BIOMEDICAL & VETERINARY SCIENCES

GRADUATE PROGRAM

ANNOUNCES

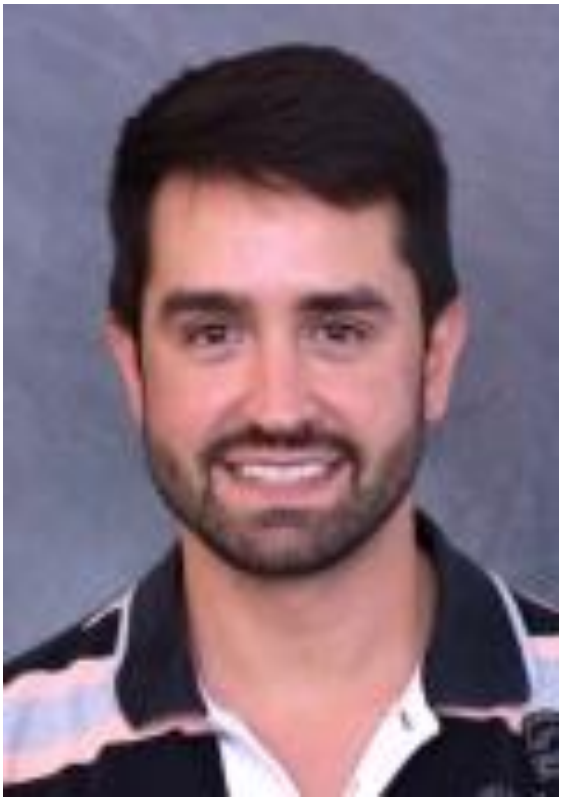
The Doctor of Philosophy Seminar and Examination of

Dr. Bruno Carvalho Menarim

“Macrophage-mediated regulation of joint homeostasis”

Monday, September 30th, 2019
10:00 am
VetMed Phase 2 Room 121

Bio



- DVM, 2004 – Midwestern State University, Parana, Brazil.
- Large Animal Surgery Residency, 2007 – Sao Paulo State University
- Master of Science in Radiology, 2008 – Sao Paulo State University
- Assistant Professor of Equine Surgery, 2008 – 20012 – Universidad Austral de Chile
- Associate Professor of Equine Surgery, 2012-2017 – Universidad Austral de ChileIn

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Lay Language Abstract

Osteoarthritis (OA) is a common cause of progressive joint deterioration in people and horses. Currently available treatments provide limited recovery of joint function, creating an urgent need more efficient therapies, however, development of new treatments require better understanding of the mechanism causing OA. A shared characteristic among many arthritic conditions is chronic inflammation. Cells called macrophages are the main drivers of joint inflammation and can exert pro- and anti-inflammatory responses. Macrophages can promote joint health by clearing aggressor agents and secreting molecules required for optimal joint function. However, when these functions are overwhelmed by damage, macrophages drive inflammation recruiting more cells to cope with increased demands for housekeeping functions. If this process is efficiently accomplished, macrophages then resolve inflammation recovering joint health, otherwise chronic inflammation happens. Macrophages in the bone marrow (BMNC - bone marrow mononuclear cells) are used to treat inflammation and produce essential molecules for joint health. Although little information exists regarding their use in joints, studies treating different organs suggest it can provide high rewards. The studies presented in this dissertation focused on understanding the dual function of macrophages in driving and controlling joint inflammation, and harnessed the therapeutic potential of macrophages.

In the first study, macrophages were investigated in normal and OA-affected joints, and curiously exhibited a hybrid pro- and anti-inflammatory identity in both groups. The indicators of this mixed identity were more markedly expressed in arthritic joints showing gross inflammation. Low levels of a macrophage-derived anti-inflammatory protein called IL-10 were detected in OA joints. The combined findings of this study suggest that anti-inflammatory mechanisms from macrophages in OA-affected joints may be overwhelmed, preventing inflammation to be resolved, and that recovering this anti-inflammatory function may aid in the treatment of OA.

In the second study we investigated how the incubation of bone marrow macrophages (BMNC) in fluid from normal and inflamed joints affect the response of macrophages. Similarly, to observed in the first study, BMNC incubated in both normal and inflamed joint fluid induced macrophages do develop a hybrid identity that was ultimately similar to cells native from normal joints fluid. Macrophages proliferated more when incubated in fluid from inflamed joints. Despite of a mixed identity, macrophages in both groups produced an anti-inflammatory effect with high levels of IL-10 that were even higher in ISF cultures. These observations suggest that higher proliferation of macrophages in inflamed joint fluid helped preserve anti-inflammatory mechanisms. Therefore, our study suggests that joint injection with BMNC could maximize macrophage- and IL-10-associated mechanisms required to resolve joint inflammation.

The third and final study investigated the response of normal and inflamed joints to BMNC injection using a model of joint inflammation in horses. Inflamed joints treated with BMNC showed visual and laboratorial markers of improvement, with increasing numbers of macrophages and concentrations of IL-10 in the joint fluid, which remained lower in joints treated with placebo. BMNC provide means to recover macrophage-associated effects required to control joint inflammation and can benefit thousands of patients with OA.

Together, the results of these studies show the macrophages are biased promoters of joint health, leading to inflammation when their anti-inflammatory mechanisms are overwhelmed. Replenishing the inflamed joint with healthy macrophages maximize their anti-inflammatory effects, favoring the recovery of a healthy articular environment.

Publications

Menarim BC, Gillis KH, Oliver A, Mason C, Ngo Y, Werre SW, Barrett SH, Luo X, Byron CR, Dahlgren LA. “Autologous bone marrow mononuclear cells modulate joint homeostasis in an equine *in vivo* model of synovitis”.

The FASEB Journal. ***In press***.

Menarim BC, Gillis KH, Oliver A, Mason C, Ngo Y, Werre SW, Barrett SH, Rodgerson DH, Dahlgren LA. "Synovial macrophage activation in normal and osteoarthritic joints". *Osteoarthritis and Cartilage*. ***Submitted***.

Menarim BC, Gillis KH, Oliver A, Mason C, Ngo Y, Werre SW, Barrett SH, Luo X, Byron CR, Dahlgren LA. "Inflamed synovial fluid induce a homeostatic response in bone marrow derived macrophages: implications for joint therapy". *The FASEB Journal*. ***To be submitted***.

Khatibzadeh S, **Menarim BC**, Nichols A, Were S, Dahlgren LA. "Urinary bladder matrix does not improve tenogenesis in an in vitro equine model". *Journal of Orthopedic Research*. 37(8) 1848-1859. ***Shared 1st authorship***.

S. Bonometti, **B. C. Menarim**, A. M. Brandt, A. D. Ealy, S. E. Johnson. Growth factor modulation of equine trophoblast mitosis and prostaglandin gene expression. *Journal of Animal Sciences.* 2019. 97(2): 865–873.

S. Bonometti, **B. C. Menarim**, A. M. Brandt, A. D. Ealy, S. E. Johnson. Equine Trophectoderm Cells and Their Role in Fetal-Maternal Recognition. *Journal of Animal Science*. 2018; 96(suppl_1):43-43.

Bonometti S, **Menarim BC**, Orlandi C, Uberti B, Ramirez A. Sperm-Oviduct Interaction Factors that Compromise Fertility of Frozen Stallion Semen. *Global Journal of Reproductive Medicine* 2017;3(1):0-9.

Presentations -Invited Talks

Menarim BC. "Equine Osteoarthritis". Invited Lecture. College of Veterinary and Agricultural Sciences. University of Kentucky – Lexington - KY. April 2019.

Menarim BC. "The role of macrophage polarization in joint health, disease

and synovial tissue repair". Invited Seminar. Maxwell Gluck Equine Research Center. University of Kentucky – Lexington - KY. June 2017.

Menarim BC. "Laparoscopic Uteropexy" – restoring fertility in multiparous mares. 7th Brazilian Meeting of Equine Reproduction. Porto Feliz – SP, Brazil. June 2016

Presentations- Scientific Abstracts

2019 Inflamed synovial fluid induce a homeostatic response in bone marrow derived macrophages: implications for joint therapy. **Menarim BC,** Gillis K, Oliver A, Ngo Y, Mason C, Luo X, Were S, Dahlgren L. Gordon Research Conference – Phagocytes.

2019 Autologous bone marrow mononuclear cells modulate joint homeostasis in an *in vivo* model of synovitis. **Menarim BC,** Gillis K, Oliver A, Ngo Y, Mason C, Barrett SH, Luo X, Dahlgren L. Gordon Research Seminar – Phagocytes. ***Outstanding Poster Award***

2019 Bone marrow mononuclear cells therapy re-establish joint homeostasis in an *in vivo* model of synovitis. **Menarim BC,** Gillis K, Oliver A, Ngo Y, Mason C, Barrett SH, Luo X, Dahlgren L. 2019 Annual Meeting of the Orthopedic Research Society.

2018 Bone marrow mononuclear cells for equine joint therapy: in vivo preliminary data. **Menarim BC,** Gillis K, Oliver A, Mason C, Luo X, Dahlgren L. 29th Biomedical & Veterinary Sciences Graduate Research Symposium

2017 Equine Trophectoderm Cells and Their Role in Fetal-Maternal Recognition. S. Bonometti, **B. C. Menarim**, A. M. Brandt, A. D. Ealy, S. E. Johnson. Animal Science Society Meeting.

2017 Bone marrow mononuclear cells for equine joint therapy: *in vitro* preliminary results. **Menarim BC,** Nichols A, Byron C, Luo X, Dahlgren L. 28th Biomedical & Veterinary Sciences Graduate Research Symposium.

2016. Bone marrow mononuclear cells for equine joint therapy. **Menarim BC,** Nichols A, Byron C, Luo X, Dahlgren L. 27th Biomedical & Veterinary Sciences Graduate Research Symposium.

Awards and Academic Achievements

Outstanding Poster Award. 2019 Gordon Research Seminar – Phagocytes. **Menarim BC,** Gillis K, Oliver A, Ngo Y, Mason C, Barrett SH, Luo X, Dahlgren L.Autologous bone marrow mononuclear cells modulate joint homeostasis in an *in vivo* model of synovitis.

Examination Graduate Committee

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