New therapies to prevent post traumatic osteoarthritis

Dr. Kyla Ortved is an assistant professor of Large Animal Surgery at New Bolton Center, the large animal campus of the University of Pennsylvania School of Veterinary Medicine, located in Kennett Square, Pennsylvania. She received her DVM degree from the University of Guelph in 2006 and completed her large animal surgical residency at Cornell University in 2010. Dr. Ortved became
boarded with the American College of Veterinary Surgeons in 2011. Following her residency, Dr. Ortved went on to obtain a PhD in equine cartilage repair at Cornell University in June 2014 and joined the faculty at Cornell Ruffian Equine Specialists in July 2015 as Clinical Assistant Professor of Equine Surgery. In January 2016, Dr. Ortved became boarded with the American College of Sports Medicine and Rehabilitation. She joined the faculty at New Bolton Center in February 2016 as a large animal orthopedic surgeon. Dr. Ortved’s research program at New Bolton Center is focused on joint disease, using the horse as a model for human disease. Specifically, she is interested in developing cell and gene therapies to improve cartilage repair and prevent the development of osteoarthritis.

**Developing new therapies to prevent post traumatic osteoarthritis (PTOA) in the horse and the rider**

Joint injuries are overwhelmingly common in both human and equine athletes. Chondrocytes, the sole cell type in cartilage, are responsible for producing and maintaining the extra-cellular matrix (ECM), which affords remarkable tensile and compressive strength to the joint surface. The intrinsic healing capabilities of cartilage are poor, in part due to its avascular and hypoxic nature[1]. Therefore, post-traumatic osteoarthritis (PTOA) commonly develops following sufficient joint trauma, whether sustained during an acute injury or accumulated over time. Unfortunately, PTOA is a progressive, debilitating disease that currently lacks any effective treatment. Pain and decreased mobility are addressed with systemic non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular corticosteroids, rest and rehabilitation. The end stage therapy for OA joints in humans is total joint replacement, while select joints in the horse can be treated with surgical arthrodesis. Both of these procedures are invasive and expensive interventions. Dr. Ortved’s research program is focused on understanding the pathophysiology of PTOA and developing gene and cell-based therapies to help regenerate cartilage and prevent the development of PTOA following joint injury. Due to the many similarities in joint biomechanics and propensity for PTOA, the horse serves as an excellent large animal model for human joint disease.

Cell-based therapies aim to return damaged or injured tissue to a more normal structure and function. An overarching goal in cell-based repair is to restore the articular surface, thereby preventing further joint degradation. Although bone marrow-derived MSCs (BM-MSCs) have been the most frequently used MSC type for cartilage repair to date, full chondrogenic differentiation...
Annual Faculty Research Retreat—The annual meeting was held on June 23rd at the New Bolton Center campus. More than 150 attended the day-long event where eight faculty members spoke and 45 posters were presented. The crowd enthusiastically responded to the Marshak Lecture, entitled “How the Mouse Got its Stripes”, given by Hopi Hoekstra, PhD, from Harvard University. A new and different approach was used in judging posters. All registrants were given a voting ballot with which they voted for first, second and third place “best posters”. Certificates and prizes were awarded to the recipients. Dr. Raghavi Sudharsan of William Beltran’s laboratory won 1st Place for her poster entitled: Involvement of Innate Immune System in Late Stages of Inherited Photoreceptor Degeneration; Dr. Sushil Kumar, from Rumela Chakrabarti’s laboratory won 2nd Place for his poster entitled ΔNp63+ Cancer Stem Cells Recruit Myeloid Derived Suppressor Cells to Promote Metastasis in Triple Negative Breast Cancer; and Cynthia Otto won 3rd Place for her poster entitled Biosensing of Biofilm: Detecting the Volatile Organic Compounds (VOC) of Biofilm using a Dog’s nose.

Dr. Ronald Harty chaired the annual event with a theme of Veterinary Medicine in the Genomics Era along with his committee (Drs. Montserrat Anguera, Michael Povelones, Julie Engiles, Helen Aceto, Zhengxia Dou, Alexandr Reiter, Keiko Miyadera, Christopher and Phillip Scott). Speakers included Charles Bradley, Dieter Schifferli and Julie Engiles from the Department of Pathobiology; Kyla Ortved and Marie Eve Fecteau from the Department of Clinical Studies New Bolton Center; and Keiko Miyadera and Erika Krick from the Department of Clinical Sciences and Advanced Medicine. Christopher Hunter, chair of the Department of Pathobiology presented the 2017 Zoetis Award for Veterinary Research Excellence to Igor Brodsky. “Dr. Brodsky has made several key observations that advanced our understanding of how the innate immune system recognizes bacterial pathogens”, said Dr. Hunter.
has been disappointing. Therefore, Dr. Ortved is currently investigating the chondrogenic differentiation capability of synovial membrane-derived mesenchymal stem cells (SD-MSCs). SD-MSCs may have superior chondrogenesis due to a common progenitor cell between synovium and cartilage[2]. Recent experiments using flow cytometry in the Ortved laboratory have demonstrated a similar immunophenotype between BM-MSCs and SD-MSCs, with SD-MSCs expressing the appropriate markers of stemness including CD29, CD44, CD90, CD105 and MHCII and lacking expression of exclusion markers including CD45, CD79, and MHCII (Figure 1) [3]. They have also shown that SD-MSCs have increased proliferative capacity in vitro, making timely culture expansion of these cells achievable. Trilineage differentiation assays are being performed to assess chondrogenic differentiation, with the ultimate goal of defining a source of adult MSCs suitable for resurfacing cartilage lesions to facilitate healing.

Gene therapy also has the potential to bolster the weak healing response in articular cartilage. Previous work by Dr. Ortved has demonstrated improved cartilage repair in large, full-thickness chondral defects created in the lateral trochlear ridge of the equine femur using autologous chondrocytes transduced ex vivo with an adeno-associated virus (AAV) vector overexpressing the
anabolic protein IGF-I[4] (Figure 2). Dr. Ortved has also demonstrated that AAV vectors can be used to safely transduce equine articular cells in vivo with efficient, sustained expression of a therapeutic transgene[3]. More recently, Dr. Ortved has been investigating AAV-mediated overexpression of interleukin-10 (IL-10), an immunomodulatory cytokine. She showed that IL-10 overexpression downregulates expression of proinflammatory mediators in inflamed chondrocytes in vitro. Next, Dr. Ortved is planning on assessing the protective effects of this therapy in vivo to determine if it can mitigate the post-traumatic inflammatory response that occurs following joint injury.

Despite the robust nature of healthy cartilage, the meager healing response that follows trauma leads to serious health consequences long-term. Indeed, PTOA is often career ending in both equine and human athletes, and is one of the most common disabilities of the aging human population. Early studies in the Ortved laboratory have identified promising cell and gene therapeutic strategies that may improve repair of cartilage lesions and modulate the post-traumatic inflammatory response in the joint. As the horse is an invaluable large animal model for human joint disease, Dr. Ortved will continue to investigate joint therapies that will hopefully allow both horse and rider to ride off into the sunset a bit more comfortably.

Dr. Ortved’s research has been funded by NIH, Grayson-Jockey Club Research Foundation, Harry M. Zweig Memorial Fund for Equine Research, and the Raymond Firestone Trust. Dr. Ortved’s laboratory is located Myrin 104, New Bolton Center.

References

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**Publication Highlights**


Dr. Gary Althouse serves final term as Chair of Clinical Studies, New Bolton Center—Currently the longest-serving chair in the School, Gary Althouse finished his term of office on June 30, 2017. A steadfast advocate for the inclusion of large animal/food animal training and science, he was an exemplary School and University citizen. In the interim, before appointing a new chair, Dr. Ray Sweeney and Dr. Dean Richardson have agreed to be interim co-Chairs for the Department. As with all the chairs at Penn Vet, Drs. Sweeney and Richardson will maintain their roles as active faculty members—continuing their teaching, research and clinical service activities.

Professor Oliver Garden, chair, Department of Clinical Sciences and Advanced Medicine, has won an international award as part of one of the largest and most distinguished veterinary awards in the world, the International Canine Health Awards. The award was given to Oliver in recognition of his tireless work as a small animal internist and immunologist.

Welcome to a new faculty member—Andrew Vaughan, PhD, joined the Department of Biomedical Sciences in April. Dr. Vaughan's research is focused on defining and understanding the relevant cell types and molecular mechanisms by which the mammalian lung is able to regenerate after severe injury. He is especially interested in elucidating the means by which epithelial progenitors contribute to repaired airway and alveolar units after various lung insults (influenza, ARDS, fibrosis). His studies suggest that physiological lung function is in fact dictated by progenitor cell fate choices after injury. Dr. Vaughan and his group have developed a novel orthotopic cell transplantation assay which allows for the direct assessment of engraftment, proliferation, and differentiation potential of these stem cells. Further, he is actively investigating the roles of the Notch, Wnt, and BMP pathways in regulating the differentiation potential and fate of expanded progenitor cells post-injury. His office and laboratory are located on the 3rd floor, office 370E Old Vet.