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What's New in Orthopaedic Basic Science

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SPECIALTY UPDATE

What's New in Orthopaedic Basic Science

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Keywords: stem cells; animal model; osteoarthritis; review; cartilage; metabolomics; gene editing

Introduction

Basic science studies remain a critically important part of the knowledge discovery process in musculoskeletal science. This review highlights several of the key advances in orthopaedic basic science over the last year. The review is not intended to be all-inclusive, rather it represents the opinions of the author, but it is hoped that the information will be of interest to the JBJS readership and will provide an easily digestible summary of some of the key recent advances in basic science. It should be noted that some topics of tremendous basic science interest, most notably orthopaedic infection and neoplasia, are not covered in detail in this article because they have been the topic of separate focused review articles in this Journal[1, 2].

1. Joints and Joint Disease

1.1. Joint as an organ

It is now widely accepted that joint is best considered an organ, rather than a simple tissue, and that osteoarthritis (OA) represents a spectrum of pathologies affecting several of the core structures that make up the joint. Early understanding of OA focused on the changes that were grossly evident on joint inspection, including cartilage degradation, subchondral bone sclerosis, synovial inflammation and osteophyte formation[3]. More recently, this picture has been expanded to include the contributions of local changes in peri-articular muscles, nerves and intra-articular structures such as the fat pad. This expanded understanding of the complexity of joint structure-function should facilitate the development of more robust and productive in-vitro models for studying joint disease and its management. It will also drive the development of more effective regenerative strategies that target multiple aspects of organ function, rather than focusing on cartilage repair/regeneration alone.

1.2. Post-traumatic OA

The majority of preclinical induced (i.e. non-natural) models of OA involve the creation of traumatic instability within the joint. Although this may have limited the translational relevance of studies performed with these models, particularly with regard to the efficacy of pharmacological or biological therapies, it has facilitated significant recent

advances in our understanding of the effects of trauma on function of the joint organ. Little et al. reported on the use of mouse models of post-traumatic osteoarthritis (PTOA) and recommended a classification scheme that incorporates three types of lesions, based on the extent of the loading that initiates the damage (type I: loading that initiates immediate structural damage and instability; type II: moderate loading with no immediate instability; type III: minor loading with no immediate instability)[4]. Mouse models exist for all of the injury types, opening up the potential for detailed and comparative studies between different degrees of injury and, in particular, for teasing apart the effects of acute versus chronic instability.

Martin et al. have recommended the use of sub-classification in their work on the development of predictive models for PTOA[5]. They have identified three broad categories of models that can be used to examine the interactions between mechanical overloading and cartilage loss. At one end of the spectrum are the explant and organ (joint) culture models that allow for very precise measurement of the cellular response to controlled joint loading. In the middle are the animal models in which it is possible to study the effects of trauma and instability on joint structure/function, and to evaluate the safety and efficacy of candidate interventions. At the other end of the spectrum lies the use of *in-silico* modeling in which patient specific models, built using data from the other two types of model, can be used to predict the likely response to injury and the most appropriate treatment approach.

1.3. Cartilage Repair and Regeneration

There is a clear distinction between acute osteochondral injuries, most often the result of trauma, and chronic damage that is often associated with OA. This difference is likely to be of great significance in the context of developing biological strategies for repairing or replacing cartilage that has been lost or damaged, since the microenvironment into which biologics are injected/implanted may be significantly different in acute versus chronic settings. Improved understanding of normal cartilage development and homeostasis is critical to the development of optimal regenerative strategies. For example, the recognition that articular cartilage and synovium share common precursors has fueled interest in synovium itself as a source of cells for transplant into

osteochondral defects[6].

Jiang et al recently reported on the identification of cartilage stem/progenitor cells (CSPCs) that appear to be capable of self-repair[7]. These stem-like cells have been found in adult human, bovine and equine cartilage, suggesting that they represent a biologically conserved strategy for joint homeostasis. The proliferation of CSPCs in cell culture can be selectively enhanced through careful control of the culture conditions, with 2-dimensional, low density culturing appearing to be most favorable. CPSCs were found to be capable of forming hyaline cartilage explants in vivo using a mouse model, and follow-up studies in 15 human patients with isolated osteochondral lesions produced encouraging results[8].

Advances in cell therapies for cartilage repair continue to move in parallel with developments in biomaterials for delivering and/or retaining the cells at the site of implantation. Current therapies, whether involving local stimulation with microfracture or direct replacement with cartilage transplant, appear well suited for small, isolated defects. The management of larger, less constrained defects remains more challenging and is perhaps the area where regenerative medicine has most to offer. Much of the emphasis remains on bioengineering of scaffold structures capable of resurfacing large areas of the joint has also seen significant advances. In some cases, for example meniscus, it may be sufficient to rely on the biomaterial alone for replacement of the structure[9], but for articular cartilage a seeded construct may represent a better approach. Moutos et al. have used a woven, anatomically contoured scaffold to support the directed expansion of adipose-derived stem cells, leading to the formation of a robust hyaline cartilage that may find clinical utility in resurfacing the femoral head [[10]].

2. Crosstalk Amongst Tissues

2.1. Interactions between bone and muscle

The effects of direct muscle forces on bone mass and bone structure have been studied for many years, but it is increasingly apparent that there are significant muscle-bone

interactions that are not based on mechanical effects[11]. The recognition of both bone and muscle as secretory, endocrine organs has changed that we think about muscle-bone interactions. Starting with myostatin, the list of muscle-derived chemokines, or *myokines*, continues to expand and it has been suggested that these molecules may play a pivotal role in the health-related benefits of physical exercise on cardiac, brain, renal and hepatic function[12]. More recent work, much of it based on studies in genetically modified mice, has established that both FGF-23 and osteocalcin, produced within bone, exert important remote effects. Deletion of FGF23 expression within bone leads to disorders of phosphate metabolism[13], and deletion of osteocalcin produces disturbances in energy metabolism through effects on glucose metabolism[14].

2.2. Interactions beyond muscle

Across medicine there is a growing interest in the role of the central nervous system and its associated neuropeptides on the function of other organs. Leptin, first identified as a modulator of appetite and satiety, has also been shown to exert influence bone mass both remotely, via direct effects on bone cells, as well as centrally in the brain[15]. The sympathetic and parasympathetic components of the autonomic nervous system have also come under increasing scrutiny both for their sensory functions as well as for their effector functions in linking the brain and the skeleton[16]. Much remains to be determined regarding the specifics of these interactions, but it is clear that the dissection of these pathways will be illuminating in terms of both improving our understanding of bone disease and in identifying potential targets for therapy.

2.3. Osteoimmunology

Interactions between bone cells and cells of the immune system have been a topic of great interest for several years, with the initial focus being on the role of T cells in inflammatory bone and joint conditions. Recognition of the hematopoietic stem cell niche, and the role played by bone cells in establishing and maintaining it, served to further highlight the significance of bone-immune cell interactions *in vivo*. Recent work has identified the importance of T-cell mediated interactions in defining skeletal responsiveness to parathyroid hormone[17] and the potential role of activated NK cells in controlling osteoclastic activity within inflammatory bone lesions[18].

2.4. Bone and the microbiome

In the context of remote regulators of bone turnover, another more recent area of research interest is the influence of gut microbiota[19]. The microbiome has been shown to be a key regulator of many homeostatic processes that occur outside the gastrointestinal tract, including important effects on the host immunity, and studies in mice have shown that the gut microbiota can influence bone mass. This has led to interest in the use of probiotics to modulate bone mass[20, 21], although much remains to be determined in order to identify the optimal combination of probiotic, timing and duration of treatment

3. Mechanism(s) of action of adult stem cells

Stem cells remain one of the most exciting potential vehicles for delivering therapy in musculoskeletal disease. Techniques for isolating, expanding and characterising adult stem cells from bone marrow, adipose tissue, cord blood, peripheral blood or synovium continue to evolve, but the relative scarcity of viable progenitor cells in the source tissue remains a significant challenge. Several recent papers have presented potential approaches to improve the clinical utility of MSCs at effectors of musculoskeletal tissue regeneration.

Sheyn et al. made use of recent advances in somatic cell reprogramming to generate inducible pluripotential stem cells (iPSCs) and then differentiated them into MSCs using transforming growth factor-beta[22]. The induced MSCs were found to be pluripotential *in vitro* and were more effective than bone marrow-derived, non-induced MSCs transduced with the gene for bone morphogenetic protein-6 in repairing radial defects in mice.

The use of synovial derived MSCs has been reported in two recent papers. In the first, human cells were infected into the knee joints of rats that had undergone transection of the anterior cruciate ligament one week previously[23]. A single injection of cells was found to be ineffective in modulating the progression of degenerative joint disease, but repeated weekly injections were found to be chondroprotective over a 12-week period.

Using immunohistochemistry, the authors demonstrated that the majority of the injected cells remained undifferentiated in vivo, functioning instead as local sources for chondroprotective proteins and anti-inflammatory cytokines.

The second paper explored the use of autologous synovial-derived MSCs in the regeneration of meniscal defects in a non-human primate model[24]. MSC aggregates were implanted directly into defects in the anterior half of the medial meniscus, and the animals were followed for either 8 or 16 weeks. The reparative response in the meniscus, and any attendant changes in the adjacent articular cartilage, were assessed by MRI, gross observation and histopathology. In this model, MSCs promoted meniscal regeneration and delayed progression of cartilage damage and OA.

4. The role of Clock genes and diurnal variations in gene expression.

The importance of diurnal variation has been established in many areas of musculoskeletal biology, including bone turnover. Earlier work showed that loss of clock genes eliminates the ability of bone to respond to leptin[25] but more recently attention has moved to looking at the clock genes in the context of articular cartilage. Dudek at al. reported that targeted disruption of the clock transcription factor, BMAL1, abolished normal circadian expression of a number of genes associated with cartilage homeostasis[26]. BLAL1 expression is also reduced in cartilage explants from humans with OA and from aged mice, implicating BLAL1 as an important potential factor in OA progression. Guo et al. have gone on to find that the regulation of clock-controlled genes is itself disrupted by catabolic cytokines implicated in cartilage degradation[27]. In the context of spinal disease, an interesting study in rats demonstrated that passive exposure to cigarette smoke resulted in a significant (6- to 9-hour) frame shift in the activity of clock genes in the intervertebral disc[28].

5. Gene editing with CRISPR-Cas9

Selective gene targeting using clustered regularly interspersed short palindromic repeat (CRISPR) technology and the RNA-guided nuclease, Cas9, has rapidly become the predominant gene-editing tool in genomics. In the last year there have been a number of high profile and very exciting publications that report on the use of CRISPR-Cas9 gene

editing in the study of musculoskeletal disorders. In Duchenne muscular dystrophy, a series of three complimentary papers reported on the successful use of this technology to restore dystrophin expression in a mouse model of the disease[29-31]. There has also been some very nice recent work on the use of this technology to target musculoskeletal cancers such as osteosarcoma[32].

6. Metabolomics and the identification of disease signatures and therapeutic targets

The use of wide-scale screening of tissue samples using proteomics has produced interesting observations across a range of orthopaedic conditions. Mickiewicz et al. have reported on the use of metabolomics to identify a potential signature for osteoarthritis[33]. Liu et al. compared metabolomics profiles in plasma samples from 30 clinical patients with osteonecrosis of the femoral head with those from 30 control patients, finding that 123 metabolites were differentially expressed in the two populations[34]. Interestingly, many of these candidate markers were involved in lipid-, glutathione- and energy-associated pathways that might be associated with inflammation, oxidative stress and energy deficiencies that have been implicated in the pathogenesis of osteonecrosis. In a mouse model, Shum et al. used metabolomics to demonstrate that mitochondrial oxidative function is impaired in aged animals and that the negative effects of aging on bone formation, bone mass and bone strength can be partially reversed by targeting cyclophilin D, a key determinant of mitochondrial function[35].

7. Animal models and their reproducibility

The last decade has seen a significant increase in public awareness regarding the contentious issue of animal use in biomedical research. One of the fundamental tenets animal research is that the “benefit” (to patients and society at large) should exceed the “cost” to the animal in terms of pain and distress. As a result of improvements in the level of detail at which researchers and clinicians are now able to characterise disease processes, it is becoming evident that many of the induced disease models that are used routinely fail to completely replicate the pathology that is seen in the clinic. Even more disturbing is the suggestion that even when validated animal models are used, variability in how animal models are used means that it is often impossible to make direct

comparisons between studies performed at different institutions or by different investigators. The National Institutes of Health has identified irreproducibility as a major obstacle to scientific advances[36] and, according to a recent publication, this problem of irreproducibility cost approximately $28 billion[37].

Arguments are being made that the 3Rs should now be expanded to the 4Rs or even the 5Rs to incorporate the need for **reproducibility** and (clinical) **relevance** as a model. In the meantime, the orthopaedic research community is encouraged to work collectively to identify and propagate best practices in the use of animal models in its work[38]. Journals will continue to play a pivotal role in ensuring the integrity of this process by requiring that authors (a) verify that the work has been approved by the relevant national regulatory authority, and (b) provide enough specific detail in the Methods section to ensure that the work can be replicated by other laboratories.

Upcoming Meetings and Events Related to Orthopaedic Basic Science

The 2017 meeting of the Orthopaedic Research Society annual meeting will be held March 19-22, 2017 in San Diego, CA.

Gordon Research Conference, "*Understanding Biology to Achieve Better Cartilage Health*", will be held April 2-7, 2017 in Barga, Italy.

The Bone Research Society will meet 25-27 June, 2017 in Bristol, UK.

The 2017 meeting of the European Society for Biomechanics will be held 2-5 July, 2017 in Seville, Spain.

The 2017 meeting of the American Society for Bone and Mineral Research will be held September 9 - 12, 2017 in Denver, CO.

The 24th annual meeting of the European Orthopaedic Research Society will be held 13-15 September, 2017 in Munich, Germany.

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CME Questions Submission Form

Enter all questions on this form. A total of five individual questions are required.

Manuscript number: Click here to enter text.
Article title: **What's new in orthopaedic basic science**
Question 1 **(*staff use only* – question type_____)**

I. Question Category: Check as many categories as seem appropriate. Question category may differ from manuscript category.

☑**Basic science** ☐ Ethics ☐ Elbow ☐ Foot and ankle ☐ Hand and wrist ☐ Hip reconstruction, adult	☐ Infection ☐ Knee reconstruction, adult ☐ Oncology ☐ Pain management ☐ Pediatrics ☐ Rehabilitation	☐ Shoulder ☐ Spine ☐ Sports ☐ Trauma ☐ General interest/Does not fit any other category

II. Intended Audience: Check as many categories as seem appropriate. Minimum of 1 question in each category

☑Other health care personnel (e.g., NP, PA, PT, RN)	☑MD, non-orthopaedic	☑Orthopaedic generalist	☑Orthopaedic subspecialist

III. Does this question have an image or images?

☐ Yes ☑No

(If YES – upload image(s) separately using the "CME Question Figure" item option in the Attach Files screen of Editorial Manager. Include a one to two sentence description of each figure here. All figures should be at least 5x7 inches with a resolution of 300 ppi.)

IV. Question: (A patient-care scenario is preferred when appropriate; see Guidelines)

A 62-year old man presents with chronic pain in his left knee joint. A sample of synovial fluid is collected from the affected knee as part of the diagnostic work-up for this patient. Beyond standard cytology, what other test could be performed on this sample that might provide supporting evidence for a diagnosis of osteoarthritis?

V. Options: *(in alphabetical or logical order)*

A.	Measurement of total RNA by ELISA
B.	Proteomic analysis to characterise protein expression
C.	Measurement of total DNA by ELISA
D.	Bacterial culture and sensitivity testing
E.	Western blot for osteocalcin

VI. Answer: (must be *clearly* the best of the options)

☐ A. ☑ B. ☐ C. ☐ D. ☐ E.

VII. Answer Location: Please list the heading of the manuscript section where the correct answer is located (e.g. "Results" or "Anatomy and Physiology").

Section on metabolomics

VIII. Core Competencies addressed by this CME question:

☐ **Patient Care:**	Provide care that is compassionate, appropriate, and effective treatment for health problems and to promote health.
☑ **Medical Knowledge:**	Demonstrate knowledge about established and evolving biomedical, clinical, and cognate sciences and their application in patient care.
☐ **Practice-Based Learning and Improvement:**	Show and ability to Investigate and evaluate patient care practices, appraise and assimilate scientific evidence, and improve the practice of medicine.
☐ **Interpersonal and Communication Skills:**	Demonstrate skills that result in effective information exchanges and teaming with patients, their families and professional associates (e.g. fostering a therapeutic relationship that is ethically sound, used effective listening skills with non-verbal and verbal communication; working as both a team member and at times a leader).
☐ **Professionalism:**	Demonstrate a commitment to carrying out professional responsibilities, adherence to ethical principles, and sensitivity to a diverse patient population.
☐ **Systems-Based Practice:**	Demonstrate awareness of and responsiveness to the larger context and systems of health care. Be able to call on system resources to provide optical care (e.g. coordinating care across sites or serving as the primary case manager when care involves multiple specialties, professions or sites).

Question 2

(*staff use only* – question type_____)

I. Question Category: Check as many categories as seem appropriate. Question category may differ from manuscript category.

☑**Basic science** ☐ Ethics ☐ Elbow ☐ Foot and ankle ☐ Hand and wrist ☐ Hip reconstruction, adult	☐ Infection ☐ Knee reconstruction, adult ☐ Oncology ☐ Pain management ☐ Pediatrics ☐ Rehabilitation	☐ Shoulder ☐ Spine ☐ Sports ☐ Trauma ☐ General interest/Does not fit any other category

II. Intended Audience: Check as many categories as seem appropriate. Minimum of 1 question in each category

☐ Other health care personnel (e.g., NP, PA, PT, RN)	☑MD, non-orthopaedic	☑Orthopaedic generalist	☑Orthopaedic subspecialist

III. Does this question have an image or images?

☐ Yes ☑No

(If YES – upload image(s) separately using the "CME Question Figure" item option in the Attach Files screen of Editorial Manager. Include a one to two sentence description of each figure here. All figures should be at least 5x7 inches with a resolution of 300 ppi.)

Question: (A patient-care scenario is preferred; see Guidelines)

What does the term CASPR-Cas9 refer to?

IV. Options: *(in alphabetical or logical order)*

A.	A popular method for selectively editing genes in cells and tissues
B.	A key molecule in the apoptosis pathway
C.	A monoclonal antibody for treating osteoarthritis
D.	A cell surface receptor implicated in bone remodeling
E.	A new small molecule inhibitor of osteosarcoma

V. Answer: (must be *clearly* the best of the options)

☑A. ☐ B. ☐ C. ☐ D. ☐ E.

VII. Answer Location: Please list the heading of the manuscript section where the correct answer is located (e.g. "Results" or "Anatomy and Physiology").

Section on CASPR-Cas9 gene editing

VIII. Core Competencies addressed by this CME question:

☐ **Patient Care:**	Provide care that is compassionate, appropriate, and effective treatment for health problems and to promote health.
☑ **Medical Knowledge:**	Demonstrate knowledge about established and evolving biomedical, clinical, and cognate sciences and their application in patient care.
☐ **Practice-Based Learning and Improvement:**	Show and ability to Investigate and evaluate patient care practices, appraise and assimilate scientific evidence, and improve the practice of medicine.
☐ **Interpersonal and Communication Skills:**	Demonstrate skills that result in effective information exchanges and teaming with patients, their families and professional associates (e.g. fostering a therapeutic relationship that is ethically sound, used effective listening skills with non-verbal and verbal communication; working as both a team member and at times a leader).
☐ **Professionalism:**	Demonstrate a commitment to carrying out professional responsibilities, adherence to ethical principles, and sensitivity to a diverse patient population.
☐ **Systems-Based Practice:**	Demonstrate awareness of and responsiveness to the larger context and systems of health care. Be able to call on system resources to provide optical care (e.g. coordinating care across sites or serving as the primary case manager when care involves multiple specialties, professions or sites).

Question 3

(*staff use only* – question type_____)

I. Question Category: Check as many categories as seem appropriate. Question category may differ from manuscript category.

☑Basic science ☐ Ethics ☐ Elbow ☐ Foot and ankle ☐ Hand and wrist ☐ Hip reconstruction, adult	☐ Infection ☐ Knee reconstruction, adult ☐ Oncology ☐ Pain management ☐ Pediatrics ☐ Rehabilitation	☐ Shoulder ☐ Spine ☐ Sports ☐ Trauma ☐ General interest/Does not fit any other category

II. Intended Audience: Check as many categories as seem appropriate. Minimum of 1 question in each category

☑Other health care personnel (e.g., NP, PA, PT, RN)	☑MD, non-orthopaedic	☑Orthopaedic generalist	☑Orthopaedic subspecialist

III. Does this question have an image or images?

☐ Yes ☑No

(If YES – upload image(s) separately using the "CME Question Figure" item option in the Attach Files screen of Editorial Manager. Include a one to two sentence description of each figure here. All figures should be at least 5x7 inches with a resolution of 300 ppi.)

IV. Question: (A patient-care scenario is preferred; see Guidelines)

A 34-year old man presents with a history of acute trauma to the knee joint. Radiographs are unremarkable but an MRI scan reveals a small (<<0.5 cm^2) defect in the cartilage of the tibial plateau. The patient is keen to use regenerative therapy for this lesion and asks your advice. What would you recommend as the preferred option for this patient?

V. Options: *(in alphabetical or logical order)*

A.	A single injection of autologous stem cells into the joint to repopulate the lesion and repair the cartilage
B.	Surgical debridement and replacement of the resulting defect with a woven synthetic scaffold
C.	Surgical debridement and replacement of the resulting defect with a woven synthetic scaffold seeded with stem cells
D.	No treatment – the lesion will heal on its own
E.	Standard surgical debridement followed by microfracture

VI. Answer: (must be *clearly* the best of the options)

☐ A. ☐ B. ☐ C. ☐ D. ☑E.

VII. Answer Location: Please list the heading of the manuscript section where the correct answer is located (e.g. "Results" or "Anatomy and Physiology").

Section of cartilage repair

VIII. Core Competencies addressed by this CME question:

☐ **Patient Care:**	Provide care that is compassionate, appropriate, and effective treatment for health problems and to promote health.
☑ **Medical Knowledge:**	Demonstrate knowledge about established and evolving biomedical, clinical, and cognate sciences and their application in patient care.
☐ **Practice-Based Learning and Improvement:**	Show and ability to Investigate and evaluate patient care practices, appraise and assimilate scientific evidence, and improve the practice of medicine.
☐ **Interpersonal and Communication Skills:**	Demonstrate skills that result in effective information exchanges and teaming with patients, their families and professional associates (e.g. fostering a therapeutic relationship that is ethically sound, used effective listening skills with non-verbal and verbal communication; working as both a team member and at times a leader).
☐ **Professionalism:**	Demonstrate a commitment to carrying out professional responsibilities, adherence to ethical principles, and sensitivity to a diverse patient population.
☐ **Systems-Based Practice:**	Demonstrate awareness of and responsiveness to the larger context and systems of health care. Be able to call on system resources to provide optical care (e.g. coordinating care across sites or serving as

	the primary case manager when care involves multiple specialties, professions or sites).

Question 4

(*staff use only* – question type_____)

I. Question Category: Check as many categories as seem appropriate. Question category may differ from manuscript category.

☑Basic science ☐ Ethics ☐ Elbow ☐ Foot and ankle ☐ Hand and wrist ☐ Hip reconstruction, adult	☐ Infection ☐ Knee reconstruction, adult ☐ Oncology ☐ Pain management ☐ Pediatrics ☐ Rehabilitation	☐ Shoulder ☐ Spine ☐ Sports ☐ Trauma ☐ General interest/Does not fit any other category

II. Intended Audience: Check as many categories as seem appropriate. Minimum of 1 question in each category

☐ Other health care personnel (e.g. NP, PA, PT, RN)	☐ MD, non-orthopaedic	☐ Orthopaedic generalist	☐ Orthopaedic subspecialist

III. Does this question have an image or images?

☐ Yes ☑No

(If YES – upload image(s) separately using the "CME Question Figure" item option in the Attach Files screen of Editorial Manager. Include a one to two sentence description of each figure here. All figures should be at least 5x7 inches with a resolution of 300 ppi.)

IV. Question: (A patient-care scenario is preferred; see Guidelines)

Improvements are needed in the reproducibility of the animal models that are used in research. For a surgical model in rats, which of the following approaches is likely to have the **greatest** impact on reproducibility?

V. Options: *(in alphabetical or logical order)*

A.	Using animal models that have been published previously
B.	Using animal models that have been validated by multiple laboratories and that have been published previously
C.	Collecting samples at more time points for each animal
D.	Collecting more samples at each time point for each animal
E.	Using fewer animals for each experimental group

VI. Answer: (must be *clearly* the best of the options)

☐ A. ☑B. ☐ C. ☐ D. ☐ E.

VII. Answer Location: Please list the heading of the manuscript section where the correct answer is located (e.g. "Results" or "Anatomy and Physiology").

Section on animal models and reproducibility

VIII. Core Competencies addressed by this CME question:

☐ **Patient Care:**	Provide care that is compassionate, appropriate, and effective treatment for health problems and to promote health.
☑ **Medical Knowledge:**	Demonstrate knowledge about established and evolving biomedical, clinical, and cognate sciences and their application in patient care.
☐ **Practice-Based Learning and Improvement:**	Show and ability to Investigate and evaluate patient care practices, appraise and assimilate scientific evidence, and improve the practice of medicine.
☐ **Interpersonal and Communication Skills:**	Demonstrate skills that result in effective information exchanges and teaming with patients, their families and professional associates (e.g. fostering a therapeutic relationship that is ethically sound, used effective listening skills with non-verbal and verbal communication; working as both a team member and at times a leader).
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	the primary case manager when care involves multiple specialties, professions or sites).

Question 5

(*staff use only* – question type_____)

I. Question Category: Check as many categories as seem appropriate. Question category may differ from manuscript category.

☑Basic science ☐ Ethics ☐ Elbow ☐ Foot and ankle ☐ Hand and wrist ☐ Hip reconstruction, adult	☐ Infection ☐ Knee reconstruction, adult ☐ Oncology ☐ Pain management ☐ Pediatrics ☐ Rehabilitation	☐ Shoulder ☐ Spine ☐ Sports ☐ Trauma ☐ General interest/Does not fit any other category

II. Intended Audience: Check as many categories as seem appropriate. Minimum of 1 question in each category

☐ Other health care personnel (e.g., NP, PA, PT, RN)	☑MD, non-orthopaedic	☑Orthopaedic generalist	☑Orthopaedic subspecialist

III. Does this question have an image or images?

☐ Yes ☑No

(If YES – upload image(s) separately using the "CME Question Figure" item option in the Attach Files screen of Editorial Manager. Include a one to two sentence description of each figure here. All figures should be at least 5x7 inches with a resolution of 300 ppi.)

IV. Question: (A patient-care scenario is preferred; see Guidelines)

There is often a disconnect between the results seen with a new drug therapy in preclinical animal models of osteoarthritis and those seen in the later clinical trials. It has been suggested that the most common reason for failure of these models to be predictive is:

V. Options: *(in alphabetical or logical order)*

A.	Mice and rats have different gastrointestinal tracts to humans, making it hard for them to metabolise oral drug formulations
B.	Mice and rats are much smaller than humans, making it impossible to accurately predict drug dosages
C.	Rats and mice are much smaller than humans, so their joints do not experience the same loading
D.	Most of the animal models used to study OA involve the creation of traumatic instability within the joint, something that is not a feature of uncomplicated primary OA in humans
E.	Animals are more resilient and do not feel pain in the same way as human patients

VI. Answer: (must be *clearly* the best of the options)

☐ A. ☐ B. ☐ C. ☑D. ☐ E.

VII. Answer Location: Please list the heading of the manuscript section where the correct answer is located (e.g. "Results" or "Anatomy and Physiology").

Section on "Post-traumatic OA"

VIII. Core Competencies addressed by this CME question:

☐ **Patient Care:**	Provide care that is compassionate, appropriate, and effective treatment for health problems and to promote health.
☑ **Medical Knowledge:**	Demonstrate knowledge about established and evolving biomedical, clinical, and cognate sciences and their application in patient care.
☐ **Practice Based Learning and Improvement:**	Show and ability to Investigate and evaluate patient care practices, appraise and assimilate scientific evidence, and improve the practice of medicine.
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Selected Abstracts

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