monday, May 19th 2014

Welcome and Opening Remarks

12:00 - 12:10	**Welcome from the Director Research Joint Medical Service German Bundeswehr** **Weller** (München, Germany)
12:10 - 12:20	**Presentation NATO-HFM-Panel and the purpose of the workshop – Future NATO STO activities** **Mees** (Koblenz, Germany)
12:20 - 12:30	**Welcome remarks from the chairman** **Scherer** (Fort Detrick, USA)
12:30 - 12:35	**Organizational remarks** **Willy** (Berlin, Germany)
12:35 - 12:40	**Break**

Introductory Session I

Chairmen: **Weller** (Munich, Germany), **Scherer** (Fort Detrick, USA)

12:40 - 12:55	**Introduction to the US military research program** **Scherer** (Fort Detrick, USA)
12:55 - 13:10	**Bone loss and injury: What is the unique military need, and how best to impact a very crowded field?** **Pfister** (Fort Detrick, USA)
13:10 - 13:25	**Introduction to the Armed Forces Institute of Regenerative Medicine (AFIRM) by the consortium Co-Director** **Tuan** (Pittsburgh, USA)
13:25 - 13:35	**Regenerative Medicine Coalition e.V. (RMC)** **Volk** (Berlin, Germany)
13:35 - 13:45	**ESTROT (European Society of Tissue Regeneration in Orthopaedic and Trauma) – perspective** **Calori** (Milan, Italy)
13:45 - 14:10	**Discussion** **All**
14:10 - 14:25	**Break**

Open Questions and Future Perspectives

Chairmen: **Kohn** ((Piscataway, NJ, USA), **Willy** (Berlin, Germany)

14:25 - 14:40	**Bone and muscle regeneration: Perspective and remaining challenges** **Duda** (Berlin, Germany)
14:40 - 14:55	**Novel strategies for engineering skeletal tissues with stem cells and natural origin scaffolds** **Gomes** (Guimarães, Portugal)
14:55 - 15:10	**Stem cells for tissue regeneration: Hope, reality and future** **Tuan** (Pittsburgh, USA)
15:10 - 15:25	**How is clinical experience driving future therapies?** **Soria** (Sevilla, Spain)
15:25 - 15:55	**Discussion** **All**
15:55 - 16:25	**Break**

Bone Defect Management I

Chairmen: **Boccaccini** (Erlangen, Germany), **Kollig** (Koblenz, Germany)

16:25 - 16:40	**Tools for healing of severe bone defects** **Bégué** (Clamart/Paris, France)
16:40 - 16:55	**Diamond concept for treatment of infected non unions** **Schmidmaier** (Heidelberg, Germany)
16:55 - 17:10	**From regeneration to substitution: Algorithm of treatment of non-unions and bone defects** **Calori** (Milan, Italy)
17:10 - 17:25	**Scientific and commercial considerations in the design of bioactive scaffolds for bone regeneration** **Kohn** (Piscataway, NJ, USA)
17:25 - 17:40	**Application of adult stem cells and biomimetic scaffolds for skeletal tissue engineering and regeneration** **Tuan** (Pittsburgh, USA)
17:40 - 19:00	**Discussion** **All & Working groups**
20:00	**Dinner**

Tuesday, May 20th 2014

Introductory Session II

Chairman: **Borchers** (Stuttgart, Germany)

08:00 - 08:20 Advances in reconstructive transplantation driven by a decade of combat
Davis (San Antonio, USA)

08:20 - 08:35 Discussion
All

08:35 - 08:40 Break

Bone Defect Management II

Chairmen: **Bégué** (Paris, France), **Schmidmaier** (Heidelberg, Germany)

08:40 - 08:55 KN: Synthetic bone substitute that can duplicate the mechanical strength, elasticity and bioactivity of bone
Zreiqat (Sydney, Australia)

08:55 - 09:10 Epigenetic changes of Ad-MSCs will improve osteogenic regeneration
Nüssler (Tuebingen, Germany)

09:10 - 09:25 Negative impact of CD8+ effector T cells on bone fracture regeneration
Schmidt-Bleek (Berlin, Germany)

09:25 - 09:40 Development of calcium phosphate based biomaterials for bone regeneration and their application in maxillofacial and orthopedic surgery
Loca (Riga, Latvia)

09:40 - 09:55 Novel biomaterials with angiogenic potential (e.g. bioactive glasses) for bone regeneration
Boccaccini (Erlangen, Germany)

09:55 - 11:25 Discussion
All & Working groups

11:25 - 12:25 Break / Lunch

Central and Peripheral Nerve Defects

Chairmen: **Feigal** (San Francisco, USA), **Vajkoczy** (Berlin, Germany)

12:25 - 12:40 KN: Central and peripheral nerve defect treatment
Feigal (San Francisco, USA)

12:40 - 12:55 Challenges of peripheral nerve injuries to the wounded warrior for regenerative medicine
Rosen (Hanover, USA)

12:55 - 13:10 Stem cell therapy in spinal cord injury
Özdemir (Denizli, Turkey)

13:10 - 13:25 Cell based therapies for cerebrovascular diseases and TBI
Deten (Leipzig, Germany)

13:25 - 13:40 Actual and future perspectives of ocular neuroregeneration and rescue
Scott (Birmingham, UK)

13:40 - 14:25 Discussion
All

14:25 - 14:55 Break

Soft Tissue Defect Management

Chairmen: **Schaser** (Berlin, Germany), **Pfister** (Fort Detrick, USA)

14:55 - 15:10	**Engineering of vascularized human implants and their first application** **Walles** (Wuerzburg, Germany)
15:10 - 15:25	**Novel extracellular matrix proteins for cardiovascular tissue regeneration - *In vitro* elastogenesis - deciphering the key for elastin fiber generation for engineering tissues and organs** **Schenke-Layland** (Stuttgart, Germany)
15:25 - 15:40	**Using of autologous cultured keratinocytes in coverage of large tissue defects** **Marinescu** (Bucharest, Romania)
15:40 - 15:55	**MSC as drug cells for cell therapy of burns** **Lataillade** (Clamart/Paris, France)
15:55 - 16:10	**Tissue engineering based strategies in tendon repair - Role of complement & influence of inflammation** **Schulze-Tanzil** (Berlin, Germany)
16:10 - 16:25	**Generation of cartilage for repairing joints damaged due to injury** **Feigal** (San Francisco, USA)
16:25 - 16:40	**Engineered skeletal muscle for craniomaxillofacial reconstruction** **Sundback** (Boston, USA)
16:40 - 16:55	**Cell therapy in organ transplantation** **Soria** (Sevilla, Spain)
16:55 - 17:10	**"New" approach in the fight against bacterial infections** **De Vos** (Brussels, Belgium)
17:10 - 18:25	**Discussion** **All**
18:25 - 18:30	**Break**

Nutritional Considerations

Chairmen: **Lataillade** (Clamart/Paris, France), **Schenke-Layland** (Tübingen, Germany)

18:30 - 18:45	**Nutrition – An important factor in regeneration** **Nüssler** (Tuebingen, Germany)
18:45 - 19:00	**The respective role of hypoxia and glucose as determinants of the survival of human mesenchymal stem cells upon implantation** **Petite** (Paris, France)
19:00 - 19:30	**Discussion** **All**
20:00	**Dinner**

Wednesday, May 21st 2014

Introductory Session III

Chairman: **Davis** (San Antonio, USA)

08:00 - 08:20	**Blast injury – potential implications for regenerative medicine** **Watts** (Salisbury, UK)
08:20 - 08:40	**Discussion** **All**
08:40 - 08:45	**Break**

Industrial, Regulatory and Socio-Political-Economic Issues

Chairmen: **Gomes** (Guimarães, Portugal), **Volk** (Berlin, Germany)

08:45 - 09:00	**Regulation and pharmaceuticalization of cellular therapies** **Soria** (Sevilla, Spain)
09:00 - 09:15	**Socio-economic barriers to technology transfer in regenerative medicine** **Kohn** (Piscataway, NJ, USA)
09:15 - 09:30	**CIRM's experience and future directions in product development; implications for the wounded warrior** **Feigal** (San Francisco, USA)
09:30 - 10:00	**Discussion** **All**
10:00 - 10:20	**Break**

Diagnostic Methods, Biomarkers and Monitoring Techniques

Chairmen: **Walles** (Wuerzburg, Germany), **Marinescu** (Bucharest, Romania)

10:20 - 10:35	**Biomarkers in regenerative therapy & immune regeneration in critically ill patients - biomarkers for stratification of ICU patients into risk groups and reconstitution of "immunoparalysis" by immunostimulation of sepsis patients** **Volk** (Berlin, Germany)
10:35 - 10:50	**Non-invasive optical tools for cell, tissue and organ monitoring** **Schenke-Layland** (Stuttgart, Germany)
10:50 - 11:05	**Imaging of decellularized and recellularized human dermal matrices by real time non invasive HD-OCT and RCM** **Draye** (Brussels, Belgium)
11:05 - 11:20	**Inflammation signals for bone regeneration** **Zreiqat** (Sydney, Australia)
11:20 - 12:05	**Discussion** **All**
12:05 - 13:15	**Break**

Regenerative Laboratory Techniques

Chairmen: **Tuan** (Pittsburgh, USA), **Duda** (Berlin, Germany)

13:15 - 13:30	**Bioprinting and development of cell/matrix-based bioinks** **Borchers** (Stuttgart, Germany)
13:30 - 13:45	**Bioreactors - towards physiologically relevant *in vitro* cell cultivation** **Charwat** (Vienna, Austria)
13:45 - 14:00	**New modular system for generation of antigen-specific T-cells for adoptive therapy** **Volk** (Berlin, Germany)
14:00 - 14:15	**Large animal modeling in regenerative medicine: application examples** **Ferrara** (Leipzig, Germany)
14:15 - 15:00	**Discussion** **All**
15:00 - 15:20	**Break**

Closing Remarks

15:20 - 15:50	**Technical evaluation report** **Kohn** (Piscataway, NJ, USA)
15:50 - 16:05	**Initial thoughts from the workshop** **Willy** (Berlin, Germany)
16:05 - 16:35	**Discussion** **All & comments**
16:35 - 16:45	**Closing remarks** **Scherer** (Fort Detrick, USA / Berlin, Germany)

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Useful information for your stay

Address of our meeting site

The HFM-RWS 243 NATO Workshop will take place in:
Julius-Leber-Kaserne Berlin
Offizierheimgesellschaft "OHG"
Julius-Leber-Kaserne Berlin e,V.
Kurt-Schumacher-Damm 41
13405 Berlin

Phone: +49 30 4981 ext. 0
info@ohg-berlin.de
www.ohg-berlin.de

We will provide a shuttle service that picks you up at the hotel and takes you to the OHG.
If you wish to travel with your own car or by taxi you will have to present a valid ID at the gate.
There will be signs on the campus that guide you to the OHG.
There is a big parking lot in front of the OHG if you wish to park your car there.

Address of the hotel

Dorint Airport-Hotel Berlin-Tegel
Gotthardstr. 96
13403 Berlin
Deutschland

Phone: +49 30 498 84 - 518
Fax: +49 30 49 884 - 555
Judy.Jaekel@dorint.com
www.dorint.com

All rooms provide air condition, free sparkling water, 24 hours free WLAN and daily newspaper. Breakfast included.

Contacts

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Meeting arrangements

Venue
The NATO HFM-RWS 243 Workshop on Regenerative Medicine will take place from May 19th – 21st 2014 in Berlin, Julius-Leber-Kaserne.

Registration
Workshop information material and registration documents will be handed out to you at the registration desk of the workshop.
Workshop registration will start on Monday 19th of May 2014 at 08.00 hrs. Please bring valid identification documents.
All participants are kindly asked to register at the information desk at the meeting site in order to obtain a badge for access to the Meeting area.
A badge will be issued to each registered participant. You are requested to wear your badge at all times in the Meeting area, at the reception and the dinners.
For security reasons, please remove your badge when leaving the meeting venue. Please make sure to bring it with you to the meetings each day as badges cannot be reissued at the meeting site.

Internet access for attendees
The Julius-Leber-Kaserne meeting area provides free Wi-Fi access. You will find the log in data in your information package.

Working language will be English
No simultaneous interpretation will be provided.

Dress Code at the meeting site
Civilian business attire.

Smoking
Not permitted in the meeting area.

Conference fee
In order to provide food and drinks we must charge a conference fee at the amount of 60 Euros per participant.
We would like to ask you to pay the conference fee upon registration cash in EURO.

Meals and refreshments

Breakfast
Breakfast is included in the room rate at the hotel.

Second breakfast
A small breakfast buffet including coffee and tea will be provided at the meeting venue on monday.

Lunch
Lunch buffets will be provided at the Offizierheimgesellschaft Julius-Leber-Kaserne, Berlin.

Coffee break
During afternoon break, tea, coffee, juice, and cookies will be available at no charge to the registered attendees.

Events

Monday 19 May 2014
The registration office will be opened from 08.00 hrs to 12.00 hrs
The official workshop program will start at 12.00 hrs and end at 20.00 hrs. A brunch meal will be served at the meeting site.
Dinner for all participants from 20:00 - 22:30 hrs (included in conference fee).
Join us for a get together at the restaurant "Zur Letzten Instanz", the oldest German Restaurant in town.
Zur letzten Instanz, Waisenstraße 14-16, 10179 Berlin, phone: + 49 30 242 55 28

Tuesday 20 May 2014
Workshop program from 08.00 to 19.00 hrs
Dinner for all participants from 20.00 – 22.30 hrs (included in conference fee) at a famous Italian restaurant "La Piazza Italiana", Oranienburger Chaussee 2, 16548 Berlin Frohnau, phone: +49 30 404 46 13

Wednesday 21 May 2014
Workshop program from 08.00 to 17.00 hrs
"Last night get together" in Berlin (own expenses). If you wish to end your stay in Berlin with a German beer or cocktail at a fancy bar we would like to invite you to join us. The location und time have yet to be determined.

Transportation in Berlin

By taxi

It is recommended to take a taxi to get from the Berlin Tegel Airport to your hotel.
There will be many taxis waiting in line in front of the airport building. In Berlin we do not have problems with being charged overprice.
For later reimbursement of your travel costs (at home), you can always ask your taxi driver for a receipt.

Berlin Taxi Hotlines are:

+49 30 20 20 20
+49 30 21 01 01
+49 30 44 33 22
+49 30 26 30 00
+49 30 21 02 02
+49 30 26 10 26

The fare from the airport to the Dorint Airport Hotel should be approximately 15 Euros.

By bus

The bus travel time between Berlin Tegel Airport and the Dorint Aiport Hotel takes about 10 minutes.
Take the bus 128, direction U Osloer Straße and exit at the station "Kapweg".
From here the hotel is about 100 meters away. One single bus ticket costs 2,60 Euros. You can buy the ticket at the Airport or on board the bus. The bus stops are outside the main entrance of the airport terminals.

Berlin city public transport system

Berlin Public Transport, BVG, contains buses, subway trains (marked with a blue U), metro trains (marked with a green S) and trams.
The city is divided into three zones. Tickets can be purchased at BVG Centers, the metro platform barriers or newsagent kiosks.
There are also ticket machines at most of the metro and commuter railway stations, as well as in a number of other locations.

Caution

You cannot purchase a ticket onboard the subway and metro trains. Onboard buses and trams a ticket purchase is possible.
It is your responsibility as a passenger to ensure that you have a valid ticket. Failure to show a valid ticket on demand will render a penalty fare of 40 Euros.
A single one way ticket costs 2.60 Euros. A day pass costs 6.70 Euros.
Read more at www.bvg.de

Car rentals

At Berlin Tegel Airport there are several companies that offer rental cars.

Sixt: +49 1806 252 525
Avis: +49 30 410 131 48
Europcar: +49 30 417 85 20
Hertz: +49 30 417 046 74

Shuttle busses from Hotel to Meeting Site

We will provide a shuttle bus from the Dorint Airport hotel to the meeting site and the evening locations. You will receive all the information regarding the shuttle schedule with your information package at the workshop registration desk.

General information

Climate

Berlin has a temperate oceanic climate. Summers are warm and sometimes humid with average high temperatures of 22–25 °C (72–77 °F) and lows of 12–14 °C (54–57 °F). Winters are relatively cold with average high temperatures of 3 °C (37 °F) and lows of –2 to 0 °C (28 to 32 °F). Spring and autumn are generally chilly to mild. Berlin's built-up area creates a microclimate, with heat stored by the city's buildings. Temperatures can be 4 °C (7 °F) higher in the city than in the surrounding areas. Annual precipitation is 570 millimeters (22 in) with moderate rainfall throughout the year. Light snowfall mainly occurs from December through March, but snow cover does not usually remain for long. Bring a warm outdoor jacket just in case. A current weather forecast can be found at: www.wetter.com

Electricity

The voltage in Germany is the EU standard of 230 Volts. If you wish to use your own personal electrical appliances an adapter is necessary for participants used to other voltages.

Currency

The currency in Germany is the Euro (€). One Euro is 100 Cents. The most regularly used bank notes are in denominations of 5, 10, 20, 50 and 100. Please check exchange rates before travelling. Please note that prices are indicated including taxes and service.
Tipping at a restaurant/bar is voluntary. About 10% tip is expected.

Banks, Credit Cards, Exchange

Most shops and hotels accept major international credit cards such as Visa and MasterCard. Please note that American Express is not always accepted. You can exchange your foreign currency at any bank or exchange office. Please be careful to check all the commissions applied. Banks are open from Monday to Friday from 08:00hrs to16:00 or 18:00 hrs. ATMs can be found throughout the city.

Telecommunications and Post

The international dialing code to Germany is +49. In Germany the post is mostly run by DHL. DHL post offices can be found throughout the city.

Emergency Numbers

112 Centre for Rescue Services (Ambulance, Fire brigade) (free of charge)
110 Police Department (free of charge)

Opening Hours for shops

In Berlin shops are usually open from Monday to Friday from 08.00hrs to 20.00 hrs (some to 22:00 hrs).
On Saturdays, they are open from 08:00 (10:00) hrs to 12:00 (16:00) hrs.
Supermarkets are open from Monday to Sunday from 08:00 hrs to 20:00 hrs.
In some bigger train stations shops are open 24/7.

50 Open Questions

As you can remember, in the very beginning of the planning of this workshop we asked you to fill out a questionnaire consisting of 8 questions, Q1 to Q8. We read, sorted and grouped all of your answers and notes. Now we would like to present to you the essence of your remaining open questions:

- What does success look like in the field of regenerative medicine and how can you measure / track it?
- Role of autologous versus allogeneic therapies?
- Is degeneration always irreversible?
- How can we ensure successful translation from preclinical research to clinical application?
- How can we ensure compatibility of regenerative medicine therapies with conventional approach, do both fields best benefit mutually?
- What are the odds of developing a malignant process using regenerative medicine?
- What is the ideal nerve graft?
- What is the role of regenerative medicine in the re-mapping of nerve regeneration and connection?
- What is the role of regenerative medicine in reducing atrophy of muscles?
- What is the role of life support in regeneration?
- How we can get enough financial support of new technical and medical innovation?
- How can we ensure broad, successful and reproducible application of new regenerative medicine therapies?
- What is the key trigger that signals regeneration of bone in large bone defects?
- How can we adjust inflammation to benefit and support regeneration?
- What is the role of the inflammatory stage in the regenerative cascade?
- How can we develop personalized strategies for regenerative approaches by biomarkers?
- How are cells influenced by matrix properties (bio-physical, structure, biochemical)?
- How to guide tissue regeneration to a functional and effective end-point?
- How can we explore the potential of newly created regenerated tissues that have therapeutic activities?
- How can we stimulate healing of degenerative tendons?
- What is the best combination of technologies and rehabilitation strategies that leads to greater function improvement following nerve injury and/or volumetric muscle loss?
- How can we create advanced (responsive, intelligent) biomaterials mimicking the extra cellular matrix characteristics (chemically and structurally)?
- How can we improve processes for biofabrication approaches (e.g. organ printing as final aim)?
- How to provide large volumes of functional tissue?
- How to provide vascularized bioartificial tissue?
- How to create the interface of tissues?
- How to source the most effective and appropriate cell type for specific tissue regenerative applications?
- How can we grow and preserve cartilage?
- How can we improve recovery at the cellular level by the effects of positive thoughts and emotions?
- How can we achieve a reliable vascularization of tissue-engineered organs?
- Can ECM alone be suitable for tissue engineering/regenerative medicine approaches?
- How can we create a microvascular bed and an appropriate perfusion of any engineered tissue?
- How can we create nerve connection to tissue (innervation), in particular in regards to the innervation of muscle tissue?
- How to enhance survival of transplanted cells?
- How to enhance vascularization of scaffolds?
- How to master scaffold resorption?
- How can we develop a rapid fabrication of custom made and drug eluting implants?
- How can we further develop highly effective orthobiologics to stimulate intrinsic healing responses of the body for example autologous platelet derived preparations (platelet rich plasma etc.)?
- How can we improve cartilage repair *in situ,* based on induced chondrogenesis of various (autologous) stem cell or chondrogenic precursor cell populations?
- How can we design versatile and biomimetic biomaterials to improve cartilage and tendon repair?
- How can we find a balance between sufficient mechanical properties and the bioresorption rate of implant materials in orthopedic surgery?
- How can we engineer complex tissues (while we can grow single tissues (bone, tendon, ligament, blood vessels etc) in the laboratory? (Yet, we cannot combine them to create complex tissues that consist of more than one or two tissue types)
- What are the right indications for MSC and how can we further improve their efficacy?
- What do stem cells really modulate in healing? What is their actual role?
- Which cell types can be designed for an off-the-shelf approach of stem cell-based therapies?
- Can stem-cell and micro-tissue engineering help us progress to preserve/regenerate nerve growth and limbs?
- What is the role of stem cell age in regeneration?
- How can we develop a standard for the method of isolation and expansion of stem cells?

50 Visions (Year 2038)

As you can remember, in the very beginning of the planning of this workshop we asked you to fill out a questionnaire consisting of 8 questions, Q1 to Q8. We read, sorted and grouped all of your answers and ideas. And now we would like to present to you the essence of your answers:

- Regenerative Medicine works and can be applied economically.
- Custom made therapy
- Ways to create and increase self-regeneration (cell-free cell-therapy, etc)
- Guiding inflammation to support regenerative processes
- Gene therapy and therapeutic approaches to cure patients
- MSC based therapies
- Real restorative therapies are available for traumatic and degenerative diseases.
- Megaprostesis implantation
- Functional restoration of large bone defects
- Successful regeneration of whole limbs
- Artificial organs for limb replacement, replacement of major parts ..., parts to include nerves and muscles ..., firstly digits and then hands and arms
- Replacement of organ transplantation by endogenous regeneration and/or exogenous stem cell derived products
- The use of purely synthetical substitutes for the regeneration of skeletal tissue
- Possibility to restore tissue of relatively simple structure and function such as supporting tissue e.g. bone/cartilage/connective tissue as well as skin, fatty tissue and functional parts of organs such as heart valves, etc.
- Translation of vascularized composite tissue allotransplantation (VCA) technologies to smaller and smaller tissue units to enable a greater adoption and an impact to a military patient population
- Functional reconstruction of ligaments, even in the shoulder girdle
- Synthetic graft opportunities for ACL reconstruction
- Techniques to restore articular cartilage (healing, transplantation, regeneration)
- Biologic treatments for tendon injury
- Availability of responsive/intelligent, biomimetic biomaterials to support tissue regeneration with vascularization potential (angiogenesis)
- Biological implants, based on the assembly of functional tissue from autologous or donor cells will be available, which help the body to restore biological functions.
- Restore or retain greater limb function following peripheral nerve injury
- Electronic nano-replacements of nerve defects so that signals from nerve cells can be enhanced and bridged in case of spine-injuries or peripheral nerve damage
- Stem cell therapy in patients with damaged spinal cords
- To restore/substitute cells that have disappeared or degenerated in diseases like diabetes, muscular dystrophies, neurodegenerative diseases, etc.
- Prevent scar formation, rather than rely upon scar remediation
- Reduced scaring in muscle and skin injuries
- Achievement of scarless wound healing in a comprehensive sense, including scarless healing of myocardial tissue after heart attacks, prevention of proliferative vitreoretinopathy after retinal detachment surgery, and elimination of surgical adhesions
- The two approaches (complex tissue transplantation with induction of immunological tolerance as one approach and the engineering of replacement body parts as the other approach) will converge, since engineered body parts will become more complex and more "tissue like" and may include components derived from living tissue
- Cadaver-derived body parts may be decellularized and simplified prior to use and thus become more similar to engineered body parts
- Combination of stem cells with appropriate bioactive scaffolds to allow the *in vitro* and/or *in vivo* fabrication of tissues and organs with suitable structure and function for long term care
- Availability of technologies for tissue and organ printing
- 3D polycultural tissue printing
- A more personalized therapeutic approach for each patient will be achieved facilitating an optimized healing process of a damaged musculoskeletal tissue: e.g. 3D printing of tailored cell-based implants might have successfully entered the clinic
- The healing process could be monitored by a set of highly relevant biomarkers and highly sophisticated imaging techniques
- Automated production of skin transplants
- Optimized drug delivering systems
- To reach a convenient regulation and pharmaceuticalization of the product
- Non-invasive methods to control tissue development *in vitro*
- Development of rapid sourcing and enrichment methods for autologous stem cells at the point of care
- One step neo-tissue assembly for point-of-care application
- Application of tissue engineering technologies to create physiologically relevant tissue analogues that may be used for disease diagnosis, toxicity testing and drug screening (Tissue-engineering-based personalized medicine)
- Non-invasive monitoring of life parameters (combination of optics, regenerative medicine and information technology)
- Combination of technologies to design biomaterials as off-the-shelf products that can then be patient-tailored
- Rapid fabrication of custom made and drug eluting implants (*in situ* in the operation room)
- Computational modeling and *in vitro* test systems
- Improved tissue regeneration through nutritional supplementation
- Improved tissue regeneration through small molecules

Introductory Session I / Chairmen: **Weller** (Munich, Germany), **Scherer** (Fort Detrick, USA)

Title: **Introduction to the US military research program**
Author: Scherer JM
Affiliation: Clinical and Rehabilitative Medicine Research Program, US Army Medical Research and Materiel Command
City/Country: Fort Detrick, USA

Abstract:
The goal of this presentation is to provide an overview of the US Department of Defense Medical Research Program with a focus on the Clinical and Rehabilitative Medicine Research Program, Joint Program Committee 8 and Joint Technology Coordinating Group 8. The research areas of the program will be presented with an emphasis on Regenerative Medicine. The strategy and challenges of bringing medical solutions into clinical practice and how funding is applied to overcome these challenges will also be discussed.

Title: **Bone loss and injury: What is the unique military need, and how best to impact a very crowded field?**
Author: Pfister B
Affiliation: Clinical and Rehabilitative Medicine Research Program, US Army Medical Research and Materiel Command
City/Country: Fort Detrick, USA

Abstract:
Epidemiological studies of combat wounds from the current armed conflicts have shown that wound distribution resides to the greatest extent in the head, neck and extremity body regions. A large percentage of these injuries present with hard tissue damage and loss. The treatment of segmental bone defects has long been a high prioity research topic for military medicine. The field has rapidly grown in the number of approaches that hope to provide osteoconductive, osteoinductive and /or osteogenic solutions for segmental bone defects. With an ever increaseing number of these solutions clinically avalible why is the treatment of segmental bone defects still viewed as a significant military medical problem? This session will explore what conclusions can be drawn about the unique military need that might help inform future research efforts.

Title: **Introduction to the Armed Forces Institute of Regenerative Medicine (AFIRM) by the consortium Co-Director**
Author: Tuan RS
Affiliation: Center for Cellular and Molecular Engineering, Center for Military Medicine Research, McGowan Institute for Regenerative Medicine, University of Pittsburgh School of Medicine
City/Country: Pittsburgh, Pennsylvania, USA

Abstract:
The Armed Forces Institute for Regenerative Medicine (AFIRM) was originally established by the U.S. Department of Defense in 2008 as a consortium of academic, government, and industry partners to develop regenerative medicine therapies focusing on the needs of the wounded warrior It is through this unique partnership that it has focused on approaches for treatment of burns, craniofacial injuries, compartment syndrome, extremity injuries, and to promote scarless wound healing. AFIRM has created a pipeline of technologies from the laboratory benchtop through clinical trial stage. The research effort of AFIRM was recently expanded through AFIRM II to include two additional areas of focus specifically treatment of genitourinary injuries and advancing composite tissue allotransplantation.

Title: **Regenerative Medicine Coalition e.V. (RMC)**
Author: Volk HD
Affiliation: Institute of Medical Immunology, Berlin-Brandenburg Center for Regenerative Therapies (BCRT), Charité Universitätsmedizin Berlin
City/Country: Berlin, Germany

Abstract:
No abstract available yet

Title: **ESTROT (European Society of Tissue Regeneration in Orthopaedic and Trauma) – perspective**
Author: Calori GM
Affiliation: Reparative Orthopaedic Surgery Department - G. Pini Institute - University of Milan
City/Country: Milan, Italy

Abstract:
ESTROT (European Society of Tissue Regeneration in Orthopaedics and Trauma) is a medical-scientific society in the field of Orthobiology recognized by EFORT (European Federation of National Associations of Orthopaedics and Traumatology); it includes all national societies of Orthopedics and Traumatology and therefore it represents 31 countries in Europe and others around the world. It is a non-profit organisation whose main objectives are: to relieve sickness in musculoskeletal disorders, to cover all matters relating to the progress and development of the field of tissue regeneration, to ensure the highest possible standards of management for the musculoskeletal patient requiring a regenerative approach to restore function of the affected limb, to educate the community in general, medical practitioners and associated professionals in particular in the most effective methods of tissue restoration of the injured patient, to promote and support advances in regenerative approaches for restoration of loss of hard and soft tissue, to encourage, develop and support evidence based regenerative treatment approaches, to guide European Tissue Regeneration Policies and to guide alliances of similar organizations from other continents.
Regenerative Medicine is being increasingly utilized in Orthopedic surgery in both civilian and military field. Nowadays soldiers are highly trained and qualified. Being able to recover them from trauma, bone loss, bone and joint infections avoiding amputations and giving the best care is strategic . With innovative treatments we can heal extremely severe cases through regenerative medicine. Utilizing biotechnologies as stem cells, growth factors, bone and cartilage substitutes, in respect of the scientific guide-lines, it is possible to regenerate large loss of substance and expecially it dresses well in the treatment of critical size bone defects. However, when the patient's conditions and the injury are so severe that regeneration is not suitable, it is possible to implant new prosthesis that allow the surgeon to replace entire limbs. Thanks to these megaprosthesis, also in patients infected and who have lost entire skeletal segments, it is possible to return them to function and mobility. This is definitely strategic from the military and civil point of view.

Open Questions and Future Perspectives

Chairmen: **Kohn** (Piscataway, NJ, USA), **Willy** (Berlin, Germany)

Title: **Bone and muscle regeneration: Perspective and remaining challenges**
Author: Duda GN
Affiliation: Julius Wolff Institute and Center for Musculoskeletal Surgery, Berlin-Brandenburg Center for Regenerative Therapies, Charité - Universitätsmedizin Berlin
City/Country: Berlin, Germany

Abstract:
Bone is a unique and highly regenerative tissue in vertebrates. Unlike to most injuries that lead to fibrotic scar formation and incomplete restoration of the tissue structure and function, bone healing restores pre-fracture properties under optimal conditions. This is distinctly different to muscle injury, which has a distinctly different inflammatory reaction to injury compared to bone. Thus, understanding the underlying differences between bone and muscle injuries in the early regenerative phases appears to be mandatory to allow an understanding on the mechanisms of scarless repair. Consequently, the investigation of bone regeneration and its comparison to regeneration in other tissues such as muscle has significant impact on our understanding of how such processes of regeneration are driven. An understanding of the underlying mechanisms and processes of bone regeneration might serve as blue-print to other organ systems where regeneration appears even more challenging.
The formation of callus tissue - as intermediate material to reconstitute the body's own structure and function - proved to be mechano-responsive in both, the type and the amount of tissue formed. Demanding mechanical conditions such as in instable fracture fixations lead to a delay of bone bridging, a prolonged cartilaginous phase of endochondral ossification, a reduced and delayed angiogenesis and a prolonged inflammatory phase. All of the relevant cascades of bone healing and formation are directly influenced by mechanical means. The way tissues are formed, the way they mature and aspects of their reorganization are directly influenced by mechanical constrains. Even though the general nature of mechano-sensitivity are widely known, details of their interplay and specially how the mechano-sensitivity at the various length scales from macroscopic mechanics to sub-cellular signaling are yet not fully understood.
Further, the process of bone healing seems to recapitulate aspects of the embryonic skeletal tissue formation and development. It is yet unclear if the processes of formation and repair are indeed similar. To what degree the key-regulator, the mechano-sensitivity, remains constant with time and across processes such as development, maintenance and regeneration is also relatively unknown. Using mesenchymal stromal (or stem) cells (MSCs) as a key element of regenerative capacity, studies from our and other groups in humans and animals have demonstrated an age dependent regeneration potential that seems to decline with increasing age. The reduced mechano-sensitivity of one of the key-elements of regeneration – mesenchymal stroma cells - combined with a shift in material characteristics and change in tissue straining in aged species compared to their younger counterparts illustrates the importance to characterize mechano-senstivity of biological systems not as static and somehow stable systems but as adaptive systems with changing capacities in all stages of aging.
Mechano-biology seems to be apparently a central aspect of the phases of bone healing and regeneration; it plays a key role in maintenance and seems to be also important in early developmental phases. A further understanding of the underlying mechanism of the link between biology and mechanics and their direct interactions at the various lengths scales and across aging seems to be essential to understand healing cascades, their interaction and limitations in healing in clinically demanding situations. This understanding is mandatory to allow effective stimulation of regenerative cascades even under compromised healing conditions.

Title: **Novel strategies for engineering skeletal tissues with stem cells and natural origin scaffolds**
Author: Gomes M
Affiliation: 3B's Research Group - Biomaterials, Biodegradables and Biomimetics, University of Minho, Headquarters of the European Institute of Excellence on Tissue Engineering and Regenerative Medicine
City/Country: Braga/Guimarães, Portugal

Abstract:
Designing successful tissue engineered substitutes involves a challenging and continuous effort to balance the interplay of the scaffold with the stem cells and the culturing environment. The scaffold design requirements evolved significantly with the growing knowledge in this field that has evidenced the importance of developing stimulating scaffolds, with forms/composition tailored to specific applications, enabling to maximize interactions with cells and/or tissues. We have developed and studied several scaffolds based on natural origin polymers which have been used in different approaches for the regeneration of skeletal tissues (namely bone, cartilage and tendon), involving the culturing of stem cells from different sources, in some cases under dynamic culturing environments. The outcomes of these studies highlight the influence of the scaffold structure and of the cell-source specific behavior and differentiation stage on the resulting *in vitro* and *in vivo* functionality of tissue engineered constructs. These findings trigger our growing interest on *in vitro* biomechanically-stimulating culture environments that can be achieved modulating the scaffold architecture and composition and the stem cells. Thus, novel scaffold designs incorporating additional structural (biomimetic architectures), biochemical (such as growth factors provided in platelets lysates) or physical (e.g. magnetism) features, are being developed to create skeletal tissue substitutes with enhanced functionality, addressing specific tissue requirements.

Title: **Stem cells for tissue regeneration: Hope, reality and future**
Author: Tuan RS
Affiliation: Center for Cellular and Molecular Engineering, Department of Orthopaedic Surgery, and Center for Military Medicine Research, University of Pittsburgh School of Medicine
City/Country: Pittsburgh, Pennsylvania, USA

Abstract:
The inherently limited regenerative ability of most adult tissues is a clinical challenge to the restoration of tissue function, particularly in the event of traumatic injuries and chronic degeneration. Recent research breakthroughs have advanced medicine from palliative and therapeutic to a regenerative phase. Approaches that combine cells, scaffolds, and biological signals, are increasingly gaining attention. This lecture will use cartilage regeneration as an example to illustrate the hope, reality, and future of the new discipline of stem cell-based biomedicine. Mesenchymal stem cells (MSCs), harvested from adult tissues such as bone marrow and adipose, have multi-lineage differentiation potential, including chondrogenesis, and are considered a promising candidate cell type for cartilage repair. Using MSCs, nanofibrous and hydrogel biomimetic scaffolds, and growth factors, engineered cartilage constructs may be produced either ex vivo or in situ. Current challenges concern the mechanical properties of these constructs, their integration with host tissue, and their long-term phenotype. Another technical limitation is the finite life span and ultimately limited availability of adult stem cells. Induced pluripotent stem cells (iPSCs) derived by reprogramming of adult somatic cells represent another autologous stem cell source, although the performance capacity of their mesenchymal derivatives remains unclear. Adult stem cells, with their multi-differentiation potential and recently discovered trophic activities, when used in combination with biomimetic scaffolds, present a powerful platform for regenerative, therapeutic, and disease modeling applications in biomedicine.

Title: **How is clinical experience driving future therapies?**
Authors: Soria B, Mateos-Fernández JA, Quesada E, Rodríguez B, Soria-Juan B, Hmadcha A
Affiliation: CABIMER, Andalusian Center for Molecular Biology and Regenerative Medicine
City/Country: Sevilla, Spain

Abstract:
In Translational Regenerative Medicine Programs scientists, healthcare professionals and administrators try to fit the knowledge generated with healthcare needs; however the main driver for knowledge generation in not translation but knowledge in itself. Peer review of the funding system and academic promotion is mostly based in excellence and translational medicine is not necessarily published in High Impact journals. In contrast healthcare administrators demand cost-effective treatments and business managers commercial viability. Furthermore, translational regenerative medicine is facing a new landscape with undefined bottlenecks such as: Poor definition of "cellular medicament", poor intellectual property protection, lack of criteria and accredited markers for biodistribution, pharmacodynamy, toxicity, dose, etc, excessive cost of cell manufacturing, insufficient training of healthcare professionals, absence of a Catalogue of Adverse Reactions, lack of standards for Risk Management procedures, lack of Big Pharma commitment, lack of an innovation business model, etc. Changing the paradigma for Translational Medicine should include exploring the "attractors" that should drive our efforts. For example, a comparison between (US) Armed Forces Needs and Societal Healthcare Needs demonstrates that there are similarities (pain management, prostheses, robotics, visual system restoration) and differences: Acute Care (min to h) with low-level expertise vs. Research in Rare Diseases; Solid Organ and bone marrow transplantation vs. Face and Hand transplantation; Skin acute inflammation, Trauma and Burns vs. Psoriasis, Atopic Dermatitis or Epidermiolysis bullosa; Head-neck, extremities and genitourinary injuries vs traffic, domestic and work accidents; On-the self products vs. personalized medicine treatments, etc.

Bone Defect Management I

Chairmen: **Boccaccini** (Erlangen, Germany), Kollig (Koblenz, Germany)

Title: **Tools for healing of severe bone defects**
Author: Bégué T
Affiliation: Service de Chirurgie Orthopédique, Traumatologique et Réparatrice, Hôpital Antoine Béclère, Université Paris-Sud
City/Country: Clamart/Paris, France

Abstract:
In severe trauma of the lower limb with additional bone defects, acute management needs to refer to Damage Control Orthopaedics (DCO). In such clinical cases, surgeons face challenging situations and decision about treatment of the bone loss. Severe bone defects are defined as critical when exceeding 5 cm and they cannot be treated by conventional bone grafting due to graft resorption and additional procedures needs for complete fusion.
The induced membrane technique, so-called Masquelet technique, is dedicated to treat very huge bone defects up to 25 cm, using a two-stage procedure with a cement spacer insertion for six to eight weeks then filling the chamber created around by autologous cancellous morcelized bone graft.
Ilizarov techniques can be used either by immediate shortening, acute shortening followed by compression-distraction techniques, or bone transport. Advantages and pitfalls include difficulty for shortening over 3 cm, length of external fixation with infection pin sites, docking site non-union, and extrusion of transferred bone due to retraction of soft tissue in the defect.
Free vascularized fibula transfer is the last option for acute reconstruction for traumatic bone loss in case of femoral bone loss with a double-barreled technique or tibial defect over 12 cm.
Tissue engineering will modify solutions by combining mesenchymal stem cells, specific scaffolds, and growth factors such as bone morphogenetic proteins (BMP).

Title: **Diamond concept for treatment of infected non unions**
Author: Schmidmaier G
Affiliation: Department of Traumatology, University Clinic of Heidelberg
City/Country: Heidelberg, Germany

Abstract:
No abstract available yet

Title: **From Regeneration to substitution: Algorithm of treatment of non-unions and bone defects**
Author: Calori GM
Affiliation: Reparative Orthopaedic Surgery Department - G. Pini Institute - University of Milan
City/Country: Milan, Italy

Abstract:
Non-union and bone defects of long bones are difficult complications treating fractures. We propose a new classification and a new strategy that could give significant information to the orthopaedist for a good management of these complicated cases and permit to create comparable study groups for research purpose.
In 2008 we published a new classification for nonunions: the Non-Union Scoring System (NUSS). The NUSS doesn't consider only the radiographic aspects of the non-union but take in consideration all the risk factors that contribute to this complication analyzing the whole patient (bone quality, primary injury, number, invasiveness and adequacy of previous interventions, soft tissues status, ASA grade, clinical infection status, smoking status, use of drugs, blood test, diabetes).
All the factors included in the scoring system have an impact on the complexity and difficulty of treatment of any nonunion. The NUSS recognizes four group of complexity:

- score from 0 to 25 should be considered a straightforward nonunion and should respond well to standard treatments; usually the problems is mainly biomechanic; the more common treatment is choosing a different system of fixation.
- score from 26 to 50 should require more specialised care; usually the problem is both biological and mechanical. The treatment require the correction of the fixation associated with a biological stimulation obtained with CEMP, ESWT or biotechnologies such as mesenchimal stromal cells or growth factors or scaffold in monorail therapy.
- score from 51 to 75 require specialised care and specialised treatments; it's a complex problem characterized by a impairment of both biological and mechanic conditions, usually is required the resection of the nonunion and consequently a bone defect must be treated. Next to traditional treatments, such as bone transport with external fixator, autologous iliac's crest grafts or microvascular fibula's graft, in this situation is indicated the use of biotechnologies (cells, scaffold and growth factors) according to the principles of the "biological chamber" and the "polytherapy".
- score from 76 to 100 may be candidates for the primary amputation, arthrodesis, prosthesis, o mega-prosthesis depending on the severity of the loss of substance and the anatomical localization.

We think that a "ladder strategy" based on the complexity of patients that starts from reconstruction and ends with substitution of the affected limb could be a good option in these difficult cases in order to return these patients to function.

Title: **Scientific and commercial considerations in the design of bioactive scaffolds for bone regeneration**

Author: Kohn J
Affiliation: Rutgers University, Armed Forces Institute of Regenerative Medicine
City/Country: Piscataway, NJ, USA

Abstract:
The design of bone regeneration scaffolds is one of the most widely investigated areas in the field of tissue engineering. The key challenge of this significant research effort is to create an engineered bone scaffold that can equal or surpass the clinical performance of autologous bone grafts. This goal has not yet been met. From the very large number of failed approaches, we conclude that a "materials-only" approach (polymers, ceramics, or combinations of polymers and ceramics) will not provide the required biological signals to support bone regeneration in critical size defects in human patients. The goal of current research efforts is therefore to create "bioactive" engineered scaffolds that enhance the formation bone tissue within the defect area. Toward this goal, various cell populations are seeded within the scaffold, growth factors and cell signaling molecules are used, and a variety of nanoparticular drug delivery systems are explored. For example, there are 2803 research publications that describe the use of nanoparticular drug carriers in bone regeneration scaffolds. Surprisingly, it seems that none of these research efforts resulted in a commercial product or clinical trial. All of these advanced design strategies show some level of success in animal models, but run into significant commercial difficulties. It turns out that the scientific necessity of creating complex, bioactive scaffolds is in direct contradiction to the requirements of the US FDA regulatory process that favors simple, proven technologies and incremental innovations over breakthrough technologies. In addition, patients do not usually die of bone defects. Therefore, contrary to cancer treatments, new ways to heal bone defects rarely meet the FDA's requirements for expedited review. In addition, there are many different bone void fillers already approved for clinical use. These products perform adequately for most patients, creating only limited opportunities to introduce improved products that would be significantly more expensive. In summary, this talk makes the observation that the scientific need to create complexly designed bone regeneration scaffolds is in direct conflict with the commercial need to keep designs simple (for regulatory purposes) and the products of low cost (for marketing purposes). This divergence of design criteria can explain in part the apparent lack of translation of current research efforts into commercial products.

Title: **Application of adult stem cells and biomimetic scaffolds for skeletal tissue engineering and regeneration**

Author: Tuan RS
Affiliation: Center for Cellular and Molecular Engineering, Center for Military Medicine Research, McGowan Institute for Regenerative Medicine, University of Pittsburgh School of Medicine
City/Country: Pittsburgh, Pennsylvania, USA

Abstract:
The intrinsically low reparative capacity of cartilage is a clinical challenge to effective treatment of degenerative joint diseases, such as osteoarthritis, the main cause of physical disability. Tissue engineering and regenerative medicine, combining cells, scaffolds, and biological signals, represents a potentially promising approach. Mesenchymal stem cells (MSCs), harvested from adult tissues such as bone marrow and adipose, have multi-lineage differentiation potential, including chondrogenesis, and are considered a promising candidate cell type for cartilage repair. A biocompatible biomaterial scaffold that ideally also enhances proliferation and differentiation of the seeded cells is critical to successful cell-based tissue engineering. We have shown that biomimetic scaffolds that simulate the structure of native extracellular matrix, e.g., the nanoscalar fibrous nature of collagen, are effective in MSC-based skeletal tissue engineering both *in vitro* and *in vivo*. Our recent work on the use of custom-designed, photo-crosslinked hydrogel scaffolds, which allows cell encapsulation during fabrication, demonstrates high fidelity reproduction of internal structure and excellent cell retention, viability, and differentiation. Specifically, applying a 3D printing approach and a custom-designed microbioreactor, we have constructed a microtissue analogue of the osteochondral junction, based entirely on MSC-derived components, to model the pathogenesis of osteoarthritis. Adult stem cells, with their multi-differentiation potential and recently discovered trophic activities, when used in combination with biomimetic scaffolds, present a powerful platform for regenerative, therapeutic, and disease modeling applications in biomedicine.

Introductory Session II

Chairman: **Borchers** (Stuttgart, Germany)

Title: **Advances in reconstructive transplantation driven by a decade of combat**
Author: Davis MR
Affiliation: Reconstructive Surgery and Regenerative Medicine United States Army Institute of Surgical Research
City/Country: San Antonio, USA

Abstract:
Background: Vascularized composite allotransplantation (VCA) holds great promise for reconstructing previously unreconstructable composite tissue defects. By obviating the need for systemic immunosuppresion through mitigation of ischemia-reperfusion injury (IRI) and development of allograft specific immunomodulation, the field of VCA can be unlocked to allow widespread use.
Methods: Porcine models of gracilis myocutaneous flap auto- and allo-transplantation as well as orthotopic forelimb allotransplantation were utilized to investigate methods of mitigation of ischemia-reperfusion injury. Suspended animation using H2S and warm *ex vivo* hyperbaric oxygen (HBO) perfusion were investigated. Allograft specific immunomodulation using sudermally delivered drug eluting microparticles were investigated as a method for obviating the need for systemic immunosuppression.
Results: Robust porcine models of VCA have been established and validated including a true orthotopic forelimb transplant model. H2S as well as warm *ex vivo* hyperbaric perfusion show statistically significant ability to abate IRI in VCA. Subdermally placed drug eluting microparticles containing sirolimus and T-cell modulators can produce allograft specific immunomodulation obviating induction requirement and producing short term allograft tolerance (+21 days over controls).
Conclusions: VCA can be potentiated through mitigation of IRI using both H2S and a warm *ex vivo* HBO perfusion device. Allograft specific immunomodulation holds great promise for unlocking the field of VCA through obviating the need for systemic immunosuppression.

Bone Defect Management II

Chairmen: **Bégué** (Paris, France), **Schmidmaier** (Heidelberg, Germany)

Title: **KN: Synthetic bone substitute that can duplicate the mechanical strength, elasticity and bioactivity of bone**
Author: Zreiqat H, Roohani-Esfahani SI, Dunstan1 CR, Li JJ, Lu Z
Affiliation: Faculty of Engineering and IT and Bosch Institute, The University of Sydney
City/Country: Sydney, Australia

Abstract:
During the past two decades, research on ceramic scaffolds for bone regeneration has progressed rapidly; however, currently available porous scaffolds remain unsuitable for load-bearing applications. The key to success is to apply microstructural design strategies to develop ceramic scaffolds with mechanical properties approaching those of bone. Here we report on the development of a unique microstructurally designed ceramic scaffold, strontium–hardystonite–Gahnite (Sr–HT–Gahnite), with 85% porosity, 500 lm pore size, a competitive compressive strength of 4.1 ± 0.3 MPa and a compressive modulus of 170 ± 20 MPa. The *in vitro* biocompatibility of the scaffolds was studied using primary human bonederived cells. The ability of Sr–HT–gahnite scaffolds to repair critical-sized bone defects was also investigated in a rabbit radius under normal load, with b-tricalcium phosphate/hydroxyapatite scaffolds used in the control group. Studies with primary human osteoblast cultures confirmed the bioactivity of these scaffolds, and the *in vivo* regeneration of segmental critical size bone defects in a rabbit model demonstrated that this material induces new bone defect bridging, with clear evidence of regeneration of original radial architecture and bone marrow environment.

Title: **Epigenetic changes of Ad-MSCs will improve osteogenic regeneration**
Author: Nüssler AK
Affiliation: Siegfried Weller Institute for Trauma Research, BG Trauma Center, University of Tübingen
City/Country: Tübingen, Germany

Abstract:
The therapeutic value of adipose-derived mesenchymal stem cells (Ad-MSCs) for bone regeneration is currently discussed critically. A possible reason for the reduced osteogenic potential of Ad-MSCs may be their age-related deterioration. It is already widely known that, in long-term *in vitro* culture, epigenomic changes in DNA methylation cause gene silencing and affect the growth as well as the differentiation potential of stem cells. We have observed an age-related decline in the proliferation of primary human Ad-MSCs. In Ad-MSCs that had been isolated from old donors (> 60 a), decreased Nanog, Oct4 and Lin28A expression as well as increased Sox2 gene expression were accompanied by an impaired osteogenic differentiation potential in comparison to Ad-MSCs that had been isolated from younger donors (< 45 a). Furthermore, we evaluated the distribution of 5-hydroxymethylcytosine (5hmC) and 5-methylcytonsine (5mC) as well as the TET gene expression in these Ad-MSCs in order to assess the evidence of active DNA demethylation. Here, we observed a decrease of 5hmC in Ad-MSCs from older donors. The incubation of these cells with 5-Azacytidine induced their proliferation and improved their osteogenic differentiation potential. The increase in AP activity and matrix mineralization was associated with an increased presence of 5hmC as well as with an increased TET2 and TET3 gene expression. Our data show, for the first time, a decrease of DNA hydroxymethylation in Ad-MSCs which correlates with donor-age. Moreover, they prove that treatment with 5-Azacytidine provides a possible approach for the rejuvenation of Ad-MSCs from aged donors.

Title: **Negative impact of CD8+ effector T cells on bone fracture regeneration**
Author: Schmidt-Bleek K
Affiliation: Julius Wolff Institute, Charité - Universitätsmedizin Berlin
City/Country: Berlin, Germany

Abstract:
Approximately 5–15% of fracture patients worldwide suffer from incomplete bone healing.
Bone is a unique tissue with a considerable healing competence. Unlike several other tissues, a complex interplay of various cellular, humoral and mechanical factors enable the scarless repair of bone injuries, restoring pre-fracture properties under optimal conditions.
Multiple factors influence the healing process and determine the healing outcome. There is growing evidence that especially the adaptive immune system plays an important role in fracture healing.
An unbalanced immune reaction was hypothesized to disturb the healing cascade and jeopardizes the successful healing outcome. In particular, we used a sheep bone osteotomy model with mechanically-induced impaired/delayed bone healing. These animals showed significantly higher T cell percentages, especially CD8+ effector T cells, in the bone fracture hematoma compared to the corresponding control animals. These results suggested that CD8+ effector T cells are unfavorable factors for regeneration. Based on these findings, we performed a Proof-of-Concept study with human tibial fracture patients over a period of 18 weeks. Here we found, that delayed fracture healing significantly correlates with enhanced levels of CD8+ TEMRA in peripheral blood. Accordingly, depletion of CD8+ T cells in a clinically relevant mouse osteotomy model resulted in enhanced endogenous fracture regeneration, whereas a transfer of CD8+ T cells impaired the healing process.
These observations open (a) a window for a new biomarker stratification of patients, as well as (b) also new therapeutic opportunities towards an immune-modulatory strategy to enhance healing.

Title: **Development of calcium phosphate based biomaterials for bone regeneration and their application in maxillofacial and orthopedic surgery**
Author: Loca D
Affiliation: Rudolfs Cimdins Riga Biomaterials Innovations and Development Centre
City/Country: Riga, Latvia

Abstract:
In last decades musculoskeletal diseases and disorders are becoming a great problem all over the world and every year the number of patients suffering from these diseases dramatically increases. In orthopedic trauma surgery, osteoporosis carries an increased risk of surgical complications. Fragility of large bone fracture defects produce challenges in operative stabilization and treatment of osteoporotic fractures, opening the new possibilities and applicability for multifunctional biomaterials.
Synthetic calcium phosphates (CaP) are chemically similar to the bone mineral phase, hence they are good candidates as bone substitution materials. Osteoconductivity and biocompatibility are their main advantages. Mostly CaP bioceramic is used in form of hydroxyapatite (HAp, Ca10(PO4)6(OH)2), β-tricalcium phosphate (TCP, Ca3(PO4)) or biphasic calcium phosphates (BCP), which is mixture of HAp and TCP. The use of BCP bioactive ceramics is based on an optimum balance between more stable phase – hydroxyapatite and more soluble phase – β-tricalcium phosphate. Varying the ratio of HAp and TCP, bioactivity and resorbability of BCP can be controlled. Depending on the CaP bioceramic composition, it can be used in maxillofacial surgery, plastic surgery and orthopedics, not only as a local support of bone fractures but also as an ideal material for new bone formation. Additional beneficial properties can be introduced in CaP biomaterials, using ion substitution strategy or incorporating various pharmacologically active agents within the biomaterial matrix, in such a way creating multifunctional materials for local ion or drug delivery.

Title: **Novel biomaterials with angiogenic potential (e.g. bioactive glasses) for bone regeneration**
Author: Boccaccini AR
Affiliation: Institute of Biomaterials, Department of Materials Science and Engineering, University of Erlangen-Nuremberg
City/Country: Erlangen, Germany

Abstract:
The development of 3D multifunctional scaffolds for bone tissue engineering and regenerative medicine will be discussed, presenting recent progress and remaining challenges. After a comprehensive summary of current research in the field, recent results on the development and characterisation of nanostructured bioactive glass based scaffolds will be highlighted. Suitable and emerging technologies for fabrication of scaffolds will be discussed including a comparison of the simple but versatile foam replica technique and more advanced methods based on rapid prototyping, electrophoretic deposition and electropspinning techniques. Approaches to engineer the bioactive glass scaffold microstructure and surface will be shown including coating and infiltration by biodegradable polymers containing functionalised nanoscale inorganic particles or nanofibres. The cellular response to scaffolds in specific *in vitro* tests will be also discussed with focus on the effects of bioactive glass dissolution products on cell behaviour in relation to osteogenesis and angiogenesis. *In vivo* investigations focusing on assessing the vascularisation potential of the new scaffolds will be discussed and the present challenges of this branch of tissue engineering, e.g. the development of vascularised bone, will be highlighted. In this context, the effect of nanoscale bioactive glass particles on angiogenesis in comparison with conventional or micrometer scale particles will be emphasized. In addition a new family of bioactive silicate scaffolds doped with trace elements (e.g. Sr, Co, Cu) and investigations on the effect of these elements on the scaffold biological performance will be presented to confirm the hypothesis that scaffolds with specific ion release capability ("bioinorganics" or therapeutic metallic ions) are attractive for vascularized bone tissue engineering. Areas of future research in the field of bioactive materials based on smart composite systems for engineering tissues requiring enhanced vascularisation will be addressed, including the emerging fields of tissue engineering therapeutics and regeneration of complex tissue interfaces where the incorporation of functional nanoparticles is suitable to improve the scaffold performance.

Central and Peripheral Nerve Defects

Chairmen: **Feigal** (San Francisco, USA)

Title: **KN: Central and peripheral nerve defect treatment**
Author: Feigal EG
Affiliation: California Institute for Regenerative Medicine
City/Country: San Francisco, CA, USA

Abstract:
No abstract available yet

Title: **Challenges of peripheral nerve injuries to the wounded warrior for regenerative medicine**
Author: Rosen JM
Affiliation: Dartmouth-Hitchcock Medical Center and the Thayer School of Engineering at Dartmouth College
City/Country: Hanover, New Hampshire, USA

Abstract:
Blast injuries create wounds as a result of massive energy transfer from weapons to the warfighter. These injuries create unique challenges for the regeneration of peripheral nerves. Peripheral nerve injuries more than other single tissue in the extremity limit the functional recovery of limbs. Among these challenges large segmental defects are the most difficult to treat. They reduce the number of axons that regrow across the defect and they increase the time required to regenerate from the proximal site of injury to the distal sensory and motor end organs.
Over the past five years we have concentrated our efforts on replacing segmental nerve defects, speeding nerve regeneration and preserving end organ function of muscles. Regenerative medicine has several unique roles to play in replacing segmental nerve defects. Segmental nerve defects can be replaced with tissue engineered artificial nerve grafts. These artificial nerves are composed of a conduit filled with a matrix. The matrix can be composed of living cells or bioactive agents. The proper construction of this artificial nerve graft should enhance nerve regeneration.
However to revolutionize this process we are also involved in projects to speed nerve regeneration by stretching nerve axons. This can increase the regeneration speed by a factor of 10X or more. This would allow the nerve to regenerate to the muscle end plates earlier than previously possible and limit atrophy of the muscles especially for proximal nerve injuries. At the same time we are involved in projects to stimulate the muscle end plates to reduce muscle atrophy. Our goal is to use Regenerative Medicine tools to engineer improved artificial nerve grafts and to optimize the overall nerve recovery process for the wounded warrior.

Title: Stem cell therapy in spinal cord injury
Author: Özedmir M
Affiliation: Faculty of Medicine Department of Neurosurgery, Pamukkale University
City/Country: Denizli, Turkey

Abstract:
Spinal cord injury is a devastating, traumatic event, and experienced mainly among young people. Until the modern era, spinal cord injury was so rapidly fatal that no seriously injured persons would survive long enough for regeneration to occur. Treatment of spinal cord injury can be summarized as follows: prevent further cord injury, maintain blood flow, relieve spinal cord compression, and provide secure vertebral stabilization so as to allow mobilization and rehabilitation, none of which achieves functional recovery. Previous studies have focused on analyzing the pathogenesis of secondary injury that extends from the injury epicenter to the periphery, as well as the tissue damage and neural cell death associated with secondary injury. Now, there are hundreds of current experimental and clinical regenerative treatment studies. One of the most popular treatment method is cell transplantation in injured spinal cord. For this purpose bone marrow stromal cells, mononuclear stem cells, mesenchymal stem cells, embryonic stem cells, neural stem cells, and olfactory ensheathing cells can be used. As a result, cell transplantation has become a promising therapeutic option for spinal cord injury patients. In this paper we discuss the effectiveness of stem cell therapy in spinal cord injury.

Title: Cell based therapies for cerebrovascular diseases and TBI
Author: Deten A
Affiliation: Fraunhofer Institute for Cell Therapy and Immunology IZI, Translational Centre for Regenerative Medicine (TRM)
City/Country: Leipzig, Germany

Abstract:
Cell-based regenerative approaches are among the most promising experimental approaches to treat acute neuronal injury. Particularly, the application of adult (stem) cell populations that can be obtained autologously and may be applied without the necessity for extensive cultivation and/or processing may be clinically practicable. The approach holds great potential to support endogenous regeneration of acute neurological diseases such as stroke and traumatic brain injury as suggested by strong evidence from experimental studies. However, therapeutic mechanism may not primarily include the replacement of lost or damaged tissue rather than anti-inflammatory and cytokine-based, modulatory "bystander" effects. The presentation will review potential therapeutic mechanisms from selected trials, also highlighting important cell populations and sources. It may also point on potential pitfalls during clinical translation as well as on relevant hurdles that may impede the translational process.

Title: Actual and future perspectives of ocular neuroregeneration and rescue
Author: Scott RAH
Affiliation: Royal Centre for Defence Medicine, Birmingham and Midland Eye Centre
City/Country: Birmingham, UK

Abstract:
Traumatic optic nerve injury results in retinal ganglion cell apoptosis and failure to regenerate axons, contributing to severe visual impairment. There are currently no effective treatments to promote functional repair of the damaged optic nerve. The mammalian target of rapamycin (mTOR) cellular signalling pathway is involved in numerous cellular processes associated with cell survival and growth and is implicated as a key determinant of neuronal survival and axon regeneration after optic nerve injury. RTP801 is a negative regulator of mTOR signalling, activated in response to cellular stress.
We hypothesise that targeted knock-down of RTP801 with a small interfering RNA (siRNA) treatment promotes retinal ganglion cell survival and axonal regeneration in an established optic nerve injury model. To investigate this we performed bilateral optic nerve crush injuries on adult male rats and administered intravitreal injections of siRTP801 in the right eye and a control siRNA in the left on days 0, 8 and 16 after the injury. Surviving retinal ganglion cells and regenerating axons were quantified at day 24 with immunohistochemistry of retinal and optic nerve sections stained for the markers Brn3a and GAP43 respectively.
We found that intravitreal siRTP801 treatment promoted significant retinal ganglion cell survival compared to control siRNA after optic nerve crus and increased the number of GAP43 positive regenerating axons in the distal optic nerve at 400 microns, 800 microns and 1200 microns beyond the crush site. In conclusion we found that knock-down of RTP801, a negative regulator of mTOR cellular signalling, promotes retinal ganglion cell survival and axon regeneration after optic nerve crush injury. This demonstrates its potential as a novel translatable treatment of optic nerve injuries.

Soft Tissue Defect Management

Chairmen: **Schaser** (Berlin, Germany), **Pfister** (Fort Detrick, USA)

Title: **Engineering of vascularized human implants and their first application**
Author: Walles H
Affiliation: Institute of Tissue Engineering und Regenerative Medizin, University of Würzburg
City/Country: Würzburg, Germany

Abstract:
No abstract available yet

Title: **Novel extracellular matrix proteins for cardiovascular tissue regeneration - *In vitro* elastogenesis - deciphering the key for elastin fiber generation for engineering tissues and organs**
Author: Schenke-Layland K
Affiliation: Department of Cell and Tissue Engineering, Fraunhofer Institute for Interfacial Engineering and Biotechnology IGB
City/Country: Stuttgart, Germany

Abstract:
No abstract available yet

Title: **Using of autologous cultured keratinocytes in coverage of large tissue defects**
Author: Marinescu BM
Affiliation: Plastic Reconstructive Surgery and Burns Department, University Emergency Military Hospital "Dr Carol Davila"
City/Country: Bucharest, Romania

Abstract:
No abstract available yet

Title: **MSC as drug cells for cell therapy of burns**
Author: Lataillade JJ
Affiliation: Percy Military Hospital Blood Transfusion Center
City/Country: Clamart/Paris, France

Abstract:
No abstract available yet

Title: **Tissue engineering based strategies in tendon repair - Role of complement & influence of inflammation**
Author: Schulze-Tanzil G
Affiliation: Laboratory for Experimental Orthopaedic Surgery, Campus Benjamin Franklin, Charité – Universitätsmedizin Berlin
City/Country: Berlin, Germany

Abstract:
Intrinsic repair of ruptured tendons can be associated with unwanted results such as scar formation and altered biomechanical tissue properties. The role of inflammation and activation of the complement cascade in tendon healing remains uncertain. Advanced understanding of the impact of posttraumatic inflammatory and catabolic processes should help to reduce healing times and to reconstruct natural structure of tendon in response to injury. Natural and synthetic polymers play a pivotal role as artificial matrices for tendon tissue engineering based tendon reconstruction and some of them entered already the clinical praxis. Biomaterials can provoke a distinct inflammatory tissue response in tendon.
We found that complement components such as the anaphylatoxin receptors C5aR and C3aR and cytoprotective complement regulatory proteins (CRPs) are expressed by the tenocytes and in tendon. Complement factors are intimately regulated by proinflammatory cytokines, complement split fragments and mechanical stress. Further, we developed cell-based strategies of experimental tendon reconstruction using polymer scaffolds and natural extracellular tendon matrix and characterized them *in vitro* and *in vivo*.
Future directions of tissue engineering assisted tendon reconstruction are to develop biomimetic polymer scaffolds, suitable to fully restore the tissue and its mechanocompetence and to achieve stable implant integration into bone and last but not least to control inflammation. Additionally, suitable polymer devices could also help to achieve more rapid tenocyte expansion procedures for cell based strategies. For clinical applications there still remains the request to establish reconstructive strategies performed in one step.

Title: Generation of cartilage for repairing joints damaged due to injury
Author: Feigal EG
Affiliation: California Institute for Regenerative Medicine
City/Country: San Francisco, CA, USA

Abstract:
No abstract available yet

Title: Engineered skeletal muscle for craniomaxillofacial reconstruction
Author: Sundback C
Affiliation: Center for Regenerative Medicine, Massachusetts General Hospital, Harvard Medical School
City/Country: Boston, MA, USA

Abstract:
Military trauma causes extensive damage to craniofacial tissue, impacting a warfighter's return to duty and quality of life. Engineered autologous skeletal muscle represents a viable reconstruction option. Muscle engineered on decellularized extracellular matrices has been utilized in clinical applications to reconstruct volumetric limb muscle loss. However the resulting muscle architecture is not well matched to that of delicate facial muscles and vascularization and innervation are insufficient.
Our MGH team has engineered 3D skeletal muscle constructs using a self-assembly process which produces a native-like muscle architecture that can be vascularized and innervated. Vascular cells are co-cultured with myogenic cells to produce muscle constructs with densely aligned muscle fibers and integrated endothelial networks. Upon implantation, these endothelial networks connect with the host vasculature in less than six hours and mature to leak tight vessels within several weeks. Introduction of nerve tissue during muscle construct fabrication leads to extensive innervation of muscle fibers. Electrical stimulation with neural-like signals up to 72 hours increases the specific contraction force of the engineered muscle constructs to the range of human orbicularis oculi (eyelid muscle). Approaches are under development to scale our muscle constructs toward a full sized facial skeletal muscle. Important milestones have been achieved toward developing replacement skeletal muscle for facial reconstruction.

Title: Cell therapy in organ transplantation
Authors: Soria B, Mateos-Fernández JA, Quesada E, Martín F, Lachaud C, Hmadcha A
Affiliation: CABIMER, Andalusian Center for Molecular Biology and Regenerative Medicine
City/Country: Sevilla, Spain

Abstract:
Solid Organ Transplantation: In the ONEstudy (www.onestudy.org) several cells types (nTreg, Tr1, Mreg, tolerogenic dendritic cells) are being used in a Phase I/II clinical trial to evaluate safety and feasibility in living-donor kidney transplantation. Cell therapy in combination with conventional immunosuppressors and monoclonal antibodies favour Treg survival, whereas blockade of IL-2-CD25 or CD28-CD80/CD86 pathways may induce Tcell anergy experimentally. Both the creation of donor-cell mixed chimerism and the modulation of regulatory T cells may be used.In fact, mesenchymal stromal cells and umbilical cord derived Tregs have been clinically used to reduce one of the most aggressive immune responses, the graft-versus host disease.
Face and Hand Transplantation: Vascularized composite allografts (VCAs) have emerged as a clinical reality for human face and hand reconstructive transplantation. The challenge of VCA, in contrast to solid organ transplantation, has been the composite nature of the transplant, which often includes skin, muscles, and bone. It is anticipated that cell-based tolerance and immunogenetics will facilitate defining personalized regiment to better tackle tolerance induction in face and hand transplantation.
Use of mesothelial cells in tissue engineering of serosal membranes, corneal endothelium and transient skin surrogate: The mesothelium is the outermost tissue layer lining the parietal surface of coelomic cavities (pleural, pericardial and peritoneal) and the visceral organs where they are housed. Among their main biological functions described so far is to secrete glycosaminoglycans and lubricants to provide a protective and slippery surface for the optimal sliding of visceral organs inside coelomic cavities, such as the beating heart or the expanding lungs. In addition, mesothelial cells also play a central role in a variety of intraserosal and submesothelial processes, including the transport of water and solutes, inflammation, host response, angiogenesis, tissue repair, and extracellular matrix remodeling

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Title: **"New" approach in the fight against bacterial infections**
Authors: De Vos D, Merabishvili M, Jennes S, Rose T, Soentjens P, Neirinckx P, Verbeken G, Pirnay JP
Affiliation: Laboratory for Molecular and Cellular Technology, Queen Astrid Military Hospital
City/Country: Brussels, Belgium

Abstract:
Antibiotic resistance is now a major threat to public health (WHO, 30/04/2014, Geneva). Bacteriophages, lifelike entities making up a major part of our biosphere, where essential for the emergence of life and it's continuous evolution. Felix d'Hérelle proposed "phage therapy" already in the early 20th century. It was further developed at the Eliava Institute, in Georgia, and used routinely in the previous Soviet Republics till now. The Western world however forgot it almost at the advent of antibiotics. Today, phage therapy is back in the picture as a potential complementary or alternative antibacterial.
The main problem is a lack of modern evidence based studies. Phage therapy is applied today in Europe under the "Helsinki Declaration", and/or a national specific regulation as in Poland. Several groups however setup studies in animals, while the idea of using bacteriophages as an anti-bacterial has already reached the stage of applications in the food sector. Clinic application is imminent at least at the stage of clinical studies such as the recently started FP7- multi-centric - study Phagoburn.
We conducted a pilot clinical safety study in burn patients, published the method for preparing the phage therapy cocktail as well as the ways to approach it in the regulatory context. Sporadically and under the "Helsinki Declaration" a handful of patients with 'untreatable' bone and soft tissue infections were treated. Over the years we realized that the current pharmaco-economic model (costly, time-consuming and strong intellectual property requirements) and regulatory frame is not compatible with sustainable (co-evolutionary) phage therapy.

Nutritional Considerations

Chairmen: **Lataillade** (Paris, France), **Schenke-Layland** (Tübingen, Germany)

Title: **Nutrition – an important factor in regeneration**
Author: Nüssler AK
Affiliation: Siegfried Weller Institute for Trauma Research, BG Trauma Center, University of Tübingen
City/Country: Tübingen, Germany

Abstract:
The prevalence of malnutrition rises with increasing age of the patients. As society is getting older, malnutrition is gaining importance in clinical research. In Germany, malnutrition concerns up to 56% of hospital patients, leads to a 43% longer stay and to a higher complication rate. In trauma patients, malnutrition causes disorders in wound healing (DWH). Patients with DWH exhibit a higher concentration of micronutrients. However, the prevalence of malnutrition in trauma patients is still unknown. Burn patients receive nutrition therapy during their entire treatment, as they feature high oxidative stress, an intense inflammatory response, and a prolonged metabolic and catabolic response. Furthermore, they have higher nutrient requirements and a low amount of antioxidants.
Studies have proven that the prevalence of malnutrition increases with age and due to severe injury: The prolonged intake of an imbalanced diet causes symptoms of deficiency. Therefore, the effect of nutritional supplements on the healing of femoral fractures was analyzed. The application of glutamine led to a noticeable improvement of monocytes during fracture healing and to a reduction of the hospital stay of about two days. In intensive care patients, the administration of nutritional supplements has led to a decreased mortality rate. In older patients, the administration of nutrition supplements has led to a noticeable increase of antioxidative enzymes in mononuclear cells. It has been demonstrated that pre-incubation with antioxidants protects the osteoblasts against the detrimental effects of reactive oxygen species (ROS) generated by cigarette smoke. The administration of natural flavonoids even improves the antioxidative defense of the cells.

Title: **The respective role of hypoxia and glucose as determinants of the survival of human**
Author: Petite H
Affiliation: Department of Bone& Joint Bioengeneering and Biomechanics, Université Paris Diderot
City/Country: Paris, France

Abstract:
No abstract available yet

Introductory Session III

Chairman: **Davis** (San Antonio, USA)

Title: **Blast injury – potential implications for regenerative medicine**
Author: Watts S
Affiliation: Combat Casualty Care research programme, British Military Medical Research
City/Country: Salisbury, Wiltshire, UK

Abstract:
Injury from explosive devices is a frequent cause of traumatic injury on the battlefield and may be a problem in the civilian sector as a result of terrorist incidents.
Due to the improvements in pre-hospital care and body armour there are an increasing number of casualties surviving severe battlefield trauma. Many of the casualties will require reconstructive surgery and long-term medical care.
Over the last decade there has been a great deal of investment in technologies relating to prosthetics for example. For those casualties who have undergone limb salvage procedures long-term outcomes are often poor and there has been little focus of research to improve tissue salvage, viability and functionality.
Blast is known to modify the response to haemorrhage and it is known that blast injury to one organ can cause an inflammatory response which 'spills over' to other organs causing secondary damage. In addition work from this laboratory has demonstrated that blast injury per se causes activation and damage to the endothelium with inflammatory consequence to the surrounding tissue.
The presentation will describe the mechanism of blast injury and how blast modifies the response to haemorrhage. Blast effects of specific organs / tissue will be explored along with the implications for exacerbated tissue damage as a result of blast.

Industrial, Regulatory and Socio-Political-Economic Issues

Chairmen: **Gomes** (Guimarães, Portugal), **Volk** (Berlin, Germany)

Title: **Regulation and pharmaceuticalization in cellular therapies**
Authors: Soria B, Gálvez P, Bermejo M, Mateos-Fernández JA, Quesada E, Rodríguez B, Hmadcha A
Affiliation: CABIMER, Andalusian Center fo Molecular Biology and Regenerative Medicine
City/Country: Sevilla, Spain

Abstract:
1.Safety: Clinical trials with human mesenchymal stem cells (hMSC) have increased in recent years. Development and manufacturing of those cellular medicaments have to be carried out under standardized conditions and require an extensive characterization of the cellular component to ensure the quality and safety of final cellular medicine. In this sense the fact that cellular medicaments are "living organisms" that may change their phenotype after interacting with patient fluids represent a new challenge in the obtention, expansion and pharmaceuticalization of the product. In order to ensure patient safety identity, purity, potency, viability, tumourigenicity, quality control and genetic stability of the cells must be studied. Evenmore, we have observed that during the *in vitro* expansion of hMSC chromosomal instability probably due to exposure to pharmaceutical drugs (unpublished).
2.Regulation: Since development of cell therapy medicinal products constitutes an alternative therapeutic strategy to conventional treatments, both the European Medicament Agency (EMA) and the Food and Drug Administration (FDA) have developed a regulatory body by which a "cellular medicament" have to fulfil .
3.Pharmaceuticalization: Manufacturing of hMSC as cell-based products for clinical use should be performed with appropriate controls that ensure safety and quality of the cellular medicine. Control of the risks of contamination by adventitious agents that can affect the quality and safety of cells and patients, thus, it is necessary to implant a quality control program covering the entire procedure of the *in vitro* expansion, from the source of cells, starting materials and reagents, such as intermediate products to the final cellular medicine. Additionally, new package, transport and administration procedures are being developed.

Title: Socio-economic barriers to technology transfer in regenerative medicine
Author: Kohn J
Affiliation: Rutgers University, Armed Forces Institute of Regenerative Medicine
City/Country: Piscataway, NJ, USA

Abstract:
Generally speaking, the effectiveness of the technology transfer process from academic laboratories to commercial entities is difficult to assess, but there seems to be consensus that the process requires fundamental improvements.
This talk will discuss a number of socio-economic barriers that exist in the USA. It must be noted that only some barriers will be highlighted and that the information presented is relevant to the USA and may not be applicable to European or Asian countries.
One example for a cultural barrier is that inventors working at academic institutions are provided with two contradictory messages: On one hand, entrepreneurial activities are recognized as important and desirable, but on the other hand, there is significant institutional mistrust of any commercial activity so that faculty inventors engaging in technology transfer are subject to increased scrutiny and supervision, which in turn tends to discourage faculty from engaging in technology transfer activities. Another important socio-economic barrier to technology transfer is "risk avoidance". In all layers of academic institutions and government, officials are increasingly reluctant to make any risky decision. Risk avoidance has is also become a common investment strategy for venture capital funds and large companies. New regenerative therapies are therefore delayed by a lack of willingness to provide early-stage support, reducing the ability of researchers to obtain solid safety and efficacy data in human patients.
The Armed Forces Institute of Regenerative Medicine (AFIRM) effectively addressed this specific barrier. AFIRM provided extensive follow-up funding designed to advance research breakthroughs into the clinic, resulting in a large number of clinical trials. Thus, AFIRM demonstrated that well-designed government funding strategies can overcome specific barriers. However, AFIRM has not yet brought regenerative products to the market. This is due in part to the increasingly complex and costly regulatory process. In spite of providing clinical trial resources, the regulatory process delayed a number of clinical trials. In the USA, this process is again predominantly shaped by "excessive risk avoidance", even at the cost of denying patients the potential benefits of a new therapy. There are widespread concerns that an "out-of-control" regulatory approval process will become the greatest barrier to medical innovation in the USA.
In summary, as we look into the future, the socio-economic barriers to bringing new regenerative therapies to the patient will be increasing rather than decreasing, making the technology transfer process more difficult, costly, and time-consuming. Government funding strategies must take these barriers into account when supporting the development of regenerative therapies.

Title: CIRM's experience and future directions in product development; implications for the wounded warrior
Author: Feigal EG
Affiliation: California Institute for Regenerative Medicine
City/Country: San Francisco, CA, USA

Abstract:
Advancing science into therapies for patients is a complex and expensive path to travel, and the uncertainty of success, particularly for innovative technologies, makes the funding of the translational steps towards and into the clinic, particularly challenging. This talk will present CIRM's experience in advancing stem-cell based therapies to the clinic, and provide information on the scope of programs, collaborations with investigators, work with the FDA and industry, and future initiatives and funding opportunities to help investigators make progress in their research, and could leverage or serve as a collaborative interface for interactions in areas relevant for the wounded warrior.

This year, California will commemorate the 10th anniversary of the passage of Proposition 71 – the state ballot initiative that led to the creation of the California Institute for Regenerative Medicine (CIRM), a state agency charged with accelerating stem cell research through the dispersal of $3B in funds for stem cell research. Since its launch in 2006, CIRM has helped to build 12 state-of-the art research facilities in California, attracted 130 stem cell biology research leaders to the state, supported training of nearly a thousand scientists and skilled laboratory staff, awarded funding to support over 600 research projects leading to over 1800 published papers, and funded over 90 translational projects. These preclinical proof of concept and development candidates extend across a broad spectrum of therapeutic approaches (namely stem cell products, gene-modified stem cells, small molecules, and biologics), as well as therapeutic areas. Twenty-six of these projects are moving towards or into clinical testing, with two clinical trials already launched and enrolling patients. CIRM expects to advance 10 projects – all with funding initiated within the past four years – into the clinic by the end of 2014. One of CIRM's newest initiatives planned for launch this year is the Alpha Stem Cell Clinics network — envisioned to be a hub for statewide, national and international clinical trials, and eventually, centers of excellence for delivery of approved therapies.

Diagnostic Methods, Biomarkers and Monitoring Techniques

Chairmen: **Walles** (Wuerzburg, Germany), **Marinescu** (Bucharest, Romania)

Title: **Biomarkers in regenerative therapy & immune regeneration in critically ill patients - biomarkers for stratification of ICU patients into risk groups and reconstitution of "immunoparalysis" by immunostimulation of sepsis patients**

Author: Volk HD
Affiliation: Institute of Medical Immunology, Berlin-Brandenburg Center for Regenerative Therapies (BCRT), Charité Universitätsmedizin Berlin
City/Country: Berlin, Germany

Abstract:
No abstract available yet

Title: **Non-invasive optical tools for cell, tissue and organ monitoring**

Author: Schenke-Layland K
Affiliation: Department of Cell and Tissue Engineering, Fraunhofer Institute for Interfacial Engineering and Biotechnology IGB
City/Country: Stuttgart, Germany

Abstract:
No abstract available yet

Title: **Imaging of decellularized and recellularized human dermal matrices by real time non invasive HD-OCT and RCM**

Authosr: Draye JP, Boone MALM, Verween G., Aiti AL, Verbeken G, De Vos D, Rose T, Jennes S, Pirnay JP, Jemec G, del Marmol V
Affiliation: Burn Wound Centre / Laboratory for Molecular and Cellular Technology, Queen Astrid Military Hospital
City/Country: Brussels, Belgium

Abstract:
Patients with severe and extensive burns have limited amount of donor sites. For those patients availability of dermal substitutes could be useful. The purpose of this study was to evaluate the use of noninvasive assessment by High-Definition Optical Coherence Tomography (HD-OCT) and Reflectance Confocal Microscopy (RCM) to characterize the quality of Decellularised Human Dermal Matrices (DHDMs) and repopulated DHDMs by human fibroblasts. Cryopreserved allogenic human skin (0.3-0.4 mm thick), obtained from deceased human donors was used to prepare DHDMs in a two step procedure. To easily remove the epidermis, the allogenic skin samples were first incubated in the presence of either Dispase II or NaCl. The dermal matrices were subsequently incubated either in 0.5% Triton X-100 or in 0.1% Sodium Dodecyl Sulfate. For recellularisation human adult dermal fibroblasts were seeded at a density of 50,000 cells/cm^2 on the DHDMs. After *in vitro* incubation (up to 19 days) the repopulated dermis samples were evaluated by MTT proliferation test, histology and HD-OCT. Treatment by NaCl/Triton X-100 showed to be the most appropriate for the preparation of the DHDMs. It had small impact on collagen and elastic fibers of the DHDMs, and collagen type IV and VII of the epidermal basement membrane were immunodetected. Imaging by HD-OCT and RCM showed that the three dimensional architecture of dermal matrices was well preserved. Histology and MTT test showed that these NaCl/Triton X-100 processed matrices could be repopulated *in vitro* by human dermal fibroblasts. HD-OCT showed that these repopulated matrices were extensively remodelled upon increasing incubation time (up to 19 days) in the presence of fibroblasts. Conclusively, HD-OCT and RCM allow a unique real-time and non invasive imaging of tissue-engineered skin.

Title: **Inflammatory signaling for bone regeneration**
Author: Zreiqat H, Lu Z, Dunstan CR
Affiliation: Faculty of Engineering and IT and Bosch Institute, The University of Sydney
City/Country: Sydney, Australia

Abstract:
Introduction: There is a major medical need for developing novel and effective approaches for repairing non-union and critical-sized bone defects. It is known that inflammation plays a crucial role in initiating bone repair and regeneration with coincidence of inflammation boost at 24 h after bone fracture in response to injury, but its underlying mechanisms remain to be determined. The aims of this study were to investigate whether the duration of exposure to tumour necrosis factor-alpha (TNF-α), one of main inflammatory factors, is crucial for the initiation of bone regeneration and to determine its underlying mechanism(s).

Methods and Results: We demonstrated that short-term (24 hours) TNF-α treatment significantly up-regulated bone sialoprotein and osteocalcin gene expression levels in human primary osteoblasts (HOBs) by day 7. In contrast, continuous TNF-α treatment down-regulated bone sialoprotein and osteocalcin gene expression. In addition, in an indirect co-culture system, HOBs pre-treated with TNF-α for 24 h induced significantly greater osteogenic differentiation in adipose tissue-derived stem cells (ASCs) than the HOBs without TNF-α treatment. We further showed that BMP-2 paracrine loop was involved in TNF-α pretreatment-promoted osteogenic gene expression in HOBs. We further investigated the direct effect of short-term preconditioning with TNF-α on proliferation, mobilization and differentiation of ASCs. We showed that (1): TNF-α pre-conditioning increased proliferation, mobilization, and osteogenic differentiation of ASCs; (2): TNF-α pre-conditioning induced osteogenic differentiation in ASCs partially via a mechanism of extracellular-signal-regulated kinases (Erk)1/2-BMP-2 signaling pathway.

Conclusion: Taken together, we provide evidence that exposure duration is a critical element in determining TNF-α's effects on bone regeneration, and short-term (1-3 days)of TNF-α preconditioning, mimicking the short boost of inflammation normally occurring after bone injury, might serve as a feasible approach for directing stem cells/osteo-progenitor cells into osteogenic differentiation.

Regenerative Laboratory Techniques

Chairmen: **Tuan** (Pittsburgh, USA), **Duda** (Berlin, Germany)

Title: **Bioprinting and development of cell/matrix-based bioinks**
Author: Borchers K
Affiliation: Fraunhofer-Institute for Interfacial Engineering and Biotechnology IGB
City/Country: Stuttgart, Germany

Abstract:
The future vision of implants comprises individually tailored prostheses and even the generation of bio-artificial tissue substitutes generated from the patient's own cells. Thus the research activities in the field of "biofabrication" – fabrication of biocompatible or biofunctional or biobased prostheses and devices – are steadily growing.
In order to mimic biological structures that are composed of various cell types and various types of extra cellular matrix (ECM) we need fabrication processes that do not set any limits to the generation of shapes. Simultaneously, we need matrix-materials that allow for the tailoring of their physical, chemical, and biological properties.
Additive fabrication processes, which built up 3D objects layer by layer due to a 3D digital model, are expected to be of great use for biomedical application as they enable flexible and individual shaping. Making additive technologies accessible for biocompatible and biological materials is one major challenge today.
In our approach we focus on applying biopolymers from the native ECM for the assembly of cell-matrix constructs in order to provide to the cells an environment as close to their natural environment as possible. We use the water soluble form of collagen ("gelatin") as a base for bioinks. Bioinks comprise cells and biopolymer solution that can form ECM-like 3D matrices for the cells in order to support their native functionality.
By chemical modification of the biomacromolecules we can control the gelation behaviour and the viscosity of the solution such that they can be dispensed by drop-on demand inkjet printing.
Additionally, modified gelatin can be chemically crosslinked to form stable hydrogels with adjustable stiffness and swellability, thereby mimicking the mechanical properties of different types of tissue.

Title: **Bioreactors - towards physiologically relevant *in vitro* cell cultivation**
Authors: Charwat V, Kasper C
Affiliation: Department of Biotechnology, University of Natural Resources and Life Sciences, Vienna
City/Country: Vienna, Austria

Abstract:
ESTROT (European Society of Tissue Regeneration in Orthopaedics and Trauma) is a medical-scientific society in the field of Orthobiology recognized by EFORT (European Federation of National Associations of Orthopaedics and Traumatology); it includes all national societies of Orthopedics and Traumatology and therefore it represents 31 countries in Europe and others around the world. It is a non-profit organisation whose main objectives are: to relieve sickness in musculoskeletal disorders, to cover all matters relating to the progress and development of the field of tissue regeneration, to ensure the highest possible standards of management for the musculoskeletal patient requiring a regenerative approach to restore function of the affected limb, to educate the community in general, medical practitioners and associated professionals in particular in the most effective methods of tissue restoration of the injured patient, to promote and support advances in regenerative approaches for restoration of loss of hard and soft tissue, to encourage, develop and support evidence based regenerative treatment approaches, to guide European Tissue Regeneration Policies and to guide alliances of similar organizations from other continents.
Regenerative Medicine is being increasingly utilized in Orthopedic surgery in both civilian and military field. Nowadays soldiers are highly trained and qualified. Being able to recover them from trauma, bone loss, bone and joint infections avoiding amputations and giving the best care is strategic. With innovative treatments we can heal extremely severe cases through regenerative medicine. Utilizing biotechnologies as stem cells, growth factors, bone and cartilage substitutes, in respect of the scientific guide-lines, it is possible to regenerate large loss of substance and expecially it dresses well in the treatment of critical size bone defects. However, when the patient's conditions and the injury are so severe that regeneration is not suitable, it is possible to implant new prosthesis that allow the surgeon to replace entire limbs. Thanks to these megaprosthesis, also in patients infected and who have lost entire skeletal segments, it is possible to return them to function and mobility. This is definitely strategic from the military and civil point of view.

Title: **New modular system for generation of antigen-specific T-cells for adoptive therapy**
Author: Volk HD
Affiliation: Institute of Medical Immunology, Berlin-Brandenburg Center for Regenerative Therapies (BCRT), Charité Universitätsmedizin Berlin
City/Country: Berlin, Germany

Abstract:
No abstract available yet

Title: **Large animal modeling in regenerative medicine: application examples**
Author: Ferrara F
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City/Country: Leipzig, Germany

Abstract:
Experimental *in vivo* studies on novel paradigms in regenerative medicine often rely on well-established rodent models. Particularly in the field of stroke research, those models have not accurately predicted the impact of such paradigms in subsequent clinical trial. The reasons for this are considered numerous, but may also include the primary use of lissencephalic rodent species. Primate models are restricted to a number of highly specialized centres and are increasingly perceived as ethically challenging. Next to those, a number of alternative models have been established including ovine stroke models featuring transient or permanent middle cerebral artery occlusion. These models may not only overcome limitations of animal models featuring lissencephalic brains, but may also provide additional benefits with respect to the application of clinically relevant imaging technology. This presentation will review the rationale for applying these models and will describe their utilization by selected application examples, highlighting advantages and limitations of large animal neurological research.