WORKSHOP
Animal Models of Comorbidities in Fracture-Healing Research
Organized by: ORS Preclinical Models Section and ORS International Section of Fracture Repair

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Workshop Title

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Abstract

A variety of comorbidities and risk factors contribute to bone fracture-healing complications. There is evidence that postmenopausal osteoporosis, concomitant tissue injury and ischemia may strongly interfere with bone regeneration, however, molecular mechanisms are still unclear. To study these, appropriate animal models are needed.

For decades, bone healing has been studied in large animals, including dogs, rabbits, or sheep. In recent years, mice and rats have become increasingly popular as a model organism for fracture healing research. Both large and small animals can be used to study comorbidities and risk factors, modelling the human clinical situation. Attention has to be paid to choose the appropriate model and to be aware of species differences between large animals, rodents and humans. This workshop will focus on the common comorbidities postmenopausal osteoporosis, polytrauma and ischemic injury and critically discusses the translational aspect of animal models.

Content

1. Altering vascularization during bone healing - Kurt Hankenson (Professor for Orthopaedic Surgery, University of Michigan, USA)

Vascularization is required for proper bone regeneration, and limb ischemia is a significant risk factor for fracture non-union development. Models of induced limb ischemia are useful for probing mechanisms of healing with loss of blood vessels and possible mechanisms of recovery. Other conditions also show decreases in vascular response, including diabetes and aging. The impact of decreased blood vessels in
fracture healing will be discussed and methods of promoting fracture blood flow considered.

Main conclusions:

- Tissue oxygenation influences many facets of fracture healing biology, including vascularization and mesenchymal proliferation, osteoblast and chondrocyte differentiation, and bone formation and remodeling
- While therapeutics to increase vessel in-growth may be attractive, because of the complexity of bone healing it is necessary to consider off-target deleterious effects of any potential therapeutic
- Mice are able to rapidly recover from significant ischemic events, and thus may be less useful for studying therapeutic options, except in the earliest periods of healing

2. Large and small animal models of postmenopausal osteoporosis during bone healing - Anita Ignatius (Head of the Institute of Orthopedic Research and Biomechanics, Ulm University, Germany)

Osteoporotic patients display a higher risk for fracture-healing complications. Thereby, the lack of estrogen after menopause contributes to delayed bone regeneration. A well established clinically relevant disease model is the induction of postmenopausal osteoporosis by ovariectomy (OVX) in female rodents. A limitation of this animal model is that the total BMD loss is less than in humans and that the bone structure in rodents in general is different from humans. In large animals, such as sheep, the effect of OVX is low and additional approaches, for example glucocorticoid treatment or calcium and vitamin D restriction, are used to induce bone loss and to study osteoporotic fracture healing. In this workshop, we will discuss small and large animal models of OVX induced osteoporotic fracture healing and a recently established ovine model combining OVX and hypothalamic-pituitary disconnection to study metaphyseal fracture healing.

Main conclusions:

- Fracture healing is delayed in rodent models of OVX due to reduced callus formation
- Estrogen deficiency in OVX mice leads to a disturbed immune response towards fracture which may contribute to impaired fracture healing
- OVX and the surgical disconnection of the hypothalamus and pituitary gland in sheep lead to considerable bone loss mimicking the low turnover state in senile osteoporotic patients and significantly impairs fracture healing.

3. Polytrauma models - Hans Christoph Pape (Head of Orthopaedic Surgery Department, University Medical Center Zurich, Switzerland)

Polytrauma commonly accompanies orthopaedic injury due to accidents with automobiles, industrial and construction worksite accidents, war and blast injuries, and injuries caused by natural disasters. Orthopaedic aspects of polytrauma include open fractures, multiple fractures, and extensive soft tissue damage including loss or damage to surrounding muscle and vascular compromise. Injuries to other sites including head or spinal cord, internal organs, and dermal burns have their own effects on orthopaedic outcomes and post-operative complications. This workshop will provide an overview of how polytrauma affects orthopaedic treatments and outcomes and what are suitable animal models.