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Biomarkers for equine joint injury and osteoarthritis

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CWM provided the initial 10,000-word summary, which was reviewed by all the other authors. CWM also wrote the first draft. All authors have read and approved the final manuscript.

ABSTRACT

We report the results of a symposium aimed at identifying validated biomarkers that can be used to complement clinical observations for diagnosis and prognosis of joint injury leading to equine osteoarthritis (OA). Biomarkers might also predict pre-fracture change that could lead to catastrophic bone failure in equine athletes. The workshop was attended by leading scientists in the fields of equine and human musculoskeletal biomarkers to enable cross-disciplinary exchange and improve knowledge in both. Detailed proceedings with strategic planning was written, added to, edited and referenced to develop this manuscript. The most recent information from work in equine and human osteoarthritic biomarkers was accumulated, including the use of personalized healthcare to stratify OA phenotypes, transcriptome analysis of anterior cruciate ligament (ACL) and meniscal injuries in the human knee. The spectrum of "wet" biomarker assays that are antibody based that have achieved usefulness in both humans and horses, imaging biomarkers and the role they can play in equine and human OA was discussed. Prediction of musculoskeletal injury in the horse remains a challenge, and the potential usefulness of spectroscopy, metabolomics, proteomics, and development of biobanks to classify biomarkers in different stages of equine and human OA were reviewed. The participants concluded that new information and studies in equine musculoskeletal biomarkers have potential translational value for humans and vice versa. OA is equally important in humans and horses, and the welfare issues associated with catastrophic musculoskeletal injury in horses add further emphasis to the need for good validated biomarkers in the horse.

Keywords: Biomarkers, Traumatic arthritis, Osteoarthritis

INTRODUCTION:

Osteoarthritis (OA) is the most common disease affecting the joints in humans and is an important cause of pain, disability and economic loss[1-3]. Traumatic joint injury and OA are equally important in the equine athlete[4], not only for joint disease but also for bone failure. In September 2014 the third Dorothy Russell Havemeyer Foundation Symposia on Equine Musculoskeletal Biomarkers was held (the second Havemeyer Foundation Symposium has been reported[5]). The aim was to identify validated biomarkers that could be used to complement clinical observations for diagnosis and prognosis of joint injury leading to OA, to predict pre-fracture subchondral bone disease which can lead to catastrophic bone failure in equine athletes, and to discuss development of a point of care diagnostic platform.

The definition of a biomarker varies but a recent consensus suggests it is "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention"[6]. Further, this definition stated that "biomarkers can be anatomic, physiologic, biochemical or molecular parameters associated with the presence and severity of specific diseases and are detectable by a variety of methods including physical examination, laboratory assays, and imaging". Biomarkers have been differentiated into "dry" (e.g. imaging parameters) and "wet" biomarkers (genetic and biochemical entities that can be detected in blood, serum, urine, synovial fluid (SF) and tissues) in OA[7].

There has been much work in biomarkers in OA in humans for over 25 years[8, 9]. The quest is still ongoing to define a validated and qualified biomarker panel that could be used to complement

clinical observations for diagnosis, prognosis and response to treatment, with the most recent data from the NIH Osteoarthritis Initiative reported[10]. The first report demonstrating a relationship between biomarkers and osteochondral change in equine joints was published in 1999[11]. Panels of some biomarkers have been validated in experimental equine OA[12,13], and the status of equine biomarkers was reviewed in 2005[14] and more recently in 2015[15]. The Dorothy Russell Havemeyer Foundation Symposia in 2005, 2009 and recently in 2014 have allowed exchange of updated information in human and equine musculoskeletal biomarkers as well as planning best paths for the future in both disciplines. The current narrative review represents the key findings from the presentations by the attendees, the issues and questions arising from their discussion and the formal break-out sessions held at the 2014 Symposia.

Equine musculoskeletal biomarkers: current knowledge and future needs

Previous studies have promoted development of targeted molecular diagnostics and predictive biomarkers as models for personalized equine orthopedic medicine[5, 14, 15]. Diagnostics are sought that are non-invasive, repeatable/reproducible and have specificity and sensitivity for early stages of OA.[16] Spontaneous joint disease is a common clinical problem in the horse and surveys estimate that up to 60% of lameness is related to OA[17]. There is therefore a need for diagnostics designed to predict risk of clinical injury and not just manage the extent of OA, bone disease, catastrophic fracture, and tendon/ligament injury, but to monitor the health and training of competition horses and prevent such injuries. This workshop focused on the current status of diagnostic and point of care platforms for predictive biomarkers.

Biomarkers in human OA - current state of the art in osteoarthritis biomarkers:

There is an urgent need for qualified biomarkers to monitor OA development, predict the long-term clinical treatment response and outcome, and identify individuals with the highest risk of disease progression[7, 9, 16, 18]. Osteoarthritis biomarkers could assist clinical trials by delivering essential early information of treatment response, speeding up compound evaluation, and thereby making OA a more manageable target for new drug development. Since a disease starts when detected by the best marker available to define it, herein lies the power of biomarkers. This is especially important for OA, a disease with a prolonged asymptomatic molecular and pre-radiographic phase. Biomarkers could provide an early warning of biochemical and structural alterations leading to earlier treatment prior to irreversible disease, which is likely recalcitrant to therapy.

An Osteoarthritis Research Society International (OARSI) White Paper[7] was produced in response to the Food and Drug Administration (FDA) call for a critical appraisal of fundamentals of the science related to biomarkers of OA, particularly relating to drug development. A subsequent OARSI White Paper reviewed FDA guidance on biomarkers and made recommendations for their use in preclinical development and phase I to IV clinical trials[18]. These documents catalyzed the OA Biomarker Consortium study managed by the Foundation for the National Institutes of Health (FNIH)[10] and highlight how advances in the field of OA research and treatments can be accelerated by a systematic paradigm that encompasses development, validation, qualification and regulatory approval of OA-related biomarkers for clinical trial and clinical use (also see http://oarsi.org).

In addition to robust disease definitions, there is a recognized need for a consensus on a nomenclature defining the disease. According to the FDA[19] the "currently used disease classification systems define diseases primarily on the basis of their signs and symptoms". Consequently, many disease subtypes with distinct molecular causes are still classified as one entity, with little ability to stratify or link distinct phenotypes. The National Academy of Sciences has called for a "New Taxonomy" of disease to advance our understanding of disease pathogenesis and improve health, that defines and describes diseases on the basis of their intrinsic biology in addition to traditional signs and symptoms[20]. Biomarkers are key to this new taxonomy for heterogenous diseases such as OA. To aid in this, a standardized nomenclature has been proposed, describing disease (molecular, anatomic and physiological aspects) and illness aspects of OA[21].

Use of personalized health care (PHC) to stratify OA phenotypes

OA is a heterogeneous disorder, with numerous drivers of disease progression. However, up to 50% of OA patients in clinical studies and approximately 85% in the background population do not show both symptom and structural progression over 2 years[22,23]. It is therefore important to identify the individuals that progress and determine the drivers of progression. This would enable enriching of clinical trial populations, and when effective treatment is available to slow disease progression, to identify those in need of it. There is a need to pair the paramount risk factor for progression with personalized treatment approaches, in which "one size does not fit all". A number of drivers for PHC in OA have been identified[24]: 1) Identification of patients who respond optimally, with the highest efficacy and lowest safety concerns, to a given treatment; 2) Specific development strategy for a selected subpopulation of patients; and 3) Efficient use of

healthcare resources. To date, three different OA subpopulations have been identified: 1) Inflammation mediated OA; 2) Subchondral bone turnover driven OA; and 3) Trauma driven OA. Biomarkers can identify different pathophysiological processes potentially leading to identification of these phenotypes (**Figure 1** (from Lotz et al 2013[24,25]).

Transcriptome analyses of meniscus and anterior cruciate ligament injuries may provide insights into early OA

These were novel discovery studies seeking to determine signaling pathways and specifically expressed transcripts that are different between samples. As with most transcriptomic profiling studies, these investigations are usually undertaken as "hypothesis-free" discovery studies, and do not rely on previous investigations to develop preliminary hypotheses. Clinical studies of athletes and revision anterior cruciate ligament (ACL) reconstruction patients indicate that having a partial meniscectomy, increasing age and elevated BMI are all associated with degenerative changes in knee articular cartilage. Englund and colleagues have suggested that weakening of the meniscus due to processes similar to OA may be sentinel for the disease[26]. However, little is known about the molecular signatures in injured meniscus. An extensive analysis of gene expression from meniscal fragments recovered from meniscal repair surgery was evaluated for association with the presence or absence of a concomitant ACL injury, age, BMI and articular cartilage disease in the patient[27-30]. Transcripts associated with extracellular matrix (ECM) synthesis were down regulated in obese individuals (BMI >30) perhaps indicating a higher risk of developing meniscus degeneration. Transcripts up-regulated in obese compared to lean or overweight patients were associated with increased apoptosis and suppression of ECM deposition. Patients >40 years of age demonstrated repression of genes for skeletal development,

cartilage development and cartilage ECM synthesis and elevation of genes involved in cell cycle and cell division, immune response and inflammation pathways. Results such as these may provide a molecular rationale for the known clinical effects of partial meniscectomy, increasing age, and increasing obesity on the development of cartilage degeneration[31-33].

Further investigation of the relative gene expression levels in the ACL at various times after injury from acute (<3 months) to chronic (>12 months) showed that processes representing angiogenesis were repressed in acute tears. In intermediate tears, processes representing stem cell proliferation concomitant with cellular component organization were elevated. In chronic tears, processes denoting myosin filament organization were elevated while those representing cellular component organization and ECM organization were repressed. An ACL tear appears to stimulate local repair processes early after rupture that recede over time. Further transcriptome analysis of injured and OA joint tissues may provide candidates for molecular biomarkers as well as targets for treatment that would reduce the risk of developing OA [29,32-33].

Fluid ("wet") biomarker assays that are antibody based

Biomarker assessment by immunologic assay has been the standard for analysis in both humans and horses (reviewed recently)[14, 15]. Progress continues with development of biomarkers for human OA and their use in clinical trials[7, 16, 18] and knowledge has advanced in parallel in the horse (Table S1).[5,15] Studies in the horse have shown significant exercise related changes in serum biomarkers of collagen metabolism in young horses[33]. Equine serum markers have also been shown to distinguish changes associated with exercise from pathologic change in exercising horses, and to correlate to clinical parameters of pain in an equine OA model[12]. A clinical study

in 238 racehorses, employing monthly musculoskeletal examinations and blood samples, showed that it was possible to correctly predict horses that would sustain an injury 74% of the time[34].

Recent work evaluating proteinases has shown that: 1) the presence of lumican and a 29kD lumican catabolite increased with the onset and progression of OA[35,36]; 2) a splice variant of one of the aggrecanases (ADAMTS4) was identified that appears to be specifically synthesized by human OA synovium and is associated with aggrecan degradation in the superficial zone of articular cartilage[37]; and 3) synovial fluid ADAMTS4 activity is a marker of inflammation and effusion[38]. Such findings have biologic/disease rationale as confirmed by OA onset in a STR/ORT mouse model being significantly reduced using monoclonal antibodies directed against substrate recognition domains of ADAMTS5[39].

An anti-cathepsin K antibody has demonstrated significant involvement of cathepsin K in naturally occurring equine and human OA[40-43]. In equine OA cartilage an alternate equine type II collagen specific cathepsin K cleavage site was identified in the N-terminal region of the C-terminal collagen fragment using proteomic and immunological techniques[43]. A novel ELISA assay (C2K77) has been developed to measure the activity of cathepsin K in culture media and is being validated in body fluids[44].

While trauma is pivotal in the pathogenesis of human knee OA, seemingly equivalent injuries do not invariably result in post-traumatic (ptOA). For instance, only 50% of patients with ACL rupture develop ptOA 10-15 years later, and these numbers are not substantially affected by surgical reconstruction and "restoration" of joint biomechanics[45-48]. This suggests that factors

other than joint instability may play a role in the risk, rate of onset, and progression of ptOA after injury. Differences between non-ptOA inducing (sham) and ptOA-inducing joint injury in mice showed differing phases of synovial inflammation with distinct cyclically increased macrophage, CD4 and CD8 T-cell infiltration into the synovium without associated systemic change. Data from Jaffa mice (protected from cartilage damage) suggest that proteolysis of aggrecan by ADAMTS plays a critical role in regulating the inflammatory response in the joint, particularly in macrophage activation and M1/M2 polarization. As has been done in inflammatory arthropathies, monitoring the pattern of cell influx into the joint after injury may be diagnostic and enable differentiation between OA-inducing and non-inducing joint trauma[49-51].

Examination of proteins from harvested media in an interleukin-1 beta cartilage explant model analysed by liquid chromatography mass tandem spectrometry (LC-MS/MS) identified cartilage oligomeric matrix protein (COMP) as a potential OA diagnostic in horses. The unique fragments of COMP include the amino acid sequences that form a new terminal (neo-epitope) sequence; polyclonal antibodies that react specifically with this new cleavage site have now been developed[52]. It was concluded that an increase in the COMP neo-epitope in synovial fluid from horses with acute lameness suggested that this has the potential to be a unique candidate biomarker for the early molecular changes in articular cartilage associated with OA.

Imaging biomarkers in the horse

Imaging lacks evidence as a biomarker technique for predicting and characterizing musculoskeletal injuries, especially to inform prognosis. Hurdles include limited ability to discern normal tissue adaptation from early disease, limited use of frontline volumetric imaging

techniques (usually due to cost), lack of prospective data on imaging biomarkers in relation to disease presence and outcome in the horse, modest correlation between pain and imaging results, and limited follow-up/longitudinal imaging[13,53]. However, progress is being made and novel techniques including digital radiography, ultrasound, nuclear scintigraphy, computed tomography (CT) and MRI are developing. The use of digital radiography, nuclear scintigraphy, CT and MRI to distinguish changes with exercise vs. OA has been published[13].

Digital radiography technology allows image manipulation to improve lesion detection but a 30-40% change in bone mineral density is still needed to detect lesions, allowing for significant tissue changes to occur prior to detection[54]. Radiological changes in OA are slow to develop, and thereby inhibit intervention in a timely fashion. Joint space width has been used for decades as a measure of joint disease severity, yet it lacks predictive ability for clinical outcomes in humans[55]. Joint space width measurements in equine femorotibial joints have recently been assessed for accuracy and standardization of positioning, as in humans, is essential for maximum accuracy[56]. Radiography, however, continues to be a useful outcome measure in a common model of OA[13].

Nuclear scintigraphy has been useful in defining the presence of disease compared to increased uptake that occurs with exercise alone in horses[57]. Although nuclear scintigraphy appears helpful in early diagnosis of disease, it lacks the specificity to fully define the lesion, but may be useful for screening and monitoring OA onset or progression in both horses and humans.

Computed tomography has been used clinically to detect occult lesions in subchondral bone. Detection of altered patterns of subchondral bone density by computed tomographic

osteoabsorptiometry (CTO) has been used to define joint disease in horses[13]. It appears that CTO density patterns can characterize insidious disease processes, such as palmar osteochondral disease. Intra-articular application of contrast has also been used and provides critical information concerning soft tissues of joints[58], especially those such as the equine femorotibial joint that can rarely be imaged using MRI[59]. Dual energy CT has also been studied and appears to have value in characterization of soft tissues and detection of bone marrow edema[60].

MRI has revolutionized the detection of subtle joint disease in all species, and in particular, the detection of soft tissue and articular lesions. However, its resolution is limited and subtle bone and joint lesions can sometimes be missed[61]. MRI has significant potential as a predictive marker of disease as shown by many studies including the MRI component of the OARSI/FNIH study[61]. A recent review has shown that measures of quantitative cartilage morphology, cartilage defect and bone marrow lesions, bone shape and attrition and subchondral bone area were the most promising as imaging biomarkers[62].

Quantitative MR imaging has improved characterization of articular cartilage matrix (GAG, collagen and water) in humans and research animals, with limited use in the horse. dGEMRIC imaging uses intraarticular or IV administration of gadolinium based contrast medium measured in relation to the fixed-charged matrix components, giving an indication of GAG concentration in the cartilage matrix[63]. T1rho has been used in people but not horses, and can give information on GAG content, but can also be influenced by collagen content[64]. Therefore T2 mapping is often necessary for comparison. Sodium MR imaging is also correlated to GAG, but requires special equipment and high field strength for scanning[65]. T2 and T2* imaging can be used to

characterize collagen content within articular cartilage, but often require long scan times[66]. Diffusion weighted techniques measure water diffusion through the matrix and appear to have promise in best characterizing matrix integrity[67].

Standing low-field MRI systems have been useful in the horse for identifying osseous pathology, which appears to carry various (but ill-defined) risks of sustaining catastrophic injury[68,69], but their usefulness is limited to the distal limb; because of low quality resolution only rudimentary visualization of the articular cartilage is possible limiting early identification of cartilage pathology.

All imaging modalities to date focus on identifying tissue changes after the initiating insult. Much like genetic markers, using biomechanical modeling to identify those horses with joints that may be geometrically predisposed to disease has potential uses for identifying risk and modulating exercise to lower risk and/or severity of disease[70].

The use of spectroscopy as a biomarker:

In the case of naturally occurring equine traumatic OA, the Fourier transform infrared spectroscopy (FTIR) approach has been confirmed as highly accurate for synovial fluid when compared to arthroscopy[71]. The limitations of such studies are that they have been conducted on clinically apparent cases and have not been tested in a preclinical population of horses for which prospective synovial fluid analysis would be impractical[35].

One of the significant advantages of FTIR as a biomarker tool is that the spectra generated from serum or any other body fluid, encompass not only known markers but also unknown markers[71]. Current work has used transmission FTIR that is expensive but more cost effective clinical platforms are being developed[72].

Metabolomics and proteomics:

There has been increasing interest in profiling the metabolome, consisting of the low molecular weight end products of cell metabolic processes which indicate the cellular function of a given cell type or tissue under specific conditions[73,74]. The principal analytical techniques used in metabolomics are mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy[75]. Compared to MS, NMR spectroscopy is non-destructive and requires little sample preparation, and can generate a comprehensive metabolomics profile from intact biofluids and tissues[76]. However, in certain instances this technique is insufficient to provide information that will fully characterize a metabolite and MS analysis has the advantage of higher sensitivity.

In OA, metabolomic fingerprinting has been performed on urine samples from Hartley guinea-pigs, which spontaneously develop OA[77,78]. MS-based proteomics techniques have also been used to determine the underlying mechanisms of musculoskeletal aging, OA and tendon injury in equine SF from normal and OA racing Thoroughbreds as well as equine cartilage and tendon from normal or diseased young and old donors (Table S1).

Proteomic analysis of the OA cartilage secretome identifies molecules with roles in the pathologic processes and allows the global study of secreted proteins while also potentially enabling biomarker discovery. In one study an equine degradome using a mass spectrometry-based absolute quantification method using a concatamer of selected quantotypic peptides representative of proteins (QconCAT) was designed to measure specific cleaved ECM proteins[79]. There was a significant decrease with age of the mean concentration of aggrecan G3 that is explained by loss of G3 soon after cartilage aggrecan synthesis and a steady decline in turnover producing a loss of G3 in the resident aggrecan molecules. The result is that the average size of aggrecan decreases with age, and a large proportion of aggrecan lacks a G3 domain[80].

Matrix assisted laser desorption ionization imaging mass spectrometry (MALDI-IMS) was used to examine proteins *in situ* at high spatial resolution in an examination of full-thickness equine cartilage slices; identified ECM proteins included COMP, fibromodulin, biglycan, and type II collagen. In addition, a number of OA and age specific markers were identified[81].

Proteomic profiling of equine synovial fluid from normal and OA metacarpophalangeal joints using label-free quantification approaches following protein equalization techniques identified 754 proteins in synovial fluid, 593 with a significant Mascot score. Proteins identified included those relating to matrix proteins, inflammatory factors, complement activation proteins and proteases. A subset of 10 proteins were identified which were differentially expressed in OA synovial fluid. This distinct set of proteins could provide potential biomarkers to stratify OA[82]. Although frequently used in clinical research , substantial challenges remain before this technology can be employed as a biomarker in a clinical setting

Next Generation Sequencing (NGS) and a computational strategy to support biomarker and therapeutic discovery

With NGS approaches it is possible to identify subtle unique genomic variations encoded in each individual's genome and identify the transcriptionally active genes in individual tissues. This provides the ability to explore associated differences in coding or transcriptional activity with clinical observations, ultimately affording cause-effect relationships that impact aspects of the individual's health status. Knowledge of the extent of an individual's unique genomic variation, which genes are transcriptionally active and the pathway assignments of each gene provides information about the metabolically active processes and how the host's tissues metabolic activity differs after injury compared to a healthy state. Further, this global approach holds the promise to not only discern early pre-symptomatic disease, but also identify susceptible individuals.

In addition to global post-genomic experimental techniques, powerful analytical strategies are required to fully utilize the resulting large and complex datasets. To address this need, iterative feature removal (IFR) analysis was developed to identify molecular features that can be used as classifiers for metabolic activity and as diagnostics[83]. The IFR process works by repeatedly building a predictive model on training data using a classifier that assigns non-zero weights to only a minimal subset of non-redundant features. IFR assists investigators with process discovery in a way that alternative feature selection approaches cannot. IFR analysis, when applied to global biological datasets, allows for more comprehensive evaluation of linked metabolic processes. When applied to transcriptional data, IFR identified sets of genes that were

highly predictive even when the sets were comprised of genes that, taken individually, appeared non-discriminatory. The efforts here not only identify biomarkers that are classifiers for disease, but also provide biomarkers that hold the potential to screen for disease susceptibility.

Due to the global analysis offered by NGS, this strategy can also be used to identify pathways associated with therapeutic intervention and healing. Based on observations that IGF-I could function as an anabolic factor for the treatment of OA, a gene therapy approach was taken to produce IGF-I and NGS was used to map the biological response associated with the observed healing effects in an equine study[84]. Analysis of the resulting transcriptional response to IGF-I therapy revealed that genes and metabolic pathways associated with specific extracellular matrix collagen types were differentially regulated, as in cartilage development and chondrocyte differentiation. NGS analysis afforded a differential expression fingerprint that could potentially be used to monitor treatments of OA.

Biobanks to classify biomarkers in different stages of equine OA:

In order to validate existing and develop new wet biomarkers it is critical that sufficient well-documented equine samples are available to the research community. Potential biomarkers can be tested using standard samples from biobanks and classified according to: Burden of disease (B), Investigative (I), Prognosis (P), and Efficacy of treatment (E), Diagnostic (D) and Safety (S) (BIPEDS)[85]. Safety was added in a second OARSI White Paper[18]. Four equine biobanks are actively archiving specimens or are proposed:

1. Young horses sampled every third month during a training program with speed training gradually increasing during the study period. This biobank can test potential biomarkers for D (acute lameness) and P (initiation and progression).
2. Joints, sampled at one abattoir or necropsy. The articular cartilage should be characterized as being macroscopically? normal or with mild, moderate, or severe lesions. Radiographic examination of the dissected bones should be included categorising the bone according to the extent of sclerosis. These structural OA joints can be used for testing biomarkers as B (degree of structural OA) and D (Structural OA).
3. Horses in conventional training/racing and undergoing arthroscopy of different joints. The SF is aspirated during arthroscopy, and material from synovial membrane, synovial capsule and osteochondral fragment, when appropriate, is immersed in buffered formalin.
4. Clinically lame horses examined by routine lameness examination sometimes including the lameness locator test[86], evaluating acute and chronic lameness before and after local anaesthesia. These fluids can test biomarkers for clinical OA as P (prognosis), E (efficacy) and D (diagnosis).

These biobanks will consist of serum and synovial fluid (SF), and where possible tissues from synovial membrane/capsule and articular cartilage (including subchondral bone). Samples of the SF would be analysed for total protein (g/L) and total number of leucocytes, and the remainder centrifuged for 20 min, 16,000g and aliquots' (100µ/L) frozen at -80°C and stored until analysed. Signed ethical approvals and consent of the owners is mandatory for all samples.

CONCLUSIONS:

New information and studies in equine musculoskeletal biomarkers have potential translational value for humans and vice versa. Osteoarthritis is equally important in both humans and horses and the welfare issues associated with catastrophic musculoskeletal injury in horses add further emphasis to the need for good validated biomarkers in the horse. Further progress in identifying useful human and equine biomarkers requires exploratory studies to identify promising candidates combined with the development of reliable assays. To prove clinical utility and acquire regulatory approval for a biomarker is a demanding task, requiring retrospective hypothesis-generating and prospective hypothesis-testing studies in several study populations. The equine athlete offers a unique "at risk" population with a high incidence of naturally occurring clinically important musculoskeletal disease including OA, that is ideal for the discovery and validation of biomarkers across the BIPEDS spectrum. In addition, by having established inducible models in the same species, the biomarkers can be used in development of new therapeutics which simultaneously validates their utility in monitoring disease progression and response to treatment. To take advantage of this opportunity will require establishing standardised methods of sample collection, reproducible biomarker measurement, and well-documented biobanks akin to those in human medicine. Meeting these challenges will not be insubstantial, but the potential rewards for the equine industry and how this will inform human health, are enormous.

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Conflict of Interest Disclosure

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Figure Legend:

Figure 1: Overview of currently used markers in the rheumatology, divided into areas Inflammation, signalling, matrix destruction, matrix production and differentiation, proteases and synovial inflammation. Reproduced from Lotz M, Martel-Pelletier J, Christiansen C, et al. Value of biomarkers in osteoarthritis: current status and perspectives. Ann Rheum Dis 2013;72:1756-63.

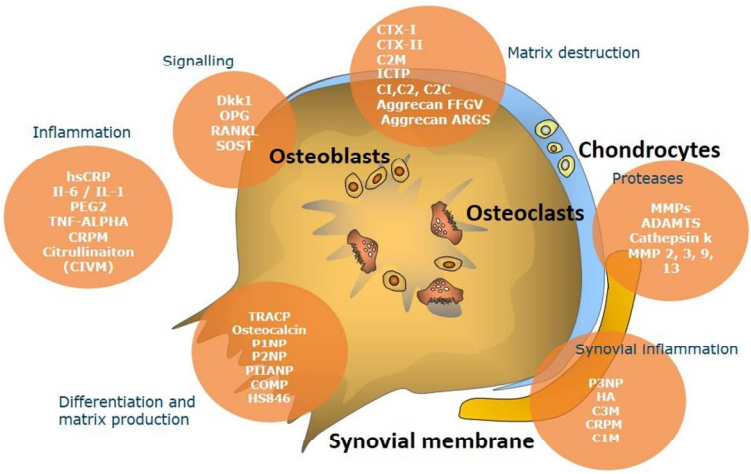

Figure 1

338x190mm (96 x 96 DPI)