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WORKSHOP 2

Large Animal Models for Orthopaedic Research: Possibilities and Limitations

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Selecting a valid animal model for musculoskeletal research;
-Scientific, veterinary, and practical considerations-

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Central to the acceptance of animals as models of human physiology and pathology is the belief that all animals are so closely linked by the bonds of evolutionary and genetic kinship that information gained from one is applicable to others (Warbasse 1910). However, when one examines the vast heterogeneity that exists in the animal kingdom, from gross anatomy to molecular levels, such a generalization seems implausible. A more tempered concept was forwarded in 1929 by the distinguished Danish physiologist, August Krogh, who wrote, “For a large number of problems there will be some animal of choice, or a few such animals, in which it can be most conveniently studied” (Krogh 1929). This has become known as the “August Krogh Principle” and has served as a rationale for the use of animal models in biomedical research. Although the development and recognition of accepted animal models for the study of specific biological phenomenon supports the August Krogh Principle, it has also been noted that the uncritical application of this principle can lead to fallacious generalizations, because extrapolating experimental findings across species is not always valid (Krebs 1975; Krebs and Krebs 1980). Subtle variations in anatomy and physiology, gait (kinematic and kinetic profile), nutrition (i.e. ruminant versus monogastric), age, and even reproductive cycles among various species can greatly impact the response of a specific species to experimental manipulations of the musculoskeletal system. Thus, the researcher is frequently left with the dilemma of which animal model(s) most accurately represent(s) and reproduce(s) the human condition being investigated and to what extent the results obtained from these models are correctly extrapolated to humans.

The selection of an animal model for biomedical research is based on many criteria that encompass a wide variety of factors. Some of these considerations include the appropriateness (analogy) of the model to the human condition, the background data available on the model, the “generalizability” of the data obtained from the model, the ease of experimental manipulation, the cost and availability of the specific animal, and the ethical implications of using animals in biomedical research (Arnoczky 1990).

In selecting an animal model, the investigator must evaluate the overall fidelity and distinctiveness of the animal model to the human condition, since even the most carefully designed experiment can be vitiated by an animal model lacking in integrity. ***Fidelity*** refers to the overall faithfulness of the animal model to the human condition, and ***distinctiveness*** means that the animal model possesses a distinguishing characteristic(s) that mimics a particular property in the human condition. Considerations such as the degree to which anatomic, physiologic, and kinematic factors are analogous help determined the extent to which the results of the investigation may or may not be extrapolated to the human. Often times the degree to which a specific animal model is analogous to a specific condition in humans depends on what “level” we wish to compare them. As noted previously, the acceptance of animal models in biomedical research must be predicated on the fundamental belief that, at some level, the information gained from one species is applicable to others. This belief stems from the concept that since life is evolutionary, all animals share certain common features; the more basic the feature or function, the more common (and similar) its occurrence among species. For example, the blood clotting mechanism is essentially the same in all warm blooded mammals. Thus, when comparing various levels of biological phenomenon among species, it is often concluded that the more basic the feature, function, or response being studied, the more valid the comparison. Conversely, the more the function or response is directly affected by species dependent variables (activity, diet, estrus cycle, etc) the less the results can be (or should be) extrapolated. Therefore, when evaluating the validity of a particular animal model, the investigator must determine not only the level of comparison the specific aim(s) of the study wishes to achieve, but also to what degree the results will be directly affected by species-dependent variables.

The ultimate validation of any animal model is the confirmation that the results obtained in that model (or the processes observed in that model) are exactly the same as those seen in the human. In addition, the level(s) (molecular, cellular, tissue, organ) at which these results are comparable must also be determined. This can often be accomplished through the evaluation of human biopsy materials, "second looks", and follow-up imaging studies. However, in the absence of any direct human material, an alternative method of validating the "generalizability" of results obtained from an animal model is the comparison of the results to those obtained from other animal models. Similar results obtained in several different species would suggest a common physiologic or pathologic pathway. Such a finding would provide strong support for the cautious extrapolation of the results to the human species.

Thus, the validation of a specific animal model can be done directly through comparison to available human data, or indirectly through the demonstration of a common biological process across several species. In addition, it must be remembered that an animal model may only be valid at a specific level of comparison. The investigator must carefully identify this (these) level(s) and make comparisons and/or extrapolations within the limits of the model.

The selection of specific animal models for musculoskeletal research is not always based on compelling scientific grounds. Often times, other factors such as cost, availability of animals and animal housing, ease of handling, or the size of the animal are the determining factors why one species is chosen over another. Finally, another important consideration in the selection of animal models is the animal welfare movement, which has strongly discouraged the use of certain animals (dogs, cats, primates) in biomedical research. While these considerations do not justify the selection of an inappropriate animal model for a specific investigation, they are valid issues and therefore play a significant role in the selection criteria.

Paramount in the use of animal models in biomedical research is the strict adherence to the principles of human and ethical treatment that have been established and incorporated into the Public Health Service (PHS) Policy on the Human Care and Use of Laboratory Animals. The most current information on these policies as well as other animal welfare information can be found on the USDA website www.aphis.usda.gov/ac/. Additional information on the use of animals in biomedical research can be found at the Foundation for Biomedical Research's website www.fbresearch.org.

Summary

In most instances, there is no compelling evidence to suggest that one animal model is superior to all others in studying all aspects of a specific musculoskeletal condition. No matter what animal model is used, it is the responsibility of the investigator to carefully define the valid levels of comparison for each model and to interpret the results within these established confines. As the data base for each animal model increases and as more information becomes available from the evaluation of human material, the validity of each of these models will become more clearly defined.

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Equine Models for Studying Osteoarthritis, Articular Cartilage Repair and Tendinopathy

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General advantages of horses as a model

Osteoarthritis (OA), traumatic cartilage lesions and tendinopathy are all significant clinical problems in the horse.

Models of osteoarthritis

The author has previously used filipin, sodium monoidoacetate and endotoxin of synovitis/OA and there are inconsistencies. The osteochondral chip fragment – exercise model currently used mimics a clinical entity in the horse, is consistent and humane, and there is significant early disease at 72 days. Another destabilizing model of OA has been developed in the equine metacarpophalangeal joint. This model waits 6 weeks after cutting the collateral ligament for OA change to be present and then a trial treatment could be started. It is an 8 week model with exercise and shows osteophyte formation and growth and histopathologic change in the articular cartilage.[1]

Osteochondral chip fragment-exercise model: An 8 mm fragment is created off the distal radial carpal bone in the middle carpal joint under arthroscopic guidance. The parent bone is burred back to make a defect of 15 mm and the debris is left in the joint. Two weeks after creation of the chip fragment, the horse's exercise on a high-speed treadmill begins with 2 minutes trot, 3 minutes gallop and 2 minutes trot out to day 72, when the study is complete. At the present time, there have been 14 studies evaluating various treatments for OA done with this model. Outcome parameters used include clinical evaluation (lameness, response to joint flexion and midcarpal joint synovial effusion), radiographic examination (radiographic lysis, proliferation and osteofied formation), CT, nuclear imaging, MRI, PG2, synovial fluid protein and synovial fluid GAG levels, serum biomarkers (GAG, COL2-3/4C_{short} , CPII, CS846, 234CEQ), gross pathologic change (erosions occur on the opposing third carpal bone), synovial membrane histopathology (cellular infiltration, intermal hyperplasia and increased vascularity), histopathologic change in articular cartilage (chondrone formation and superficial fibrillation), histochemistry (loss of SOFG staining for GAG), GAG levels and GAG synthesis in cartilage and PT-PCR of synovial membrane. Strengths of the model are that typical pathologic lesions of early OA occur, and mimic natural equine disease, induction can be done arthroscopically, is humane (low grade lameness), can use a full range of clinical outcome parameters and can measure many of the parameters sequentially. Weaknesses are cost (however, statistical power of 0.8 is achieved with eight in each group), the equine carpus is not the human knee, it is a model of early OA, and the horse is a quadruped. A model of OA using contusive impacts on the MFC of horses has recently been described and supports trauma as a contributing factor in the natural pathogenesis of osteoarthritis.[5]

Reference(s):

1) Simmon EJ, Bertone AL, Weisbrode SE. Instability-induced osteoarthritis in the metacarpophalangeal joint of horses. Am J Vet Res, 1999;60:7-13. 2) Frisbie DD, Kawcak C, Trotter GW, Powers BE, Walton RM, McIlwraith CW. Effects of triamcinolone acetonide on an *in vivo* equine osteochondral fragment exercise model. Equine Vet J 1997;29:349-359; 3) Kawcak CE, Norrdin RW, Frisbie DD, McIlwraith CW, Trotter GW. Effects of osteochondral fragmentation and intra-articular triamcinolone acetonide treatment on subchondral bone in the equine carpus. Equine Vet J 1997;30:66-71; 4) Frisbie DD, Ghivizzani SC, Robbins PD, Evans CH, McIlwraith CW. Treatment of experimental equine osteoarthritis by in vivo delivery of the equine interleukin-1 receptor antagonist gene. Gene Therapy 2002; 9:12-20.

5) Bolam CJ, Hurtig MB, Cruz A, McEwen BJE. Characterization of experimentally induced post-traumatic osteoarthritis in the medial femorotibial joint of horses. Am J Vet Res, 2006 67:433-7.

Models of articular cartilage healing

We have used two different models of articular cartilage healing: one in the femorotibial compartment and one in the femoropatellar compartment.

Femorotibial model: This model creates a 1cm^2 defect on the medial femoral condyle and has been used to evaluate the benefit of microfracture to articular cartilage healing, both long term[6], and short term[7], (in the latter study RTPCR was used to evaluate expression of Type II collagen and aggrecan). In this model the calcified cartilage layer can be differentially removed or left in place and retention of the calcified cartilage has been shown to lead to inferior healing.[8]

Femoropatellar model: The creation of two 15mm lesions on the medial trochlear ridge have been used as a model to evaluate different tissue engineering techniques[9], The defects can be created arthroscopically, but the tissue repair techniques may need to be done in some instances by arthrotomy which is quite effective. Advantages of the model include comparable articular cartilage thickness to the human knee[10], the ability to create defects arthroscopically, the ability to apply controlled exercise, and the ability to do intermittent regular arthroscopic examinations in articular healing studies.

Reference(s):

6) Frisbie DD, Trotter GW, Powers BE, Rodkey WG, Steadman JR, Howard RD, Park RD, McIlwraith CW. Arthroscopic subchondral bone plate microfracture technique augments healing of large osteochondral defects in the radial carpal bone and medial femoral condyle of horses. Vet Surg 1999;28:242-255.7) Frisbie DD, Oxford JT, Southwood L, Trotter GW, Rodkey WG, Steadman JR, Goodnight JL, McIlwraith CW. Early events in cartilage repair after subchondral bone microfracture. Clin Orthop 2003;407:215-227.8) Frisbie DD, Morisset S, Ho CP, Rodkey WG, Steadman JR, McIlwraith CW. Effects of calcified cartilage on healing of chondral defects treated with microfracture in horses. Am J Sports Med (11):1824-1831, November 2006.9) Frisbie DD, Bowman SM, Calhoun HA, DiCarlo EF, Kawcak CE, McIlwraith CW. Evaluation of autologous chondrocyte concentration via a collagen membrane in equine articular defects – results at 12 and 18 months. Osteoarthritis & Cartilage, 2006 Submitted.10) Frisbie DD, Cross MW, McIlwraith CW. A comparative study of articular cartilage thickness in the stifle of animal species used in human pre-clinical studies compared to articular cartilage thickness in the human knee. Vet Comp Orthop Traumatol 2006; 19:142-6.

Models of tendonitis

Injection of 0.1ml of 1000IU per ml of collagenase (total dose of 0.2mls) into the center of the superficial digital flexor tendon (SDF) using ultrasound guidance at two locations has been a commonly used method of developing tendonitis in the horse. It is the only model that has been published. It has advantages in that the model has been used to compare a number of treatments for SDF tendonitis which is an important clinical problem in the horse. However there is variability and initially there is some pain. Work is ongoing (Schramme personal communication, 2006) to develop a traumatic model using a resector into the central portion of the SDF.

Reference:

11) Dahlgren LA, van der Meulen LMC, *et al.* Insulin-like growth factor-1 improves cellular and molecular aspects of healing in a collagense-induced model of flexor tendonitis. J Orthop Res, 2002;20:910-919.

Large Animal Models of Total Hip and Knee Replacement

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Background: Total hip replacement (THR) and total knee replacement (TKR) are common clinical procedures in human medicine. Although much of the preclinical work on the biocompatibility of candidate implant materials (metal, ceramic, polymer) can be performed in small animals, definitive evaluation of these materials or of the surgical techniques used for THR and TKR ultimately require the use of *simulated use models*. In this context, the most popular models are the sheep and the dog. While the use of canines can be problematic in some countries, for the purposes of this presentation I will consider the dog as the standard model and then provide comparisons with sheep and, where appropriate, goats.

Total Hip Replacement in Dogs: THR surgery is performed as a clinical procedure in the dog and, as a consequence, there is a large body of literature regarding surgical technique, post-operative care and clinical outcomes [1]. Commercial implant systems are available for both cemented and cementless applications and the components from the two systems are interchangeable, making it possible to perform hybrid THR if indicated. The femoral components are fabricated from Ti6Al4V and the acetabular components from UHMWPE (with a Ti6Al4V outer shell for cementless application). The presence of adequate cancellous bone in the proximal femur makes the dog an excellent model for research studies on primary cemented or cementless femoral.

Total Hip Replacement in Sheep and Goats: Hemiarthroplasty and arthroplasty of the ovine [2-4] and caprine [5-6] hip joints have been reported. The proximal femur contains relatively little cancellous bone and cemented, rather than cementless, fixation is recommended for the femoral component (G. Blunn, personal communication). There are currently no commercial implants but it is possible to use either canine implants [7] or custom implants. Technically, the procedure for THR is more demanding in small ruminants, with dislocation being more common in these species than in dogs. Given the potential for complications with THR in small ruminants [3], researchers anticipating the use of these animals in THR studies are encouraged to contact groups with experience with the procedure prior to initiating any live animal surgeries. As with any surgical project, the value of cadaver trials cannot be overemphasized.

Total Knee Replacement in Dogs: TKR is a more recent development in the dog and the majority of published reports are from research rather than clinical studies. The main focus of these studies has been on tibial implant fixation [8-11], although acute studies have also been used to examine the effects of cement on embolization [12]. All of these studies utilized custom implants. A commercial canine TKR system has now been developed and is currently in clinical trial. The first generation system consists of a press-fit Ti6Al4V femoral component and an all-polyethylene tibial component that is implanted with cement.

Total Knee Replacement in Sheep: There have been a limited number of reports on total knee replacement in sheep [13-15]. All involved the use of a custom prosthesis developed for sheep and none of these implant systems are available commercially. Surgical access to the ovine knee (stifle) joint is greatly facilitated by osteotomy of the tibial crest; the osteotomized fragment is subsequently re-attached with pins, alone or in combination with cerclage wire. It is not necessary to immobilize the operated limb but it is critically important to house animals on non-slip surfaces and to restrict their activity for at least 4-6 weeks post-surgery.

General Surgical Considerations in THR and TKR

Screening of animals: Animals destined for THR/TKR studies need to be screened for skeletal maturity and clinical or radiographic signs of musculoskeletal disease. If possible, vendors should be asked to provide radiographs prior to shipment so that animals that are not suitable are not shipped to the study site. These pre-operative films can also be used to determine the optimal implant size for each animal.

Strict asepsis: Aseptic procedures are critical in total joint replacement surgery. For both hip and knee replacement surgery we wrap the hind limb in stockingette or sterile Coban in order to isolate the surgical site. We do not obtain intraoperative cultures from THR or TKR cases because they can be of limited value in predicting subsequent joint infection.

Unilateral versus bilateral surgery: Bilateral total joint replacement is not recommended. Quite apart from the ethical concerns, the practical reality is that a complication in one leg will compromise data from both legs. If absolutely necessary, it is possible to perform staged surgeries in animals as long as the interval between surgeries is at least 8-12 weeks.

Post-Operative Care: Aggressive analgesic regimens are indicated in any animal undergoing a major orthopedic procedure. We use a combination of non-steroidal anti-inflammatory drugs (carprofen in dogs, flunixin meglumine in sheep) and opiate analgesics (morphine and/or fentanyl) in all THR and TKR cases. Transdermal fentanyl patches can be used in the sheep but we have moved away from them in dogs since we found an unacceptable risk of breakthrough pain (Allen MJ and Breur GJ, unpublished data). There is no requirement for post-operative casts or bandages following THR but a Robert Jones bandage for 3-7 days is useful in controlling swelling and protecting stifle joints following TKR surgery in sheep and dogs. Physical therapy (PT), involving both passive ROM activity and active exercises, plays an important role in the rehabilitation of clinical patients (human and veterinary) but may be impractical in a laboratory setting when large groups of animals may be undergoing surgery at any one time. Without any form of PT, we have found that return to function takes 4-6 weeks in THR dogs but 6-12 weeks in TKR dogs and sheep. We are currently investigating whether PT will accelerate return to function following canine TKR.

Outcome Measures in Preclinical THR and TKR Studies:

Routine follow-up for all THR and TKR animals should consist of clinical examination, radiography and visual assessment of the animal's gait. As dictated by the specific aims of the study, these assessments may be supplemented by more focused investigations such as:

Force plate analysis: The use of force plates, alone or in combination with video gait analysis, provides useful information regarding the temporal pattern of return to full limb function.

Radiostereometric analysis: RSA is the benchmark for assessing implant fixation in human THR and TKR. In a preclinical setting, RSA offers the potential for real-time, non-invasive monitoring of implant migration; perhaps more importantly, it permits serial evaluation in the same animal, thereby reducing the number of animals that are required for a long-term study. RSA methods have been described and validated in canine THR [16], canine TKR [17] and ovine TKR [15].

Bone densitometry: DEXA is very useful in assessing the response of periprosthetic bone. In canine TKR, the reproducibility of DEXA is 2-6% [11] and comparable to that reported in human TKR.

Bone marker analysis: Serum and urinary markers of bone turnover offer a means of non-invasive assessment of bone turnover following total joint replacement. Potential applications for these assays could include the documentation of increased osteoblastic activity following anabolic therapies, or increased osteoclastic activity in preclinical models of aseptic loosening. However, the sensitivity of bone markers in assessing focal skeletal disease remains to be determined.

Histology/Histomorphometry: Undecalcified histology is preferred. For studies on cemented fixation, embedding in Spurr's resin provides a means of preserving the cement mantle. Since THR and TKR specimens typically include metallic or polymeric implants, ground sections are typically used; it should be noted that it is possible to obtain high-quality ground sections from specimens that have been frozen (e.g. in order to run mechanical tests) prior to fixation.

References:

[1] Olmstead ML. Journal of Small Animal Practice 36: 395-399, 1995; [2] Radin EL *et al*., J Bone Jt Surg [Am] 64-A: 1188-1200, 1982; [3] Brumby SA *et al*. Clin Orthop 355: 229-237, 1998; [4] van der Meulen MC *et al*. J Orthop Res 20: 669-675, 2002; [5] Bhumbra RP *et al*. Clin Orthop 372: 192-204, 2002. [6] Malkani AL *et al*., Orthopedics 28: 49-58, 2005; [7] El-Warrak AO *et al*. Vet Surg 33: 495-504, 2004; [8] Turner TM *et al*. J Orthop Res 7: 893-901, 1989. [9] Matthews LG and Goldstein SA. Clin Orthop 276: 50-55, 1992; [10] Sumner DR *et al*. J Biomech 27: 929-939, 1994; [11] Allen *et al*. 52nd Annual Meeting of the ORS, Poster #674, 2006; [12] Markel DC *et al*. J Arthroplasty 14: 227-232, 1999; [13] Claes L *et al*. Proc 15th Annual Meeting of the Society for Biomaterials: 229, 1989; [14] Allen MJ *et al*. Vet Surg [15] Bellemans J. Acta Orthop 288: 1-35, 1998; [16] Allen MJ *et al*. J Orthop Sci 9: 66-75, 2004; [17] Allen MJ *et al*. 53rd Annual Meeting of the ORS: Poster #1892, 2007.

Comparative Orthopaedic Research Using Sheep

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Introduction

General advantages of sheep as a model compared to other species: Skeletally mature female sheep (and goats) have become a convenient large animal model for a variety of orthopaedic problems. This is because of availability, ease of handling and housing, animal cost as well as acceptance to society as a research animal. The main limitation of these species compared with other large animals (dogs and pigs) is the complex G.I. system for studies involving oral medications. Below are some examples using sheep and goats. For more detail about the studies, readers are encouraged to consult the references cited as a start.

Critical- and non-critical- sized defects of the tibia/distraction osteogenesis/allograft incorporation

Models for critical-sized defects are of interest for evaluation of bone graft substitutes, growth factors [1], scaffolds, stem cells or any combination of these and biostimulation [2]. The large defects of the tibia (5 cm) or metatarsal bone (3 cm) are very slow to heal without some type of augmentation/stimulation. They do present a challenge to implant fixation strength because animal restraint and compliance. Higher morbidity should be anticipated when designing such studies. Goats are suitable for studying distraction osteogenesis [3].

Reference(s): 1. G.E .Pluhar, A.S. Turner, *et al*. Comparison of Two Biomaterial Carriers for Osteogenic Protein-1 (BMP-7) in a Model of Ovine Critical Size Defects. *J Bone Joint Surg* **88-B [7]:** 960-966, 2006 2. Santoni, B., Ehrhart N., *et al.* Effects of Low intensity pulsed ultrasound (LIPUS) and longitudinal perforation (LAP) on allograft remodeling: A histological investigation. *Proc 52nd Orthop Res Soc*, Chicago Il (Abstr.) p. 1735, 2006 3. Welch, R. D., J. G. Birch, *et al*. Histomorphometry of distraction osteogenesis in a caprine tibial lengthening model. *J Bone Miner Res* **13**(1): 1-9, 1998

Rotator cuff research (growth factors, sutures, biologics and scaffolds)/tendon reattachment to bone; acute and chronic models

Although the anatomy of the shoulder of quadrupeds is quite different to humans, tenotomy of the infraspinatus of goats [1] and sheep [2, 3] and subsequent reattachment to the proximal humerus, is useful to address the biomechanical, histological and biochemical processes of rotator cuff repair. Sheep have been selected because the similarity of the infraspinatus tendon to the human supraspinatus tendon [2]. To reproduce a chronic rotator cuff injury, the end of the infraspinatus can be covered with Gor-Tex and the animals reoperated upon at a variable time later [4].

Reference: 1. St. Pierre, P., E. J. Olson, *et al*. (1995). “Tendon-healing to cortical bone compared with healing to a cancellous trough a biomechanical and histological evaluation in goats.” *J Bone Joint Surg* **77A**: 1858-1866. 2**.** Gerber, C., A. G. Schneeberger, *et al*. (1999). “Experimental Rotator Cuff Repair” *J Bone Joint Surg* **81A**(9): 1281-1290.; 3. Schlegel TF, Hawkins RJ, *et al*. The Effects of Augmentation with Swine Small Intestine Submucosa on Tendon Healing Under Tension: Histologic and Mechanical Evaluations in Sheep. *Am.J.Sports Med.* **34(2):** 275-280, 2006.; 4. Coleman SH, Fealy S, *et al*. Chronic Rotator Cuff Injury and Repair Model in Sheep. *J Bone Joint Surg Am.* **85-A [12]:** 2391-2402, 2003.

Achilles tendon defect

We have used sheep as a model to evaluate scaffolds and biologics to augment Achilles tendon defects, similar to the model used in dogs [1].

Reference: 1. Badylak,S.F., Tillius, R. *et al* The use of xenogenic small intestinal submucosa as a biomaterial for Achille’s tendon repair in a dog model. *J. Biomed. Mater. Res*. **29:** 977-985 (1995).

Meniscal surgery, (transplant, synthetic meniscus evaluation, repair and defects)

The pioneering work perfomed by Arnoczky in meniscal biology was performed in dogs [1,2]. The large knee joint of certain breeds of sheep and goats, make them also ideal for meniscus or other knee surgeries [3,4].

Reference(s): 1. Arnoczky, S. P. (1994). Meniscus. *Knee Surgery*. F. H. Fu, C. D. Harner and K. G. Vince.

Baltimore, Williams & Wilkins. **1:** 131-140; 2. Arnoczky, S. P. (1990). Animal model for knee ligament research. *Knee Ligaments: Structure, Function, Injury, and Repair*. e. a. D. Daniel, Raven Press, Ltd.**:** 401-417; 3. Allen, M. J., J. E. F. Houlton, et al. (1998). "The surgical anatomy of the stifle joint in sheep." *Vet Surg* **27**: 596-605; 4. Kelly, B.T.,Potter, H.G. *et al.* Meniscal Allograft Transplantation in the Sheep Knee: Evaluation of Chondroprotective Effects *Am.J.Sports Med***.** **34**:1464-1477, 2006.

Spine fusion (anterior interbody (cervical or lumbar) and TLIF(lumbar))

Human spine research in a quadruped may be questioned by some. However, it has been shown that the main loading component in spines of humans and quadrupeds is axial compression and secondary loading components are anterior shear and axial torsion [1]. Larger animals such as dogs [2], goats [3] and sheep [4-6] and are better suited to for spine fusion protocols because the vertebrae sizes are more adaptable to available implants and vertebroplasty techniques [7].

Reference(s): 1. Smit, T. H. (2002). "The use of a quadruped as an in vivo model for the study of the spine- biomechanical consideration." *Eur Spine J* **11**:137-144; 2. Kahanovitz, N., S. P. 2. Arnoczky, *et al.* (1994). "The effect of electromagnetic pulsing on posterior lumbar spinal fusions in dogs." *Spine* **19(6)**: 705-709; 3. Allen, M. J., J. E. Schoonmaker, *et al*. (2004). "Preclinical evaluation of a poly (vinyl alcohol) hydrogel implant as a replacement for the nucleus pulposus." *Spine* 29(5): 515-523; 4. Drespe IH, Polzhofer GK, et al. Animal models for spine fusion *The Spine Journal (*Focus Issue on Biologics in Spinal Surgery) **5**: 209S-216S, 2005; 5. Sandhu, H.S., Toth, J.M. *et al.* Histological evaluation of the efficacy of rhBMP-2 when compared to autograft bone in sheep spinal anterior interbody fusion using titanium cage. *Spine* **27**: 567-575, 2002. 6. Toth JM, Wang, M., *et al,* Polyetheretherketone (PEEK) as a biomaterial for spinal applications. *Biomaterials* **27**: 324-334, 2005. 7. Kobayashi, D. Togawa, T. *et al.* Histological and radiographic evaluation of polymethylmethacrylate with two different concentrations of barium sulfate in a sheep vertebroplasty model. *J Biomed Mater Res* **75A**: 123–127, 2005. **Also see ORS '07, posters 126 & 1603.**

Tibial plateau fracture model

A model for evaluating augmentation of tibial plateau fractures is well described in goats [1,2] and we have used the same model in sheep.

Reference(s): 1. Welch, R. D., H. Zhang, et al. (2003). "Experimental tibial plateau fractures augmented with calcium phosphate cement or autologous bone graft." *J Bone Joint Surg Am* **85-A**(2): 222-31. 2. Welch, R. D., B. H. Berry, *et al*. (2002). "Subchondral defects in caprine femora augmented with in situ setting hydroxyapatite cement, polymethylmethacrylate, or autogenous bone graft: biomechanical and histomorphological analysis after two-years." *J Orthop Res* **20**: 464-472.

Osteoporosis (therapies and implant evaluation)

The OVX rat has occupied a vital niche in the early screening of pharmaceutical agents for osteoporosis, but a larger model higher up the phylogenetic scale is needed before human clinical trials. The other need for a large animal model with some of the characteristics of osteoporosis is the design of prosthetic devices with different coatings to promote osseointegration and stability, despite decreased bone mass [1, 2]. However, inducing the severe bone loss characteristic of elderly women and men is a challenge. Dietary-induced metabolic acidosis (implicated in human osteoporosis) in sheep, combined with OVX, can induce a relatively rapid osteopenia (6 months)[3].

Reference(s): 1.Turner A.S. Animal Models of Osteoporosis – Necessity and Limitations. European Cells and Materials 1: 66-81, 2001.2. Turner A.S., MacLeay J.M. Osteoporosis: Advantages and disadvantages of commonly used animal models. Adv. Osteoporotic Fract. Mgmt. 1 (3): 80-86, 2002. 3. MacLeay J.M. Olson, J.D., et al. Effect of dietary-induced metabolic acidosis and ovariectomy on bone mineral density and markers of bone turnover. J. Bone Miner. Metab. **22**: 561-568, 2004.

Also see ORS '07, posters 308, 1346, 1394 & 1395.

General Reference:

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