Cornell University
College of Veterinary Medicine

Choosing the best animal model – preclinical cartilage and meniscal studies.

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Disclosures: Kensey Nash Board of Scientific Advisors, Arthrex consultant

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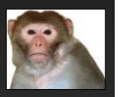
Choosing an Animal Model - Cartilage

- Drug, neutraceutical
  - Rat, mouse, rabbit, dog

- Device or product to repair/replace cartilage



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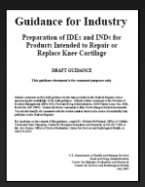
Foundation

- FDA Guidance for Industry - 07/2007
- Products intended to repair or replace knee cartilage
- Pre-clinical animal models
  - excluding non-human primates
  - excluding models for OA


Guidance for Industry

Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage

DRAFT GUIDANCE

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FDA Guidelines

- Goats, sheep, horses are most frequently used
- Choose after consideration of clinical use
  - Dimensions of product
  - Delivery of product
  - Number of outcome measures desired
    - balance of *n* and $

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Challenges and goals

- All animal models are challenging and expensive
- Ideal animal model should include:
  - Represent intended human clinical use
  - Low cost
  - Assessable outcome measures
    - Known clinical entity, antibodies, probes

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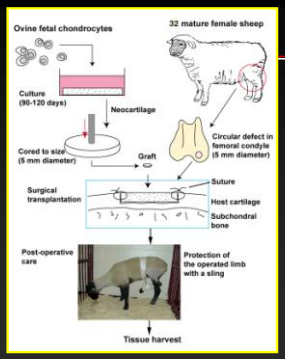

Courtesy, MD Markel. From Lu et al, 2005

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Anatomic comparisons

horse human sheep rabbit

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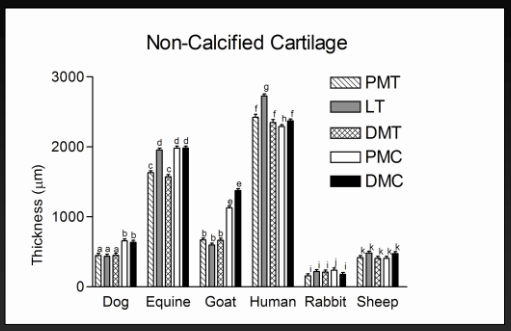

Frisbie, et al. Vet Comp Orthop Traumatol, 2006. 19:142-6

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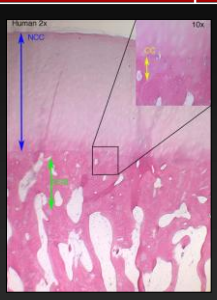
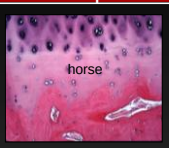
Cartilage and subchondral bone – between species comparison





Frisbie, et al. Vet Comp Orthop Traumatol, 2006. 19:142-6

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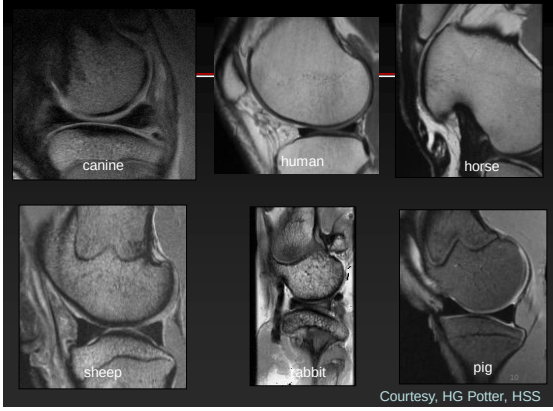

Courtesy, HG Potter, HSS

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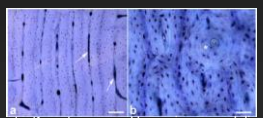
Bone attributes – similarities between animals and humans

secondary osteonal bone

	Canine	Sheep Goat	Pig	Rabbit
Macrostructure	++	+++	++	+
Microstructure	++	+	++	+

+ least similar, ++ moderately similar, +++ most similar



plexiform bone

Haversian remodeling of plexiform bone

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Pearce AI, et al. Euro Cells and Materials. 2007; 13:1-10.

Location within location

8 weeks 16 weeks

LTR
Large lesions
Thickness
Collar of cartilage
Injectable

Fortier et. al. J Orthop Res. 2001 Jul;19(4):720-8.

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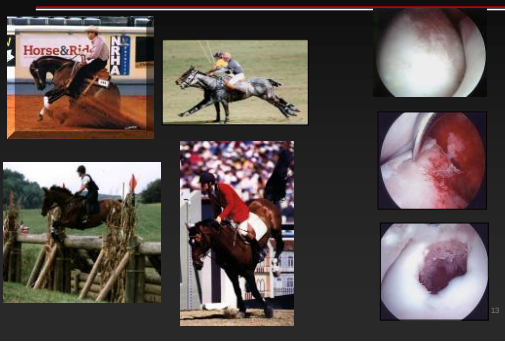
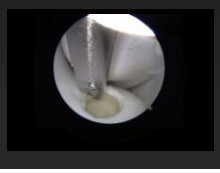
Horses as patient-models.



BMAC

Biphasic scaffold

- Kensey Nash -Bioresorbable biphasic scaffold
  - β-TCP/PLA - collagen
  - Soak in bone marrow aspirate
  - Advantages: off the shelf, bone + cartilage
  - Disadvantages: increase defect size, few cells



Conclusions

- Small animal species typically perform better than large animal species
- Full thickness defects perform better than partial thickness defects
- Partial thickness defects may be a better model for OA than full thickness defects

Meniscus - sheep as a model

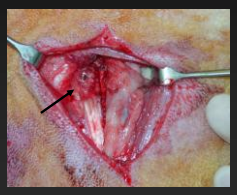
- Anatomic size, cellularity, vascularity, collagen structure
  - sheep, rabbit, human
  - Chevrier JOR 2009
- Compressive biomechanical properties
  - human, bovine, monkey, canine, sheep, and porcine
  - Joshi J Biomed Mater Res 1995
- Goat?

Considerations for approach

- Medial vs. lateral
- What are you trying to model?

Lateral meniscal approach

– takedown and repair of the LCL

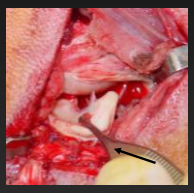



Kelly et al, AJSM, 2006

Kelly et al, AJSM 2007

Rodeo, HSS

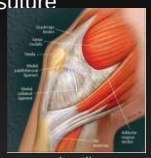
Excise and Replace the lateral meniscus



Rodeo, HSS

Going medial - what NOT to do

- Bone block approach if you need to suture meniscus
- Transect MFPL
- Bilateral
- ? Epidural



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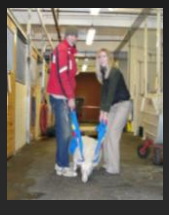

Penn Veterinary Medicine

Ovine Hemicondylotomy Approach to the Medial Meniscus

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The University of Pennsylvania

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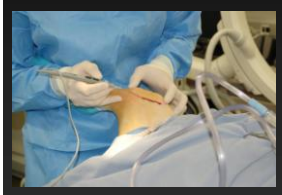
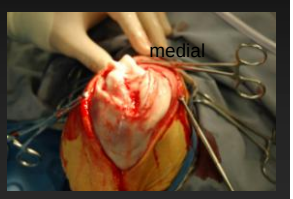
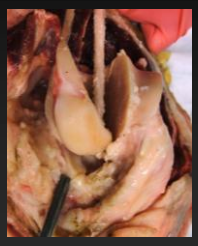
[3] School of Veterinary Medicine New Bolton Center

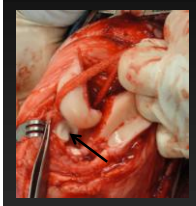
Many Species. One Medicine.™

1. Medial skin incision
2. Lateral parapatellar arthrotomy, patella luxated medially

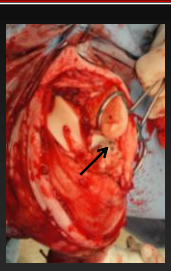



Practice, practice, practice

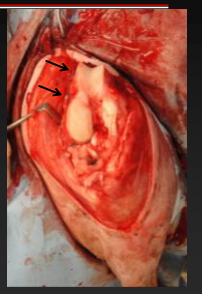


tear



repair

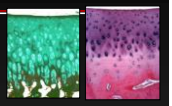


2 lag-screw fx fixation

Achilles Tenotomy?
LAF and SAR modified

Schaer, UPenn

Thoughts for all animal models



- Age of skeletal maturity is critical
  - >2 years of age is general guideline
- Dimensions of critical size defect must be known
- Choice of full or partial thickness defects
- Importance of validating that subchondral has not been penetrated
  - very difficult for smaller animals
- Difficult to ensure removal of calcified cartilage

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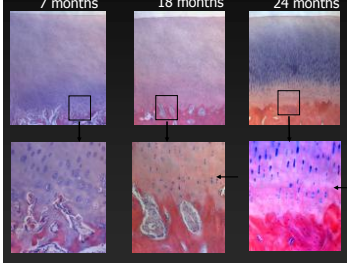
	Rabbit (Leporine)	Dog (Canine)	Pig (Porcine)	Sheep (Ovine)	Goat (Caprine)	Horse (Equine)	Human
Breed	New Zealand White	Mixed, Beagle	Minipig	Suffolk, Texel	Dairy, Boer, Cross, Spanish	Mixed, Thoroughbred, Quarter Horse	N/A
Age at Skeletal Maturity (years)	0.75	1-2	0.8-1	2-3	2-3	2-4	16-21
Weight at Skeletal Maturity (kg)	3-4	15-30	20-40	35-80	40-70	400-500	70
Defect Commonly Used	FC, TG, TP, P	FC, TG, P	FC, TG	FC, TG	FC, TG, TP, P	FC, TG, RC	FC
Cartilage Thickness at Femoral Condyle (mm)	0.25-0.75	1.3		1.7	1.5-2	2-3	2-3
Critical Size Defect (mm)	3			7		9	

FC- femoral condyle; TG- trochlear groove; TP- tibial plateau; P- patella; RC- radial carpal

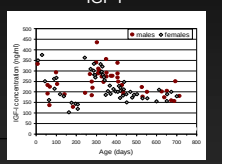
Cellular, Tissue, and Gene Therapies Advisory Committee, 2005

Equine cartilage structure with age

7 months 18 months 24 months



IGF-I



Fortier, et al. Equine Vet J 2005; 37:37-42.

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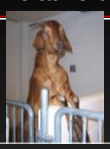
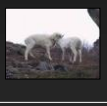
Relative disadvantages

- Goats



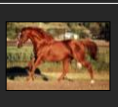
  - Caseous Lymphadenitis
    - *Coryne pseutoTB*
  - Behavior
  - Low cartilage thickness

- Sheep



  - Scrapie (TSE)
  - Shoulder ramming
  - Lowest cartilage thickness

- Horses



  - Cost
  - Immediate loading (MFC)
  - Emotive

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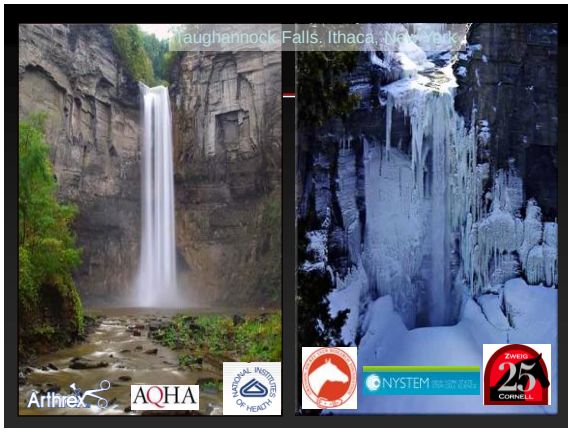
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