

YOUNG INVESTIGATOR GRANTS  
RESEARCH GRANTS

**RESEARCH BOOK**

2008

# Research Book 2008

# RESEARCH BOOK

# 2008

Research Program History .....	4
Current Research Committee Members .....	5
Supporting Promising Researchers.....	8
Review Process.....	9
Research Grants 2005.....	10
Research Grants 2006.....	16
Young Investigator Grants 2007 .....	20
Research Grants 2007.....	22
Young Investigator Grants 2008 .....	24
Research Grants 2008.....	29
Young Investigator Grants 2009 .....	35
Research Grants 2009.....	38
Publications .....	46
Presentations.....	46
Index to Grantees .....	48
Index to Institutions.....	49
Announcement Research Grants.....	50

# Research Program History

The objective of Research Grants is to encourage investigators by providing seed and start-up funding for promising research projects in the field of orthopaedic trauma surgery through Grants of up to US\$ 50,000 for a research project extending over a maximum of two years.

The **Mission of OTC** is to foster evidence-based research that increases knowledge to solve clinical problems and improve orthopaedic trauma care. Through the OTC Research Grant Program funding support is provided on topics such as:

- Promotion of fracture healing, including treatment and enhancement of fracture repair
- Treatment of fractures in osteoporotic bone
- New technologies in fracture fixation, including computer-assisted surgery
- Prophylaxis and treatment of infections in fracture
- Prospective clinical trials in fracture care
- Numerical methods in trauma surgery

The target groups addressed through the program are senior researchers who are eligible to research grants of up to US\$ 50,000, and also young investigators who can obtain grants of up to US\$ 10,000.

The evaluation and selection of grant projects is strictly based upon blinded proposals submitted by applicants, in accordance with OTA criteria. The OTC

Research Committee, with currently nine members of high academic standing, oversees and directs the program. This committee identifies research topics to be covered, develops the procedures for reviewing proposals, and establishes the criteria for approving proposals and awarding grants.

Further information on the OTC Research Grant Program can be obtained under **[www.otcfoundation.org](http://www.otcfoundation.org)** by clicking on 'Research Grants'.

The budget for OTC Grants is limited and applicants are often three times higher than the total grant volume. Therefore the OTC is not able to fund all of the research proposals. The number of funded proposals varies from year to year depending on the availability of funds.

During the years 2005, 2006 and 2007 the Research Grants were administered by the AIOD. With the transition from AIOD to the OTC Foundation at the beginning of 2008, such grants are provided as OTC Research Grants. The essence of the program has been maintained, including the Research Committee.



## Current Research Committee Members

### **PETER PATKA, MD PHD, THE NETHERLANDS (CHAIR)**

Rotterdam University Chair in Trauma Surgery  
<http://www.erasmusmc.nl/heelkunde/traumatologie>

Dr Patka is a graduate in Medicine of the Charles University of Prague (1969) and the Free University of Amsterdam (1976). He completed his medical and surgical training at the Free University of Amsterdam, and broadened his clinical trauma exposure by training with world experts at the Kanton Spital



**PETER PATKA**  
 MD PHD,  
 THE NETHERLANDS (CHAIR)

St. Gallen in Switzerland. Dr Patka was in charge of Trauma Surgery at the VU Medical Centre in Amsterdam. Since 2004, he has been Professor and Chair in Trauma Surgery and head of the Trauma Center South West Netherlands at the Erasmus MC. Dr. Patka's clinical interests include the management of patients with complex trauma and the restoration of traumatic bone loss, encompassing both clinical and basic research of bone substitution and bone growth stimulation.

### **VOLKER ALT, MD PHD, GERMANY**

Orthopaedic Trauma Surgeon University Hospital Giessen

Dr. Alt is an active orthopaedic trauma surgeon at the University Hospital in Giessen, Germany. His main research interest is both clinical and experimental work



**VOLKER ALT**  
 MD PHD,  
 GERMANY

on fracture healing, bone infections and biomaterials. A further focus of his work is on health economics in trauma surgery. He was awarded with the Gerhard-Küntschner-Prize in 2006 and is working as official reviewer for several journals in the field of orthopaedic trauma surgery and biomaterials.

### **PETER AUGAT, PHD, GERMANY**

Professor of Biomechanics

Peter Augat graduated in Physics at the University of Ulm, Germany and started his career in orthopaedic research at the Institute of Orthopaedic Research



**PHD,  
 GERMANY**

and Biomechanics at the University of Ulm. As an Assistant Adjunct Professor in Radiology at the University of California in San Francisco, he worked on quantitative imaging and osteoporosis. Prof Augat is now the Director of the Institute of Biomechanics at the Trauma Center in Murnau, Germany.

# Current Research Committee Members

## **MOHIT BHANDARI, MD MSC FRCS, CANADA**

Canada Research Chair in Musculoskeletal Trauma  
[http://fhs.mcmaster.ca/surgery/faculty/directory/bhandari\\_mohit.html](http://fhs.mcmaster.ca/surgery/faculty/directory/bhandari_mohit.html)

A University of Toronto graduate in Medicine, Dr. Bhandari completed both his orthopaedic and Master's of Clinical Epidemiology and Biostatistics training at McMaster University. To broaden his



**MOHIT BHANDARI**  
MD MSC FRCS,  
CANADA

clinical trauma exposure, he trained with world experts in Los Angeles, California and Minneapolis. Dr. Bhandari's clinical interests include the management of patients with complex lower extremity fractures and fractures of the pelvis and acetabulum.

## **LOUIS WING-HOI CHEUNG, BSC PHD, CHINA**

Research Associate Professor, Deputy Director of Musculoskeletal Research Laboratory, Department of Orthopaedics&Traumatology, The Chinese University of Hong Kong, [www.ort.cuhk.edu.hk](http://www.ort.cuhk.edu.hk)

Graduated in Biochemistry Department, Dr. Cheung completed his PhD degree in Orthopaedics and biostatistics training at the Chinese University of Hong-



**LOUIS WING-HOI CHEUNG**  
MD PHD,  
CHINA

Kong. Dr. Cheung's research interests include biophysical interventions, enhancement of osteoporotic fracture healing, biological response to mechanical stimulation, and tissue engineering for cartilage regeneration.

## **THEODORE MICLAU, III, MD, USA**

Orthopaedic traumatologist, vice Chairman and Director of Orthopaedic Trauma

Theodore Miclau completed his residency in orthopaedic surgery at the University of North Carolina at Chapel Hill in 1994, during which he spent one year at the AO Research Institute in Davos, Switzerland studying fracture healing. After finishing an orthopaedic trauma fellowship at the Baylor College of Me-



**THEODORE MICLAU**  
III, MD  
USA

dicine (Houston, TX), he visited trauma centers in St. Gallen, Hannover, and Berlin. In 1996, dr. Miclau was appointed as orthopaedic traumatologist at the San Francisco General Hospital. Since 2004, he is Vice Chairman and Director of Orthopaedic Trauma of the UCSF Department of Orthopaedic Surgery.

**EMIL H. SCHEMITSCH, MD PHD,  
CANADA**

Professor of Surgery, University of Toronto

Dr. Emil Schemitsch, Professor of Surgery, University of Toronto, Canada is head of the Division of Orthopaedic Surgery at St. Michael's Hospital (University of Toronto) and scientist at the Keenan Research Centre (Li Ka Shing Knowledge Institute, St. Michael's Hospital). He completed his orthopaedic training at the University of Toronto. To broaden his clinical



**EMIL H. SCHEMITSCH**  
MD PHD,  
CANADA

exposure, Dr. Schemitsch trained at the University of Washington (Harborview Medical Center) and Harvard University. Dr. Schemitsch's clinical interests include the management of patients with complex lower extremity fractures, hip and knee reconstruction and computer assisted surgery.

**A.H.R.W. SIMPSON, MD PHD, UK**

Professor of Orthopaedics and Trauma

Hamish Simpson read Advanced Physics (Cambridge University) and Medicine (at Oxford and Cambridge Universities), and carried out his surgical training in Oxford, Bath, and Toronto. Professor Simpson's current research interest relates to Fracture Repair especially in Osteoporotic Bone, Bone & Joint Infection and Tissue Engineering of both cartilage



**A.H.R.W. SIMPSON**  
MD PHD,  
UK

and bone. Professor Simpson currently chairs an UK Medical Research Council Data Monitoring Committee and is Chairman of the Scottish Committee for Orthopaedics and Trauma.

**ESTHER M.M. VAN LIESHOUT, PHD,  
THE NETHERLANDS**

(scientific coordinator)

Research Coordinator in Trauma Surgery,  
Erasmus MC Rotterdam

Esther van Lieshout graduated in Medical Biology at the University of Nijmegen/St. Radboud Hospital (1994), where she completed her PhD training in 1998. To broaden her scientific exposure, she trained



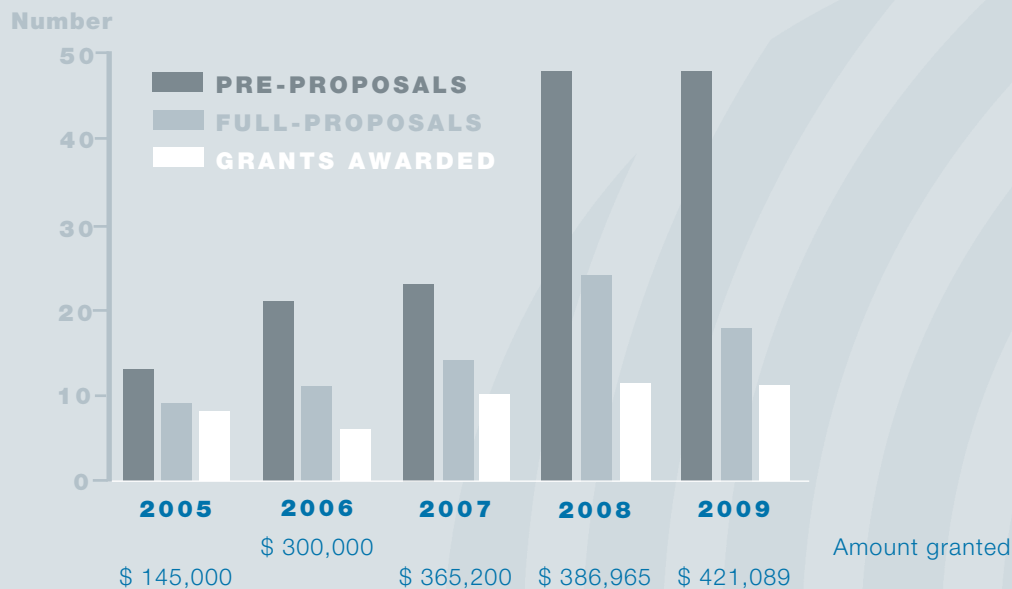
**ESTHER M.M.  
VAN LIESHOUT**  
PHD,  
NETHERLANDS

with experts in Copenhagen, Denmark. Dr. Van Lieshout is senior scientist and research coordinator Traumatology at the Erasmus MC (Rotterdam, the Netherlands). Her research interests include bone healing biology and efficacy of interventions in trauma care. She supervises several basic scientific and clinical research projects.

# Supporting Promising Researchers

Through a Young Investigator Grant or a Research Grant, OTC supports researchers active in areas related to trauma care. For the 2009 grants, approximately 50 Pre-proposal applications were received and 18 were invited for submitting a Full-length proposal. Of these, 11 were accepted, following a well-defined review and selection process. The approval rate improved from 46% for the 2008 grants to 61% for 2009. Currently, the OTC supports 46 projects with a total sum of US\$ 1,618,254. Biological research in areas like bone healing and clinical research account for the majority of projects. A relatively new area of awarded research is biomechanics.

## NUMBER OF PROJECTS SUPPORTED BY OTC





# Review Process

**Basis requirements for applicants:**

- The (co)-principle investigator should be trauma or orthopaedic surgeon
- Non-trauma/orthopaedic surgeons may serve as Principle Investigator, if affiliated with a trauma/orthopaedic department and with an orthopaedic surgeon as co-principle investigator
- Candidates may receive only one OTC Research Grant per institution in each category and in each year

Both laboratories and clinical projects are suitable, but in either case clinical relevance must be explicitly and clearly described.

**Pre-proposal applications:**

Preliminary screening of application is based on a pre-proposal application, containing a brief (maximum three pages) description of the research idea. Pre-proposals are reviewed in a blinded fashion by all research committee members, and are rated and ranked based on scientific merit and orthopaedic trauma impact. For those proposals receiving an average rate of three or higher (on a scale of 1 to 5) are invited to submit a full-length proposal. Applicants or proposals that do not meet this threshold receive feedback on their proposal.

**Full-length proposals:**

Full-length proposals are evaluated in a non-blinded fashion for their scientific merit, orthopaedic trauma impact, methodology, feasibility, experience of the research team, and the budget requirements. For each application, three appointed reviewers provide an in-depth review, which is discussed with all research committee members. Committee members are absent during discussion or projects in which they have a conflict of interest. The best-rated applications are offered a Grant contract. Applicants of unsuccessful applications receive feedback on their proposal, which may help them improving the quality of their proposal or the design of their study.

## Research Grants 2005

### Introduction of investigator/scientific focus:

Prof. Leung is an orthopaedic surgeon, specialized in traumatology. He is a chair professor and head of Traumatology section in the Dept. of Orthopaedics & Traumatology, The Chinese University of Hong Kong. His research work includes fracture healing and fixation, biological responses of tissues to mechanical stimulations and image guided orthopaedic surgery. He also plays an active role in several orthopaedic societies. He has published many books, internatio-

nal peer-reviewed papers and conference abstracts. His scientific focus in recent years is low-magnitude high-frequency vibration treatment on orthopaedic indications like fracture healing. Intensive animal and clinical research in this area are undergoing.

### Summary of results:

Mechanical environment plays an essential role in

## EFFECT OF HIGH-FREQUENCY, LOW-MAGNITUDE VIBRATION THERAPY ON THE HEALING OF FEMORAL FRACTURE IN A RAT MODEL

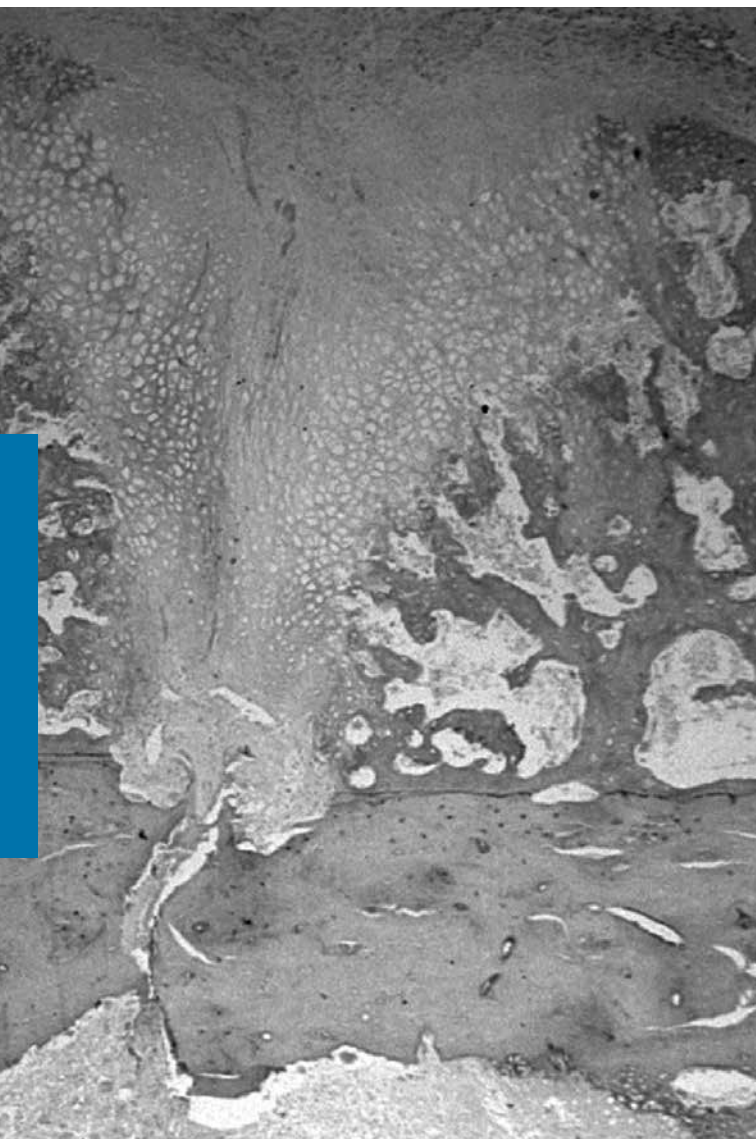
**DR. K.S. LEUNG**

The Chinese University of Hong Kong,  
Hong Kong, China

Research Grants

# 2005





fracture healing. Low-magnitude high-frequency vibration (LMHFV), a noninvasive biophysical stimulation, was proven beneficial for bone formation in osteoporosis. Therefore, this OTC foundation-funded project aims to investigate the effect of LMHFV on fracture healing in rat model fixed with intramedullary nail. The hypothesis of the present study is that LMHFV can accelerate the fracture healing and influence fracture healing-related gene expression. Following standard closed femoral shaft fracture, 75 3-month-old female SD rats received LMHFV (35Hz, 0.3g, 20 minutes/day, 5 days/week) or sham treatment with the power switched off. Radiographic healing was compared between the vibration and control groups using image analysis. On 1, 2 and 4 weeks post-treatment, mRNA expressions of chondrogenesis and osteogenesis related matrix collagens (type II and I collagens, respectively) and growth factors (BMP-2, TGF-b1 and VEGF) were quantified (n=6 for each group) using real-time PCR. Histomorphological changes in terms of total callus area and cartilage area were measured, with type I and II collagens located immunochemically. Results showed that chondrogenesis was augmented with a two-fold increase in type II collagen expression and a significantly larger area of cartilage in the fracture callus after one week's treatment of LMHFV. From week 2 to week 4, a faster decrease of type II collagen expression was accompanied with a more

significant increase of type I collagen expression in the treatment group. On 4 weeks post-treatment, the vibration group presented a higher rate of osseous bridging histologically, indicating the faster bone remodelling. Besides, upregulation of BMP-2, TGF-b1 and VEGF was observed in the treatment group along the whole process. All these evidences support that LMHFV stimulates the formation of matrix collagens and growth factors that are closely related to chondrogenesis and osteogenesis, and hence accelerates fracture healing. LMHFV therefore holds great potential in clinical applications for fracture healing.

## Research Grants 2005

### FLUID LAVAGE OF OPEN WOUNDS (FLOW): A MULTICENTER RANDOMIZED TRIAL

**Principal Investigator:****MOHIT BHANDARI, MD MSC FRCSC**Methods and Coordinating Center: McMaster  
University, Hamilton ON, CanadaCollaborating Centers: 42 Sites  
USA, Canada, Europe, Australia, China, India

Traffic accidents ranked among the top 10 causes of global disability in 1990. By 2020, disability from traffic accidents is estimated to rank in the top 3 of all cause disability from disease – second only to ischemic heart disease and depression. The most serious injuries are those fractures that break through the skin. These so called open, or compound, fractures have serious consequences for patients including infections, wound healing problems and failure of fracture healing - many of which necessitate a secondary intervention, or re-operation. For this reason, open fractures are designated as surgical emergencies and require

urgent treatment. In North America, an estimated 250,000 open fractures occur annually. The single most important step in the initial management of these complex injuries is a thorough wound irrigation to remove any contaminants. However, there is currently no clinical evidence on the optimal approach to irrigating the wounds during the initial operative procedure. Options for the type of irrigating fluid used and the pressure at which the fluid is delivered to the surface of the open wound and bone remain controversial.

We primarily aim to investigate whether the irrigation solution (soap vs. normal saline) or irrigation pressure

(low vs. high; gravity flow vs. high) will decrease the risk of re-operation among adult patients with open fracture wounds. We secondarily aim to determine the effect of irrigating solution and irrigation pressure on patient function and quality of life, and non-operatively managed infection, wound healing and fracture healing problems.

We are conducting a multi-centre, multi-national, patient and outcome assessor blinded, randomized controlled trial using a 2x3 factorial design. Surgeons across 42 sites are recruiting 2,264 patients for the study.

We received pilot trial funding from OTC in 2005 towards the completion of a 100 patient pilot trial. Our pilot trial was highly successful and proved feasibility for a larger pivotal trial, which has subsequently received 3 million dollars from the Canadian Institutes of Health Research and the U.S. Departments of Defence. Our ability to raise large scale funding was significantly improved by the OTC pilot grant.

This study represents a major international effort to identify a simple and easily applicable strategy for emergency wound management. The importance of the question and potential low cost argues strongly for global participation, especially in regions like India and China where disability from traumatic injuries is staggering.

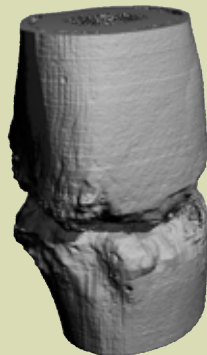
## ASSESSMENT OF ANGIOGENESIS IN THE DEVELOPMENT OF NON-UNIONS BY VOLUMETRIC CT-SCANNING

### Principal Investigator:

**DR. V. ALT**

University Hospital Giessen-Marburg, Giessen,  
Germany

**Abstract:** This application focuses on the interactions of new blood vessel and new bone formation in physiological diaphyseal fracture healing and development of non-unions as non-unions are still one of the most important complications in trauma surgery. An established osteotomy model for hypotrophic diaphyseal long bone non-unions will be used. The most important method of the current project is volumetric CT scanning enabling dynamic visualization of new blood vessel and bone formation without sacrificing the animal which will provide morphological landmarks for comparison to standard methods, e.g. histology and biomechanical testing. As this innovative imaging method has never been used in fracture healing before, the current project will also serve to establish volumetric CT scanning in the field of trauma research.



**Summary of results:** According to the the surgical procedure of Kobuku et al. (2003) for the establishment of aseptic non-union an osteotomy was created at the midshaft of the tibia of rats (36 animals) which was stabilized by an intramedullary K-wire. In the non-union group (18 rats) coagulation of the osteotomy surrounding periost was done to impair osteogenesis, which was not performed in the control group (18 rats).

The coagulation of the osteotomy site led to inhibited fracture healing with development of non-unions and implant instability in all animals whereas the control group showed uneventful fracture healing. Immunohistochemistry with PECAM and anti-VEGF-R1 staining is being carried out at the moment for relation of the bone formation to the immunohistochemical staining. The method of volumetric CT scanning was unable to identify vessels during the in vivo perfusion in either group. Most likely the diameter of the blood vessels is beyond the detection threshold of 20 micrometers of the VCT.

## EARLY DIAGNOSIS OF AVASCULAR NECROSIS OF FEMORAL HEAD IN POST-TRAUMATIC HIP DISLOCATION

### Principal Investigator:

**DR. R.K. SEN**

Postgraduate Institute of Medical Education & Research,  
Chandigarh, India

**Abstract:** To evaluate the usefulness of intra-operative aspiration of the femur head, for early diagnosis of its avascularity, in patients of hip dislocation. The aspiration and needle biopsy will be taken from of the superior outer third (expected avascularity) and inferior part (as control area) of femoral head, in patients requiring surgery for relocation of dislocated femur head. Aspiration volume of marrow will be estimated and marrow analyzed cytologically and for histological characteristics from both areas. Subsequent screening by serial clinical, radiological examination and MRI will be made at 6, 12, 24 and 48 weeks post surgery for AVN. Total 10 cases will be studied in 2 years with statistical analysis for correlation of aspiration volume & marrow characteristics with eventual development of AVN.

## Research Grants 2005

### MAP KINASE ACTIVATION IN OSTEOBLASTS EXPOSED TO A PULSED ELECTROMAGNETIC FIELD

**Principal Investigator:****DR. B.J. PUNT**

Erasmus MC, Rotterdam, the Netherlands

**Abstract:** Since the 1950s and 1960s, clinical applications of Pulsed ElectroMagnetic Field stimulation also include the treatment of delayed union and non-union. There are several observational studies that demonstrate the positive effect of electric or electromagnetic stimulation in the treatment of delayed unions and non-unions. The clinical effectiveness of bone-growth stimulation proved to be easier to demonstrate than the mechanisms on cellular and molecular levels behind it. The effect of electric and electromagnetic field stimulation is hypothesized to be propagated and amplified by signal transduction pathways, ultimately leading to modification of cell behavior. A possible signalling candidate is the phosphorylation cascade involved in the activation of mitogen-activated protein kinases (MAPKs). The MAPK pathway plays a crucial role in cell proliferation and differentiation by transmitting extracellular signals from membrane to nucleus. The aim of this study is to determine whether human osteoblasts respond to Pulsed ElectroMagnetic Field stimulation with increased levels of phosphorylated MAPK. We will use fetal human osteoblast (SV-HFO). These cells will be

exposed to 1 Gauss Pulsed Electromagnetic Field for 15 minutes, 7, 14 and 21 days. A non-exposed cell line will be used as reference. After exposure the cells will be lysed and the activation of MAP Kinase will be detected using an antibody in Western Blot analysis.



### THE EFFECT OF ARGININE DEFICIENCY ON THE DEVELOPMENT OF (AVASCULAR) NON-UNION

**Principal Investigator:****DR. P.R. BRINK**University Hospital Maastricht,  
Maastricht, the Netherlands

**Abstract:** Avascular non-union during fracture healing is an increasingly and disabling problem related to the presence of decreased blood flow. The amino acid arginine as a precursor of nitric oxide (NO), as a strong blood flow regulator, is hypothesized to be deficient during non-union. The proposed study in a mice model of femoral non-union investigates the effects of modulation of the arginine-NO metabolism on the development of non-union. This line of the proposed research during a 2-year period will elucidate the pathophysiological mechanisms behind the disturbances in arginine-NO during the avascular non-union and has not been investigated before. Subsequent therapeutic applications will be directed at nutritional supplementation.



## THE ADDITIONAL TREATMENT OF FRESH FRACTURES OF THE LOWER LEG WITH PULSED ELECTROMAGNETIC FIELDS

### Principal Investigator:

**DR. B.J. PUNT**

Erasmus MC, Rotterdam, the Netherlands

**Abstract:** The concept of electrical stimulation to elicit fracture healing has a long history. The early work of Fukada and Yasuda in 1957 demonstrated that mechanical loading of a bone produced electrical potentials in bone tissue (Fukada E 1957). In 1971 it was Friedenbunrg and his colleagues who were the first to use this technique in clinical practice (Friedenberg, Harlow et al. 1971). They successfully treated a non-union of the medial malleolus with electric stimulation. There are several observational studies that demonstrate the positive effect of electric or electromagnetic stimulation in the treatment of delayed unions and non-unions (Bassett, Mitchell et al. 1981; Brighton, Black et al. 1981; Dunn and Rush 1984; Brighton and Pollack 1985; de Haas, Beaupre et al. 1986; Sharrard 1990; Scott and King 1994). In 1971 Jorgensen was the first to treat patients with fresh tibia fractures. He reported a reduction of 30 % in consolidation time compared to the conventional treatment. In our study we will analyze the effect of the additional treatment of fresh fractures of the lower leg with Pulsed Electromagnetic Fields. Will there be a reduction in consolidation

time? Will the use of PEMF reduce the occurrence of delayed and nonunion? Does a reduction in consolidation time mean an earlier return to work? Will the additional treatment with PEMF result in a better Quality of life? We will conduct a multi center double-blind randomized trial concerning patient with a fresh lower leg fracture. After treatment of the fracture by intramedullary nailing, an additional treatment with PEMF for 6 weeks will be given. One group will receive an active stimulator and the other group a dummy. Data will be collected using case report forms, which will contain regular x-rays and pain scores. Also the quality of life will be registered using the SF 36 score.

## OPTIMAL TREATMENT OF FEMUR FRACTURES IN POLY-TRAUMA PATIENTS: ASSESSMENT OF THE IMPACT OF CENTER-SPECIFIC CHARACTERISTICS ON OUTCOMES AND DEVELOPMENT OF A NOVEL PREDICTION RULE TO GUIDE TREATMENT

### Principal Investigator:

**DR. S. MORSHED**

University of California San Francisco,  
San Francisco, CA, USA

**Abstract:** We will assess the impact of center-specific variations on outcomes of care for femoral shaft fractures in multiply injured patients and develop a generalizable clinical prediction model to improve patient care. Specific aims: 1) analysis of the National Trauma Data Bank (NTDB) to assess risk associated with individual baseline characteristics and aggregate-level factors; 2) use the NTDB to generate a predictive model followed by internal and external validation on an independent test set from San Francisco General Hospital; and 3) conduct a prospective pilot study testing feasibility of implementation and overall accuracy and reliability of our model.

# Research Grants 2006

## OPTIMIZATION OF LOCKED SCREW DEVICES

**PROF. DR. L. CLAES**

Ulm University, Ulm, Germany

### Introduction of investigators / scientific focus:

The institute of orthopaedic research and biomechanics in the center of musculo-skeletal research at Ulm University focuses on research in the fields of fracture healing, osteoporosis, tissue engineering, cell biology as well as knee and spine biomechanics.

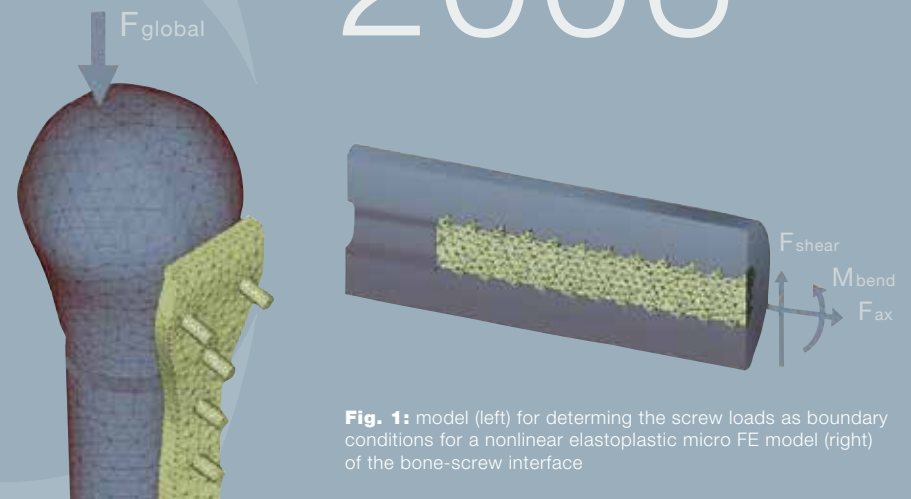
16

Research Grants



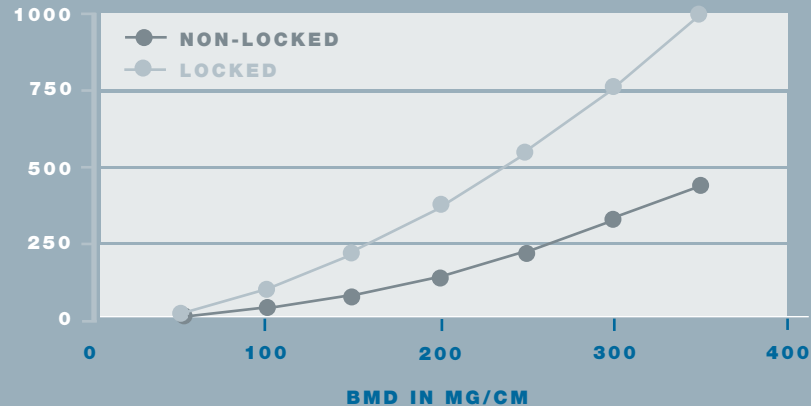
PROF. DR. L. CLAES (LEFT) AND DR. T. WEHNER (RIGHT)

# 2006



**Fig. 1:** model (left) for determining the screw loads as boundary conditions for a nonlinear elastoplastic micro FE model (right) of the bone-screw interface





**Fig. 2:** Ultimate load (Fult) of the bone-implant complex in relation to the bone mineral density (BMD)

#### Abstract:

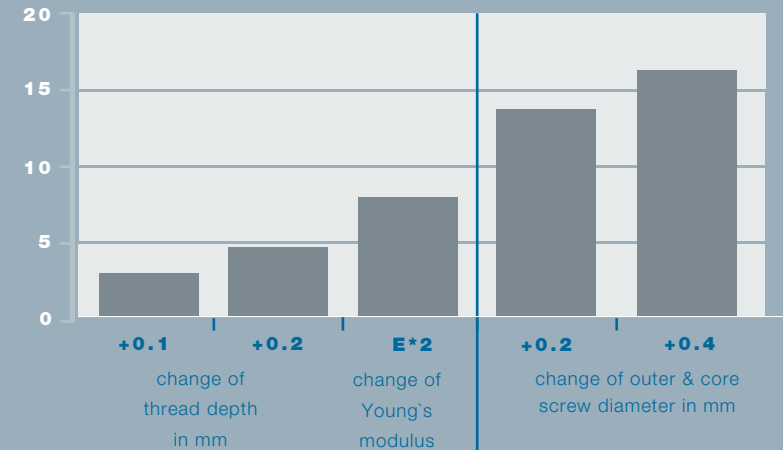
Conventional implants have a critical primary stability in weak, osteoporotic bone, which leads to a large number of complications. Locked plate fixations help to improve this stability but there is still a need for optimization. We developed idealized nonlinear 3D finite element models, which could be used to determine the ultimate loading capability of both (i) conventional non-locked and (ii) locked plate fixations at the proximal humerus (**Fig. 1**).

Therefore, it was possible to directly compare both fixation systems under physiological loading conditions. By changing the mechanical properties of the

bone material in relation to the bone mineral density, it was possible to determine the influence of the bone quality on the ultimate load of the bone-implant complex (**Fig. 2**).

The ultimate load of the locked plate fixation was greater than for the non-locked fixation, which could be confirmed by in vitro tests with human cadaver specimens. With these finite element models, it was possible to vary the design parameters for optimizing the locked plate fixation. The strength of the screw-bone interface, and therefore the ultimate loading

capability of the bone-implant complex, could be increased by enlarging the thread depth and increasing the stiffness of the screw (**Fig. 3**).



**Fig. 3:** Change of the ultimate load (Fult) of the bone-implant complex related to variations of the screw design

# Research Grants 2006

## CELL-BASED GENE THERAPY TO ACCELERATE FRACTURE HEALING

### Principal Investigator:

**DR. E.H. SCHEMITSCH**

St. Michael's Hospital - University of Toronto, Toronto, ON, Canada

**Abstract:** Bone fracture disrupts the circulation locally and leads to delays in bone healing or nonunion. The present research proposal seeks to develop a novel approach, namely cell-based gene therapy to promote fracture healing using bone marrow derived endothelial progenitor cell transfer with genes of vascular endothelial growth factor and endothelial nitric oxide synthase. It is hypothesized that this method will be used to deliver a combination of cell and gene therapy to promote angiogenesis and osteogenesis at a fracture location. This work will lead to effective strategies to increase fracture healing.

## TREATMENT OF INTRA-ARTICULAR CALCANEAL FRACTURES; A RANDOMIZED CONTROLLED TRIAL

### Principal Investigator:

**DR. T. SCHEPERS**

Erasmus MC, Rotterdam, the Netherlands

**Abstract:** Calcaneal fractures are a disabling injury and optimal treatment has yet to be determined. This study aims to demonstrate a clinically significant difference of 10 points using the most cited and clinically relevant American Orthopaedic Foot and Ankle Society hindfoot score (total 100 points) after 2 and 5 years. Open reduction and internal fixation (ORIF), percutaneous reduction and fixation and conservatively treated patients will be compared in an adequately powered, multicenter randomized controlled trial with 3 treatment arms. Clinical outcome will be measured using the AOFAS score, standard physical exam and radiographic criteria after 2 and 5 years.

### ALCOHOL CONSUMPTION



## AND FRACTURE HEALING

### Principal Investigator:

**DR. H.W. SAMPSON**

Texas A&M University Health Science Center,  
College of Medicine, Collage Station, TX, USA

**Abstract:** Understanding the pathophysiology of fracture healing in the alcoholic patient would contribute greatly to the discovery of optimum treatment methods. Several pertinent questions will be addressed in this proposal. What level of alcohol consumption is detrimental to fracture healing and what stage of healing is most vulnerable. Does alcohol consumption effect fracture healing by processes that are genomic, or through perturbation of cytokines or other growth factors? How can fractures in alcoholics, best be treated? Will termination of alcohol consumption or presently FDA approved or investigative anti-resorptive or anabolic agents be affective in treating alcohol-induced fracture healing problems?

## IMPROVING FRACTURE REPAIR IN AGING PATIENTS: THE INFLUENCE OF AGE ON THE EFFECTIVENESS OF MESENCHYMAL STEM CELL STIMULATED NONUNION REPAIR

### Principal Investigator:

**DR. D.J. HAK**

University of Colorado at Denver and Health Sciences  
Center, Denver, CO, USA

**Abstract:** The aim of this study is to examine potential methods to improve bone regeneration and repair in aging patients. The effect of bone marrow derived mesenchymal stem cells will be examined in the treatment of experimental atrophic nonunions, and their effectiveness compared in old and young animals. Atrophic nonunions will be created in a rat femoral fracture model by cauterizing the periosteum. Bone Marrow derived mesenchymal stem cells will be harvested from inbred Fisher 344 rats and expanded in vivo. The ability of these cells to heal the nonunion will be investigated in young (3 month) and old (18 month) animals. The influence of bone marrow stem cell donor age, number of stem cells implanted, and the benefit of rhBMP transduction of bone marrow stem cells will also be evaluated in old animals. Fracture repair will be assessed through serial radiographs, histology, and biomechanical testing.



## ROLE OF BMP-2 IN STEM CELL RECRUITMENT AND DIFFERENTIATION DURING FRACTURE REPAIR

### Principal Investigator:

**DR. C. COLNOT**

University of California San Francisco,  
San Francisco, CA, USA

**Abstract:** Our long-term objective is to understand the mechanisms of skeletal stem cell recruitment and differentiation during fracture healing. The objective of our proposal is to examine the extent to which exogenous BMP-2 enhances fracture repair via direct effects on skeletal stem cells and indirect effects on angiogenesis. Our first aim will determine the extent to which exogenous BMP-2 affects chondrogenesis, osteogenesis, and angiogenesis during fracture repair. Our second aim will determine the extent to which exogenous BMP-2 affects the recruitment of genetically labeled skeletogenic stem cells from a variety of endogenous niches, including the periosteum and endosteum.

# Young Investigator Grants 2007

## BONE ENGINEERING USING A COMPOSITE BIODEGRADABLE SCAFFOLD FOR TREATMENT OF A SEGMENTAL TIBIAL BONE DEFECT IN A CANINE MODEL

### Principal Investigator:

**DR. P.R.T. KUZYK**

St. Michael's Hospital - University of Toronto,  
Toronto, ON, Canada

**Abstract:** The purpose of this study is to evaluate the osteoconductive and angiogenic ability of a novel polymer-ceramic composite scaffold when utilized for the treatment of a large segmental bone defect in the tibia. We will use a canine model with three different treatments for the tibial defect: Group 1 will be left empty, Group 2 will have a cancellous autograft from the iliac crest, and Group 3 will have the scaffold. We hypothesize that there will be no bone growth across the defect site in Group 1 (empty). Group 2 (iliac crest) will have complete bridging bone across the defect site. Group 3 (scaffold) will have some bone growth within the defect, proving osteoconductivity. Angiogenesis will be evaluated using a barium compound perfused through the femoral artery at the time of sacrifice. Micro-CT will be used to quantify blood vessel volumes within the defect and surrounding tissue.

## CONTINUOUS DELIVERY OF VASCULAR ENDOTHELIAL GROWTH FACTOR THROUGH AN IMPLANTED OSMOTIC PUMP IN A MODEL OF RABBIT TIBIAL NON UNION WITH A SEGMENTAL BONE DEFECT

### Principal Investigator:

**DR. M.A. RUIZ IBÁN**

Hospital Ramon y Cajal, Madrid, Spain

**Abstract:** The treatment of long bone segmental defects produced after non-union is challenging. The use of cortical allografts has poor results. The aim of the study is to determine if continuous addition of Vascular endothelial growth factor (VEGF) to a segmental defect treated with a structural allogenic graft improves healing of the graft. A long bone non-union model in the rabbit modified to obtain a segmental defect will be used. The VEGF will be added with an implanted osmotic pump in the interior of the graft and results will be compared with two different control groups.

Young Investigator Grants

# 2007



## CELL-BASED GENE THERAPY TO ACCELERATE FRACTURE HEALING

### Principal Investigator:

**DR. E.H. SCHEMITSCH**

St. Michael's Hospital - University of Toronto,  
Toronto, ON, Canada

**Abstract:** Bone fracture disrupts the circulation locally and leads to delays in bone healing or nonunion. The present research proposal seeks to develop a novel approach, namely cell-based gene therapy to promote fracture healing using bone marrow derived mesenchymal stem cell and endothelial progenitor cell transfer with genes of vascular endothelial growth factor and endothelial nitric oxide synthase. It is hypothesized that this method will be used to deliver a combination of cell and gene therapy to promote angiogenesis and osteogenesis at a fracture location. This work will lead to effective strategies to increase fracture healing.

## FLUID IRRIGATION TECHNIQUES IN PATIENTS WITH OPEN FRACTURE WOUNDS: A MULTI-CENTER BLINDED RANDOMIZED CONTROLLED TRIAL (F.L.O.W.): A PILOT STUDY

### Principal Investigator:

**DR. M. BHANDARI**

McMaster University, Hamilton, ON, Canada

**Abstract:** Traffic accidents ranked among the top 10 causes of global disability in 1990. By 2020, disability from traffic accidents is estimated to rank in the top 3 of all cause disability from disease. The most serious injuries are those fractures that break through the skin. Open fractures have serious consequences for patients including infections, wound healing problems and failure of fracture healing which necessitate a secondary intervention. For this reason, open fractures are designated as surgical emergencies and require urgent treatment. In North America, an estimated 250,000 open fractures occur annually. The single most important step in the initial management of these complex injuries is a thorough wound irrigation to remove any contaminants. There is currently no clinical evidence on the optimal approach to irrigating the wounds during the initial operative procedure. Options for the type of irrigating fluid used and the pressure

at which the fluid is delivered to the surface of the open wound and bone remains controversial. We aim to evaluate whether the type of irrigation solution (soap vs. normal saline) or irrigation pressure (high pressure vs. low pressure) will decrease the risk of re-operation among adult patients with open fracture wounds. We secondarily aim to determine the effect of irrigating solution and irrigation pressure on patient function and quality of life. We propose to conduct a multicenter, blinded, randomized controlled trial using a 2x2 factorial design to investigate whether irrigation solution (soap versus normal saline solution) or irrigation pressure (low versus. high) will decrease the rate of reoperations among patients with open fracture wounds. Surgeons across 30 sites (Canada, USA, Africa, and Asia) will recruit 1060 patients for the study. Patients will be randomized to one of 4 treatment arms (Soap + Low pressure; Soap + High pressure; Saline +Low pressure; Saline +High pressure). Using a factorial design, we will assess rates of re-operation at 12 month across Soap vs. Saline and High vs. Low pressure irrigation. Outcomes will be blinded adjudicated by an independent committee. Patients, data collectors, and outcome assessors will be blinded. Function and quality of life will be assessed at follow up of 6 weeks, 3, 6, 9 and 12 months.

# Research Grants 2007

## OPERATIVE VERSUS NON-OPERATIVE TREATMENT FOR UNSTABLE LATERAL MALLEOLUS FRACTURES

### Principal Investigator:

#### DR. D.W. SANDERS

London Health Sciences Centre - Victoria Hospital,  
London, ON, Canada

**Abstract:** Unstable, undisplaced lateral malleolus fractures are common traumatic injuries requiring orthopaedic care. However, the best treatment for these very common fractures is not only unknown, it is extremely controversial. This multi-center, randomized controlled clinical trial compares functional outcomes, radiographic outcomes, and complications between operative and non operative care. The study will determine whether recovery is improved or hastened when operative treatment is performed; and what the risks of operative care in this population entail. Results of this study will guide care for thousands of trauma patients annually.

### DOES VIBRATION THERAPY ENHANCE

## FRACTURE HEALING THROUGH BONE REMODELING?

### Principal Investigator:

#### DR. K.S. LEUNG

The Chinese University of Hong Kong,  
Hong Kong, China

**Abstract:** Fracture at lower extremities is a serious injury and healing usually takes long time. To accelerate fracture healing, mechanical stimulation is a critical factor as stated in Wolff's law. Low-magnitude, high-frequency vibration is a biophysical modality to provide whole-body mechanical stimulation. Our previous study of applying vibration treatment on femoral fractured rat model indicated a significant accelerated fracture healing with increased callus formation and maturation rate. Therefore, this study aims at verifying our postulation that the acceleration of fracture healing is via enhanced bone remodeling. Bisphosphonate, an agent to decrease bone resorption by osteoclast inhibition leading to reduced bone turnover and retarded remodeling, will be used to counteract the enhanced bone remodeling by vibration treatment, in order to prove the involvement of increased bone remodeling in the mechanism of vibration treatment. The findings will help to understand the rationale of the application of vibration treatment on fracture healing.

### THE USE OF BONE MORPHOGENETIC PRO-

## TEINS IN INFECTED NON-UNIONS

### Principal Investigator:

Dr. V. Alt

University Hospital Giessen-Marburg, Giessen, Germany

**Abstract:** Infected non-unions of long bone remain a critical problem in orthopaedic trauma surgery. The purpose of the current project is to study the effect of additional use of BMP-2 and BMP-7 on infected non-unions of the tibia with indwelling intramedullary implants in rats, particularly to look whether rhBMP-2 or rhBMP-7 can reduce infection rates and enhance new bone formation compared to irrigation, debridement and nail exchange only. An intramedullary nail-associated infected non-union of the tibia in rats is established and subsequently revised after two weeks with surgical débridement, irrigation and reosteosynthesis by exchange nailing without BMPs (group 1), with BMP-2 (group 2) or BMP-7 (group 3). 4 weeks after the revision procedure the infection rate and new bone formation is evaluated using microbiological, histological, biomechanical and radiological methods. Statistical analysis will be performed to study potential significant differences in infection rates and new bone formation.

### TREATMENT OF INTRA-ARTICULAR



## CALCANEAL FRACTURES; A RANDOMIZED CONTROLLED TRIAL

### Principal Investigator:

**DR. T. SCHEPERS**

Erasmus MC, Rotterdam, the Netherlands

**Abstract:** Calcaneal fractures are a disabling injury and optimal treatment has yet to be determined. The aim of this study is to demonstrate which of three management strategies yields the best clinical outcome. Open reduction and internal fixation (ORIF), percutaneous minimal invasive reduction and fixation (MIRF) and conservative treatment will be compared in an adequately powered, multicenter randomized controlled trial with 3 treatment arms. Clinical outcome will be measured after 1, 2 and 5 years using the American Orthopaedic Foot and Ankle Society hindfoot score (AOFAS) score, standard physical exam and radiographic criteria. A difference of 10 points using the most cited and clinically relevant AOFAS score (total 100 points) is considered clinically relevant.

### ROLE OF BMP-2 IN STEM CELL RECRUIT-

## MENT AND DIFFERENTIATION DURING FRACTURE REPAIR

### Principal Investigator:

**DR. C. COLNOT**

University of California San Francisco,  
San Francisco, CA, USA

**Abstract:** Our long-term objective is to understand the mechanisms of skeletal stem cell recruitment and differentiation during fracture healing. The objective of our proposal is to examine the extent to which exogenous BMP-2 enhances fracture repair via direct effects on skeletal stem cells and indirect effects on angiogenesis. Our first aim will determine the extent to which exogenous BMP-2 affects chondrogenesis, osteogenesis, and angiogenesis during fracture repair. Our second aim will determine the extent to which exogenous BMP-2 affects the recruitment of genetically labeled skeletogenic stem cells from a variety of endogenous niches, including the periosteum and endosteum.

### SYNDESMOTIC STABILIZATION OF WEBER

## C ANKLE INJURIES: IS FIBULAR PLATING ALWAYS NEEDED?

### Principal Investigator:

**DR. C. BORN**

Rhode Island Hospital; Providence, RI, USA

**Abstract:** Our hypothesis is that treatment of midlevel Type C fibula fractures with indirect fracture reduction and anatomic stabilization of the mortise using only syndesmotic screw fixation will yield outcomes equivalent to those same injuries treated with formal open direct plating of the fibula and adjuvant syndesmotic screw fixation, and will have fewer complications and enjoy faster recovery times.



# Young Investigator Grants 2008

## Introduction of principal investigator/scientific focus:

After finishing his PhD thesis in fracture healing, entitled "New developments in fracture healing: imaging and treatment methods", Taco J Blokhuis stayed active in research in fracture healing. During his training as a trauma surgeon, which followed the PhD, focus has been placed on clinical research. Since January 2007, he started at the University Medical Center in Nijmegen, and changed to the University Medical Center Utrecht (UMCU) since January 2009. In his current position, a minimum of two days per week is spent on research activities, mainly pre-

## FRACTURE HEALING IN OSTEOPOROSIS

clinical. The current research project, fracture healing in osteoporosis, is part of these research activities. Other items are the influence of systemic inflammation on fracture healing, and carrier materials in BMP application. The borderline between basic science and clinical application makes a close collaboration between basic scientists and clinicians imminent. Close cooperation with the departments of orthopaedics at the UMCU and the UMC Nijmegen, as well as the biochemistry department of the Radboud University Nijmegen, are therefore part of the multidisciplinary approach in this field.

## Young Investigator Grants

# 2008



**DR. T.J. BLOKHUIS**

University Medical Center Utrecht, the Netherlands



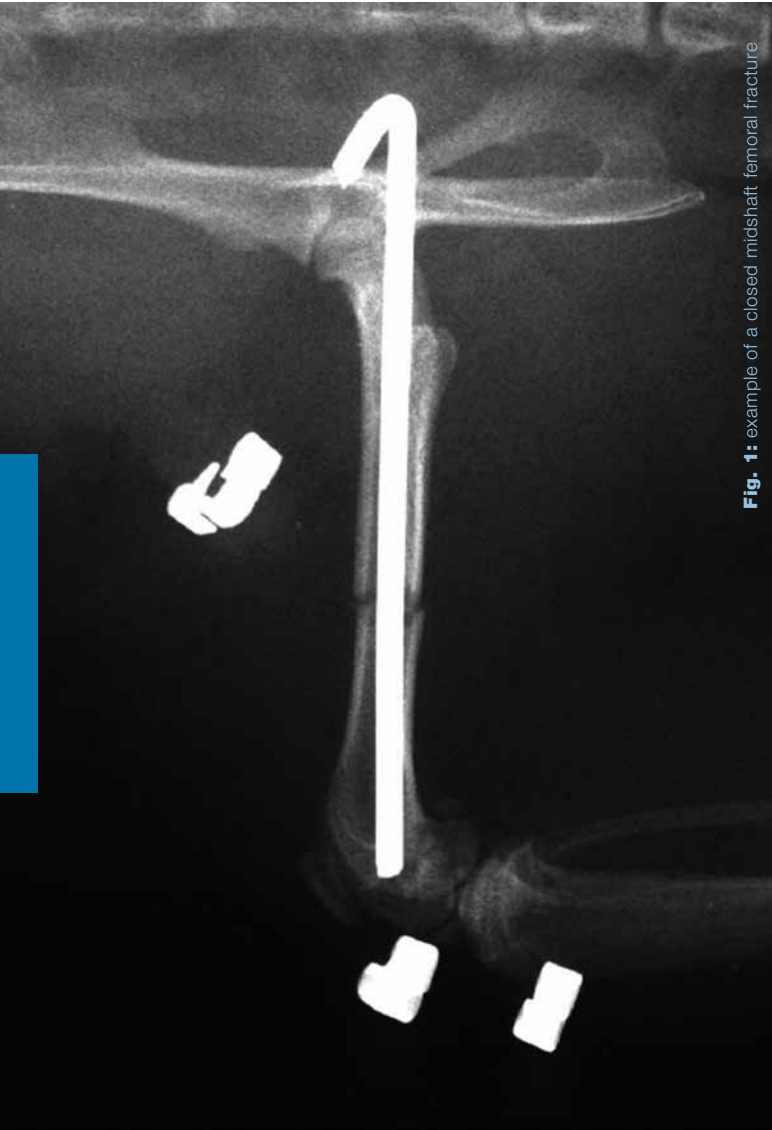


Fig. 1: example of a closed midshaft femoral fracture

#### Synopsis and progress so far:

Osteoporosis is an increasing cause of morbidity. It increases the incidence of fractures, but fixation and healing of fractures is influenced by osteoporosis as well. This leads to a high failure rate, prolonged hospital stay and associated costs and morbidity. The mechanism by which fracture healing is influenced by osteoporosis is unclear, and this project is designed to further investigate, and stimulate, the fracture healing process in the presence of osteoporosis. A rat model with closed femoral fractures is used. After an ovariectomy and 6 weeks of low-calcium diet, a closed midshaft fracture is created (figure 1), and the healing of the femoral fractures was investigated at two and four weeks, compared to fracture healing in non-osteoporotic controls. A significant delay in fracture healing in the estrogen

deficient animals was observed, with the strongest effect at two weeks after the fracture. A larger study was then performed in which the effect of treatment of these fractures was examined using a single injection of bisphosphonates (systemic, intravenously), rhBMP-7 (local, percutaneously), or both combined.

Callus formation, mechanical strength, and histology are the primary endpoints. Callus formation will be determined with radiographs and histology. As a baseline measurement of osteoporosis, micro-CT and PET-CT will be used to measure bone density and bone volume.

The mechanical tests have shown a significant increase in strength in animals treated with BMP-7 compared to no treatment. No additional benefit of the bisphosphonate treatment was seen. The evaluation of the other endpoints is ongoing.

# Young Investigator Grants 2008

## THE ROLE OF A NEW INTEGRIN LIGAND, CCN-1, IN BONE FRACTURE HEALING

### Principal Investigator:

**DR. D.A. SCHNEIDER**

University Hospital Heidelberg,  
Heidelberg, Germany

**Abstract:** Non-unions with non-healing unstable bone remain a critical problem in trauma surgery. Angiogenesis and neovascularization are indispensable during fracture repair and are dependent on the functional crosstalk between osteoblasts and endothelial cells within the bone microenvironment. We want to find out, how osteoblasts may regulate angiogenesis during fracture repair and to point out the role of the integrin ligand CCN1 (Cyr61), a secreted, extracellular matrix-associated protein of the CCN family, as the potential osteoblast-derived mediator of bone linked angiogenesis. CYR61 functions through integrin-mediated pathways to promote cell adhesion, migration, and proliferation. We want to describe the role of CYR61 in angiogenesis during bone fracture healing as a mediator of the crosstalk between osteoblasts and endothelial cells in bone angiogenesis and bone fracture healing. For this reasons we will: 1) analyze the role, the timecourse and the expression pattern of CCN1 during bone fracture healing by the use of an established model of bone fracture in mice. The expression of CCN1 and of endothelial markers of angiogenesis will be assa-

ayed by means of immunohistochemistry. 2) analyse the expression pattern of CCN1 in several osteoblast cell lines (primary human and mouse osteoblasts and osteosarcoma cell lines). As a second step, we will assess the signal transduction ways for the secretion of CYR-61 in osteoblasts. 3) analyse, if CCN1 can regulate the expression of VEGF in osteoblasts and identify a potential autocrine regulatory loop. 4) elucidate proangiogenic effects of CCN1 and effects on endothelial cells and the pathways and integrins involved and 5) analyze the difference in the degree of angiogenesis and neovascularisation between normally healing bone fractures and non-unions and see, if this difference might be due to a difference in the expression pattern of osteoblast-derived CCN1. Finally, we will make the proof of principle in bone fractures and non unions with low and high CCN1 expression. As a very long term objective we see the application of our findings in an adequate clinical approach. These findings help to define the mechanisms by which CYR61 acts as an angiogenic regulator, and emphasize the importance of CYR61 in bone angiogenesis thus

providing indispensable informations for the understanding of the process of bone fracture healing, offering a potent tool for accelerating bone fracture healing and avoiding non unions. Would an therapeutical increase of the local concentration of CCN1 at the fracture site lead to an improvement of the fracture healing process in non-unions.



## RADIOLOGICAL METHODS FOR EVALUATION OF REPARATIVE PROCESS IN REPAIR OF CLOSED DIAPHYSEAL TIBIAL FRACTURES

### Principal Investigator:

#### DR. R. STEPANOV

Ilizarov Scientific Center for Restorative Traumatology and Orthopaedics, Kurgan, Russian Federation

**Abstract:** 60 (sixty) patients with closed diaphyseal tibial fractures of type A and B [7] that are accurately reduced using the Ilizarov method will be studied with the methods of MRI, CT and DEXA. The use of CT will provide a quantitative evaluation (Hounsfield units) of the degree of bone callus maturity using the direct study of the area of interest excluding the surrounding soft tissues and independent of their volume and density. CT enables to assess the structure, and make prognosis for bone callus development even at its early stages. The study is supposed to include individuals aged 18-65 years old, matched males (30) and females (30) that have no associated chronic diseases: 20 patients aged 18-35, 20 aged 36-50 and 20 aged 51-65 years. The studies should be conducted by one month after the operation (fixation with the Ilizarov fixator), after removal of the fixator and at long-term follow-up (1-2 years). Radiographic loading by CT: minimally required number of slices (up to 10-12 depending on the extension of the fracture line), pitch – 0.5 cm, Voltage (Kv) - 130,

Current (mAs) – 70. Voluntary consent of patients to participate in the research associated with roentgenologic radiation ( , DEXA) will be signed. The results of CT and DEXA will be processed with the methods of non-parametric statistical analysis using criteria of Wilcoxon and Bradley and dispersion (variance) analysis. The use of current methods of diagnosis such as CT, MRI and densitometry will offer the researchers and surgeons the objective criteria for evaluation of osteogenesis activity, stages and terms of bone tissue reorganization after tibial fractures, and provide data for planning additional treatment or rehabilitative measures in case of impairment of the reparative process. The results of the research should reveal the dynamics of density values for various bone regions and structures in the fracture area and their relationship with fixation duration when using KT and densitometry studies. MRI will demonstrate the condition of non-mineralized portion of the tibia (bone marrow, vessels) and stages of its remodeling and would allow to judge on the degree of

normalization of the structural relationship in the bone, surrounding soft tissues for defining the term of complete remodeling and restoration of all the structural and functional relations.

# Young Investigator Grants 2008

## PATIENT FUNCTION FOLLOWING FEMORAL NECK SHORTENING AND VARUS COLLAPSE AFTER CANCELLOUS SCREW FIXATION OF ISOLATED FEMORAL NECK FRACTURES: A PROSPECTIVE MULTI-CENTER COHORT STUDY

### Principal Investigator:

**DR. M. ZLOWODZKI**

University of Minnesota, Minneapolis, MN, USA

**Abstract: AIMS:** The purpose of the present study is to assess the incidence of femoral neck shortening and varus collapse after internal fixation of isolated femoral neck fractures with multiple cancellous screws in ambulatory patients and to determine its impact on patient function using multiple validated functional outcome as well as radiographic measures in a prospective cohort of patients. We hypothesize that 1) femoral neck shortening and varus collapse following hip fracture fixation is common and 2) that femoral neck shortening and varus collapse has an adverse effect on patients' physical function despite successful fracture healing.



**METHODS:** The proposed study is a prospective multi-center cohort study in a consecutive series of patients with femoral neck fractures presenting to two University affiliated hospitals in the USA and Denmark. Patients will be followed for 1 year after the surgery.

**Eligibility criteria:** Eligible patients for the study will include those who are skeletally mature, have an isolated fracture of the femoral neck which will undergo internal fixation with cancellous screws. Patients will be evaluated clinically and radiographically 6 months and 12 months after the fracture treatment.

**Outcome parameter:** Fracture union/nonunion, the occurrence of infection, osteonecrosis and all secondary surgical procedures will be recorded. The primary subject of this study is fractures that unite. The primary outcome parameter of this study will be the SF-36 physical functioning subscore (PF). Secondary outcome parameters related to physical function will be the SF-36 role physical subscore (RF), the SF-36 physical component summary measure (PCS) and the EuroQol EQ-5D index score. Other secondary

outcome parameter will include the remaining seven SF-36 subscores and a self-reported health status on a visual analogue scale which is part of the EQ-5D. Radiographs will be independently assessed by three independent reviewers who will be blinded to the functional score results. Before the start of the study, we will categorize the degree of femoral neck shortening along the femoral neck and varus collapse into three categories: none/mild (within 5 mm / 5°), moderate (5-10 mm / 5-10°) and severe (>10 mm / >10°). Femoral neck shortening and varus malalignment will be assessed relative to the contralateral intact hip. Radiographic outcome parameters will be correlated with functional outcome scores.

**SAMPLE SIZE:** Based on conservative estimates and a prior retrospective pilot study we will need 206 patients to detect clinically relevant differences in functional outcomes between different degrees of femoral neck shortening.

## Research Grants 2008

### BIOMECHANICAL COMPARISON OF PLATE SYSTEMS WITH ANGULAR STABILITY FOR THE DISTAL FEMUR

#### Principal Investigator:

**DR. U. SCHMIDT**

Krankenhaus der Barmherzigen Schwestern,  
Ried im Innkreis, Austria

**Abstract:** Current locking plate systems exhibit significantly different mechanical properties which finally result in differences concerning fatigue strength and the corresponding displacements at failure. These parameters of the plate systems under static and dynamic compressive loads as well as the remaining strength after dynamic loading will be investigated. Plates will be loaded in a fracture model with eccentric forces representing the clinical worst case of type 33 – A3 fractures. This will induce bending moments that could possibly lead to implant failure. Within the frame of current investigations only the stability of the plate systems are investigated. The overall strength of the fixation (plate and screws) is not in the focus of this comparative study.

### A MULTICENTER RANDOMIZED CLINICAL TRIAL OF NON-OPERATIVE VERSUS OPERATIVE TREATMENT OF ACUTE ACROMIO-CLAVICULAR JOINT DISLOCATION

#### Principal Investigator:

**DR. M.D. MCKEE**

St. Michael's Hospital - University of Toronto,  
Toronto, ON, Canada

**Abstract:** The literature on the treatment approaches for a complete dislocation of the Acromioclavicular (AC) joint (Rockwood Types III, IV and V) reveals a conflicting assortment of treatment methods. Although two randomized trials have been performed, they were hampered by outdated surgical methods (trans-articular Kirschner wires) and a lack of statistical power, among other methodological flaws. There is a need for a properly powered, randomized, controlled trial to evaluate the differences in patient outcome following either non-operative or operative treatment for acute acromioclavicular joint dislocation. This study will provide comprehensive evaluation of two treatment methods. One hundred and twenty two patients will be randomized into two groups: non-operative and operative. The non-operative group will be treated with a sling for comfort/immobilization. The operative group will undergo a surgical procedure using the clavicle hook plate. Both groups will be followed for

2 years. Outcome assessments will be thorough and will include a radiographic assessment, a surgeon based shoulder score (Constant), a patient based upper extremity score (DASH) and a general health status score (SF-36).

Research Grants

2008

# Research Grants 2008

## A NOVEL ANIMAL MODEL FOR COMPARTMENT SYNDROME: PATHOPHYSIOLOGY AND THERAPEUTICS

### Principal Investigator:

#### DR. A. BADHWAR

London Health Sciences Centre - Victoria Hospital,  
London, ON, Canada

**Abstract:** Compartment Syndrome is a devastating complication of skeletal trauma. The sequelae include morbidity related to myonecrosis to amputation and systemic complications. Our laboratory has developed a novel animal model of skeletal muscle compartment syndrome, in which we demonstrated pronounced inflammatory activation associated with microvascular dysfunction and cell death using intravital videomicroscopy. In a second study, pre-treatment with indomethacin prior to inducing compartment syndrome decreased muscle cell damage and as such, may represent a potential therapeutic intervention. In this protocol, the molecular mechanisms underlying the microvascular dysfunction and inflammatory components of compartment syndrome will be investigated. The effects of indomethacin and other potential therapeutic interventions (including reduction in metabolic rate, xanthine oxidase inhibition and the induction of acute neutropenia) will be investigated. Techniques used in these studies include intravital videomicroscopy, DNA and RNA analysis, and metabolic assessments. Current treat-

ment for compartment syndrome is restricted to fasciotomy. The results of these proposed studies will add to the knowledge base surrounding compartment syndrome, and eventually help define alternative therapeutic interventions.



## A PROSPECTIVE RANDOMIZED TRIAL COMPARING OPEN REDUCTION AND INTERNAL FIXATION, NON-SPANNING EXTERNAL FIXATION, AND CLOSED REDUCTION WITH PERCUTANEOUS FIXATION IN DISPLACED DISTAL RADIUS FRACTURES WITH JOINT CONGRUITY

### Principal Investigator:

**DR. G.K. BERRY**

McGill University Health Centre - Montreal General  
Hospital, Montreal, Quebec, Canada

**Abstract:** Fractures of the distal radius, the most common fracture to occur in adults, are increasing in incidence and cost due to ageing of the population and the link with senile osteoporosis. Young adults also suffer these injuries albeit involving higher-energy mechanisms. Closed reduction and casting is often unsuccessful in maintaining adequate alignment and length, both of which are crucial to a successful outcome. Thus, there has been a trend toward surgical treatment of these fractures. In fractures with preserved joint congruity, 3 fixation options exist: percutaneous pinning and cast (Kapandji technique), non-spanning external fixation, and volar locked-plates. Which technique is most efficacious in restoring function remains unknown due to a lack of adequate scientific evidence. A recent Cochrane Group report concluded: "There is a need for good quality evidence for the surgical management of these fractures". Because of a high rate of complications with dorsal plate placement and with the advent of new fixed-

angle screw-plate designs, volar fixation has become the standard approach for distal radius fractures with joint congruity. The locking nature of the screw-plate construct produces excellent fixation even in osteopenic bone and permits early range of motion exercises. In contrast to external fixation and percutaneous pinning, no tethering of muscle, tendon or capsule occurs with plate fixation and thus motion of the wrist and fingers is uninhibited. These advantages would suggest that plate fixation with a volar fixed-angle device should permit earlier and more aggressive rehabilitation and more rapid and certain regain of function when compared to stabilization with external fixation or percutaneous pinning, although this has yet to be studied in a systematic way. The aim of this prospective randomized clinical trial is to compare the functional, clinical and radiographic outcomes of these 3 fixation methods. The trial will be run through the Canadian Orthopaedic Trauma Society (COTS),

a group of orthopaedic surgeons devoted to clinical outcome research with a proven track record. A total of 108 patients per treatment arm will be recruited over a 2 year period and followed for 2 years using validated outcome measures to evaluate functional, radiographic and clinical outcome. The results will guide surgeons in the choice of optimal technique in ensuring best functional, radiographic and clinical outcome in patients suffering from this common fracture.



# Research Grants 2008

## PROSPECTIVE RANDOMIZED CONTROLLED TRIAL OF THE EFFICACY OF LOW-MAGNITUDE, HIGH-FREQUENCY VIBRATION TREATMENT ON OSTEOPOROTIC HIP FRACTURE HEALING

### Principal Investigator:

**DR. K.S. LEUNG**

The Chinese University of Hong Kong, Hong Kong,  
China

**Abstract:** Osteoporotic hip fracture is very common in elderly, which usually accompanies with long-time recovery and limited mobility due to the low reparative capacity of osteoporotic bones. Interventions to provide mild mechanical stimulation to accelerate fracture healing, therefore, have great implication on medico-social benefits. Low-magnitude, high-frequency vibration (LMHFV) treatment is a biophysical modality proven to be effective in enhancing bone quality, muscle performance and circulation in normal bone. Our previous study of LMHFV on femoral fracture in rats showed acceleration of fracture healing resulted from enhanced callus formation and maturation. Application of LMHFV on osteoporotic fractures could shorten the period of complete callus bridging by 30%, with upregulation of expression of collagen I, II and BMP-2. Our clinical trial on normal elderly also demonstrated improved muscle performance with good compliance, which is also a critical factor for fracture healing. In this study, we therefore hypothesize that LMHFV can enhance hip fracture healing by enhancing fracture impaction, maintaining bone

mineral density, enhancing muscle recovery, thus improving implant mechanical stability and rehabilitation in elderly patients. The objectives are to study the efficacy of LMHFV on osteoporotic hip fracture healing in elderly patients and to document the safety issue related to such an application on post-operative hip fracture patients.





## EFFECT OF MANNOSE-BINDING LECTIN POLYMORPHISMS ON SUSCEPTIBILITY TO INFECTIOUS COMPLICATIONS IN TRAUMA PATIENTS

### Principal Investigator:

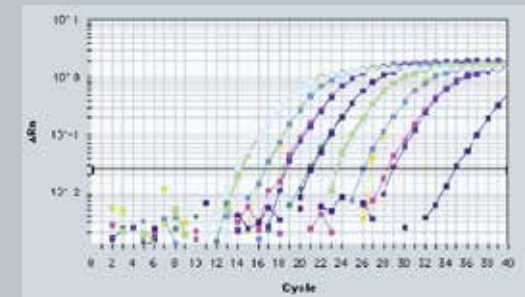
**DR. E.M.M. VAN LIESHOUT**

Erasmus MC, Rotterdam, the Netherlands

**Abstract:** Infection and sepsis are serious complications that occur in up to 10% of trauma patients. Sepsis, bloodstream infections, (ventilator-associated) pneumonia and surgical site infections seriously hamper recovery, and may eventually lead to death. The innate immune system is the first line of defense against invading microorganisms. It consists of the classic, alternative and the lectin pathway. The central molecule in the lectin pathway is Mannose-Binding Lectin (MBL). Binding of MBL to carbohydrates present on pathogens activates the lectin pathway of complement activation, resulting in opsonization and antimicrobial protection. Three frequently occurring single nucleotide polymorphisms (SNPs) are described in exon 1 of the MBL-2 gene. They are associated with abnormal polymerization of the MBL molecule, decreased serum concentrations, and strongly impaired function of MBL protein. In addition, SNPs in the promoter region and the 5' untranslated region of the MBL-2 gene reduce the promoter activity and, hence, result in reduced

protein levels. Clinical studies have shown that SNPs in the MBL-2 gene are associated with increased susceptibility to infections, especially in immune-compromised persons. Injury challenges the immune system of trauma patients, therefore an optimal immune status is important. The aim of this study is to determine to what extent MBL-2 polymorphisms are a risk factor for (serious) infectious complications and subsequent mortality in trauma patients with an Injury Severity Score (ISS) of 16 or higher. The hypotheses are that trauma patients (ISS $\geq$ 16) with low MBL levels due to SNPs in the MBL-2 gene display a higher rate of (1) serious infectious complications and (2) mortality due to these complications than patients with wildtype genotype and protein levels. Four hundred and fifty consecutive trauma patients (ISS $\geq$ 16, age 18-70 years, formerly healthy) who are admitted to the Erasmus MC will be enrolled upon given informed consent. Two blood samples (10 ml each) will be taken, one without anticoagulant and one with EDTA. Serum MBL levels will be measured using an enzyme-linked immunosorbent assay (ELISA). Upon routine DNA extraction from EDTA blood, SNPs in exon 1 and the promoter region of MBL-2 will be typed by pyrosequencing and conven-

tional polymerase chain reaction, respectively, following validated and published protocols. Primary clinical endpoints are bloodstream infection, pneumonia, systemic inflammatory response syndrome, sepsis and septic shock. Secondary endpoints are death within 3 months, surgical site infection and osteitis after osteosynthesis treatment of fractures. Definitions for these endpoints follow international agreements. Both univariate and multivariate analyses will be performed.



# Research Grants 2008

## DO BISPHOSPHONATES INHIBIT DIRECT OSTEOAL (BUT NOT INDIRECT) FRACTURE HEALING?

### Principal Investigator:

**DR. A.H.R.W. SIMPSON**

The University of Edinburgh, Edinburgh, UK

**Abstract:** Fractures repair by two broad mechanisms. Direct osteonal healing requires absolute stability at the fracture site and is achieved by rigid internal fixation. Indirect healing by callus formation relies on some mobility at the fracture site. Bisphosphonates are a class of drug with proven efficacy to prevent fragility fractures and their mode of action is via inhibition of osteoclast activity that prevents bone resorption. However in direct healing osteoclasts are of pivotal importance in the initiation of the fracture healing process. As there are a great number of ageing patients with osteoporosis on bisphosphonates who will continue to sustain fragility fractures, there is a need to enhance our understanding of the effects of bisphosphonates on fracture healing. Specifically, this study will ascertain whether bisphosphonates inhibit direct osteonal fracture healing. This is a crucial research question as the literature concerning bisphosphonate effects on fracture healing has been solely derived from models of indirect fracture healing by callus formation. This study will provide information that will assist trauma surgeons in choosing the most appropriate method

of fracture fixation for patients on bisphosphonates. This research will be conducted in a well-established unit with significant experience of the experimental protocols to be used within this study. A rat model of tibial osteotomy stabilised by both external and rigid internal fixation techniques is well established in our laboratory. Skeletally mature male ex-breeder rats will be used as this more closely resembles adult human bone. The effects of bisphosphonates will be assessed on direct and indirect fracture healing and compared to that of controls. Different regimens of bisphosphonate dosing will be used to assess the effect of timing of bisphosphonate delivery relative to the fracture in order to reflect the clinical scenarios of patients sustaining fractures whilst on bisphosphonate therapy and others who may be due to start therapy immediately after fracture. Fracture healing and cell function will be assessed using established radiographic, mechanical, histological, immunocytochemical and image analysis techniques.

## Young Investigator Grants 2009

### EFFECT OF MULTIPLE AND DELAYED ADMINISTRATIONS OF CELL-BASED VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) GENE THERAPY ADMINISTRATIONS ON A SEGMENTAL BONE DEFECT

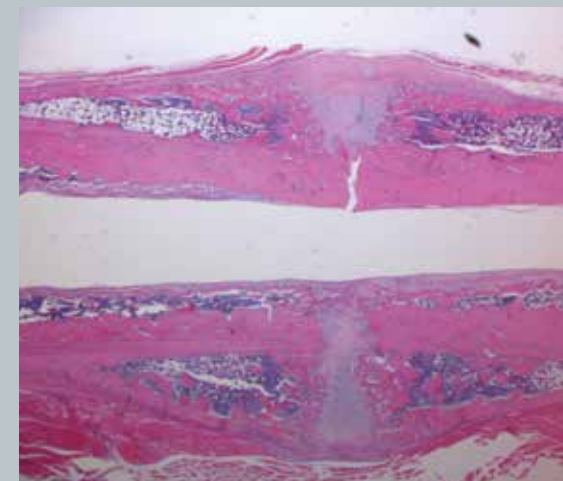
#### Principal Investigator:

#### DR. E. QAMIRANI

St. Michael's Hospital - University of Toronto, Toronto, ON, Canada

**Abstract:** Fracture healing can be a lengthy process that might have a detrimental effect on the patient and the medical system if it is complicated by delayed union or nonunion of the fracture. Therefore, developing strategies to accelerate bone healing and prevent complications related to it is of utmost importance to orthopedic trauma care. Vascular endothelial growth factor (VEGF) plays a key role during bone healing through its angiogenic and osteogenic effects. The objective of this proposed study is to evaluate the in vivo effect of cell-based VEGF therapy on a segmental bone defect. The first specific aim is to evaluate the effect of early administration of mesenchymal cell (MSC)-based VEGF gene therapy on fracture healing as compared to delayed administration. The second specific aim is to determine the effect of multiple cell-based VEGF therapy treatments during the entire fracture healing process as compared to a single administration. To achieve these aims, single injections of VEGF-transfected MSCs will be administered at a segmental bone defect in rat

femurs at different time intervals during fracture healing (days 0, 3, 7, and 14 after the creation of the defect). In addition, rats that will receive multiple injections of VEGF-transfected MSCs on each described time interval will be compared to rats that receive a single injection. Non-transfected MSCs or saline will be injected as control in matched groups of rats. Fracture healing among the different treatment and control groups will be evaluated eight weeks after the creation of the bone defect by radiography (plain radiographs and Micro CT), immunohistochemistry, and biomechanical testing. In addition, callus VEGF levels will also be determined. The duration of this study is expected to be 12 months. This proposed project will not only increase the current understanding of the complex fracture-healing process, but will also provide new treatment strategies for accelerating bone healing and preventing complications related to it.



# Young Investigator Grants 2009

## PREDICTING ACETABULAR FRACTURE PROGNOSIS THROUGH QUANTITATIVE WEIGHT-BEARING AREA DAMAGE EVALUATION

### Principal Investigator:

**DR. O. LUBOVSKY**

Sunnybrook Health Sciences Center -  
University of Toronto, Toronto, ON, Canada

**Abstract:** Displaced acetabular fractures occur in young adults involved in high-energy trauma and can lead to disabling post-traumatic arthritis. Some fracture patterns induce worse prognosis than others. Decisions must be made as to whether to treat with surgery and if so, what kind of surgical approach (open/close reduction, acute or delayed arthroplasty). In addition to clinical and qualitative measures, quantitative assessment of CT scan data may be useful in estimating the prognosis of acetabular fractures. This study aims to develop a method for automated quantitative CT based assessment of acetabular fracture patterns through evaluation of the initial damage to the weight bearing area of the fractured acetabulum and compare these findings to functional outcome at 6, 12 and 24 months from injury. We hypothesize that a negative correlation exists between the initial damage to the weight bearing area of the acetabulum and functional outcome in acetabular fractures.

Previous work has demonstrated uneven load distribution patterns around the acetabulum when intact and especially after fracture. Bone density, which may be used to represent relative weight bearing, can be derived from the intensity values in the CT data. We have previously developed a 3D CT based algorithm to map these density patterns of intact acetabular bone on its geometry to calculate the functional orientation of the acetabulum. In this study, based on a pelvic and acetabular trauma database that is maintained at our institution, we will conduct a retrospective analysis of acetabular cup surface bone density maps for patients with unilateral acetabular fractures. In the injured acetabulum, the original injury fracture fragments will be segmented and reconstructed to generate acetabular cup surface bone density maps. The acetabuli will then be further divided into 3 concentric circles and quadrants to yield 12 mapped regions. Characterization of the extent of injury in each of the 12 regions by the % of region damaged will enable us to quantify the weight

bearing area damage.

This measure of damage will then be correlated with functional outcome at 6, 12 and 24 months post injury. Future work will use this data in the development of a comprehensive scoring system for predicting outcome following acetabular fracture.

## QUANTITATIVE ASSESSMENT OF THE BONE MORPHOGENIC PROTEINS AND GRANULIN-EPITHELIN PRECURSOR (A NOVEL MUSCULOSKELETAL GROWTH FACTOR) FROM ALTERNATE BONE-GRAFT HARVESTING SITES

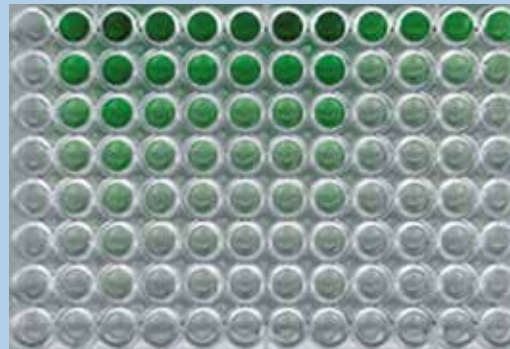
### Principal Investigator:

**DR. M.R. FAJARDO**

NYU Hospital for Joint Diseases, New York, NY, USA

**Abstract:** Autogenous bone graft is a common procedure in orthopedic surgery. The bone morphogenic proteins, GEP, and other related growth factors play an important role in the bone grafts efficacy. It is unknown whether a bone graft donor site is rich in these growth factors, and if concordantly, one harvest site is advantageous over the other. The objective of this study is to determine if the concentration of bone morphogenic proteins, GEP, and other growth factors are different in terms of the bone graft harvest location. This will initially be screened at the mRNA level by quantitative real time polymerase chain reaction and confirmed at the

protein level by enzyme linked immunosorbent assays (ELISA). In identifying a superior bone graft harvesting site; this can lead to less surgery, less donor site morbidity, and increased surgical efficacy. This study's results can influence the manner in which orthopedic surgeons attain bone graft. The characterization of GEP can lead to its use as a bone graft substitute. The null hypothesis is that all surgical harvest sites are equal in terms of growth factor concentrations.



## Research Grants 2009

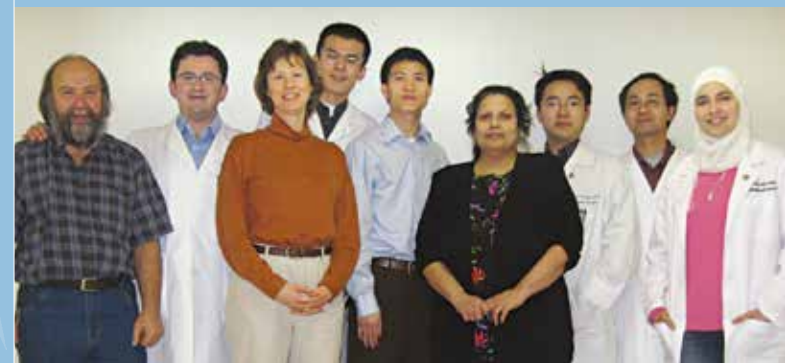
Open fracture associated infection is a significant clinical complication affecting millions of people annually. Patients with open fractures have a high risk of infection due to bacterial contamination and soft tissue damage. The objective of this project is to develop local encapsulated interleukin-12 (IL-12) therapy to prevent *Staphylococcus aureus*-induced infection in an open fracture. The proposed work is innovative because (i) it develops a non-antibiotic approach for infection prevention by stimulating the body's natural immune system to fight pathogens

### **NANOTECHNOLOGY BASED IL-12 MICROCAPSULES FOR INFECTION PREVENTION IN OPEN FRACTURES - A PILOT STUDY**

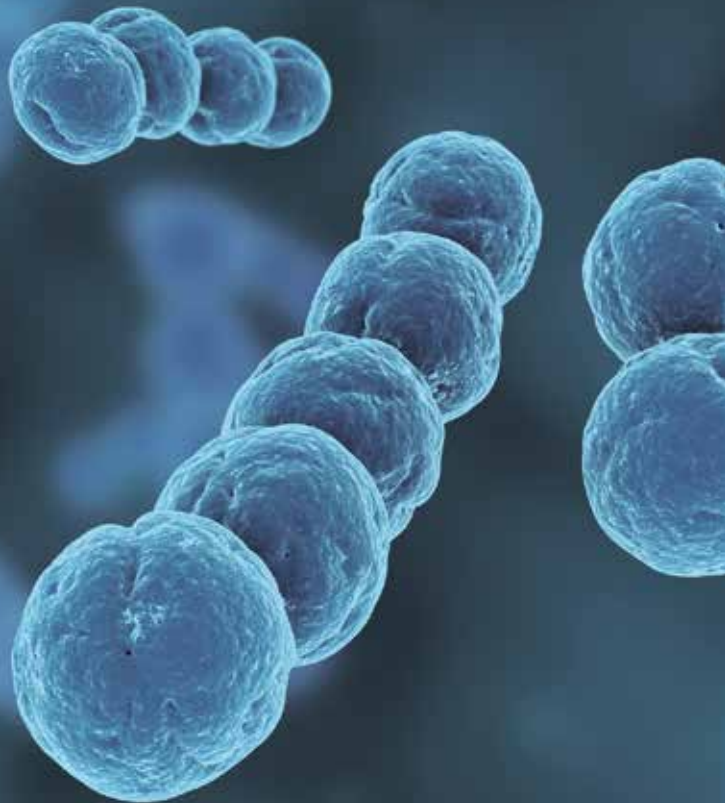
and (ii) the nanotechnology based microcapsules are injectable and can easily be combined with other drug microcapsules. This project will carry out some pilot experiments to determine the effects of local IL-12 microcapsule treatment on infection prevention and bone healing.

A team with expertise in bioengineering, nanotechnology, biochemistry, molecular biology, orthopaedic surgery, and immunology has been established to carry out this project. Dr. Bingyun Li is an Assistant Professor in the department of Orthopaedics at West Virginia University. He was an invited speaker and panelist for a premier nanomedicine event in 2008 and has given more than 10 invited talks nationally and internationally. The research in Dr. Li's group focuses on developing advanced methods for

## Research Grants 2009



**BINGYUN LI, PHD AND FRANKLIN D. SHULER MD, PHD**  
West Virginia University, Morgantown, WV, USA



infection prevention and wound healing. Dr. Li has extensive experience with advanced orthopaedic materials and drug delivery. He, as well, contributed to early studies in the design of polypeptides for electrostatic layer-by-layer self-assembly. He has published more than 30 articles in journals with high impact factors. The Co-PI, Franklin D. Shuler, MD, PhD, is the Director of Orthopaedic Research and an Orthopaedic Traumatologist. He is a regional and nationally known expert in Orthopaedic Trauma and served as a panelist and speaker for the AAOS Instructional Course Lecture on postoperative infections. He is the PI or Co-PI on several active multi-center, multi-national, randomized, controlled clinical trials and has numerous publications. His laboratory focuses on establishing new and novel biomarkers for the detection of impact related cartilage damage in trauma patients.

The success of the project will lead to a new approach to treat patients with severe open fractures with high risk of contamination (e.g. Gustilo grade III open fractures). Antibiotic resistance is becoming more and more problematic; the developed approach may reduce antibiotic use and antibiotic resistance. It may also change the way orthopaedic surgeons treat infection; local IL-12 therapy could be an alternative to antibiotic therapy.



## Research Grants 2009

### DIFFERENTIALLY LOADED RADIOSTEREOMETRIC ANALYSIS TO MEASURE FRACTURE STIFFNESS OF HEALING FEMORAL FRACTURES IN VIVO

#### Principal Investigator:

**DR. M. CHEHADE**

Royal Adelaide Hospital - University of Adelaide,  
Adelaide, Australia

**Abstract:** The 2007 International Society for Fracture Repair Symposium identified the lack of an accurate and objective assessment tool to monitor fracture healing as a fundamental hindrance to advances in fracture management. Development of such a tool must be a priority because up to 10% of extremity fractures do not heal properly, with consequent distress and cost. If it were possible to a) accurately determine when a fracture has healed, b) predict when it is not going to heal and c) define optimal management protocols, clinical outcomes could be vastly improved, with less suffering, quicker return of function and reduced costs. Also, new methods to promote fracture healing could be objectively assessed. The goal of fracture repair is restoration of function, which requires the ability to withstand loading and measures of fracture healing, with the need to assess the ability of the healing bone to function under load. The aim of this two-year study is to further develop a novel method to monitor fracture stiffness (ability to endure load) during healing in a clinical research setting. This will be done by detecting changes in fracture displacement, using ra-

diostereometric analysis (RSA), while simultaneously measuring applied axial loads; a technique termed differentially loaded RSA.



## REGULATION OF VEGF EXPRESSION DURING CELL-BASED GENE THERAPY FOR BONE HEALING

### Principal Investigator:

#### DR. E.H. SCHEMITSCH

St. Michael's Hospital - University of Toronto,  
Toronto, ON, Canada

**Abstract:** **Background:** The repair of large bone defects caused by trauma, tumor and disease remains a major clinical challenge in orthopedics. Cell-based hVEGF gene transfer, without viral vector, has been effective in the treatment of bone segmental defects by inducing the development of new blood vessels and improving osteogenesis in a rabbit model in our previous studies (Li, Schemitsch JOR, 2008). Nevertheless, there is concern regarding on-going gene over expression from delivered transfected cells that remain active at the fracture site. Therefore, we will study the regulation and duration of gene expression and cell activity so that we may provide evidence to show safety and improve the potential for use of cell-based gene therapy in the human fracture situation.

**Aims:** 1) To quantify the exogenous VEGF concentration during the course of fracture healing, and to detect the relationship between the exogenous VEGF and endogenous VEGF and other factors, which have relevance to fracture healing;  
2) To investigate whether the VEGF expression would vary with angiogenesis increasing in a fracture gap;

and 3) To determine whether the effect of transfected fibroblast cells would be reduced by increasing bone formation.

**Methods:** Fibroblast based VEGF gene therapy for a rat femur segmental bone defect model will be studied. 147 Fisher 344 rats will be randomly divided into three groups based on fibroblast cell transfection with VEGF or  $\beta$ -gal, each group subdivided into 7 sub-groups based on the time point of specimens being collected. Group 1) Fibroblast cells-VEGF (n=49), 2) Fibroblast cells- $\beta$ -gal (n=49), and 3) Saline only (n=49). The animals will be sacrificed and specimens will be measured and examined at 1, 2, 3, 6, 12, 24, and 52 weeks using radiographs, histochemistry, histology, microarray analysis, RT-PCR, ELISA or Western blotting, Micro-CT, and biomechanical testing. The data will undergo statistical analysis.



## Research Grants 2009

### CAN LOW INTENSITY PULSED ULTRASOUND ACCELERATE SYSTEMIC RECRUITMENT OF OSTEOBLASTIC CELLS FOR FRACTURE HEALING?

#### Principal Investigator:

**DR. W.H. CHEUNG**

The Chinese University of Hong Kong, Hong Kong, China

**Abstract:** In fracture repair, recruitment of reparative MSCs (mesenchymal stem cells), vascularization and mechanical modulation are three key determinants for success healing. In bone fracture, recruitment of MSCs is predominantly from local bone marrow and periosteum. Our previous study has proven that some osteoblasts involved in fracture repair were systemically mobilized and recruited to the fracture from remote bone marrow sites via peripheral circulation. This is substantiated by other studies that mesenchymal precursor cells engrafted into bone marrow and bone preferentially. A murine model study also showed that bone marrow cells homed to the marrow after systemic injection and localized in fracture callus. This evidence supports the preferential, active homing of mesenchymal or osteoblastic cells to the fracture sites. Recent research on low intensity pulsed ultrasound (LIPUS) shows promising evidences that acoustic wave provides micro-motion mechanical stimulation onto the healing tissues. LIPUS is shown to increase cellular activities and cytokine production in many cell types. It can also enhance blood flow. Clinically, many RCTs prove its

efficacy in accelerating fracture healing by 30%, including our previous study on complex fracture healing. LIPUS is therefore effective in modulating the mechanical micro-environment to stimulate fracture healing. Based on above scientific evidences, we hypothesize that LIPUS can enhance the systemic recruitment of intravenously administered MSCs for fracture healing. This is justified by enhanced production of chemoattractive cytokines, increased blood flow to enhance circulating MSCs and promoted cellular activities and differentiation of MSCs to osteogenic lineage after LIPUS treatment. The objectives of this study are to investigate the effect of LIPUS on intravenously administered MSCs homing to the fracture site and to evaluate its efficacy to accelerate fracture healing. The homing effect to fracture callus will be assessed by in vivo bioluminescence imaging on the luciferase-marked MSCs while the status of fracture healing is monitored by comparing with groups without LIPUS or no-treatment control groups. The findings of this study may potentially help to develop an alternative approach to treat non-unions or accelerate fracture healing clinically.

### BONE REGENERATION IN CRITICAL-SIZE GAP INDUCED BY ENDOTHELIAL PROGENITOR CELLS

#### Principal Investigator:

**DR. D. LEWINSON**

Rambam Health Care Campus, Haifa, Israel

**Abstract:** In approximately 10% of all fractures the defect is too large for the body's natural healing response and delayed or non-unions develop at the trauma site. The gold standard treatment for healing these bone defects is transplantation of autologous bone tissue. This process has several drawbacks including limited body sites from which bone may be harvested and donor site morbidity. The present preclinical study will test the feasibility of a new approach for healing large bone defects in which implantation of peripheral blood derived endothelial progenitor cells (EPC) induce bone regeneration. We have previously shown the potential of sheep EPC to induce bridging of a 3.2 cm gap in tibia by 3 months. The direct implantation of EPC to the traumatized site reduces the hazard of homing to other organs and allows efficient beneficial effect. Human EPC (hEPC) will be harvested from healthy volunteers and grown in-vitro. To test their bone induction ability, they will be applied to a 5 mm gap created in immunodeficient rats' tibiae. Doses of low (50,000) and high (500,000) hEPC will be mixed with scaffold of hyalu-

ronic acid-fibrinogen hydrogel and will replace the scar tissue formed 1 week post trauma. Localization of fluorescence labeled hEPC in the healing bones will be tested 1 & 2 w post implantation by confocal microscopy of frozen sections (performed during first 6 m). The possible transformation of hEPC into osteoblasts and their angiogenic /vasculogenic potential will be studied by double staining with antibodies directed specifically against human osteocalcin and rat PCAM-1. Histomorphometric evaluation of the regeneration process (H&E, alcian blue-hematoxylin) and of the vasculature (PCAM-1 immunohistochemistry) will be conducted 2 & 4 w post implantation (performed during 1st year). To evaluate the quality of the new bone formed, 8 w post implantation  $\mu$ CT scans will be performed. Mechanical resistance to torsion 12 w post surgery will compare the maximum failure torque of bones healed by hEPC to uninjured bones and to sham-operated bones. The results of this study will pave the way to a clinical study in which autologous hEPC will heal large bone defects in trauma patients. This approach eliminates disease transmission, immunologic rejection and minimizes infections that accompany non autologous cell-based therapies or use of animal-derived conductive materials.

## PHENOTYPICALLY UNMODIFIED MESENCHYMAL STEM CELLS FOR BONE REGENERATION

### Principal Investigator:

**DR. Z. ZHANG**

Saint Louis University, St. Louis, MO, USA

**Abstract:** The functionality of mesenchymal stem cells (MSCs) may determine the healing of a fracture. Current knowledge of MSCs is largely accumulated from characterization of MSCs in vitro. The cultured MSCs are a heterogenic population of cells. During culture, MSCs are modified phenotypically and functionally by the in vitro environment. Recent discovery of a new MSC marker, CD271, makes it possible to select MSCs without altering their phenotypes. The working hypothesis of this project is that unmodified MSCs are more effective in fracture repair than culture-isolated MSCs, since prolonged exposure to in vitro conditions modifies MSC functionalities.

In this study, bone marrow will be collected during intramedullary fixation of tibial fractures. MSCs will be selected based on the surface marker of CD271 (CD271-MSCs). For study control, MSCs will be isolated with a traditional protocol, i.e. plastic adhesion (PA-MSCs). In the first part of this project, the CD271-MSCs will be characterized with a panel of cell surface markers in comparison with PA-MSCs. In the second part, phenotypically modified PA-MSCs and unmodified CD271-MSCs will be implanted into

“critical size” bone defects in nude rats for comparison of their osteogenic capacity in vivo. Bone regeneration in the bone defects will be quantitatively measured with micro-CT and histomorphometry. The regenerated bone will also be subjected to 3-point bending tests. The long-term goal of this study is to address the importance of unmodified MSC phenotype in fracture healing, and to improve the outcomes of MSC applications in orthopedic traumatology.

# Research Grants 2009

## CAN MULTI-PLANAR FIXATION IMPROVE THE STRENGTH OF LOCKED PLATING CONSTRUCTS?

### Principal Investigator:

**DR. M. BOTTLANG**

Legacy Research & Technology Center, Portland, OR,  
USA

**Abstract:** Locked plating provides superior fixation strength in metaphyseal bone. However, diaphyseal fixation remains prone to fixation failure by screw breakage or screw pull-out. Several recent studies have described the principal cause for diaphyseal fixation failure to be plate elevation, which imposes excessive bending forces to the screw-bone interface under torsional loading. The proposed research will determine, if this characteristic weakness of locked diaphyseal fixation in torsion can be overcome by a staggered, multi-planar arrangement of locking screws in the osteosynthesis plate.

Specifically, the proposed research will test the hypothesis, that multi-planar fixation of a locking plate in the diaphysis can provide significantly greater fixation strength compared to the traditional fixation technique with locking screws being placed along a linear hole pattern. To test this hypothesis, two specific aims will be completed, correlating to the two specific failure modes observed clinically.

Specific Aim 1 will measure the effect of multi-planar fixation on the strength of diaphyseal plating constructs with uni-cortical locking screws. Specific Aim 2 will measure the effect of multi-planar fixation

on the strength of diaphyseal plating with bi-cortical locking screws.

After successful completion, results of this research will provide conclusive evidence if multi-planar fixation can improve the fixation strength of locked plating. If true, this research would provide a readily applicable strategy to improve the strength of locking plate fixation in diaphyseal bone, while retaining the benefits of plate elevation for less-invasive, biological fixation. As a consequence, this research strategy has a strong potential to reduce the incidence of diaphyseal fixation failures seen with locked plating.



## ANKLE FRACTURE PLATING: A MULTICENTER RANDOMIZED TRIAL COMPARING LATERAL AND ANTIGLIDE PLATING IN DISPLACED LATERAL MALLEOLUS FRACTURES

### Principal Investigator:

**DR. L. PHIEFFER**

The Ohio State University Medical Center, Columbus,  
OH, USA

### Abstract:

Ankle fractures are one of the most common injuries requiring orthopaedic care. The role of operative fixation of unstable, displaced lateral malleolus fractures is well-established. However, the optimal type of fixation remains the subject of debate. The choices for fibular stabilization most commonly involve the use of plates and screws which can be placed on either the lateral or posterior side of the bone, with or without lag screws. Lateral plating remains the most popular option, but since the description of posterior plating, reports in the literature have demonstrated some advantages of posterior over lateral plating. These include less dissection, less palpable hardware, and decreased likelihood of intra-articular screw placement. Despite the proposed advantages, no prospective study has directly compared the outcomes of these two methods.

This prospective, multicenter RCT will assess the functional and radiographic results of patients who have sustained a closed ankle fracture requiring

surgical fixation with lateral malleolar fracture pattern amenable to direct lateral or posterior antiglide plating techniques. A total of 144 subjects will be enrolled and followed for a period of one year. Follow up will be clinical, radiographic, and patient-based. General outcome will be determined by the SF-12v2 survey, and disease-specific outcomes will be assessed by the Short Musculoskeletal Functional Assessment (SMFA) and the AOFAS Clinical Rating System Score.

The results of the proposed study will help clarify the advantages and disadvantages of these techniques utilizing patient based, objective physical examination, and radiologic outcomes measures. This will aid orthopedic surgeons in deciding the best treatment options for these common injury patterns.



# Publications

## PUBLICATIONS

**Leung KS, Shi HF, Cheung WH, Qin L, Ng WK, Tam KF, Tang N.** Low-Magnitude High-Frequency Vibration Accelerates Callus Formation, Mineralization, and Fracture Healing in Rats. *J Orthop Res* 2008; 27(4):458-65.

**Morshed S, Miclau T 3rd, Bembom O, Cohen M, Knudson MM, Colford JM Jr.** Delayed internal fixation of femoral shaft fracture reduces mortality among patients with multisystem trauma. *J Bone Joint Surg Am.* 2009;91(1):3-13.

**Petrisor B, Jeray K, Schemitsch E, Hanson B, Sprague S, Sanders D, Bhandari M,** On Behalf Of The Flow Investigators. Fluid lavage in patients with open fracture wounds (FLOW): an international survey of 984 surgeons. *BMC Musculoskeletal Disorders* 2008;9:7.

**Zlowodzki M, Brink O, Switzer J, Wingerter S, Woodall J, Petrisor BA, Kregor PJ, Bruinsma DR, Bhandari M.** The effect of shortening and varus collapse of the femoral neck on function after fixation of intracapsular fracture of the hip. A multi-centre cohort study. *J Bone Joint Surg Br.* 2008;90(11):1487-1494.

## PRESENTATIONS

**Bhandari M, Petrisor B, Jeray K, Schemitsch E, Hanson B, Sprague S, Sanders D.** Fluid Lavage in Open Fracture Wounds (FLOW): An International Survey. European Federation of National Associations of Orthopaedics and Traumatology (EFORT), (May 29-June 1, 2008, Nice, France). Poster Presentation.

**Blokhuis TJ.** Fracture Healing in Osteoporosis. OTC Annual General Meeting (June 26-28, 2008, Nice, France). Oral Presentation.

**Cheung WH, Shi HF, Qin L, Lee KM, Leung KS.** Effect of Low Magnitude, High Frequency Vibration Therapy on Fracture Healing – Rat Model. International Symposium on Vibration Therapy (December 2006, Hong Kong, China). Oral Presentation.

**Cheung WH, Shi HF, Qin L, Leung KS.** Augmentation of callus formation and mechanical properties of fracture healing in ovariectomized rats by low-magnitude high-frequency vibration treatment. 55th Annual Meeting of Orthopaedic Research Society (February 2009, Las Vegas, USA). Oral presentation.

**Kuzyk PR, Davies JE, Schemitsch EH.** The Effect of Intramedullary Reaming on a Diaphyseal Bone Defect of the Tibia. 55th Annual Meeting of the Orthopaedic Research Society (February 2009, Las Vegas, USA). Poster Presentation.

**Kuzyk PR, Davies JE, Schemitsch EH.** The Effect of Intramedullary Reaming on a Diaphyseal Bone Defect of the Tibia. British Trauma

Society Annual Clinical Meeting (May 2009, Newcastle, UK). Oral Presentation.

**Kuzyk PR, Davies JE, Schemitsch EH.** The Effect of Intramedullary Reaming on a Diaphyseal Bone Defect of the Tibia. Canadian Orthopaedic Association Annual Meeting (July 2009, Whistler, Canada). Oral Presentation.

**Kuzyk PR, Schemitsch EH, Davies JE.** A Biodegradable Scaffold for the Treatment of a Diaphyseal Bone Defect of the Tibia. 55th Annual Meeting of the Orthopaedic Research Society (February 2009, Las Vegas, USA). Poster Presentation.

**Kuzyk PR, Schemitsch EH, Davies JE.** A Biodegradable Scaffold for the Treatment of a Diaphyseal Bone Defect of the Tibia. British Trauma Society Annual Clinical Meeting (May 2009, Newcastle, UK). Oral Presentation.

**Kuzyk PR, Schemitsch EH, Davies JE.** A Biodegradable Scaffold for the Treatment of a Diaphyseal Bone Defect of the Tibia. Canadian Orthopaedic Association Annual Meeting (July 2009, Whistler, Canada). Oral Presentation.

**Morshed S.** Femoral nailing in bicarbonate-defined hypoperfused trauma patients predicts pulmonary dysfunction. American Academy of Orthopedic Surgeons (March 2008, San Francisco, CA, USA). Oral Presentation.



## Presentations

**Morshed S, Miclau T, Bembom O.** Delayed femoral shaft fracture internal fixation in multi-system trauma patients decreases mortality in the National Trauma Data Bank. Orthopedic Trauma Association Meeting (October 2007, Boston, MA, USA). Oral Presentation.

**Petrisor B, Jeray K, Schemitsch E, Hanson B, Sprague S, Sanders D, Bhandari M, FLOW investigators.** Fluid Lavage of Open Fracture Wounds (FLOW): A survey of 984 surgeons. Orthopaedic Trauma Association (October 2007, Boston, MA, USA). Poster Presentation.

**Petrisor B, Jeray K, Schemitsch EH, Hanson B, Sprague S, Sanders D, Bhandari M.** Fluid Lavage in Open Fracture Wounds (FLOW): An International Survey. International society for fracture repair (July 14-16, 2009, Lake Tahoe, Nevada, USA). Poster Presentation.

**Petrisor B, Jeray K, Schemitsch E, Hanson B, Sprague S, Sanders D, Bhandari M.** Fluid Lavage in Open Fracture Wounds (FLOW): An International Survey. Canadian Orthopaedic Ass. (6- 4-8, 2008, Quebec City, Can.). Oral Presentation. Poeze M. Effect of NO metabolism on bone metabolism in non-union. Research Meeting University Hospital Maastricht September 2007, Maastricht, the Netherlands. Oral Presentation.

**Punt BJ, Jansen JHW, Fontijne WPJ, Weinans H.** Stimulatie van Osteoblasten door Pulserende Elektromagnetische Velden Traumadagen (Nov. 3-4, 05, Ede, The Netherlands) Oral Presentation.

**Shi HF, Cheung WH, Qin L, Lee KM, Chan KW, Leung KS.** Expression of type I/II collagen and BMP-2 gene in low-magnitude high-frequency vibration treated rat fracture healing. 2nd International Congress of Chinese Orthopaedic Association (November 2007, Zhengzhou, China). Poster Presentation.

**Shi HF, Cheung WH, Qin L, Lee KM, Chan KW, Leung KS.** Regulation of Type I/II Collagen and BMP-2 in Low-magnitude High-frequency Vibration Treatment on Fracture Healing – A Rat Study. 27th Annual Congress of The Hong Kong Orthopaedic Association (November 2007, Hong Kong, China). Oral Presentation.

**Shi HF, Cheung WH, Qin L, Lee KM, Leung KS.** Effect of Low-magnitude, High-frequency Vibration Therapy on Fracture Healing in Rats. 53rd Annual Meeting of Orthopaedic Research Society (February 2007, San Diego, USA). Poster Presentation.

**Shi HF, Cheung WH, Qin L, Lee KM, Leung KS.** Low-Magnitude, High-Frequency Vibration accelerates Fracture Healing in Rats. 16th IAA Human In Space Symposium (May 2007, Beijing, China). Oral Presentation.

**Shi HF, Cheung WH, Qin L, Lee KM, Leung KS.**

Low Magnitude, High-Frequency Vibration therapy accelerates fracture healing in rats. 1st International Congress of Chinese Orthopaedic Association (November 2006, Beijing, China). Oral Presentation.

**Shi HF, Cheung WH, Qin L, Lee KM, Leung KS.** Low-magnitude, High-frequency Vibration Therapy Accelerates Fracture Healing in Rats. 26th Annual Congress of The Hong Kong Orthopaedic Association (November 2006, Hong Kong, China). Poster Presentation.

**Yu YY, Lieu S, Colnot C.** Distinct effects of BMP-2 on cell differentiation in periosteum and endosteum during bone healing. 54th Annual Meeting of the Orthopaedic Research Society (May 2008, San Francisco, USA). Poster Presentation.

**Yu, YY, Miclau, T, Marcucio, RS, and Colnot, C.** Expression of bone morphogenetic proteins activation pathway and its antagonists during tibial fracture healing. 55th Annual Meeting of the Orthopaedic Research Society (February 2009, Las Vegas, USA). Poster Presentation.

# Index to Grantees

Alt, V.....	13, 22	Schneider, D.A.....	26
Badhwar, A.....	30	Sen, R.K.....	13
Berry, G.K.....	31	Simpson, A.H.R.W.....	34
Bhandari, M.....	12, 21	Stepanov, R.....	27
Blokhuis, T.....	24	Van Lieshout, E.M.M.....	33
Born, C.....	23	Zhang, Z.....	43
Bottlang, M.....	44	Zlowodzki, M.....	28
Brink, P.R.....	14		
Cehade, M.....	40		
Cheung, W.H.....	42		
Claes, L.....	16		
Colnot, C.....	19, 23		
Fajardo, M.R.....	37		
Hak, D.J.....	19		
Kuzyk, P.R.T.....	20		
Leung, K.S.....	10, 22, 32		
Lewinson, D.....	42		
Li, B.....	38		
Lubovsky, O.....	36		
McKee, M.D.....	29		
Morshed, S.....	15		
Phieffer, L.....	45		
Punt, B.J.....	14, 15		
Qamirani, E.....	35		
Ruiz Ibán, M.A.....	20		
Sampson, H.W.....	18		
Sanders, D.W.....	22		
Schemitsch, E.H.....	18, 21, 41		
Schepers, T.....	18, 23		
Schmidt, U.....	29		

## Index to Institutions

Erasmus MC, Rotterdam, the Netherlands.....	14, 15, 18, 23, 33	University Medical Center Utrecht, Utrecht, the Netherlands.....	24
Hospital Ramon y Cajal, Madrid, Spain.....	20	University of California San Francisco, San Francisco, CA, USA.....	15, 19, 23
Ilizarov Scientific Center for Restorative Traumatology and Orthopaedics, Kurgan, Russian Federation.....	27	University of Colorado at Denver and Health Sciences Center, Denver, CO, USA .....	19
Krankenhaus der Barmherzigen Schwestern, Ried im Innkreis, Austria.....	29	University of Minnesota, Minneapolis, MN, USA.....	28
Legacy Research & Technology Center, Portland, OR, USA .....	44	West Virginia University, Morgantown, WV, USA.....	38
London Health Sciences Centre - Victoria Hospital, London, ON, Canada .....	22, 30		
McGill University Health Centre - Montreal General Hospital, Montreal, Canada.....	31		
McMaster University, Hamilton, ON, Canada .....	12, 21		
NYU Hospital for Joint Diseases, New York, NY, USA.....	37		
Postgraduate Institute of Medical Education & Research, Chandigarh, India .....	13		
Rhode Island Hospital, Providence, RI, USA.....	23		
Rambam Health Care Campus, Haifa, Israel.....	42		
Royal Adelaide Hospital - The University of Adelaide, Adelaide, Australia.....	40		
Saint Louis University, St. Louis, MO, USA .....	43		
St. Michael's Hospital-University of Toronto, Toronto, ON, Canada .....	18, 20, 21, 29, 35, 41		
Sunnybrook Health Sciences Center - University of Toronto, Toronto, ON, Canada.....	36		
Texas A&M University Health Science Center, Collage Station, TX, USA .....	18		
The Chinese University of Hong Kong, Hong Kong, China.....	10, 22, 32, 42		
The Ohio State University Medical Center, Columbus, OH, USA .....	45		
The University of Edinburgh, Edinburgh, UK.....	34		
Ulm University, Ulm, Germany.....	16		
University Hospital Giessen-Marburg, Giessen, Germany.....	13, 22		
University Hospital Heidelberg, Heidelberg, Germany .....	26		
University Hospital Maastricht, Maastricht, the Netherlands.....	14		

# Announcement

## Osteosynthesis and Trauma Care Foundation is offering

Research Grants up to US \$ 50,000 in the  
field of orthopaedic trauma surgery and  
Young Investigator's Grants of US \$ 10,000

### Topics for

## Research Grant Proposals

- Promotion of fracture healing, including treatment and enhancement of fracture repair
- Treatment of fractures in osteoporotic bone
- New technologies in fracture fixation, including computer-assisted surgery
- Prophylaxis and treatment of infections in fracture
- Prospective clinical trials in fracture care
- Numerical methods in trauma surgery

## Timelines

- Website application available **October**
- Pre-proposal submission deadline **May 15**
- Full-length grant application deadline **October 15**
- Grant Award notification **December**





