# Final Report on “Bone Stem Cells”
# a European Science Foundation Workshop
# "Regenerative Medicine" (REMEDIC) Research Networking Programme
# 8-10 October 2009, Bertinoro (Forlì), Italy

SUMMARY

The Workshop “Bone Stem Cells” was organized in Bertinoro (Italy) on October 8-10 2009, at the same time of the Meeting of the Steering Committee of the Research Networking Programme (RNP) on Regenerative Medicine (REMEDIC). The Workshop was specifically targeted to PhD students and young researchers. The participants, including the scientific secretarial staff, were 54 from 12 European countries, with three high-level invited speakers (T. Mitsiadis, Zürich, CH, “Tooth repair and formation using stem cells: lesson from embryogenesis”; L. Di Silvio, London, UK, “Stem cells for bone regeneration: is there hope or is it all hype?”; M. Dominici, Modena, I, “Mesenchymal stem cells between regeneration and destruction”). Two more lectures were given by members of the Steering Committee of REMEDIC (D. Pioletti, Lausanne, CH, “Biomechanical aspects in the development of bone tissue engineering; K. Le Blanc, Stockholm, Sweden, “Mesenchymal stem cells as treatment of graft-versus-host disease”). Y. Konttinen (Helsinki, Finland), E. Gòmez Barrena (Madrid, Spain) and G. Van Osch (Rotterdam, NL) from REMEDIC had also a role as chairpersons.

The Workshop was carried out jointly with the European Orthopaedic Research Society (EORS), which was particularly interested to the feasibility and consequences of stem cell research in bone engineering.

The Workshop was aimed to answer to some questions that should be clarified before the basic biological knowledge is translated into the clinical field: the most suitable source of stem cell for bone regeneration, specific markers for the identification of adult bone stem cells, the best in vitro and in vivo models, the orthopaedic indications and the possible contraindications and side-effects.

Moreover, the Workshop was specifically intended to serve as a forum for young investigators that are actively involved in bone stem cell research, with the aim of launching and encouraging a pluralistic and informative debate.

The principal topics of the Workshop were

- isolation, differentiation and characterization of bone stem cells
- stem cell strategies for bone engineering
- stem cell strategies for tooth engineering
- clinical indications for stem cell therapies in orthopaedics

Each topic was introduced by an overview lecture, where the most recent knowledge has been exposed and indications were given for the future research.

The presentations from young researchers and PhD students were 40, previously selected by the Steering Committee of REMEDIC on the basis of the curriculum and of the scientific quality of the abstract. On the same basis, the Steering Committee of REMEDIC assigned 20 travel grants.

Most presentations concerned on isolation, differentiation and characterization of bone stem cells and strategies for bone engineering. The difference between bone marrow cells and alternative sources of human stem cells, derived from adipose tissue, umbilical cord, umbilical blood and placenta were object of presentations and discussion.

Stem cell strategies for tooth engineering were treated in the lecture of prof. Mitsiadis and in presentations concerning a clinical trial with dental pulp stem cells and the use of these cells as models for studying the induction towards neural and astrocytic growth pathways.

One session was devoted to the orthopaedic application. In this session, the BMP trascriptional activity during fracture healing was treated, and clinical indications were proposed for the use of autologous bone marrow stromal cells mixed with platelet rich plasma and bone allografts.

DESCRIPTION OF THE SCIENTIFIC CONTENT OF AND DISCUSSION AT THE EVENT

The Workshop "Bone Stem Cells" was organized within the framework of the Research Networking Programme on Regenerative Medicine (REMEDIC), managed by the European Science Foundation. One of the aims of REMEDIC is to promote the exchange of ideas and know-how across disciplines in the area of mesenchymal (stromal) and other stem cells. Remedic supports EU-wide co-operation in regenerative medicine to produce new knowledge and innovation, and promotes its dissemination through seminars and schools. The Workshop was carried out jointly with the European Orthopaedic Research Society (EORS), which was particularly interested to the feasibility and consequences of stem cell research in bone engineering.

The Workshop was aimed to contribute to clarify many issues still existing on the use of stem cells for bone regeneration.

A few objects of discussion were: the most suitable source of stem cell for bone regeneration, specific markers for the identification of adult bone stem cells, the best in vitro and in vivo models, contraindications and side-effects of stem cells use in orthopaedic indications.

Each topic was introduced by an overview lecture, where the most recent knowledge was exposed and indications were given for the future research.

Following the overview lecture, the presentations from young researchers and PhD students, selected by the Steering Committee of REMEDIC, were discussed. The participants, including the scientific secretarial staff and 3 invited speakers, were 54 from 12 European countries (32 from Italy, 3 from Finland, 2 from The Netherlands, 3 from UK, 3 from Denmark, 1 from Belgium, 3 from Germany, 2 from Spain, 2 from Switzerland, 1 from Portugal, 1 from Romania, 1 from Hungary). Contemporaneously to the Workshop, also the meeting of the Steering Committee of REMEDIC was held; the members of the Steering Committee, which were more involved in bone stem cell research, had also a role in the Workshop as invited speakers or chairpersons.

**Session 1** was introduced by prof. Pioletti (Lausanne, Switzerland), a member of the Steering Committee of Remedic. The lecture, "Biomechanical aspects in the development of bone tissue engineering", concluded that not only the biomechanical analysis, but a multi-level approach is necessary to design an orthopaedic scaffold that links the external loading to the mechanical stimulus transmitted at the cell surface.

The selected presentations of the young researchers focused on new scaffolds for bone engineering and on predictive parameters for the osteogenic differentiation of human mesenchymal stem cells. Cama G. (Genoa, Italy) described the synthesis and the characterization of a new macroporous brushite bone cement, where the osteoblast cell line MG63 was able to adhere and spread. An innovative material, containing boron nitride nanotubes, was proposed as a non-viral vector to convey electrical/mechanical signals to cellular systems through their piezoelectric properties (Danti S., Pisa, Italy). Bidimensional systems for the osteogenic differentiation of human embryonic stem cells (hESC), bone marrow stromal cells (BMSC) and adipose tissue derived cells were compared with 3D microcarriers (Declercq H, Ghent, Belgium). The 3D cultures, formed by the differentiated cell seeded on microcarriers, were encapsulated in a bone defect. ESC- and adipose tissue derived cells on microcarriers induced a heterogeneous bone formation, which was limited to specific areas.

Janicki P (Heidelberg, Germany) identified parameters able to predict the ability of human MSC to form bone in vivo. BMSC, mixed with beta-tricalcium phosphate granules and fibrin glue, were subcutaneously implanted into immunodeficient mice. A low generation time prior to transplantation and high ALP activity during osteogenic differentiation in vitro correlated positively to ectopic bone formation in vivo. In contrast, slowly growing MSC had not the ability to survive inside the host and to differentiate into osteoblasts. The amount of deposited mineralized matrix in vitro did not correlate with the capability to form bone in vivo.

In **Session 2** (chairperson Ciapetti G, Bologna, Italy), innovative scaffolds for the osteogenic differentiation of MSC were discussed: high porosity hydroxyl-apatite (Manfrini M, Ferrara, Italy), a composite formed with poly-epsilon-caprolactone and hydroxyapatite particles, previously coated with sucrose (Lazzarini E, Genoa, Italy), a self-mineralizing porous scaffold based on high density chitosan and polyvynil-pyrrolidone loaded with calcium and phosphate (Palazzo B, Brindisi, Italy), and a porous beta-metacalcium phosphate scaffold incorporating bone mineral protein-7 (BMP-7) and platelet derived growth factor (PDGF) (Buranawat B, London, UK).

**Session 3** was introduced by the lecture of prof. Mitisiadis (Zurich, Switzerland): "Tooth repair and formation using stem cells: lesson from embryogenesis".

The presentations concerned on alternative sources of osteogenic cells, such as mesenchymal stem cells isolated from umbilical cord blood or amniotic fluid (Marzorati S, Monza, Italy) or from Wharton's jelly of umbilical cord (Torreggiani E, Ferrara, Italy). They were demonstrated to be good sources for bone repair and regeneration, even if some peculiar differences with BMSC were observed, which should be further considered before the clinical application.

Adipose-derived stem cells are a relatively new source of osteogenic cells. A continuous adipose stem cell line derived from mice displayed a stem-mesenchimal phenotype and was able to differentiate into osteoblasts on titanium scaffolds (Mele S, Novara, Italy).

Adipose-derived stem cells were investigated to assess the effect of strontium ranelate on osteoblast differentiation (Tognarini I, Florence, Italy). Strontium ranelate, a drug used in the osteoporosis treatment, increased the OPG/RANKL ratio, consistent with osteoclastogenesis inhibition.

In **Session 4** (chairperson Konttinen Y, Helsinki, Finland), the use of adipose-derived stem cells was further discussed. They differentiated into osteoblasts when seeded on nanostructured Ti6Al4V and TI13Nb13V (Marini F, Florence, Italy).

Other presentations focused on the role of integrins in osteoblast differentiation. The downregulation of alpha11beta1 integrin reduced adhesion, spreading, migration and survival rates of MSC on collagen I-coated surfaces (Docheva D, Munich, Germany). Mechanical stimulation of beta1-integrin receptors of human BMSC induced an immediate transient activation of the PI-3K/Akt signalling pathway and an increased expression of vascular endothelial growth factor (VEGF) and of the chondrogenic marker Sox9 (Kasten A, Rostock, Germany).

A presentation showed preliminary data on the ability of human MSC to form bone in vivo via endochondral ossification. Bone formation can occur via the endochondral route following in vitro chondrogenic priming of human mesenchymal stem cells (Both S, Nijmegen, the Netherland).

**Session 5** was introduced by the lecture of prof. Le Blanc (Stockholm, Sweden) "Mesenchymal stem cells as treatment of graft-versus-host disease". In patients with malignant blood diseases, the cotransplantation of MSC and hematopoietic stem cells from HLA-matched donors suppressed the immunological response responsible for graft-versus-host disease (GVHD).

Lacza Z (Budapest, Hungary) standardized a method for seeding MSC from bone marrow or from dental pulp on lyophilized bone allografts with a rotating bioreactor and a pre-incubation with fibronectin, albumin, fetal calf serum or collagen I solutions.

Other two presentations focused on stem cells from dental pulp. Egbuniwe O (London, UK) characterized a dental pulp stem cell model in order to investigate not only odontoblast differentiation, but also the induction towards neural and astrocytic growth pathways. D'Aquino R (Naples, Italy) presented the preliminary results of a clinical trial where dental pulp was implanted in mandible bone defects together a collagen sponge. The lamellar bone at the injury site completely regenerated and the bone defect was wholly restored.

Krattinger N (Lausanne, CH) standardized the culture conditions of human bone foetal cells: they differentiated into mature osteoblasts without the supplementation with beta-glycerophosphate, while PDGF and fibroblast growth factor-2 increased the proliferation rate and dexamethasone increased alkaline phosphatase (ALP) activity.

The topic of **session 6** (chairperson Gòmez-Barrena E, Madrid, Spain) were the preclinical models and the clinical application of bone stem cells. A promising preclinical model for cellular therapy in osteogenesis imperfecta. was presented by Panaroni C (Milan, Italy). The model consisted in knock-in osteogenesis imperfecta mice carrying the α1(I)-Gly349Cys substitution (BrtlIV mice) with a dominant transmission, which induces moderately severe and lethal osteogenesis imperfecta. Adult bone marrow cells from CMV/eGFP CD-1 transgenic mice were intrauterine transplanted in pregnant wild type females crossed with BrtlIV heterozygous males. The transplantation eliminated the perinatal lethality of heterozygous BrtlIV mice, which synthesized up to 20% of type I collagen and had significant improvement of bone density. Therefore, *in utero* transplantation can be considered as a promising approach for the treatment of osteogenesis imperfecta.

Doomberg J (Amsterdam, The Netherlands) evaluated the physiological spatio-temporal pattern of BMP signaling during bone healing in an established murine tibia fracture model. The application of an external fixator without creating a tibia fracture resulted in decreased signaling of mechanically induced BMP transcriptional activity. After creating fractures, an initial decrease in BMP transcriptional activity was shown, followed by an increased BMP signaling.

The presentation of Rani N (Bologna, Italy) concerned on orthopaedic indication of BMSC. Clinical trials are in progress involving the application of autologous BMSC mixed with platelet gel and lyophilized bone allografts in osteonecrosis of the femoral head and nonunions.

Patella S (Bari, Italy) observed that platelet rich plasma previously treated with shock waves better improved mouse osteoblast proliferation and differentiation in vitro.

**Session 7** was introduced by the lecture of prof. Di Silvio (London, UK) “Stem cells for bone regeneration: is there hope or is it all hype ?”. The properties of stem cells were resumed, as well as the advantages and the drawbacks of adult and embryonic cells. The role of stem cells in bone engineering was discussed, with particular emphasis to the scaffold vascularization. Co-cultures of MSC and endothelial cells in porous calcium-phosphate scaffolds were presented, and the methods for distinguish the contribute of each cell type were described. The clinical application of strategies combining cells, matrices/scaffolds and inductive stimula requires a suitable source of stem cells, the knowledge about the basic mechanism of differentiation, the development of a system for cell delivering and the clear identification of the pathological conditions that may have benefits from this treatment.

The following presentations concerned on suitable scaffolds for MSC adhesion and growth, such as composites made of electrospun fibers of poly-L-lactic acid loaded with nanoparticles of hydroxyapatite (Vadalà G, Rome, Italy), multilayer polycaprolactone and poly-l-lactide (PLA) micron-size 3D-scaffolds with chitosan/polyethylene oxide and PLA nano-size fibres (Ainola M, Helsinki, Finland), collagen type I and β-tricalcium phosphate cross-linked scaffolds (Oprita J, Bucharest, Romania).

Bertoldi S (Milan, Italy) described an alternative source of bone stem cells. Placenta-derived stem cells were able to differentiate into osteoblasts. When seeded scaffolds on polyurethane foams coated or not with α-tricalcium phosphates, chorion mesenchymal cells seemed to colonize better than amnion cells.

In **Session 8** (chairperson Van Osch G, Rotterdam, The Netherlands), preliminary results on isolation and characterization of cells derived from the intervertebral disc were described, in order to obtain models for the study of disc degeneration (Di Gesualdo, Firenze, Italy). Narcisi R (Genoa, Italy) investigated the role of transforming growth factor-beta (TGF-beta) in chondrocyte cultures. Human articular chondrocytes, expanded in the presence of TGF-beta 1 and transferred in 3D cultures acquired a pre-hypertrophic phenotype. However, if the same cells were osteoinducted, they strongly mineralized and displayed increased levels of osteogenic markers. Roseti L (Bologna, Italy) described how the knowledge in bone engineering is transferred to the clinical practice. The organization of a production facility for the preparation of engineered constructs for cartilage and bone, according to the EU guidelines of "Good Manufacturing Practices", was presented. Rasini V

(Modena, Italy) focused on the standardization of immunohistochemistry techniques on paraffin embedded mouse bone specimens, to be applied to in vivo models.

**Session 9** was introduced by the lecture of Dominici M (Modena, Italy) "Mesenchymal stem cells between regeneration and destruction".

The following presentations focused on molecular aspects of bone cells. Saeed H (Odense, Denmark) described the role of telomerase in maintenance of stem cell functions. Lamghari M (Porto, Portugal) studied the role of the neuropeptide Y1 receptors in bone generation. This nuropeptide receptor may be considered to mediate the effects of nervous system on bone metabolism. Alessio N (Naples, Italy), through the silencing of the ATPase subunit of SWI/SNF (BRG1), induced a significant increase of senescence and a decrease of apoptosis of MSC. Lozano D (Madrid, Spain) evaluated the role of N- and C-fragments of parathyroid hormone related protein (PTH-rP) in diabetes-related osteopenia. Both fragments restored the osteogenic phenotype in cultures of mouse MSC, which had been previously compromised by high concentrations of glucose.

Also the presentations of **session 10** (chairperson Baldini N, Bologna, Italy) concerned on the analysis of molecular aspects of bone cells. Chen L (Odense, Denmark) demonstrated that dlk1 gene and the secret form of Dlk1 protein (FA1) inhibited chondrogenic cell differentiation probably through the suppression of Akt activation. With microarray analysis, Baglio R (Bologna, Italy) found that 232 genes were differentially expressed during the phases of osteoblastogenesis, from the BMSC isolation to mineralization. Qiu W (Odense, Denmark) revealed a novel function of TNFRSF19 in determining cell fate of human MSC through Wnt and C/EPB. Squillaro T (Siena, Italy) demonstrated that the downregulation of MECP2 protein, a regulator of chromatin status, induced arrest of the cells cycle in MSC. This result could provide new insights on Rett syndrome, caused by a mutation of MECP2 gene.

A poster presented by Kauppinen K (Oulu, Finland) described a new technique based on focused ion beam/scanning electron microscopy, in which the electron and ion beams are focused in the same point of the sample, which can be successfully applied in imaging of the hard/soft material interfaces, such as bone/osteoblast and implant/new bone interfaces.

A feedback form was given to all participants, to survey the quality of the event. Ten filled forms were returned. The positive aspects of the workshop were considered the variety of the topics of bone biology which were faced, the different skills and expertise of the researchers; the high competence and the interdisciplinary of contributions; the clear and interesting keynotes; the long time for discussion and the high interaction among participants. Also the specific targeting for young researchers and phD students was considered a positive aspect, as well as the informal ambient that helped to exchange information. At last, the travel grants for young students were particularly appreciated. Only a participant complained of the very poor participation of professors in general. However, everybody would recommend the workshop to their colleagues. Some changes could have improved the workshop: a more general keynote about stem cells biology (i.e. about markers for differentiation and gene expression), and a longer length of key-notes. Accommodation was excellent for 8 participants and good for the other 2. The judgement on the single sessions was constantly excellent or good, except for session 5 and 7 (fair 1/10).

## ASSESSMENT OF THE RESULTS AND IMPACT OF THE EVENT ON THE FUTURE DIRECTION OF THE FIELD

*Assessment of the results*

The aim of the Workshop was to elucidate some critical aspects of bone engineering, such as the most suitable source of stem cell for bone regeneration, specific markers for the identification of adult bone stem cells, the best in vitro and in vivo models, the orthopaedic indications and the possible contraindications and side-effects. Moreover, the workshop was specifically intended to launch and encourage a pluralistic and informative debate among young and senior researchers interested in the feasibility and consequences of stem cell application in the orthopaedic field.

As source of stem cells, adult bone marrow cells are generally used by most researchers and also by orthopaedic surgeons in clinical studies so far. However, their limited developmental potential and the loosening of their ability to proliferate and differentiate with time may represent drawbacks for clinical applications. Embryonic stem cells have infinite lifespan and unlimited supply but present ethical problems. Stem cells from cord blood or from amniotic fluid are promising alternatives but need a better knowledge of the differences with bone marrow cells. Adipose tissue derived cells have been better investigated and could represent a useful source for bone engineering, even though some differences with bone marrow cells should be taken into account. Foetal osteoblasts could have both the advantages of a larger availability than adult bone marrow cells and less ethical problems than embryonic cells, but also this model requires further characterization.

About the specific markers of osteogenic differentiation, the cues should be focused to informs a stem cell to move from an uncommitted state into a more committed phenotype. The comparison of in vitro and in vivo data is necessary. In fact, some well-known in vitro markers, such as the demonstration of a mineralized matrix, did not correlate with the capability to form bone in vivo.

Many in vitro models have been presented; some of these models tried to standardize culture conditions. In vivo models for bone engineering were not particularly discussed. The use of knock-out mice and GFP reporter transgenic mice can be useful in investigate particular pathways.

Only few presentations concerned on orthopaedic applications. The clinical use of rhBMP may be hampered by the lack of a clear knowledge of the spatio-temporal pattern of BMP signaling during bone healing. Researches in progress could elucidate this aspect in a next future. A presentation concerned on the use of platelet rich plasma to improve the effects of bone marrow stromal cells, particularly in nonunions and in osteonecrosis of the femoral head. Other orthopaedic applications could be object of clinical trials in the next years, when the scaffold design will be improved and further knowledge on stem cells will be reached. However, large-scale applications should taken into account the issue of resource allocation, particularly when conventional treatments are available. Also dental applications of pulpal stem cells are in progress. In the future, an innovative clinical application of stem cells could be the treatment of intervertebral disc degeneration, but the research in this field is only at the beginning. However, the applications which forecast the implant of a cell-seeded scaffold in patients must taken into account the EU rules for cellular therapy, particularly the regulation to perform all manipulations in a clean room, according to the cGMP guidelines. Particular applications of MSC are the in utero transplantation for the treatment of genetic bone diseases and the cotransplantation with hematopoietic stem cells in blood malignancies to prevent the graft versus host disease.

Another aim of the Workshop was to encourage a pluralistic and informative debate among young and senior researchers interested in stem cell application in the orthopaedic field. A heated debate, run by the young researchers, constantly followed the scientific presentations, and informal discussions were present out of the scientific sessions, which may favour the generation of a network of scientific collaborations in Europe.

*Impact of the event on the future direction of the field*

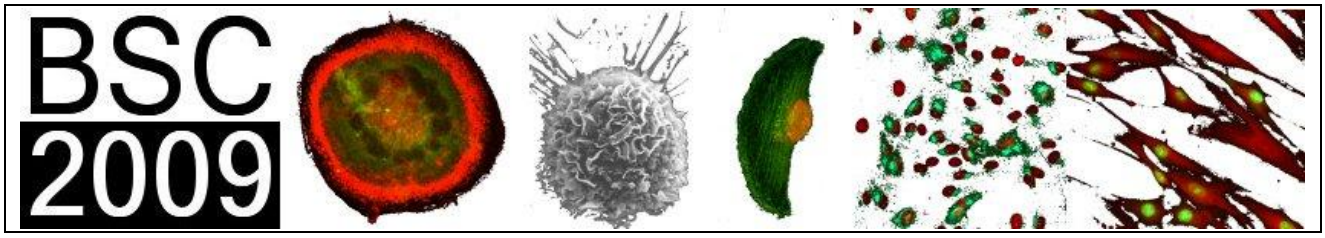
The young researchers attending the Workshop have increased their knowledge on bone stem cells, also for the interdisciplinary of the event that allowed the comparison of different competences. This newly acquired knowledge will be transferred to their Labs and probably will affect their future work. The lecture of prof. Le Blanc "Mesenchymal stem cells as treatment of graft-versus-host disease" has opened up new horizons to scientists that are not skilful in bone marrow transplantation for blood malignancies. In fact, immunological aspects of MSC and their interaction with haematopoietic stem cells are seldom considered by the researchers in bone engineering field. Another application of bone stem cells which is less known is their use for intrauterine treatment in genetic bone diseases, such as osteogenesis imperfecta.

Most presentations concerned on basic research, that is fundamental for bone stem cells knowledge, limited so far especially for the markers of osteogenic differentation that should have the same meaning in vitro and in vivo. Actually basic research, after having consolidated some fundamental aspects of osteogenesis, tends towards the study of molecular pathways that can explain the behaviour of stem cells, particularly the mechanism that reduce their ability to proliferate and differentiate with time. We do not know the role of many genes involved in osteogenesis. A presentation showed the differential activation of over 200 genes during osteoblast differentiation in vitro. Only 76 genes were related to specific steps of osteogenic differentiation or to correlated processes, such as angiogenesis, cell communication, or development, but the involvement in osteogenesis was not known for more than 100 genes. The study of these genes could give further information on bone development.

Few reports described clinical trials, even though the event had been largely disseminated among orthopaedic surgeons. Probably EU rules for cellular therapy, needed for reducing the risk for the patient, may limit the number of clinical trials, because specialized production facilities are required to perform all manipulations in GMP.

About the training element, the organization of the Workshop left a wide share to young researchers, even though under the supervision of seniors which chaired the sessions and gave the lectures. In such a way, young researchers generally showed a profound knowledge of the subject and took interest also to other aspects of bone stem cells. A high scientific value was present in most reports.

In order to discuss more deeply bone stem cell biology, among the topic of the Workshop a lower prominence was given to other components of tissue engineering, i.e. scaffold and inductive signals. These two subjects were secondary treated, the scaffolds as a support for stem cell adhesion and proliferation, and inductive signals as modulators of differentiation. Likewise, other topics related to osteogenesis, such as vascularization and pericyte biology, were not treated during the Workshop. Owing their importance for the clinical application, all these subjects should be specifically discussed in next seminars or workshops.




# Bone Stem Cells

## A European Science Foundation Workshop

"Regenerative Medicine" (REMEDIC) Research Networking Programme

*8-10 October 2009, Bertinoro (Forlì), Italy*

EUROPEAN SCIENCE FOUNDATION
SETTING SCIENCE AGENDAS FOR EUROPE

EUROPEAN ORTHOPAEDIC RESEARCH SOCIETY

## Faculty

**Nicola Baldini**, Dept. of Human Anatomy and Musculoskeletal Pathophysiology, University of Bologna & Istituto Ortopedico Rizzoli, Bologna, Italy
**Lucy Di Silvio**, King's College London, UK
**Massimo Dominici**, Laboratory of Cell Biology and Advanced Cancer Therapies, Dept. of Oncology, Hematology and Respiratory Diseases, University of Modena & Reggio Emilia, Modena, Italy
**Enrique Gómez-Barrena**, Universidad Autónoma de Madrid and Hospital Fundación "Jimenez Diaz", Madrid, Spain
**Yrjö T. Konttinen**, Dept. of Medicine, University of Helsinki, Finland
**Katarina Le Blanc**, Division of Clinical Immunology, Karolinska Institute, Stockholm, Sweden
**Thimios Mitsiadis**, Institute of Oral Biology, University of Zürich, Switzerland
**Dominique Pioletti**, Laboratory of Biomedical Orthopaedics, École Polytechnique Federale de Lausanne, Switzerland
**Gustav Steinhoff**, Dept. of Cardiac Surgery, Medical Faculty, University of Rostock, Germany
**Gerjo JVM Van Osch**, Connective Tissue Cells and Repair Group, Dept. of Orthopaedics & Otorhinolaryngology, Erasmus MC, University Medical Center Rotterdam, The Netherlands

## Local Organizing Committee

**Nicola Baldini**, University of Bologna & Istituto Ortopedico Rizzoli, Bologna (Chair)
**Sofia Avnet**, Istituto Ortopedico Rizzoli, Bologna
**Elisabetta Cenni**, Istituto Ortopedico Rizzoli, Bologna
**Francesca Perut**, Istituto Ortopedico Rizzoli, Bologna
**Manuela Salerno**, Istituto Ortopedico Rizzoli, Bologna

## ESF-REMEDIC Steering Committee

**Yrjö T. Konttinen**, Biomedicum Helsinki, Finland (Chair)
**Gerjö van Osch**, Erasmus University Medical Center, Rotterdam, The Netherlands (Vice-Chair)
**Reinhold G. Erben**, Institute of Pathophysiology, Vienna, Austria
**Kristina Arvidson**, University of Bergen, Norway
**Enrique Gómez-Barrena**, Hospital Fundación "Jimenez Diaz", Madrid, Spain
**Moustapha Kassem**, University Hospital of Odense, Denmark
**Katarina Le Blanc**, Karolinska University, Hospital Huddinge, Stockholm, Sweden
**Frank Luyten**, University of Leuven (K.U. Leuven), Belgium
**Gustav Steinhoff**, Medical Faculty, University of Rostock, Germany
**Eva Syková**, Academy of Sciences of the Czech Republic, Prague, Czech Republic
**Ana Paula Pêgo**, Institute of Biomedical Engineering (INEB), University of Porto, Portugal
**Dominique Pioletti**, École Polytechnique Federale de Lausanne, Switzerland
**Laurentiu Popescu**, Academy of Medical Sciences, "V. Babes" National Institute of Pathology Bucharest, Romania
**Ivo Vanicky**, Institute of Neurobiology, Slovak Academy of Sciences, Kosice, Slovakia
**Ms. Eija Kaila**, Biomedicum Helsinki, Finland (Coordinator)
**Isabel Varela-Nieto**, Consejo Superior de Investigaciones Cientificas (CSIC), Instituto Investigaciones Biomedicas "Alberto Sols", Madrid, Spain (EMRC Rapporteur)
**Maria Manuela Nogueira** (European Science Foundation, Science Officer)
**Blanche Facchini** (ESF Administrator)

***Thursday 8 October***

**9:00-9:20** **Dominique Pioletti** (Lausanne, CH)
Biomechanical aspects in the development of bone tissue engineering.

## Session 1

Chairperson: Dominique Pioletti

9:20 Cama G (Genova, I)
Macroporous brushite bone cement.

9:45 Declercq H (Ghent, B)
2D and 3D differentiation of human stem cells for bone tissue engineering.

10:10 Janicki P (Heidelberg, D)
Prediction parameters for the functional suitability of human mesenchymal stem cells for ectopic bone formation.

10:35 Danti S (Pisa, I)
Osteoblast function/differentiation modulated by intracellular nanotransducers based on piezoelectric nanotubes.

**11:00-11:30 coffee-break**

## Session 2

Chairperson: Gabriela Ciapetti

11:30 Manfrini M (Ferrara, I)
Adhesion and proliferation of human mesenchymal stem cells are influenced by different biomaterials.

11:55 Lazzarini E (Genova, I)
A model of bioinspired composite material with improved bone forming efficiency.

12:20 Palazzo B (Novara I)
Self-mineralizing polymer based porous scaffolds for bone tissue engineering.

12:45 Buranawat B (London, UK)
A biomimetic bone scaffold for potential use as a carrier for stem cells.

**13:10-14:10 lunch**

**14:10-14:30** **Katarina Le Blanc** (Stockholm, S)
Mesenchymal stem cells as treatment of graft-versus-host disease

## Session 3

Chairperson: Katarina Le Blanc

14:30 Marzorati S (Monza, I)
Characterization of different mesenchymal stromal cells isolated from umbilical cord blood (UCB-fMSC), amniotic fluid (AF-fMSC) and bone marrow (BM-MSC) and comparison of their osteogenic potential.

14:55 Torreggiani E (Ferrara, I)
Mesenchymal stem cells from Wharton's jelly: encapsulation in alginate microbeads and osteogenic differentiation.

15:20 Tognarini I (Firenze, I)
Strontium-inducing adipose tissue mesenchymal stem cells: effects on differentiation into osteoblastic phenotype.

15:45 Mele S (Novara, I)
Proliferation and differentiation potential of mouse adipose derived stromal cells on titanium scaffolds.

**16:10-16:40 coffee-break**

## Session 4

Chairperson: Yrjö Konttinen

16:40 Docheva D (München, D)
Mesenchymal stem cells "face-to-face" with the bone matrix: the role of α11β1 integrin.

17:05 Kasten A (Rostock, D)
Stimulation of VEGF expression due to mechanical β1-integrin stress.

17:30 Marini F (Firenze, I)
Adipose tissue derived mesenchymal stem cells: effects of two nanostructured titanium alloys on osteogenic differentiation.

17:55 Both S (Nijmegen, NL)
Endochondral bone formation by human mesenchymal stem cells.

**20:00 Dinner**

***Friday, 9 October***

**9:00-9:20** **Thimios Mitsiadis** (Zürich, CH)
Tooth repair and formation using stem cells: lesson from embryogenesis

## Session 5

Chairperson: Thimios Mitsiadis

9:20 Lacza Z (Budapest, H)
Development of a single-step procedure for a human bone graft containing bone allograft and autologous mesenchymal stem cells.

9:45 Egbuniwe O (London, UK)
Human dental pulp stem cells as models for studying potential nerve regeneration.

10:10 D'Aquino R (Napoli, I)
Repair of human mandible bone defects by the grafting of dental pulp stem cells and collagen sponge biocomplexes: a successful clinical study.

10:35 Krattinger N (Lausanne, CH)
Effects of culture conditions on the proliferation capacity of bone human fetal cells.

**11:00-11:30 coffee-break**

## Session 6

Chairperson: Enrique Gómez-Barrena

11:30 Panaroni C (Milano, I)
In utero transplantation of adult bone marrow decreases perinatal lethality and rescues the bone phenotype in the knock-in murine model for classical, dominant osteogenesis imperfecta.

11:55 Doornberg JN (Amsterdam, NL)
Real time monitoring of BMP smads transcriptional activity in bone during fracture healing treated with an external-fixator.

12:20 Rani N (Bologna, I)
Treatment of nonunion in long bones using platelet gel and packed autologous stromal cells.

12:45 Patella S (Bari, I)
Shock waves on human platelet-rich plasma (PRP) and osteoblasts.

**13:10-14:10 Lunch**

**14:10-14:30** **Lucy Di Silvio** (London, UK)
Stem cells for bone regeneration: is there hope or is it all hype?

## Session 7

Chairperson: Lucy Di Silvio

14:30 Vadalà G (Roma, I)
Poly-l-lactic/hydroxyapatite electrospun nanocomposite induces chondrogenic differentiation of mesenchymal stem cells.

14:55 Ainola M (Helsinki, FIN)
Bioactive 3D tissue-engineering product for cartilage/bone repair.

15:20 Bertoldi S (Milano, I)
Ability of Polyurethane Foams to Support Placenta-Derived Stem Cells Proliferation and Differentiation into the Osteoblastic Lineage

15:45 Oprita EI (Bucharest, R)
Collagen/nano-β-TCP cross-linked scaffolds for human mesenchymal stem cells used in bone tissue engineering.

**16:10-16:40 coffee-break**

## Session 8

Chairperson: Gerjö Van Osch

16:40 Di Gesualdo F (Firenze, I)
A novel candidate gene therapeutic and mesenchymal stem cell-derived chondrocytes as possible tools against intervertebral disc degeneration.

17:05 Narcisi R (Genova I)
The presence of transforming growth factor-β1 induces the endochondral phenotype switching on cultured human articular chondrocyte.

17:30 Roseti L (Bologna, I)
Autologous chondrocyte-based therapy for the repair of cartilage damages.

17:55 Rasini V (Modena, I)
Multiparametric immunohistochemical approaches to detect bone proteins on paraffin embedded specimens in a mouse model.

**20:00 Dinner**

## Saturday 10 October

**8:30-8:50** **Massimo Dominici** (Modena, I)
Mesenchymal stem cells between regeneration and destruction.

## Session 9

Chairperson: Massimo Dominici

8:50 Saeed H (Odense, DK)
Telomerase deficiency leads to decreased bone mass and impaired mesenchymal stem cells (MSC) and osteo-progenitors functions in telomerase deficient (TERC-/-) mice.

9:15 Lamghari M (Porto, P)
Neuropeptide Y1 receptor as a potential candidate for bone regeneration therapies.

9:40 Alessio N (Napoli, I)
Silencing of BRG1, the ATPase subunit of SWI/SNF chromatin remodeling complex, induces senescence of mesenchymal stem cells.

10:05 Lozano D (Madrid, E)
Both N- and C-terminal fragments of parathyroid hormone-related protein restore the altered osteogenic differentiation induced by high glucose in mesenchymal cells from the mouse bone marrow.

**10:30-11:00 coffee-break**

## Session 10

Chairperson: Nicola Baldini

11:00 Chen L (Odense, DK)
Dlk1/pref-1/FA1 inhibits chondrocyte differentiation through Akt-dependent pathway.

11:25 Baglìo SR (Bologna, I)
Temporal gene expression of human bone marrow stromal cells during osteoblast differentiation.

11:50 Qiu W (Odense, DK)
Dual function of TNFRSF19 in osteogenesis and adipogenesis.

12:15 Squillaro T (Siena, I)
Partial silencing of methyl cytosine protein binding 2 (MECP2) in mesenchymal stem cells induces senescence along with increase of damaged DNA.

**12:40-13:40 Adjourn and Lunch**

Roche

CENTRO RESIDENZIALE
UNIVERSITARIO
Bertinoro

SERVIZIO SANITARIO REGIONALE
EMILIA - ROMAGNA
Istituto Ortopedico Rizzoli di Bologna
Istituto di Ricovero e Cura a Carattere Scientifico

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
A.D. 1088