

Animal Models for Bone Repair

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INTRODUCTION: Animal models for bone repair provide information on the potency and efficacy of osteoconductive materials, osteoinductive factors, and the clinical relevance of tissue engineered products *in toto*. Important considerations include: choice of the appropriate animal and having well described, sensitive and repeatable analytical techniques.

REVIEW:

Rodents -Rat and mouse models of large bone defects are primarily chosen for proof of principle studies where complex modeling of human conditions are required. For example, current studies running in our institute include the use of Arginine deficient mice in a non-union osteotomy model to evaluate the role of arginine in non-union, and large bone defects in normal and ovariectomised rats to evaluate tissue engineered constructs in normal and osteoporotic animals simultaneously. The challenge with these models is in the technical aspects of having a reproducible fixation method. We have also developed systems for generation of defects and the placement of radiolucent PEEK plates with angular stable screws. With this instrumentation, very low levels of complications may be expected, and a reproducible defect created. Other models described in the literature also use plates, external fixateurs or intramedullary nails.

Rabbits - Rabbits are very commonly used for models of bone healing and the efficacy of osteoinductive agents and osteoconductive scaffolds. The reason for the popularity of this model is that these models are very well described, the turn around time for data is short due to the normal rapid healing process and the animals are easy to obtain, house and handle. Furthermore the surgical approach to the long bones frequently used is simple, and the radius (or ulna), being a paired bone, requires no osteosynthesis. At our institution, both radial and ulna defect models are commonly performed (the decision for either model is commonly based on the preferred cross sectional shape of the oste-otomised/ectomised bone). The rapid healing in these models compared with humans, make them a valuable

bioassay for screening of comparable technologies, but questionable for direct transfer of information to the human clinical situation. A tibial model is also being developed in our institution as a non-union model for cases in which it is not desirable to have the influence of the paired bone at the repair site.

Small Ruminants - Sheep in particular have been used extensively for studying bone healing. The healing properties and size similarities with humans make this model appropriate for studies destined as proof of efficacy or safety prior to registration or human clinical trials. The preferred model at our institution for large bone defects is a mid diaphyseal tibial osteotomy, and for osteotomy healing a new model has been developed involving osteotomy of the distal femur which is particularly good for evaluation of biomaterials used for implant anchorage. This model uses a custom designed stainless steel locking "J" shaped plate. The plate was made following creation of a CT dataset for ovine distal femora.

Dogs - Different osteotomy/ectomy models have been described in dogs with good results. The use of companion animals such as dogs for invasive research is a difficult ethical issue. However, the long history of the use of dogs in orthopaedic research has resulted in a formidable bank of comparative data, and sometimes the FDA, or other regulatory agencies may request that efficacy or safety studies are performed in dogs. We have developed a radial osteotomy model to mimic wrist injuries in people, but the first choice large animal model for bone healing at our institution are small ruminants.

Analysis

Typical analytical methods include *in vivo* radiographs, thin section cabinet radiography with image analysis, computed tomography (*in vivo* and post-mortem), and normalised biomechanical material property evaluations.