Colorado State University

ORTHOPAEDIC RESEARCH CENTER

2014 REPORT

MISSION

TO INVESTIGATE THE PATHOGENESIS, DIAGNOSIS, TREATMENT, AND PREVENTION OF MUSCULOSKELETAL DISEASE AND INJURY FOR THE BETTERMENT OF BOTH ANIMALS AND HUMANS.

PREFACE

“Our principal focus continues to be solving the significant problems in equine musculoskeletal disease”

IT IS MY PLEASURE TO PRESENT OUR 2014 REPORT from the Orthopaedic Research Center (including the Orthopaedic Bioengineering Research Laboratory) at Colorado State University. Our principal focus continues to be solving the significant problems in equine musculoskeletal disease as can be seen in this report but we also continue to investigate questions relevant to human joint disease and techniques and devices for human osteoarthritis and articular cartilage repair when the technique can potentially benefit the horse. The increased number of translational projects and funding support from the National Institute of Health (NIH) support our mission of helping both horses and humans.

As part of that evolution the big news this year is the gift of $42.5 million from John and Leslie Malone to support the development of an Institute of Biologic Translational Therapies. The vision of the IBTT is to investigate next generation remedies based on living cells and their products including patient-derived stem cells to treat musculoskeletal disease and other ailments. At the ORC we have developed expertise at analyzing and developing medical treatments for animal patients, then providing knowledge gained to boost human medical advancements. The progression is known as translational medicine and is successful because of similarities in animal and human physiology and disease. This gift is the largest cash gift ever given to Colorado State University and is truly transformational for our Orthopaedic Research Program and will take us to a higher level. As reported previously, the Malones have also given us a $6 million Presidential Chair in Equine Sports Medicine and Rehabilitation. In order to complete funding to build the IBTT Colorado State University is contributing $10 million, and at the time of going to press, we have attained another $20 million gift which allows us to completely fund the new building.

We have also had substantial gifts from Barbara Cox Anthony Estate (Barbara Cox Anthony had previously donated $3 million Endowed Chair that I have the honor of sitting in, as well as a second University Chair in Oncology). The latest gift has funded the re-roofing of the Orthopaedic Research Laboratories and provided, which allowed for improvement of those facilities and renovations as well as additional support for research projects. We thank Barbara Cox Anthony’s son, Jim Kennedy, for his continued support of the program. Another new donor is the Louis L. Borick Foundation which is allowing us to purchase and house the first standing equine computed tomographic unit (CT) that was installed in July in the US and I particularly thank Robert Borick for his support.

There have been a number of exciting research projects and these are summarized in this report. Particularly notable are collaborative projects with MIT looking at the combination of microfracture in a self-assembling hydrogel to promote the repair of defects of the equine stifle (directly comparable to the human knee) that has been published in the prestigious Journal of Bone and Joint Surgery, two very positive studies on the value of intra-articular MSCs for traumatic injury to the equine femorotibial joint as well as demonstration of enhancement of cartilage repair. The development of the new standing CT from Epica™ is the beginning of an ongoing collaborative project with the company to develop a standing CT for the limb. The current standing CT will enable standing evaluation of necks and is going to be part of a major project looking at cervical pain and its pathogenesis as well as improving our diagnostic ability with cervical problems in sport horses. Use of CT for standing evaluation in the limb is an ultimate goal that we have and a joint venture with Epica™ will hopefully result in this in the near future. Two other significant studies in cartilage repair, one with examining chondroprogenitor cells derived from the surface of articular cartilage and another evaluating bone marrow-derived stem cells placed into articular defects have both also been published in the Journal of Bone and Joint Surgery.

We have continued to have new developments in the faculty, staff and facilities. Our first two graduates from the residency program in Equine Sports Medicine and Rehabilitation Drs. Dora Ferris and Erin Contino, both passed the examination and are now Diplomates of the College of American Veterinary Sports Medicine and Rehabilitation. Dr. Myra Barrett joined us as a faculty member and is the first tenure track position specifically in equine imaging. Dr. Mindy Story joined us as an Assistant Professor in Equine Sports Medicine and Rehabilitation and Dr. Erin Contino also joined our faculty as an equine fellow in imaging and is going to become an Assistant Professor in the Equine Sports Medicine and Rehabilitation Program within this current year. We have also seen a number of other staff changes including Chrissy Battaglia joining us as a Research Scientist/Lab Manager and her contributions have already made a significant change to efficiency within the laboratory.

Accomplishments at the ORC over the past year are detailed in this report. Because of our increasing level of productivity we have converted from a two year report to a one year report to keep the information current. Our accomplishments in this report could not be achieved without our team of faculty and staff as well as the excellent support of equine funding agencies (Grayson-Jockey Club Research Foundation, American Quarter Horse Association and United States Equestrian Federation), corporation funding and individual donors. With this help we continue to achieve our goals and also make new ones as new clinical questions arise.

Best wishes,

Wayne McIlwraith

CONTENTS

continued...

TABLE OF CONTENTS

FOCUS 2
EARLY DIAGNOSIS OF BONE AND JOINT DISEASE

FOCUS 3
IMPROVEMENT IN THE UNDERSTANDING OF THE PATHOGENESIS OF EXERCISE-INDUCED TRAUMATIC DISEASE

FOCUS 4
CONTINUED DEVELOPMENT OF NOVEL THERAPIES FOR TRAUMATIC SYNOVITIS, CAPSULITIS, AND OSTEOARTHRITIS IN THE HORSE

FOCUS 5
VALIDATION OF REHABILITATION AND PHYSICAL THERAPY TECHNIQUES FOR MUSCULOSKELETAL DISEASE

MUSCULOSKELETAL TISSUE HEALING

This focus addresses articular cartilage, tendon, ligament, and menisci healing.

EARLY DIAGNOSIS OF MUSCULOSKELETAL DISEASE

This includes the development of novel imaging techniques (present and future), body fluid markers, and also molecular monitoring. The uses of these early diagnostic techniques include:

a. Evaluation of the pathogenesis of bone and joint disease

b. Early detection of disease processes

c. Monitoring of therapy, with the long-term goal of preventing severe arthritis or failure

IMPROVEMENT IN THE UNDERSTANDING OR THE PATHOGENESIS OF EXERCISE-INDUCED AND DEVELOPMENTAL MUSCULOSKELETAL DISEASE

These investigations use molecular tools such as reverse transcriptase PCR for evaluation of tissues in various stages of the disease, biomechanical and modeling studies, and imaging techniques, including magnetic resonance imaging (MRI) and computed tomography (CT), to monitor early events in bone disease.

CONTINUED DEVELOPMENT OF NOVEL THERAPIES FOR TRAUMATIC SYNOVITIS, CAPSULITIS, AND OSTEOARTHRITIS

This focus includes evaluation of biologic inhibitors of critical mediators in joint disease, novel protein therapies, including platelet-rich plasma (PRP), gene therapy techniques, and mesenchymal stem cell therapies.

VALIDATION OF REHABILITATION AND PHYSICAL THERAPY TECHNIQUES FOR MUSCULOSKELETAL DISEASE

These include objective assessment of integrative therapies, including manipulation and acupuncture for management of musculoskeletal disease and pain, as well as rehabilitative techniques of swimming, underwater treadmilling, and hyperbaric therapy.

MUSCULOSKELETAL RESEARCH PROGRAM

The Musculoskeletal Research Program has been designated as a Program of Research and Scholarly Excellence at Colorado State University (initially designated in 2004, renewed in 2008, 2012, and again in 2014).

THE MUSCULOSKELETAL RESEARCH PROGRAM COVERS ALL ORTHOPAEDIC RESEARCH AT COLORADO STATE UNIVERSITY AND INCLUDES:

1. Orthopaedic Research Center, including Orthopaedic Bioengineering Research Laboratory

2. Preclinical Surgical Research Laboratory

3. Orthopaedic Oncology

SCHOOL OF BIOMEDICAL ENGINEERING

Most of the faculty within the Musculoskeletal Research Program are also faculty in the School of Biomedical Engineering. Colorado State University's School of Biomedical Engineering (SBME) was formed in March 2007 to address society's needs in bioengineering, one of the fastest emerging areas of scientific discovery. The SBME is an interdisciplinary program built on strong faculty and research programs in the Colleges of Applied Human Sciences, Engineering, Natural Sciences, and Veterinary Medicine and Biomedical Sciences. Drs. Christian Puttlitz, Tammy Donahue, Wayne McIlwraith, David Frisbie, Chris Kawcak, Seth Donahue, Laurie Goodrich, Kevin Haussler and John Kisiday of the Orthopaedic Research Center are core faculty members of the program in biomedical engineering research, which is rapidly expanding to all areas of human health. New technologies being developed at CSU are enabling people to continue active and healthy lifestyles.

SBME students have the opportunity to collaborate with faculty from these four colleges and eleven departments, including the highly ranked Professional Veterinary Medicine program.

SBME now offers bachelor of science (B.S.), master of engineering (M.E.), master of science (M.S.), and doctor of philosophy (Ph.D.) degrees. The M.S. and Ph.D. programs focus on three main research areas: biomechanics and biomaterials; molecular, cellular, and tissue engineering; and medical diagnostics, devices, and imaging. Within these three areas, students participate in cutting-edge research from therapies and imaging modalities for fighting cancer to improving equipment used in open heart surgery. In order to allow flexibility to explore the multiple research possibilities, fully funded (stipend and tuition) lab rotation fellowships are available for first-year Ph.D. students.

ORTHOPAEDIC RESEARCH CENTER ADVISORY BOARD

GAIL HOLMES (CHAIR)
Quarter Horse Owner and Breeder

RICK ARTHUR, D.V.M.
Racetrack Veterinarian, California

Past President, American Association of Equine Practitioners

THOMAS BAILEY
Cutting Horse Owner and Breeder, Iron Rose Ranch

LARRY BRAMLAGE, D.V.M.
Past President, American Association of Equine Practitioners, American College of Veterinary Surgeons

Specialist Equine Surgeon, Rood & Riddle Equine Hospital

LINDY BURCH
Hall of Fame/Cutting Horse Trainer and Breeder

MARK DEDOMENICO, M.D.
Thoroughbred Owner and Breeder

Pegasus Thoroughbred Training and Rehabilitation Center

RON ELLIS
Thoroughbred Racehorse Trainer

JOHN HALLEY, M.V.B. (D.V.M.)
Veterinarian for Coolmore and Ballydoyle, Ireland

BOBBY LEWIS, D.V.M.
Elgin Veterinary Hospital

Past President, American Association of Equine Practitioners

RICHARD MANDELLA
Racing Thoroughbred Trainer, Racing Hall of Fame

WAYNE MCILWRAITH, B.V.Sc. (D.V.M.), PH.D.
Past President, American Association of Equine Practitioners, American College of Veterinary Surgeons, and Veterinary Orthopaedic Society

Director, Orthopaedic Research Center

MARIA I. NIARCHOS-GOUAZÉ
Thoroughbred Owner, Europe & USA

DAN ROSENBERG
Rosenberg Thoroughbred Consulting

BARRY SIMON, D.V.M.
Thorn BioScience

MELANIE SMITH TAYLOR
Olympic Gold Medalist, Show Jumping

JON WINKELRIED
Cutting Horse Breeder

Marvine Ranch

MARTIN WYGOD
Thoroughbred Owner, California

President and CEO, WebMD

EDITORIAL AND SCIENTIFIC ADVISORY BOARDS OF ORC FACULTY 2014

DONAHUE, SETH W.
Aursos, Inc. Scientific Advisory Board

MCILWRAITH, C.W.
Cartilage Associate Editor

Veterinary Record Editorial Board

Equine Veterinary Journal Advisory Board

Equine Veterinary Education Assistant Editor

New Zealand Equine Trust Board of Trustees (Chair)

Steadman Philippon Research Institute Scientific Advisory Board

PUTTLITZ, C.M.
Computational Methods in Ortho Biomechanics (Co-Chair)

Journal of Histotechnology

REISER, R.F.
Journal of Strength and Conditioning

DONORS

With grateful acknowledgment to those who are so critical to the continued success of our program.

$5,000,000 and above

Dr. John C. Malone and Mrs. Leslie A. Malone, Malone Family Foundation

$1,000,000 to $4,999,999

Barbara Cox Anthony, James M. Cox, Jr. Foundation

Thomas Bailey, Iron Rose Ranch

Abigail Kawananakoa, Kawananakoa Foundation

Herbert A. Allen, Allen & Co.

Ken and Virginia Atkinson,* Ken and Virginia Atkinson Estate

Steadman Hawkins Research Institute

Alice Walton, Walton Family Foundation

$100,000 to $999,999

James M. Cox, Jr. Foundation

Stavros S. Niarchos Foundation

Mr. Jon & Abby Winkelried Family

Marilyn M. Simpson Trust

Mr. Kenneth E. Atkinson

Louis L. Borick Foundation

Mark P. Dedomenico

Dr. Wayne McIlwraith and Dr. Nancy Goodman McIlwraith

Steadman Philippon Research Institute

Dea Family Foundation/Mr. Peter A. & Mrs. Cathy L. Dea

Mr. John & Mrs. Susan Magnier Family/Coolmore Stud Corporation

Mr. Walter C. & Mrs. Jaynn M. Emery

IDEXX Laboratories, Inc.

Robert B.* and Beverly J. Lewis

Fahd A. Al-Sobayil, Ph.D. Family

Luitpold Pharmaceuticals, Inc.

Ms. Gail Holmes

Attache International Marketing, Inc.

The Peter Jay Sharp Foundation

Pfizer, Inc.

Mr. Frederick & Mrs. Melissa Westerman Family

Mr. George R. Pidgeon, Sr.

Equine Sports Medicine, LLC.

Mr. Tommy Manion

Mr. Keith Goett Family

Dan Lufkin, Lufkin Family Foundation

Prince Sultan bin Muhammed

$25,000 to $99,999

Mr. John M. Sparks*, T.A. Family

Thoroughbred Charities of America, LTD.

Progenteq Limited

Bayer Corporation

Steve and Paula Reynolds, TBR Ranch

Mr. Jack E. Waggoner Family

John Andreini, Andreini & Company

Rosenthal Ranch Trust

Gooding Family Foundation

Thoroughbred Corporation/ Prince Ahmed Salman*

EquuSys Incorporated

Ms. Elaine Hall

Martin J. and Pamela S. Wygod

Burnett Ranches, LTD

Volodar and Zory Kuzyk/Oak Creek Ranch

Oaktree Charitable Foundation

E E Ranches, Inc.

Equus Foundation, Inc.

Mace Siegel

Southern California Equine Foundation, Inc.

Mr. Stephen Grove

Dellora A. & Lester J. Norris Foundation

Raymond James Charitable Endowment Fund

Pavillard Scholarship

$10,000 to $24,999

Holmes Cutting Horses

Slate River Ranch LLC

Esperanza Ranch

Rood and Riddle Foundation, Inc.

Mr. Peter D. Stent Family

Mr. George R. Hearst, Jr. Family

Buffalo Ranch

Vincent A. Baker, D.V.M.

Ms. Sandy Bonelli

Nutramax Laboratories

S&S Farms

Smart Little Lena Syndicate

Strawn Valley Ranch

HMT High Medical Technologies USA, Inc.

Susan Allen

Mr. Glenn Drake Family

Dual Peppy Partners

Ms. Lindy Burch

Mr. Winston Hansma Family

Arthro Dynamic Technologies, Inc.

Platinum Performance

Britt Land & Cattle Company, Inc.

California Authority of Racing Fairs

Circle C Ranch Company

Del Mar Thoroughbred Charities

Heather S. Dedomenico Estate

Hollywood PK Racetrack Charities

Los Angeles Turf Club, Inc.

Mr. Benny Martinez Family

Rocky Mountain LAE Inc.

Barry W. Simon, D.V.M. and Kari H. Simon

THORN BioScience, LLC.

Thoroughbred Owners of California

Verdad Foundation

Calmark Corporation

Doolin Family Foundation

Spectravet, Inc.

continued...

DONORS

$1,000 to $9,999

Wichita Ranch

Robert L. and Melanie Taylor II

Gayle and Judith Trotter

Bet On Me 498 Syndicate

SR Instant Choice Partnership

American Livestock Insurance Company

Ms. Nancy G. Dickenson

American Association of Equine Practitioners

Celavie Biosciences, LLC

BiTerra Quarter Horse, LLC

Mr. Andrew H. Chavers Family

GCH Land and Cattle Company LLC

William J. Keller

Niangua River Ranch Land & Cattle Co.

Tokoroa & Dists. Veterinary Servs. Ltd.

California Thoroughbred Breeders Association

Capps Radio Ranch

CARE Research, Inc.

Essar Charitable Foundation

Mrs. Marylynn A. Fischer Family

James P. Morehead, D.V.M. Family

R&P Medical

Sanuwave Services, LLC

Sulzer Biologics

Jorg A. Auer

Ms. Sandy Haskins Family

C. George Dewell, D.V.M. Family

Mr. Jimmy W. Guest Family

Hacienda Colima Quarter Horses

Mr. Ken Hill

Mr. Kobie Wood Family

Mr. T.D. Kelsey Family

Jeffrey S. Matthews – Franklin Street Partners

Dorothy Russell Havemeyer Foundation., Inc.

Animal Health Options-ProMotion Studies

Coalson Acres Ranch

David D. Frisbie

Mr. Don Lester Family

Mr. Charles A. Bess Family

Mr. Cooper Williams

Mr. Buckeye Blake Family

Graystone Ranch

Mr. Bill Lacy Family

Smart Lil Highbrow Partnership

BioVision Technologies, LLC

Biovision Veterinary Endoscopy

Abrakadabracre Partnership

Banuelos Ranches

Equine Trust Foundation

Jenkins Veterinary Services, P.C.

Lectric Company, Ltd.

Mr. Neil J. Mulholland

New Zealand Equestrian Federation

Pacific Coast Horse Shows Association

Rancho Petersen

Trefethen Vineyard Winery, Inc.

Wildenstein Family, LLC

Ms. Candace Gregory

Twin Willows Ranch, LLC

R.A. and Farall Canning

Ms. Joy Smith

Mill Creek Veterinary Service

Mr. Billy Emerson

Ms. Karen Long

Thiry-O'Leary Foundation

A.J. & Lynda Scribante Charitable Foundation

Mr. Charles Henry Scoggin, M.D.

Watercolors Racing, LLC.

Mr. Duncan M. Alexander

Blessed Twice Ltd. Partnership

Fairlea Ranch

Mr. Mike Hollibaugh Family

Christopher E. Kawcak, D.V.M., Ph.D.

Morning Sun Ranch

Performance Horse Partners

Round & D'Angelo Partnership

Smart Little Jerry Syndicate, LTD

Mr. Wes Smith Family

Terry Riddle Inc.

Mr. Maynard M. Brittan

Worldwide Medical, Inc.

Rick A. Pederson, LLC.

Glenwood Veterinary Clinic, Inc.

J. Mark Beverly, D.V.M.

Dr. Edward and Darci Blach

Brokaw Family Foundation

Dr. Stacy Smitherman Family

Valley Oak Ranch

Vernon Cutting Horses

David C. Davis, D.V.M. Family

Hidden Paint Ranch

Jim Holmes Cutting Horses

Mr. William T. O'Donnell, Jr. Family

Robert K Shideler, D.V.M.*

Londonderry Equine Clinic

Merial Inc.

Mr. Ronald W. Williams

Bartlett and Ann Baker

Mr. Ron Crockett

Mr. Shannon Hall

Mr. Paul L. Hansma

Brad R. Jackman and A. Lindsay Croom

Land 'O Lakes Farmland Feed

Little Rush Syndicate LLC

Dr. Terry Swanson/Littleton Equine Medical Center

George S. Martin, D.V.M.

John & Bonnie O'Neil

Smokin Trona Syndicate, LLC.

Mrs. Linda K. Souders

Transoceanic Marine, Inc.

Advanced Regenerative Therapies (ART)

Denise Opdahl

Fossil Creek Veterinary Hospital

Henry and Lorie Gordon

Vaughn and Jill Cook, D.V.M.

Joelle Rogers

Dr. Chip Beckett

Kim Ellis

Maggie McHugh

Manfred Menzi

Midge Leitch

$100 to $999

Dr. James P. and Amy .J Foley

Heidi Gordon on behalf Denise Steensland, Employee's Community Fund

Shawn and Kristi L. O'Neal

Teresa M. and Gary Stewart

Summer Hills Veterinary Hospital

Atlantic Mutual Companies

Hagyard Equine Medical Institute

Dain Rauscher Foundation

Pamela Silverman

Von Hemel Racing Stable

James A. and Juanita B. Winn*

Cauleen Glass – In memory of Denison P. Glass

George W. Platt*

Studio and TV Hire Corporation

Joe Petalino

Steve Rael

John D. Roven

Dennis A. Luedke D.V.M.,

continued...

DONORS

Glenwood Veterinary Clinic

Double JK Ranch

Richard E. Mandella

Lester Pedicord

Gary Praytor

Harris Equine Hospital/John M. Harris, Jr.

Scarmardo Enterprises

Dennis Bogott

Marilynn Dammon, King's Hill Stables

Cecil and Hatie Davis

Ron Ellis Racing Stable

Fenton International

Mrs. Alysa Tothill Levine

David K. and Linda McKelvie

Marilyn Berg-Voth

Kenneth and Elizabeth Thomazin

Roy Voth

Martha Goodrich

Elizabeth Armstrong

Joe H. Carter, D.V.M and Terri Carter

Dearborn Stables

Joy Dreier

Lorna and Shannon Dueck/Dueck Dressage

Pierre Famille Inc.

Kate A. Gaughan

Cindy Guagenti

Alex Harthill

Lawrence Horan

James Irving

Jane M. Jennings

James F. Kelly

Michael Ochsner

Cynthia Piper

Ranch and Coast Equine Practice, Inc.

Edgar R. Sander

Donald N. and Judith M. Stone Family

Patrick H. Young

James J. Corbett

Stillwater Veterinary Clinic

Placer County 4-H

William Jo Simonds

Wallace Souza

Dorothy L. Thielen

Bryan K. Hobson

Hong Kong Jockey Club

Lazy E Ranch, LLC

Alamo Pintado Equine Clinic

Alamogordo Animal Hospital

Dennis R. and Kerrie Allen, Jr.

Bend Equine Medical Center

Bishben Cutting Horses

Blue Castle Racing

Columbia Equine Hospital

Claire Cox

Barrie and Brenda Gerolamy

Goff (Lon) Custom Homes

Steven and Cynthia Gregory

Ed Halpern

Harrington Equine Hospital

Heidi J. Hamlen

Robert A. Jackson

Gerard Kelly

Jessica A. Kidd

Virginia L. Pabst

Robert E. Pexton and Anita Edmondson

The Ruffian Stables

Gary Striker and Yvette Croteau

Ute Vaske

Simon Development and Construction Company

Ms. Cynthia Chesnutt

Equine Sports Medicine and Surgery, Inc.

Loni D. Gattinger

John W. Kaufman, D.V.M.

Susan Locke

London Equine Hospital Professional Corp.

Rosewood Hanoverians

Tiffany Farms and Stables

Wisconsin Equine Clinic

Clover Valley Veterinary Hospital

G.W. Ranch

Carolyn J. Hannaford

Jud E. and Catherine Miller

Okotoks Animal Clinic

Connie Inglish

Mary B. Lint*

Lois and Joan Luft

James C. Shircliff

Dr. William and Sandra Sutter

John V. and Neola J. Martz

Myron Yoknis

Rick Abbot

Ashford Stud

Fernando Canonici

Contract Veterinary Sales

Denali Stud

Falcon Seaboard, Snaffle Bit Ranch

Melissa Lyons Gardner

J Diamond 3

Joseph M. Singer

Three Chimneys Farm

Marshal and Anne Younglund

North American Specialty Insurance Company

Sharmin E. Bock

JD and Paula S. Vanderlinden

Charles Boles

Mr. Michael Dinnell Family

Mountain Park Ranch Inc

Les H. Mayes, D.V.M.

Mr. Brett L. Shawcroft Family

Lindsey Cutting Horses

Mr. Gerald L. Dancy

Dutton Farms

Oklahoma Equine Hospital

Circle B Bar T

** Deceased*

FACULTY

C. Wayne McIlwraith

B.V.Sc. (Dist.), M.S., Ph.D., D.Sc. (Purdue), Dr. med. vet. (hc) (Vienna), D.Sc. (hc) (Massey), L.Dr. (Turin), Dvetmed (hc) (London), FRCVS, Diplomate ACVS, Diplomate ECVS, Diplomate ACVSMR, University Distinguished Professor, Director of the Orthopaedic Research Center, Barbara Cox Anthony University Chair in Orthopaedics; Department of Clinical Sciences

Research Interests: Equine orthopaedic surgery and joint disease (arthritis), biomarkers and cartilage repair research including stem cells

Dr. McIlwraith has been Director of the ORC since its inception, advancing the Orthopaedic Research Center's reputation through research and publications, scientific presentations at key meetings throughout the world, and also through his fundraising efforts. He is a Diplomate of the American College of Veterinary Surgeons and the American College of Veterinary Sports Medicine & Rehabilitation; a Past-President of the American College of Veterinary Surgeons, the American Association of Equine Practitioners, and the Veterinary Orthopedic Society; and a recognized leader in the field of equine orthopaedic research and surgery. He consults worldwide as a specialist equine surgeon, and has received national and international honors for his contributions to joint research and clinical orthopaedics. Dr. McIlwraith is the co-author of five textbooks: Techniques in Large Animal Surgery (two editions): Equine Surgery: Advanced Techniques (two editions); Arthroscopic Surgery in the Horse (four editions); Joint Disease in the Horse (second edition just published); and Equine Welfare. He has authored or co-authored over 445 refereed publications and textbook chapters, and has presented more than 600 seminars both nationally and internationally to equine practitioners, veterinary specialty meetings, and human orthopaedic meetings.

Honors include: Colorado State University AAEP Faculty Award for Excellence in Teaching Equine Medicine and Surgery, 1981-82; Colorado State University Alumni Outstanding Faculty Award, 1983; DLT Smith Visiting Scientist, University of Saskatchewan, 1992; Inducted into the George H. Glover Gallery of Distinguished Faculty and Alumni, CSU, 1993; Awarded the Tierklinik Hochmoor Prize at Equitana, 10th Equine Veterinary Conference, Essen, Germany, 1993, for international contributions to Equine Orthopaedics; the Schering-Plough Award from World Equine Veterinary Association for Equine Applied Research for outstanding research work in equine locomotor disorders in Yokohama, Japan, 1995; Jacques Jenny Lecturer, Veterinary Orthopaedic Society, 1997; John Hickman Award for Equine Orthopaedics for leading work in arthroscopic surgery and equine joint disease research, British Equine Veterinary Association and Equine Veterinary Journal, Harrogate, England, 1997; Dr. med. vet. (honoris causa), University of Vienna, 1995; D.Sc., Purdue University, 2001; D.Sc. (hc), Massey University, 2003, Laurea Dr. (hc), Turin University 2004; Inducted into UK Equine Research Hall of Fame 2005; Frank Milne Lecturer (Lifetime Contribution Award), AAEP 2005; Founders Award for Lifetime Achievement, ACVS, 2006; Elastikon Equine Research Award, Johnson & Johnson and Grayson-Jockey Club Research Foundation, 2008-2009; Colorado State University Scholarship Impact Award 2007, University Distinguished Professor, Colorado State University 2009; Distinguished Life Member, AAEP, 2009; Dr. vet. med. (honoris causa), Royal Veterinary College, University of London, 2010; Life Member, New Zealand Equine Veterinary Association, 2011; Jacob Markowitz Award, Academy of Surgical Research, 2013; Marshall R. Urist M.D. Award for Excellence in Tissue Regeneration Research, Orthopaedic Research Society, 2014; American Association Equine Practitioners Distinguished Service Award, 2014.

Nicole Ehrhart

D.V.M., M.S., DACVS, Professor, Department of Clinical Sciences

Research Interests: Stem Cell Therapy, Tissue Engineering, Guided Bone Regeneration, Allograft Healing, Limb Preservation, Bone Substitutes

Dr. Ehrhart is one of 30 fellowship-trained veterinary surgical oncologists in the world. She is a full professor in surgical oncology at the highly acclaimed Animal Cancer Center and has been a member of the CSU faculty since 2002. She is the director of the Laboratory of Comparative Musculoskeletal Oncology and Traumatology and has been actively involved in limb preservation research, regenerative medicine, tissue engineering, and sarcoma research for the last sixteen years. She has been an invited speaker at various venues for MD researchers in translational research, both nationally and internationally. She holds joint faculty positions in the School of Biomedical Engineering, the Cell and Molecular Biology program, the Gates Regenerative Medicine Center at the University of Colorado, and The University of Colorado Cancer Center. In addition to her research, she has held several prestigious positions in the American College of Veterinary Surgeons (Scientific Program Chair, Residents Forum Chair, and Examination Committee) and Veterinary Orthopedic Society (President). She has authored numerous publications on limb preservation and translational cancer research. She is currently the director of the Musculoskeletal Oncology section of the University-wide Cancer Supercluster.

David D. Frisbie

D.V.M., M.S., Ph.D., Diplomate ACVS & ACVSMR, Professor, Department of Clinical Sciences

Research Interests: Treatment and diagnosis of joint disease, biologic treatment of musculoskeletal injuries, gene therapy

Dr. Frisbie began his professional career after obtaining both a B.S. in biochemistry and a D.V.M. from the University of Wisconsin. He then went to New York, where he completed a Surgical Internship at Cornell University and began his research in joint disease. After completing his internship, Dr. Frisbie came to CSU, where he continued his joint research, completed a surgical residency in Large Animal Surgery, and obtained a master's degree in joint pathobiology. After completion of his residency, Dr. Frisbie began his work on a novel way to treat joint disease using gene therapy, which was the focus of his Ph.D. During work on his Ph.D., Dr. Frisbie became board certified in Large Animal Surgery and is a Diplomate of the American College of Veterinary Surgeons. He joined the faculty as an assistant professor in Equine Surgery in the Department of Clinical Sciences in 1999, was promoted to associate professor (with tenure) in 2007, and then to professor in 2013. He is also a Diplomate of the American College of Veterinary Sports Medicine and Rehabilitation.

His current joint disease research is in two basic fields: 1) treatment of joint disease (therapeutics he has evaluated include Adequan®; corticosteroids, such as Vetalog® and Depo-Medrol®; Orthokine® (IRAP®); and stem cells), and new methods of diagnosing joint disease, such as standing arthroscopy of the equine stifle; and 2) biologic methods for treating musculoskeletal injuries, including tendon and ligaments, as well as joints. This research focus has blossomed into the testing of multiple biologic agents, allowing for side-by-side comparisons, as well as pioneering novel techniques for treating joint, tendon, and ligamentous injuries.

Honors include: Pfizer Animal Health Award for Research Excellence, 2001; American Association Equine Practitioners Presidential Award, 2011.

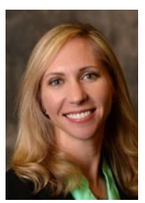
Laurie Goodrich

D.V.M., M.S., Ph.D., Diplomate ACVS, Associate Professor, Department of Clinical Sciences

Research Interests: Gene therapy, stem cell therapy

Dr. Laurie Goodrich joined the faculty at CSU College of Veterinary Medicine in April of 2005 as an assistant professor in Equine Surgery and Lameness. Prior to joining the faculty, she obtained her D.V.M. from the University of Illinois, and completed an internship in Large Animal Surgery and Medicine at Virginia-Maryland Regional College of Veterinary Medicine. Following her internship, Dr. Goodrich joined the faculty at Virginia for one year as an equine ambulatory clinician before going on to complete her residency in Equine Surgery at the Equine Medical Center in Leesburg, Va. She also obtained a Master of Science in Pharmacology during her residency. Dr. Goodrich subsequently joined the large animal surgery faculty at Cornell University's College of Veterinary Medicine and became Board Certified in Large Animal Surgery in 1999. At Cornell, she rotated as Chief-of-Service for the Orthopedic, Soft Tissue, and Emergency Surgery Services. In 2000, she began a Ph.D. in Cartilage Repair and Gene Therapy. Her research included the transplantation of genetically modified chondrocytes (cells of cartilage) into the defects of cartilage to improve cartilage healing. She completed her Ph.D. in the fall of 2004. Since commencing her position at CSU, Dr. Goodrich has focused on gene therapy and regenerative medicine for musculoskeletal disease in joint and bone repair. Specifically, her main focuses have included using IGF-I, IL-1ra, and BMP gene therapy to enhance cartilage repair, reduce inflammation in osteoarthritis, and improve bone repair, respectively. Further, she has investigated stem cell therapy applications for enhancement of cartilage repair. She is now an associate professor in equine surgery and lameness. Dr. Goodrich's clinical interests are broad and include joint disease, lameness, arthroscopy, fracture repair, laparoscopy, wound healing, neoplasia, and pain management.

Honors include: Orthopaedic Research Society, New Investigator Research Award, Semi-Finalist, 2006; Recipient five-year NIH KO8 Training Grant, 2008-2013; Clinician of the Year Award for Teaching Excellence, 2011; Elastikon Equine Research Award, 2011.



Myra Barrett

D.V.M., M.S., Diplomate ACVR, Assistant Professor of Radiology, Department of Environmental & Radiological Health Sciences

Research Interests: Equine musculoskeletal imaging and comparative imaging

Dr. Barrett earned her D.V.M. from Colorado State University. After graduating, she completed a year-long internship at Oakridge Equine Hospital in Edmond, Okla. Dr. Barrett underwent a non-conforming radiology residency in order to particularly focus on equine diagnostic imaging. The residency was based at CSU, but included training with multiple equine imaging experts in the U.S. and internationally. At the same time, Dr. Barrett obtained a master's degree through the ORC. She remained at CSU and is currently an assistant professor of radiology. Dr. Barrett works closely with the Equine Surgery and Sports Medicine services. She has spoken at multiple large national meetings and is regularly involved in continuing education courses. Dr. Barrett is dedicated to the advancement of the specialty of equine diagnostic imaging and is currently the president-elect of the Large Animal Diagnostic Imaging Society, a subgroup of the American College of Veterinary Radiology.

Kevin K. Haussler

D.V.M., D.C., Ph.D., Diplomate ACVSMR, Associate Professor, Department of Clinical Sciences

Research Interests: Etiopathogenesis and objective assessment of musculoskeletal pain, spinal dysfunction, and sacroiliac joint disorders; spinal kinematics and conservative management of spinal-related disorders; clinical research in the areas of veterinary chiropractic, acupuncture, physiotherapy modalities, and musculoskeletal rehabilitation

Dr. Haussler obtained a B.S. in agriculture from the University of Nebraska - Lincoln in 1984. He graduated in 1988 from The Ohio State University, College of Veterinary Medicine, followed by a small animal internship at the Sacramento Animal Medical Group in 1989. Dr. Haussler was a relief veterinarian for multiple small animal practices, emergency clinics, and humane societies from 1989 to 1994, when he became interested in pursuing further specialized training in the diagnosis and management of pain and musculoskeletal disorders in animals. He enrolled in Palmer College of Chiropractic - West, a human chiropractic program, to learn how to apply human chiropractic techniques and principles to the treatment of animals with musculoskeletal-related disorders. Dr. Haussler started veterinary chiropractic practice with equine and small animal patients in 1992. After graduating with a Doctor of Chiropractic (D.C.) degree from Palmer College of Chiropractic - West in 1993, Dr. Haussler obtained a Ph.D. comparative pathology from the University of California - Davis, School of Veterinary Medicine in 1997. The focus of his Ph.D. research was the evaluation of the anatomy, pathology, and biomechanics of the lower back and pelvis of Thoroughbred racehorses. He then went on to complete a post-doctorate investigating in-vivo equine spinal kinematics in 1999 at the Department of Anatomy, College of Veterinary Medicine at Cornell University. As a Lecturer at Cornell University until 2005, he was responsible for teaching equine anatomy, biomechanical research, and initiation of a clinical Integrative Medicine Service at the Cornell University Hospital for Animals in both the large and small animal clinics that provided chiropractic, acupuncture, and physical therapy services. Dr. Haussler's research studies included evaluation of in vivo equine spinal kinematics, paraspinal muscle morphometry and histochemistry, and the initiation of equine chiropractic research assessing pain and spinal flexibility.

Currently, Dr. Haussler is an assistant professor with continued research interests in objective assessment of musculoskeletal pain and spinal dysfunction, and evaluation of rehabilitation approaches to both large and small animals.

Honors include: James M. Wilson Award for Equine Research, School of Veterinary Medicine, University of California, Davis, 1997

Erin Contino

D.V.M., M.S., DACVSMR

Dr. Contino recently joined our faculty as an Equine Fellow in Imaging and is going to become an Assistant Professor in the Equine Sports Medicine and Rehabilitation Program in 2015. Erin is a Colorado State University D.V.M. graduate, who after interning at Pioneer Equine Hospital, did a three year Sports Medicine and Rehabilitation Residency at CSU (completed June 30, 2014) and then passed the examination to become a Diplomate of the American College of Sports Medicine and Rehabilitation in August of this year. Before and during her time as a D.V.M. student she also completed an M.S. degree at the Orthopaedic Research Center.

Christopher E. Kawcak

D.V.M., Ph.D., Diplomate ACVS & ACVSMR, Professor, Iron Rose College Chair in Musculoskeletal Research, Department of Clinical Sciences

Research Interests: Subchondral bone histomorphometry, biomechanical modeling of joint loading, and imaging of early subchondral disease in pathogenesis of joint disease

Dr. Kawcak joined our faculty in 1998 as an Assistant Professor after completing his Ph.D. He is now a Professor in the Iron Rose Ranch Chair in the ORC, and is Director of Equine Clinical Services in the James L. Voss Veterinary Teaching Hospital. His collaborations with the Biomedical Engineering Program at CSU, the Southwest Research Institute in San Antonio, Texas, The I-STAR Laboratory at Johns Hopkins University, the Department of Chemical and Materials Engineering, The University of Auckland, and other laboratories worldwide have allowed for more sophisticated assessment of joint disease and healing. Dr. Kawcak is currently involved with research projects evaluating the effects of exercise on the incidence of musculoskeletal injury, the development of computerized models of joints and joint diseases, and development of a new standing computed tomography machine for horses. He has over 100 publications and has been an invited speaker in the U.S. and Europe, and is involved with the American Association of Equine Practitioners, the American College of Veterinary Surgeons, and the American College of Veterinary Sports Medicine and Rehabilitation.

Honors Include: Ken Atkinson Scholar in the College of Veterinary Medicine and Biomedical Sciences, 1995-98; Pfizer Award for Research Excellence, 2003; Elastikon Equine Research Award, Johnson & Johnson Consumer Products Company and Grayson-Jockey Club Research Foundation, 2007.

Dr. Melissa King

D.V.M., Ph.D., Diplomate ACVSMR, Assistant Professor, Department of Clinical Sciences; Lead Clinician, Equine Sports Medicine and Rehabilitation Service

Research Interests: Equine sports medicine and rehabilitation

Dr. Melissa King received her D.V.M. from CSU in 1997 and then completed an internship at Rood & Riddle Equine Hospital in Lexington, Ky. Upon completion of her internship, Dr. King returned to northern Colorado to begin her career as an equine ambulatory clinician focusing on equine sports medicine. In 2011, Dr. King completed a Ph.D. at the ORC assessing the efficacy of underwater treadmill exercise to diminish the progression of carpal osteoarthritis. Currently, Dr. King is an assistant professor and the lead clinician for the Equine Sports Medicine and Rehabilitation Service at CSU. Dr. King is actively involved in clinical research to advance the quality and effectiveness of rehabilitation for the equine athlete.

John Kisiday

Ph.D., Associate Professor, Department of Clinical Sciences

Research Interests: Mechanobiology of cartilage and repair tissue, tissue engineering

Dr. John Kisiday was hired as an assistant professor in Clinical Sciences in a research and teaching appointment at the ORC in January 2005 after doing his Ph.D. at MIT in bioengineering, and a collaborative post-doctorate of fellowship with CSU and MIT. He is now an associate professor in Clinical Sciences. Dr. Kisiday is currently involved with research projects evaluating the potential of bone marrow mesenchymal stem cells to heal orthopaedic injuries, with an emphasis on cartilage repair. He has collaborated with ORC faculty to bring autologous mesenchymal stem cell treatments to the clinic. In the laboratory, he is investigating factors that influence mesenchymal stem cell differentiation with the goal of increasing the effectiveness of clinical treatments.

Honors include: Young Investigator Award, Engineering Tissues Workshop, Hilton Head, 2003; NIH Biotechnology Pre-doctoral Training Grant, 2001-2003; MIT President Pre-doctoral Fellowship, 1999

Valerie Moorman

D.V.M., Ph.D., Diplomate ACVS, Assistant Professor, Equine Surgery and Lameness

Research Interests: Early detection of musculoskeletal injury and methods of quantitative lameness detection

Valerie Moorman graduated from North Carolina State University with a B.S. in Animal Science in 2000. She graduated from North Carolina State University College of Veterinary Medicine in 2004. She then completed an internship in large animal medicine and surgery at Auburn University in June 2005 and continued as a large animal ambulatory clinical instructor through June 2006. She then completed a combined equine surgery residency and master's program at Oklahoma State University in July 2009. She became a Diplomate of the American College of Veterinary Surgeons in March 2010, and in July 2009, she began a Ph.D. program at the Orthopaedic Research Center at CSU, where she worked to develop a hoof-mounted motion analysis system. From July 2009 until June 2012, she also provided after-hours surgical emergency coverage at the CSU James L. Voss Veterinary Teaching Hospital. From July 2012 until July 2013, she served as staff veterinarian at the ORC. In July 2013, she was named an Assistant Professor of Equine Surgery and Lameness in the Department of Clinical Sciences at Colorado State University.

Richard Slayden

Ph.D., Associate Professor of Microbiology, Executive Director and founding member of the Center for Environmental Medicine at CSU

Dr. Slayden has 14 years of drug discovery and genomics experience with bacterial pathogens (F. tularensis, Burkholderia pseudomallei, Y. pestis, M. tuberculosis) and mouse models of infection. In the last several years, Dr. Slayden has employed Next Generation Sequencing techniques and metagenomics strategies to perform systems-based transcriptional studies to investigate molecular marks and metabolic tendencies of complex biological systems, including animal models of infection. During this time, Dr. Slayden has formed multi-disciplinary collaborations in the areas of microbiology, infectious disease, mathematics, and computational modeling to study host-pathogen interactions. Using this approach, Dr. Slayden has successfully characterized the host response to different infections and the unique in vivo transcriptional patterns and metabolism of bacterial pathogens.

Dr. Melinda Story

DVM, Diplomate ACVS, Assistant Professor, Department of Clinical Sciences

Research Interests: Assessment and treatment of spinal dysfunction and pain; clinical research interest in the areas of acupuncture and chiropractic therapy

Dr. Melissa King received her D.V.M. from CSU in 1997 and then completed an internship at Rood & Riddle Equine Hospital in Lexington, Ky. Upon completion of her internship, Dr. King returned to northern Colorado to begin her career as an equine ambulatory clinician focusing on equine sports medicine. In 2011, Dr. King completed a Ph.D. at the ORC assessing the efficacy of underwater treadmill exercise to diminish the progression of carpal osteoarthritis. Currently, Dr. King is an assistant professor and the lead clinician for the Equine Sports Medicine and Rehabilitation Service at CSU. Dr. King is actively involved in clinical research to advance the quality and effectiveness of rehabilitation for the equine athlete.

Seth W. Donahue

Ph.D., Associate Professor, Department of Mechanical Engineering

Research Interests: Naturally occurring models of bone metabolism and mechanical adaptation in extreme environments, and bone regeneration for metabolic diseases, fracture, and large bone defects

Dr. Donahue's research interest is the role of mechanical forces in bone cell metabolism, tissue engineering, bone adaptation, bone fracture, and osteoporosis. He has established hibernating bears as a model for preventing immobilization-induced osteoporosis. He has published 46 peer-reviewed journal manuscripts and conference abstracts on his hibernating bear research and its translational potential\s. He won the American Society of Biomechanic's Post-Doctoral Young Investigator Award for his research on bears. Dr. Donahue's laboratory cloned the gene for black bear parathyroid hormone, obtained a U.S. patent on it, and uses the recombinantly produced protein to reverse osteoporosis, improve fracture healing, and repair large bone defects in animal models.

Raoul F. Reiser, II

Ph.D., Associate Professor, Department of Health & Exercise Science

Research Interest: Musculoskeletal biomechanics

Dr. Reiser completed his B.S. in mechanical engineering at Cornell University, his M.A. in kinesiology with a specialization in biomechanics at the University of Texas at Austin, and his Ph.D. in mechanical engineering at CSU. The emphasis of his dissertation was the biomechanics of recumbent cycling. After working as an assistant professor at the University of Wyoming in the Division of Kinesiology and Health, Dr. Reiser began work as an assistant professor at CSU in the Department of Health and Exercise Science in August of 2002, and was promoted to associate professor with tenure in 2008. His current research is mainly in the area of fall prevention in the elderly, understanding how muscle and tendons change as we age. He also continues to explore bilateral asymmetries of the low extremities and how they may relate to performance and potential injury risk.

Honors include: Elected Fellow, American College of Sports Medicine, 2007; CSU College of Engineering's Outstanding Research Assistant, 2000; GAANN Three-Year Fellowship, 1997; CSU Graduate Fellowship, 1997; NSCA Challenge Scholarship, 1996.

Susan P. James

Ph.D., Professor and Head, Department of Mechanical Engineering; Professor, School of Biomedical Engineering

Research Interests: Biomaterials for orthopaedic, cardiovascular, and ocular applications, including permanent implants and tissue engineering

Dr. Susan James joined the CSU Mechanical Engineering faculty in 1994 as an assistant professor. She is now the Head of Mechanical Engineering Department at CSU, and was the founding director of the School of Biomedical Engineering. She received her Ph.D. in polymers from MIT and her B.S. in metallurgical engineering and materials science from Carnegie Mellon. Professor James' research focuses on characterization and development of biomaterial solutions to health care problems. These include orthopaedic, cardiovascular, and ocular applications, as well as regenerative medicine and tissue engineering. She and her students invented the BioPoly® materials, now in clinical use in partial resurfacing knee implants (http://www.biopolyortho.com/). Much of her current work is on hyaluronan-enhanced plastics, which do not cause blood clotting and platelet activation like most synthetic plastics. In collaboration with several faculty, students, and researchers, she is working on developing hyaluronan-enhanced flexible leaflets for heart valve prostheses. Her group is also researching new materials for small diameter vascular grafts, and contact and intraocular lenses. Dr. James is committed to giving back and has been involved with many organizations over the years, including Africa Higher Education Partnerships (AAHEP), Women and Minorities in Engineering Program (WMEP), and SWE. She has also performed countless outreach programs for young girls to get them interested in engineering careers. Dr. James was awarded the prestigious Margaret Hazaleus award this year for her strong commitment to mentoring and helping women.

Christian Puttlitz

M.S., Ph.D., Associate Professor, Department of Mechanical Engineering and School of Biomedical Engineering

Research Interests: Orthopaedic biomechanics, tissue and biomaterials interactions

Dr. Puttlitz and his team have global interests in how engineering mechanics can be applied towards solving orthopaedic-related problems, including both experimental and computational modeling to better understand the underlying tissue-level mechanobiology. Dr. Puttlitz and his colleagues have leveraged well-known orthopaedic hardware systems to functionally isolate the ovine metatarsus to develop a Haversian bone model of microgravity. The model will be used to simulate the fracture healing cascade that is expected to occur during deep space flight. In addition, the model will be used as an evaluation platform for emerging technologies that seek to enhance fracture healing in microgravity environments. These experiments are complemented by a computational effort that merges musculoskeletal and finite element models of the ovine hindlimb in an attempt to span numerous length scales and relate the observed biological response to the localized (i.e., tissue-level) mechanics.

Dr. Puttlitz received his B.S. in material science and engineering mechanics from Michigan State University, his M.S. in bioengineering from Clemson University, and his Ph.D. in biomedical engineering from the University of Iowa. Dr. Puttlitz became a Postdoctoral Fellow in the Orthopaedic Bioengineering Research Laboratory at the University of California, San Francisco. He joined the Department of Orthopaedic Surgery faculty at UCSF as an assistant professor in 2001, and directed the Orthopaedic Biomechanics Laboratory at the San Francisco General Hospital. In 2005, he accepted a faculty position at CSU in the Department of Mechanical Engineering and is currently appointed as an associate professor. He also holds secondary appointments in the School of Biomedical Engineering and the Department of Clinical Sciences.

Honors include: Monfort Professorship, May 2011; Mark S. Bloomberg Memorial Award for Outstanding Research, Veterinary Orthopaedic Society, March 2008; Elastikon Equine Research Award, Grayson-Jockey Club Research Foundation, May 2007; Best Basic Science Award, Inman-Abbott Society, San Francisco, May 2005; Finalist, Basic Science Award at the Cervical Spine Research Society, Boston, December 2004; Finalist, Basic Science Award at the Cervical Spine Research Society, Scottsdale, December 2003; Best Poster Award at the International Society for the Study of the Lumbar Spine, Edinburgh, June 2001; Inducted into Sigma Xi, National Research Honorary Society, January 2001; Nordby-Smith Best Paper Award on Minimally Invasive Surgery at the North American Spine Society Meeting, New Orleans, October 2000; Finalist, Doctoral Student Paper Competition, American Society of Mechanical Engineers, November 1999; Inducted into Tau Beta Pi, National Engineering Honor Society, Fall 1995; Inducted into Academic All-American Society, Spring 1993; Inducted into Alpha Sigma Mu, National Materials Science and Engineering Honor Society, Spring 1992.

Tammy Haut Donahue

M.S., Ph.D., Professor, Department of Mechanical Engineering and School of Biomedical Engineering

Research Interest: Orthopaedic biomechanics

Dr. Haut Donahue joined the faculty at CSU in December 2012 after spending 11 years in Mechanical Engineering at Michigan Technological University. She earned a Ph.D. from the University of California at Davis, where she received the Allen Marr Distinguished Dissertation Award in Biomedical Engineering in 2002 and the Microstrain Award for Innovative Instrumentation in Biomechanics for her master's work. Dr. Haut Donahue was a post-doctoral fellow in the Department of Orthopaedics at Pennsylvania State University before joining the faculty at Michigan Tech. She is a member of the School of Biomedical Engineering at CSU as well.

She is an associate editor for the Journal of Biomechanical Engineering and an editorial consultant for the Journal of Biomechanics. She recently completed a four-year position on the Program Committee as Chair of the Student Paper Competition for the ASME Summer Bioengineering Conference, and is now serving as Chair of the New Investigator Mentoring Committee for the Orthopaedic Research Society.

Dr. Haut Donahue's research includes analytical and experimental biomechanics of the musculoskeletal system with ongoing research in orthopaedic biomechanics and post-traumatic osteoarthritis. An emphasis is put on prevention, treatment, and repair of injuries to the soft tissue structures of the knee, focusing primarily on the meniscus. With funding from Whitaker Foundation, NIH, NSF, as well as industrial sponsorship her research program, she has had 10 Ph.D. students, 15 M.S. student, and more than 35 undergraduates. She has national collaborations with Michigan State and Mayo Clinic, as well as international collaborations with Trinity College Dublin and UMC Utrecht. Dr. Haut Donahue has brought in more than $11 million in funding as a PI and co-PI that has led to over 45 journal publications. She is also now helping to teach the senior design program in mechanical engineering for the American Society of Engineering Education.

Honors include: The Ferdinand P. Beer and E. Russell Johnson Jr. Outstanding New Mechanics Educator Award, 2006, presented by the American Society of Engineering Education

Elwyn Firth

B.V.Sc., Ph.D., Diplomate ACVS, Professor and Director, Massey Equine Research, Massey University, Palmerston North, New Zealand

Dr. Elwyn Firth is a Professor in the Department of Exercise Science and the Liggins Institute at the University of Auckland, New Zealand. He has worked in other universities as a specialist in equine surgery and a researcher in musculoskeletal sciences. His current research interests include the effect of exercise on bone and joint growth and function, the effect of nutritional and exercise interventions on early and later responses of various body systems, and how exercise during pregnancy and early postnatal life affects metabolic outcomes in later life.

Mark W. Grinstaff

Ph.D; Distinguished Professor, Boston University, Boston, MA

Dr. Mark W. Grinstaff is the Distinguished Professor of Translational Research and a Professor of Biomedical Engineering, Chemistry, and Materials Science and Engineering, and Medicine at Boston University. Mark received his Ph.D. from the University of Illinois under the mentorship of Professor Kenneth S. Suslick and was an NIH postdoctoral fellow at the California Institute of Technology with Professor Harry B. Gray. Mark's awards include the ACS Nobel Laureate Signature Award, NSF Career Award, Pew Scholar in the Biomedical Sciences, Camille Dreyfus Teacher-Scholar, Alfred P. Sloan Research Fellowship, the Edward M. Kennedy Award for Health Care Innovation, and a Fellow of the National Academy of Inventors. He is an author or co-author on more than 200 peer-reviewed manuscripts, given more than 275 oral presentations, and an inventor or co-inventor on more than 200 issued patents or pending applications. His students and fellows have given more than 125 oral presentations and 350 posters at national and international meetings. He is a co-founder of four companies that are commercializing his ideas, and he has three products being sold and used in the clinic. His current research activities involve the synthesis of new macromolecules and biomaterials, self-assembly chemistry, imaging contrast agents, drug delivery, and wound repair.

Robert F. LaPrade

M.D., Ph.D.; Chief Medical Officer, The Steadman Philippon Research Institute; Complex Knee and Sports Medicine Surgery, The Steadman Clinic, Vail, Colo.

Dr. Robert LaPrade is an internationally recognized orthopaedic surgeon who specializes in the treatment of complex knee injuries, in particular posterolateral knee injuries. He is currently the chief medical officer for the Steadman Philippon Research Institute, the deputy director of the sports medicine fellowship, and the director of the international scholars program.

He has published over 150 peer-reviewed scientific manuscripts, over 75 invited articles and book chapters, and one textbook. He also performs editorial duties for American Journal of Sports Medicine and Knee Surgery, Arthroscopy and Traumatology (KSSTA), and is a peer reviewer for over 10 journals. He has received numerous international awards, including the OREF Clinical Research Award, considered one of the Nobel prizes of orthopaedic surgery. Dr. LaPrade was recognized for his research collaboration with Dr. Lars Engebretsen of the University of Oslo, which developed new surgeries to treat complex knee injuries. Dr. LaPrade is a member of numerous professional associations, including AOSSM, ISAKOS, and ESSKA, and is a frequent contributor to orthopaedic surgery expert groups and research committees.

William G. Rodkey

D.V.M., M.S.; Chief Scientific Officer and Senior Scientist, Director, Center for Translational and Regenerative Medicine; Research Chairman, Scientific Advisory Committee, Steadman Philippon Research Institute, Vail, Colo.

Dr. Rodkey has been chief scientific officer and director of the Center for Translational and Regenerative Medicine Research at the Steadman Philippon Research Institute in Vail, Colo., since 1990. He is also the chairman of the Scientific Advisory Committee. Dr. Rodkey's research is focused on tissue regeneration with scaffolds, and cellular therapy with an emphasis on articular cartilage, meniscus, and ligaments. Prior to joining Dr. Steadman in Vail, Dr. (Colonel, U.S. Army, retired) Rodkey was chairman of Military Trauma Research at Letterman Army Institute of Research in San Francisco and earned numerous awards and military decorations, including the United States of America Legion of Merit Medal, Meritorious Service Medal, U.S. Army Commendation Medal (with five oak leaf clusters), Humanitarian Services Medal, Order of Military Medical Merit, and the U.S. Secretary of the Army Research and Development Achievement Award. He has authored more than 200 published works and has made more than 450 presentations at national and international meetings. Dr. Rodkey has received numerous awards, including the Excellence in Research Award from AOSSM, the Cabaud Memorial Award from AOSSM twice, the Albert Trillat Award for Knee Research, and GOTS-Beiersdorf Research Award 2000. He received undergraduate and Doctor of Veterinary Medicine degrees from Purdue University and completed medical education and surgical and orthopaedic residency training at University of Florida. He is a member of AAOS, AOSSM, ISAKOS, ESSKA, ICRS, OARSI, EFORT.

Jude Samulski

Ph.D., Professor, Department of Pharmacology, University of North Carolina, Chapel Hill, N.C.

Dr. Jude Samulski is an important collaborator to our group investigating gene therapy at the ORC. He is a professor in the Department of Pharmacology and the director of the Gene Therapy Center at the University of North Carolina at Chapel Hill. Dr. Samulski earned his B.S. at Clemson University, and a Ph.D. at the University of Florida in Molecular Biology. He did two post docs at SUNY in New York and Princeton University, respectively. He then was on faculty at University of Pittsburgh from 1986-1992 and recruited to UNC as associate professor in Pharmacology, and director of the Gene Therapy Center.

Honors include: Outstanding Young Men of America Award and the President's Distinguished Research Award; American Society of Gene Therapy Outstanding Achievement Award, 2009. President of American Society of Cell and Gene Therapy, 2012

Coen Wijdicks

Ph.D.; Director, Department of BioMedical Engineering; Senior Staff Scientist, Steadman Philippon Research Institute, Vail, Colo. In late 2014 became Director of Research, Arthrex GmbH, Munich, Germany

Dr. Wijdicks is an orthopaedic researcher who currently serves as the director of the Department of BioMedical Engineering and as a senior staff scientist at the Steadman Philippon Research Institute (SPRI). His focus is in utilizing biomedical engineering principles to advance healthcare treatments by combining the design and problem solving skills of engineering with medical and biological sciences. Specifically, Dr. Wijdicks is interested in bench-to-bedside translational research for the development, optimization, and validation of surgical procedures for common injuries.

Charles Archer, Ph.D., Professor of Regenerative Medicine, School of Medicine, Swansea University, Swansea SA2 8PP

Dr. Charles Archer took up his current position in 2012. Prior to that, from 2002–2012 he was professor of Reparative Biology and Tissue Engineering at Cardiff University, and head of the Connective Tissue Biology Laboratories within Biosciences until 2006, one of the-then 16 research groups within the school. Having graduated the University College of Swansea in zoology, he remained there to pursue a Ph.D. in the effects of pulse-magnetic fields and fracture healing. He then carried out post-doctoral work at the Middlesex Hospital Medical School on cartilage morphogenesis under Prof. Louis Wolpert before moving to the Institute of Orthopaedics, University College, London, as lecturer and then senior lecturer in cell biology before moving to Cardiff in 1990. Most of his work has been on articular cartilage, from initial mechanisms of joint formation through to its morphogenesis, aging and the onset of degenerative disease. More recently, he has focused on endogenous cartilage stem cells as a therapeutic option for repair of damaged cartilage.

Frank Barry, Ph.D., Professor of Cellular Therapy at the Regenerative Medicine Institute (REMEDI), National University of Ireland Galway.

Frank Barry directs a large group of researchers who focus on the development of new repair strategies in stem cell therapy and gene therapy in orthopaedics. Previously, he was Director of Arthritis Research at Osiris Therapeutics in Baltimore, Md., and a Research Fellow at Shriners Hospital for Children, Tampa, Fla.

He has contributed to the fields of tissue engineering and regenerative medicine by developing innovative and successful cellular therapies for the treatment of acute joint injury and arthritic disease. This has included the generation of a large body of new data in ground-breaking preclinical studies, and has led to the first phase of clinical testing of mesenchymal stem cells in clinical trials for joint injury.

In a career that has spanned both industry and academic research, he has been a driver in the development of cellular therapy as a biological repair strategy. It is his belief that the application of new technologies in regenerative medicine, including cellular therapy, gene therapy, growth factor augmentation, implantable scaffolds, and nanomaterials, will have a profound impact in Orthopaedics. Frank Barry was the recipient of the 2012 Marshall Urist Award for excellence in tissue regeneration research from the Orthopaedic Research Society.

Neil David Broom, Ph.D., Professor, Department of Chemical and Materials Engineering, University of Auckland

Professor Neil Broom's initial training in metallurgy has been applied successfully to experimental tissue mechanics that has earned him an international reputation in this field. His earlier aortic valve research fundamentally altered processing procedures in the bio-prosthetic valve industry world-wide. Neil's key achievements in joint-tissue research include the development of new collagen-based physical models for cartilage to account for the structural weakening occurring in the cartilage matrix arising from both early degeneration and trauma. He has provided rigorous, experimentally-based analyses of both the role of the strain-limiting articular surface, and the biomechanically critical junction region between the compliant cartilage and bone in its physiological state. He and his team have produced evidence of primary bone formation beneath the still-intact cartilage adjacent to lesion sites thus clarifying the elusive pre-osteoarthritic state. His research has produced a structural gold standard for the international community of 'tissue engineering' researchers, challenging them to 'engineer' matrices that are biomechanically viable. Neil's most recent research has focused on the intervertebral disc (IVD). He and his team have developed new structural insights into the micro-anatomy of the disc wall to explain the mechanical basis of annular disruption and prolapse, these being linked to two of the most prevalent and debilitating clinical conditions of the modern world - low back and radicular pain. He has shown experimentally how nucleus material interacts with the disc wall and endplate, and how combinations of flexion, torsion, and rate of loading can cause nuclear fragments to migrate out through the wall and cause prolapse. This pioneering research is the first published integration of disc micro-architecture, functional posture, and loading rate, with susceptibility to failure. Neil is an elected Fellow of the Royal Society of NZ, and in 2013 was awarded the Society's MacDarmid Medal for his contributions to research that most benefits human health.

Constance R. Chu, M.D., Professor and Vice Chair Research, Department of Orthopedic Surgery, Stanford University; Director of Joint Preservation Center and Chief of Sports Medicine, VA, Palo Alto

Dr. Constance R. Chu was previously the Albert Ferguson Professor of Orthopaedic Surgery at the University of Pittsburgh. She is a clinician-scientist who is both principal investigator of several projects funded by the National Institutes of Health, and who has been recognized as a Castle-Connelly/US News and World Report "Top Doctor" in orthopedic surgery, as well as on Becker's list of 125 Top Knee Surgeons in the U.S. Her clinical practice focuses on knee reconstruction, arthroscopy, ACL and meniscus surgery, and cartilage repair. She graduated from the U.S. Military Academy at West Point and earned her medical degree from Harvard Medical School.

As director of the multi-disciplinary Joint Preservation Center structured to seamlessly integrate basic, translational and clinical research with clinical practice, Dr. Chu developed the center to advance the concept of early diagnosis and treatment of cartilage injury and degeneration as a strategy to delay or prevent the onset of disabling osteoarthritis. Towards this end, she is leading innovative translational research from bench to bedside in three main areas: quantitative imaging and biomarker development for early diagnosis and staging of joint and cartilage injury and degeneration; cartilage tissue engineering and stem cell based cartilage repair; and molecular and biological therapies for joint restoration and rejuvenation. Her research efforts have led to more than 30 professional awards and honors to include a Kappa Delta Award, considered to be the highest research honor in Orthopedic Surgery.

Dr. Chu also regularly holds leadership and committee positions in major professional organizations such as the American Association of Orthopedic Surgeons (AAOS) and the American Orthopedic Association (AOA). In her subspecialty of Orthopedic Sports Medicine, she is a past president of the Forum Sports Focus Group, a member of the prestigious Herodicus Society of leaders in sports medicine, and immediate past Chair of the American Orthopedic Society for Sports Medicine (AOSSM) Research Council. She is alumnus of the highly selective AOA American, British, Canadian (ABC) Traveling Fellowship and the AOSSM Traveling Fellowship, opportunities enacted to recognize and promote careers of emerging leaders in orthopedic surgery and orthopedic sports medicine, respectively.

Lisa Fortier, D.V.M., Ph.D., Diplomate ACVS
Lisa Fortier is a professor of surgery at Cornell University in Ithaca, N.Y.

She received her D.V.M. from Colorado State University and completed her Ph.D. and surgical residency training at Cornell University. She is boarded with the American College of Veterinary Surgeons and is an active equine orthopaedic surgeon at Cornell University and the Cornell Ruffian Equine Specialists Hospital at the Belmont race track in New York. Her laboratory studies the intracellular pathways involved in the pathogenesis of osteoarthritis, with particular emphasis on post-traumatic osteoarthritis. In addition, Lisa's research program investigates the clinical application of stem cells and biologics such as PRP for cartilage repair and tendonosis. She has received the Jaques Lemans Award from the International Cartilage Repair Society, the New Investigator Research Award from the Orthopaedic Research Society, and the Pfizer Research Award for Research Excellence from Cornell University. Lisa is the vice president of the International Veterinary Regenerative Medicine Society and past president of the International Cartilage Repair Society.

Alan J. Grodzinsky, Sc.D., Professor, Director of the Center for Biomedical Engineering, Departments of Biological Engineering, Mechanical Engineering, and Electrical Engineering and Computer Science, MIT

Dr. Grodzinsky is a professor in the departments of Biological, Electrical, and Mechanical Engineering at the Massachusetts Institute of Technology. He is also the director of the Center for Biomedical Engineering. Dr. Grodzinsky's research focuses on the mechanobiology of articular cartilage, including the response of native tissue to physiological and injurious loading, as well as the mechanobiology of neo-tissue development for applications to cartilage resurfacing.

Charles P. Ho, Ph.D., M.D.; Director of Imaging Research; member, Scientific Advisory Board; Steadman Philippon Research Institute, Vail, Colo.

Dr. Ho is experienced and active in musculoskeletal and orthopaedic sports medicine imaging and research, particularly in musculoskeletal Magnetic Resonance Imaging. He has been a member of the Radiological Society of North America, the American Roentgen Ray Society, the Society of Skeletal Radiology, the American Academy of Orthopaedic Surgeons, the American Orthopaedic Society for Sports Medicine, and the ACL Study Group, among other professional organizations. He has published numerous papers and book chapters in radiologic and orthopaedic literature, and presented numerous papers internationally in radiologic and orthopaedic conference proceedings. Dr. Ho is Director of Imaging Research and a member of the Scientific Advisory Board of the Steadman Philippon Research Institute in Vail, Colo. He has served as Radiologic Consultant for the San Francisco 49ers, the San Francisco Giants, Cleveland Indians, Denver Broncos, Colorado Rockies, the U.S. Ski Team, and the U.S. Decathlon Team.

Christopher Little, B.Sc., B.V.M.S., M.Sc., Ph.D.; Diplomate ACVS; Professor and Director, Raymond Purves Bone & Joint Research Laboratories, Kolling Institute, Institute of Bone and Joint Research, University of Sydney at Royal North Shore Hospital

Professor Christopher Little is director of the Raymond Purves Bone and Joint Research Labs at the Kolling Institute and the SubDean of Research for Sydney Medical School (Northern) at Royal North Shore Hospital, Australia. Dr. Little received his veterinary training at Murdoch University in Western Australia, where he also undertook an internship in equine medicine and surgery (1978-1984). He then completed a residency in large animal surgery and an M.Sc. studying arthritis in horses at the University of Minnesota. Chris was appointed to the faculty at the Ontario Veterinary College, University of Guelph, and during this time passed his certifying examinations to become a Diplomate of the American College of Veterinary Surgeons (1990). He then moved to back to Australia and was awarded a Ph.D. degree from the Faculty of Medicine at the University of Sydney in 1996. Following a 5-year postdoctoral position at Cardiff University (U.K.), he was awarded an Arthritis Foundation of Australia Fellowship at the University of Melbourne. In 2004, he moved to his current position in the University of Sydney Faculty of Medicine. Chris's research interests focus on defining the biochemical and molecular mechanisms of joint pathology in OA, and tendon and intervertebral disc degeneration, and are based on the belief that it is only through a better understanding of the mechanisms that drive the initiation and progression of these diseases that new therapies can be developed. In particular, he has studied changes in aggrecan and small proteoglycan biosynthesis and degradation, and the proteolytic pathways responsible in cartilage breakdown in arthritis and during tendon and disc degeneration. Chris is recognized internationally for his expertise in the development and use of animal models of bone and joint disease. He has served as an Associate Editor of Osteoarthritis and Cartilage, and as leader of the OARSI international initiative to establish standardized methods for evaluation of animal models of OA. Chris received the 2010 Barry Preston Award from the Matrix Biology Society of Australia and New Zealand, presented to an outstanding leader in the field. He has authored/co-authored 112 scientific papers and seven book chapters.

Helen McCarthy, Ph.D.

Dr. Helen McCarthy is a senior post-doctoral research scientist within the division of Pathophysiology and Repair at Cardiff School of Biosciences in the U.K. Her research interests focus on the development of translational technologies based on articular cartilage progenitor cell biology, primarily in the equine field. This work has resulted in the first large animal studies utilizing both equine (Colorado) and caprine (Davos, Switzerland) models. Her interests also lie in the biology of both the articular cartilage progenitor cell and a meniscus-specific stem/progenitor cell in human tissue and their role in tissue repair and osteoarthritis.

Alan J. Nixon, B.V.Sc., M.S., Diplomate ACVS, Professor of Orthopaedic Surgery, Director of the Comparative Orthopaedic Laboratory, Cornell University

Dr. Nixon is a Professor of Orthopaedic Surgery and Director of the Comparative Orthopaedic Laboratory at Cornell University, Ithaca, New York. His research focus is in chondrocyte metabolism and cartilage repair methods using chondrocyte or pluripotent stem cell transplantation. Dr. Nixon's research group has focused on the cloning of growth factor molecules for use in gene therapy protocols, inserting the growth factor gene into cartilage cells at the time of transplantation of synovial cells by direct joint injection. The laboratory group also studies the molecular changes associated with osteochondritis dissecans (OCD) in horses and man, and investigates treatment methods for tendonitis in athletes.

Dr. Nixon's current interests include the use of combination gene therapy using stimulatory growth factors, and, in collaboration with the ORC at CSU, the combined use of interleukin receptor antagonist gene therapy to diminish degradation in arthritic joints.

Michael "Mick" Peterson, Ph.D., Professor, University of Maine

Dr. Peterson is a professor of mechanical engineering at the University of Maine. Prior to coming to the University of Maine, he was a faculty member at CSU and was a post-doctoral researcher at Northwestern University. He has also worked in industry at General Motors and General Dynamics Corp. His Ph.D. is in theoretical and applied mechanics from Northwestern University in Illinois, and he also holds a B.S. in mechanical engineering from General Motors Institute (now Kettering University) and an M.S. in theoretical and applied mechanics from Northwestern University. He has also done additional graduate work in mechanics, materials, and mathematics from Yale University, Cornell University, and the University of Connecticut. His primary expertise is in the animal biomechanics, dynamic response of materials, and waves in solids.

Christopher B. Riley, B.Sc. (Physics), B.V.Sc. (Hons), M.Sc., Ph.D., Diplomate ACVS, PGCertInnovation Mgt, Professor, Chair and Service Chief, Equine Group, Institute of Veterinary, Animal and Biomedical Sciences, Massey University, Palmerton North, New Zealand.

Following military service in the Air Force, Dr. Riley received degrees in physics and veterinary medicine from the University of Melbourne, Australia. After an internship and private practice in Australia, he completed a surgical residency at the University of Saskatchewan in Canada. Concurrently, he completed M.Sc. and Ph.D. degrees in the fields of tendon in-vitro biology and biochemistry. Dr. Riley then worked at briefly at Iowa State University and in private practice during which time he became a Diplomate in the American College of Veterinary Surgeons. He joined the faculty at the Atlantic Veterinary College, Canada, in 1999 rising to the rank of professor, and completed an MBA course in Innovation Management in 2007 at the University of Melbourne. In 2010 he accepted an appointment as the inaugural professor and chair of Equine Health the University of Adelaide, establishing the equine curriculum, teaching and veterinary hospital facilities. He commenced his current position at Massey University in 2013 during the veterinary program's 50th Anniversary year. Dr. Riley has focused his research on the development of biomedical tests for animal diseases using the emerging technologies of infrared spectroscopy (FTIR), optoacoustics, and bioinformatics. He established the first FTIR laboratory of its kind in Canada, developed to investigate the veterinary potential biomedical infrared spectroscopy. He has continued this work with ~US $6.7 million in funded projects to date. Dr. Riley has a special interest in biomarkers for orthopaedic disease, and humoral immunity, but is also interested exploring the full potential of emerging technologies as they apply to veterinary and comparative medicine. Dr. Riley partnered with the Orthopaedic Research Center and the Institute for Biodiagnostics, National Research Council of Canada, to develop the first FTIR test for equine traumatic arthritis and osteochondrosis. More recently, he has collaborated with Prof. Sheila Laverty at the University of Montreal and Prof. James Cook at the University of Missouri to examine and characterize this technology further in rabbit and canine models of orthopaedic disease. He looks further to continued collaboration and advances in this new field of research. Currently, he is continuing work with the carpal chip fracture model established at the ORS.

Robert Lie-Yuan Sah, M.D., Sc.D., Professor of Bioengineering & Adjunct Professor of Orthopaedic Surgery, UCSD; Professor, Howard Hughes Medical Institute

Dr. Sah received his Sc.D. in medical engineering from the Massachusetts Institute of Technology and his M.D. from Harvard Medical School. He did postdoctoral work at Massachusetts General Hospital in orthopaedic bioengineering. He is currently co-director of the Center for Musculoskeletal Research at UCSD, and also co-director of an NIH pre-doctoral training grant on Translational Musculoskeletal Research at UCSD. In addition, he is on the Editorial Board of Cartilage, Osteoarthritis and Cartilage, and Tissue Engineering, and a standing review panel member for the NIH.

Honors include: Arthritis Foundation, Hulda Irene Duggan Investigator, 1993; Young Investigator Award, National Science Foundation, 1994; "Mechanical Blueprint for Cartilage," cited as one of the Great Advances in Scientific Discovery in Disease and Injury Treatment, The Science Coalition, 1998; American Academy of Orthopaedic Surgeons Kappa Delta Award, 1993 and 2001; American Society of Mechanical Engineers Van C Mow Medal, 2006; Howard Hughes Medical Institute, Society of Professors, 2006; American Institute for Medical and Biological Engineering, 2007

Roger K.W. Smith, M.A., VetMB, Ph.D., FHEA DEO, AssocECVDI, Diplomate ECVS MRCVS; Professor of Equine Orthopaedics, Royal Veterinary College, London, U.K.; RCVS and European Specialist in Equine Surgery (Orthopaedics); President, International Veterinary Regenerative Medicine Society

Roger Smith qualified as a veterinary surgeon from Cambridge University in 1987 and, after two years in practice, returned to academia to undertake further clinical training as a resident in Equine Studies at the Royal Veterinary College. Following his residency, he undertook a three-year research project culminating in the award of a Ph.D. for his studies on the extracellular matrix of equine tendon. He remained at the Royal Veterinary College, first as a lecturer in equine surgery, then as senior lecturer in equine surgery before his appointment to a professorship in December 2003. He holds the Diploma of Equine Orthopaedics from the Royal College of Veterinary Surgeons, and is both a Diplomate of the European College of Veterinary Surgeons and a Royal College of Veterinary Surgeons Specialist in Equine Surgery. He is also an Associate member of the European College of Veterinary Diagnostic Imaging and Fellow of the Higher Education Academy.

He currently divides his time equally between running a specialist orthopaedic service within the Royal Veterinary College and continuing to direct research into equine tendon disease. His main area of research is understanding the pathogenesis of tendinopathy but also has projects investigating the epidemiology of tendon disease in the horse, the development of a serological assay for tendonitis, and stem cell therapy for tendons.

J. Richard Steadman, M.D.; Founder and Managing Partner, The Steadman Clinic; and Founder and Co-Chairman, Steadman Philippon Research Institute, Vail, Colo.

Dr. Steadman graduated from the University of Texas Southwestern Medical School in Dallas. Following internship, two years in the U.S. Army, and an orthopaedics residency at Charity Hospital in New Orleans, La., Dr. Steadman moved to Lake Tahoe, Calif., where he practiced orthopaedics with increasing emphasis on the treatment of knee disorders. While living there, he was named chief physician and medical chairman for the United States Ski Team. During his time at Lake Tahoe, Dr. Steadman developed special surgical techniques which allowed several ski team members to return to competition and win Olympic medals and championships. At Lake Tahoe, Dr. Steadman started a non-profit sports medicine foundation in order to conduct research in knee surgery and rehabilitation projects. That organization exists today as the Steadman Philippon Research Institute in Vail, Colo. In 1990, Dr. Steadman moved to Vail, Colo. By this time, Dr. Steadman had limited his practice to the surgical and conservative treatment of knee disorders. Today, Dr. Steadman is regarded as a world-renowned human orthopaedic surgeon. He is a prominent knee surgeon and the inventor of two significant new techniques in orthopaedics. His Research Institute has supported several research projects at CSU. Dr. Steadman serves as a consultant regarding clinical relevance of our research work, and the CSU Orthopaedic Bioengineering Research Laboratory has done controlled studies investigating his techniques used in human orthopaedic surgery.

Stephen B. Trippel, M.D., Orthopaedic Surgeon; Professor of Orthopaedic Surgery and Anatomy and Cell Biology, Indiana University School of Medicine

Dr. Stephen Trippel is an orthopaedic surgeon with a clinical focus on adult reconstructive surgery and a research focus on musculoskeletal repair. He is professor of Orthopaedic Surgery and of Anatomy and Cell Biology at Indiana University School of Medicine and is an advisory member of the graduate faculty at Purdue University. Dr. Trippel received his M.D. from Columbia University College of Physicians and Surgeons, and completed his orthopaedic residency in the Harvard Combined Orthopaedic Residency Program. He also completed a fellowship in orthopaedic research at Massachusetts General Hospital and a Pediatric Endocrinology research fellowship at the University of North Carolina, Chapel Hill. He served on the faculty of Harvard Medical School before joining the faculty of the Indiana University School of Medicine. Dr. Trippel's current research is focused on the development of new approaches to the treatment of articular cartilage damage, including tissue engineering and gene therapy. This includes an ongoing study with the ORC investigating a novel approach to articular cartilage repair in an equine stifle joint model.

René van Weeren, D.V.M., Ph.D., Diplomate ECVS, Royal Dutch Veterinary Association; Professor of Equine Musculoskeletal Biology, Department of Equine Sciences, Faculty of Veterinary Medicine, Utrecht University, The Netherlands

Paul René van Weeren (1957) graduated in 1983 from the Utrecht University Veterinary Faculty (The Netherlands). He became a staff member of the Department of General and Large Animal Surgery in that year and obtained his Ph.D. in 1989. From 1991-1993 he worked as a visiting professor at the Escuela de Medicina Veterinaria of the Universidad Nacional in Heredia, Costa Rica. He became a diplomate of the European College of Veterinary Surgeons in 1994. He was appointed as full professor to the chair of Equine Musculoskeletal Biology in 2007, and is now mainly involved in research with focus areas articular cartilage, tendons, and biomechanics. He became head of the Department of Equine Sciences of the Faculty of Veterinary Medicine of Utrecht University in 2012.

René van Weeren has been a supervisor of 27 Ph.D. students, who have obtained their degree in the past years and currently supervises 10 Ph.D. students, who will be graduating within the next few years. He is an associate editor of Equine Veterinary Journal, member of the editorial board of The Veterinary Journal, and member of the scientific board of several others. He has been, or is, guest editor of various Special Issues or Supplements of a variety of scientific journals. He has been external examiner for Ph.D. students abroad at various occasions in Belgium, the U.K., France, Austria, Sweden, Norway, and Finland. He is author or co-author of more than 250 peer-reviewed scientific publications and has contributed various chapters to a variety of text books.

Josh Donnell

D.V.M.

Dr. Josh Donnell joined the ORC as an Equine Sports Medicine and Rehabilitation resident in July 2012. He is originally from Canyon, Texas, where he received a bachelor's degree in animal science from West Texas A&M University. Josh graduated from Texas A&M College of Veterinary Medicine in May 2010, and was an intern at Goulburn Valley Equine Hospital in Shepparton, VIC, Australia. He then worked for a year at La Mesa Equine Lameness Center and Equine Sports Medicine in Pilot Point, Texas.

Philippe Manchon

B.V.Sc

Dr. Philippe Manchon joined the Equine Sports Medicine and Rehabilitation Service's residency program in July 2013. Dr. Manchon is originally from Queensland, Australia. He received his veterinary degree at the University of Queensland, graduating in 2010, at which time he accepted a scholarship to continue his clinical training at the university's equine hospital. Dr. Manchon then pursued an internship in 2011 at Weatherford Equine Medical Center, Weatherford, Texas, and did an additional year in that practice before joining us at CSU.

Frances Peat

B.V.Sc

Dr. Peat joined the Equine Sports Medicine and Rehabilitation Services residency program in July 2013. She is the fifth resident in our program that remains unique as the only residency in Equine Sports Medicine and Rehabilitation. Dr. Peat is from New Zealand and received her veterinary degree from Massey University. She has also done a postgraduate clinical diploma at Massey. She has been in practice for five years at one of the leading equine practices in New Zealand, Matamata Veterinary Services.

Ellison Aldrich

D.V.M.

Dr. Ellison Aldrich received her B.A. in 2008 from Skidmore College in Saratoga Springs, N.Y., where she studied biology and studio art, and earned her VMD from the University of Pennsylvania in 2012. She then completed a one-year large-animal surgery internship at Tufts Cummings School of Veterinary Medicine and is now an equine surgery resident at CSU. She enjoys all aspects of equine surgery and lameness, with a primary research interest in regenerative medicine.

Aimee Colbath

D.V.M.

Dr. Aimee Colbath joined the ORC team in 2012 for a three-year surgical residency. She graduated from the University of Pennsylvania School of Veterinary Medicine in 2010. Aimee became interested in stem cell research and biologic therapies during my general large animal internship at the University of Georgia, where she worked in Dr. Peroni's research laboratory. She then moved on to a surgical internship at the Tufts Cummings School of Veterinary Medicine, where she worked in the regenerative medicine laboratory studying the effects of shipping on stem cells. Since joining CSU, her research focus has been on the immunomodulatory effects of equine stem cells.

Alexander Daniel

D.V.M.

Dr. Alexander Daniel joined the team at CSU for a three-year surgical residency program. After graduating from the Royal Veterinary College London, he worked in a private practice equine referral hospital in California. There, he developed an interest in advanced diagnostic imaging and while completing his surgical residency and master's degree at CSU, he has continued to be involved in research in this field. Other areas of research include laparoscopic surgery and the acute phase protein response after colic surgery.

Kristine Fischenich

B.S., Mechanical Engineering, The University of Mississippi

Kristine is working toward a Ph.D. in biomedical engineering. She just completed her M.S. in mechanical engineering at CSU. Her thesis work includes mechanical testing of rabbit menisci from both a traumatic ACL tear model and surgical ACL transaction model. This work is for an ongoing project looking at the progression of post-traumatic osteoarthritis. Kristine is doing initial failure testing to transition the ACL tear model from rabbits to sheep. She will graduate in May 2014.

Ben Gadomski

B.S.

Ben received his B.S. in mechanical engineering from Tri-State University in 2009. Since that time, Ben has been studying under the guidance of Dr. Christian Puttlitz in research areas including spinal implant design as well as spinal finite element modeling. Ben is currently a Ph.D. candidate working on a NASA-funded grant to investigate the role of microgravity on bone loss and fracture healing.

Livia Camargo Garbin

D.V.M., M.Sc.

Livia graduated in Veterinary Medicine at Lavras Federal University in Brazil in 2010. She completed an equine internal medicine internship in 2011 at Minas Gerais Federal University in Brazil, where she also completed her master's degree in 2012. In her master's research, Livia compared the effects of two different protocols for mesenchymal stem cell isolation and application in equine-induced desmitis. Currently, Livia is engaged in a Ph.D. program at CSU with Dr. Frisbie as her advisor. Her project involves the study of the protective effects of freeze-dried platelet-rich plasma (PRP) and insulin receptor antagonist protein (IRAP) in synovial tissues and tendon explants under an inflammatory state, in vitro.

Brad Nelson

D.V.M., M.S., Diplomate ACVS

Dr. Brad Nelson recently started in a Ph.D. program at the ORC. Brad graduated from the University of Wisconsin-Madison with a D.V.M. in 2009, and then completed an equine internship in surgery and medicine at Washington State University, followed by a residency in large animal surgery at CSU. He also received a master's degree in clinical sciences as part of the residency program. Dr. Nelson's Ph.D. research will focus on articular cartilage imaging, specifically in the use of contrast enhanced computed tomography as a method to improve the diagnosis of articular cartilage injury. Brad replaced Dr. Moorman as the staff veterinarian at the ORC.

Hannah Pauly

B.S., Biomedical Engineering, Vanderbilt University

Hannah is currently working towards a Ph.D. in biomedical engineering. Her major area of study is the attachment of the meniscus of the knee to the underlying bone. Current projects include comparing structure and function characteristics of healthy and osteoarthritic meniscal insertions using second harmonic generation microscopy and developing a tissue engineered artificial meniscal insertion. She will graduate in May 2016.

Nicole Ramo

B.S.

Nicole graduated in December of 2012 with a B.S. in mechanical engineering from Kettering University in Flint, Mich. Through Kettering's co-operative education program, Nicole worked for three-and-a-half years as a research assistant in the Bone and Joint Center of Henry Ford Hospital in Detroit. Her work culminated in an undergraduate thesis on the dynamic in-vivo joint motion of the cervical spine following fusion and arthroplasty. Continuing to research spine biomechanics at CSU, Nicole now works under Dr. Christian Puttlitz in the ORC as a Ph.D. student in the School of Biomedical Engineering.

Suwimol Tangtrongsup

M.S.

Suwimol graduated from Mahidol University, Bangkok, Thailand, and received her B.Sc. in biology in 2000 and her M.Sc. in physiology in 2003. She spent the next four years as an instructor in the Department of Physiology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand. Suwimol joined the ORC in 2009 under a scholarship from The Royal Thai Government and is currently working on a Ph.D. under Dr. John Kisiday. Her research focus is the effect of dexamethasone concentration and duration of exposure on chondrogenic differentiation of equine bone marrow-derived mesenchymal stem cells. She also studies the effect of inflammatory cytokine IL-1β on chondrogenesis of mesenchymal stem cells in the presence or absence of dexamethasone and the relationship between inflammation, oxidative stress, and chondrogenesis of mesenchymal stem cells in an agarose-gel culture system.

Benjamin Wheatley

B.S., Engineering, Trinity College

Ben joined Dr. Haut Donahue's lab in Fall 2012 as a Ph.D. student. His main research area is muscle mechanics. His current project is the development of a finite element model of skeletal muscle to predict intramuscular pressure. This goal of this project is cooperation with a clinical tool to determine muscle force. He is also working on experimental testing of muscle as a non-linear viscoelastic material.

Alyssa Ball

B.S.

Alyssa graduated from CSU in 2013 with a B.S. Degree in Biochemistry and started her M.S. graduate program (concurrently with a D.V.M. program) under the direction of Dr. Laurie Goodrich. In 2014, Dr. Goodrich and Alyssa received CRC funding for a one-year fellowship through a NIH T-32 grant to explore the use of genetically modified stem cells in equine fracture repair. After completing veterinary school, Alyssa plans to continue pursuing equine musculoskeletal research.

John Schwartz

B.S.

John Schwartz received his B.S. in journalism from Boston University in 2010 and under the direction of Dr. Laurie Goodrich started working on his M.S. in microbiology and expects to graduate in May 2015. Before coming to CSU, he spent four years working in the Orthopaedic Research Laboratory at the Feinstein Institute for Medical Research under Dr. Daniel Grande researching cartilage regeneration, tendon repair, and 3D bioprinting.

Gustavo Miranda Zanotto

D.V.M., MSc.

Dr. Gustavo Zanotto is originally from Curitiba, Brazil, where he received a D.V.M. from Paraná Federal University in 2007. Gustavo then moved to São Paulo where he completed a residency in large animal internal medicine and surgery, and received a master's degree in veterinary surgery at São Paulo University. For his master's degree, Gustavo evaluated chitosan hydrogel as a scaffold for equine stem cells. The main objective of this study was to improve the tissue engineering techniques for repair of osteochondral defects.

From 2010 to 2013, Gustavo was an assistant professor of large animal internal medicine and surgery at Anhanguera Educational School of Veterinary Medicine. Currently, Gustavo is a visiting researcher at the ORC working with Dr. David Frisbie on a project to compare the freeze-dried and fresh platelet-rich plasma in injured tendon explants. Additionally, Gustavo is doing an internship with CSU's Veterinary Diagnostic Imaging Service focusing on equine musculoskeletal imaging under the supervision of Dr. Myra Barrett-Frisbie.

Christine Battaglia

M.S.

Christine (Chrissy) began her appointment at the Orthopaedic Research Center as a Research Scientist/ Lab Manager in January 2014. Chrissy attended St. Michael's College in Colchester, VT and obtained a B.S. in environmental science. She obtained an M.S. in biochemical toxicology from Virginia-Maryland Regional College of Veterinary Medicine in Blacksburg, VA in 2001. Shortly after, Chrissy moved to Fort Collins and began working at Colorado State University in the Environmental and Radiological Health Sciences. She has worked in a variety of research areas since her arrival at CSU, including the Center for Environmental Toxicology, Neurobiology and Radiation Cancer Biology. She looks forward to participating in the exciting research advancements being made at the ORC.

Jennifer Suddreth

B.S.

Jen is originally from Altamont, Utah, and graduated from CSU in 2009 with a bachelor's degree in equine science and agricultural business. She started at the ORC on feed crew, and returned after graduation to work as an animal care technician. Jen joined the ORC full time as Research Trials Coordinator, Barn Manager and Volunteer Coordinator in June 2010. She was named the 2013 Technician of the Year, an award coordinated by the American Association for Laboratory Animal Science and the International Council for Laboratory Animal Science.

Kirk McGilvray

Ph.D.

Dr. Kirk McGilvray is currently working as a research scientist at the Orthopaedic Bioengineering Research Laboratory (OBRL). He is a Colorado native and received his B.S., M.S., Ph.D., and Post-doctoral education at CSU. His research efforts focus on comparative animal studies investigating pathways to enhance both soft tissue and bone healing following surgical intervention or trauma. He is also responsible for managing the day-to-day operations within the biomechanical testing center at the OBRL, which includes mentoring students in research techniques. Kirk's overreaching goals are to develop advance in vitro and in vivo measurement techniques that can be used to assess biological tissue in both its normal and diseased states.

Britt Madsen

B.S.

Britt is a Colorado native and graduated from CSU in 2002 with a B.S. in equine science. She managed horses for several equine operations in the area, including Chatellen Farm and Double Dove Ranch. In addition, she worked as a technician for Pilchuck Animal Hospital in Snohomish, WA and CSU's Equine Sports Medicine Service, and was a representative in the HR department of Starbucks Coffee Co. before joining the Equine Sports Medicine team as the Equine Sports Medicine Coordinator. Britt brings a balance of customer service experience and extensive equine industry connections to her new position. In her downtime, Madsen spends time at home in the garden with her daughter, Riley, and attempts to find time to ride one of her three horses.

Lynsey-Ann Bosch

B.S.

Lynsey graduated from Michigan State University with a bachelor's degree in veterinary technology, and worked at MSU as a technician throughout her education and for one year after graduation. In this position, Lynsey helped with equine emergencies, daily treatments, and out-patient appointments. She then moved with her husband to Colo. and worked at a private equine practice and at Bel-Rea Institute, a veterinary technician training college in Denver. Lynsey came to the ORC in 2005 as an administrative assistant and implemented an archiving program to digitize research study documents and associated data. Lynsey now works closely with all the PI's at the ORC editing and formatting research articles and presentations. She also helps to organize continuing education courses hosted by CSU.

Cecily Broomfield

M.S.

Cecily received a B.S. in microbiology from California Polytechnic State University in 2000, and an M.S. in agriculture from CSU in 2006. She is currently working as a research associate for the Orthopaedic Bioengineering Research Lab (OBRL).

Nate Jensrud

B.S.

Nate Jensrud joined the ORC as a research associate in March 2010. He earned his B.S. in forest resources with an emphasis in biotechnology from the University of Georgia in Athens. Nate managed a Plant Pathology laboratory at UGA for several years, studying the effects of Phytopthora ramorun, Sudden Oak Death, before moving to Colorado in 2008. He spent several seasons working for the federal government with the U.S. Forest Service and U.S. Geological Survey before coming to the ORC.

Whitney McMillan

B.S.

Whitney joined the Equine Sports Medicine and Rehabilitation service at the end of 2014 as a technician. She is a Georgia native and has a bachelor degree in Equine Science from CSU. She has been working in equine orthopedic research since 2005 and now brings her extensive experience to the Equine Sports Medicine team.

Mindy Meyers

B.S.

Melinda Meyers is a Research Associate with ten years of experience in the biomedical and biotechnology field. She received a B.S. from the University of Minnesota-Duluth and a M.S. in a focus on equine biotechnology, flow cytometry, and genetic preservation. She was recently hired as a research associate (laboratory) for the Orthopaedic Research Center.

Lindsay Richardson

B.S.

Lindsay joined the Equine Sports Medicine and Rehabilitation team as a technician in December 2014. She is originally from Illinois and has a bachelor's degree in animal science from CSU. She has several years of experience working at the Orthopaedic Research Center and assisting in equine research projects. She is currently attending the Front Range Community College Veterinary Technician Program and will become a certified veterinary technician in 2016.

Nikki Phillips

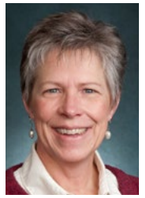
B.S.

Nikki received her B.S. in cell and molecular biology in May 1997 from Tulane University. She has been at CSU since 2001, working in the Department of Pathology for a year before working for both Clinical Sciences and Biomedical Sciences. Nikki joined the ORC in January 2008 as a research associate to assist in the ORL.

Katie Briggs

B.A.

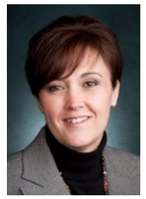
Katie received her B.A. in technical journalism from CSU, and has held a variety of marketing and publishing positions. She is the outreach coordinator for the ORC and the Equine Section of the VTH, and assists with the writing, editing, and printing of publications for both equine entities. She also coordinates fundraising and outreach events.



Paula Vanderlinden

Program Coordinator

Paula joined the ORC in March 2007 as program coordinator and Dr. McIlwraith's personal assistant. Paula manages the Annual Stallion Auction and the biannual lab report. Prior to working at CSU, Paula worked in the pharmaceutical industry.



Candice Hastings

Business Officer

Candice is the business officer for the Department of Clinical Sciences, and in May 2011, she began managing the accounting activity for the ORC.

ORC Student Hourlies in 2014

Alyssa Ball

Erin Beason

Carly Brown

Bree Copeman

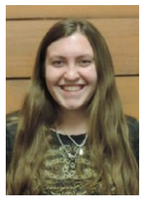
Kenzie Keefer

Jadyn McCoy

Jami Reed

LIndsay Richardson

Amy Scott



Megan Steele

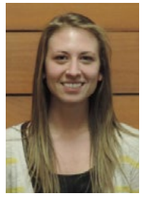
Not pictured:

Annaliese Caitlin

Ashlee Shelley

Cassie Powers

Volunteers in 2014



Fallon Elhard

Madeline Peters

Sabina Ligas

Not pictured:

Liz Hougland

Student	Degree	Date Graduated	Current Position
George Martin	M.S.	1983	Private practice, specialist equine surgeon
Gayle W. Trotter	M.S.	1983	Formally Professor in equine surgery, Colorado State University now private practice Weatherford, TX
Kenneth Sullins	M.S.	1984	Professor, University of Virginia, Marion DuPont Scott Equine Center
Alicia Bertone	M.S., Ph.D.	1987	Professor and Truman Endowed Chair, Ohio State University
John Yovich	M.S., Ph.D.	1988	Vice Chancellor, Murdoch University (now retired)
Cathy Gibson	M.S.	1989	Regulatory veterinarian, Australia
Scott Gustafson	M.S.	1989	Associate Professor, University of Oregon, Corvallis, OR
Jeff Foland	M.S.	1992	Co-owner and specialist equine surgeon, Weatherford Equine Hospital, TX
Dan Steinheimer	M.S.	1995	Specialist radiologist, Veterinary Clinics of America, Loveland, CO
Rick Howard	M.S., Ph.D.	1996	Specialist surgeon private practice, Arizona Equine Medical, AZ
Fahd Al-Sobayil	Ph.D.	1997	Assistant Professor, King Saud University, Riyadh, Saudi Arabia
Abigail Dimock	M.S.	1997	Currently a Ph.D. student, Equine Nutrition (Orthopaedic Related), Rutgers University
JoAnne Engel-Fehr	M.S.	1997	Specialist equine surgeon, Pilchuck Veterinary Hospital, WA
Becky Woodward	M.S.	1998	Graduate Researcher on S-V Dagon Research Vessel, University of British Columbia
Tina Anderson	Ph.D.	1998	Director of Marketing, Purina
Chris Kawcak	M.S., Ph.D.	1998	Professor, Iron Rose Ranch University Endowed Chair in Musculoskeletal Research, Colorado State University
David Frisbie	M.S., Ph.D.	1999	Professor, Orthopaedic Research Center, Colorado State University
Brigitte von Rechenberg	Ph.D.	1999	Dean, College of Veterinary Medicine, University of Zurich
Charles Hubbeling	Ph.D.	1999	Private consulting
Guy Beauregard	Ph.D.	1999	Senior scientist/researcher for private industry.
Andrew Green	M.S.	1999	Engineering Manager for private industry.
Elisha Rentfrow	M.S.	1999	Private consulting
Louise Southwood	M.S., Ph.D.	1998/2002	Associate Professor, University of Pennsylvania School of Veterinary Medicine
Tara Ruttley	M.S.	2000	Engineer for NASA
Carson Shellenberger	M.S.	2000	Engineer for private industry

Student	Degree	Date Graduated	Current Position
Al Kane	Post-Doc	2000	Analytic Epidemiologist, USDA; Affiliate Faculty for Colorado State University's Center of Veterinary Epidemiology and Animal Disease Surveillance Systems
Julie Dechant	M.S.	2000	Assistant Professor, University of California Davis
Troy Trumble	M.S., Ph.D.	2000, 2004	Associate Professor, University of Minnesota
Chengcheng Lui	M.S.	2001	Continuing in school
Jana Read	M.S.	2001	Employed in Quality Control
Erin Peterson	M.S.	2001	Faculty Member, Department of Animal Science, University of Maryland
Anne DePalma	M.S.	2002	
Joel Millets	M.S.	2002	Employed at Osteotech, Allograft Company
Carolyn Skurla	Ph.D.	2002	Assistant Professor, Baylor University
Awad Al-Zaben	Ph.D.	2003	Faculty Member, Electronics Engineering Department, Yarmouk University, Irbid, Jordan
Sophie Morisset	Ph.D.	2003	Assistant Professor, Department of Clinical Sciences, Université de Montréal
Thomas Young	M.S.	2003	Currently job searching
Colin Scruten	M.S.	2004	Private Practice, Alberta, Canada
Lea Rempel	Ph.D.	2004	Post-Doctoral Fellow, University of Kansas Medical School, Currently, Research Scientist, United States Meat Animal Research Center, Clay Center, NE
Chris Sorensen	Ph.D.	2004	Post-Doctoral, National Mass Spectrometry Facility, Environmental Molecular Sciences Laboratory and Biological Sciences Division, Pacific Northwest National Laboratory,Richland, WA
Brandon Santoni	Ph.D.	2006	Posdoctoral Research Fellow, ORBL, Colorado State University
Katja Duesterdieck	Ph.D.	2006	Assistant Professor, Oregon State University
Marti Shearin	D.V.M., Ph.D.	2006	Assistant Doctoral Fellow, University of Tennessee
Valerie Perino	M.S., Ph.D.	2007	Completed Ph.D., Equine Orthopaedic Research, Colorado State University
Sam Hendrix	M.S.	2008	Equine Practice, Utah
Ty Wallis	M.S.	2008	Equine Speciality Practice
Erin Contino	M.S.	2009	Final year DVM student
Ryan Carpenter	M.S.	2009	Equine Practice, Southern California
Jennifer Antonnici	Ph.D.	2010	University of California San Diego
Christina Lee	Post-Doc	2010	
Myra Barrett	M.S.	2010	Assistant Professor CVMBS, CSU
Carrie Adrian	Ph.D.	2011	Director of Rehabilitation Services, VCA Animal Hospitals

Student	Degree	Date Graduated	Current Position
Katrina Easton	D.V.M., Ph.D.	2011	University of Sydney
Melissa King	M.S., Ph.D.	2010/2011	Staff Veterinarian, Orthopaedic Research Center, Clinical Instructor Sports Medicine and Rehabilitation Service, CSU
Katie Seabaugh	M.S.	2011	Assistant Professor, Farm Practices/Field Services, University of Georgia
Lacy Kamm	M.S.	2012	Equine Surgeon, Veterinary Associates, Auckland, New Zealand
Valerie Moorman	Ph.D.	2013	Assistant Professor, Equine Medicine & Surgery, CSU
Ali Daniel	M.S.	2014	Private Referral Practice, Florida
Josh Donnell	M.S.	2015	Residency in Equine Sports Medicine, Colorado State University

Resident	Years of Residency	Date Achieved Board Certification in the American College of Veterinary Surgery
G. W. Trotter	1979-1981	1983
A. J. Nixon	1980-1983	1985
G. S. Martin	1980-1983	1986
R. M. De Bowes	Phase III, 1983-1984	1985
K. Sullins	1981-1984	1986
J. V. Yovich	1983-1986	1987
A. L. Bertone	1983-1986	1988
K.J. Easley	Phase II 1986, Phase III 1986-87	
C. Kobluk	1987-1988	1990
K. T. Gibson	1986-1989	1990
S. B. Gustafson	1986-1989	1990
M. J. Reeves	1986-1989	1990
D. French	1988-1990	1992
J. F. Foland	1989-1991	1994
R. D. Howard	1990-1992	1994
C. R. Ray	1991-1994	1998
C. E. Kawcak	1992-1995	1996
D. D. Frisbie	1993-1996	1999
L. Southwood	1995-1998	2000
T. Trumble	1996-1999	2000
J. Dechant	1997-2000	2001
J. Alldredge	2000-2003	2004
C. Scruton	2001-2004	2004
E. Farstvedt	2002-2005	2005
S. Hendrix	2003-2006	2006
J. Joyce	2005-2007	2007
T. Wallace	2006-2008	2008
R. Carpenter	2007-2009	2010
A. McCoy	2008-2010	2011
K. Seabaugh	2009-2011	2013
L. Kamm	2010-2012	2013
B. Nelson	2010-2013	2014
A. Daniel	2010-2014	2015

PROGRAM SYNOPSIS

History

The Orthopaedic Research Center (ORC) began as a multidisciplinary equine program dedicated to finding methods to treat and prevent equine musculoskeletal disease and injury. Prior to 1984, the program's research was primarily clinical. During this time, many of the techniques for arthroscopic surgery currently used to treat joint problems more effectively and to enable continued athletic function were developed at CSU. We also identified and defined a number of new clinical conditions and documented some of the best methods for diagnosis and treatment. As we developed arthroscopic surgical techniques to treat these clinical conditions, we identified limitations in terms of secondary osteoarthritis (OA) and articular cartilage loss and this led into phase two of our program of finding solutions through scientific research.

A major goal of the program has always been to find solutions to musculoskeletal problems, especially joint injuries and arthritis. The researchers strive to offer the best possible treatment of clinical cases with continual and critical assessment of the results, which are then used to modify treatments and direct the research toward disease prevention. The program's goals are to use state-of-the-art research techniques to find new methods to rehabilitate damaged joints, to prevent or decrease the occurrence of joint disease and musculoskeletal injuries and methods of early detection, and develop better treatments to prevent permanent damage to injured joints and validate manual therapies and rehabilitation techniques.

The ORC now includes the Orthopaedic Bioengineering Research Laboratory (OBRL), and we function as a single unit. The ORC and OBRL, together with the Preclinical Surgical Research Laboratory (previously Small Ruminant Orthopaedic Research), and Orthopaedic Oncology make up the Musculoskeletal Research Program, which is a Program of Research and Scholarly Excellence in the university. This designation was originally granted in 2004, renewed in 2008, and renewed again in 2012. The significant collaborations with the College of Engineering, School of Bioengineering, as well as the Department of Health and Exercise Sciences, has added considerably to our research strengths. In recent years, considerable human-based funding (Orthopaedic Foundation, NIH, and corporate grants) has added to our support.

The most recent addition to our program has been the development of an equine ambulatory sports medicine service and an equine sports medicine and rehabilitation residency program. This followed the accreditation of the new American College of Veterinary Sports Medicine and Rehabilitation specialty and four of our faculty being Charter Diplomates. This has led to both considerable clinical and research advancements in the rapidly emerging field of equine sports medicine and rehabilitation as a specialty.

Research Activities

The following are the research focuses of the ORC. Details of recent and current projects can be found on pages 114-206.

1. Musculoskeletal Tissue Healing

Until a few years ago, we have principally addressed articular cartilage healing and continue to do so, but we have enlarged the focus to include tendons, ligaments, and menisci. For instance, treatments of tendonitis including A-cell therapy, extracorporeal shock wave therapy (ESWT), and mesenchymal stem cell therapies have been assessed and a new traumatic model of tendonitis validated. Projects including a controlled study assessing meniscus repair with mesenchymal stem cells (MSCs) in fibrin, articular cartilage repair with MSCs in autologous platelet-enriched fibrin scaffolds, as well as a clinical study with meniscal injuries in the horse have most recently been published. Other projects include looking at synovial fluid lubricant properties and showing them to be transiently deficient after arthroscopic articular cartilage defect repair with platelet-enriched fibrin with and without MSCs, and the examination of the immunological activity of allogenic equine MSCs.

2. Early Diagnosis of Bone and Joint Disease

This area includes the development of novel imaging techniques (present and future), body fluid biomarkers, and also molecular monitoring. The uses of these early diagnostic techniques include a) Evaluation of the pathogenesis of musculoskeletal disease, b) Early detection of disease processes, and c) Monitoring of therapy, with the long term goal of preventing severe osteoarthritis or failure of joints, tendons, ligaments, and menisci.

Work in biomarkers has progressed into imaging biomarkers with particular emphasis on the use of ultrasonography, MRI and computed tomography (CT) in diagnosing early disease change in the limb. Considerable work has also been accomplished using subject-specific finite element modeling of the equine metacarpal phalangeal joint which helps us better understand the stresses that play a role in injury of this critical joint. Other papers under the focus of Early Diagnosis of Bone and Joint Disease include a study on in vivo diffusion characteristics following perineural injection of the deep branch of the lateral plantar nerve with mepivacaine or iohexol in horses, the use of an inertial measurement unit to assess the effect of forelimb lameness on three-dimensional hoof orientation in horses at a walk and trot and also validate a human cervical spine finite element model for risk assessment of spinal cord injury. Other clinically relevant areas include diagnostic stifle joint arthroscopy using a needle arthroscope in the standing horse, a technique developed at the ORC led by Dr. Frisbie as well as hosting a Havemeyer Foundation funded workshop on equine musculoskeletal biomarkers to assess current knowledge and future needs.

3. Improvement in the Understanding of the Pathogenesis of Exercise-Induced Traumatic Disease

Catastrophic injury is a major problem in the equine athletic industry and we, as well as researchers elsewhere, have demonstrated that the severe fractures and injuries start as microfractures in the subchondral bone. Our ongoing mission is to develop methods of detecting this damage in the clinical patient before it becomes severe, irreversible damage. Exercising horses have been followed with imaging techniques including computed tomography (CT) and MRI, nuclear scintigraphy, defined sentinels of early damage, and fluid biomarkers as a means of identifying horses at risk studied with promising results. Recently, biomechanical and modeling studies have been done to monitor early events in bone disease. Modeling has

been used to look at the pathogenesis of condylar fractures and other disease processes as well as mapping of pressure distribution and articular cartilage thickness in equine joints. Other factors that can potentially contribute to traumatic musculoskeletal injury including race track surface and conformation have also been part of this research focus.

Examples of recent research projects summarized in this section include looking at the impact of race training on volumetric bone mineral density and its spatial distribution in the distal epiphysis of the third metatarsal bone of 2-year-old horses by comparing 2-year-old Thoroughbreds with training compared to untrained controls, a finite element investigation of fracture healing under simulated microgravity loading conditions, evaluation of meniscal mechanics and proteoglycan content in a model of anterior cruciate ligament rupture, and dynamic testing of horseshoe designs with regard to their impact on synthetic and dirt Thoroughbred racetrack materials. We also hosted a second Havemeyer sponsored workshop on equine tendon disease with an overall theme of advances in the understanding of tendinopathies in horses and in humans.

4. Continued Development of Novel Therapies for Traumatic Synovitis, Capsulitis, and Osteoarthritis in the Horse

Objective evaluation of currently available pharmaceutical agents as well as new potential ones have been a significant focus of our work. These evaluations also include examination of specific biological inhibitors including gene therapy, novel protein therapies, and mesenchymal stem cells therapies. These newer therapies offer the potential of inhibiting the disease process sufficiently early so that the need for palliative drugs currently used is decreased.

Recent projects summarized in Summaries of Research Projects include evaluation of an intravenous combination of sodium pentosan polysulfate, N-acetyl glucosamine, and sodium hyaluronan, the use of genomics in drug discovery, a review of the use of firocoxib (Equioxx™) for the treatment of equine osteoarthritis, a comparison of subjective methods to identify mild forelimb lameness and its response to therapy as well as the evaluation of intravenous hyaluronan, sodium chondroitin sulfate and N-acetyl-D-glucosamine combination (Polyglycan®) versus saline for equine osteoarthritis, and development of a new technique for injection navicular bursa so that the bursa can be medicated with minimal risk of puncturing the deep digital flexor tendon (DDFT).

5. Validation of Rehabilitation and Physical Therapy Techniques for Musculoskeletal Disease

This is a newer focus that includes objective assessment of integrative therapies including physical manipulation and acupuncture for management of musculoskeletal disease and pain as well as rehabilitative techniques of swimming under water treadmilling and hyperbaric therapy. This area also includes study of the pathogenesis of musculoskeletal problems biomechanically and using gait analysis (kinetics, kinematics) and electromyography (EMG), as well as novel methods of pain detection.

In recent years, the Orthopaedic Research Center has acquired the personnel and technical abilities to do more sophisticated orthopaedic research and to address critical questions at a more basic level. Development of this expertise has allowed us to use the horse as a model to resolve problems in human arthritis where conditions are comparable to those in horses. This has led to collaborations with human health researchers, foundations, and industry.

Summaries include a chapter reviewing problems of the back and pelvis in the horse and their treatment, the physiologic effects of long term immobilization of the equine distal limb, a review chapter on chiropractic treatment for athletic horses as an equine rehabilitation technique and a review chapter on aquatic rehabilitation.

Impact

As a preeminent equine orthopaedic research program, both nationally and internationally, the Orthopaedic Research Center provides critical new findings of significant clinical impact and has been able to attract talented students who wish to pursue careers in orthopaedic research. Students choose this program because of its excellent reputation and because of the opportunities they have to be involved in research during their under-graduate and pre-veterinary programs. Many pre-veterinary students have served as volunteers in the equine orthopaedic research program over the past 10 years; this allows

students to develop a high level of research expertise during this undergraduate experience. This involvement encourages students to pursue advanced degrees and ultimately research careers rather than traditional private veterinary practice. Our program also impacts undergraduate and pre-veterinary education by applying findings from research studies to clinical veterinary medicine.

The breadth of dissemination of information from the Orthopaedic Research Center is extensive, with information distributed to graduate and undergraduate students in eight Departments within five Colleges at Colorado State University. Many faculty members from these five Colleges who are participants in the Orthopaedic Research Program are internationally recognized; they are therefore able to share research findings worldwide to academia, the equine industry, the scientific community, and private biomedical industry. The ORC's extensive collaboration with the Steadman Philippon Research Institute and biotechnology companies, as well as collaboration in five NIH research grants, has significantly impacted the treatment of humans with orthopaedic injuries and osteoarthritis. Human medicine, as well as veterinary medicine, has been positively affected by the dissemination of the ORC's findings.

Program Trends

1. Faculty and Staff. Over the last 10 years, funding for our orthopaedic research and specialized personnel availability has increased dramatically. Until 1994, orthopaedic research was being performed by faculty members within the Department of Clinical Sciences. Since that time, the ORC research involves fourteen full-time faculty members (including three Bioengineering Faculty) in our Center. To support the work of the Faculty Researchers, we now have eight research associates. We had eight Ph.D. students and six resident M.S. students in the program in 2014. Current funding is around $4 million annually.

2. Facilities. Thanks to generous private donors, the construction of the Gail Holmes Equine Orthopaedic Research Center and the remodeling of the orthopaedic research laboratories was completed 13 years ago. In addition, a state-of-the-art equine MRI facility has been in operation for eight years, and this was also funded by private donations. More recently, a state-of-the-art gait analysis facility has been added and, most recently, the roof of the ORC Laboratories has been replaced as a gabled roof, and further renovations to accommodate expansion of Bioengineering has been done. We have also received three $3 million University Endowed Chairs from Barbara Cox Anthony, Iron Rose Ranch, and Abigail K. Kawananakoa, a $1.5 million Chair in Musculoskeletal Imaging from the estate of Kenneth and Virginia Atkinson, and most recently, a $6 million Presidential Endowed Chair from John and Leslie Malone. We continue to pursue endowed funding to make all of our positions permanent.

3. Further development of an Equine Ambulatory Sports Medicine Service. An equine ambulatory sports medicine service was initiated in 2010, and has now grown to where Drs. Chris Kawcak and Melissa King have been joined by Dr. Mindy Story. There are two research associates, Whitney McMillan and Lindsay Richardson, assisting in this service offering state-of-the-art expertise in equine musculoskeletal problems in athletic horses. Britt Madsen joined the team as an administrative coordinator of the program. We have three equine sports medicine

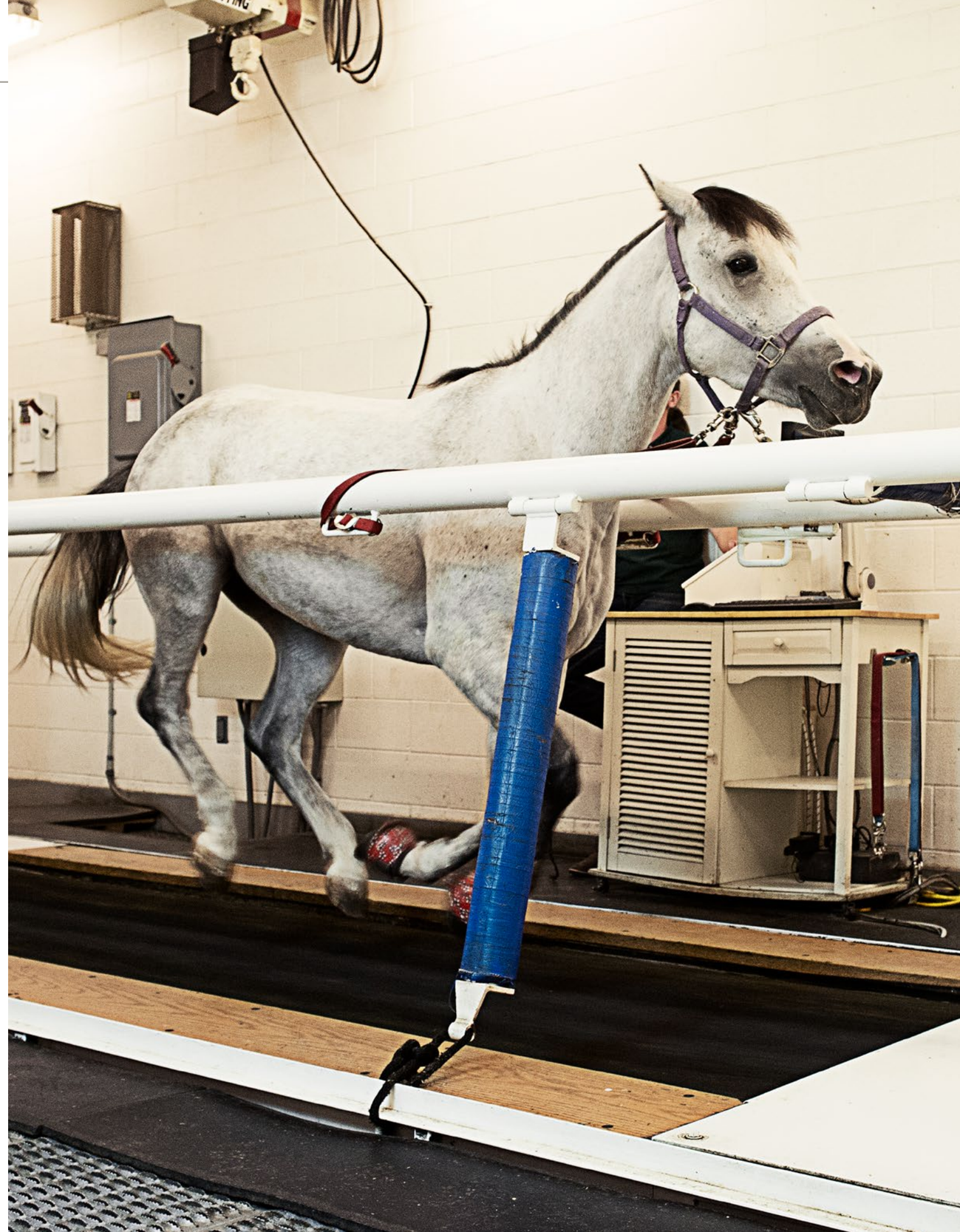
residents (one in each year) and are have graduated our second resident from her three-year program in 2014. The service commenced in 2011 and has continued to exceed our expectations in demand.

4. Establishment of Equine Sports Medicine and Rehabilitation Residencies. A new American veterinary specialty, the American College of Veterinary Sports Medicine and Rehabilitation has been developed and was accredited by the American Veterinary Medical Association in May 2009. There were 27 Charter Diplomates established by a nomination and Delphi election system. Four of our faculty, Drs. McIlwraith, Haussler, Kawcak, and Frisbie, were made Charter Diplomates of the new College. We then established an equine sports medicine and rehabilitation residency program to train future specialists in 2010. Our first resident, Dr. Dora Ferris commenced in July 2010 followed by our second resident, Dr. Erin Contino starting in July 2011, and our third resident Dr. Josh Donnell stared in July 2012.

5. Unrestricted Funding from Donors and Foundations. The period 2014 has been one of continuing to function with good support and further increase in faculty and staff positions. Donor support is critical to our continued operation and growth.

Promotion of Orthopaedic Research Center Faculty and Staff in 2014

Dr. Chris Kawcak has been made Director of Equine Clinical Services. As part of this transition and to maintain his orthopaedic research funding Dr. Valerie Moorman became an Assistant Professor in equine surgery with a major part of her job description being to aid in his research. Dr. Kevin Haussler was promoted to Associate Professor and granted tenure July 1, 2014. Dr. Myra Barrett became a tenure-track Assistant Professor and head of the Equine Imaging Service which includes all modalities of clinical diagnostic imaging of horses, training of diagnostic imaging residents, equine diagnostic imaging interns and fellows and equine sports medicine residents as well as the imaging components of ORC research. This was a major breakthrough as academic institutions have typically had departments of radiology somewhat divorced from the equine clinicians, per se, and certainly not equine focused. Dr. Erin Contino joined our faculty as an equine fellow in imaging and Dr. Tammy Haut Donahue was promoted to full Professor in 2014 as well as being named member-at-large of the Executive Committee of the American Society of Mechanical Engineers Bioengineering Division.



RESEARCH TECHNIQUES AVAILABLE AT THE ORTHOPAEDIC RESEARCH CENTER

The Orthopaedic Research Center at Colorado State University is a comprehensive research facility predominantly focusing on the prevention and repair of orthopedic disease in humans and animals. In addition to protein biomarker analysis and development, this program is supported by several molecular biology applications such as antibody purification, real time PCR assay development and gene expression analysis, cell and tissue culture techniques, adeonviral construction and cloning, gene chip microarray, biomechanical testing, and histological procedures. As the support structure for biomedical research continues to expand with modern medical discoveries and advances, the Orthopaedic Research Center will continue to provide ground-breaking research for the future.

Below is a brief list of the laboratory applications and services provided by the ORC.

1. Biomarker Analysis

Fully equipped to run any commercially available absorbance or fluorescence biomarker immunoassay in 96 or 384-well plate format, using Molecular Devices SpecraMax 384 plus, microplate absorbance/transmittance reader, as well as a Gemini-XS Fluorometer.

Extensive experience with the following biomarker assays:

Detection of Cartilage Markers:

- **Alcian Blue:** Standardize measurement of 35S labeled proteoglycan complexes.
- **C1,C2:** An assay to standardize the measurement of Types I and II collagen degradation.
- **CPII:** An assay to measure type II collagen carboxy propeptide (C-propeptide).
- **CS-846:** Measurement of Aggrecan Chondroitin Sulfate 846 Epitope.
- **Eq. Col 2 ¾ (CEQ):** An assay to quantify equine specific Type II collagen, which has also been proven to work with canine fluid.
- **GAG DMMB:** An assay for standardized measurement of glycosaminoglycans in biological fluids and/or tissues.
- **Pyd Assay:** An assay to standardize measurement of pyridinoline crosslinks in serum and urine.
- **Pyrilinks-D:** To standardize measurement of deoxypyridinoline crosslinks in urine.
- **TCA:** Assay to measure 3H content in media or cartilage digested samples.
- **YKL-40:** Assay for measurement of YKL-40, human cartilage glycoprotein 39, in serum.

Detection of Bone Markers:

- **C1,2C:** An assay to standardize measurement of Type I and II collagens (378 assay, MMP1 and MMP13).
- **Metra™ BAP:** Quantification of bone-specific alkaline phosphatase in serum and synovial fluid samples.
- **Metra™ Osteocalcin EIA:** An enzyme immunoassay for the quantification of intact (de novo) osteocalcin.
- **Serum Cross Laps® (CTX):** Assay for the quantification of degradation products of C-terminal telopeptides of Type-I collagen in serum and plasma.

Cytokine Assays:

- **HIL-1ra:** To standardize the measurement of interleukin 1 receptor antagonist concentrations in cell culture supernatant, serum and plasma.
- **IGF:** To standardize the measurement of Insulin-like Growth Factor in Serum, Cell culture and plasma.
- **TGF-α:** An assay to quantify measurement of Transforming Growth Factor-beta in serum, cell culture supernatant, plasma, and urine.
- **TNF-alpha:** An assay to quantify levels of Tumor Necrosis Factor-alpha in serum, plasma, synovial fluid, and cell culture supernatant.
- **IL-10:** An assay to quantify levels of Interleukin-10 in serum, plasma, and cell culture supernatant.
- **PDGF-BB:** An assay to quantify levels of Platelet-Derived Growth Factor-BB subunit in serum, plasma, and cell culture supernatant.
- **PGE2:** An assay to quantify levels of Prostaglandin E2 in serum, plasma, synovial fluid, cell culture supernatant, and urine.

Pre-assay sample processing including:
papain, hyaluronidase, and collogenase digestion, as well as chromatography extraction of synovial fluid, serum, and tissues.

Western, Southern, and Northern Blotting

Many other assays available. Please inquire.

- PDGF-BB: An assay to quantify levels of Platelet-Derived Growth Factor-BB subunit in serum, plasma, and cell culture supernatant.
- PGE2: An assay to quantify levels of Prostaglandin E2 in serum, plasma, synovial fluid, cell culture supernatant, and urine.

2. Biomechanical Testing

Displacement control testing for compressive, tension, and shear material properties

Tissue explants or cell-seeded scaffolds

Light to moderate load cells are suitable for testing small tissue explants or cell-seeded scaffolds

3. Molecular Biology

Evaluation of metabolic activity in living tissues

- Radiolabel protocols available

GeneChip® Microarray Analysis

- Complete Affymetrix GeneChip® 3000 scanner, fluidics 450, and hybridization system

Real Time PCR Analysis

- ABI Prism® 7000 Sequence Detection System
- Optimization of PCR Primers

RNA/DNA Extractions/Isolations

- cDNA synthesis from RNA
- RNA from cells, tissue, or whole blood
- Primer and probe design
- Gel extraction and purification
- Purification of plasmid DNA
- PCR amplification

Isolation of Synoviocytes, Chondrocytes, and Tenocytes

- Cell culture expansion of freshly collected cells

Culturing of Mesenchymal Stem Cells (bone-marrow derived or fat-derived)

- Cell culture expansion of bone-marrow derived or adipose-derived cells, including three-dimensional culturing for clinical use

Adenoviral Vector construction and cell transfection

- The development of adenoviral vectors for the delivery of genes into cells

4. Histology Services

Decalcified tissue histology

Immunohistochemistry

Paraffin and frozen Sectioning and staining of paraffin embedded samples

Histomorphometric analysis

RESEARCH TECHNIQUES AVAILABLE AT THE ORTHOPAEDIC BIOENGINEERING RESEARCH LABORATORY

The Orthopaedic Bioengineering Research Laboratory (OBRL) is an interdisciplinary research and educational effort bringing together engineers, clinicians, biologists, and scientists all over campus. The goal of the laboratory is to provide an environment for undergraduate and graduate education in Biomedical Engineering while advancing treatment and/or prevention of muscular, neuromuscular, cardiovascular, neuronal or skeletal injury and/or disease. The primary research foci include:

1. Computational Simulation of Orthopaedic Conditions and Treatments

a. Finite element analysis
b. Cadaver and animal experiments to validate and augment the computational models

2. Biomaterials Development

a. Enhancing wear resistance of polymeric orthopaedic implant bearing materials
b. Biopolymer derivative synthesis and characterization
c. Bioactive and osteoinductive bone graft materials

3. Engineering and Growth Factor Therapy for Cartilage and Bone Repair

a. In vitro cell culture assessment
b. Animal models development and application to evaluate repair
c. In vitro micro-assessment of mechanics of regenerated and normal tissue
d. Development and assessment of biomaterial carriers

4. Retrieval Analysis for Failure Assessment, Design Improvement, and Tissue Interface

a. Orthopaedic implants
b. Allograft bone composites
c. Synthetic bone graft materials and resorbable biomaterials

5. Biocompatibility and Biomaterial/ Tissue Interface

a. Interface biomechanics
b. Tissue response to biomaterials

6. Comparative Orthopaedics and Animal Models

a. Animal model development and validation
b. Comparison of human and other animal disease mechanisms and treatment efficacy

7. Biomechanical Analysis Equipment available includes: minibionix MTS machine, standard MTS, spine tester, biaxial tester

a. Range of motion/kinematics
b. Materials testing for biomechanical strength
c. Dynamic and Quasi-static analyses
d. Fatigue and life-cycle analyses

8. Histological structural analyses

a. MicroComputedTomography (µCT) – High resolution imaging of bone and / or implants to determine bone growth and healing
b. Decalcified and non-decalcified tissue histology
c. Dynamic and Static Histomorphometric analysis

SCIENTIFIC PUBLICATIONS AND PRESENTATIONS

Textbooks

Kawcak C.E., Parente E.J. McIlwraith and Turner's Equine Surgery Advanced Techniques, 3rd edition. 2014.

McIlwraith C.W., Nixon A.J., Wright I.M. Diagnostic and Surgical Arthroscopy in the Horse, 4th edition. Elsevier, London. 2014.

McIlwraith C.W., Kawcak C.E., Frisbie D.D., van Weeren P.R. Joint Disease in the Horse, 2nd edition. Elsevier. 2015.

Textbook Chapters

Barrett M.F., Frisbie D.D. Stifle. Chapter 25. In, Joint Disease in the Horse, 2nd edition. McIlwraith C.W., Kawcak C.E., Frisbie D.D., van Weeren P.R. (Eds). Elsevier. 2015:346-363.

Barrett M.F., Selberg K.T. Equine Diagnostic Imaging. In, Large Animal Medicine for Veterinary Technicians. Wiley-Blackwell. 2014.

Contino E.K., Mama K. Recognizing Pain in Horses. In, Current Therapies in Equine Medicine, 7th edition. Sprayberry K., Robinson E. (Eds). 2014.

Ehrhart N.P., Culp W. Principles of Biopsy. In, Veterinary Surgical Oncology. Seguin and Kudnig.

Frisbie D.D. Biologic Therapies. Chapter 16. In, Joint Disease in the Horse, 2nd edition. McIlwraith C.W., Kawcak C.E., Frisbie D.D., van Weeren P.R. (Eds). Elsevier. 2015:221-227.

Frisbie D.D. Hyaluronan. Chapter 13. In, Joint Disease in the Horse, 2nd edition. McIlwraith C.W., Kawcak C.E., Frisbie D.D., van Weeren P.R. (Eds). Elsevier. 2015:207-211.

Frisbie D.D. Kawcak C.E., Werpy N.M., Barrett M.F. Distal Limb. Chapter 20. In, Joint Disease in the Horse, 2nd edition. McIlwraith C.W., Kawcak C.E., Frisbie D.D., van Weeren P.R. (Eds). Elsevier. 2015:273-293.

Frisbie D.D., McIlwraith C.W., deGrauw J.C. Synovial Fluid and Serum Biomarkers. Chapter 10. In, Joint Disease in the Horse, 2nd edition. McIlwraith C.W., Kawcak C.E., Frisbie D.D., van Weeren P.R. (Eds). Elsevier. 2015:171-183.

Frisbie D.D., Selberg K.T. The Elbow and Shoulder. Chapter 23. In, Joint Disease in the Horse, 2nd edition. McIlwraith C.W., Kawcak C.E., Frisbie D.D., van Weeren P.R. (Eds). Elsevier. 2015:324-331.

Frisbie D.D., Selberg K.T. The Hip. Chapter 26. In, Joint Disease in the Horse, 2nd edition. McIlwraith C.W., Kawcak C.E., Frisbie D.D., van Weeren P.R. (Eds). Elsevier. 2015:364-367.

Frisbie D.D. Stem Cells. Chapter 17. In, Joint Disease in the Horse, 2nd edition. McIlwraith C.W., Kawcak C.E., Frisbie D.D., van Weeren P.R. (Eds). Elsevier. 2015:228-234.

Haussler K.K. Jeffcott L.B. Back and pelvis. In, Equine Sports Medicine and Surgery, 2nd edition. Hinchcliff K.W., Kaneps A.J., Geor R., (Eds). Elsevier. 2014:419-456.

Haussler K.K., King M.R. Physical Rehabilitation. Chapter 18. In, Joint Disease in the Horse, 2nd edition. McIlwraith C.W., Kawcak C.E., Frisbie D.D., van Weeren P.R. (Eds). Elsevier. 2015:235-261.

Haussler K.K. Equine rehabilitation: Chiropractic treatment for athletic horses. In, Equine Sports Medicine and Surgery, 2nd edition. Hinchcliff K.W., Kaneps A.J., Geor R. (Eds). Elsevier. 2014:1225-1229.

Kawcak C.E., Barrett M.F. Carpus. Chapter 22. In, Joint Disease in the Horse, 2nd edition. McIlwraith C.W., Kawcak C.E., Frisbie D.D., van Weeren P.R. (Eds). Elsevier. 2015:310-323.

Kawcak C.E., Barrett M.F. Fetlock. Chapter 21. In, Joint Disease in the Horse, 2nd edition. McIlwraith C.W., Kawcak C.E., Frisbie D.D., van Weeren P.R. (Eds). Elsevier. 2015:294-309.

Kawcak C.E., Barrett M.F., Werpy N.M., Selberg K.T. Principles of Diagnosis. Chapter 9. In, Joint Disease in the Horse, 2nd edition. McIlwraith C.W., Kawcak C.E., Frisbie D.D., van Weeren P.R. (Eds). Elsevier. 2015:119-170.

Kawcak C.E. Biomechanics in Joints. Chapter 2. In, Joint Disease in the Horse, 2nd edition. McIlwraith C.W., Kawcak C.E., Frisbie D.D., van Weeren P.R. (Eds). Elsevier. 2015:25-32.

Kawcak C.E. Pathologic Manifestations of Joint Disease. Chapter 4. In, Joint Disease in the Horse, 2nd edition. McIlwraith C.W., Kawcak C.E., Frisbie D.D., van Weeren P.R. (Eds). Elsevier. 2015:49-56.

Kawcak C.E. Tarsus. Chapter 24. In, Joint Disease in the Horse, 2nd edition. McIlwraith C.W., Kawcak C.E., Frisbie D.D., van Weeren P.R. (Eds). Elsevier. 2015:332-345.

King M.R., White A. Equine Musculoskeletal Evaluation. In, Physical Therapy evaluation of the Equine Rehabilitation Patient.

Mama K., Contino E.K. Postoperative Pain Control. In, Current Therapies in Equine Medicine, 7th edition. Sprayberry K., Robinson E. (Eds). 2014.

McIlwraith C.W., Frisbie D.D., Kawcak C.E., Goodrich L.R., van Weeren P.R. Equine Joint Disease: Present and Future Directions in Research. Chapter 27. In, Joint Disease in the Horse, 2nd edition. McIlwraith C.W., Kawcak C.E., Frisbie D.D., van Weeren P.R. (Eds). Elsevier. 2015:368-389.

McIlwraith C.W., Frisbie D.D. Nonsteroidal Anti-inflammatory Drugs. Chapter 11. In, Joint Disease in the Horse, 2nd edition. McIlwraith C.W., Kawcak C.E., Frisbie D.D., van Weeren P.R. (Eds). Elsevier. 2015:184-193.

McIlwraith C.W. Intraarticular Corticosteroids. Chapter 12. In, Joint Disease in the Horse, 2nd edition. McIlwraith C.W., Kawcak C.E., Frisbie D.D., van Weeren P.R. (Eds). Elsevier. 2015:194-206.

McIlwraith C.W. Pentosan Polysulfate. Chapter 15. In, Joint Disease in the Horse, 2nd edutuin. McIlwraith C.W., Kawcak C.E., Frisbie D.D., van Weeren P.R. (Eds). Elsevier. 2015:216-220.

McIlwraith C.W. Polysulfated Glycosaminoglycan (Adequan ®). Chapter 14. In, Joint Disease in the Horse, 2nd edition. McIlwraith C.W., Kawcak C.E., Frisbie D.D., van Weeren P.R. (Eds). Elsevier. 2015:212-215.

McIlwraith C.W. Subchondral Cystic Lesions. Chapter 6. In, Joint Disease in the Horse, 2nd edition. McIlwraith C.W., Kawcak C.E., Frisbie D.D., van Weeren P.R. (Eds). Elsevier. 2015:85-90.

McIlwraith C.W. Traumatic Arthritis and Posttraumatic Osteoarthritis in the Horse. Chapter 3. In, Joint Disease in the Horse, 2nd edition. McIlwraith C.W., Kawcak C.E., Frisbie D.D., van Weeren P.R. (Eds). Elsevier. 2015:33-48.

McIlwraith C.W. Use of Oral Joint Supplements in Equine Joint Disease. Chapter 19. In, Joint Disease in the Horse, 2nd edition. McIlwraith C.W., Kawcak C.E., Frisbie D.D., van Weeren P.R. (Eds). Elsevier. 2015:262-272.

Refereed Publications

Doherty A.H., Florant G.L., Donahue S.W. Endocrine Regulation of Bone and Energy Metabolism in Hibernating Mammals. Integr Comp Biol, Feb 19, 2014 [Epub ahead of print].

Abraham, A.C., Pauly, H.M., Haut Donahue, T.L., Deleterious effects of osteoarthritis on the structure and function of the meniscal enthesis, Osteoarthritis and Cartilage. 2014; 22(2):275-83.

Amsellum P.M., Selmic L.E., Wypij J.M., Bacon N.J., Culp W.T., Ehrhart N.P., Powers B.E., Stryhn H., Farese J.P. Appendicular osteosarcoma in small breed dogs- a Veterinary Society of Surgical Oncology retrospective study : 51 cases (1996-2011), J Am Vet Med Assoc. July, 15 2014;245(2):203-10.

Ozbey B., Unal E., Ertugrul H., Erturk V.B., Kurc O., Puttlitz C.M., Altintas A., Demir H.V. Wireless displacement sensing enabled by metamaterial probes for remote structural health monitoring. Sensors. 2014;14:1691-704.

Barrett M.F., McIlwraith C.W., Contino E.K., Park R., Kawcak C.E., zumBrunnen J., Frisbie D.D.. The relationship between radiographic findings and performance outcome in Quarter Horse cutting horses. Vet Radiol Ultrasound. 2014;Submitted.

Gadomski B.C., McGilvray K.C., Easley J.T., Ehrhart E.J., Palmer R.H., Santoni B., Puttlitz C.M. An in vivo ovine model of bone tissue alterations in simulated microgravity conditions. Journal of Biomechanical Engineering. 2014;136:021020.

Gadomski B.C., McGilvray K.C., Easley J.T., Palmer R.H., Santoni B.G., Puttlitz C.M. Partial gravity unloading inhibits bone healing responses in a large animal model. Journal of Biomechanics. 2014;47:2836-42.

Hindman B.J., Santoni B.G., Puttlitz C.M., From R.P., Todd M.M. Intubation biomechanics: laryngoscope force and cervical spine motion during intubation with Macintosh and Airtraq laryngoscopes. Anesthesiology. 2014;121:260-71.

Bogers S.H., Rogers C.W., Bolwell C.F., Roe W.D., Gee E.K., McIlwraith C.W. Impact of race training on volumetric bone mineral density and its spatial distribution in the distal epiphysis of the third metatarsal bone of 2-year-old horses. Vet J. 2014;201:353-358.

Park B., Awasthi D., Chowdhury S.R., Melief E.H., Kumar K., Knudson S.E., Slayden R.A. and Ojima I. Design, Synthesis and Evaluation of Novel 2,5,6-trisubstituted Benzimidazoles Targeting FtsZ as Antitubercular Agents. Bioorganic & Medicinal Chemistry. 2014;22:2602-2612. PMID: 24726304.

Coatney G.A., Abraham A.C., Fischenich K.M., Button K.D., Haut R.C., Haut Donahue, T.L. Efficacy of P188 on GAG Preservation in Lapine Menisci Following In Vivo Blunt Trauma., In Review, Journal of the Mechanical Behavior of Biomedical Materials, September, 2014.

Contino E.K., Barrett M.F., Werpy N.M. Effect of limb positioning on the radiographic appearance of the distal and proximal interphalangeal joint spaces of the forelimbs of horses during evaluation of dorsopalmar radiographs. J Amer Vet Med Assoc. 2014; 244:1186-1190.

Contino E.K., Barrett M.F., Werpy N.W. The effects of limb positioning on mediolateral interphalangeal joint balance as evaluated on dorsopalmar radiographs. J. American Veterinary Assoc. 2014;244:1186–1190.

Contino E.K., King M.R., Valdés-Martínez A., McIlwraith C.W. In vivo diffusion characteristics following perineural injection of the deep branch of the lateral plantar nerve with mepivacaine or iohexol in horses. Equine Vet J. March 10, 2014; doi: 10.1111/evj.12261. [Epub ahead of print].

Culp W.T., Olea-Popelka F., Sefton J Aldridge C.F, Withrow S.J., Lafferty M.H., Rebhun R.B., Kent M.S., Ehrhart N. J Am Vet Med Assoc. November 15, 2014;245(10):1141-6.

Donnell J.R., Frisbie D.D. Use of firocoxib for the treatment of equine osteoarthritis. Veterinary Medicine: Research and Reports. 2014;5:159-168.

Elce Y.A., Goodrich L.R. Deep digital flexor tendon rupture in two horses: A potential complication of comminuted second phalangeal fractures. Equine Veterinary Education. 2014; doi 10.111/eve.12258

Ferris D.J., Frisbie D.D., Kisiday J.D., McIlwraith C.W., Hague B.A., Major M.D., Schneider R.K., Zubrod C.J., Kawcak C.E., Goodrich L.R. Clinical outcome after intra-articular administration of bone marrow derived mesenchymal stem cells in 33 horses with stifle injury. Vet Surg. 2014;43:255-265.

Ferris R.A., Frisbie D.D., McCue P.M. Use of mesenchymal stem cells or autologous conditioned serum to modulate the inflammatory response to spermatozoa in mares. Theriogenology. 2014;82:36-42.

Fischenich K., Coatney G., Haverkamp J., Button K., Decamp C., Haut R.C., Haut Donahue T.L. Evaluation of Meniscal Mechanics and Proteoglycan Content in a Modified ACL Transection Model. Journal of Biomechanical Engineering. July, 2014;136-7. Editor's Choice Award.

Frisbie D.D., Barrett M.F., McIlwraith C.W., Ullmer J. Diagnostic stifle joint arthroscopy using a needle arthroscope in standing horses. Vet Surg. 2014;43:12-18.

Frisbie D.D., Kawcak C.E., McIlwraith C.W., Werpy N.M. Comparing intraarticular polysulfated glycosaminoglycan and triamcinolone acetonide to intraarticular polysulfated glycosaminoglycan along or placebo for treatment of osteoarthritis using an equine experimental model. Vet J. 2014. Submitted.

Frisbie D.D., McIlwraith C.W., Kawcak C.E., Werpy N.M. Evaluation of intravenous hyaluronan, sodium chondroitin sulfate and N-acetyl-D-glucosamine combination versus saline (0.9% NaCl) for osteoarthritis using an equine model. Vet J. Submitted.

Gadomski B.C., McGilvray K.C., Easley J.T., Palmer R.H., Ehrhart E.J, Haussler K.K., Browning J.C., Santoni B.G., Puttlitz C.M. An in vivo ovine model of bone tissue alterations in simulated microgravity conditions. Journal of Biomechanical Engineering. 2014;136 (2):021020-021020-9. doi:10.1115/1.4025854.

Goodrich L.R., Nixon A.J., Conway J.D., Morley P.S., Bladon B.M., Hogan P.M. Dynamic compression plate (DCP) fixation of propagating medial condylar fractures of the third metacarpal/metatarsal bone in 30 racehorses: retrospective analysis (1990-2005). Equine Veterinary Journal. 2014;46:695-700. doi 10.1111/evj 12184.

Grissom M.J., Temple-Wong M.M., Adams M.S., Tom M., Schumacher B.L., McIlwraith C.W., Goodrich L.R., Chu C.R., Sah R.L. Synovial fluid lubricant properties are transiently deficient after arthroscopic articular cartilage defect repair with platelet-enriched fibrin alone and with mesenchymal stem cells. Orthop J Sports Med. 2014.

Harrison S.M., Whitton R.C., Kawcak C.E., Stover S.M., Pandy M.G. Evaluation of a subject-specific finite-element model of the equine metacarpophalangeal joint under physiological load. J Biomech. 2014;47:65-73.

Hemphill D.D., McIlwraith C.W., Samulski R.J., Goodrich L.R. Adeno-associated viral vectors show serotype specific transduction of equine joint tissue explants and cultured monolayers. Sci Rep. 2014;4:5861.

Hill J.A., Story M.R., Surgical repair of a congenital lateral abdominal wall hernia in a neonatal foal. Equine Veterinay Education. 2014;26(10):516-519.

Cummings J.E., Beaupre A.J., Knudson S.E., Liu N., Yu W., Neckles C., Wang H., Khann A., Trunck L.A., Schweizer H.P, Tonge P.J., Slayden R.A. Substituted Diphenyl Ethers as a Novel Chemotherapeutic Platform Against Burkholderia pseudomallei. Antimicrobial Agents and Chemotherapy. 2014;58(2):931. PMID: 24379198.

Cummings J.E., Kingry L.C., Rholl D.A., Schweizer H.P., Tonge P.J. and Slayden R.A. The Burkholderia pseudomallei enoyl-ACP reductase FabI1 is Essential for in vivo Growth and is the Target of a Novel Chemotherapeutic with Efficacy. Antimicrobial Agents and Chemotherapy. 2014;58(2). PMID: 24277048.

Schiebel J., Chang A., Shah S., Lu Y, Liu L, Pan P., Hirschbeck M.W., Tareilus M., Eltschkner S., Yu W., Cummings J.E., Knudson S.E., Bommineni G.R, Walker S.G., Slayden R.A., Sotriffer C.A., Tonge P.J., Kisker C.. Rational Design of Broad-Spectrum Antibacterial Activity based on a Clinically Relevant Enoyl-ACP Reductase Inhibitor. Journal of Biological Chemistry. 2014. [Epub ahead of print]. PMID: 24739388.

Killian M.L., Haut R.C., Haut Donahue T.L. Acute Cell Viability and Nitric Oxide Release in Lateral Menisci Following Closed-Joint Knee Injury in a Lapine Model of Post-Traumatic Osteoarthritis., BMC Musculoskeletal Disorders. 2014;6;15:297.

Labus K.M., Han S.K, Hsieh A.H., Puttlitz C.M. A computational model to describe the regional interlamellar shear of the annulus fibrosis. Journal of Biomechanical Engineering 136:051009.

Koening T.J., Dart A.J., McIlwraith C.W., Horadagoda N., Bell R.J., Perkins N., Dart C., Krockenberger M., Jeffcott L.B., Little C.B. Treatment of experimentally induced osteoarthritis in horses using an intravenous combination of sodium pentosan polysulfate, N-acetyl glucosamine, and sodium hyaluronan. Vet Surg. 2014;43:612-622.

Kopesky P.W., Byun S., Vanderploeg E.J., Kisiday J.D., Frisbie D.D., Grodzinsky A.J. Sustained delivery of bioactive TGF-β1 from self-assembling peptide hydrogels induces chondrogenesis of encapsulated bone marrow stromal cells. J Biomed Mater Res A. 2014;102:1275-1285.

Dreischarf M., Zander T., Shirazi-Adl A., Puttlitz C.M., Adam C.J., Chen C.S., Goel V.K., Kiapour A., Kim Y.H., Labus K.M., Little J.P., Park W.M., Wang Y.H., Wilke H.J., Rohlmann A., Schmidt H. Comparison of eight published static finite element models of the intact lumbar spine: predictive power of models improves when combined together. Journal of Biomechanics. 2014;47:1757-66.

Mahaffey C.A., Peterson M.L., Thomason J.J., McIlwraith C.W. Dynamic testing of horseshoe designs at impact on synthetic and dirt Thoroughbred racetrack materials. Equine Vet J. 2014; doi: 10.1111/evj.12360. [Epub ahead of print].

McIlwraith C.W., Clegg P.D. Science in brief: Report on the Havemeyer Foundation workshop on Equine musculoskeletal biomarkers - current knowledge and future needs. Equine Vet J. 2014;46:651-653.

Miller R.E., Grodzinsky A.J., Barrett M.F., Hung H-H, Frank E.H., Werpy N.M., McIlwraith C.W., Frisbie D.D. Effects of the combination of microfracture and self-assembling peptide filling on the repair of a clinically-relevant trochlear defect in an equine model. J Bone Joint Surg. 2014;96:1601-1609.

Moorman V.J., Reiser R.F, Mahaffey C.A., Peterson M.L., McIlwraith C.W., Kawcak C.E. Use of an inertial measurement unit to assess the effect of forelimb lameness on three-dimensional hoof orientation in horses at a walk and trot. Am J Vet Res. 2014;75:800-808.

Pan P., Knudson S.E., Bommineni G.R., Li H-J, Lai C-T, Liu N., Miguel Garcia-Diaz M., Simmerling C., Patil S.S., Slayden R.A., Tonge P.J. Time-Dependent Diaryl Ether Inhibitors of InhA: Structure-Activity Relationship Studies of Enzyme Inhibition, Antibacterial Activity and in vivo Efficacy. ChemMedChem. 2014;9(4):776-91. PMID: 24616444. Selected Cover Article-100th Issue.

Pietsch R., Wheatley B.B., Haut Donahue T.L., Gilbrech R., Prabhu R., Liao J., Williams L.N. The Anisotropic Compressive Properties of Porcine Muscle Tissue. Journal of Biomechanical Engineering. July 1, 2014. doi 10.1115/1.4028088.

Shetye S., Troyer K., Streijer F., Lee JHT, Kwon B.K., Cripton P., Puttlitz C.M. Nonlinear viscoelastic characterization of the porcine spinal cord. Acta Biomaterialia. 2014;10:792-7.

Seabaugh K.A., Goodrich L.R., Bohn A.A., Morley P.S., Hendrickson D.A. A comparison of peritoneal fluid values in mares following bilateral laparoscopic ovariectomy using a vessel sealing and dividing device versus placement of two ligating loops. Veterinary Journal. 2014;2:297-302. doi 10.1016/

Selmic L.E., Lafferty M.H., Kamstock D.A., Garner A., Ehrhart N.P., Worley D.R. Withrow S.J., Lana S.E. Outcome and prognostic factors for osteosarcoma of the maxilla mandible and calvarium in dogs:183 cases (1987-2010). J Am Vet Med Assoc. October 2014;15;245(8):930-8.

Smith R., McIlwraith C.W., Schweitzer R., Kadler K., Cook J., Caterson B., Dakin S., Heinegård D., Screen H., Stover S., Crevier-Denoix N., Clegg P., Collins M., Little C., Frisbie D.D., Kjaer M., van Weeren P.R., Werpy N.M., Denoix J-M., Carr A., Goldberg A., Bramlage L., Smith M., Nixon A. Advances in the understanding of tendinopathies: A report on the Second Havemeyer Workshop on equine tendon disease. Equine Vet J. 2014;46:4-9.

Shetye S.S., Deault M., Puttlitz C.M.. Biaxial response of ovine spinal cord dura mater. Journal of the Mechanical behavior of Biomedical Materials 2014;34:146-53.

Stewart H., Werpy N.M., McIlwraith C.W., Kawcak C.E. Physiologic effects of long-term immobilization of the equine distal limb. Bone 2014. Submitted.

Knudson S.E., Awasthi D., Kumar K., Carreau A., Goullieux L., Lagrange S., Vermet H., Ojima I., Slayden R.A.. A Trisubstituted Benzimidazole Cell Division Inhibitor with Efficacy Against Mycobacterium tuberculosis. PLOS ONE. 2014;9(4):e93953. PMID: 24736743.

Knudson S.E., Kumar K., Awasthi D., Ojima I., Slayden R.A. In vitro-in vivo Activity Relationship of Substituted Benzimidazole Cell Division Inhibitors with Activity Against Mycobacterium tuberculosis. Tuberculosis (Edinb). 2014;doi:10.1016/j.tube.2014.03.007. [Epub ahead of print]. PMID: 24746463.

Temple-Wong M.M., Sah R.L., Frisbie D.D., McIlwraith C.W. Articular cartilage lubrication with polyglycan: effects in vitro and with in vivo supplementation following osteochondral fracture in the horse. Osteoarthritis Cartilage. 2014. Submitted.

Tuohy J.L., Selmic L.E., Worley D.R., Ehrhart N.P., Wthrow S.J. Outcome following curative-intent surgery for oral melanoma in dogs: 70 cases (1998-2011). J Am Vet Med Assoc. December 1 2014;245:1266-73.

Traynelis V.C., Sherman J., Nottmeier E., Singh V., McGilvray K., Puttlitz C.M., Leahy P.D. Kinetic analysis of anterior cervical discectomy and fusion supplemented with transarticular screws. Journal of Neurosurgery: Spine. 104;20:485-61.

Wakeman K.A., Sanchez C.R., Lung N.P., Barrett M.F., Hersman G.J. MRI of Adult Giraffe's Distal Limbs with Hoof Overgrowth. Journal of Zoo and Wildlife Medicine. 2014.45(3):668-671.

Published Abstracts/Proceedings

Aanstoos M., Rose R., Regan D., Chubb L., Ehrhart N. Mesenchymal Stromal Cell Influence on Pulmonary metastasis after removal of primary osteosarcoma. World Veterinary Orthopaedic Congress. Breckenridge, Colorado. March, 2014.

Adrian A.A., Barrett M.F., Werpy N.M., Kawcak C.E., Goodrich L.R. The Use of Arthroscopy and Ultrasonography for identification of pathologic changes in the equine stifle. Proceedings of the American Association of Equine Practitioners. Salt Lake City, Utah. 2014

Gadomski B.C., McGilvray K.C., EasleyJ.T., PalmerR.H., Puttlitz C.M. Evaluation of Haversian bone fracture healing in simulated microgravity. NASA Human Research Program Investigators' Workshop. Galveston, Texas. February 12-13, 2014.

Gadomski B.C., Lerner Z.F., Browning R.C., Puttlitz C.M. Development and validation of a finite element model of the ovine hindlimb for the investigation of microgravity loading on skeletal tissue healing. 7th World Congress of Biomechanics. Boston, Massachusetts. July 6-11, 2014.

Button K.D., Keikert K.M., DeCamp C.E., Haut Donahue T.L., Haut R.C. Comparison of a Traumatic ACL Rupture Model and Modified Transdection Model to Study Post-Traumatic Osteoarthritis. World Congress on Biomechanics. Boston, Massachusetts, July 2014

Clinton C. Dawson, Susan E. Knudson, Jason E. Cummings, and Richard A. Slayden. The RelBE complex of Mycobacterium tuberculosis is regulated in response to overall metabolic state. Keystone Symposia-Novel Therapeutics to Tuberculosis. Keystone, Colorado. March 30-April 4, 2014.

Donnell J.R., Frisbie D.D., King M.R., Goodrich L.R., Haussler K.K., Hess A.M. Comparison of subjective and objective methods to identify mild forelimb lameness in horses. Association of Equine Practitioners Annual Convention. Salt Lake City, Utah. December 6-10, 2014.

Donnell J.R., Frisbie D.D. Lameness Locator: Man vs Machine. World Veterinary Orthopaedic Congress/Veterinary Orthopaedic Society. Breckenridge, Colorado. March 1-8, 2014:121.

Ehrhart N.P., Rose R., Woodard M., Parkinson L., Chubb L. Efficacy of a Locally-Injected Amnion-Derived Tissue Product in a Murine Model of Implant-Associated Staphlococcus aureus osteomyelitis. World Veterinary Orthopaedic Congress. Breckenridge, Colorado. March, 2014

Ehrhart N.P., Chubb L., Flaumenhaft E., Rose R., Barrett C., Shi Y. Efficacy of Adipose-Derived Stromal Cells on Demineralized Bone Matrix Persist in Critical Sized Bone Defects. World Veterinary Orthopaedic Congress. Breckenridge, Colorado. March, 2014

Ehrhart N.P., Chubb L., Flaumenhaft E., Rose R., Barrett C., Shi Y. Efficacy and Fate of Adipose-Derived Stromal Cells Seeded on Demineralized Bone Matrix Persist in Critical Sized Bone

SCIENTIFIC PUBLICATIONS AND PRESENTATIONS

Defects. Orthopaedic Research Society. New Orleans, Louisiana. March, 2014

Fischenich K., Button K.D., DeCamp C., Haut R.C., Haut Donahue T.L. A Longitudinal Comparison of Mechanical Changes in the Menisci for Two Experimental Models of ACL Injury. World Congress on Biomechanics. Boston, Massachusetts. July, 2014.

Freund K., Aanstoos-Ewan M., Rose R., Webb T., Ehrhart N.P. Quantum dot labeling of canine mesenchymal stromal cells for longitudinal visualization. World Veterinary Orthopaedic Congress. Breckenridge, Colorado. March, 2014

Frisbie D.D., Donnell A.D., Donnell J.R. Western performance horses: what goes wrong in the elite athlete. World Veterinary Orthopaedic Congress/Veterinary Orthopaedic Society. Breckenridge, Colorado. March 1-8, 2014:122.

Frisbie D.D., McCarthy H.E., Archer C.W., Barrett M.F., McIlwraith C.W. Evaluation of articular cartilage progenitor cells for the repair of articular defects in an equine model. European Cells and Materials XV: Cartilage & Disc: Repair and Regeneration. Davos, Switzerland. June 16-18, 2014.

Frisbie D.D., McCarthy H.E., Archer C.W., Barrett M.F., McIlwraith C.W. Evaluation of articular cartilage progenitor cells for the repair of articular defects in an equine model. European Cells and Materials XV: Cartilage & Disc: Repair and Regeneration. Davos, Switzerland. June 16-18, 2014.

Frisbie D.D. Diagnostic arthroscopy of the equine stifle. 23rd European College of Veterinary Surgeons Annual Scientific Meeting. Copenhagen, Denmark. July 3-5, 2014.

Frisbie D.D. General overview of RM treatment options. 17th European Society of Veterinary Orthopaedics and Traumatology Congress. Venice, Italy. October 2-4, 2014.

Frisbie D.D. How to choose cases and utilize mesenchymal stem cells (MSCs) in joint injury. Association of Equine Practitioners Annual Convention. Salt Lake City, Utah. December 6-10, 2014.

Frisbie D.D. May we have the practical RM results, please? 17th European Society of Veterinary Orthopaedics and Traumatology Congress. Venice, Italy. October 2-4, 2014.

Frisbie D.D. Meet the expert session: Tips and tricks in stifle arthroscopy. 23rd European College of Veterinary Surgeons Annual Scientific Meeting. Copenhagen, Denmark. July 3-5, 2014.

Frisbie D.D. Modern diagnostics of joint injuries. 17th European Society of Veterinary Orthopaedics and Traumatology Congress. Venice, Italy. October 2-4, 2014.

Frisbie D.D. Residents Lecture: Investigation and treatment of hock related lameness. 23rd European College of Veterinary Surgeons Annual Scientific Meeting. Copenhagen, Denmark. July 3-5, 2014.

Frisbie D.D. The use of stem cells in equine sports medicine. World Veterinary Orthopaedic Congress/Veterinary Orthopaedic Society. Breckenridge, Colorado. March 1-8, 2014:123.

Frisbie D.D. What do we expect from future RM developments? 17th European Society of Veterinary Orthopaedics and Traumatology Congress. Venice, Italy. October 2-4, 2014.

Frisbie D.D. What surgeons need to know about PRP/ACP. 17th European Society of Veterinary Orthopaedics and Traumatology Congress. Venice, Italy. October 2-4, 2014.

Frisbie D.D. What's new in surgical and medical management of equine osteoarthritis. 23rd European College of Veterinary Surgeons Annual Scientific Meeting. Copenhagen, Denmark. July 3-5, 2014.

Goodrich L.R. Regenerative Medicine and Joint Disease: Thrill of Victory and Agony of Defeat. Colorado Veterinary Medical Association. Loveland, Colorado. 2014.

Goodrich L.R. Lameness originating from the stifle: Complexities and correlations. Colorado Veterinary Medical Association. Loveland, Colorado. 2014.

Goodrich L.R., Chen A.C., Werpy N.M., Kisiday J.D., Morley P., McIlwraith C.W., Sah R.L., Chu C.R. Autologous Platelet Enhanced Fibrin (APEF) compared to APEF with culture expanded bone marrow derived mesenchymal stem cells to enhance cartilage repair in an equine model. Transactions of the 60th Orthopaedic Research Society Meeting. New Orleans, Louisiana. 2014.

Haussler K.K. Equine laser therapy. 8th International Symposium on Veterinary Rehabilitation/Physical Therapy and Sports Medicine. Corvallis, Oregon. 2014:60-62.

Haussler KK. Interaction between lameness and neurologic disease. 8th International Symposium on Veterinary Rehabilitation/Physical Therapy and Sports Medicine. Corvallis, Oregon. 2014:63-65.

Haussler K.K. The use of manual therapies in equine sports medicine. 4th World Veterinary Orthopaedic Congress. Breckenridge, Colorado. 2014:144-145.

Haut Donahue T.L., Fischenich K., Pauly H., Coatne, G., Button K., Haut R C. Two New Experimental Models of Post-Traumatic Knee Joint Injury. World Congress on Biomechanics. Boston, Massachusetts. July, 2014.

Haut Donahue T.L., Pauly H.P. Meniscal Attachment Mechanics and the Effect of Osteoarthritis. World Congress on Biomechanics. Boston, Massachusetts. July, 2014.

Cummings J.E., Knudson S.E., Kumar K., Awasthi D., Ojima I., Slayden R.A. In vitro-in vivo activity relationship of substituted benzimidazole cell division inhibitors with activity against Mycobacteria tuberculosis. Keystone Symposia-Novel Therapeutics to Tuberculosis. Keystone, Colorado. March 30-April 4, 2014.

Kawcak C.E. Advances in equine orthopedic surgery. American College of Veterinary Surgeons Symposium. San Diego, California. October 16-18, 2014.

Kawcak C.E. Developments in IRAP treatment strategies. Regenerative medicine for horses six years after: what happened since 2008? Arbeitsgruppe Pferd. Bonn, Germany. February 7-9, 2014.

Kawcak C.E. Imaging biomarkers in the horse. Dorothy Russell Havemeyer Foundation Symposium on Equine Musculoskeletal Biomarkers. Steamboat Springs, Colorado. September 21-25, 2014:26.

Kawcak C.E. Update on distal interphalangeal joint therapies. American College of Veterinary Surgeons Symposium. San Diego, California. October 16-18, 2014.

King M.R. Effect of underwater treadmill exercise on postural sway in horses with experimentally induced carpal osteoarthritis. ACVS Proceedings. San Diego, California. November, 2014.

King M.R. Influence of aquatic exercise on postural sway characteristics in a model of equine carpal osteoarthritis. AAEP Proceedings. Salt Lake City, Utah. December, 2014.

Kisiday J.D., Tangtrongsup S. Chondrogenic preconditioning of equine bone marrow-derived mesenchymal stem cells in self-assembling peptide hydrogel. Transactions of the 60th Orthopaedic Research Society Meeting. New Orleans, Louisiana. 2014.

Labus K.M., Orozco G.A., García J.J., Puttlitz C.M. An anisotropic model of the biaxial mechanics of brain white matter. 7th World Congress of Biomechanics. Boston, Massachusetts. July 6-11, 2014.

Dreischarf M., Zander T., Shirazi-Adl A., Puttlitz C.M., Adam C.J., Clayton J., Chen C.S., Goel V.K., Kiapour A., Kim Y.H., Labus K.M., Little J.P., Park W.M, Wang Y.H., Wilke H.J., Rohlmann A., Schmidt H. Comparison of eight published lumbar spine finite element models. 7th World Congress of Biomechanics. Boston, Massachusetts. July 6-11, 2014.

McIlwraith C.W. Equine orthopaedic research in horses and the horse-human connection. AVMA Annual Convention. Denver, Colorado. July 25-29, 2014.

McNamara K., Dow S., Chubb L., Ehrhart N.P. Massive Cortical Allografts Elicit Definitive Host

Immune Responses Against Donor Antigens. World Veterinary Orthopaedic Congress. Breckenridge, Colorado. March, 2014

Pauly H.M., Larson B., Button K.D., DeCamp C.E., Haut R.C., Haut Donahue T.L. Micro-Computed Tomography Comparison of Trabecular Bone Changes in Rabbits Following Surgical Transection of the ACL and Menisci or Traumatic Impact to the Tibiofemoral Joint. Transactions of the ORS. New Orleans, Louisiana. March, 2014.

Reiser R.F., Nelson, J., Carter K., Dalton E., Pault J. Effect of load on standing weight-bearing and erector spinae muscle activation asymmetries. Proceedings of the 7th World Congress of Biomechanics. 2014.

Donahue S.W. Naturally occurring models for preventing disuse induced bone loss. 7th World Congress of Biomechanics. Boston, Massachusetts. Podium.

Knudson S.E., Awasthi D., Kumar K., Carreau A., Goullieux L., Lagrange S., Vermet H., Ojima I., Slayden R.A. A Trisubstituted benzimidazole cell division inhibitor with efficacy against Mycobacterium tuberculosis. Keystone Symposia-Novel Therapeutics to Tuberculosis. Keystone, Colorado. March 30-April 4, 2014.

Tangtrongsup S., Kisiday J.D. Effect of dexamethasone concentration and exposure duration on chondrogenic differentiation of equine bone marrow-derived mesenchymal stem cells. Transactions of the 60th Orthopaedic Research Society Meeting. New Orleans, Louisiana. March, 2014.

Wheatley B.B., Fischenich K.M., Haut R.C., Haut Donahue T.L. Mechanical Properties of Healthy and Damaged Menisci through Finite Element Analysis of Indentation. Transactions of the 60th Orthopaedic Research Society Meeting. New Orleans, Louisiana. March, 2014.

Wheatley B.B., Morrow D.A., Odegard G.M., Kaufman, K.R., Haut Donahue, T.L., Inverse Finite Element Analysis for Poroelastic Material Properties of Excised Skeletal Muscle. World Congress on Biomechanics. Boston, Massachusetts. July, 2014.

Zanotto G.M., Barrett M.F., Manchon P., Kawcak C.E. Ultrasonographic morphometric evaluation of hind limb proximal suspensory ligaments of 2-year-old Quarter Horses used for cutting: Preliminary study. American College of Veterinary Radiology. St. Louis, Missouri. October 21-24, 2014.

Oral Presentations

Barrett M.F. The Combined Use of Arthroscopy and Ultrasonography for the Identification of Pathologic Changes in the Equine Medial Femoral Tibial Joint. World Veterinary Orthopedic Congress & Annual Veterinary Orthopedic Society Meeting. Breckenridge, Colorado. 2014.

Barrett M.F. International Cartilage Repair Society Laboratory Skills Course – Animal Models. Lecturer. Colorado State University. Fort Collins, Colorado. August, 2014,

Barrett M.F. Kentucky Veterinary Medical Association. Invited Speaker. Louisville, Tennessee. September, 2014.

Barrett M.F. Potomac Regional Veterinary Conference. Invited Speaker. Baltimore, Maryland. November, 2014.

Barrett M.F. Standing Stifle Arthroscopy and Ultrasound Short Course. Lecturer, Lab Instructor. Colorado State University. Fort Collins, Colorado. August, 2014.

Donahue S.W. Mammalian Hibernation as a Model of Disuse Osteoporosis: The Effects of Physical Inactivity on Bone Metabolism, Structure, and Strength. American Physiological Society's Meeting on Comparative Approaches to Grand Challenges in Physiology. San Diego, California. October 6, 2014.

Haut Donahue T.L. Choosing a Post-Doctoral Mentor: What are the Elements of a Successful Post-doctoral Fellowship. Orthopaedic Research Society Annual Meeting. New Orleans, Louisiana. March, 2014.

Frisbie D.D. Criteria and evaluation of repair tissue in cartilage resurfacing, Practical descriptions of how to create cartilage defects, Case examples and research. Lab: Creation of critically sized cartilage defects using a drill or hand curette in rabbit and horse joints. ICRS 5th Laboratory Skills Workshop. Colorado State University, Fort Collins, Colorado. October 27-29, 2014.

Frisbie D.D. Equine Stifle Specialty Arthroscopy Course. Cornell University, Ithaca, NY. September 5-6, 2014.

Frisbie D.D. Instrument and equipment update including video documentation and still image capture, Standing arthroscopy of the stifle joints and eight hours laboratory. Advanced Arthroscopic Surgery Course. Colorado State University, Fort Collins, Colorado – two hours of lecture. August 23, 2014.

Frisbie D.D. Instrumentation and 4 hours of laboratory. Basic Arthroscopic Surgery Course. Colorado State University, Fort Collins Colorado – one hour of lecture. August, 2014.

Frisbie D.D. Modern diagnostics of joint injuries. 17th European Society of Veterinary Orthopaedics and Traumatology Congress. Venice, Italy. October 2-4, 2014.

Frisbie D.D. General overview of RM treatment options. 17th European Society of Veterinary Orthopaedics and Traumatology Congress. Venice, Italy. October 2-4, 2014.

Frisbie D.D. May we have the practical RM results, please? 17th European Society of Veterinary Orthopaedics and Traumatology Congress. Venice, Italy. October 2-4, 2014.

Frisbie D.D. What do we expect from future RM developments? 17th European Society of Veterinary Orthopaedics and Traumatology Congress. Venice, Italy. October 2-4, 2014.

Frisbie D.D. What surgeons need to know about PRP/ACP. 17th European Society of Veterinary Orthopaedics and Traumatology Congress. Venice, Italy. October 2-4, 2014.

Frisbie D.D. The challenges going forward with equine biomarkers – next steps. Dorothy Russell Havemeyer Foundation Symposium on Equine Musculoskeletal Biomarkers. Steamboat Springs, Colorado. September 21-25, 2014.

Frisbie D.D. Investigation and treatment of hock related lameness. 23rd European College of Veterinary Surgeons Annual Scientific Meeting – Residents Lecture. Copenhagen, Denmark. July 3-5, 2014.

Frisbie D.D. Diagnostic arthroscopy of the equine stifle. 23rd European College of Veterinary Surgeons Annual Scientific Meeting. Copenhagen, Denmark. July 3-5, 2014.

Frisbie D.D. What's new in surgical and medical management of equine osteoarthritis? 23rd European College of Veterinary Surgeons Annual Scientific Meeting. Copenhagen, Denmark. July 3-5, 2014.

Frisbie D.D. Meet the expert session: Tips and tricks in stifle arthroscopy. 23rd European College of Veterinary Surgeons Annual Scientific Meeting. Copenhagen, Denmark. July 3-5, 2014.

Frisbie D.D. Strategies to improve tendon healing. World Veterinary Orthopaedic Congress/Veterinary Orthopaedic Society. Breckenridge, Colorado. March 1-8, 2014.

Frisbie D.D. In-depth: Interactive Lameness, lameness videos: diagnosis and treatment. American Association of Equine Practitioners Annual Convention. Salt Lake City, Utah. December 6-10, 2014.

Frisbie D.D. The Old and the New: A Unique CE Program on Lameness Problems in Performance Horses – Intra-articular medications, Stifle joint problems: diagnosis and treatment, The use of stem cells to treat osteoarthritis and ligament/tendon injuries, Biologics: Clinical indications for PRP, IRAP and Problem case discussions. Lab: diagnostic local anesthetic injection techniques – three hours. McKinlay and Peters Equine Hospital and Zoetis. Newman Lake, Washington. September 26-27, 2014.

Frisbie D.D. A current look at treating joint disease. Bayer Animal Health, Northern California Equine Practitioners. Danville, California. June 26, 2014.

SCIENTIFIC PUBLICATIONS AND PRESENTATIONS

Frisbie D.D. Current outlooks upon stifle conditions and therapies pertaining to the equine athlete, two 1 hour sessions of BioVision wetlab demo. Peninsula Equine Medical Center 12th Annual Symposium/International Society of Equine Locomotor Pathology Menlo Park, California. April 4-6, 2014.

Frisbie D.D. Legend/joint disease discussion. Bayer Animal Health, BEVAC. Austin, Texas. January 31-February 2, 2014.

Adrian A.A., Barrett M.F., Werpy N.M., Kawcak C.E., Goodrich L.R. The Use of Arthroscopy and Ultrasonography for identification of pathologic changes in the equine stifle. Veterinary Orthopedic Society. Breckenridge, Colorado. 2014.

Nelson B.B., Kawcak C.E., Ehrhart E.J., Goodrich L.R. Comparison of radiofrequency probe and sharp transection for the tenoscopic-guided desmotomy of the accessory ligament of the superficial digital flexor tendon. Veterinary Orthopedic Society and 4th World Veterinary Orthopedic Congress. Breckenridge, Colorado. 2014.

Aldrich E., Goodrich L.R., Conway J.D., Monahan M., Valdes-Martinez A. Radiographic localization of the origins and insertions associated with the tendons and ligaments of the equine stifle. American College of Veterinary Surgeons. San Diego, Colorado. 2014.

Nelson B.B., Kawcak C.E., Ehrhart E.J, Goodrich L.R. Comparison of radiofrequency probe and sharp transection for the tenoscopic-guided desmotomy of the accessory ligament of the superficial digital flexor tendon. American College of Veterinary Surgeons. San Diego, California. 2014.

Colbath A.C., Dow S., Phillips J.N., McIlwratih C.W., Goodrich L.R. Comparison of the immunosuppressive properties of allogeneic and autologous equine bone marrow derived mesenchymal stem cells. American College of Veterinary Surgeons. San Diego, California. 2014.

Goodrich L.R., Chen A., Werpy N.M., Kisiday J.D., Morley P., McIlwraith C.W., Sah R.L., Chu C. Autologous platelet enhanced fibrin (APEF) scaffold supports in situ repair in the equine model. American College of Veterinary Surgeons, San Diego CA. 2014.

Goodrich L.R. Advanced arthroscopy surgery for internal fixation of fractures of the carpus and fetlock. Colorado State University Continuing Education Short Course, Fort Collins, Colorado. 2014.

Goodrich L.R. Gene Therapy and Implantation Hydrogels, International cartilage repair Society. 5th ICRS Laboratory skills course for Translational Science, Animal Models. 2014.

Goodrich L.R. Autologous platelet enhanced fibrin (APEF) scaffold supports in situ repair in the equine model. American College of Veterinary Surgeons, Invited Speaker. San Diego, California. 2014.

Goodrich L.R. Lameness originating from the stifle: Complexities and correlations. Colorado Veterinary Medical Association, Invited speaker. Loveland, Colorado. 2014.

Goodrich L.R. Regenerative Medicine and Joint Disease: Thrill of Victory and Agony of Defeat. Colorado Veterinary Medical Association, Invited speaker. Loveland, Colorado. 2014.

Hausler K.K., Focus on the Equine Spine: Advanced Course, Part 2. Eight hours lecture, five hours laboratory. Medical and surgical treatment of equine back problems, Active and passive joint stability, Equine osteopathy, Effects of saddles, saddle pads and riders, The art of equine manual therapy, Exotic animal manual therapy and rehabilitation, Laboratories, Equine chiropractic evaluation and treatment of the axial skeleton. Vledder, Netherlands. April, 2014.

Hausler K.K. Two invited lectures, eight hours laboratory. Laboratory, The horse's neck from A-Z. Equine laser therapy, Interaction between lameness and neurologic disease. 8th International Symposium on Veterinary Rehabilitation/ Physical Therapy and Sports Medicine. Corvallis, Oregon. August, 2014.

Hausler K.K. The use of manual therapies in equine sports medicine. 4th World Veterinary Orthopaedic Congress. Breckenridge, Colorado. March, 2014.

Hausler K.K., Equine Rehabilitation Certificate Program – Module II. Eight hours lecture, eight hours laboratory. College of Veterinary Medicine, University of Tennessee, Knoxville, Tennessee. January. 2014

Hausler K.K. Laboratory–Axial skeleton dissection, Principles and practice of equine manual therapy, Equine spinal evaluation techniques: Thoracolumbar region, Equine spinal evaluation techniques: Head and cervical region, Equine spinal evaluation techniques: Sacropelvic region.

Hausler K.K. Demonstration and Laboratory–Equine spinal evaluation techniques: Observation, palpation and joint mobilization, Pathology of the equine spine and pelvis, Current equine spinal and pelvic research, Current saddle fitting and tack research.

Hausler K.K. Normative sciatic nerve excursion during a modified straight leg raise test. Manual Therapy Canine Rehabilitation Rounds. Colorado State University, Fort Collins, Colorado. April, 2014;19:59-64.

Hausler K.K. Controversies in the treatment of equine back pain, Saddle, saddle pad and rider issues. Student Chapter of the American Association of Equine Practitioners, College of Veterinary Medicine. Iowa State University, Ames, Iowa. April, 2014.

Kawcak C.E. Specimen preparation and histologic processing, Regular and contrast enhanced CT, Case examples and research and 2 afternoon laboratories. Hands-on course & lectures from the lab to the clinic. ICRS 5th Laboratory Skills Course for Translational Science. Colorado State University, Fort Collins, Colorado. October 27-29, 2014.

Kawcak C.E. Arbeitsgruppe Pferd Regenerative medicine for horses six years after: what happened since 2008? Practical workshop. Bonn, Germany. February, 2014.

Kawcak C.E. Standing Stifle Diagnostic Arthroscopy Course – four hours of laboratory. Colorado State University, Fort Collins, Colorado. September, 2014.

Kawcak C.E. Advanced Arthroscopic Surgery Course – four hours of laboratory. Colorado State University, Fort Collins, Colorado. September, 2014.

Kawcak C.E. Basic Arthroscopic Surgery Course – four hours of laboratory. Colorado State University, Fort Collins, Colorado. September, 2014.

Kawcak C.E. Imaging biomarkers in the horse. Dorothy Russell Havemeyer Foundation Symposium on Equine Musculoskeletal Biomarkers. Steamboat Springs, Colorado. September, 2014.

Kawcak C.E. Recent advances in regenerative therapies. Florida Association of Veterinary Practitioners, 10th Annual Promoting Excellence Symposium. Hilton Head, South Carolina. October, 2014.

Kawcak C.E. Lameness case studies – when blocks can be misleading. Florida Association of Veterinary Practitioners, 10th Annual Promoting Excellence Symposium. Hilton Head, South Carolina. October, 2014.

Kawcak C.E. Sports medicine practice philosophy. Oregon Veterinary Medical Association conference. Corvallis, Oregon. March, 2014.

Kawcak C.E. Lameness examination. Oregon Veterinary Medical Association conference. Corvallis, Oregon. March, 2014

Kawcak C.E. Updates on therapies for musculoskeletal injuries. Oregon Veterinary Medical Association conference. Corvallis, Oregon. March, 2014.

Kawcak C.E. Rehabilitation strategies for the equine athlete. Oregon Veterinary Medical Association conference. Corvallis, Oregon. March, 2014.

Kawcak C.E. Diagnostic approach to common foot injuries – focus on internal foot structures. NC State College of Veterinary Medicine, Equine Health Symposium. Raleigh, North Carolina. February, 2014.

Kawcak C.E. Characterization of causes of lameness in the proximal metacarpal and metatarsal regions. North Carolina State College of Veterinary Medicine, Equine Health Symposium. Raleigh, North Carolina. February, 2014.

SCIENTIFIC PUBLICATIONS AND PRESENTATIONS

Kawcak C.E. Rehabilitation of foot and suspensory injuries. North Carolina State College of Veterinary Medicine, Equine Health Symposium. Raleigh, North Carolina. February, 2014.

Kawcak C.E. Anatomy and pathologic changes of equine bones and joints. University of Tennessee Certificate Program in Equine Rehabilitation. Knoxville, Tennessee. January, 2014.

Kawcak C.E. Diseases of equine bones and joints. University of Tennessee Certificate Program in Equine Rehabilitation. Knoxville, Tennessee. January, 2014.

Kawcak C.E. Diagnosis of equine joint disease. University of Tennessee Certificate Program in Equine Rehabilitation. Knoxville, Tennessee. January, 2014.

Kawcak C.E. Treatment of bone and joint disease in horses. University of Tennessee Certificate Program in Equine Rehabilitation. Knoxville, Tennessee. January, 2014.

King M.R. Influence of aquatic exercise on postural sway characteristics in a model of equine carpal osteoarthritis. American Association of Equine Practitioners Annual Convention. Salt Lake City, Utah. December, 2014.

King M.R. Effect of underwater treadmill exercise on postural sway in horses with experimentally induced carpal osteoarthritis. American College of Veterinary Surgeons Annual Convention. San Diego, California. November, 2014.

King M.R. Equine Aquatic Therapy. 8th International Symposium of Veterinary Rehabilitation/Physical Therapy and Sports Medicine. Corvallis, Oregon. August, 2014.

King M.R. Advanced Equine Lameness Evaluation and Current Therapeutic Approaches for Musculoskeletal Disorders. Animal Rehab Institute. Loxahatchee, Florida. January, 2009. February, 2010. January, 2012. January, 2013. February, 2014.

Kisiday J.D. Biochemical techniques for quantifying extracellular matrix; Centrifugation techniques for separating cell populations in blood and bone marrow. International Cartilage Repair Society Workshop. Fort Collins, Colorado. 2014.

McIlwraith C.W. New biological therapies (IRAP™, IRAPII™) and PRP (including ACP®) in equine sports medicine. World Veterinary Orthopaedic Conference, 4th World Veterinary Orthopaedic Congress. Breckenridge, Colorado. March 2-7, 2014.

McIlwraith C.W. Joint injury and repair in horses and translation to humans, Urist Lecture (recipient of the 2014 Marshall Urist Award). Orthopaedic Research Society 60th Annual Meeting. New Orleans, Louisiana. March 15-18, 2014.

McIlwraith C.W. Joint injury and repair in horses and translation to humans. North Carolina One Health Collaborative. North Carolina State University, Raleigh, North Carolina. April 15, 2014.

McIlwraith C.W. USA racetrack surface research, The Gouldie Hour (with Joe Mayhew), Cutting out catastrophic injury, a global view. New Zealand Veterinary Association conference. Hamilton, New Zealand. June 18-20, 2014.

McIlwraith C.W. Managing joint disease with stricter drug restrictions. 4th Jockey Club Welfare and Safety of the Racehorse Summit. Lexington, Kentucky. July 8-9, 2014.

McIlwraith C.W. Translational and regenerative medicine research: SPRI-CSU research and biologic therapies. Steadman Philippon Research Institute Scientific Advisory Committee meeting. Vail, Colorado. July 25-26, 2014.

McIlwraith C.W. Regenerative medicine – Keynote lecture. 2014 ACVSMR/IAVRPT Symposium. Corvallis, Oregon. August 6-8, 2014.

McIlwraith C.W. – Basic Arthroscopic Surgery course – four hours lecture, four hours laboratory. Colorado State University, Fort Collins, Colorado. August 21, 2014.

McIlwraith C.W. Lag screw fixation of carpal slab fractures, Lag screw fixation of condylar fractures, Lag screw fixation of other fractures including frontal fractures of the proximal phalanx, mid-body fractures of the sesamoid bone and sagittal fractures of the proximal phalanx. Advanced Arthroscopic Surgery course in Internal Fixation of Fractures of the Carpus and Fetlock. Colorado State University, Fort Collins, Colorado. August 22, 2014.

McIlwraith C.W. Equine Stifle Specialty Arthroscopy course – five lectures and three laboratories. Cornell University, Ithaca, New York. September 5-6, 2014.

McIlwraith C.W. Introduction and looking back to previous Havemeyer Symposiums and the way forward. 3rd Dorothy Russell Havemeyer Foundation Symposium on Equine Musculoskeletal Biomarkers – organizer and moderator. Clark, Colorado September 21-25, 2014.

McIlwraith C.W. The Ohio State University College Research Seminar Series – Joint injury and repair in horses and translation to humans, forum on funding of equine research with equine section clinicians. September 29, 2014.

McIlwraith C.W. University of Kentucky Hall of Fame Induction, Lexington, Kentucky. Induction speech for Prof. Elwyn Firth, University of Auckland, New Zealand. October 9, 2014.

McIlwraith C.W. Stifle CT and arthroscopy, Update on distal interphalangeal joint (DIP) therapies. American College of Veterinary Surgeons Symposium. San Diego, California. October 18, 2014.

McIlwraith C.W. Animal models, hands on course and lectures from the lab to the clinic – co-organizer and faculty member (three days lecture and labs). ICRS Laboratory Skills Workshop for Translational Science. Colorado State University, Fort Collins, Colorado. October 27-29, 2014.

Moorman V.J. Equine Orthopaedic Research at CSU. CSU Pre-Vet Day. Colorado State University, Fort Collins, Colorado. Fall 2014.

Moorman V.J. Advanced Equine Lab, 3 four hour laboratories on lameness examination, equine abdominal exploratory, basic surgical procedures of the distal limbs. Colorado State University, Fort Collins, Colorado. Fall 2013-2014, Spring 2014.

Moorman V.J. Let's Be Objective About Lameness, didactic lecture. 75th Annual Conference for Veterinarians, Fort Collins, Colorado. April, 2014.

Moorman V.J. Objectifying Equine Lameness, didactic lecture. SAVMA Symposium. Fort Collins, Colorado. March, 2014.

Moorman V.J. Navicular Syndrome: Where Are We Know? Didactic lecture. Third Annual Colorado State University's Equine Symposium. Fort Collins, Colorado. February, 2014.

Moorman V.J. Joint Injection Wetlab, live horse wetlab, Third Annual Colorado State University's Equine Symposium, equine veterinary practitioners; two hours. Fort Collins, Colorado. February, 2014.

Moorman V.J. Clinical Sciences III, didactic lectures on basic hoof care, basic conditions of the hoof, basic reproductive surgeries, equine osteoarthritis, and equine developmental orthopedic disease; third year veterinary students; five hrs. Colorado State University, Fort Collins, Colorado. Fall 2013-2014.

Moorman V.J. Foundations in Veterinary Medicine, Case-based discussion, first and second year veterinary students; four hours per group, two groups per semester. Colorado State University, Fort Collins, Colorado. Fall 2013-2014, Spring 2014.

Moorman V.J. Use of the inertial measurement unit to assess the effect of equine forelimb lameness on three-dimensional hoof orientation at the walk and trot. 41st Annual Conference Veterinary Orthopedic Society/4th World Veterinary Orthopaedic Conference. Poster Presentation. March, 2014.

Puttlitz C.M. Grand Rounds Seminar: Bone fracture technology development for prediction of aberrant healing and issues associated with microgravity. Invited Lecture, Department of Orthopaedic Surgery. University of California, San Francisco, San Francisco, California. April 30, 2014.

Puttlitz C.M. Evaluation of bone fracture healing in simulated microgravity: gearing up to send man/woman to Mars, Department of Exercise

Physiology. Experimental and computational development of a Haversian bone model of simulated microgravity, Mentored Research Program in Space Life Sciences. Invited Lecturer. Texas A&M, College Station, Texas. February 14, 2014.

Reiser R., Nelso, J., Carter K., Dalto E., Pault J. Effect of load on standing weight-bearing and erector spinae muscle activation asymmetries. 7th World Congress of Biomechanics. Boston, Massachusetts. July 6-11, 2014.

Baker B., Reiser R. Bone density in competitive cyclists at the start of the season. American College of Sports Medicine: Rocky Mountain Chapter Annual Meeting. Denver, Colorado. March 28-29, 2014. Student poster award winner.

Notz T., Board W., Browning R., Hunt N., Reiser R. Effects of a corset-style foot and ankle unloading brace on gait biomechanics. American College of Sports Medicine: Rocky Mountain Chapter Annual Meeting. Denver, Colorado. March 28-29, 2014.

Slayden R.A. New tools and strategies for biomarker discovery. Dorothy Russell Havemeyer Foundation Symposium. The Home Ranch, Steamboat Springs, Colorado. September 21-25, 2014.

Slayden R.A. Data Management Action Plan for Biologists. Information Science Technology Center Spring Symposia. Colorado State University, Fort Collins, Colorado. May 2, 2014.

Slayden R.A. Directors Opening Comments. Center for Environmental Medicine Spring Research Symposia. Opening Comments. Colorado State University, Fort Collins, Colorado. April 30, 2014.

Slayden R.A. Bacterial Drug Discovery in Context of the Host. ARBL Seminar Series. Colorado State University, Fort Collins, Colorado. February 17, 2014.

FUNDING, REVENUE AND EXPENSES

Investigators	Sponsor	Title	Period	Amount
Tammy Donahue (Primary PI)-1374; Thomas Heenan Bradley (Co-PI)-1374	DOD-USAF-Air Force	University Engineering Design Challenge Program	7/15/11-7/14/14	$20,000.00
Tammy Donahue (Primary PI)-1374	Mayo Clinic - Rochester	Microsensor for Intramuscular Pressure Measurement	9/10/11-6/30/15	$64,512.00
Tammy Donahue (Primary PI)-1374; Ketul C Popat (Co-PI)-1374	NSF - National Science Foundation	Development of a Novel Bioinspired Fiber Reinforced Hydrogel that Recapitulates Developmental Processes to ...	7/15/13-6/30/15	$215,000.00
Nicole P Ehrhart (Primary PI)-1678	AlloSource	Consulting Task Order #4	1/1/09-12/31/14	$88,000.00
David D Frisbie (Primary PI)-1678; C Wayne McIlwraith (Co-PI)-1678	Indiana University	Gene Transfer Treatment of Articular Cartilage Damage	3/1/12-2/28/14	$11,486.00
David D Frisbie (Primary PI)-1678; C Wayne McIlwraith (Collaborator)-1678; Christopher E Kawcak (Collaborator)-1678; Myra Frances Barrett Frisbie (Collaborator)-1681	LifeNet Health Foundation	Equine Osteochondral Defect Study	2/12/14-2/11/15	$71,324.00
David D Frisbie (Primary PI)-1678	M.I.T. Massachusetts Institute of Tech.	Cartilage Repair Using Self Assembling Peptide Scaffolds	9/1/13-8/31/14	$157,994.00
Laurie R Goodrich (Primary PI)-1678; C Wayne McIlwraith (Collaborator)-1678	AlloSource	The Evaluation of Laser Enhanced Cartilage Discs for the Regeneration of Chondral Defects in the Equine Model - Pilot	5/1/14-6/30/14	$14,193.00
Laurie R Goodrich (Primary PI)-1678; C Wayne McIlwraith (Collaborator)-1678	AlloSource	The Evaluation of Laser Enhanced Cartilage Discs for the Regeneration of Chondral Defects in the Equine Model - In Vivo	6/1/14-7/31/15	$324,904.00
Christopher E Kawcak (Primary PI)-1678; Bradley Bernard Nelson (Co-PI)-1678	Grayson-Jockey Club Research Foundation	Contrast CT for Cartilage Injury in Impact OA Model	4/1/14-3/31/15	$15,000.00
Christopher E Kawcak (Primary PI)-1678; Bradley Bernard Nelson (Co-PI)-1678; C Wayne McIlwraith (Collaborator)-1678; Laurie R Goodrich (Collaborator)-1678; Myra Frances Barrett Frisbie (Collaborator)-1681	Grayson-Jockey Club Research Foundation	Contrast Enhanced CT for Detection of Cartilage Injury	4/1/14-3/31/16	$109,476.00
Christopher E Kawcak	CRC, CVMBS CSU	Postmortem Racing Project	7/1/13-6/30/14	$12,500.00

Investigators	Sponsor	Title	Period	Amount
John D Kisiday (Primary PI)-1678	Morris Animal Foundation	Chondrogenic Priming of Equine Bone Marrow-Derived Mesenchymal Stem Cells	3/1/14-2/28/16	$38,087.00
John D Kisiday (Primary PI)-1678	University of Wyoming	Mesenchymal Stem Cell Differentiation in Composite Hydrogel Tissue Scaffolds	5/1/13-4/30/14	$45,630.00
Ross H Palmer (Primary PI)-1678; Howard B Seim (Co-PI)-1678	Cytex Therapeutics, Inc.	Cytex-Osteochondral Tissue Repair Using 3D Woven Poly Scaffold	9/1/13-8/31/14	$149,384.00
Ross H Palmer (Primary PI)-1678; Jeremiah T Easley (Co-PI)-1678	Prosidyan, Inc.	Evaluation of Novel Bone Graft Substitute Materials in an Ovine Study - Phase 2	1/13/14-1/12/15	$141,204.00
Christian M Puttlitz (Primary PI)-1374	Cayenne Medical, Inc.	Tendon/Bone Interface Augmentation of Primary Rotator Cuff Repair in a Sheep Model - A Pilot Sudy	3/10/14-2/28/15	$53,739.00
Christian M Puttlitz (Primary PI)-1374; Stewart D Ryan (Co-PI)-1678; Raymond Clifton Browning (Co-PI)-1582	NASA - Natl Aeronautics & Space Admin.	A Large Animal Model of Fracture Healing in Simulated Microgravity Environments	8/24/11-8/23/14	$208,373.00
Christian M Puttlitz (Primary PI)-1374; Jens C Eickhoff (Collaborator)-1877	HHS-NIH-National Institutes of Health	Intubation Mechanics of the Stable and Unstable Cervical Spine	5/15/11-2/28/15	$9,925.00
Christian M Puttlitz (Primary PI)-1374; Jens C Eickhoff (Collaborator)-1877	HHS-NIH-National Institutes of Health	Intubation Mechanics of the Stable and Unstable Cervical Spine	5/15/11-2/28/15	$193,694.00
Christian M Puttlitz (Primary PI)-1374; Jens C Eickhoff (Collaborator)-1877	HHS-NIH-National Institutes of Health	Intubation Mechanics of the Stable and Unstable Cervical Spine	5/15/11-2/28/15	$175,371.00
Christian M Puttlitz (Primary PI)-1374; Stewart D Ryan (Co-PI)-1678; Raymond Clifton Browning (Co-PI)-1582	NASA - Natl Aeronautics & Space Admin.	Fracture Healing in Haversian Bone Under Conditions of Simulated Microgravity	8/24/11-8/23/14	$60,000.00
Richard A Slayden (Primary PI)-1682	HHS-NIH-NIAID-Allergy & Infect Diseases	RP-06 Development of Novel Broad Spectrum Chemotherapeutics against Priority Pathogens	5/1/09-4/30/14	$311,632.00
Richard A Slayden (Primary PI)-1682	Stony Brook University	FtsZ Inhibitors for Anti-TB Chemotherapy Novel Antimicrobials Targeting Cell Division	12/1/08-11/30/14	$33,297.00
Richard A Slayden (Primary PI)-1682	Anacor Pharmaceuticals, Inc.	Overcoming Resistance by the Application of Born to Ribosomal Inhibitors	10/16/13-4/16/17	$207,653.00
TOTAL				**$2,732,378.00**

REVENUE AND EXPENSES, FY14

Donations	Amount
Platinum Performance Vet, Inc.	$65,000.00
Jon and Abby Winkelreid Foundation	$66,700.00
Spectravet, Inc.	$15,000.00
Dearcorn, Eric	$10.00
Gail Holmes	$50,184.00
Verdad Foundation	$2,500.00
Dea Family Foundation	$40,000.00
Morgan Stanley Smith Barney Gift Inc.	$10,000.00
Advanced Regnerative Therapies	$5,000.00
King, Wayne C.	$25.00
Boese, Sylvia Linda	$25.00
Dolan, Bonnie	$60.00
Durbin, Charles L.	$50.00
First State Bank of Colorado	$50.00
Guerrieri, Paul	$15.00
Kester, Kenneth H.	$20.00
Dearcorn, Eric	$10.00
Brown, Alta Mae	$25.00
Stevens Humphreys, Mary	$35.00
Lucas, Robert C.	$50.00
William & Karen Ciocchetti LVNG. TR.	$20.00
Allen, Robert Dee	$500.00
Burkholder, Craton R.	$200.00
Davis, Charlie A.	$50.00
Blakeslely, Cindy Sue	$20.00
Bruce, Ardith	$30.00
Ezevich, Paul	$50.00
Micros, Myrna	$15.00
Muller, Jack Duane	$100.00
Pomfret, Michael T.	$30.00
Sharp, Larry	$25.00
Taylor, Art F.	$30.00
Collyer, Paul	$50.00
Shomaker, Wayne J.	$50.00
Cherry Creek Equine	$400.00
Cherry Creek Equine	$50.00
Edwards, Glen	$100.00
Fell, Judy K.	$200.00

Donations	Amount
Johnson, Shelia D.	$20.00
Moore, Lorene	$100.00
Steadman Philippon Research Institute	$15,000.00
Dearcorn, Eric	$10.00
Lemon, Frank	$25.00
Platinum Performance, Inc.	$3,500.00
Rogge, E. Sam	$25.00
O'loughlin, John	$50.00
Celavie Biosciences, LLC	$2,550.00
Gomez, Johnny	$25.00
Grant, Jennifer	$25.00
Stephen Reynolds	$30,000.00
Baker, Sara W.	$25.00
Wiker, Nina Maud	$50.00
Biovision Veterinary Endoscopy	$1,000.00
Ross, Frank	$25.00
Prichard, James Thomas	$100.00
Goodman McIlwraith, Nancy, Lynn	$15,000.00
John M. Sparks DVM, PC	$500.00
The Louis L. Borick Foundation	$150,000.00
Cole, Harvey Warren	$25.00
Mrs. Karen Long	$2,170.00
A.J. and Lynda Scibante Charitable Foundation	$2,170.00
Charles H. Scoggin, M.D.	$2,170.00
Thiry-O'Leary Foundation	$2,170.00
Terri Kinney/Linda Ghent	$20.00
Cash	$20.00
Robert Percival	$40.00
Jennifer Schrader	$50.00
Dr. Allen L. Robinson	$100.00
Dellora A. & Lester J. Norris Foundation	$5,000.00
Kiely, Jeanine Marie	$25.00
Wells, Gordan Wesley	$50.00
Estate of Barbara Cox-Anthony	$395,061.00
Ms. Kathy A. McAlister	$20.00
Julie A. Inghram	$25.00
Oak Creek Ranch	$5,000.00
Oak Creek Ranch	$5,000.00

continued...

Donations	Amount
Glenn T. Hammons, M.D.	$50.00
Stallion Auction FY13	$16,729.00
Ms. Courtney C. Grey	$25.00
Mr. Stephen A. Grove	$25,000.00
Buebel, Gary	$100.00
McCall, Marc R.	$50.00
Dr. Mark C. Rick	$50.00
Estate of Barbara Cox-Anthony	$395,061.00
Total Donations	**$1,330,890.00**

New Endowments	Amount
John and Leslie A. Malone	$6,046,194.00
Total	**$6,046,194.00**

Interest on Endowments	Amount
McIlwraith Scholarship	$6,836.00
Cox Anthony Chair	$150,132.00
Iron Rose Ranch Chair	$145,296.00
Atkinson Chair	$56,008.00
Kawananakoa Chair	$115,448.00
Malone Chair	$155,956.00
Total Interest	**$629,676.00**

Medical Center Clinical Services	Amount
Anesthesia	$25,733.00
Per Diem	$1,913.00
IRAP	$20,683.00
MRI	$38,774.00
PRP	$8,413.00
Shockwave	$13,494.00
Surgery	$58,163.00
Xray	$96.00
Client Services Total	**$167,269.00**

ORC ESM	**$15,086.00**
ORC CORE Lab Revenue	**$3,750.00**

REVENUE AND EXPENSES, FY14

Research Projects	Amount
Indiana Univ Trippel NIH	$129,777.00
University of Wyoming	$45,630.00
MIT	$885,317.00
NexVet	$313,625.00
Arthrodynamics	$115,640.00
Allosource	$339,097.00
Grayson	$124,476.00
Morris	$38,087.00
LifeNet	$71,324.00
Research Accounts Total	**$2,062,973.00**

Continuing Education Activities	**$43,500.00**
Stallion Auction	**$16,729.00**

State Funds	Amount
Kawcak CRC Grant	$16,000.00
PRSE Grant	$24,000.00
State Funds Total	**$40,000.00**

Expenses	Amount
Faculty Salaries	$927,767.00
Research Associate Salaries	$222,028.00
Administrative Salaries	$78,347.00
Residents	$101,000.00
Graduate Student Salaries	$40,000.00
Hourly EORC students	$70,050.00
Total Salaries	**$1,439,192.00**
Faculty Travel	$52,093.00
Building Repairs	$810,000.00
Materials & Supplies	$248,867.00
Other Direct	$652,743.00
Equipment	$54,891.00
Expense Subtotal	**$3,257,786.00**
Facility & Administrative Overhead Costs	$158,222.00
Expense Total	**$3,416,008.00**
ACCOUNT BALANCE	**$893,865.00**

HEADLINES

NEWS 2014

Philanthropists John and Leslie Malone, fascinated by the healing power of stem cells, have committed a record $42.5 million to Colorado State University to develop regenerative medical therapies for animals and people.

John and Leslie Malone with Maikel

It is the largest cash gift in university history, a remarkable commitment to improved human and animal health and well-being.

The donation will launch the CSU Institute for Biologic Translational Therapies to investigate next-generation remedies based on living cells and their products, including patient-derived stem cells, to treat musculoskeletal disease and other ailments. Colorado State veterinarians are experts at analyzing medical treatments for animal patients, then providing knowledge gained to boost human medical advancements; the progression is known as translational medicine and is successful because of similarities in animal and human physiology and disease.

"We are tremendously grateful to John and Leslie Malone for their generous philanthropy, foresight and dedication to scientific discovery," Colorado State President Tony Frank said. "In addition to being the largest cash gift in the university's history, their commitment positions us to build on our foundation as a leader in translational medicine, where advances in veterinary medicine very rapidly move into the sphere of benefitting human health."

The new institute will be unique in its focus on developing regenerative treatments from inception in the laboratory setting, through clinical trials, to commercialization of new technologies.

Malones' horses inspire gift

The largesse was inspired in part by stem-cell treatments the Malones' world-class dressage horses have received to help repair stressed and injured joints, the couple said. They discussed the gift at their sweeping horse farm near Denver.

"You put so much training into them, it would be wonderful to have them enjoy their health for a longer period," Leslie Malone said. She led through her immaculate barn a promising dressage competitor named Blixt, a gelding that suffered lameness, underwent successful arthroscopic surgery at the Colorado State Orthopaedic Research Center, received stem-cell injections, and now is back to training.

"We think this whole area of research is very exciting in what it portends for humans and animals," John Malone said. "When you say, 'Who's in the best position to do something about this?' – to take cutting-edge research and apply it pragmatically to the problems we see that people and horses are encountering on a day-to-day basis – it became pretty logical. CSU was the right place to go."

The Malones' gift will provide $10 million for operations and $32.5 million for construction of an institute building, to feature laboratories, specialized surgical suites, and conference space for veterinarians and physicians. The lead gift requires $32.5 million in matching donations for building construction.

Gift will shape future therapeutics

"We are truly appreciative and humbled by John and Leslie Malone's contribution to Colorado State University. This is a transformational gift that will make a difference in our society today and in the future," Brett Anderson, vice president for advancement, said.

The Malones, dedicated to dressage and racehorses, first encountered Colorado State through its Orthopaedic Research Center, led by Dr. Wayne McIlwraith, University Distinguished Professor and renowned equine arthroscopic surgeon.

In 2013, the philanthropic couple donated $6 million to endow the Leslie A. Malone Presidential Chair in Equine Sports Medicine, a way to foster prevention, diagnosis and treatment of injuries in performance horses.

They soon focused on the Orthopaedic Research Center's work in biological therapies – with gene therapy, stem cells, specialized tissue replacement and novel proteins. These therapies, used alone and in combination with minimally invasive surgery, could provide more effective and longer-lasting treatment for equine athletes and people with osteoarthritis and orthopaedic injuries.

"We are so thankful for John and Leslie's support and consider them real partners," McIlwraith said.

Veterinary medicine has a unique role

Colorado State has demonstrated the value of treating animal patients with naturally occurring disease as a vital step in developing new treatments for human patients, noted Dr. Mark Stetter, dean of the CSU College of Veterinary Medicine and Biomedical Sciences.

The approach provides a logical and clinically relevant step in the benchtop-to-bedside research path for new therapeutics: Veterinarians design clinical trials to treat animals with chronic or acute illness; knowledge gained in the course of this treatment helps spark new therapies for pets and people.

"We are extremely grateful to Dr. and Mrs. Malone for supporting the unique role of veterinary medicine by so significantly supporting strides in animal medicine that may be translated into new options in human healthcare," Stetter said.

Biological therapies are the next horizon

John Malone, a dedicated athlete in his school days, described his own orthopaedic aches and pains while explaining the vision he and his wife have for advancing regenerative treatments.

"This is a very exciting and very broad area of research, and it's going to pay big dividends in both human and animal medicine," Malone said. "It seems entirely appropriate to assist in the development of this research at one of the top vet schools in the country."

The institute established with the Malones' lead gift will allow Colorado State to vault ahead in its work.

"We've really gone through a transformation in recent years, with more participation in human medicine," said McIlwraith, leader of the Orthopaedic Research Center. "This has occurred because of the comparability of equine joints and equine joint problems with human joint problems, extending into tendon and ligament injuries, which are big concerns in both humans and horses. This new institute takes us to another level with all of this work."

Professor Anthony Hollander

"Stem cells, cartilage and how to save a life"

March 18, 2014

Professor Anthony Hollander, the Arthritis Research UK Professor of Rheumatology and Tissue Engineering at the University of Bristol and head of The School of Cellular and Molecular Medicine, visited Colorado State University in March 2014. He has many years of experience in cartilage biology, and his research is particularly focused on osteoarthritis. He also has more general expertise in the wider fields of stem cells and tissue engineering. In 2010, the Times newspaper ranking of Britain's 100 most important scientists included him at 39th on the list.

Dr. Brian Johnstone, PhD

"Tissue engineering cartilage: – the good, the bad and the ugly"

April 21, 2014

Dr. Brian Johnstone, Ph.D., director of research for the Department of Orthopaedics and Rehabilitation at Oregon Health & Science University, presented a special seminar during his visit to the CSU Gail Holmes Equine Orthopaedic Research Center in April 2014. Dr. Johnstone began his career in skeletal biology in London, U.K., at the Kennedy Institute of Rheumatology, where he subsequently completed his Ph.D. Since coming to the U.S., he has developed a research program centered on stem cell differentiation for musculoskeletal tissues. His laboratory developed the method for in vitro differentiation of stem cells into chondrocytes; a method that was patented and facilitated the field of cartilage tissue engineering from stem cells. He was elected to the presidential line of the Orthopaedic Research Society in 2007 and served as president for 2011-2012.

Peter Millett, MD

"Rotator cuff tears and repairs: state of the art and clinical outcomes"

May 9, 2014

Dr. Peter Millett, surgeon and partner with the Steadman Clinic, specializes in disorders of the shoulder, knee, and elbow. He treats patients with rotator cuff tears, ligament and cartilage injuries, and arthritis, and brings expertise in total shoulder replacement surgery, arthroscopy, and the treatment of shoulder fractures. A particular interest of Dr. Millett's is advanced, arthroscopic surgery where minimally invasive techniques are used to restore damaged ligaments, joints, and bones. His clinical practice is based in Vail, Colo., where he sees approximately 75 patients in the clinical setting and performs approximately 20 shoulder, knee, and elbow surgeries weekly.

Brian Cole, MD, MBA

"Stem Cells, GF, and PRP in the management of OA and Cartilage Defects" and "Overview of cartilage restoration in humans."

June 12, 2014

Dr. Brian Cole is a professor in the Department of Orthopedics with a conjoint appointment in the Department of Anatomy and Cell Biology at Rush University Medical Center in Chicago, Ill. In 2011, he was appointed chairman of surgery at Rush Oak Park Hospital. He is the section head of the Cartilage Research and Restoration Center at Rush University Medical Center, a multidisciplinary program specializing in the treatment of arthritis in young active patients. He also serves as the head of the Orthopedic Master's Program and trains residents and fellows in sports medicine and research.

Sheila Laverty, MVB, MRCVS, Diplomate ACVS

"Imaging the Foal Epiphysis to Understand OCD"

September 26, 2014

Sheila Laverty, full professor in the Department of Veterinary Clinical Sciences, University of Montreal, chief of the Division of Equine Surgery, and director of the Comparative Orthopaedic Research Laboratory, presented the seminar "Imaging the foal epiphysis to understand OCD." She is a Diplomate of the American and European Colleges of Veterinary Surgery, and her recent honors include the institutional Pfizer research excellence awards in 2002 and 2009. She was co-theme leader of the Diagnostics and Therapeutics theme of the Canadian Arthritis Network (a research center of excellence - 150 researchers - funded by the Canadian government for 12 years to study osteoarthritis in people) and also served on its research advisory and management committees. She is also theme leader of the musculoskeletal section of Thécell (Quebec government- funded cell therapy research network).

Andy Christenson

"3D Printing in Medicine and Virtual Surgical Planning".

November 18, 2014

Andy Christensen is the vice president of Personalized Surgery & Medical Devices at 3D Systems. He works to create a more cohesive health care offering spanning provision of software technology, 3-D printing technology, personalized surgery services, and implant production. He is a current board member of the World Craniofacial Foundation and has been involved with the Society of Manufacturing Engineers Rapid Technologies and Additive Manufacturing technical community for many years. He is also a recipient of the SME/RTAM Industry Achievement Award, a prestigious award given for groundbreaking work in the additive manufacturing industry.

Honors and Awards

Dr. Wayne McIlwraith received the Marshall R. Urist, MD Award from the Orthopaedic Research Society for Excellence in Tissue Regeneration Research in March 2014. As stated by the ORS, “This prestigious award honors an investigator who established him/herself as a cutting-edge researcher in tissue regeneration research and has done so with a sustained ongoing body of focused research in this area of tissue regeneration as it relates to the musculoskeletal system.” This is the first time the award has been given to a veterinarian, and it is a great honor for the research productivity of the ORC.

McIlwraith C.W. Marshall R. Urist, MD Award for Excellence in Tissue Regeneration Research, Orthopaedic Research Society, 2014

McIlwraith C.W. American Association of Equine Practitioners Distinguished Service Award, 2014

Ehrhart, N. Chair World Veterinary Orthopaedic Congress, 2014

Puttlitz C.M. Editor’s Choice: one of the 9 highest impact papers in Journal of Biomechanical Engineering, 2014

Reiser R.F. Best Teacher Award, College of Health and Human Sciences, Colorado State University, 2014

Professional Associations

Barrett, M.F. American College of Veterinary Radiology, American Association of Equine Practitioners, American Veterinary Medical Association, Colorado Veterinary Medical Association, Texas Veterinary Medical Association

Donahue, S.W. American Society of Bone and Mineral Research, American Society of Biomechanics, International Bone and Mineral Society, Orthopaedic Research Society

Haut Donahue, T.L. American Society of Biomechanics, American Society of Mechanical Engineers, Biomedical Engineering Society, Orthopaedic Research Society, American Society for Engineering Education

Ehrhart, N. American Veterinary Medical Association, The American College of Veterinary Surgeons, Veterinary Cancer Society, Veterinary Orthopedic Society

Frisbie, D.D. International Cartilage Research Society, Orthopaedic Research Society, American College of Veterinary Surgeons, American Association of Equine Practitioners, Osteoarthritis Research Society International, American Veterinary Medical Association, Veterinary Orthopaedic Society, American College of Veterinary Sports Medicine and Rehabilitation

Goodrich, L.R. Veterinary AO Society, International Cartilage Repair Society, American Society of Gene, Therapy, Orthopaedic Research Society, American College of Veterinary Surgeons, Veterinary Orthopedic Society, California Veterinary Medical Association, American Veterinary Medical Association

Haussler, K.K. American Veterinary Medical Association, American College of Veterinary Sports Medicine and Rehabilitation, American Association Equine Practitioners, Colorado Veterinary Medical Association, International Veterinary Academy of Pain Management, Phi Zeta National Honor Society

Kawcak, C.E. AOVET, American Veterinary Medical Association, American Association of Equine Practitioners, American College of Veterinary Surgeons, American College of Veterinary Sports Medicine and Rehabilitation, Osteoarthritis Research Society, International Orthopaedic Research Society, Veterinary Orthopaedic Society

Kisiday, J.D. Orthopedic Research Society

McIlwraith, C.W. Royal College of Veterinary Surgeons, American College of Veterinary Surgeons, American Association of Equine Practitioners, American Veterinary Medical Association, Phi Zeta Veterinary Honor Society, Gamma Sigma Delta Honor Society of Agriculture, Colorado Veterinary Medical Association, Orthopaedic Research Society, Veterinary Orthopaedic Society, American Association of Veterinary Clinicians, European College of Veterinary Surgeons, International Society of Arthroscopy and Knee Surgery, International Cartilage Research Society, American Academy of Orthopaedic Surgeons, American College of Veterinary Sports Medicine and Rehabilitation

Moorman, V.J. American College of Veterinary Surgeons, American Veterinary Medical Association, American Association Equine Practitioners

Puttlitz, C.M. Orthopaedic Research Society, Cervical Spine Research Society, American Society of Biomechanics, American Society of Mechanical Engineers, International Society of Biomechanics, Spine Arthroplasty Association, North American Spine Society

Reiser, R.F. National Strength and Conditioning Association (NSCA), International Society of Biomechanics in Sports (ISBS), American College of Sports Medicine (ACSM), International Sport Engineering Association (ISEA)

Slayden R.A. American Society of Microbiology, American Chemical Society

Story, M.R. American College of Veterinary Surgeons, American Association of Equine Practitioners, American Veterinary Medical Association, Colorado Veterinary Medical Association, International Veterinary Chiropractic Association

Smooth Talkin Style
2015 NCHA Open Horse of the Year

SUMMARIES OF RESEARCH PROJECTS

Synovial Fluid Lubricant Properties Are Transiently Deficient After Arthroscopic Articular Cartilage Defect Repair With Platelet-Enriched Fibrin Alone and With Mesenchymal Stem Cells

This is a summary of an article published in Orthopedic Journal of Sports Medicine, by Drs. M.J. Grissom, M.W. Temple-Wong, M.S. Adams, B.L. Schumacher, C.W. McIlwraith, L.R. Goodrich, C.R. Chu and R.L. Sah. Orthop J Sports Med. 2014 Jul;2(7). doi: 10.1177/2325967114542580.

Take Home Message

We found that synovial fluid lubrication is deficient shortly following arthroscopic cartilage repair surgery, and supplementation with high molecular weight hyaluronan (HA) may be beneficial. The patellofemoral joint of horses can be operated on arthroscopically, and is analogous to surgical repair of cartilage damage in the human knee joint.

Introduction

Following various types of naturally occurring traumatic injury to an articular joint, the lubricating ability of synovial fluid is impaired. We see this damage through change (indicators) in the concentration and structure of lubricant molecules, hyaluronan (HA) and proteoglycan-4 (PRG4).

Our objectives were to compare these indicators at the pre-injury state, again at 10 days, and at 3 months following surgery to create chondral defects. We looked at friction of normal cartilage-on-cartilage boundaries, the concentration and quality of HA and PRG4 and molecular weight, the relationship between lubrication function and composition, and the ability of certain HA to restore lubricating ability in samples deficient in lubrication function.

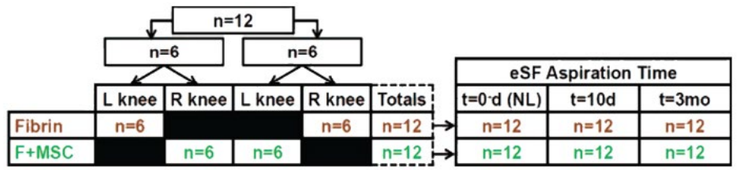
Materials and Methods

Bilateral experimental cartilage defects (15 mm in diameter) were created by removing cartilage including the calcified layer and extending down to, but not through, the subchondral bone in the stifle of adult horses. One side was injected with prepared Fibrinogen and the other with Fibrinogen plus Mesenchymal stem cells. Three times these joints were aspirated for equine synovial fluid, day 0, day 10 and 3 months following surgery to be tested.

Results

The composition of the synovial fluid samples from left and right knees of individual animals were similar in the initial preinjury state, Day 0.

Boundary lubrication function was diminished 10 days after surgery and returned to normal at the 3 month post-surgery check. This lubrication deficiency of equine synovial fluid for the Day 10 samples was associated with decreased concentration of HA, with a shift toward lower Molecular Weight forms of HA, as well as increases in volume, increased concentration of protein, and increased concentration of PRG4.



Discussion

The finding of time-dependent alterations in lubrication after surgery is consistent with and extends previous studies of properties of synovial fluid after joint injury. The elevated Day 10 coefficient of friction was consistent with observations of diminished lubricating ability obtained from acutely injured horses. The restoration of normal lubricating ability by the long, 3 month, duration postsurgery may be analogous to the normal lubricating properties of equine synovial fluid after chronic injury and human synovial fluid from patients with various grades of osteoarthritis. The finding of the decrease in HA concentration and shift in HA toward low-molecular weight forms at 10 days postsurgery provides new information with potential therapeutic implications.

The finding that the in vitro addition of high-molecular weight HA to equine synovial fluid restores lubricant function, suggests that intra-articular lubricant supplementation may help maintain and/or restore the boundary lubrication function of synovial fluid, following arthroscopic joint repair surgery.

References

1. Antonacci JM, Schmidt TA, Serventi LA, et al. Effects of equine joint injury on boundary lubrication of articular cartilage by synovial fluid: role of hyaluronan. Arthritis Rheum. 2012;64:2917-2926.

2. Asari A, Miyauchi S, Sekiguchi T, et al. Hyaluronan, cartilage destruction and hydrarthrosis in traumatic arthritis. Osteoarthritis Cartilage. 1994;2:79-89.

3. Davis WHJ, Lee SL, Sokoloff L. Boundary lubricating ability of synovial fluid in degenerative joint disease. Arthritis Rheum. 1978;21:754-760.

4. Di Marco C, Letizia GA. Hyaluronic acid in the treatment of pain due to knee joint immobilisation. Clin Drug Invest. 1995;10:191-197

Examination of immunologic activity of allogeneic equine mesenchymal stem cells

This is a summary of an article published in the Equine Veterinary Journal by Drs. B. Ranera, D. Antczak, D. Miller, T. Doroshenkova, A. Ryan, W. McIlwraith and F. Barry. Equine Veterinary Journal, 2015. DOI:10.1111/evj.12414.

Take Home Message

The results of this study demonstrate immunosuppression of stimulated lymphocytes by mismatched equine bone marrow-derived MSCs which supports their potential use for clinical treatments with allogeneic MSCs.

Introduction

A number of recent publications have given the take home mesenchymal stem (stromal) cell (MSC) therapy as a treatment for musculoskeletal injury in the horse[1,2], the majority focusing on the use of an autologous MSCs derived from adult tissues.[1,3-5] As well as benefitting the equine field, these studies are of relevance in human stem cell therapies. The use of autologous MSCs has been the focus of attention in publications evaluating articular cartilage repair and tendon healing in horses[6-7] the efficacy of autologous MSCs is also supported by clinical studies in horses[4,8] in experimental evidence that suggests intra-articular therapy at 4 weeks (the period of time required for MSC isolation and expansion) can be beneficial in articular cartilage repair[6] however, earlier treatment might be crucial for recovery[9], an allogeneic MSCs (allo-MSCs) offered immediate available treatment. There have been recent preclinical studies of equine allo-MSCs[10-12], but there are no reports on the safety and efficacy of the therapy in the horse.

The benefits of in vivo MSC treatments appear to be closely associated with trophic factors released by the cells, rather than their ability to differentiate.[13] Moreover, MSCs display 2 important properties related to the host immune system that might contribute positively to their effects following transplantation, namely immunomodulatory effects and lack of immunogenicity.[14] Absence of the major histocompatibility complex (MHC) II molecule and co-stimulatory antigen CD86 on the surface of the equine MSCs[10] prevents triggering of an immune response. Thus, allo-MSC treatments may not produce an inflammatory response.

The aim of this study was to determine the immunoregulatory effects of equine bone-marrow-derived MSCs (BM-MSCs) on MHC-mismatched lymphocytes and their influence on the T cells subsets in an in vitro system prior to clinical application.

Materials

In an in vitro experiment phytohaemagglutinin-stimulated peripheral blood mononuclear cells (PBMCs) from 3 Thoroughbreds (recipients) were co-cultured with mismatched BM-MSCs from 3 Connemara ponies (donors). Proliferation of lymphocytes was monitored by carboxyfluorescein succinimidyl ester labelling and analyzed by flow cytometry. In total, 6 horses were haplotyped using microsatellites to confirm mismatching. Optimization of the conditions to stimulate Thoroughbred lymphocytes and titration of equine anti-CD4 and anti-CD8 antibodies were performed. Connemara pony and Thoroughbred BM-MSCs were isolated, expanded and characterized by tri-lineage differentiation. Finally, BM-MSCs from both breeds were set up in co-culture at different ratios with stimulated Thoroughbred lymphocytes. Proliferation of CD4+ and CD8+ cells was determined by flow cytometry.

Results

A high proportion of CD4/CD8 double-positive lymphocytes were found in freshly isolated PBMCs, although this percentage decreased after 4 days of culture. Mismatched BM-MSCs inhibited proliferation of stimulated lymphocytes in a dose-dependent manner, with the greatest suppression occurring at a 1:10 ratio of BM-MSCs to PBMCs. Proliferation of CD4+ and CD8+ subpopulations decreased in 1:10 co-culture, with statistical significance in the case of CD8+ cells, while that of the CD4/CD8 double-positive population was similar to the phytohaemagglutinin control.

Discussion

Similar to human and mouse cells[15-40] equine MHC-mis-matched MSCs were able to inhibit the proliferation of T lymphocytes in vitro. Several studies using MSCs from different sources have indicated that this occurs in a dose-dependent manner.[41-42] The majority of the cells including the MSCs express the MHC 1 molecule which is actively involved in the rejection of transplants. Thus, the inhibition of the equine cytotoxic T cells by BM-MSCs might be advantageous for allogeneic transplant due to the injected MSCs reducing the presence of cytotoxic T cells from the host at the site of injection, thus avoiding lysis and therefore being able to exert their beneficial properties for longer[43] however, CD4/CD8 double-positive lymphocytes displayed similar proliferation with and without MB-MSCs without altering their proportion in the total lymphocytes. This population has never been studied before in co-culture systems with BM-MSCs; their stability might indicate that none of the factors released by the cells in the co-culture affects the differentiation to a single-positive lymphocyte subset.

In summary, we analysed the immunosuppressive capability of equine BM-MSCs on stimulated PBMCs from MHC-mismatched horses using the CFSE-labelling technique. We demonstrated that equine BM-MSCs were able to suppress the proliferation of stimulated PBMCs because the CFSE profile showed a reduction in the number of generations of lymphocytes in the stimulation index decreased in the presence of BM-MSCs. This immunosuppression occurred in a dose-dependent fashion, with the most marked inhibition at the ratio of 1:10, and in a MHC-independent way, because the autologous and allogeneic BM-MSCs exhibited a similar capability to inhibit proliferation. These in vitro results are an important step towards performing clinical studies and demonstrating that treatment for musculoskeletal injuries based on allogeneic MSCs is safe and beneficial.

Conclusions

The results demonstrate dose-dependent immunosuppression of stimulated lymphocytes by mismatched equine BM-MSCs, supporting their future application in allo-MSC clinical treatments.

References

1. Frisbie, D.D. and Smith, R.K. (2010) Clinical update on the use of mesenchymal stem cells in equine orthopaedics. Equine Vet. J. 42, 86-89.

2. Schnabel, L.V., Fortier, L.A., McIlwraith, C.W. and Nobert, K.M. (2013) Therapeutic use of stem cells in horses: which type, how, and when? Vet. J. 197, 570-577.

3. de Mattos Carvalho, A.B., Badial, P.R., Álvarez, L.E.C., Yamada, A.L.M., Borges, A.S., Deffune, E. Hussni, C.A., Alves, A.L.G. (2013) Equine tendonitis therapy using mesenchymal stem cells and platelet concentrates: a randomized controlled trial. Stem Cell Res. Ther. 4, 84.

4. Ferris, D.J., Frisbie, D.D., Kisiday, J.D., McIlwraith, C.W., Hague, B.A., Major, M.D., Schneider, R.K., Zubrod, C.J., Kawcak, C.E. and Goodrich, L.R. (2014) Clinical outcome after intra-articular administration of bone marrow derived mesenchymal stem cells in 33 horses with stifle injury. Vet. Surg. 43, 255-265.

5. Smith, R.K., Werling, N.J., Dakin, S.G., Alam, R., Goodship, A.E. and Dudhia, J. (2013) Beneficial effects of autologous bone marrow-derived mesenchymal stem cells in naturally occurring tendinopathy. Plos One 8, e75697.

6. McIlwraith, C.W., Frisbie, D.D. and Kawcak, C.E. (2012) Evaluation of intramuscularly administered sodium pentosan polysulfate for treatment of experimentally induced osteoarthritis in horses. Am. J. Vet. Res. 73, 628-633.

7. Schnabel, L.V., Lynch, M.E., van der Meulen, M.C., Yeager, A.E., Kornatowski, M.A. and Nixon, A.J. (2009) Mesenchymal stem cells and insulin-like growth factor-I gene-enhanced mesenchymal stem cells improve structural aspects of healing in equine flexor digitorum superficialis tendons. J. Orthop. Res. 27,1392-1398.

8. Godwin, E.E., Young, N.J., Dudhia, J., Beamish, I.C. and Smith, R.K. (2012) Implantation of bone marrow-derived mesenchymal stem cells demonstrates improved outcome in horses with

overstrain injury of the superficial digital flexor tendon. Equine Vet. J. 44, 25-32.

9. Richardson, L.E., Dudhia, J., Clegg, P.D. and Smith, R. (2007) Stem cells in veterinary medicine – attempts at regenerating equine tendon after injury. Trends Biotechnol. 25, 409-416.

10. Carrade, D.D., Owens, S.D., Galuppo, L.D., Vidal, M.A., Ferraro, G.L., Librach, F.,Buerchler, S., Friedman, M.S., Walker, N.J. and Borjesson, D.L. (2011) Clinicopathologic findings following intra-articular injection of autologous and allogeneic placentally derived equine mesenchymal stem cells in horses. Cytotherapy 13, 419-430.

11. Lange-Consiglio, A., Tassan, S., Corradetti, B., Meucci, A., Perego, R., Bizzaro,D. and Cremonesi, F. (2013) Investigating the efficacy of amnion-derived compared with bone marrow-derived mesenchymal stromal cells in equine tendon and ligament injuries. Cytotherapy 15, 1011-1020.

12. Pigott, J.H., Ishihara, A., Wellman, M.L., Russell, D.S. and Bertone, A.L. (2013) Inflammatory effects of autologous, genetically modified autologous, allogeneic, and xenogeneic mesenchymal stem cells after intra-articular injection in horses. Vet. Comp. Orthop. Traumatol. 26, 453-460.

13. Caplan, A.I. (2007) Adult mesenchymal stem cells for tissue engineering versus regenerative medicine. J. Cell. Physiol. 213, 341-347.

14. Le Blanc, K. and Ringden, O. (2007) Immunomodulation by mesenchymal stem cells and clinical experience. J. Intern. Med. 262, 509-525.

15. Djouad, F., Plence, P., Bony, C., Tropel, P., Apparailly, F., Sany, J., Noël, D. and Jorgensen, C. (2003) Immunosuppressive effect of mesenchymal stem cells favors tumor growth in allogeneic animals. Blood 102, 3837-3844.

16. Di Nicola, M., Carlo-Stella, C., Magni, M., Milanesi, M., Longoni, P.D., Matteucci, P., Grisanti, S. and Gianni, A.M. (2002) Human bone marrow stromal cells suppress T-lymphocyte proliferation induced by cellular or nonspecific mitogenic stimuli. Blood 99, 3838-3843.

17. Maccario, R., Podesta, M., Moretta, A., Cometa, A., Comoli, P., Montagna, D., Daudt, L., Ibatici, A., Piaggio, G., Pozzi, S., Frassoni, F. and Locatelli, F. (2005) Interaction of human mesenchymal stem cells with cells involved in alloantigen-specific immune response favors the differentiation of CD4+ T-cell subsets expressing a regulatory/suppressive phenotype. Haematologica 90, 516-525.

18. Bartholomew, A., Sturgeon, C., Siatskas, M., Ferrer, K., McIntosh, K., Patil, S., Hardy,W., Devine, S., Ucker, D., Deans, R., Moseley, A. and Hoffman, R. (2002) Mesenchymal stem cells suppress lymphocyte proliferation in vitro and prolong skin graft survival in vivo. Exp. Hematol. 30, 42-48.

19. Sullivan, C., Murphy, J.M., Griffin, M.D., Porter, R.M., Evans, C.H., O'Flatharta, C., Shaw, G. and Barry, F. (2012) Genetic mismatch affects the immunosuppressive properties of mesenchymal stem cells in vitro and their ability to influence the course of collagen-induced arthritis. Arthritis Res. Ther. 14, R167.

20. Ibrahim, S., Saunders, K., Kydd, J.H., Lunn, D.P. and Steinbach, F. (2007) Screening of anti-human leukocyte monoclonal antibodies for reactivity with equine leukocytes. Vet. Immunol. Immunopathol. 119, 63-80.

21. Tseng, C.T., Miller, D., Cassano, J., Bailey, E. and Antczak, D.F. (2010) Identification of equine major histocompatibility complex haplotypes using polymorphic microsatellites. Anim. Genet. 41, Suppl. 2, 150-153.

22. Ranera, B., Remacha, A.R., Álvarez-Arguedas, S., Castiella, T., Vázquez, F.J., Romero, A., Zaragoza, P., Martín-Burriel, I. and Rodellar, C. (2013) Expansion under hypoxic conditions enhances the chondrogenic potential of equine bone marrow-derived mesenchymal stem cells. Vet. J. 195, 248-251.

23. Borjesson, D.L. and Peroni, J.F. (2011) The regenerative medicine laboratory: facilitating stem cell therapy for equine disease. Clin. Lab. Med. 31,109-123.

24. Burk, J., Badylak, S.F., Kelly, J. and Brehm, W. (2013) Equine cellular therapy –from stall to bench to bedside? Cytometry A 83, 103-113.

25. Ranera, B., Lyahyai, J., Romero, A., Vázquez, F.J., Remacha, A.R., Bernal, M.L., Zaragoza, P., Rodellar, C. and Martín-Burriel, I. (2011) Immunophenotype and gene expression profiles of cell surface markers of mesenchymal stem cells derived from equine bone marrow and adipose tissue. Vet. Immunol. Immunopathol. 144, 147-154.

26. Ranera, B., Ordovás, L., Lyahyai, J., Bernal, M.L., Fernandes, F., Remacha, A.R., Romero, A., Vázquez, F.J., Osta, R., Cons, C., Varona, L., Zaragoza, P., Martín-Burriel, I. and Rodellar, C. (2012) Comparative study of equine bone marrow and adipose tissue-derived mesenchymal stromal cells. Equine Vet. J. 44, 33-42.

27. Muul, L.M., Heine, G., Silvin, C., James, S.P., Candotti, F., Radbruch, A. and Worm, M. (2011) Measurement of proliferative responses of cultured lymphocytes. Current Protocols in Immunology. 7.10.1-7.10.26.

28. Rasooly, L., Rose, N.R., Shah, D.B. and Rasooly, A. (1997) In vitro assay of Staphylococcus aureus enterotoxin A activity in food. Appl. Environ. Microbiol. 63, 2361-2365.

29. Le Blanc, K., Tammik, L., Sundberg, B., Haynesworth, S.E. and Ringden, O. (2003) Mesenchymal stem cells inhibit and stimulate mixed lymphocyte cultures and mitogenic responses independently of the major histocompatibility complex. Scand. J. Immunol. 57, 11-20.

30. Cavatorta, D.J., Erb, H.N. and Felippe, M.J. (2012) Activation-induced FoxP3 expression regulates cytokine production in conventional T cells stimulated with autologous dendritic cells. Clin. Vaccine Immunol. 19, 1583-1592.

31. Horohov, D.W., Kydd, J.H. and Hannant, D. (2002) The effect of aging on T cell responses in the horse. Dev. Comp. Immunol. 26, 121-128.

32. Wattrang, E., Palm, A.K. and Wagner, B. (2012) Cytokine production and proliferation upon in vitro oligodeoxyribonucleotide stimulation of equine peripheral blood mononuclear cells. Vet. Immunol. Immunopathol. 146, 113-124.

33. Park, S.A., Reilly, C.M., Wood, J.A., Chung, D.J., Carrade, D.D., Deremer, S.L., Seraphin, R.L., Clark, K.C., Zwingenberger, A.L., Borjesson, D.L., Hayashi, K., Russell, P. and Murphy, C.J. (2013) Safety and immunomodulatory effects of B. Ranera et al. Properties of allogeneic mesenchymal stem cells Equine Veterinary Journal •• (2015) ••–•• © 2015 EVJ Ltd 7 allogeneic canine adipose-derived mesenchymal stromal cells transplanted into the region of the lacrimal gland, the gland of the third eyelid and the knee joint. Cytotherapy 15, 1498-1510.

34. Wagner, B., Hillegas, J.M. and Antczak, D.F. (2006) A monoclonal antibody to equine interleukin-4. Vet. Immunol. Immunopathol. 110, 363-367.

35. Bismarck, D., Schütze, N., Moore, P., Büttner, M., Alber, G. and Buttlar, H. (2012) Canine CD4+CD8+ double positive T cells in peripheral blood have features of activated T cells. Vet. Immunol. Immunopathol. 149, 157-166.

36. Blue, M.L., Daley, J.F., Levine, H. and Schlossman, S.F. (1985) Coexpression of T4 and T8 on peripheral blood T cells demonstrated by two-color fluorescence flow cytometry. J. Immunol. 134, 2281-2286.

37. Luhtala, M., Lassila, O., Toivanen, P. and Vainio, O. (1997) A novel peripheral CD4+CD8+ T cell population: inheritance of CD8α expression on CD4+ T cells. Eur. J. Immunol. 27, 189-193.

38. Pescovitz, M.D., Sakopoulos, A.G., Gaddy, J.A., Husmann, R.J. and Zuckermann, F.A. (1994) Porcine peripheral blood CD4+/CD8+ dual expressing T-cells. Vet. Immunol. Immunopathol. 43, 53-62.

39. Zuckermann, F.A. (1999) Extrathymic CD4/CD8 double positive T cells. Vet. Immunol. Immunopathol. 72, 55-66.

40. Oh, W., Kim, D.S., Yang, Y.S. and Lee, J.K. (2008) Immunological properties of umbilical cord blood-derived mesenchymal stromal cells. Cell. Immunol. 251,116-123.

41. Najar, M., Raicevic, G., Boufker, H.I., Fayyad Kazan, H., De Bruyn, C., Meuleman, N., Bron, D., Toungouz, M. and Lagneaux, L. (2010) Mesenchymal stromal cells use PGE2 to modulate activation and proliferation of lymphocyte subsets: combined comparison of adipose tissue, Wharton's Jelly and bone marrow sources. Cell. Immunol. 264, 171-179.

42. Yañez, R., Lamana, M.L., García-Castro, J., Colmenero, I., Ramírez, M. and Bueren, J.A. (2006) Adipose tissue-derived mesenchymal stem cells have in vivo immunosuppressive properties applicable for the control of the graft-versus-host disease. Stem Cells 24, 2582-2591.

43. Ramasamy, R., Tong, C.K., Seow, H.F., Vidyadaran, S. and Dazzi, F. (2008) The immunosuppressive effects of human bone marrow-derived mesenchymal stem cells target T cell proliferation but not its effector function. Cell. Immunol. 251, 131-136.

RESEARCH | FOCUS 1 - Musculoskeletal Tissue Healing

Evaluation of a subject-specific finite-element model of the equine metacarpophalangeal joint under physiological load

This summary is from a paper by S. Harrison, R. Whitton, C. Kawcak, S. Stover and M. Pandy. J. Biomechanics, 2014; 47:65-73.

Take Home Message

The equine fetlock undergoes a number of different types of injuries, some of which may be life threatening. In order to better understand the mechanisms that cause injury, the investigators developed a computational model of the fetlock joint to better understand the stresses that play a role in injury. This paper shows the normal stresses within the fetlock joint of a galloping horse. The results of this study are leading to development of models that demonstrate the stresses that lead to injury.

Introduction

The metacarpophalangeal (MCP) joint, commonly referred to as the fetlock, is a site that commonly fails and becomes injured in the horse. Osteochondral injuries commonly occur beginning in the palmar aspect of the joint where the cannon bone articulates with the proximal sesamoid bones. Consequently injury at this site can lead to cartilage damage, bone damage, fracture, or catastrophic injury sometimes leading to euthanasia of the horse. These injuries are caused by a phenomenon as repetitive stress injury in which the high number of cyclic loads seen by the joint and the tremendous force placed across the joint combined lead to damage. The chronic tissue level damage ultimately leads to a clinically relevant injury. There are many factors that can lead to injury, such as bone geometry, shoeing, limb conformation and tissue strength. In order to best study the influence of each of these factors on the stresses that lead to injury, a computational model of the MCP was developed. The ultimate goal of this work is to create a computational model in which these various factors can be put into the model to identify the result in stress that could lead to injury. This study was a large collaborative effort between the Orthopaedic Research Center, the University of Melbourne and the University of California at Davis.

Materials and Methods

A patient specific model was developed using a single horse that underwent a series of analyses. Kinematic data were obtained from the horse at a walk, a trot and canter on a high-speed treadmill. Computed tomography and MRI of the whole limb was performed to gather anatomical features of the limb. This allowed for a subject specific, rigid body musculoskeletal model to be created using the bone geometries and muscle tendon paths. Mechanical properties of tendons and ligaments and the relationship between the tendon and ligament strains and limb pose were determined from loading experiments. Joint torque and tendon forces were calculated.

These data allowed for the creation of a subject specific finite element deformable model of the MCP joint. The distal third metacarpus, proximal first phalanx and the proximal sesamoid bones were included in the model. Bone and cartilage properties were inserted into the model.

Once created, this model was validated against the results of cadaver experiments. This allowed for calculation of contact pressures and stresses to be determined in the articular cartilage of each articulation. This model allows any input to be changed to determine that influence on resulting cartilage and bone pressures and stresses (Figure 1).

Results

The error rate between the model and results of cadaver was less than 5%. That percent error is well within acceptable limits for these types of studies. As expected, the net joint torque, joint contact force, cartilage pressure and stresses all increased with locomotion speed.

In general, the medial aspect of the joint experienced larger mean pressures, peak pressures and stresses. The highest stresses were seen in the palmar aspect of the metacarpus between the articulation of the third metacarpal bone and proximal sesamoid bones. This was seen particularly at the parasagittal groove in the palmar aspect of the joint (Figure 2).

Discussion

The results of this study were the first to demonstrate the stresses that occur within the fetlock joint. This is important in further understanding the stresses that lead to injury within that joint. Future studies will focus on changing inputs within the model that emulate changes in conformation, limb conformation, hoof conformation, ground characteristics and shoeing (as examples) and their influence on the joint stresses. These studies can help make suggestions to the industry for managing various factors to reduce injury in racehorses.

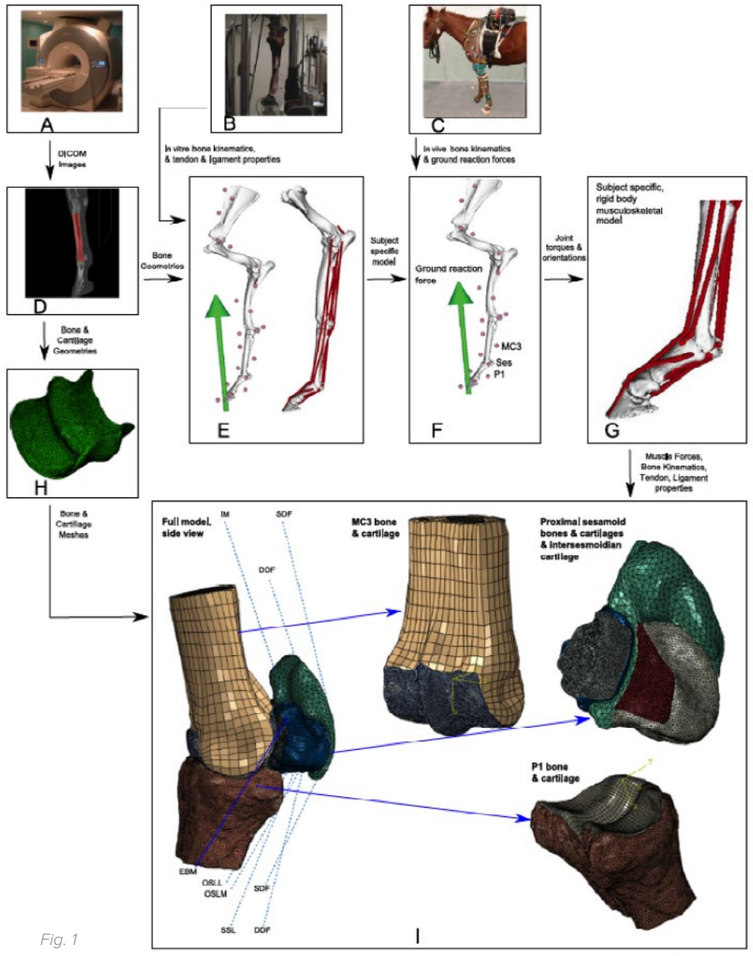
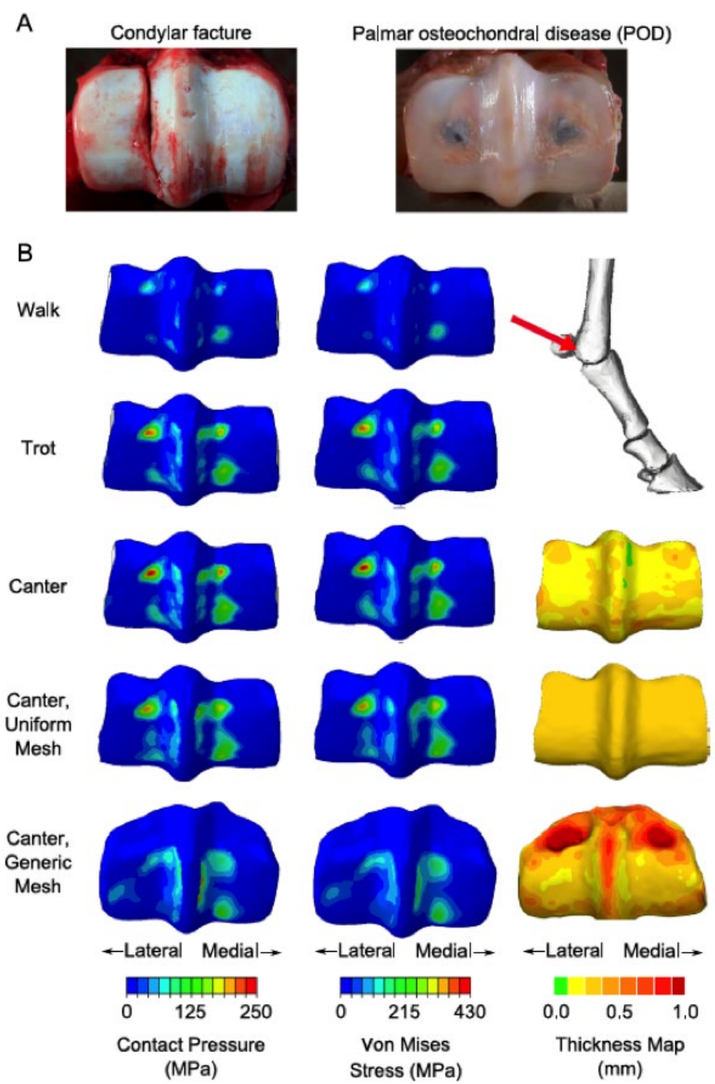


Fig. 1

Fig. 2



In vivo diffusion characteristics following perineural injection of the deep branch of the lateral plantar nerve with mepivacaine or iohexol in horses

This is a summary of an article by Drs. E. Contino, M. King, A. Valdes-Martinez and W. McIlwraith published in Equine Vet Journal 2015 Mar;47(2):230-4. doi: 10.1111/evj.12261. Epub 2014 Apr 20.

Take Home Message

Diagnostic analgesia of the deep branch of the lateral plantar nerve (DBLPN) can result in inadvertent involvement of the tarsal sheath and/or tarsometatarsal joint.

Introduction

Proximal suspensory ligament (PSL) desmitis is a common injury in sport horses. Accurate diagnosis of the condition can be difficult, partly because diagnostic analgesia of this region lacks specificity. Perineural analgesia of the DBLPN to diagnose PSL desmitis has been proposed as a more specific method of isolating pain of the proximal aspect of the suspensory ligament but the technique has not been evaluated in vivo.

Materials and Methods

The DBLPN was injected perineurally with 3 mL of either mepivacaine (n=8) or contrast media (n=8) in live horses. Contrast-injected limbs were radiographed 5, 15, and 30 minutes post injection and diffusion characteristics were described. In mepivacaine-injected limbs, synovial fluid from the tarsometatarsal joint was obtained 10 and 20 minutes post injection and mepivacaine concentrations were analyzed.

Results

At 5, 15, and 30 minutes post injection, the contrast media extended 19.6, 20.6 and 21.0 mm proximal and 38.0, 43.5 and 51.9 mm distal to the injection site, respectively. Three of 8 (37.5%) limbs had evidence of contrast media in the tarsal sheath. Two of 8 (25%) limbs had tarsometatarsal joint mepivacaine concentrations sufficient to produce analgesia (>300 mg/L) at 10 minutes post injection.

Discussion

Analgesia of the DBLPN is commonly used to diagnose PSL desmitis however, this technique can result in inadvertent involvement of the tarsal sheath and/or tarsometatarsal joint.[1] This is important to consider when evaluating the response to analgesia of the DBLPN and reiterates that subtarsal analgesia is not specific to the PSL.

References

1. Contino E., King M.R., Valdes-Martinez A., McIlwraith C.W. In-vivo Characteristics Following Perineural Injection of the Deep Branch of the Lateral Palmar Nerve with Mepivacaine or Iohexol in Horses. Equine Vet J. Accepted 2014.

Use of an inertial measurement unit to assess the effect of forelimb lameness on three-dimensional hoof orientation in horses at a walk and trot

This is a summary of two papers (references 2 and 3 at the end of the article) by Drs. Moorman, Reiser, Peterson, McIlwraith and Kawcak.

Take Home Message

A hoof-mounted inertial measurement unit (IMU) detected significant changes in hoof orientation following induction of mild lameness at the walk and trot. This technology should be further evaluated for use in clinical cases of lameness.

Introduction

Lameness is a significant problem to the equine industry, with up to 14% of horses per year requiring veterinary care and an annual cost of over $600 million spent on the diagnosis and treatment of these animals.[1] Mild lameness can result in poor or decreased performance, and can be the first indication of a more severe injury. Thus, early diagnosis of lameness is critical to diminish potential tissue damage and minimize days lost from training or competition. Mild lameness can be challenging to diagnose, as it is intermittent and is only appreciated under certain conditions. To improve the diagnosis of mild lameness, horse-mounted motion analysis systems have been developed to supplement the subjective lameness examination. While several horse-mounted systems have been evaluated to detect lameness, the limits of their detection have not been fully elucidated. The inertial measurement unit (IMU) has been used to determine changes in orientation and linear accelerations when mounted to a subject, and is thus an appropriate tool to examine equine kinematics. We hypothesize that a hoof-mounted IMU would detect changes to hoof orientation following induction of lameness, and that significant orientation changes would be detectable at mild lameness. We also hypothesize that hoof orientation changes following lameness would normalize following peri-neural anesthesia. This study was performed by Drs. Valerie Moorman, Raoul Reiser, Wayne McIlwraith, and Chris Kawcak at the ORC, in collaboration with Drs. Christie Mahaffey and Mick Peterson at the University of Maine.

Materials and Methods

A sole-pressure model of weight-bearing lameness was induced in a single forelimb of six clinically normal horses. Three increasing grades of lameness were induced, and following the most severe lameness, peri-neural anesthesia was performed to resolve the lameness. An IMU was rigidly mounted with hoof acrylic to the lateral hoof wall on the lame limb to determine three-dimensional (3-D) linear accelerations and orientations. Horses were examined in hand at the walk and trot both before (baseline), following induction of each lameness grade, and following peri-neural anesthesia. Linear acceleration profiles from the IMU were used to divide the stride into break-over, initial swing, terminal swing, and total swing. 3-D orientations were compared following each lameness grade and peri-neural anesthesia to the baseline condition of the lame limb. Repeated measures, mixed model ANOVA was used to analyze the orientations with significance set at $P < 0.05$.

Results

Following lameness induction, there were significant increases in external rotation and abduction and a significant decrease in sagittal plane rotation of the hoof during break-over at the trot. During the initial 25% of swing, the hoof had a more adducted and extended position, and had larger ranges of motion in the sagittal, frontal, and transverse planes at the trot. At the trot, significant changes to internal/external rotation and adduction/abduction of the hoof were seen after mild lameness during both stance and swing phases of stride. At the walk during the initial 25% of stride, the hoof was more internally rotated and abducted following lameness. After peri-neural anesthesia, the changes to external rotation and sagittal rotation of the hoof at the trot returned to baseline. In addition, there was a significant increase in the standard deviations of the sagittal plane orientations, with 12 of 19 (> 60%) sagittal variables having larger standard deviations compared to both baseline and lameness conditions.

Discussion/Conclusions

From this investigation, we identified several significant changes to 3-D hoof orientations both during stance and swing phases of stride following the induction of a weight-bearing lameness. While significant orientation changes with lameness were detected at both the walk and trot, there were a larger number of orientation changes at the trot, indicating that examining horses at the trot is preferable for evaluating lameness. Several of these orientations returned to baseline, indicating that they may useful in identifying a positive response to peri-neural anesthesia. In addition, a consistent increase in standard deviation of the sagittal plane orientations was identified following peri-neural anesthesia at both the walk and trot. These increases may result from changes in proprioception. This increase in variability may be useful in assessing peri-neural anesthesia clinically. The hoof-mounted IMU should be further investigated for its use in detecting orientation changes associated with lameness, and it may be useful as a supplemental tool for clinical lameness evaluation, especially in cases where lameness is mild.

References

1. USDA. National economic cost of equine lameness, colic, and equine protozoal myeloencephalitis in the United States. Information sheet. Fort Collins, Colo: USDA, APHIS, Veterinary Service, National Health Monitoring System, 2001.

2. Moorman V.J., Reiser R.F., Peterson M.L., McIlwraith C.W., Kawcak C.E. The effect of equine forelimb lameness on hoof kinematics at the trot. Am J Vet Res 2013;74:1183-1191. doi: 10.2460/ajvr.74.9.1183.

3. Moorman V.J., Reiser R.F., Peterson M.L., McIlwraith C.W., Kawcak C.E. The effect of equine forelimb lameness on hoof kinematics at the walk. Am J Vet Res 2013;74:1192-1197. doi: 10.2460/ajvr.74.9.1192.

Validation of a Human Cervical Spine Finite Element Model for Risk Assessment of Spinal Cord Injury during Endotracheal Intubation

This study was done by B.J. Hindman, B.G. Santoni, C.M. Puttlitz, R.P. From, M.M. Todd and was presented at the Orthopaedic Research Society and funded by the National Institute or Health (NIH).

Take Home Message

A high fidelity finite element model of the human cervical spine has been developed and validated in order to assess the risk of serious spinal cord damage during endotracheal intubation in the presence of cervical spine injury.

Introduction

Endotracheal intubation can increase the risk of cervical spinal cord injury when performed in the presence of cervical spine instability. It has been postulated that the force exerted by the laryngoscope blade on surrounding airway tissues and the cervical vertebral levels, can induce pathologic (i.e. supraphysiologic) motion in the presence of cervical spine injury, resulting in spinal cord compression or permanent damage. While several experimental studies have sought to investigate the effects of laryngoscope use of spinal cord damage, the majority of these studies have utilized stable (not injured) cervical spines. Further, it is intractable to rigorously characterize the motion and internal mechanical parameters (i.e. tissue stresses and strains) for all possible forms of cervical spine instability during intubation using cadaveric models. Specifically, cadaver tissue models do not allow for direct measurement and spatial mapping of spinal cord stresses and strains. A more feasible approach for comprehensively studying spinal mechanics in the presence of destabilizing injuries is to use computational (i.e. finite element) models of the cervical spine that includes the spinal cord. Parametric series investigations with finite element models will also help identify which features of specific injuries may put the patient at a higher risk of cord impingement or damage during intubation maneuvers. In the current study, a finite element model of the cervical spine (including the spinal cord) was developed and validated to investigate intubation mechanics of the stable and injured cervical spine.

Methods

The osseous geometry of the seven cervical vertebrae (C1 to C7) and the base of the occiput (C0) was extracted from computed tomography scans of a healthy cadaveric specimen (64 year old female, Height: 170 cm, Weight: 74 Kgs) by image segmentation via AMIRA visualization software (ver. 4.0 & 5.0, FEI, Hillsboro, OR). The resultant surface dataset was imported into TrueGrid (XYZ Scientific Applications, Inc., Livermore, CA) and meshed with 8-noded hexahedral elements. The final mesh resolution was chosen based on our previously developed and validated lower cervical spine finite element model.[1] The geometry of the spinal cord was extracted from the visible human database and meshed with identical hexahedral elements. The final spinal cord and osseous tissue meshes were then integrated in ABAQUS (Fig. 1, ver. 6.11, D'assault Systems, Waltham, MA).

Fig. 1: The full human cervical spine (C0-C7) finite element model.

Linearly elastic and transversely orthotropic material models were used to simulate the mechanical response of cortical and trabecular bone, respectively. Trabecular bone properties were based on CT attenuation data using available regression formulae utilizing Hounsfield attenuation units. All major ligaments were modeled as tension-only nonlinear springs and were assigned previously published uniaxial force-displacement relationships. The annulus fibrosus was modeled as a linearly elastic solid with a Young's modulus of 5 MPa and a Poisson's ratio of 0.4. The nucleus pulposus was also modeled as a nearly incompressible linearly elastic solid with a Poisson's ratio of 0.49 and a Young's modulus of 1.5MPa. The spinal cord was modeled as a hyperelastic Ogden material.

A typical intubation procedure is associated with a specific set of boundary conditions at the superior (C0) and the inferior (C7) ends of the cervical spine. It has been reported that the sliding of the skull on the operating table along with the gravitational effects of the weight of the head can influence upper cervical spine motion during intubation.[2] Since the FE model did not include the entire skull geometry, C0 (base of skull) was constrained to translate in the superior-inferior direction and was allowed to rotate freely around all axes. The weight of the torso tends to neutralize motion at C7. Thus, the model was fixed at the C7 vertebra.

The intubation blade applies an anteriorly-directed force to the airway canal and the surrounding soft tissue structures with magnitude and location dependent on the type of intubation blade employed.[2] Our recent studies reported on the mechanics during intubations of live patients and cadavers with the Macintosh intubation blade. These experimental results were used to drive the FE model simulations. The Macintosh intubation protocol was simulated with the center of the applied intubation force (F = 48.4 N) at the center of the C3 vertebra and directed anteriorly at an angle of 70° with the horizontal (Fig. 2).

Sagittal range-of-motion data (via lateral C-arm fluoroscopy) collected during related in vivo and cadaver intubation experiments on stable cervical spines were used to validate the FE model. These data consisted of extension values for vertebral levels C0 to C5. Initially, only the average recorded force from the instrumented intubation blade[2] at the point of maximum extension (during intubation) was applied to the model. The ROM predictions from the model were then compared to the experimental results for validation purposes. Additionally, ROM data was collected from unstable c-spine cadavers. Instability was achieved by a C2 Type II injury (bony fracture) on one set of cadavers and by a C3C4 disc/ligament disruption on second set of cadavers. Ligamentous injuries were created by removal of the relevant springs at the location of injury. Disk compromise was simulated by an 80% reduction in the Young's modulus along with the removal of homeostatic pressurization for that particular intervertebral disk. Model predictions were compared to the experimentally observed ROM data (C0-C5).

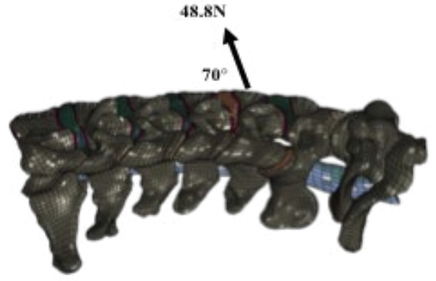


*Fig. 2: Thickness of defects repaired with APEF alone or APEF with BMDMSCs. Defects treated with APEF alone had greater thickness; however, when defects were normalized for thickness, repair tissue of APEF alone scaffolds had similar material properties to APEF with BMDMSCs. *denotes significance*

Results

Intervertebral range of motion (ROM) model predictions for the intact cervical spine fell within one standard deviation of in vivo intact patient data, indicating a high level of predictive accuracy for the finite element model (Fig. 3). Model ROM predictions for the C2 Type II and C3C4 disc injuries were in good agreement with experimental data (Fig. 4).

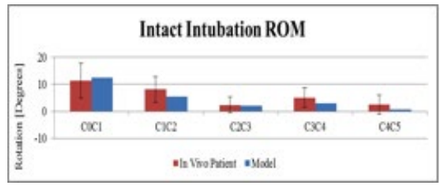
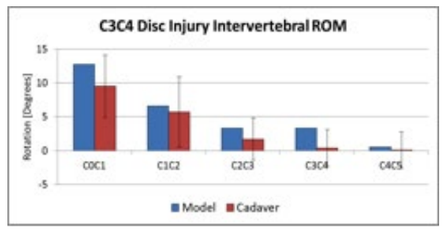


Fig. 3: Intervertebral range of motion (ROM) model predictions for the intact cervical spine fell within one standard deviation of in vivo patient data.



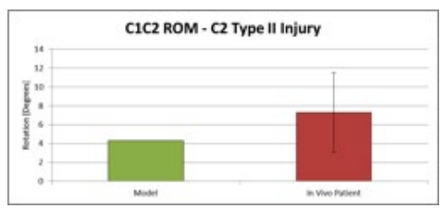


Fig. 4: (Top) Intervertebral range of motion (ROM) model predictions for the C3C4 intervertebral disc injury fell within one standard deviation of cadaver data. (Bottom) Model predictions of C1C2 ROM for the C2 Type II injury fell within one standard deviation of in vivo patient data.

Discussion

The data provided herein demonstrate a high level of agreement between finite element model predictions and in vivo patient and cadaver data for the intact cervical spine as well as the C2 Type II and C3C4 intervertebral disc injury scenarios. A parametric study of common cervical spine injuries will be modeled during intubation to investigate which injuries pose the highest risk of spinal cord damage during endotracheal intubation.

Acknowledgments

Funding provided by the National Institutes of Health (5R01EB012048-04).

References

1. Womack et al., 2011. Cartilage thickness distribution affects computational model predictions of cervical spine facet contact parameters. J Biomech Engr. 133(1), 011009.

2. Hindman et al., 2014. Laryngoscope force and cervical spine motion during intubation with Macintosh and Airtraq laryngoscopes. Anesthesiology. 121(2), 260-271.

Diagnostic stifle joint arthroscopy using a needle arthroscope in standing horses

This is a summary of an article published in Veterinary Surgery, by Drs. D. Frisbie, M. Barrett, W. McIlwraith and J. Ullmer. (reference 3 at the end of the article)

Take Home Message

An 18 ga arthroscope can be used for diagnostic examination of the equine stifle in standing horses.

Introduction

The prevalence of stifle injuries in most equine athletic disciplines is not accurately known. Scant attention was given to athletic injuries of the equine stifle in part because of diagnostic limitations and lack of successful treatment options. It has been suggested athletic injuries to the stifle may account for >40% of injuries in sport horses.[1] Although many consider routine arthroscopy the gold standard for stifle joint diagnostics, complete observation of intra-articular structures such as the meniscus are limited.[2] Computed tomography (CT) using contrast arthrography has been used to image the stifle; however, availability of this modality and magnetic resonance imaging is limited. Thus other methods to safely and quickly evaluate the stifle would be advantageous to facilitate more accurate clinical diagnosis of stifle disease. Our purpose was to assess the use of an 18 ga disposable arthroscope to safely and efficiently provide complete observation of the stifle joint in the standing horse.

Methods

This study had 3 phases. In phase 1, 18 ga and standard 4mm arthroscopic examination of cadaveric stifles was compared and in phase 2, exploratory stifle examination was performed.[3]

Phase 1 - Five cadaver limbs with intact stifles were used. Limbs were positioned in a flexed or extended position using a custom limb stand. Each stifle had routine arthroscopic examination including the caudal portion of the medial and lateral femorotibial (LFT) joints.[4] In 2 limb specimens, the 18 ga arthroscope was used first followed by the 4mm arthroscope to complete exploration of each joint compartment. The other 3 limbs were only assessed using the 18 ga arthroscope. No initial distention of any of the joint compartments was used; however, communication of joint compartments could allow for fluid distention after the first exploratory (based on anatomic location).[3]

Phase 2 - Six clinically normal horses (both stifles were assessed) were studied.[3]

Phase 3 - Three clinically lame horses with suspected stifle disease had diagnostic arthroscopy using the 18 ga arthroscope.[3]

Results

Phase 1 - Complete examination of the intraarticular structures (as defined by McIlwraith and coworkers4) was identified using both the 18 ga and 4mm arthroscope. Further, ultrasonographic confirmation of the intra-articular structures was obtained in 2 limbs (Fig. 1). Complete examination of the remaining 3 limbs was also completed without incident.

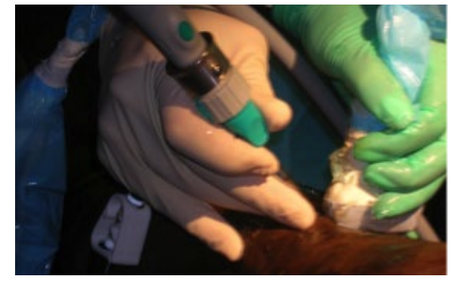


Fig. 1: Simultaneous arthroscopic and ultrasonographic examination using a cadaver limb.

Phase 2 - In the first 2 horses, simultaneous arthroscopy and ultrasonography were performed as in phase 1 to confirm the extent of the exploratory examination and intra-articular structures (Fig. 2). Greater observation of the condyles was possible in both cranial femorotibial joints when the limb was flexed (18 ga or 4mm arthroscope) compared to the standing position. The only notable difference between using the 18 ga arthroscope standing and routine arthroscopic examination was the degree of change in the appearance of the meniscus when weight bearing versus nonweight bearing (Fig. 3).

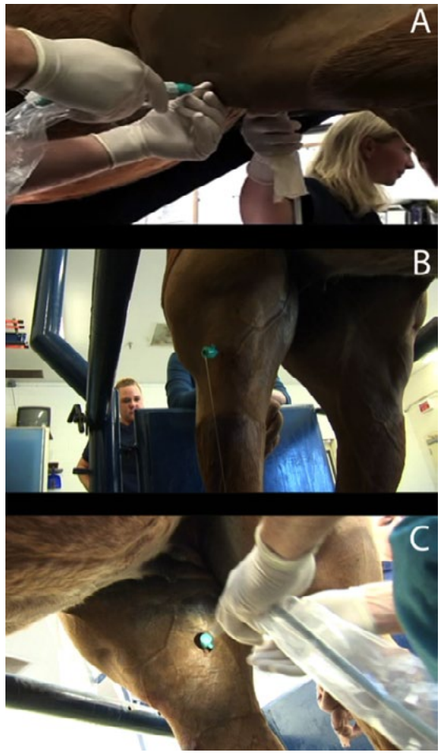


Fig. 2: (A) Simultaneous diagnostic arthroscopy and ultrasonographic examination in a standing horse with the operated limb flexed. (B) Synovial fluid draining from a stiff (2.5 mm) cannula inserted in the cranial MFT joint from a lateral portal in a standing horse. (C) Cannula placement in the caudal MFT joint in standing horse.

Phase 3 - Three horses with a history of stifle disease or suspected stifle disease had standing arthroscopy with the 18 g arthroscope using the protocol described for phase 2. All horses had at least 3 months follow-up and diagnoses were obtained with no complications being observed.

Discussion

As expected, the field of view is smaller than that of a 4mm arthroscope but this was not considered a limitation. In fact, the 18 ga arthroscope provided a better exploratory of the stifle joint than would be obtained with a 2.7mm arthroscope. Ultrasonography was helpful especially in placement of portals to enter the caudal compartment of the femorotibial joint in both the standing and flexed position. Likewise cartilage defects were noted on the medial femoral condyle of 1horse before arthroscopic examination, such observations might help adjustment of portal selection in clinical cases.

In standing horses we were able to confirm that an 18 ga arthroscope could be used to perform complete diagnostic examination of the 3 compartments of the stifle joint. Further, we found that in some areas of the joint where space was limited the small diameter of the 18 ga arthroscope was an advantage, despite the smaller field of view. Diagnostic arthroscopy of the stifle joint was tolerated, even with range of equine temperaments in the standing horse. Finally, the use of the 18 ga arthroscope played a unique and beneficial role in the 3 clinical cases where it was used.

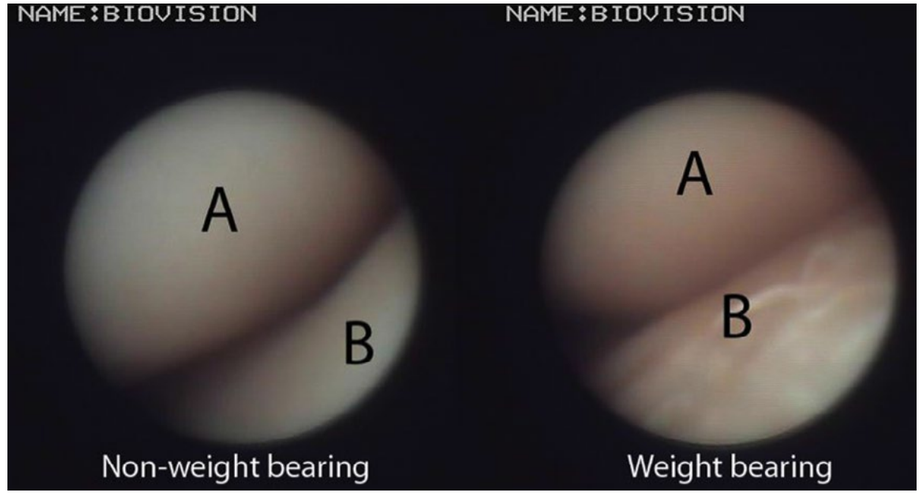


Fig. 3: Comparison of the cranial aspect of the medial femorotibial joint in a nonweight bearing and weight bearing position in the same horse. The configuration of the medial meniscus changes considerably when the joint is being loaded. The medial femoral condyle (A) and medial meniscus (B) are visible.

References

1. Singer E.R., Barnes J., Saxby F., et al: Injuries in the event horse: Training versus competition. Vet J 2008;175:76–81.

2. Trumble T.N., Stick J.A., Arnoczky, et al: Consideration of anatomic and radiographic features of the caudal pouches of the femorotibial joints of horses for the purpose of arthroscopy. Am J Vet Res 1994;55:1682–1689.

3. Frisbie D.D., Barrett M.F., McIlwraith C.W., Ullmer J. Diagnostic stifle joint arthroscopy using a needle arthroscope in standing horses. Vet Surg 2014;43:12-18.

4. McIlwraith C.W., Nixon A.J., Wright I.M.: Diagnostic and surgical arthroscopy of the femoropatellar and femorotibial joints. In Diagnostic and Surgical Arthroscopy in the Horse (ed 3). Edinburgh, NY, Mosby Elsevier, 2005, pp 197–268.

RESEARCH | FOCUS 2 -Early Diagnosis of Bone and Joint Disease

Science in brief: Report on the Havemeyer Foundation workshop on equine musculoskeletal biomarkers – current knowledge and future needs

This is a reproduction of an article previously published in Equine Veterinary Journal by C.W. McIlwraith and P.D. Clegg: Equine Veterinary Journal, 2014; 46, 651-653.

In 2009, a Dorothy Russell Havemeyer Foundation workshop on equine musculoskeletal biomarkers was held in Steamboat, Colorado, USA. The goal of this effort was to develop a validated biomarker platform that could be used practically for diagnosis and prognosis of musculoskeletal disease, assessment of therapy, disease prediction and study of musculoskeletal disease. This editorial identifies the key outcomes from this meeting and indicates key future directions for this discipline.

The potential benefit of biomarkers of disease in horses is comparable with that in human medicine where working groups have been used to identify the needs and strategies for biomarker development.[1–3] It has been stated that a disease starts when detected by the best biomarker available to define it[2]; this usually requires the presence of a symptom or clinical sign, which often occurs well into the progression of an illness or disease. However, there are often early, presymptomatic biomarkers of illness and disease which if detected may allow for earlier treatment. This forms the basis for the power and importance of applying biomarkers to osteoarthritis (OA), a disease often characterised by a prolonged, asymptomatic molecular phase, a preradiographic phase and a recalcitrant later radiographic stage with evident structural joint changes, frequent pain and loss of function.[2]

The equine athlete may also have somewhat unique applications for biomarkers of musculoskeletal health that may not be so relevant in man. Issues in people are who gets monitored for OA biomarkers or in which groups will it be of most cost–benefit? The 'low hanging fruit' are likely to be in predicting patients that will have rapid progression of existing joint disease and thus may benefit most from available therapies; monitoring response to therapy for existing disease and identifying which patients will and which will not progress to OA following injury. These applications would also apply to the horse. However in horses, a greater need may be in monitoring currently healthy athletes to predict, and thereby hopefully prevent, catastrophic injuries such as long bone fractures or tendon/ligament tears, as well as impending joint disease[4]. Advances in this area would be extremely useful in equine medicine, not only from the perspective of preventing disease and maximising performance, but also in minimising racing-associated injuries. There is little research in biomarker monitoring of human athletes and in this area the equine community could lead the way and provide novel insights for translation to man.

State of knowledge in equine musculoskeletal biomarkers was reviewed by McIlwraith in 2005.[5] Since that time, specific reviews relating to specific aspects of equine musculoskeletal biomarkers have also been published.[6–10]

Definitions

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention.[11] This is in contrast to the term clinical endpoint which is a marker or variable that measures how a patient feels, functions or survives. A biomarker can become a surrogate endpoint when it is appropriately qualified to substitute for a clinical endpoint. The evolution in molecular biology and imaging has led to the expansion of the notion of what constitutes a potential biomarker to include, not only proteins and protein fragments, but also metabolites, carbohydrate biomarkers, genomic biomarkers (RNA and DNA), cellular biomarkers (that may be captured for instance in a cell pellet extracted from body fluids) and imaging biomarkers.[1,2]

Biomarkers have also been classified, based upon their characteristics, into 2 major groups: the so called soluble or 'wet' biomarkers (fluid biomarkers) and 'dry biomarkers' which consist of visual analogue scales (VAS), questionnaires, performed tasks or imaging.[1,2]

In a recent review on biomarkers in OA, it was noted that the OA disease process is increasingly being considered a continuum, beginning with an inciting event, such as genetic variation or injury, progressing through molecular, preradiographic and radiographic stages culminating in end-stage disease.[3] Based on this reclassification of the disease as a continuum of a series of stages, it is proposed that biomarkers could play a pivotal role in disease detection and monitoring, particularly during the critical, early molecular stages when other tools are not readily able to identify nascent OA.[2]

Development of a biomarker sample bank

It was agreed by the Havemeyer group that this should be a major priority. While biobanking is emerging as an important research tool in the human field, it is now also gaining momentum in veterinary medicine.[12,13] A biobank is a repository of biological material that has been collected and stored in a standardised fashion and whose phenotype, origin, date of collection and location can be easily determined.[13] These specimens can be stored at one or more site and distributed to the biobank users based on preset guidelines. Not only sample collection and storage methods but also data recording (quality, completeness, consistency) relating to samples at different storage sites must be harmonised[14,15] and a powerful informatics programme that permits efficient and reliable management of all the biobank's specimens is essential for its success.[15] A key element of a biobank is that all necessary legal and ethical permissions are in place to allow appropriate use of materials for research purposes. This is obviously complicated in the case of an international biobank where different legislative frameworks and cultural issues may have an impact.[16]

Types of biomarkers

There are a number of putative biomarkers and it is important that we recognise limitations of existing technologies, as well as the potential of novel approaches.

Protein biomarkers: Historically, biomarker assays rely on immunological assays using antibodies raised against nonequine species and a significant homology in amino acid sequences between equine and other species is a minimal requirement for the antibody to cross-react. To prove the specificity of a nonequine antibody on specific equine epitopes, a gel electrophoresis and a western blot is mandatory and a single band of the appropriate molecular weight should be identified. Also the protein (usually fractionated on a gel) should ideally be analysed with mass spectrometry to fully identify the protein. In many historical publications, the specificity of the nonequine antibody is not clearly stated, leading to some uncertainty about presented data.

Genetic biomarkers: Genetic sequence variants hold particular promise for predicting disease risk and guiding appropriate decisions and treatments. Genetic biomarkers are defined as genetic variations (mutations or polymorphisms) that can predict disease susceptibility, disease outcome, or treatment response. The use of genetic biomarkers to estimate risk is potentially more straightforward than using nongenetic ones because genetic biomarkers can be detected almost without error and do not vary in an individual over time. Also, unlike nongenetic markers, they only need to be determined once, and this can be early in life allowing appropriate decisions on treatments or adjustments to begin earlier, potentially increasing their effects.[17] This revolution in genomic resources, which has the potential to have a dramatic impact on the horse, started with the publication of a high-quality draft sequence of equine genome.[18] In musculoskeletal diseases, recent genomic studies have been performed relating to osteochondrosis[19] and tendon injury.[20]

Post genomic technologies and biomarkers: Transcriptomics: The sequencing of the equine genome opens up a number of post genomic technologies to equine researchers and the potential for novel tests that can be both prognostic and predictive of disease processes in the horse.[21] Analysis of the transcriptome by PCR, microarray or next-generation sequencing[22,23] is a powerful technique, although it has specific limitations as identification of specific regulation of a particular gene does not always relate to a cellular response of protein transcription. Tran-

RESEARCH | FOCUS 2 -Early Diagnosis of Bone and Joint Disease

scriptomic analysis can also be used to determine noncoding RNAs and microRNA which have been suggested as biomarkers in a number of diseases including osteoarthritis.[24]

Proteomics: Proteomic analysis has been increasingly used in equine research and studies are now using mass-spectrometry techniques has been used to identify specific biomarkers that may be associated with equine musculoskeletal disorders.[25–28]

Metabolomics: In the post genomic era it has become clear that solely mapping the genes, mRNA and proteins of the living system does not reveal its phenotype. Consequently, researchers have turned their interest to the metabolome (or the metabolic compliment to functional genomics) and thus metabolomics is a rapidly expanding post genomic science that utilises analytical techniques to measure low molecular weight metabolites in biological samples. The principal analytical techniques used in metabolomics are mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy. Techniques generate huge amounts of data in complex spectral profiles that must be then analysed using bioinformatics and statistical methods. Currently there is no published data on metabolomic profiling and its potential use as a biomarker in equine musculoskeletal disease, but recent publications in human OA and animal OA models suggest it may have potential.[29–31]

Imaging biomarkers: In recent years computed tomography (CT) and magnetic resonance imaging (MRI) have allowed for 3D characterisation of joints. Although this has improved diagnostic capabilities, pathological tissues must still be present in order for these imaging modalities to be useful. In the past the pathological changes must have been structural in nature to be detected, although now they may be physiological. For example, bone marrow lesions on MRI and uptake of contrast agent into diseased tissues on CT examinations are indicative of methods that show the physiological change when structural changes may not be present.[32–34] Therefore, with the introduction of 3D imaging techniques, higher resolution and the ability to image physiological changes has improved early diagnosis of disease.

A correlative study between the various available imaging techniques and the development of experimental OA in the horse has been reported.[35] The paper serves as an example of the potential to have multiple imaging biomarkers for clinical OA. At the moment a true imaging biomarker that could be used to predict onset and/or progression of joint disease does not exist in any species, including man. There is nowa need to determine the role, as well as any cost–benefit analysis, of performing imaging screening to predict future injury risk, particularly relating to many of the newer imaging techniques. While such approaches, particularly using radiography, have been frequently performed by veterinary surgeons for decades, there is little evidence for actual benefit to the horse.

Summary

There are exciting prospects relating to biomarkers for equine musculoskeletal disease and injury risk characterisation and prediction, but there is still considerable work to do before having a clinically useful biomarker panel. Work will continue with colleagues in human medicine to learn from their research but we can hopefully contribute back to them with data from the horse. The horse provides a clinically relevant study group with some unique applications of biomarkers in prediction of disease susceptibility, changes with exercise (or over training) and possibly athletic ability.

Acknowledgments

The authors would like to thank Christopher Little, Sheila Laverty, David Frisbie, Mark Vaudin, Stina Ekman, Eva Skiöldebrand, Joanna Price, Christopher Riley, Christopher Kawcak, Roger Smith and Chris Riley for assistance in writing this paper. The meeting was also attended by Troy Trumble, Jack Quinn, Elwyn Firth and John Kisiday as well as prominent experts from the human biomarker research field Robin Poole, Dick Heinegård, Bruce Caterson and Virginia Byers Kraus. A full report for the meeting can be found at http://csu-cvmbs.colostate.edu/documents/ research-equine-musculoskeletal-biomarkers-white-paper.pdf

C. W. McIlwraith and P. D. Clegg†

Gail Holmes Equine Orthopaedic Research Center, Colorado State University, Fort Collins, USA †Department of Musculoskeletal Biology, Institute of Ageing and Chronic Disease, University of Liverpool, Chester, UK.

References

1. Kraus, V.B. (2011) Osteoarthritis year 2010 in review: biochemical markers. Osteoarthritis Cartilage 19, 346-353.

2. Kraus, V.B., Burnett, B., Coindreau, J., Cottrell, S., Eyre, D., Gendreau, M., Gardiner, J., Garnero, P., Hardin, J., Henrotin, Y., Heinegard, D., Ko, A., Lohmander, L.S., Matthews, G., Menetski, J., Moskowitz, R., Persiani, S., Poole, A.R., Rousseau, J.C. and Todman, M. (2011) Application of biomarkers in the development of drugs intended for the treatment of osteoarthritis. Osteoarthritis Cartilage 19, 515-542.

3. Kraus, V.B., Nevitt, M. and Sandell, L.J. (2010) Summary of the OA biomarkers workshop 2009–biochemical biomarkers: biology, validation, and clinical studies. Osteoarthritis Cartilage 18, 742-745.

4. Frisbie, D.D., McIlwraith, C.W., Arthur, R.M., Blea, J., Baker, V.A. and Billinghurst, R.C. (2010) Serum biomarker levels for musculoskeletal disease in two- and three-year-old racing Thoroughbred horses: a prospective study of 130 horses. Equine Vet. J. 42, 643-651.

5. McIlwraith, C.W. (2005) Use of synovial fluid and serum biomarkers in equine bone and joint disease: a review. Equine Vet. J. 37, 473-482.

6. Garvican, E.R., Vaughan-Thomas, A., Innes, J.F. and Clegg, P.D. (2010) Biomarkers of cartilage turnover. Part 1: markers of collagen degradation and synthesis. Vet. J. 185, 36-42.

7. Garvican, E.R., Vaughan-Thomas, A., Clegg, P.D. and Innes, J.F. (2010) Biomarkers of cartilage turnover. Part 2: non-collagenous markers. Vet. J. 185, 43-49.

8. Mobasheri, A. and Henrotin, Y. (2010) Identification, validation and qualification of biomarkers for osteoarthritis in humans and companion animals: mission for the next decade. Vet. J. 185, 95-97.

9. Mobasheri, A. and Cassidy, J.P. (2010) Biomarkers in veterinary medicine: towards targeted, individualised therapies for companion animals. Vet. J. 185, 1-3.

10. de Grauw, J.C. (2011) Molecular monitoring of equine joint homeostasis. Vet. Q. 31, 77-86.

11. Group, B.D.W. (2001) Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin. Pharmacol. Ther. 69, 89-95.

12. Castelhano, M.G., Acland, G.M., Ciccone, P.A., Corey, E.E., Mezey, J.G., Schimenti, J.C. and Todhunter, R.J. (2009) Development and use of DNA archives at veterinary teaching hospitals to investigate the genetic basis of disease in dogs. J. Am. Vet. Med. Ass. 234, 75-80.

13. Schrohl, A.S., Wurtz, S., Kohn, E., Banks, R.E., Nielsen, H.J., Sweep, F.C. and Brunner, N. (2008) Banking of biological fluids for studies of disease-associated protein biomarkers. Mol. Cell Proteomics 7, 2061-2066.

14. Founti, P., Topouzis, F., van Koolwijk, L., Traverso, C.E., Pfeiffer, N. and Viswanathan, A.C. (2009) Biobanks and the importance of detailed phenotyping: a case study–the European Glaucoma Society GlaucoGENE project. Br. J. Ophthal. 93, 577-581.

15. Amin,W., Singh, H., Pople, A.K., Winters, S., Dhir, R., Parwani, A.V. and Becich, M.J. (2010) A decade of experience in the development and implementation of Equine musculoskeletal biomarkers C. W. McIlwraith and P. D. Clegg 652 Equine Veterinary Journal 46 (2014) 651–653 © 2014 EVJ Ltd tissue banking informatics tools for intra and inter-institutional translational research. J. Pathol. Inform. 1, 12.

16. Blow, N. (2009) Biobanking: freezer burn. Nat. Methods 6, 173-178.

17. Webbon, P. (2012) Harnessing the genetic toolbox for the benefit of the racing Thoroughbred. Equine Vet. J. 44, 8-12.

18. Wade, C.M., Giulotto, E., Sigurdsson, S., Zoli, M., Gnerre, S., Imsland, F., Lear, T.L., Adelson, D.L., Bailey, E., Bellone, R.R., Blocker, H., Distl, O., Edgar, R.C., Garber, M., Leeb, T., Mauceli, E., MacLeod, J.N., Penedo, M.C., Raison, J.M., Sharpe, T., Vogel, J., Andersson, L., Antczak, D.F., Biagi,

T., Binns, M.M., Chowdhary, B.P., Coleman, S.J., Della Valle, G., Fryc, S., Guerin, G., Hasegawa, T., Hill, E.W., Jurka, J., Kiialainen, A., Lindgren, G., Liu, J., Magnani, E., Mickelson, J.R., Murray, J., Nergadze, S.G., Onofrio, R., Pedroni, S., Piras, M.F., Raudsepp, T., Rocchi, M., Roed, K.H., Ryder, O.A., Searle, S., Skow, L., Swinburne, J.E., Syvanen, A.C., Tozaki, T., Valberg, S.J., Vaudin, M., White, J.R., Zody, M.C., Lander, E.S. and Lindblad-Toh, K. (2009) Genome sequence, comparative analysis, and population genetics of the domestic horse. Science 326, 865-867.

19. Corbin, L.J., Blott, S.C., Swinburne, J.E., Sibbons, C., Fox-Clipsham, L.Y., Helwegen, M., Parkin, T.D., Newton, J.R., Bramlage, L.R., McIlwraith, C.W., Bishop, S.C., Woolliams, J.A. and Vaudin, M. (2012) A genome-wide association study of osteochondritis dissecans in the Thoroughbred. Mamm. Genome 23, 294-303.

20. Tully, L.J., Murphy, A.M., Smith, R.K., Hulin-Curtis, S.L., Verheyen, K.L. and Price, J.S. (2014) Polymorphisms in TNC and COL5A1 genes are associated with risk of superficial digital flexor tendinopathy in National Hunt Thoroughbred racehorses. Equine Vet. J. 46, 289-293.

21. Ramery, E., Closset, R., Bureau, F., Art, T. and Lekeux, P. (2008) Relevance of using a human microarray to study gene expression in heaves-affected horses. Vet. J. 177, 216-221.

22. Kamm, J.L., Frisbie, D.D., McIlwraith, C.W. and Orr, K.E. (2013) Gene biomarkers in peripheral white blood cells of horses with experimentally induced osteoarthritis. Am. J. Vet. Res. 74, 115-121.

23. Peffers, M.J., Liu, X. and Clegg, P.D. (2013) Transcriptomic signatures in cartilage ageing. Arthritis Res. Ther. 15, R98.

24. Zen, K. and Zhang, C.Y. (2010) Circulating MicroRNAs: a novel class of biomarkers to diagnose and monitor human cancers. Med. Res. Rev. 32, 326-348.

25. Desjardin, C., Balliau, T., Valot, B., Zivy, M., Wimel, L., Guerin, G., Cribiu, E. and Schibler, L. (2012) A method for proteomic analysis of equine subchondral bone and epiphyseal cartilage. Proteomics 12, 1870-1874.

26. Chiaradia, E., Pepe, M., Tartaglia, M., Scoppetta, F., D'Ambrosio, C., Renzone, G., Avellini, L., Moriconi, F., Gaiti, A., Bertuglia, A., Beccati, F. and Scaloni, A. (2012) Gambling on putative biomarkers of osteoarthritis and osteochondrosis by equine synovial fluid proteomics. J. Proteomics 75, 4478-4493.

27. Clutterbuck, A.L., Smith, J.R., Allaway, D., Harris, P., Liddell, S. and Mobasheri, A. (2011) High throughput proteomic analysis of the secretome in an explant model of articular cartilage inflammation. J. Proteomics 74, 704-715.

28. Peffers, M.J., Cillero-Pastor, B., Eijkel, G.B., Clegg, P.D. and Heeren, R.M. (2014) Matrix assisted laser desorption ionization mass spectrometry imaging identifies markers of ageing and osteoarthritic cartilage. Arthritis Res. Ther. 16, R110.

29. Blanco, F.J. and Ruiz-Romero, C. (2012) Osteoarthritis: metabolomic characterization of metabolic phenotypes in OA. Nat. Rev. Rheumatol. 8, 130-132.

30. Adams, S.B., Jr, Setton, L.A., Kensicki, E., Bolognesi, M.P., Toth, A.P. and Nettles, D.L. (2012) Global metabolic profiling of human osteoarthritic synovium. Osteoarthritis Cartilage 20, 64-67.

31. Maher, A.D., Coles, C., White, J., Bateman, J.F., Fuller, E.S., Burkhardt, D., Little, C.B., Cake, M., Read, R., McDonagh, M.B. and Rochfort, S.J. (2012) 1H NMR spectroscopy of serum reveals unique metabolic fingerprints associated with subtypes of surgically induced osteoarthritis in sheep. J. Proteome Res. 11, 4261-4268.

32. Powell, S.E. (2012) Low-field standing magnetic resonance imaging findings of the metacarpo/metatarsophalangeal joint of racing Thoroughbreds with lameness localised to the region: a retrospective study of 131 horses. Equine Vet. J. 44, 169-177.

33. Vallance, S.A., Bell, R.J., Spriet, M., Kass, P.H. and Puchalski, S.M. (2012) Comparisons of computed tomography, contrast-enhanced computed tomography and standing low-field magnetic resonance imaging in horses with lameness localised to the foot. Part 2: lesion identification. Equine Vet. J. 44, 149-156.

34. Tranquille, C.A., Parkin, T.D. and Murray, R.C. (2012) Magnetic resonance imaging-detected adaptation and pathology in the distal condyles of the third metacarpus, associated with lateral condylar fracture in Thoroughbred racehorses. Equine Vet. J. 44, 699-706.

35. Kawcak, C.E., Frisbie, D.D.,Werpy, N.M., Park, R.D. and McIlwraith, C.W. (2008) Effects of exercise vs experimental osteoarthritis on imaging outcomes. Osteoarthritis Cartilage 16, 1519-1525. C. W. McIlwraith and P. D. Clegg Equine musculoskeletal biomarkers Equine Veterinary

Impact of race training on volumetric bone mineral density and its spatial distribution in the distal epiphysis of the third metatarsal bone of 2-year-old horses

This is a summary of an article published in the Veterinary Journal by Drs. S.H. Bogers, C.W. Rogers, C.F. Bolwell, W.D. Roe, E.K. Gee and C.W. McIlwraith. Veterinary Journal, September 2014; 201: 353-358. Doi 10.1016/j/tvjl.2014.06.018.

Take Home Message

Rapid focal changes in bone mineral density occur in the distal metatarsus of 2-year-old racing Thoroughbreds with training compared to untrained controls. They are less than a previous study has shown in the distal McIII.

Introduction

During high speed activity such as race training and racing the distal McIII epiphysis objected to large compressive forces (Harrison et al, 2010), which have been documented to result in cartilage loss, significant remodeling of the epiphysis and localized increases in volumetric bone mineral density (BMD) (Riggs, 2002; Firth et al, 2005) that often contribute to lameness (Tull and Bramlage, 2011). These bone and cartilage responses are often site-specific and focal, reflecting the heterogeneity of load on the distal McIII epiphysis. Within affected bones, the localized sclerosis is greater at the palmar aspect of the condyles and least at the sagittal ridge, creating the possibility for development of the shear along planes of different densities, in this case primarily at the axial margin of the condyles (Riggs, 2002). The focal and site-specific responses observed in the distal McIII epiphysis are thought to be related to cyclic loading of the joint and are associated with fractures (Whitton et al., 2010).

The statistical technique of spatial analysis has been extensively used in the discipline of epidemiology (Pfeiffer et al., 2008), but to date has not been widely used to quantitatively describe tissue (bone) responses to exercise (Rose et al., 2012). This method facilitates quantitative description of what previously has been described qualitatively such as the high levels of clustering of certain BMD pixels, whether such clusters are arranged in uniform or random patterns, and if the dispersion of pixels is related to the BMD of neighboring pixels. The aim of this study was to use spatial analysis (Fig. 1) to quantify differences in BMD in clearly defined populations of control and race-trained 2-year-old Thoroughbreds.

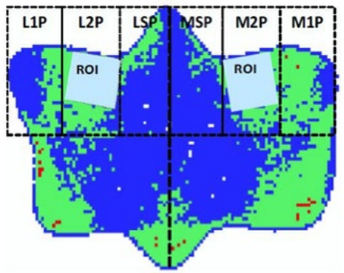


Fig. 1: Stylized representation of the regions of interest (RO1) for spatial analysis and classification of pixels into low (blue), medium (green) and high (red).

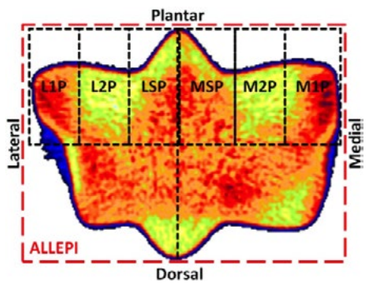


Fig. 2: Regions of interest (ROI) were selected dividing the plantar half of the peripheral quantitative computed tomographic image into three sections on both lateral and medial aspects of the midline.

Materials

The left distal MtIII of 14 2-year old Thoroughbred fillies from a previously controlled exercise trial were available for an analysis (Firth, et al., 2004; Firth and Rogers, 2005). The fillies were selected for race training for yard rest (control). Training protocols were consistent with conventional flat race training programs for 2-year-olds in New Zealand (Bolwell et al. 2010). Specimens were scanned using axial peripheral quantitative computed tomography (pQCT; XCT 2000, Stratec Medical). There were 15 2 mm contiguous scans, with a pixel size of 0.5 mm. Further details are described in the full publication which is available. The BMD data (mg/cm3) were extracted using the scanner's proprietary software for the entire slice and for the six regions of interest (ROI)(Fig 2), representing regions subject to different loads during training (Riggs et al., 1999; Harrison et al., 2014).

Results

There were no significant differences in the total BMD, between control and exercise groups in the entire transverse slice or in the ROI. The median proportion of pixels for bone density categories 1000-1100 mg/cm3 was great in exercised compared to control horses in medial plantar condyle (M2P) and lateral sagittal ridge and groove (LSP) (Fig. 3)

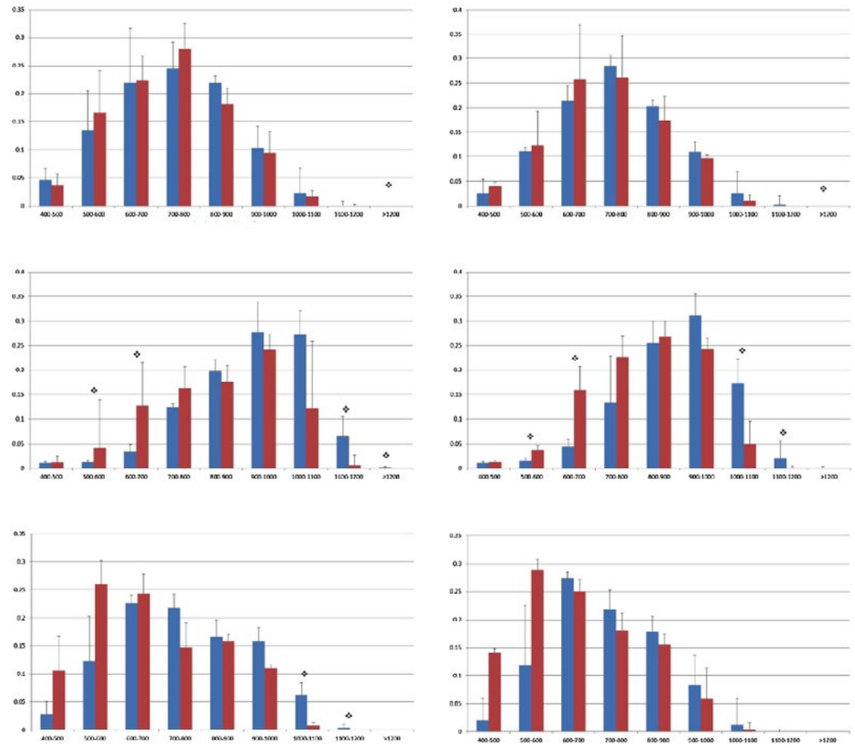


Fig. 3: The median relative proportion of voxels for each bone density threshold (mg/cm3) for particular regions of interest: (a) L1P, (b) M1P, (c) L2P, (d) M2P, (e) LSP, and (f) MSP for exercised (blue) and non-exercised (red) horses.

All exercised horses showed a strong to marked clustering of high BMD threshold pixels in P2P; however, only three control horses demonstrated clustering that was weak to strong. In M2P, five of the exercised horses had a moderate to marked clustering and there was no significant 'high' BMD clustering in the control group.

Discussion

The lack of significant differences in BMD of the total slice between groups may reflect the less dramatic changes in BMD to the exercise load identified in the MtIII rather than that observed in the McIII and or partial dilution of what are focal responses to load when the entire slice is examined. The selected ROI exhibited differences in BMD distribution histograms, reflecting differences in the loads and loading pattern of each region. Condylar regions, despite being contact areas, are loaded via the inter-sesamoidean ligament rather than via the sesamoid bones directly (Easton and Kawcak, 2007). The effect of the exercise program on these ROI was a significant, but small, increase in the proportion of pixels in the highest density category, and no dramatic change in the profile of the distribution between groups. Inclusions of the BMD response to exercise in these horses were site-specific with the central condylar regions exhibiting the greatest response to exercise, a finding consistent with previous studies. The use of spatial analysis quantified and supported previous findings that the response is rapid and focal in nature, even with a relatively moderate training load. The non-invasive serial CT measurements can be used to numerically describe the gradient of focal and rapid responses to training in the distal MtIII epiphysis of young horses.

References

1. Allen, D.W., 2009. GIS Tutorial II, ESRI Press, Redlands, CA, USA.

2. Bolwell, C.F., Russell, L.J., Rogers, C.W., Firth, E.C., 2010. A cross-sectional survey of training practices of 2-year-old racehorses in the North Island of New Zealand.Comparative Exercise and Physiology 7, 37–42.

3. Bolwell, C.F., Rogers, C.W., French, N.P., Firth, E.C., 2012. Risk factors for interruptions occurring before the first trial start of 2-year-old Thoroughbred racehorses in training. New Zealand Veterinary Journal 60, 241–246.

4. Boyde, A., Firth, E.C., 2005. Musculoskeletal responses of 2-year-old Thoroughbred horses to early training. 8. Quantitative back-scattered electron scanning electron microscopy and confocal fluorescence microscopy of the epiphysis of the third metacarpal bone. New Zealand Veterinary Journal 53, 123–132.

5. Clark, P.J., Evans, F.C., 1954. Distance to nearest neighbor as a measure of spatial relationships in populations. Ecology 35, 445–453.

6. Drum, M.G., Kawcak, C.E., Norrdin, R.W., Park, R.D., McIlwraith, C.W., Les, C.M., 2007. Comparison of gross and histopathologic findings with quantitative computed tomographic bone density in the distal third metacarpal bone of racehorses. Veterinary Radiology and Ultrasound 48, 518–527.

7. Easton, K.L., Kawcak, C.E., 2007. Evaluation of increased subchondral bone density in areas of contact in the metacarpophalangeal joint during joint loading in horses. American Journal of Veterinary Research 68, 816–821.

8. Firth, E.C., Rogers, C.W., 2005. Musculoskeletal responses of 2-year-old thoroughbred horses to early training. Conclusions. New Zealand Veterinary Journal 53, 377–383.

9. Firth, E.C., Rogers, C.W., Perkins, N.R., Anderson, B.H., Grace, N.D., 2004. Musculoskeletal responses of 2-year-old Thoroughbred horses to early training. 1. Study design, and clinical, nutritional, radiological and histological observations. New Zealand Veterinary Journal 52, 261–271.

10. Firth, E.C., Rogers, C.W., Doube, M., Jopson, N.B., 2005. Musculoskeletal responses of 2-year-old Thoroughbred horses to early training. 6. Bone parameters in the third metacarpal and third metatarsal bones. New Zealand Veterinary Journal 53, 101–112.

11. Firth, E.C., Rogers, C.W., van Weeren, P.R., Barneveld, A., McIlwraith, C.W., Kawcak, C.E., Goodship, A.E., Smith, R.K.W., 2011. Mild exercise early in life produces changes in bone size and strength but not density in proximal phalangeal, third metacarpal and third carpal bones of foals. The Veterinary Journal 190, 383–389.

12. Firth, E.C., Rogers, C.W., van Weeren, P.R., Barneveld, A., McIlwraith, C.W., Kawcak, C.E., Goodship, A.E., Smith, R.K.W., 2012. The effect of previous conditioning exercise on diaphyseal and metaphyseal bone responses to imposition and withdrawal of training in young Thoroughbred horses. The Veterinary Journal 192, 34–40.

13. Fonseca, A.A., Cherubini, K., Veeck, E.B., Ladeira, R.S., Carapeto, L.P., 2008. Effect of 10% formalin on radiographic optical density of bone specimens. Dentomaxillofacial Radiology 37, 137–141.

14. Getis, A., Ord, J.K., 1992. The analysis of spatial association by use of distance statistics. Geographical Analysis 24, 189–206.

15. Greenacre, M., 2007. Correspondence Analysis in Practice, Second Ed. Taylor and Francis Group, Boca Raton, USA.

16. Griffith, D.A., 2009. Spatial Autocorrelation, in: www.elsevierdirect.com. Elsevier Inc., Richardson, TX, USA, pp. 5–7.

17. Harrison, S.M., Whitton, R.C., Kawcak, C.E., Stover, S.M., Pandy, M.G., 2010. Relationship between muscle forces, joint loading and utilization of elastic strain energy in equine locomotion. Journal of Experimental Biology 213, 3998–4009.

18. Harrison, S.M., Chris Whitton, R., Kawcak, C.E., Stover, S.M., Pandy, M.G., 2014. Evaluation of a subject-specific finite-element model of the equine metacarpophalangeal joint under physiological load. Journal of Biomechanics 47, 65–73.

19. Parkin, T.D.H., Clegg, P.D., French, N.P., Proudman, C.J., Riggs, C.M., Singer, E.R.,Webbon, P.M., Morgan, K.L., 2006. Catastrophic fracture of the lateral condyle of the third metacarpus/metatarsus in UK racehorses – fracture descriptions and pre-existing pathology. The Veterinary Journal 171, 157–165.

20. Perkins, N.R., Reid, S.W.J., Morris, R.S., 2004. Effect of training location and time period on racehorse performance in New Zealand. 2. Multivariable analysis. New Zealand Veterinary Journal 52, 243–249.

21. Perkins, N.R., Reid, S.W.J., Morris, R.S., 2005. Risk factors for musculoskeletal injuries of the lower limbs in Thoroughbred racehorses in New Zealand. New Zealand Veterinary Journal 53, 171–183.

22. Pfeiffer, D.U., Robinson, T.P., Stevenson, M.A., Stevens, K.A., Rogers, D.J., Clements, A.C.A., 2008. Spatial Analysis in Epidemiology, Oxford University Press, Oxford, UK.

23. Reed, S.R., Jackson, B.F., McIlwraith, C.W.,Wright, I.M., Pilsworth, R., Knapp, S.,Wood, J.L.N., Price, J.S., Verheyen, K.L.P., 2012. Descriptive epidemiology of joint injuries in Thoroughbred racehorses in training. Equine Veterinary Journal 44, 13–19.

24. Riggs, C.M., 2002. Fractures – A preventable hazard of racing thoroughbreds? The Veterinary Journal 163, 19–29

25. Riggs, C.M., Boyde, A., 1999. Effect of exercise on bone density in distal regions of the equine third metacarpal bone in 2-year-old thoroughbreds. Equine Veterinary Journal 30, 555–560.

26. Riggs, C.M., Whitehouse, G.H., Boyde, A., 1999. Pathology of the distal condyles of the third metacarpal and third metatarsal bones of the horse. Equine Veterinary Journal 31, 140–148.

27. Rogers, C.W., Firth, E.C., 2004. Musculoskeletal responses of 2-year-old Thoroughbred horses to early training. 2. Measurement error and effect of training stage on the relationship

between objective and subjective criteria of training workload. New Zealand Veterinary Journal 52, 272–279.

28. Rose, D.C., Agnew, A.M., Gocha, T.P., Stout, S.D., Field, J.S., 2012. Technical note: The use of geographical information systems software for the spatial analysis of bone microstructure. American Journal of Physical Anthropology 148, 648–654.

29. Rubio-Martinez, L.M., Cruz, A.M., Gordon, K., Hurtig, M.B., 2008. Mechanical properties of subchondral bone in the distal aspect of third metacarpal bones from Thoroughbred racehorses. American Journal of Veterinary Research 69, 1423–1433.

30. Tull, T.M., Bramlage, L.R., 2011. Racing prognosis after cumulative stress-induced injury of the distal portion of the third metacarpal and third metatarsal bones in Thoroughbred racehorses: 55 cases (2000–2009). Journal of the American Veterinary Medical Association 238, 1316–1322.

31. Verheyen, K.L.P., Price, J.S., Wood, J.L.N., 2003. Epidemiology of fractures in British racehorses in training. Journal of Bone and Mineral Research 18, 1364.

32. Whitton, R.C., Trope, G.D., Ghasem-Zadeh, A., Anderson, G.A., Parkin, T.D.H., Mackie, E.J., Seeman, E., 2010. Third metacarpal condylar fatigue fractures in equine athletes occur within previously modelled subchondral bone. Bone 47, 826–831.

A FINITE ELEMENT INVESTIGATION OF FRACTURE HEALING UNDER SIMULATED MICROGRAVITY LOADING CONDITIONS

This is a summary of two articles published in the Journal of Biomechanical Engineering (reference 1 and 2 at the end of this summary) by B. Godomski, K. McGilvray, J. Easley, R. Palmer, E. Ehrhart, K. Haussler, R. Browning, B. Santoni and C. Puttlitz.

Take Home Message

Simulated microgravity loading condition lead to decreased hydrostatic pressure and strain levels of the healing fractures and contributes to subsequent alterations in the healing process, with animals exposed to a simulated microgravity environment subsequently healing via intramembranous bone formation rather than the typical endochondral ossification process experienced by animals healing in an Earth gravitational environment.

Introduction

The literature is deficient with regard to how the localized mechanical environment of skeletal tissue is altered during microgravity unloading and how these alterations affect bone remodeling and healing. Limited research has been performed to investigate the direct role of these reduced gravitational forces as they relate to fracture healing. The few in vivo studies that have been performed have consistently demonstrated that weight-bearing maintains skeletal integrity of healthy bones and ultimately accelerates the healing of long bone fractures by promoting rapid callus formation, while the lack of mechanical loading experienced during weightlessness leads to the inhibition of fracture healing. Alterations in the localized mechanical environment within mineralized tissues due to microgravity unloading remain inadequately described due to the experimental limitations associated with such tasks. However, the use of computational techniques may aid in elucidating the mechanical underpinnings of skeletal adaptation and healing in microgravity environments. Thus, the purpose of this study was to computationally characterize the local mechanical environment responsible for the inhibited fracture healing observed under experimental simulated microgravity conditions.

Methods

The effects of simulated microgravity on bone remodeling and fracture healing were previously investigated in two animal studies using a large animal (sheep) model.[1,2] Animal use approval was granted by the Colorado State University Animal Care and Use Committee (Approval #11-2938A). In the first study, a trans-biarticular fixator was applied to the hindlimb of five skeletally mature sheep for 8 weeks (ExFix group). This unloading technique was shown to simulate a 0.25g environment, or a 75% reduction in loading and a loss of metaphyseal bone mineral density of 25% per month. The second experiment investigated fracture healing using this simulated microgravity model. Following a 21 day simulated microgravity period and a resultant loss of bone mineral density of approximately 18%, a 3.0mm mid-metatarsal ostectomy was performed and stabilized with an orthopaedic locking plate instrumented with a rosette strain gage. An Earth gravity (Control, n=5) group was included in which an ostectomy was created, plated, and casted, allowing full loading to be transmitted through the bone. Both groups were euthanized after 28-days and post-sacrifice mechanical, micro-computed tomography (μCT), and histomorphometric analyses were performed to quantify fracture healing.

A high fidelity FE model of the ovine hindlimb extending from the tibia to the proximal phalanges was prepared from CT imagery data of a fully mature ewe. Each bone was segmented based on attenuation values to generate surface representations, and 8-noded hexahedral elements were morphed to the surface geometry of each bone to create a mesh consisting of 215,000 elements. Articular cartilage was modeled as a 0.5mm, three-element thick layer extruded from the osteochondral surfaces. Transversely isotropic, linearly elastic material properties were assigned to the cortical and cancellous bone, and a hyperelastic

Mooney-Rivlin material definition was assigned to the articular cartilage. A total of 8 ligaments of the metatarsophalangeal and hock joints were represented via spring elements. The external fixation components were then added to the model to create an ExFix group configuration while the base model was utilized to simulate the Control group.

To determine the appropriate model mesh resolution, strain energy density predictions from the model's hard and soft tissue constituents were compared between low, medium, and high mesh density models under identical loading conditions wherein the number of elements for each model was approximately doubled to create the next highest resolution model to ensure that the appropriate number of elements was utilized. Mode validation was performed by comparing metatarsal surface strain predictions to in vitro and in vivo experimentally-obtained strain measurements. Model predictions typically fell within one standard deviation of experimentally-derived data while the parametric convergence study demonstrated medium resolution model predictions to be within 5% of those predicted by the high resolution model. Therefore, the medium resolution model (215,000 elements) was used for the subsequent analysis.

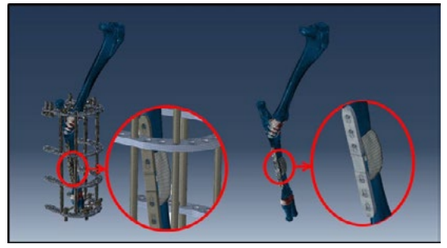


Fig. 1: The (right) ExFix and (left) Control FE fracture models were generated by creating a 3mm ostectomy and callus (red insets) at the mid-diaphysis of the metatarsus.

A 3mm mid-diaphyseal ostectomy was created in the ExFix and Control models (Figure 1). Callus dimensions for each model were taken from histological data. The callus material was modeled as a linearly elastic and isotropic, and a parametric FE analysis was performed to calibrate the model four-point bending stiffnesses to the experimentally-derived results. Each model was then loaded with muscle forces from a previously-developed musculoskeletal model[3] corresponding to 100N, 200N, and 300N GRF standing loads as well as a gait speed of 0.75m/s (corresponding to the maximum speed of the housed animals, or 600N). The local strain components and hydrostatic pressure within the fracture gap and periosteal callus predicted by each model were then compared with histological results.

Results

The in vivo study demonstrated inhibited healing in animals exposed to simulated microgravity as compared to those that healed in a 1g Earth gravitational environment. µCT results indicated decreased callus bone volume in simulated microgravity specimens versus 1g specimens. 1g specimens routinely displayed endochondral ossification bone formation in the periosteal callus as well as lower levels of intramembranous bone formation around the periosteal callus perimeter, while the simulated microgravity specimens appeared to heal directly through intramembranous bone formation without evidence of a cartilage intermediary (endochondral ossification, Figure 2).

As expected, model hydrostatic pressure and strain predictions were greatest for a GRF of 600N (0.75m/s gait speed) in both FE models and decreased as a function of GRF. Both models predicted peak hydrostatic pressures and strains within the cortices of the fracture gap (Figure 3) contralateral to the orthopaedic fixation plate, with both parameters decreasing radially toward the callus periphery.

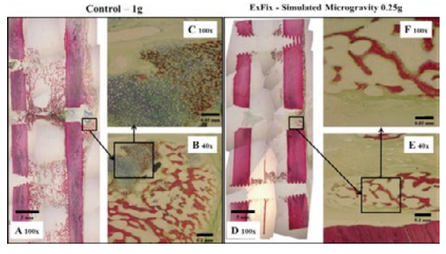


Fig. 2: (A,B,C) Experimental 1g control specimens routinely displayed endochondral ossification bone formation in the periosteal callus as well as lower levels of intramembranous bone formation around the callus perimeter. (D,E,F) The simulated microgravity specimens appeared to heal directly through intramembranous bone formation.

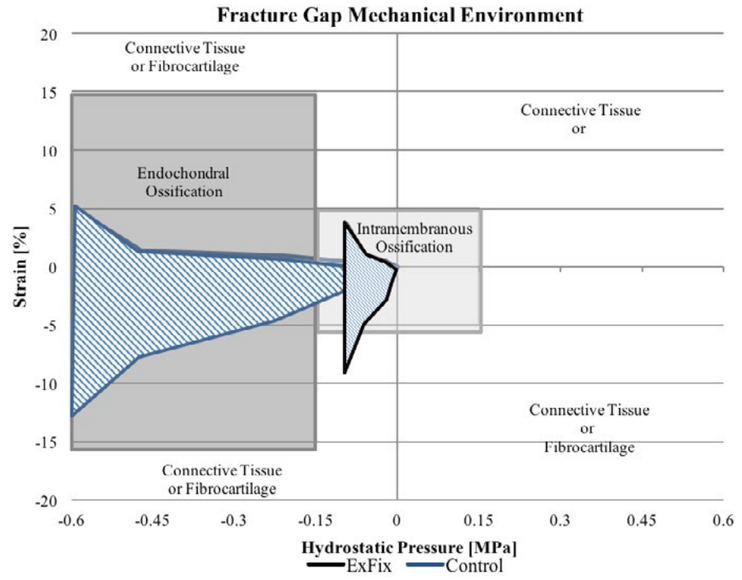


Fig. 3: The Control model predicted peak hydrostatic pressure and strain within the endochondral ossification envelope for the range of GRFs while all hydrostatic pressure and strain predictions fell within the intramembranous ossification zone for the ExFix model.

Discussion

The mechanical unloading experienced during simulated microgravity induced inhibited fracture healing via fundamental changes to the bone formation sequelae. Previous studies have elucidated specific envelopes of pressure and strain that lead to either endochondral or intramembranous ossification (Figure 3).

The predictive data of this FE study suggests that both hydrostatic pressure and strain of the healing fracture contributed to alterations in the healing process, with animals exposed to a simulated microgravity environment subsequently healing via intramembranous bone formation rather than the typical endochondral ossification process experienced by animals healing in an Earth gravitational environment. These findings will help direct future countermeasures for enhancing bone healing in microgravity environments.

Acknowledgments

Funding provided by the National Aeronautics and Space Administration (NNX11AQ81G).

References

1. B.C. Gadomski, K.C. McGilvray, J.T.Easley, R.H. Palmer, E.J. Ehrhart, K.K. Haussler, R.C. Browning, B.G. Santoni, C.M.Puttlitz. "An in vivo ovine model of bone tissue alterations in simulated microgravity conditions." J Biomech Engr 136, 2014.

2. B.C. Gadomski, K.C. McGilvray, J.T.Easley, R.H. Palmer, E.J. Ehrhart, K.K. Haussler, R.C. Browning, B.G. Santoni, C.M.Puttlitz. "Partial Gravity Unloading Inhibits Bone Healing Responses in Haversian Bone Systems." J Biomech 47, 2014.

3. Z.F.Lerner, B.C. Gadomski, A. Ipson, K.K. Haussler, C.M.Puttlitz, R.C. Browning. "Modulating tibiofemoral contact force in the sheep hindlimb via treadmill walking: Predictions from an OpenSim musculoskeltal model. J Orthopaed Res, 2015

Evaluation of Meniscal Mechanics and Proteoglycan Content in a Modified ACL Transection Model

Fischenich, K., Coatney, G., Haverkamp, J., Button, K., Decamp, C., Haut, R.C., Haut Donahue, T.L. Journal of Biomechanical Engineering, Jul; 136(7), 2014.

Take Home Message

This study is one of the first to monitor meniscal changes after inducing combined meniscal and ACL transections. With no surgical intervention to repair damaged tissue, 12 weeks post trauma there is a decrease in elastic moduli as well as a decrease in GAG coverage. Thus, it would appear that damage to the soft tissue of the knee is exasperated over 12 weeks and further damages the remaining meniscal tissue. Thus, interventions to treat the acute damages should be investigated that also focus on not only the visibly torn tissues, but the remaining meniscal tissue as well.

Introduction

Post traumatic osteoarthritis (PTOA) is a form of secondary osteoarthritis which develops as a result of traumatic loading that causes tears of the soft tissues in the knee. This study introduces a modified transection model to monitor PTOA development in which both meniscal and anterior cruciate ligament (ACL) transections have occurred. Specifically mechanical and histological properties of the menisci were investigated.

Methods

Six skeletally mature Flemish Giant rabbits were used in this study. Once the rabbits were anesthetized, the right limb underwent open joint surgery where the ACL and both menisci were transected. The medial meniscus then received a radial transection in the white zone of the central region with a longitudinal transection extending though the main body. The lateral meniscus was transected radially in the white zone of the central region and with a minor longitudinal cut extending anteriorly. The left limb served as a control and rabbits were sacrificed 12 weeks post-surgery. Gross morphological assessments, elastic moduli, and glycosaminoglycan (GAG) coverage of the menisci were determined to quantify the amount of tissue damage.

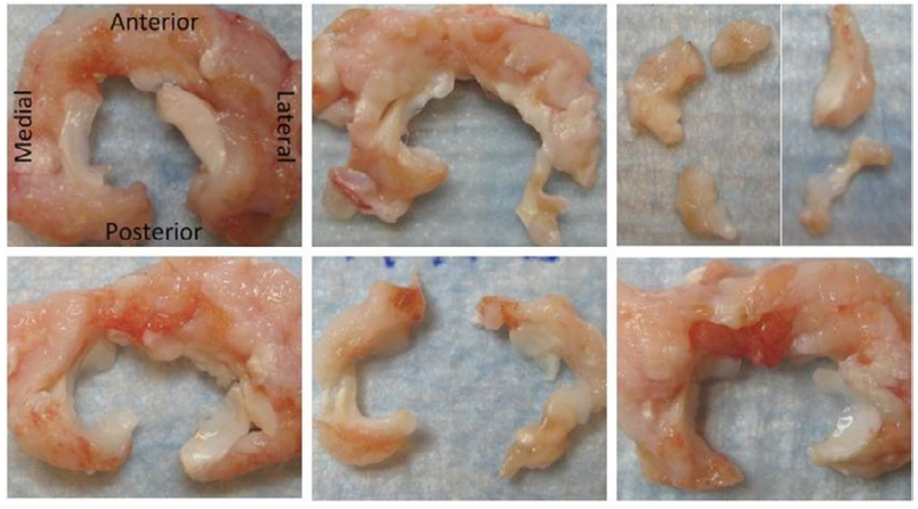


Fig. 1: Menisci twelve weeks post-surgery. (animals 1-6 left to right and top to bottom, all specimens are oriented identical to the first image).

Results

Gross morphology showed extensive damage to the structure of the transected menisci (Figure 1). Extensive damage rendered some regions mechanically untestable. Averaging data for a given hemijoint, there was a significant decrease in both the instantaneous and equilibrium moduli of both the lateral and medial menisci. Instantaneous elastic moduli decreased 72% from control to transected limb in both hemijoints, while the equilibrium elastic moduli decreased 81% in the lateral hemijoint and 71% in the medial hemijoint (Figure 2). Overall, GAG coverage decreased significantly between control and transected limbs for both the lateral (66% decrease) and medial menisci (51% decrease). (Figure 3).

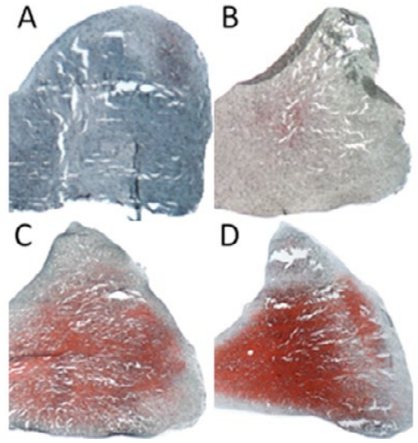


Fig. 2: Safranin-O-Fast Green staining intensity: (A) No stain = 0 (B) Slight staining = 1 (C) Moderate staining = 2 (D) Strong staining = 3. The ACLT animals showed reduced GAG coverage and had a mean score of less than 1 for GAG intensity. Control joints, without transections showed strong GAG staining with an overage score of 2.5.

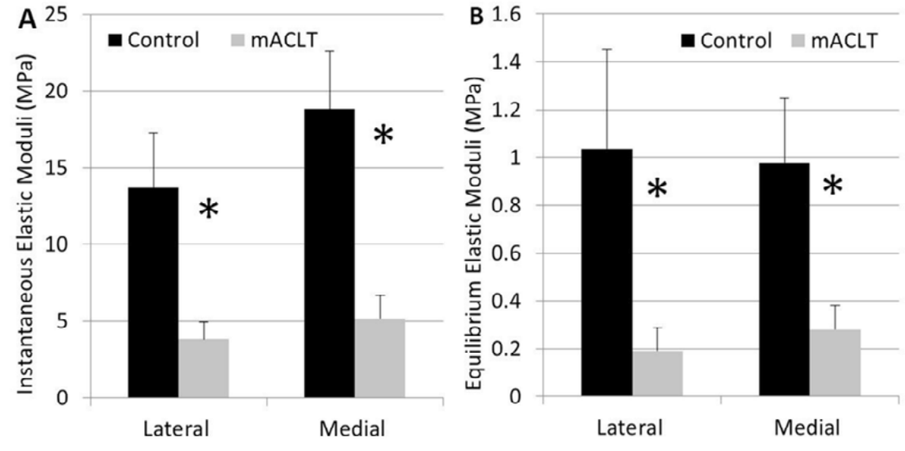


*Fig. 3. 3A) Instantaneous and 3B) equilibrium elastic moduli by hemijoint (mean with standard error) *denotes significant difference between control and modified ACL transection model.*

Dynamic testing of horseshoe designs at impact on synthetic and dirt Thoroughbred racetrack materials

This is a summary of a study that was published in Equine Veterinary Journal in 2014. doi: 10.1111/evj.12360 by Drs. C. Mahaffey, M. Peterson, J. Thomason and W. McIlwraith.

Take Home Message

This comparison of 3 different Thoroughbred racing shoes indicate that shoeing has little effect, and that a track's surface material in its preparation has a significant effect on the dynamic loading during the impact phase of the stance.

Introduction

Safety concerns in horse racing are often focused on surfaces and other variables at the track surface and hoof interface.[1] The previous research is demonstrated that surface characteristics including composition, cushion depth, moisture in dirt tracks, temperature in synthetic tracks, and the effects of maintenance all influence the mechanics of a surface.[2-5] Different surfaces, from one facility to the next, may provide different performance conditions experienced by the horse and rider. One way that trainers may attempt to control the surface hoof interface is to use different kinds of horseshoes for various track surfaces and conditions. Accordingly, different horseshoe designs have been developed in an attempt to optimize footing for equine athletes. For example, common toe grabs and heel calks at varying heights are used in order to manipulate traction. Other shores, such as the V-Grip shoe available through Victory Racing Plates (Baltimore, Maryland, USA), are intended to affect slide and traction in a horse's gait.

Horseshoe performance is assumed to be dependent on the surface and the gait but there are limited data on horseshoe performance on different surfaces independent of gait variation. 3 different shoes were tested on synthetic and dirt surfaces at typical operating conditions of temperature and moisture content for the respective material samples in this study.

Materials and Methods

This study quantifies the dynamic loading for 3 aluminum racing horseshoe designs on Thoroughbred racetrack surfaces using a biomechanical surface tester. Samples were tested under laboratory conditions replicating a track surface by compacting material into a latex-lined mold, surrounded by silica sand for represented boundary conditions. Peak loading and loading rates were measured vertically and horizontally (craniocaudal), simulating aspects of primary and secondary impacts of the hoof in a galloping horse.

Results and Discussion

Maximum vertical and shear loads and loading rates were not significantly different between shoes types with the exception of a reduced craniocaudal loading rate for the V-grip shoe on the synthetic surface. All other statistical significance was related to the surface material. It was noted that the 7° C synthetic material sample had a higher shear strength and lower cohesion than the 20° C sample under compacted conditions for drained triaxial testing. The dirt shear strength was examined at maximum stress whereas the synthetic shear strength was reported at 10% stress because the material, unlike dirt, does not have a clear failure. The highest cohesion for compacted dirt material occurred at 16% moisture (by mass) at which moisture content the dirt surface sample also achieved the maximum dry density. The 14% moisture contented resulted in the greatest total shear strength of 176.5 kPa in the dirt.

Under controlled laboratory conditions testing a synthetic and dirt Thoroughbred racetrack material, horseshoe design had no significant effect in 33 out of 36 combinations of peak loads and loading rates measured for 3 shoe types on 3 surface types. The 3 exceptions were for the V-grip shoe, which had a significantly lower craniocaudal maximum loading rate for the surfaces. These results support that a track's surface material and its preparation has a much greater effect on loading during the primary and secondary impact in a gallop than do horseshoes- the primary impact occurring at the peak dorsoventral load of the surface tester, and the secondary impact occurring at the peak craniocaudal load of the surface tester.1 The moisture content (affecting dry density and thus shear strength) and temperature are documented as having significant effects on the loading of dirt[25] and synthetic materials[20] respectively.

Conclusions

These 3 different Thoroughbred racing shoes do not have a significant impact on loading and loading rate with the exception of the V-grip shoe on a synthetic surface. Although the V-grip may reduce craniocaudal peak load rates in a synthetic material with relatively high wax and/or low oil content, the reduction in load rate is less than the difference found between materials. This study indicates that shoeing has little effect, and that a track's surface material and its preparation has a significant effect, on the dynamic loading during the impact phase of the stance.

References

1. Peterson, M.M., Roepstorff, L., Thomason, J.J., Mahaffey, C. and McIlwraith, C.W. (2011) Racing Surfaces White Paper. p 34.

2. Mahaffey, C.A., Peterson, M.L. and Roepstorff, L. (2013) The effects of varying cushion depth on dynamic loading in shallow sand thoroughbred horse dirt racetracks. Biosystems Engineering 114, 178-186.

3. Mahaffey, C.A., Peterson, M.M. and McIlwraith, C.W. (2012) Archetypes in Thoroughbred Dirt Racetracks Regarding Track Design, Clay Mineralogy, and Climate. Sports Engineering 15, 21-27.

4. Bridge, J.W., Peterson, M.L., Radford, D.W. and McIlwraith, C.W. (2010) Thermal transitions in high oil content petroleum-based wax blends used in granular sport surfaces. Thermochimica Acta 498, 106-111.

5. Peterson, M.L. and McIlwraith, C.W. (2008) Effect of track maintenance on mechanical properties of a dirt racetrack: A preliminary study. Equine Vet. J. 40, 602-605.

6. Benoit, P., Barrey, E., Regnault, J.C. and Brochet, J.L. (1993) Comparison of the Damping Effect of Different Shoeing by the Measurement of Hoof Acceleration. Cells Tissues Organs 146, 109-113.

7. Scheffer, C.J.W. and Back, W. (2001) Orthopaedics: Effects of 'navicular' shoeing on equine distal forelimb kinematics on different track surface. Veterinary Quarterly 23, 191-195.

8. Anthenill, L.A., Stover, S.M., Gardner, I.A. and Hill, A.E. (2007) Risk factors for proximal sesamoid bone fractures associated with exercise history and horseshoe characteristics in Thoroughbred racehorses. Am. J. Vet. Res. 68, 760-771.

9. Hill, A.E., Stover, S.M., Gardner, I.A., Kane, A.J., Whitcomb, M.B. and Emerson, A.G. (2001) Risk factors for and outcomes of non-catastrophic suspensory apparatus injury in Thoroughbred racehorses. J. Am. Vet. Med. Assoc. 218, 1136-1144.

10. Gross, D.K., Stover, S.M., Hill, A.E. and Gardner, I.A. (2004) Evaluation of forelimb horseshoe characteristics of Thoroughbreds racing on dirt surfaces. Am. J. Vet. Res. 65, 1021-1030.

11. Hernandez, J.A., Scollay, M.C., Hawkins, D.L., Corda, J.A. and Krueger, T.M. (2005) Evaluation of horseshoe characteristics and high-speed exercise history as possible risk factors for catastrophic musculoskeletal injury in Thoroughbred racehorses. Am. J. Vet. Res. 66, 1314-1320.

12. Barrett, R.S., Neal, R.J. and Roberts, L.J. (1998) The dynamic loading response of surfaces encountered in beach running. Journal of Sports Science and Medicine 1, 1-11.

13. Ehrlich, P.J. and Lanyon, L.E. (2002) Mechanical strain and bone cell function: a review. Osteoporosis International 13, 688-700.

14. Kulin, R.M., Jiang, F. and Vecchio, K.S. (2011) Effects of age and loading rate on equine cor-

tical bone failure. Journal of the Mechanical Behavior of Biomedical Materials 4, 57-75.

15. Torcasio, A., van Lenthe, G.H. and Van Oosterwyck, H. (2008) The importance of loading frequency, rate and vibration for enhancing bone adaptation and implant osseointegration. European Cells and Materials 16, 56-68.

16. Peterson, M.L., McIlwraith, C.W. and Reiser, R.F. (2008) Development of a system for the in-situ characterisation of thoroughbred horse racing track surfaces. Biosystems Engineering 101, 260-269.

17. Polytrack® (2010) Polytrack® Product Information.

18. Cushion Track (2010) Cushion Track Product Information. Accepted Article This article is protected by copyright. All rights reserved. 16

19. ASTM (2005) Standard Test Methods for Laboratory Determination of Water (Moisture) Content of Soil and Rock by Mass. In: Book of Standards Volume: 04.08, ASTM International, West Conshohocken, PA.

20. Bridge, J.W., Peterson, M.L., McIlwraith, C.W. and Beaumont, R.M. (2010) Temperature Effects on Triaxial Shear Strength of Granular Composite Sport Surfaces. Journal of ASTM International 7, 12.

21. Peterson, M.L., Reiser II, R.F., Kuo, P.-H., Radford, D.W. and McIlwraith, C.W. (2010) The effect of temperature on 6 furlong times on a synthetic racing surface. Equine Vet. J. 42, 351-357.

22. ASTM (2007) Standard Test Methods for Laboratory Compaction Characteristics of Soil Using Standard Effort (12 400 ft-lbf/ft3 (600 kN-m/m3)). In: Book of Standards Volume: 04.08, ASTM International, West Conshohocken, PA.

23. Fung, Y. (1993) Biomechanics: mechanical properties of living tissues, Springer-Verlag.

24. ASTM (2004) Standard Test Method for Consolidated Undrained Triaxial Compression Test for Cohesive Soil. In: Book of Standards Volume: 04.08, ASTM International, West Conshohocken, PA.

25. Ratzlaff, M.H., Hyde, M.L., Hutton, D.V., Rathgeber, R.A. and Balch, O.K. (1997) Interrelationships between moisture content of the track, dynamic properties of the track and the locomotor forces exerted by galloping horses. J. Equine Vet. Sci. 17, 35-42.

26. Steffanus, D. (2003) Grip and Slide. In: Thoroughbred Times, Thoroughbred Times, Lexington, Kentucky.

27. Duckworth, A.H. (2007) Synthetic Surfaces: Right Direction. In: The Blood Horse. pp 6987-6988. Accepted Article This article is protected by copyright. All rights reserved. 17

28. Setterbo, J.J., Garcia, T.C., Campbell, I.P., Reese, J.L., Morgan, J.M., Kim, S.Y., Hubbard, M. and Stover, S.M. (2009) Hoof accelerations and ground reaction forces of Thoroughbred racehorses measured on dirt, synthetic, and turf track surfaces. Am. J. Vet. Res. 70, 1220-1229.

29. Setterbo, J.J., Chau, A., Fyhrie, P.B., Hubbard, M., Upadhyaya, S.K., Symons, J.E. and Stover, S.M. (2012) Validation of a Laboratory Method for Evaluating Dynamic Properties of Reconstructed Equine Racetrack Surfaces. PLoS ONE 7, e50534.

30. Setterbo, J., Yamaguchi, A., Hubbard, M., Upadhyaya, S. and Stover, S. (2011) Effects of equine racetrack surface type, depth, boundary area, and harrowing on dynamic surface properties measured using a track-testing device in a laboratory setting. Sports Engineering 14, 119-137.

31. Kerdok, A.E., Biewener, A.A., McMahon, T.A., Weyand, P.G. and Herr, H.M. (2002) Energetics and mechanics of human running on surfaces of different stiffnesses. J. Applied Physiology 92, 469-478.

32. Ferris, D.P. and Farley, C.T. (1997) Interaction of leg stiffness and surface stiffness during human hopping. J. Applied Physiology 82, 15-22.

33. Pfau, T., Witte, T.H. and Wilson, A.M. (2006) Centre of mass movement and mechanical energy fluctuation during gallop locomotion in the Thoroughbred racehorse. The Journal of Experimental Biology 209`, 3742-3757.

34. The Jockey Club (2012) Supplemental Tables of Equine Injury Database Statistics.

35. Parkin, T.D.H. (2007) Epidemiology of training and racing injuries. Equine Vet. J. 39, 466-469.

36. Schaer, B.L.D., Ryan, C.T., Boston, R.C. and Nunamaker, D.M. (2006) The horse-racetrack interface: a preliminary study on the effect of shoeing on impact trauma using a novel wireless data acquisition system. Equine Vet. J. 38, 664-670.

37. Colahan, P., Leach, D. and Muir, G. (1991) Center of pressure location of the hoof with and without hoof wedges. Equine Exercise Physiology 3, 113-119. Accepted Article This article is protected by copyright. All rights reserved. 18

38. Tan, H. and Wilson, A.M. (2011) Grip and limb force limits to turning performance in competition horses. Proceedings

RESEARCH | FOCUS 3 -Improvement in the Understanding of the Pathogenesis of Exercise-Induced Traumatic Disease

Advances in the understanding of tendinopathies: A report on the Second Havemeyer Workshop on equine tendon disease

This is a reproduction of an article previously published in 2014 in Equine Veterinary Journal by R. Smith, (co-organizer), W. McIlwraith (co-organizer),R. Schweitzer, K. Kadler, J. Cook, B. Caterson, S. Dakin, D. Heinegård, H. Screen, S. Stover, N. Crevier-Denoix, P. Clegg, M. Collins, C. Little, D. Frisbie, M. Kjaer, R. van Weeren, N. Werpy, J.-M. Denoix, A. Carr, A. Goldberg, L. Bramlage, M. Smith and A. Nixon. Equine Vet Journal, 2014; 46: 4-9.

Introduction

The second workshop on equine tendon disease funded by the Havemeyer foundationwas held at Estes Park, Colorado, USA from 23 to 26 September 2012. A list of workshop participants can be found in Appendix S1.

The following is a summary of the presentations and discussion.

Tendon development (Ronen Schweitzer and Karl Kadler)

Tendons are formed during the second half of embryonic development when tendon precursor cells deposit narrow-diameter (~30 nm) collagen fibrils that are parallel to the long axis of the tissue. During post natal development, the narrow fibrils are replaced by large-diameter (up to 500 nm) fibrils. The ability of tendon to transmit force frommuscle to bone, and to dissipate forces during locomotion, is directly attributable to the collagen fibrils. How the fibrils are synthesised, how they are aligned parallel to the tendon long axis, and how this arrangement can be reinstated during tendon healing are poorly understood. Ultrastructural studies of tendon lesions show the reappearance of narrow-diameter collagen fibrils and cells with slender cytoplasmic protrusions (called fibripositors) that normally only occur in tendon during embryonic development. Recapitulation of development is a hypothesis that is gaining increasing support from researchers of tendon disease. A better understanding of the genetic, molecular and environmental cues during embryonic development is expected to provide better insights into how to improve the rate and fidelity of tendon repair in mature horses. Tendon development can conveniently be considered to have an early 'cellular' phase and a subsequent 'matrix' phase. In the matrix-dominated phase of tendon development 3D scanning electron microscopy of mouse tendon suggests that fibripositors of the cells are the site of new fibril formation and the mechanical interface between the cell and the extracellular matrix. It is hypothesised that fibripositors exert pulling forces on collagen fibrils, and their cellular forces require functional myosin II, which is an intracellular molecular motor that is part of the actinomyosin system. A detailed understanding of how cells set the tensional homeostasis of tendon is expected to lead to new strategies for regulating collagen fibril assembly in health and in tendinopathy.

Tendon physiology and pathogenesis (Jill Cook, Bruce Caterson, Stephanie Dakin and Dick Heinegård)

Tendons are diverse and specialised musculoskeletal tissues. The tendon cell is responsible for maintaining this complex tissue, and mechanical load and the local environment significantly influence tendon phenotype and metabolism. Tendon disease is a result of mechanical overload, especially storage and release of energy[1]. Tensile and/or compressive overload will induce different tendon responses[2]; for example, core lesions in the equine superficial digital flexor tendon (SDFT) may be due to tensile overload, whereas compressive overload may induce pathology in the deep digital flexor tendon (DDFT). Recent work suggests that the primary response to overload may be inflammation[3] and/or local tendon cell activation and proliferation.[4] Vascular disruption may initiate a more inflammatory response, whereas mechanical overload without vascular damage may induce a cell driven pathology. Inflammation at the cellular level has been shown in early-stage naturally occurring equine injury[3], and a mechanism for incomplete resolution of inflammation after injury is suggested. High levels of inflammation have also been described in early-stage human rotator cuff tears.[5] Conversely, a noninflammatory response to overload may be driven by the tendon cell, resulting in many extracellular matrix changes. Tendon cell activation, proliferation and the enhanced production and deposition of proteoglycan may result in the formation of functionally compromised tissue. Changes in cell morphology will induce different patterns in collagen expression and this, combined with increased proteoglycan expression, will compromise the collagen network, resulting in altered physiological function of the tissue. Future challenges include differentiating the beneficial and detrimental effects of inflammation and local cellular response, characterising proteoglycan deposition and its effect upon collagen fibril formation and orientation and change in collagen expression patterns induced by the change in cell phenotype. Therapies or loading regimes that regulate cell proliferation and proteoglycan production in response to acute overload would be advantageous.

Biomechanics and mechanobiology (Hazel Screen, Sue Stover, Nathalie Crevier-Denoix and Peter Clegg)

To characterise the biomechanics of any organ it is necessary to take into account the whole hierarchy of the structure. Whole body biomechanics will facilitate understanding of the loading environment experienced by any tissue. It is then necessary to characterise the strain transfer throughout the tissue hierarchy to understand tissue function and deformation, and the resulting cellular responses.

Whole body biomechanics

High tendon strains, which result from high tendon loads, promote the development of tendon injury; minimising these should reduce the incidence of tendinopathy. Tendon loads are directly related to the ground reaction forces and, as such, modification of the nature of the surface, or of the geometry or properties of the hoof and horseshoe, could all reduce the risk of injury. The capacity to determine in vivo tendon strains during a range of physiological loads has recently enabled advancement in our understanding of tendon biomechanics, with the ultimate aim of both preventing and improving treatments for SDFT injury. Limb kinetics and kinematics can be measured simultaneously with hoof accelerations.[6,7] and superficial digital flexor muscle activity can also be measured at different gaits using electromyography.[8] Incorporating all these data into computer models can provide exciting insights into forelimb locomotion, enhancing our understanding of the factors that affect tendon and ligament mechanics.[9,10] In addition, a novel ultrasound tensometer (called Tensonics) has recently been developed[11,12], enabling SDFT mechanics to be measured in horses during both trot and gallop activities[13]. This technique has been recently tested in preliminary studies to measure loading of the Achilles tendon during walk in human subjects[14] and to follow-up equine tendon lesion recovery.[15,16] It uses the linear correlation between tendon modulus and the speed of ultrasound[17] to establish tendon force characteristics in real time, enabling the tendon load environment to be determined across different training surfaces and at different exercise speeds. Using this range of analytical techniques, it has been shown that ground reaction forces, hoof acceleration, limb kinematics and tendon loads all differ for horses at different gaits and on different surfaces[6, 18–24], and that limbmechanics at sites distant to the site of tendon injury affect propensity for injury.[25] Test instruments that simulate hoof impact have been used to measure static and dynamic properties of racing surfaces [23,26] and, in the USA, a national track surface testing laboratory provides standard tests for measurements of the composition and mechanical behaviour of surface materials.[http://www.racingsurfaces.org]

Tendon biomechanics

As tendon is a hierarchical fibrocomposite material, strain transfer through tendon is complex, with data showing that tendon extension is governed by sliding between collagenous components throughout the hierarchy.[27–29] Based on these data, recent studies have focused on elucidating micromechanical distinctions between differing functional tendons. In high-strain energy storing tendons, fascicles have a helical structure, which will lead them to act as small springs, enabling efficient elastic extension and recoil.[30] Furthermore, in these tendons there is considerable interfascicular sliding, facilitating the large strain requirements of this tissue without overloading the collagen components.[30] In contrast, in the low-strain stiffer positional tendons, more viscoelastic and less fatigueresistant behaviour is governed by fibre and fibril sliding.[31] With fascicle sliding proposed to be key in high-strain tendons, understanding how the noncollagenous matrix between fascicles mediates sliding mechanics may be key to preventing failure. It is likely that molecules such as elastin, elastic fibres, lubricin and a variety of proteoglycans will have key roles.[32–34] Failure at the noncollagenous interface

RESEARCH | FOCUS 3 -Improvement in the Understanding of the Pathogenesis of Exercise-Induced Traumatic Disease

will first alter load on the cell, and, through mechanotransduction, will potentially alter cell phenotype to a more degradative state. Second, failure of the noncollagenous matrix will propagate through the tissue hierarchy, ultimately resulting in both biochemical and mechanical failure of the structure. Risk of tendon injury increases with ageing.[35,36] As the SDFT ages the effectiveness of the fascicular spring reduces, and there is a stiffening of the interfascicular matrix.[30,37] These changes will result in localised stiffening within the hierarchy and probably alterations in cell loading. Injury risk is likely to be increased in individuals with less effective loading mechanisms in energy storing tendons, through injury or suboptimal conditioning during development, for example.

Tendinopathy genetics (Malcolm Collins)

Tendinopathy in man is a multifactorial condition and there is increasing evidence from both familial and case-control association studies that genetic sequence variants play an important role in its aetiology. For example, a fivefold increased risk of developing a rotator cuff injury following a sibling's injury has been reported in a family study.[38] Investigators have also reported an association of several DNA sequence variants with chronic Achilles tendinopathy in man. The associated genes encode: 1) structural components of the extracellular matrix (COL5A1 and TNC); 2) extracellular matrix proteinases (MMP3) and their inhibitors; 3) cytokines and growth factors (GDF5); 4) enzymes in the apoptotic pathway (CASP8); and 5) microRNAs (MIR608).[39–41] These associated genetic sequence variants do not cause tendinopathy: they merely alter the risk for injury. Tendinopathy is caused by a poorly understood complex interaction of environmental exposure, such as volume and intensity of training, and other nongenetic factors with the genetic background.[39] All the published association studies to date have used a case-control candidate gene approach to identify genetic risk factors implicated in chronic Achilles tendinopathy in either South African and/or Australian Caucasian populations.[40] Although the results of these early genetic association studies with Achilles tendinopathy have been promising, investigators have, when investigating other multifactorial conditions, such as osteoarthritis, often failed to repeat the association in other populations. This is a common observation and major limitation of any genetic association study.[42] A poorly defined or heterogeneous pathology is a common reason why genetic associations are often not repeated in independent follow-up studies. The inclusion of only homogeneous clinically well-defined forms of tendinopathy as cases in genetic association studies is therefore an important consideration.[43] The selection of appropriately matched controls is also as important as the selection of the cases.[40] Other limitations to the candidate gene approach include assumptions that the protein or nonprotein product of the gene is directly involved in the aetiology of the pathology, and missing genes that may be involved in currently unknown processes. Whole genome screening methods therefore need to be considered to capture all the potentially important biological pathways.

The initial genetic association studies in equine tendinopathy have also been promising. Some of the genes associated with human chronic Achilles tendinopathy have recently been shown to also associate with SDFT in racehorses.[44] The identification of genetic risk factors for equine tendinopathy has been made possible by the sequencing of the entire domestic horse genome. In addition, a high density equine single nucleotide polymorphism genotyping array has been developed and evaluated.[45]

Experimental models (Roger Smith, Chris Little, David Frisbie, Michael Kjaer and René van Weeren)

Our understanding of human and equine tendinopathy requires experimental models that accurately mimic natural disease. The similarities in naturally occurring tendinopathy between horses and man indicate that there are valid correlates between specific tendinopathies where the tendons were matched by function rather than anatomical location. Thus equine SDFT was analogous to the human Achilles tendinopathy and certain intrathecal lesions (i.e. DDFT tears) were analogous to human rotator cuff disease. The study of naturally occurring equine tendinopathy offers the prospect of additional insight into human tendinopathies, although expense, numbers and natural variability are major disadvantages.

The important role of altered biomechanics, both stress-deprivation and increased loading, in driving tendon pathology has been demonstrated using in vitro and in vivo models. Focal injury in the sheep infraspinatus and equine SDFT, induced by mid-body hemi-transection, resulted in tendinopathy throughout the length of the tendon. The characteristic histopathological features of increased cellularity, tenocyte rounding, neovascularisation, fibril disorganisation and proteoglycan accumulation occurred on both the stress-deprived and the overloaded sides. Despite similar histological appearances, the gene expression signature differed with the 2 loading conditions. The stress-deprivation pathology can be modelled in vitro by culturing tendon explants without tensile loading. Mesenchymal stem cells (MSCs) were effective in reducing surgically induced tendon pathology, but the timing of injection was critical, with maximal long-term effect with delayed administration. In vitro changes in MSC expression suggest that both the tenocytes and the condition of the extracellular environment determine the secretome of the injected cells, and that the MSCs are responding to feedback from their immediate environment.

High-throughput in vitro models to screen therapeutics would be helpful. However, our current understanding of clinical disease and progression of degeneration/healing is poor, leaving the creation of a suitable model difficult. The ideal experimental in vivo model should create a core lesion in the form of a compartment that does not include the paratenon. The classic surgical and collagenase models as published in the 1980s do not meet this requirement and are deemed inferior to the modifications for a core lesion produced mechanically with the help of arthroscopic instruments (the 'Schramme' model;[46]). The application of a low dose of collagenase in a mechanically created canal in the core of the tendon has also been described recently.[47] The Schramme model has been used successfully in a number of trials looking at the effect of intratendinous application of platelet-rich plasma (PRP) and the effect of casting on the propagation of lesions.[48,49]

Diagnosis of tendon disease (Natasha Werpy and Jean-Marie Denoix)

Multiple imaging modalities are available for imaging tendon injury, including ultrasonography (US), magnetic resonance imaging (MRI) and computed tomography (CT). The goal of imaging is to provide the most information possible about the character and progression of the injured tissue. Using US to assess tendinopathy is inexpensive and can frequently be performed in the standing horse. However, a decreased sensitivity to certain abnormalities in soft tissue structures has been shown. Therefore, improving and validating advanced US techniques is an important goal R. Smith and W. McIlwraith Advances in the understanding of tendinopathies: 2nd Havemeyer Workshop Equine Veterinary Journal 46 (2014) 4–9 © 2013 EVJ Ltd 5 of tendon imaging. Doppler, US tissue characterisation, elastography, microbubbles and angle contrast are all potential improvements to the standard US technique. The latter uses changes in the ultrasound beam angle to improve identification and characterisation of normal tendon and ligament architecture as well as differentiation of pathological change in soft tissue injury. Fusion imaging, which allows correlation of different imaging modalities and has increased availability, can be used as a tool to improve US techniques.

Magnetic resonance imaging provides superior soft tissue detail to US and CT. However, high-field MRI requires general anaesthesia and is expensive. In addition, recheck MRI examination in combination with other modalities is necessary to optimise lesion characterisation. Standing low-field MRI can be used to image tendon injury but its resolution will limit the identification of certain lesions, although those performed under general anaesthesia can provide information that cannot be detected with US. Although standing low-field MRI avoids general anaesthesia, weightbearing can obscure certain lesions and image detail can be reduced because of motion artefact. Furthermore, comparison of CT and MRI for lesion characterisation is needed. Standard MR images do not necessarily provide a clear distinction for chronicity, especially when evaluating tendinopathy characterised by increased signal intensity on proton density and/or T1-weighted images without a concurrent signal increase on T2-weighted or STIR images. These lesions are the most challenging in clinical cases because they can be identified in asymptomatic as well as in symptomatic cases with both acute and chronic injury. Ideally, correlation of multiple imaging modalities with histologic evaluation will allow the diagnosis and accurate characterisation of tendon injury while providing potential methods for more frequent monitoring without the expense and potential risks of general anaesthesia.

State of the art treatment in humans (Andy Carr and Andy Goldberg)

Two of the commonest tendons to cause symptoms and disability in man are the Achilles tendon and the rotator cuff tendons of the shoulder.

Rotator cuff tears increase in prevalence with age, although only half the tears in the general population are symptomatic, with larger tears being more likely to cause symptoms. Causes of pain are not well understood and studies of pain mechanisms are limited. It is clear that pain is not directly correlated with structural abnormality, and recent studies with quantitative sensory testing show evidence of central pain sensitisation.[50] This opens up opportunities for novel treatment strategies. In addition, an improved understanding of peripheral nociceptive variability is likely to lead to alternative and improved ways of managing shoulder pain, for example inhibition of nerve growth factor, a neurotrophin capable of sensitising peripheral nociceptors. Evidence for the effectiveness of conservative treatment is conflicting. Exercise therapy provided with formal instruction from specialist physiotherapists has been shown to improve symptoms and reduce the need for interventional treatment. Corticosteroid injections are commonly used and appear to improve symptoms in the short term, although there is evidence that symptoms return in the longer term and may be associated with accelerated tissue damage.[51] Cohort studies of surgical treatment, including acromioplasty and rotator cuff repair, show improvement in symptoms. However, some randomised trials question whether surgery is more effective than exercise, and whether acromioplasty has any added value.[52] Combined imaging and clinical reviews of rotator cuff repair surgery reveal that in spite of patients being symptomatically improved by surgery a large percentage re-rupture. Failure of the repair is associated with a poorer prognosis and is more common in the elderly and with larger tears. There is therefore a strong unmet clinical need to develop new, more effective therapies.

Achilles tendinopathy affects both athletes and sedentary individuals and conservative treatments include physiotherapy, corticosteroid injections, extracorporeal shockwave therapy, high volume injections, dry needling and PRP. Other than physiotherapy none of the treatments have any supporting evidence base[53], and many patients consider surgery that has unpredictable results.[54] Thus, there is a need for improved nonsurgical treatments. Studies of MSCs to treat equine SDFT injuries represent a natural disease model for their translation into a human study in the Achilles tendon and potentially rotator cuff disease, and a trial is under way assessing the use of autologous culture expanded mesenchymal stem cells in Achilles tendinopathy.

State of the art treatment in horses (Larry Bramlage and Matt Smith)

Tendinopathy in the horse can be broadly divided into intrathecal and extrathecal injuries. The former are quite consistent in lesion configuration and morphology, whereas with extrathecal lesions there are a number of distinct and different presentations. Intrasynovial tendinopathies involve tendon subjected to compressive rather than tensile forces. The periphery of the tendon is usually affected, in contrast to the most commonly encountered central lesions in extrathecal tendinopathies. However, the latter may present with several different ultrasonographic patterns. The most frequently encountered intrathecal injuries involve the lateral margin of the DDFT within the digital flexor tendon sheath, and the dorsal margin of the DDFT within the navicular bursa. Sports and pleasure horses are predominantly affected, with comparatively few racehorses compared to extrathecal injuries.

It is commonly accepted that preceding degenerative changes are a feature of extrathecal tendinopathies, but their role in intrasynovial injuries is uncertain. To date, histological evidence for preceding degeneration has not been evaluated. In contrast to extrathecal injuries, bilateral disease is uncommon and there is no demonstrable association between age and exercise. However, morphologically lesions appear similar to rotator cuff injuries in man, where preceding tendinopathic changes are well established. Histopathological examination of affected tendons should be pursued to elucidate this further.

Tendinitis can represent a secondary disease process, and careful clinical examination should always be performed to identify underlying processes, i.e. causes of contralateral limb lameness. Endoscopic debridement and annular ligament desmotomy are well accepted in the treatment of intrasynovial tendinopathies. Debridement facilitates tendon healing, and second-look endoscopic procedures have confirmed that this can be achieved. Healing can be unreliable, but results of treatment are still fair to good. Advances in treatment strategies are necessary; in man, endoscopic repair techniques are employed for rotator cuff tears, and this requires attention in the horse. Percutaneous tendon splitting and superior check ligament desmotomy appear to have promise in certain presentations of extrathecal injury, although those most appropriate for each procedure remain to be well defined. Current observations indicate that both appear most effective in the more acute stage of tendinitis with active lesions, and should be considered early, prior to the conversion of the lesion into irreversible fibrous tissue. Traumatic lacerations represent a different entity and are not considered further here. Biological and surgical treatments are compatible and may be combined rather than considered mutually exclusive. Pretreatment diagnosis of intrasynovial lesions remains difficult, although improvements in ultrasonographic technique, and contrast radiography, have advanced predictability. Failure of treatment particularly with extrathecal injuries, usually does not occur until well into the training stages of rehabilitation, making early assessment of prognosis difficult. Current rehabilitation strategies are largely arbitrary and relatively little is known about optimum programmes for different injury presentations. There are limitations in the ability of ultrasound to differentiate stages of healing and readiness for increases in exercise.

New treatments: research evidence to guide selection of biological treatments for tendinopathy (Wayne McIlwraith and Alan Nixon)

The selection of recombinant forms of growth factors (which ones, how much and in what vehicle), bone marrow aspirate, cultured stem cells, PRP or mixtures of several, for injection to acute and subacute tendinopathy is still based only on empirical evidence, with limited experimental and controlled case studies to support the choices. Available products include:

1. Bone marrow aspirate. Anecdotal evidence supports the injection of bone marrow aspirate.[55] It is quick and economical, and contains high levels of transforming growth factor-β and platelet-derived growth factor.[56] Both growth factors induce collagen synthesis. Systems that concentrate the growth factors and cells in marrow may be more useful.
2. PRP, generated by differential centrifugation or filtration of autologous whole blood.[57] PRP provides a more concentrated source of platelet-derived growth factor and transforming growth factor-β than marrow, and numerous other growth factors such as vascular endothelial growth factor and platelet-derived angiogenesis factor, thromboxane, and fibronectin/vitronectin. Commercial systems vary in platelet concentration and white blood cell numbers. PRP potentially contributes to healing of tendon and ligament[58]; however, the potential proinflammatory effect of white blood cells has been recognised and may be detrimental.[59,60] There is emerging evidence that more than just the platelets in PRP are playing a role. Recent research favoured PRP for tendonitis and marrow aspirate for suspensory desmitis.[56,58] A controlled study with mechanically induced tendonitis showed significantly enhanced biomechanical and histological parameters at 24 weeks.[48] Small case series indicate improved response after PRP injection into suspensory lesions.[61] There are no large scale reports of PRP effects in SDFT tendonitis in racehorses. A recent study evaluated PRP as a treatment for proximal sesamoiditis – suspensory ligament branch desmitis. Two-year-old horses treated with PRP were more likely to start a race than horses treated with saline, but their earnings were similar. Additionally, some PRP-treated horses developed cosmetic blemishes at the injection site.[62]
3. Interleukin-1 receptor antagonist protein (IRAP; Dechra, Dusseldorf, Germany) and IRAP II (Arthrex, Bonita Springs, Florida, USA). Comparing the response to PRP and bone marrow aspirate in vitro, a recent study using tenocytes cultured from SDFTs showed that both bone marrow aspirate and PRP derived by plasma centrifugation (ACP; Arthrex, Bonita Springs, Florida, USA) stimulated secreted collagen production more than other commercial PRP devices, IRAP and IRAP II, and plasma. However, IRAP and IRAP II were the strongest stimulators of cell proliferation.[63] IRAP and IRAP II have been used as a treatment but there are no published reports of their use in clinical tendinopathy cases.

4. Centrifuged bone marrow aspirate concentrate. Heparinised bone marrow can be separated and the stem cells and small leucocyte population concentrated using a modified floating specific density shelf along the same principle as PRP. These devices concentrate MSCs and growth factors, but there are no clinical reports defining outcome after injection to tendon or ligament in horses.

5. Cultured MSCs. Several studies suggest that equine MSCs can be derived from bone marrow or fat.[64,65] Experimental studies indicate that MSC injection and injection of MSCs overexpressing IGF-I improve tendonitis repair in a collagenase model of equine SDF tendonitis.[66] A surgical model failed to show improved tendon fibre architecture after MSC injection to core lesions.[67] However, small clinical studies show improved return to function after MSC injection to SDF tendon damage[68], and a more recent, larger scale study showed that cultured MSCs reduced reinjury rate after tendonitis in a retrospective study, predominantly involving National Hunt horses.[69] The use of 10–20 million cultured MSCs admixed with PRP or bone marrow aspirate would appear to hold the most promise from a theoretical standpoint. However, no case series involving the mixture of MSCs and PRP has been published to date.

6. Concentrated adipose tissue digest (adipose derived nucleated cells e.g. stromal vascular fraction) contains MSCs and other nucleated cells and proteins active in tissue healing. Equine studies showed that it appears to improve tendon healing in collagenase induced lesions.[65] Reduced further degeneration may be a key component of fat derived nucleated fractions, reducing apoptosis, enzymatic propagation and necrosis.

7. Fetal derived embryonic stem cells (ESCs). Fetal derived stem cells can be exposed in culture to agents that select for an ESC-like cell, capable of continued propagation without senescence. These cells have improved repair in a tendonitis model in horses[70,71], but no clinical data have been published.

8. Induced pluripotent stem cells. Developing pluripotent cells from mature fibroblasts or other mesenchymal tissue by genetic transformation is a new and interesting progression of research. These induced pluripotent stem cells essentially behave like ESCs without the stigma of embryo harvest. They have been developed in the horse, but no clinical application in musculoskeletal tissue repair has been published.

[1]Department of Veterinary Clinical Sciences and Services, The Royal Veterinary College, UK; [2]Clinical Sciences, Orthopaedic Research Center, Colorado State University, USA; [3]SOM-Cell and Developmental Biology Department, Oregon Health and Science University, USA; [4]Faculty of Life Sciences, University of Manchester, UK; [5]Department of Physiotherapy, School of Primary Health Care, Monash University, Victoria, Australia; [6]Cardiff School of Biosciences, UK; [7]Faculty of Medicine, Lund University, Sweden; [8]The School of Engineering and Materials Science, Queen Mary, University of London, UK; [9]University of California, USA; [10]Ecole Vétérinaire d'Alfort, UMR INRA-ENVA BPLC (Biomécanique du Cheval), France; [11]University of Liverpool, UK; [12]Department of Human Biology, UCT/MRC Research Unit for Exercise Science and Sports Medicine (ESSM), South Africa; [13]Raymond Purves Bone and Joint Research Laboratories, Kolling Institute of Medical Research, E25 - Royal North Shore Hospital, University of Sydney, New SouthWales, Australia; [14]Clinical Sciences, Colorado State University, USA; [15]Department of Clinical Medicine, Section of Orthopaedics and Internal Medicine, Bispejerg Hospital, Denmark; [16]Equine Sciences, Utrecht University, the Netherlands; [17]Veterinary Medicine and Surgery, University of Florida, USA; [18]CIRALE, France; [19]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Nuffield Orthopaedic Centre, University of Oxford, UK; [20]Royal National Orthopaedic Hospital, UK; [21]Rood and Riddle Equine Hospital, Kentucky, USA; [22]Newmarket Equine Hospital, UK; [23]Clinical Sciences, Cornell University, New York, USA

References

1. Kjaer, M., Langberg, H., Miller, B.F., Boushel, R., Crameri, R., Koskinen, S., Heinemeier, K., Olesen, J.L., Døssing, S., Hansen, M., Pedersen, S.G., Rennie, M.J. and Magnusson, P. (2005) Metabolic activity and collagen turnover in human tendon in response to physical activity. J. Musculoskelet. Neuronal Interact. 5, 41-52.

2. Cook, J.L. and Purdam, C.R. (2012) Is compressive load a factor in the development of tendinopathy? Br. J. Sports Med. 46, 163-168.

3. Dakin, S.G.,Werling, D., Hibbert, A., Abayasekara, D.R., Young, N.J., Smith, R.K. and Dudhia, J. (2012) Macrophage sub-populations and the lipoxin A4 receptor implicate active inflammation during equine tendon repair. PLoS One 7, e32333.

4. Cook, J.L. and Purdam, C.R. (2009) Is tendon pathology a continuum? A pathology model to explain the clinical presentation of load-induced tendinopathy. Br. J. Sports Med. 43, 409-416.

5. Murphy, R.J., Kliskey, K., Wheway, K., Beard, D.J. and Carr, A.J. (2012) Rotator cuff tendinopathy: immunohistochemical changes across the spectrum of pathology. Proceedings of the 58th Annual Meeting of the Orthopaedic Research Society, 157.

6. Setterbo, J.J., Garcia, T.C., Campbell, I.P., Reese, J.L., Morgan, J., Kim, S.Y., Hubbard, M. and Stover, S.M. (2009) Hoof accelerations and ground reaction forces of Thoroughbred racehorses measured on dirt, synthetic, and turf track surfaces. Am. J. Vet. Res. 70, 1220-1229.

7. Crevier-Denoix, N., Robin, D., Pourcelot, P., Falala, S., Holden, L., Estoup, P., Desquilbet, L., Denoix, J.-M. and Chateau, H. (2010) Ground reaction force and kinematic analysis of limb loading on two different beach sand tracks in harness trotters. Equine Vet. J., Suppl. 38, 544-551.

8. Harrison, S.M., Whitton, R.C., King, M., Haussler, K.K., Kawcak, C.E., Stover, S.M. and Pandy, M.G. (2012) Forelimb muscle activity during equine locomotion. J. Exp. Biol. 215, 2980-2991.

9. Swanstrom, M.D., Zarucco, L., Hubbard, M., Stover, S.M. and Hawkins, D.A. (2005) Musculoskeletal modeling and dynamic simulation of the Thoroughbred equine forelimb during stance phase of the gallop. J. Biomech. Eng. 127, 318-328.

10. Harrison, S.M., Whitton, R.C., Kawcak, C.E., Stover, S.M. and Pandy, M.G. (2010) Relationship between muscle forces, joint loading and utilization of elastic strain energy in equine locomotion. J. Exp. Biol. 213, 3998-4009.

11. Pourcelot, P., Defontaine, M., Ravary, B., Lematre, M. and Crevier-Denoix, N. (2005) A non-invasive method of tendon force measurement. J. Biomech. 38, 2124-2129.

12. Crevier-Denoix, N., Ravary-Plumioen, B., Evrard, D. and Pourcelot, P. (2009) Reproducibility of a non-invasive ultrasonic technique of tendon force measurement, determined in vitro in equine superficial digital flexor tendons. J. Biomech. 42, 2210-2213.

13. Ravary-Plumiöen, B., Pourcelot, P., Vergari, C., Desquilbet, L. and Crevier-Denoix, N. (2012) Effects of ground surface on the equine superficial digital flexor tendon loading at the walk and trot. Comput. Methods Biomech. Biomed. Eng. 15 (Suppl. 1), 143-144.

14. Vergari, C., Pradon, D., Ravary-Plumioen, B., Pourcelot, P. and Crevier-Denoix, N. (2012) Achilles tendon force and axial speed of sound: a calibration method under clinical conditions. Comput. Methods Biomech. Biomed. Eng. 15 (Suppl. 1), 355-356.

15. Vergari, C., Pourcelot, P., Ravary-Plumioën, B., Dupays, A.G., Denoix, J.-M., Mitton, D., Laugier, P. and Crevier-Denoix, N. (2012) First application of axial speed of sound to follow up injured equine tendon. Ultrasound Med. Biol. 38, 162-167.

16. Vergari, C., Pourcelot, P., Ravary-Plumioën, B., Dupays, A.-G., Jacquet, S., Audigié, F., Denoix, J.-M., Laugier, P., Mitton, D. and Crevier-Denoix, N. (2012) Axial speed of sound for the monitoring of injured equine tendon: a preliminary study. J. Biomechanics 45, 53-58.

17. Vergari, C., Ravary-Plumioen, B., Evrard, D., Laugier, P., Mitton, D., Pourcelot, P. and Crevier-Denoix, N. (2012) Axial speed of sound is related to tendon's nonlinear elasticity. J. Biomechanics 45, 263-268.

18. Crevier-Denoix, N., Pourcelot, P., Ravary, B., Robin, D., Falala, S., Uzel, S., Grison, A.-C.,

Valetter, J.-P., Denoix, J.-M. and Chateau, H. (2009) Influence of track surface on the equine superficial digital flexor tendon in two horses at high speed trot. Equine Vet. J. 41, 257-261.

19. Robin, D., Chateau, H., Pacquet, L., Falala, S., Valette, J.-P., Pourcelot, P., Ravary, B., Denoix, J.-M. and Crevier-Denoix, N. (2009) Use of a 3D dynamometric horseshoe to assess the effects of an all-weather waxed track and a crushed sand track at high speed trot: preliminary study. Equine Vet. J. 41, 253-256.

20. Chateau, H., Robin, D., Falala, S., Pourcelot, P., Valette, J.P., Ravary, B., Denoix, J.M. and Crevier-Denoix, N. (2009) Effects of a synthetic all-weather waxed track versus a crushed sand track on 3D acceleration of the front hoof in three horses trotting at high speed. Equine Vet. J. 41, 247-251.

21. Chateau, H., Holden, L., Robin, D., Falala, S., Pourcelot, P., Estoup, P., Denoix, J.-M. and Crevier-Denoix, N. (2010) Biomechanical analysis of hoof landing and stride parameters in harness trotter horses running on different tracks of a sand beach (from wet to dry) and on an asphalt road. Equine Vet. J., Suppl. 38, 488-495.

22. Peterson, M.L. and McIlwraith, C.W. (2008) Effect of track maintenance on mechanical properties of a dirt racetrack: a preliminary study. Equine Vet. J. 40, 602-605.

23. Setterbo, J.J., Fyhrie, P.B., Hubbard, M., Upadhyaya, S.K. and Stover, S.M. (2013) Dynamic properties of a dirt and a synthetic equine racetrack surface measured by a tract-testing device. Equine Vet. J. 45, 25-30.

24. Bridge, J.W., Peterson, M.L., Radford, D.W. and McIlwraith, C.W. (2010) Thermal transitions in high oil content petroleum-based wax blends used in granular sport surfaces. Thermochim. Acta 498, 106-111.

25. Whitlock, D., Garcia, T.C., Vallance, S.A. and Stover, S.M. (2012) Possible role of carpal hyperextension in superficial digital flexor tendinopathy. Equine Vet. J. 44, 559-563.

26. Peterson, M.L., McIlwraith, C.W. and Reiser, R.F. (2008) Development of a system for the in-situ characterization of thoroughbred horse racing track surfaces. Biosystems Engineering 101, 260-269.

27. Screen, H.R., Lee, D.A., Bader, D.L. and Shelton, J.C. (2004) An investigation into the effects of the hierarchical structure of tendon fascicles on micromechanical properties. Proc. Inst. Mech. Eng. H. 218, 109-119.

28. Screen, H.R. (2008) Investigating load relaxation mechanics in tendon. J. Mech. Behav. Biomed. Mater. 1, 51-58.

29. Gupta, H.S., Seto, J., Krauss, S., Boesecke, P. and Screen, H.R. (2010) In situ multi-level analysis of viscoelastic deformation mechanisms in tendon collagen. J. Struct. Biol. 169, 183-191.

30. Thorpe, C.T., Udeze, C.P., Birch, H.L., Clegg, P.D. and Screen, H.R. (2012) Specialization of tendon mechanical properties results from interfascicular differences. J. R. Soc. Interface 7; 9, 3108-3117.

31. Screen, H.R., Toorani, S. and Shelton, J.C. (2013) Microstructural stress relaxation mechanics in functionally different tendons. Med. Eng. Phys. 35, 96-102.

32. Funakoshi, T., Schmid, T., Hsu, H.P. and Spector, M. (2008) Lubricin distribution in the goat infraspinatus tendon: a basis for interfascicular lubrication. J. Bone Joint Surg. Am. 90, 803-814.

33. Kohrs, R.T., Zhao, C., Sun, Y.L., Jay, G.D., Zhang, L.,Warman, M.L., An, K.N. and Amadio, P.C. (2011) Tendon fascicle gliding in wild type, heterozygous, and lubricin knockout mice. J. Orthop. Res. 29, 384-389.

34. Smith, K.D., Vaughan-Thomas, A., Spiller, D.G., Innes, J.F., Clegg, P.D. and Comerford, E.J. (2011) The organisation of elastin and fibrillins 1 and 2 in the cruciate ligament complex. J. Anat. 218, 600-607.

35. Kasashima, Y., Takahashi, T., Smith, R.K., Goodship, A.E., Kuwano, A., Ueno, T. and Hirano, S. (2004) Prevalence of superficial digital flexor tendonitis and suspensory desmitis in Japanese Thoroughbred flat racehorses in 1999. Equine Vet. J. 36, 346-350.

36. Perkins, N.R., Reid, S.W. and Morris, R.S. (2005) Risk factors for injury to the superficial digital flexor tendon and suspensory apparatus in Thoroughbred racehorses in New Zealand. N. Z. Vet. J. 53, 184-192.

37. Thorpe, C.T., Udeze, C.P., Birch, H.L., Clegg, P.D. and Screen, H.R. (2013) Capacity for sliding between tendon fascicles decreases with ageing in injury prone equine tendons: a possible mechanism for age-related tendinopathy? Eur. Cell. Mater. 8, 48-60.

38. Harvie, P., Ostlere, S.J., The, J., McNally, E.G., Clipsham, K., Burston, B.J., Pollard, T.C. and Carr, A.J. (2004) Genetic influences in the aetiology of tears of the rotator cuff. Sibling risk of a full-thickness tear. J. Bone Joint Surg. Br. 86, 696-700.

39. Collins, M. and Raleigh, S.M. (2009) Genetic risk factors for musculoskeletal soft tissue injuries. Med. Sport Sci. 54, 136-149.

40. Raleigh, S.M. and Collins, M. (2013) Gene variants that predispose to Achilles tendon injuries: an update on recent advances. In: Achilles Tendon, Ed: A. Cretnik, InTech - Open Access Publisher, Rijeka, Croatia. pp 25-40.

41. September, A.V., Posthumus, M. and Collins, M. (2012) Application of genomics in the prevention, treatment and management of Achilles tendinopathy and anterior cruciate ligament ruptures. Recent Pat DNA Gene Seq. 6, 216-223.

42. Gibson, W.T. (2009) Genetic association studies for complex traits: relevance for the sports med cine practitioner. Br. J. Sports Med. 43, 314-316.

43. Mokone, G.G., Gajjar, M., September, A.V., Schwellnus, M.P., Greenberg, J., Noakes, T.D. and Collins, M. (2005) The guanine-thymine dinucleotide repeat polymorphism within the tenascin-C gene is associated with Achilles tendon injuries. Am. J. Sports Med. 33, 1016-1021.

44. Tully, L.J., Murphy, A.M., Smith, R.K., Hulin-Curtis, S.L., Verheyen, K.L. and Price, J.S. (2013) Polymorphisms in TNC and COL5A1 genes are associated with risk of superficial digital flexor tendinopathy in National Hunt Thoroughbred racehorses. Equine Vet. J. Epub ahead of print; doi: 10.1111/evj.12134. PubMed PMID:23906005.

45. McCue, M.E., Bannasch, D.L., Petersen, J.L., Gurr, J., Bailey, E., Binns, M.M., Distl, O., Guérin, G., Hasegawa, T., Hill, E.W., Leeb, T., Lindgren, G., Penedo, M.C., Røed, K.H., Ryder, O.A., Swinburne, J.E., Tozaki, T., Valberg, S.J., Vaudin, M., Lindbald-Toh, K.,Wade, C.M. and Mickelson, J.R. (2012) A high density SNP array for the domestic horse and extant Perissodactyla: utility for association mapping, genetic diversity, and phylogeny studies. PLoS Genet. 8, e1002451.

46. Schramme, M., Hunter, S., Campbell, N., Blikslager, A. and Smith, R. (2010) A surgical tendonitis model in horses: technique, clinical, ultrasonographic and histological characterisation. Vet. Comp. Orthop. Traumatol. 23, 231- 239.

47. Watts, A.E., Nixon, A.J., Yeager, A.E. and Mohammed, H.O. (2012) A collagenase gel/physical defect model for controlled induction of superficial digital flexor tendonitis. Equine Vet. J. 44, 576-586.

48. Bosch, G., van Schie, H.T., de Groot, M.W., Cadby, J.A., van de Lest, C.H., Barneveld, A. and van Weeren, P.R. (2010) Effects of platelet-rich plasma on the quality of repair of mechanically induced core lesions in equine superficial digital flexor tendons: a placebo-controlled experimental study. J. Orthop. Res. 28, 211-217.

49. David, F., Cadby, J., Bosch, G., Brama, P., van Weeren, R. and van Schie, H. (2012) Short-term cast immobilisation is effective in reducing lesion propagation in a surgical model of equine superficial digital flexor tendon injury. Equine Vet. J. 44, 570-575.

50. Gwilym, S.E., Oag, H.C., Tracey, I. and Carr, A.J. (2011) Evidence that central sensitisation is present in patients with shoulder impingement syndrome and influences the outcome after surgery. J. Bone Joint Surg. Br. 93, 498-502.

51. Hart, L. (2011) Corticosteroid and other injections in the management of tendinopathies: a review. Clin. J. Sport Med. 21, 540-541.

52. Shi, L.L. and Edwards, T.B. (2012)) The role of acromioplasty for management of rotator cuff problems: where is the evidence? Adv. Orthop. 467571.

53. Magnussen, R.A., Dunn, W.R. and Thomson, A.B. (2009) Nonoperative treatment of midportion Achilles tendinopathy: a systematic review. Clin. J. Sport Med. 19, 54-64.

54. Maffulli, N., Sharma, P. and Luscombe, K.L. (2004) Achilles tendinopathy: aetiology and management. J. R. Soc. Med. 97, 472-476.

55. Herthel, D.J. (2001) Enhanced suspensory ligament healing in 100 horses by stem cell and other bone marrow components. Proc. Am. Ass. Equine Practnrs. 47, 319-321.

56. Schnabel, L.V., Sonea, H.O., Jacobson, M.S. and Fortier, L.A. (2008) Effects of platelet rich plasma and acellular bone marrow on gene expression patterns and DNA content of equine suspensory ligament explant cultures. Equine Vet. J. 40, 260-265.

57. Kon, E., Buda, R., Filardo, G., Di Martino, A., Timoncini, A., Cenacchi, A., Fornasari, P.M., Giannini, S. and Marcacci, M. (2010) Platelet-rich plasma: intra-articular knee injections produce favorable results in degenerative cartilage lesions. Arthroscopy 18, 472-479.

58. Schnabel, L.V., Mohammed, H.O., Miller, B.J., McDermott, W.G., Jacobson, M.S., Santangelo, K.S. and Fortier, L.A. (2007) Platelet rich plasma (PRP) enhances anabolic gene expression patterns in flexor digitorum superficialis tendons. J. Orthop. Res. 25, 230-240.

59. Sundman, E.A., Cole, B.J. and Fortier, L.A. (2011) Growth factor and catabolic cytokine concentrations are influenced by the cellular composition of platelet-rich plasma. Am. J. Sports Med. 39, 2135-2140.

60. Kisiday, J.D., McIlwraith, C.W., Rodkey, W.R., Frisbie, D.D. and Steadman, J.R. (2012) Effects of platelet-rich plasma composition on anabolic and catabolic activities in equine cartilage and meniscal explants. Cartilage 3, 245-254.

61. Waselau, M., Sutter, W.W., Genovese, R.L. and Bertone, A.L. (2008) Intralesional injection of platelet-rich plasma followed by controlled exercise for treatment of midbody suspensory ligament desmitis in Standardbred racehorses. J. Am. Vet. Med. Ass. 232, 1515-1520.

62. Garrett, K.S., Bramlage, L.R., Spike-Pierce, D.L. and Cohen, N.D. (2013) Injection of platelet- and leukocyte-rich plasma at the junction of the proximal sesamoid bone and the suspensory ligament branch for treatment of yearling Thoroughbreds with proximal sesamoid bone inflammation and associated suspensory ligament branch desmitis. J. Am. Vet. Med. Ass. 243, 120-125.

63. Hraha, T.H., Doremus, K.M., McIlwraith, C.W. and Frisbie, D.D. (2011) Comparison of clinically relevant platelet-rich plasma methods in acellular bone marrow preparations on equine digital flexor tenocytes in vitro. Proceedings Vet. Orthop. Soc. p 5.

64. Fortier, L.A., Nixon, A.J., Williams, J. and Cable, C.S. (1998) Isolation and chondrocytic differentiation of equine bone marrow-derived mesenchymal stem cells. Am. J. Vet. Res. 59, 1182-1187.

65. Nixon, A.J., Dahlgren, L.A., Haupt, J.L., Yeager, A.E. and Ward, D.L. (2008) Effect of adipose-derived nucleated cell fractions on tendon repair in horses with collagenase-induced tendinitis. Equine Vet. J. 69, 928-937.

66. Schnabel, L.V., Lynch, M.E., van der Meulen, M.C., Yeager, A.E., Kornatowski, M.A. and Nixon, A.J. (2009) Mesenchymal stem cells and insulin-like growth factor-I gene-enhanced mesenchymal stem cells improve structural aspects of healing in equine flexor digitorum superficialis tendons. J. Orthop. Res. 27, 1392-1398.

67. Caniglia, C.J., Schramme, M.C. and Smith, R.K. (2012) The effect of intralesional injection of bone marrow derived mesenchymal stem cells and bone marrow supernatant on collagen fibril size in a surgical model of equine superficial digital flexor tendonitis. Equine Vet. J. 44, 587-593.

68. Pacini, S., Spinabella, S., Trombi, L., Fazzi, R., Galimberti, S., Dini, F., Carlucci, F. and Petrini, M. (2007) Suspension of bone marrow-derived undifferentiated mesenchymal stromal cells for repair of superficial digital flexor tendon in race horses. Tissue Eng. 13, 2949-2955.

69. Godwin, E.E., Young, N.J., Dudhia, J., Beamish, I.C. and Smith, R.K. (2012) Implantation of bone marrow-derived mesenchymal stem cells demonstrates improved outcome in horses with overstrain injury of the superficial digital flexor tendon. Equine Vet. J. 44, 25-32.

70. Smith, R.K. and Webbon, P.M. (2005) Harnessing the stem cell for the treatment of tendon injuries: heralding a new dawn? Br. J. Sports Med. 39, 582-584.

71. Watts, A.E., Yeager, A.E., Kopyov, O.V. and Nixon, A.J. (2011) Fetal derived embryonic-like stem cells improve healing in a large animal flexor tendinitis model. Stem Cell Res. Ther. 2, 4.

Damage Modeling of Spinal Dura Mater

This is a summary of a study that was presented at the Biomechanics, Bioengineering, and Biotransport Conference by Nicole Ramo, Snehal Shetye, and Dr. Christian Puttlitz.

Take Home Message

Understanding how the spinal dura mater accumulates sub-failure damage and ultimately fails is important for the study of spinal cord injuries. The results of this study show that the components of the tissue incur damage differently and the accumulation of damage may be dependent on loading rate. These findings are the first step toward understanding the damage process in spinal tissues and may provide insight into the prevention and treatment of injuries.

Introduction

The spinal dura mater is the outermost and strongest of the tissues that make up the spinal cord-meningeal complex (SCM). Accordingly, it plays an important role in the overall behavior of the SCM – including that during traumatic loading scenarios such as vertebral burst fracture events.[1] Despite its functional importance, little work has been done to characterize the sub-failure and failure properties of the dura mater. While a variety of mathematical models have been used to describe the failure of multiple biological tissues[2–4], this technique has not been extended to any tissue of the SCM until now. This work is currently being prepared for publication by Dr. Christian Puttlitz's research group.

Methods

Mechanical Testing

Longitudinal dura mater samples were collected from sheep euthanized at Colorado State University's Preclinical Surgical Research Laboratory for unrelated studies. Uniaxial tension-to-failure tests were performed using the custom built test stand shown in figure 1A. Digital images were acquired with the grips at 0° (testing orientation) and turned 90° (as shown in Figure 1B) to measure initial sample length and thickness. Each sample was pulled to failure at 0.01mm/s, 1mm/s, or 6mm/s while the actuator displacement and reaction force was recorded.

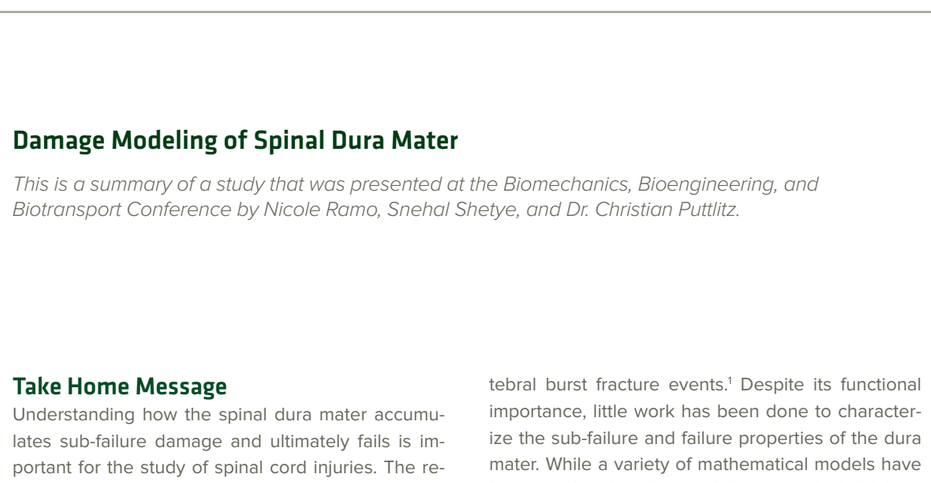


Fig. 1: A) Testing stand with labeled components; B) five thickness measurements taken with grips turn 90°; example of test with sample at (C) initial length, (D) prior to failure, and (E) immediately following mid-substance failure.

Damage Modeling

A hyperelastic non-linear directional damage model for fibrous biological soft tissues[3,5] was used to fit the data in this study:

$$\boldsymbol{\psi} = (1 - D_m)\hat{\boldsymbol{\psi}}^m_{iso} + (1 - D_f)\hat{\boldsymbol{\psi}}^f_{ani}$$

The damage parameters, D_m and D_f, relate to how the ground matrix and collagen fibers, respectively, accumulate damage with 0 representing no damage and 1 representing complete failure. The ground matrix was modeled as isotropic with the following exponential form:

$$\hat{\boldsymbol{\psi}}^m_{iso} = \frac{c_1}{c_2}\{exp[\frac{c_2}{2}(I_1 - 3)] - 1\}$$

While the collagen fibers were modeled with a piecewise function based on the straightening of the fibers:

$$\hat{\psi}^f_{ani} = \begin{cases} 0, & if\ I_4 < I_{4_0} \\ \frac{c_3}{c_4}\{exp[c_4(I_4 - I_{4_0})] - c_4(I_4 - I_{4_0}) - 1\}, & if\ I_{4_0} < I_4 < I_{4_{ref}} \\ c_5\sqrt{I_4 - I_{4_0}} + c_6 ln(I_4 - I_{4_0}) + c_7, & if\ I_4 > I_{4_{ref}} \end{cases}$$

where I_{4_0} and $I_{4_{ref}}$ characterize the location and length of the toe region.

Results and Discussion

Figure 2 shows plots of the damage parameters for each loading rate group. For the quasi-static and 1mm/s groups, D_m left zero prior to D_f doing so, meaning that the matrix started to damage before the fibers. For all three groups, D_m also reached one prior to D_f doing so, meaning that the matrix completely failed before fiber failure. It can also be seen in Figure 2 that the D_m curves demonstrate a reduced slope as compared to the D_f curves, indicating more gradual relative failure of the matrix.

However, in the highest speed group, the fibers started to damage before the fibers in the other groups but did not fail completely until after the fibers in the other groups. As 6mm/s is above what the dura mater experiences during voluntary neck motion, this may represent a protective mechanism in which the fibers also exhibit a gradual failure taking on more damage before complete failure.

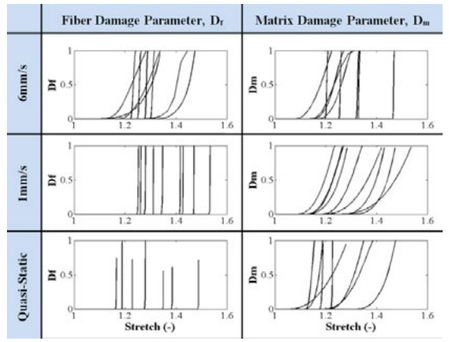


Fig. 2: Results of fitting procedure for damage parameters (in a subset of quasi-static tests, the force did not completely return to zero following failure, therefore the damage parameter does not extend all the way to one)

References

1. Hall R. M., Oakland R. J., Wilcox R. K. & Barton D. C. Spinal cord-fragment interactions following burst fracture: an in vitro model. J. Neurosurg. Spine 2006; 5:243–50.

2. Calvo B. et al. On modelling damage process in vaginal tissue. J. Biomech. 2009; 42:642–51.

3. Martins P. et al. Mechanical characterization and constitutive modelling of the damage process in rectus sheath. J. Mech. Behav. Biomed. Mater. 2012;8:111–22.

4. Liao H. & Belkoff S. M. A failure model for ligaments. J. Biomech. 1999; 32:183–8.

5. Calvo B. & Pena E. An uncoupled directional damage model for fibred biological soft tissues. Formulation and computational aspects. Int. J. ... 2007; 2036–2057; doi:10.1002/nme.

Adeno-Associated Viral Vectors Show Serotype Specific Transduction of Equine Joint Tissue Explants and Cultured Monolayers

This is a summary of a paper published by Drs. D. Hemphill, W. McIlwraith, R. Samulski and L. Goodrich. Scientific Reports, 2014; 4:5861. doi:10.1038/srep05861.

Take Home Message

Gene therapy is currently being considered as a promising treatment for musculoskeletal diseases with considerable emphasis placed on arthritis.[1,2,3,4] Intra-articular gene therapy would target tissue using a vector that can infect articular cartilage and the synovial lining of the joint which contain the cell types chondrocytes and synoviocytes, respectively.[5,6] This study should encourage clinicians to perform AAV 5 neutralization tests before administration of AAV gene therapy vectors to horses.

Introduction

The objective of this study was to determine whether transduction efficiencies in the monolayer culture model are an accurate representation of transduction efficiencies in tissue explants, a model more closely related to in vivo transduction. We hypothesized that there may be differences in transduction efficiencies due to the increased amount of extracellular matrix in explant tissues. Further, to maximize transduction efficiency in vivo, we sought to investigate whether neutralizing antibodies existed in the joint fluid or the serum of the horse. We hypothesized that neutralizing antibodies would most likely exist to some of the AAV serotypes that have efficient transduction in equine synoviocytes and chondrocytes.

Materials and Methods

Tissues were harvested post mortem from four horses, whose joints displayed no OA pathology. Synovium was aseptically excised from the inside of the fetlock joint capsule and cartilage from the patella. Similarly sized explants approximating 5 mm squares were cut from the larger pieces and kept in wells of 48 well plates. The day of transduction was considered day zero. On days 4, 8, 12, 16, and 20, fluorescent microscopy pictures were taken of the cells and explants.

On day thirty, explants were individually digested and plated immediately into wells according to a prior digestion protocol and the suspensions analyzed by flow cytometry.

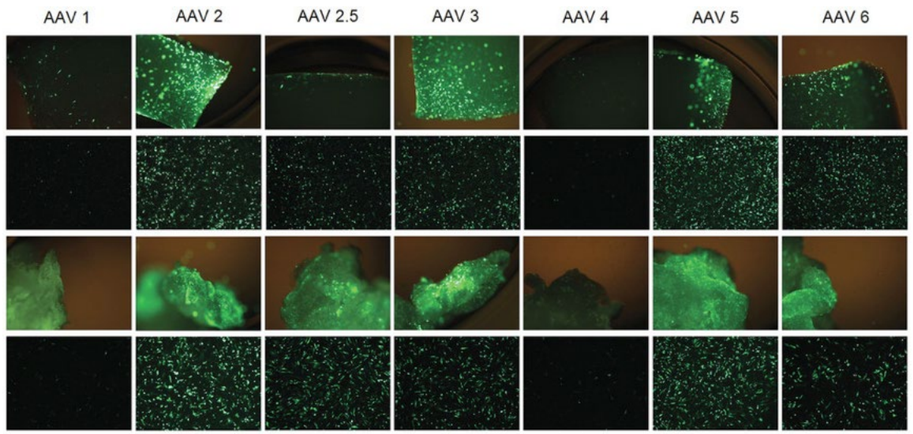


Fig. 1: Fluorescence micrographs of the cell and culture types tested showing the presence or not of AAV transduction with the vectors tested. Pictures are from a single animal twelve days after transduction. From top row to bottom row: cartilage explants, chondrocyte monolayers, synovial explants, and synoviocyte monolayers.

Results

It was found that AAV 2 and 2.5 transduced cells more efficiently in explants than in monolayers. Through experiments involving assessing enzyme degradation of cell surface proteoglycans, this change could not be attributed to differences in the extra cellular matrix (ECM), but a similar change in AAV 5 transduction efficiency could be readily explained by differences in cell surface sialylated glycan. Unexpectedly it was found that in a small but diverse sample of horses evidence for serum neutralizing antibodies was only found to AAV 5. This suggests a unique relationship between this capsid and the equine host or an unresolved relationship between similar bovine AAV and the AAV 5 capsid immune response.

Discussion

This study reveals that AAV transduction efficiency can differ between explants and monolayers. One of the contributing factors could be the increased amount of extracellular matrix found in the explant. This suggests that monolayer cultures could provide an adequate, relative model for testing transduction efficiency for AAV serotypes in vivo, but explants may offer a more accurate model. Additionally, we have shown there is a possibility of serum neutralization to AAV 5 in some horses. This should encourage clinicians to perform AAV 5 neutralization tests before administration of AAV gene therapy vectors to horses.

References

1. Ghivizzani, S. C. et al. Direct adenovirus-mediated gene transfer of interleukin 1 and tumor necrosis factor alpha soluble receptors to rabbit knees with experimental arthritis has local and distal anti-arthritic effects. Proc. Natl. Acad. Sci. U.S.A 95, 4613–4618 (1998).

2. Evans, C. H., Gouze, J. N., Gouze, E., Robbins, P. D. & Ghivizzani, S. C. Osteoarthritis gene therapy. Gene Ther. 11, 379–389, doi:10.1038/sj.gt.3302196 (2004).

3. Goodrich, L. R. et al. Direct adenovirus-mediated IGF-I gene transduction of synovium induces persisting synovial fluid IGF-I ligand elevations. Gene Ther. 13, 1253–1262, doi:10.1038/sj.gt.3302757 (2006).

4. Goodrich, L. R., Hidaka, C., Robbins, P. D., Evans, C. H. & Nixon, A. J. Genetic modification of chondrocytes with insulin-like growth factor-1 enhances cartilage healing in an equine model. J. Bone Joint Surg. Br. 89B, 672–685, doi:10.1302/0301-620x.89b5.18343 (2007).

5. Watanabe, S. et al. Adeno-associated virus mediates long-term gene transfer and delivery of chondroprotective IL-4 to murine synovium. Mol. Ther. 2, 147–+ (2000).

6. Madry, H., Cucchiarini, M., Terwilliger, E. F. & Trippel, S. B. Recombinant adeno-associated virus vectors efficiently and persistently transduce chondrocytes in normal and osteoarthritic human articular cartilage. Hum. Gene Ther. 14, 393–402 (2003).

Treatment of Experimentally Induced Osteoarthritis in Horses Using an Intravenous Combination of Sodium Pentosan Polysulfate, N-Acetyl Glucosamine, and Sodium Hyaluronan (PGH)

This study has been published in Veterinary Surgery in 2014 (Reference 1 below)

Take Home Message

Radiographic scores, macroscopic joint pathology and macroscopic cartilage pathology scores were significantly reduced in horses treated with PGH confirming disease modifying effects with this drug combination.[1]

Introduction

Osteoarthritis (OA), a common cause of lameness in athletic horses, has a substantial economic cost.[1,2] Common medications used to minimize OA in horses include non-steroidal anti-inflammatory drugs, corticosteroids, polysulfated glycosaminoglycans (PSGAGs), sodium pentosan polysulfate (PPS), N-acetyl glucosamine (NAG), and hyaluronan (HA).[3-10] The rationale for the development of this product is that by combining drugs with different mechanisms of action it may be possible to target different pathways that contribute to OA thereby providing broader efficacy or synergy in the treatment of joint disease.[11-14]

Materials and Methods[16]

Standardbred horses were entered into the study and the CSU osteochondral fragment- osteoarthritis (OA) model created. Treatment group contained pentosan polysulfate (PPS) at 75 mg/mL, n-acetyl glucosamine (NAG) at 120 mg/mL and hyaluronan (HA) at 2 mg/mL. The combination was abbreviated as PGH. Treatment commenced at day 10 and the treated group were administered 0.04 mL/kg PGH IV every 7 days, until the study completion day 70. This treatment protocol was equivalent to 3 mg/kg PPS, 4.8 mg/kg NAG and 0.12 mg/kg HA. Control horses received an equivalent volume of saline IV until study completion (day 70). Horses underwent a standardized treadmill exercise program. Clinical and radiographic findings and synovial fluid analysis were evaluated throughout the study. Macroscopic, histologic, histochemical and biochemical findings were evaluated after necropsy. Comparisons of interest included OA in non-OA joints of saline treated horses and OA joints of PGH treated horses and OA joints of saline treated horses. Results were statistically analyzed with significance set at $P<0.05$.

Results

OA caused increases in clinical assessment scores, synovial fluid variables radiographic, macroscopic, and histologic cartilage scores, synovial fluid and cartilage chondroitin sulfate 846-epitope and glycosaminoglycan concentration. Total radiographic scores, total macroscopic joint pathology and macroscopic cartilage pathology scores were significantly reduced in horses treated with PGH compared with saline treated horses. However, there was no difference in lameness scores, lameness scores after limb flexion or in the degree of effusion in OA limbs between saline and PGH treated horses.

Discussion and Conclusions

This drug combination showed benefits to radiographic and macroscopic scores in the cartilage. However, in a previous study with PPS alone (3 mg/kg) administered intramuscularly there was also significant reduction of articular cartilage fibrillation histologically. It was concluded that the combination product did not provide any additional benefit and was perhaps inferior to the use of PPS alone[17]

References

1. Koenig T.J., Dart A.J., McIlwraith C.W., Horadagoda N, Bell R.J., Perkins N., Dart C., Krockenberger M., Jeffcott L.B., Little C.B. Treatment of experimentally induced osteoarthritis in horses using an intravenous combination of sodium pentosan polysulfate, N-acetyl glucosamine, and sodium hyaluronan. Vet Surg 2014;43:612-622.

2. Rossdale P., Hopes R., Digby N., et al: Epidemiological study of wastage among racehorses 1982 and 1983. Vet Rec 1985;116: 66–69

3. Todhunter R., Lust G.: Pathophysiology of synovitis: clinical signs and examination in horses. Compend Contin Educ Pract Vet 1990;12:980–992

4. Auer J., Fackelman G., Gingerich D., et al: Effect of hyaluronic acid in naturally occurring and experimentally induced osteoarthritis. Am J Vet Res 1980;41:568–574

5. Foland J., McIlwraith C.W., Trotter G., et al: Effect of betamethasone and exercise on equine carpal joints with osteochondral fragments. Vet Surg 1994;23:369–376

6. Frisbie D., McIlwraith C.W., Kawcak C., et al: Evaluation of topically administered diclofenac liposomal cream for treatment of horses with experimentally induced osteoarthritis. Am J Vet Res 2009;70:210–215

7. Frisbie D.D., Kawcak C.E., Baxter G.M., et al: Effects of 6-alphamethylprednisolone acetate on an equine osteochondral fragment exercise model. Am J Vet Res 1998;59:1619–1628

8. Frisbie D.D., Kawcak C.E., McIlwraith C.W.: Evaluation of the effect of extracorporeal shock wave treatment on experimentally induced osteoarthritis in middle carpal joints of horses. Am J Vet Res 2009;70:449–454

9. Frisbie D.D., Kawcak C.E., McIlwraith C.W., et al: Evaluation of polysulfated glycosaminoglycan or sodium hyaluronan administered intra-articularly for treatment of horses with experimentally induced osteoarthritis. Am J Vet Res 2009;70:203– 209

10. Frisbie D.D., Kawcak C.E., Trotter G.W., et al: Effects of triamcinolone acetonide on an in vivo equine osteochondral fragment exercise model. Equine Vet J 1997;29:349–359

11. Kwan C., Bell R., Koenig T., et al: Effects of intra-articular sodium pentosan polysulphate and glucosamine on cytology, total protein concentration and viscosity of synovial fluid in horses. Aust Vet J 2012;90:315–320

12. Goodrich L.R., Nixon A.J.: Medical treatment of osteoarthritis in the horse—a review. Vet J 2006;171:51–69

13. McCarty M.F., Russell A.L., Seed M.P.: Sulfated glycosaminoglycans and glucosamine may synergize in promoting synovial hyaluronic acid synthesis. Med Hypotheses 2000;54:798–802

14. Pearson W., Lindinger M.: Critical review of research evaluating glucosamine-based nutraceuticals for treatment of joint pain and 620 Veterinary Surgery 43 (2014) 612–622 © Copyright 2014 by The American College of Veterinary Surgeons Treatment of Experimentally Induced Osteoarthritis in Horses Koenig et al. degenerative joint disease in horses. Proceedings of the 4th European Equine Health and Nutrition Congress, Vol. 4. 2008, pp 81–91

15. Trumble T.N.: The use of nutraceuticals for osteoarthritis in horses. Vet Clin North Am Equine Pract 2005;21:575–597

16. Frisbie D., Ghivizzani S., Robbins P., et al: Treatment of experimental equine osteoarthritis by in vivo delivery of the equine interleukin-1 receptor antagonist gene. Gene Ther 2002;9:12–20

17. Howard R.D., McIlwraith C.W.: Hyaluranon and its use in the treatment of equine joint disease, in VandenBerg W, Van Der Kraan P, Van Lent P (eds): Joint disease in the horse. Austin, TX, Birkhauser, 1996, pp 257–269

18. McIlwraith C.W., Frisbie D.D., Kawcak C.E.: Evaluation of intramuscularly administered sodium pentosan polysulfate for treatment of horses with experimentally induced osteoarthritis. Am J Vet Res 201: 273: 628–633

19. Pearson W., Lindinger M.: Low quality of evidence for glucosamine-based nutraceuticals in equine joint disease: review of in vivo studies. Equine Vet J 2009;41:706–712

20. Block J.A., Oegema T.R., Sandy J.D., et al: The effects of oral glucosamine on joint health: is a change in research approach needed? Osteoarthritis Cartilage 2010;18:5–11

21. Dechant J.E., Baxter G.M.: Glucosamine and chondroitin sulphate as structure modifying agents in horses. Equine Vet Educ 2007;19:90–96

22. Miller K.L., Clegg D.O.: Glucosamine and chondroitin sulfate. Rheum Dis Clin North Am 2011;37:103–118

23. Neil K.M., Caron J.P., Orth M.W.: The role of glucosamine and chondroitin sulfate in treatment for and prevention of osteoarthritis in animals. J Am Vet Med Assoc 2005;226:1079–1088

24. Vista E.S., Lau C.S.: What about supplements for osteoarthritis? A critical and evidenced-based review. Int J Rheum Dis 2011;14:152–158

25. Kawcak C., Frisbie D., Trotter G., et al: Effects of intravenous administration of sodium hyaluronate on carpal joints in exercising horses after arthroscopic surgery and osteochondral fragmentation. Am J Vet Res 1997;58:1132–1135

26. Frisbie D.D., Kawcak C.E., Werpy N.M., et al: Clinical, biochemical, and histologic effects of intra-articular administration of autologous conditioned serum in horses with experimentally induced osteoarthritis. Am J Vet Res 2007;68:290– 296

27. Anonymous. Definition and classification of lameness, in Guide for veterinary service and judging of equestrian events (ed. 4). Lexington, KY, Am Assoc Equine Pract, 1991, p 19

28. Billinghurst R., Brama P., vanWeeren P., et al: Significant exerciserelated changes in the serum levels of two biomarkers of collagen metabolism in young horses. Osteoarthritis Cartilage 2003;11:760–769

29. Farndale R.W., Buttle D.J., Barrett A.J.: Improved quantitation and discrimination of sulphated glycosaminoglycans by use of dimethylmethylene blue. Biochim Biophys Acta 1986;883:173–177

30. Burkhardt D., Hwa S.Y., Ghosh P.: A novel microassay for the quantitation of the sulfated glycosaminoglycan content of histological sections: its application to determine the effects of Diacerhein on cartilage in an ovine model of osteoarthritis. Osteoarthritis Cartilage 2001;9:238–247

31. Stegemann H., Stalder K.: Determination of hydroxyproline. Clin Chim Acta 1967;18:267–273

32. Steel C.M.: Equine synovial fluid analysis. Vet Clin North Am Equine Pract 2008;24:437–454

33. Persson L.: On the synovial fluid of horses. Acta Vet Scand Suppl 1971;35:1–77

34. Van Pelt R.: Interpretation of the synovial fluid findings in the horse. J Am Vet Med Assoc 1974;165:91–95

35. Little C., Ghosh P.: Potential use of pentosan polysulfate for the treatment of equine joint disease, in McIlwraith C, Trotter G (eds): Joint disease in the horse. Philadelphia, PA, Saunders, 1993, pp 281–292

36. McIlwraith C.W.: The use of intra-articular corticosteroids in the horse: what is known on a scientific basis? Equine Vet J 2010;42:563–571

37. Frisbie D.D., Kawcak C.E., McIlwraith C.W., et al: Assessment of intravenous or intra-articular hyaluronic acid, chondroitin sulfate, and N-acetyl-D-glucosamine in treatment of osteoarthritis using an equine experimental model. Proc Am Assoc Equine Pract 2009;55:61–62

38. Dart A., Perkins N., Dowling B., et al: The effect of three different doses of sodium pentosan polysulphate on haematological and haemostatic variables in adult horses. Aust Vet J 2001;79:624–627

39. Little C., Ghosh P., Bellinger C.: Meniscectomy increases aggrecan, decoran (PGS2) and biglycan (PG-S1) metabolism in cartilage. Proceedings of the 39th Annual Meeting Orthopedic Research Society, Vol. 18. 1993, p 707

40. Smith M.M., Ghosh P., Numata Y., et al: The effects of orally administered calcium pentosan polysulfate on inflammation and cartilage degradation produced in rabbit joints by intraarticular injection of a hyaluronate-polylysine complex. Arthritis Rheum 1994;37:125–136

41. Clegg P.D., Jones M.D., Carter S.D.: The effect of drugs commonly used in the treatment of equine articular disorders on the activity of equine matrix metalloproteinase-2 and 9. J Vet Pharmacol Ther 1998;21:406–413

42. Francis D.J., Forrest M.J., Brooks P.M., et al: Retardation of articular cartilage degradation by glycosaminoglycan polysulfate, pentosan polysulfate, and DH-40J in the rat air pouch model. Arthritis Rheum 1989;32:608–616

43. Frean S.P., Cambridge H., Lees P.: Effects of anti-arthritic drugs on proteoglycan synthesis by equine cartilage. J Vet Pharmacol Ther 2002;25:289–298

44. Ghosh P., Armstrong S., Read R., et al: Animal models of early osteoarthritis: their use for the evaluation of potential chondroprotective agents, in VandenBergW, van der Kraan P, van Lent P (eds): Joint destruction in arthritis and osteoarthritis. Austin, TX, Birkhauser, 1993, pp 195–206

45. Nethery A., Giles I., Jenkins K., et al: The chondroprotective drugs, Arteparon and sodium pentosan polysulphate, increase collagenase activity and inhibit stromelysin activity in vitro. Biochem Pharmacol 1992;44:1549–1553

46. Rogachefsky R.A., Dean D.D., Howell D.S., et al: Treatment of canine osteoarthritis with insulin-like growth factor-1 (IGF-1) and sodium pentosan polysulfate. Osteoarthritis Cartilage 1993;1:105–114

47. Jimenez S.A.: The effect of glucosamine on human chondrocyte gene expression. Proceedings of the 9th European League Against Rheumatism Symposium Vol. 9. 1996, pp 8–10 Veterinary Surgery 43 (2014) 612–622 © Copyright 2014 by The American College of Veterinary Surgeons 621 Koenig et al. Treatment of Experimentally Induced Osteoarthritis in Horses

48. Lohmander L.S., Ionescu M., Jugessur H., et al: Changes in joint cartilage aggrecan after knee surgery and in osteoarthritis. Arthritis Rheum 1999;42:534–544

49. Rikzalla G., Reiner A., Bogoch E., et al: Studies of the articular cartilage proteoglycan aggrecan in health and osteoarthritis: evidence for molecular heterogeneity and extensive molecular changes in disease. J Clin Invest 1992;90:2268–2277

50. Laverty S., Ionescu M., Marcoux M., et al: Alterations in cartilage type-II procollagen and aggrecan contents in synovial fluid in equine osteochondrosis. J Orthop Res 2000;18:399–405

51. Lohmander L.S., Dalén N., Englund G., et al: Intra-articular hyaluronan injections in the treatment of osteoarthritis of the knee: a randomised, double blind, placebo controlled multicentre trial. Hyaluronan Multicentre Trial Group. Ann Rheum Dis 1996;55:424–431

52. Balazs E.A., Denlinger J.L.: Sodium hyaluronate and joint function. J Equine Vet Sci 1985;5:217–228

53. Trotter G.W.: Polysulfated glycosaminoglycan (Adequan), in VandenBergW, van der Kraan P, van Lent P (eds): Joint disease in the horse. Austin, TX, Birkhauser, 1996, pp 270–280

Genomics in Drug Discovery

This is, in part, a reproduction of an article by Richard A. Slayden, Dean Crick, Michael M. McNeil and Patrick J. Brennan (2003) Microbial Genomics in Drug Discovery. Pp. 111-134, and Luke C. Kingry, Ryan M. Troyer, Nicole L. Marlenee, Helle Bielefeldt-Ohmann, Richard A. Bowen, Alan R. Schenkel, Steven W. Dow and Richard A. Slayden. Genetic Identification of Unique Immunological Responses in Mice Infected with Virulent and Attenuated Francisella tularensis. Microbes and Infection. 2011, 13(3):261-75, in addition to unpublished information.

Take Home Message

There is a traditional observation in antimicrobial drug discovery that there is a poor correlation between the in vitro potency of a drug candidate and its efficacy. To better understand why chemotherapeutics work and why there is a disconnect between in vitro potency and efficacy, a complexity sciences approach consisting of host-pathogen interactions analyses has been employed. This research summary highlights how investigating the unique dynamics and response of the host and the pathogen during infection and disease progression provides insights in regards to vulnerabilities that can be exploited for target identification and drug discovery. The result of this approach has revealed new clinically relevant therapeutic options for treating and managing infectious disease.

Introduction

The sequencing of the human genome and pathogen genomes has had a significant impact on drug discovery with the promise being to understand infection and disease progression at a genetic level, thus revealing key vulnerabilities and identification of points of intervention. It has become clear that pathogen virulence, host exposures and external environmental stresses, in combination, influence host susceptibility, infection potential and disease progression. Genomic information and host-pathogen interaction information is now an integral part of the modern drug discovery pipeline, and provides insight into the global metabolic capabilities and cause and effect relationships that can be used to guide inhibitor design in a manner that may bias development towards relevant states of infection and disease progression.

Materials and Methods[16]

We have employed host-pathogen interaction studies to understand the dynamics of the host response to infection and the pathogen response to the changing host environment. We routinely employ Next Generation Sequencing (NGS) technology and bioinformatics analysis to identify transcriptionally active genes in the host, and transcriptionally active and essential genes of pathogens from different tissues and states of disease. The host response is monitored transcriptionally throughout disease with pathogens of different virulence. In terms of the pathogens, we use a 2-pronged approach of global, saturating mutagenesis approach and SIFT (Sorting Intolerant From Tolerant) analysis to determine which genes encode essential proteins for early and late stages of disseminated disease, and transcriptional analysis of bacterial genes during infection in the lungs and spleen throughout disease progression. Together, the complimentary studies in this report define the unique and minimal bacterial metabolism required for acute disease and dissemination, and thus clinically relevant drug targets and candidates for vaccine development to combat and prevent infection and diagnostic markers to manage disease.

Results

Host response to F. tularensis infection.

A critical question in understanding F. tularensis pathobiology is to determine which critical host responses are altered during the first 4-5 days following infection. We coupled whole genome transcriptional analysis with analysis of tissue pathology and organ bacterial burden to gain a more complete understanding of disease progression and host response to infection with a fully virulent and a less virulent strain of F. tularensis. Quantification of bacterial burden in the lungs revealed that Schu4 had increased growth compared to LVS, such that by 120 h the bacterial load of Schu4 in the lungs significantly exceeded that of mice infected with the LVS strain. In addition, F. tularensis Schu4 demonstrated increased dissemination to the spleen, as indicated by detection within 48 h of infection and significantly increased bacterial burden in the spleen at later time points following infection. Tissue damage was markedly more severe in the spleen following infection with Schu4, particularly at later time points of infection. Notably, both Schu4 and LVS established similar levels of infection in the lung, but eventually the Schu4 infection progressed to more severe pulmonary pathology, presumably due to more rapid replication and avoidance of host immune responses. The results of the global transcriptional analyses of the host response to infection with Francisella Schu4 or LVS strains indicate highly virulent strains are capable of subverting the host innate immune response and cell-mediated immunity. These altered responses included apoptosis, antigen processing and presentation, the inflammatory response, and leukocyte receptor signaling. The down regulation of multiple host defense mechanisms by F. tularensis is consistent with previous observations.

Transcriptionally active bacterial open reading frames throughout infection.

To investigate the active metabolism of F. tularensis during infection bacterial transcripts were obtained from bacteria isolated from the lungs and spleen during acute infection. Transcriptionally active bacterial transcripts where identified and quantified from infected lungs 48 and 96 hours post infection and from infected spleens 96 hours post infection via Next Generation Sequencing. These specific time points were chosen based on our characterization of the host response to F. tularensis infection, which provided landmarks for bacterial dissemination and disease progression. Greater transcriptional diversity was observed in F. tularensis in infected tissue which expressed 45% of the total number ORFs encoded in the genome as compared to in-vitro grown F. tularensis that only expressed 27% of the total number of ORFs encoded. The increased number of transcriptionally active bacterial genes during in vivo growth is consistent with the notion that there is need for a more complex transcriptional repertoire, and thus metabolic capability to survive the host environment compared to growth on defined artificially rich media. Analysis of the transcriptional profiles from infected tissues at different times of infection show the extent of F. tularensis transcriptional diversity from bacteria growing in the host as compared to laboratory conditions (Figure 1). The overlap between expression profiles between in vivo and in vitro growing F. tularensis is attributed to the differences in growth conditions and availability of nutrients.

Minimal essential coding capacity of F. tularensis required for infection and dissemination.

The minimal essential coding capacity of F. tularensis Shu4 required for acute infection and dissemination in the murine model of infection was defined using whole genome saturation mutagenesis coupled with the murine model of infection. The genome of F. tularensis strain Schu4 was randomly mutagenized using mitomycin C treatment. Following exposure to mitomycin C, the viable bacterial population was amplified by passage on nutrient rich solid media and sequenced via NGS. Whole genome sequencing identified 196,044 single nucleotide polymorphisms (SNPs) across the genome. This bacterial population [input pool] of F. tularensis Shu4 was then used to infect Balb/C mice via the intranasal route. At 96 hours post-infection, surviving F. tularensis were recovered from the lungs and spleen and subjected to whole genome sequencing. Sequencing revealed 179,782 SNPs in the bacteria population recovered from the lungs and 77,806 SNPs in bacteria recovered from the spleen. Non-synonymous changes within in open reading frames that were present in the input pool and identified in the recovery pool from the spleen, representing mutations carried through the entire infection, were further analyzed. Based on these stringent criteria, 5,201 mutations were present in 38.9% of the annotated open reading frames in the F. tularensis genome.

Discussion

Development of novel antimicrobials in the post-genomic age has proven to be more complicated than simply understanding the genetic coding capacity of an individual or group of pathogens. The transcriptional diversity demonstrated by Francisella throughout the infection reflects the highly adaptive nature of transcriptional regulation required by pathogens throughout the disease process. In addition, the differing transcriptional profiles throughout the disease indicate the need for such studies to understand the genetic requirements and thus the most clinically relevant drug targets that are active throughout the infection. Through a complexity sciences approach utilizing RNA-Seq, saturating chemical mutagenesis, and in silico mutational analysis we have generated a list of F. tularensis genes that are expressed throughout infection and in vitro and do not tolerate mutation, thus providing a prioritized list of potential therapeutic targets for F. tularensis. As similar studies are conducted

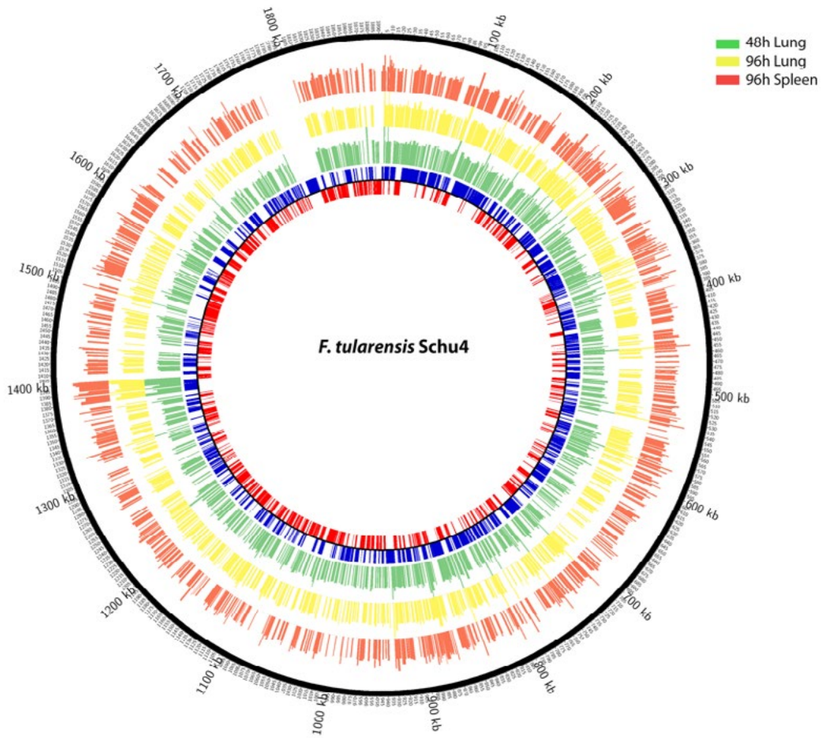


Fig. 1: Fluorescence micrographs of the cell and culture types tested showing the presence or not of AAV transduction with the vectors tested. Pictures are from a single animal twelve days after transduction. From top row to bottom row: cartilage explants, chondrocyte monolayers, synovial explants, and synoviocyte monolayers.

using other pathogens and infection models researchers will have more understanding of broad-spectrum targets for therapeutic intervention that will combat the ever-increasing problem of antimicrobial resistance, which has important implications for in vitro drug screening and the translation between in vitro potency and in vivo efficacy when developing therapeutics for pulmonary pathogens that disseminate to secondary sites.

Acknowledgments

Acknowledgment is required for past and present members of the Slayden laboratory for contribution of the work in this research summary. In addition to the listed works, Dr. Luke Kingry and Mr. Jason Cummings contributed to the unpublished information. The Infectious Diseases Research Center Next Generation Sequencing Core at Colorado State University, particularly Dr. Richard Casey and Ms. Erin Petrilli, assisted in this work. This work was supported, in part by a grant to Richard Slayden (NIH, NIAID grant AI065357).

Use of firocoxib for the treatment of equine osteoarthritis.

This is a review published by Drs. J. Donnell and D. Frisbie in Veterinary Medicine: Research and Reports, 2014; 5: 159-168.

Inhibition of PGE2 remains a fundamental treatment for decreasing clinical signs (i.e. pain and lameness) associated with OA in horses.[1-4] The inhibition of PGE2 by NSAIDs classifies them as symptom-modifying drugs with little to know support that they have a disease modifying effect. The COX-2 preferential NSAID firocoxib has shown to be safe, have an average bioavailability orally, have a large volume of distribution, and cause a reduction in lameness at the recommended dose in horses.[5-9]

Current clinical reports suggest that when using firocoxib (paste, table or injectable form) at the recommend dose (0.1 mg/kg) a clinical improvement is seen in at least 7 days and is comparable to phenylbutazone alone at this time period.[8,9] One report has documented an objective improvement in lameness at the recommended dose as early as 2 days and as early as 10 hours with a 0.25 mg/kg dose10. In the authors' opinion when administered at the recommended dose firocoxib has a longer onset of action (assessed by clinical improvement in lameness) compared to phenylbutazone. This may be explained by the increase duration for time to steady state concentration at the recommend dose, which is routinely recommended by the authors. Administration of a loading dose (0.3 mg/mg) could potentially produce an earlier clinical improvement, similar to that seen with phenylbutazone, when administering firocoxib.[11]

Firocoxib continues to be a noteworthy and well-accepted treatment for reducing clinical signs associated with OA in the horse. With promising disease modifying effects of other therapeutics described as COX- 2 preferential NSAIDs (meloxicam and carprofen) further controlled studies are needed to evaluate disease-modifying potential of firocoxib on OA.

References

1. May S.A., Lees P. Nonsteroidal anti-inflammatory drugs. In: McIlwraith C.W., Trotter G.W., eds. Joint disease in the horse. Philadelphia: W.B. Saunders, 1996:223–237.

2. Frisbie D.D., Al-Sobayil F., Billinghurst R.C., et al. Changes in synovial fluid and serum biomarkers with exercise and early osteoarthritis in horses. Osteoarthritis Cartilage 2008;16:1196-1204.

3. Frisbie D.D., Kawcak C.E., Baxter G.M., et al. Effects of 6alpha-methylprednisolone acetate on an equine osteochondral fragment exercise model. Am J Vet Res 1998;59:1619-1628.

4. Kawcak C.E., Frisbie D.D., Trotter G.W., et al. Effects of intravenous administration of sodium hyaluronate on carpal joints in exercising horses after arthroscopic surgery and osteochondral fragmentation. Am J Vet Res 1997;58:1132-1140.

5. Cox S., Villarino N., Sommardahl C., et al. Disposition of firocoxib in equine plasma after an oral loading dose and a multiple dose regimen. Vet J 2013;198:382-385.

6. Hovanessian N., Davis J.L., McKenzie H.C., 3rd, et al. Pharmacokinetics and safety of firocoxib after oral administration of repeated consecutive doses to neonatal foals. J Vet Pharmacol Ther 2013.

7. Knych H.K., Stanley S.D., Arthur R.M., et al. Detection and pharmacokinetics of three formulations of firocoxib following multiple administrations to horses. Equine Vet J 2013.

8. Orsini J.A., Ryan W.G., Carithers D.S., et al. Evaluation of oral administration of firocoxib for the management of musculoskeletal pain and lameness associated with osteoarthritis in horses. American Journal of Veterinary Research 2012;73:664-671.

9. Koene M., Goupil X., Kampmann C., et al. Field Trial Validation of the Efficacy and Acceptability of Firocoxib, a Highly Selective Cox-2 Inhibitor, in a Group of 96 Lame Horses. Journal of Equine Veterinary Science 2010;30:237-243.

10. Back W., Macallister C.G., Heel M.C.V., et al. The use of force plate measurements to titrate the dosage of a new COX-2 inhibitor in lame horses. Equine Veterinary Journal 2009;41:309-312

11. MacKay R.J., French T.W., Nguyen H.T., et al. Effects of large doses of phenylbutazone administration to horses. Am J Vet Res 1983;44:774-780

Comparison of subjective and objective methods to identify mild forelimb lameness in horses. In, Proceedings Association of Equine Practitioners 2014.

This is a summary of a publication by Drs. J. Donnell, D. Frisbie, M. King, L. Goodrich and K. Haussler.

Take home message
Subjective evaluation and inertial-sensors agree on mild forelimb lameness more frequently than either with force platforms. Subjective evaluation more reliably identified the limb with an OCF fragment 15 days post induction.

Introduction
The goal of this study was to compare subjective and objective lameness detection methods to identify the presence of mild lameness using an established model of osteoarthritis.

Materials and Methods
A unilateral carpal osteochondral fragment (OCF) was created in 16 horses. Three different assessment methods (force platforms, inertial sensors and subjective evaluation) were used to detect forelimb lameness at 4 time points. Agreement was measured for identification of OCF limb using each individual method and for identification of the same limb identified as lame between methods. Pearson correlations were calculated between all output parameters.

Results
Fifteen days post OCF; agreement was 87% for subjective evaluation, 63% for force platforms and 50% for inertial sensors identifying the OCF limb. Agreement between methods for identifying the same forelimb as lame was 53% between subjective evaluation and inertial sensors and 33% for subjective evaluation and force platforms.

Discussion
Induction of an OCF caused mild lameness 15 days post induction, which was more reliably detected by subjective evaluation, albeit potentially biased. Potential bias associated with perceived treatment effect and study time line by the subjective evaluator was not able to be determined because the lack of a gold standard. A limitation of the objective methods is the inability to evaluate multiple variables, which impacted the force platforms more than the inertial sensors.

Evaluation of intravenous hyaluronan, sodium chondroitin sulfate and N-acetyl-D-glucosamine combination (Polyglycan®) versus saline (0.9% NaCl) for osteoarthritis using an equine model

This study was done by Drs. D. Frisbie, C. McIlwraith, C. Kawcak and N. Werpy

Take Home Message

Caution in using PG via an IV route should be considered especially when more beneficial in vivo results were observed using an intraarticular route of administration in a previous study.

Introduction

Joint disease, specifically OA, is one of the most prevalent and debilitating diseases affecting horses and has a notable economic impact on the equine industry.[1-4] Various medications have been evaluated and or used for the treatment of OA in horses including HA and glucosamine as well as combinations of these products.[5]

In a recent survey of equine practitioners 18% of the respondents indicated that they had used an HA, sodium chondroitin sulfate and N-acetyl-D-glucosaminea combination for the treatment of OA.[6] This formulation, which is not approved by the Food and Drug Administration, is typically administered as a 5 mL dose that contains 25 mg hyaluronic acid sodium salt, 500 mg sodium chondroitin sulfate and 500 mg of N-acetyl-D-glucosamine. The product's label is for IA use as a post-surgical joint lavage and a recent publication confirms beneficial effects when administered using this route.[7] Interestingly, practitioners reported administration routes of 60.1% IV, 21.8% IA and 18% IM, despite the IA labeling recommendations.

The purpose of this study was to assess the ability of this product when administered IV before or after the onset of disease to have symptom and/or disease modifying effects in a model of equine OA as well as monitor for any adverse effects.

Methods

Horses had OA induced in one middle carpal joint and the opposite joint served as a control. Horse were assigned to one of four treatments goups; a placebo group used in testing the prophylactic effects of Polygylcan (PG-PCB) (n = 8), an active prophylactic Polyglycan (PPG) group (n = 8) whose treatment began on day of OA induction, a PCB group to test the effects on established disease (n = 8) and an active Polyglycan (PG) group (n = 8) also testing effects where treatment was given 14 days post-disease induction.

Beginning on Day 16, horses were exercised on a high-speed treadmill 5 days per week and continued each week until the end of the study. PPG horses received 5 mL of PG IV every fifth day of the study starting on Day 0 and horses in the PG-PCB group received 5 mL saline (0.9% NaCl) IV on the same schedule. Horses in the PG group received 5 mL of IV PG on Days 16, 23, 30, 37 and 44 and the PCB horses received 5 mL of IV saline (0.9% NaCl) on the same schedule. The PPG and PG-PCB horses were assessed at a similar time as a group of horses evaluating the IA effect of this product.[7] The PG-PCB horses acted as the controls in the previous study[7] and this group as well as the PPG received 5 mL of saline (0.9% NaCl) as well as 125 mg of amikacin sulphate injection in both middle-carpal joints on Days 0, 7, 14 and 28. The PG and PCB horses did not receive any IA treatments.

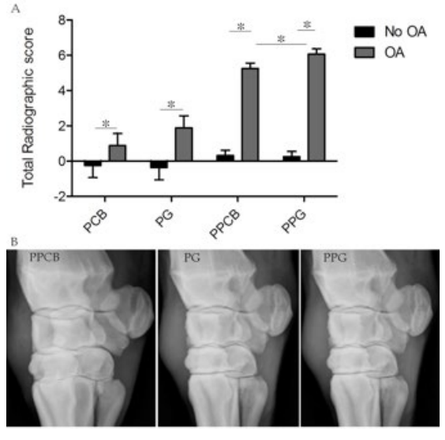


Fig. 1: (A) Plot of mean ± standard error of the mean of total radiographic score for all treatment groups at Day 70. Comparisons between groups mark using a line and asterisk denote a statistically significant difference between comparisons. (B) Radiographs taken at day 70 from the OA affected limbs of the various treatment groups.

Clinical outcomes included lameness exams, flexion, effusion, radiologic evaluation, MRI evaluation, synovial fluid total protein concentration, cytologic evaluation, and total WBC count, synovial fluid GAG concentration and PGE2, gross observation of joints, histologic examination, articular cartilage GAG content and articular cartilage matrix metabolism.

Results

Horses in the PPG group had significantly more response to carpal flexion in the OA affected limb (1.75 ± 0.09) when compared to the opposite (0.09 ± 0.09) limb as well as the OA affected limb of the PG-PCB treated horses (1.30 ± 0.09).

A significantly increased degree of pathologic change was observed for OA affected joints of the PPG group when compared to OA affected joints of the PG-PCB horses respectfully in the cumulative radiographic score (Fig 1).

On MRI evaluation, more radial carpal bone edema was noted for PG treated horses (1.3 ± 0.19) at Day 70 compared to PCB (0.7 ± 0.19).

Significantly less full thickness articular cartilage erosion was seen when PPG (0.63 ± 0.23) was compared to PG-PCB (1.38 ± 0.23) in OA affected joints.

Discussion

The IV administration of Polyglycan was assessed with treatment being initiated at the time of disease induction/prior to onset of disease (PPG) and 14 days post disease induction (PG) and then compared to the respective control groups. It should be noted that the PPG and PG-PCB horses were part of a study that also assessed an IA route of administration and as such IA controls were utilized. This included IA saline and amikacin, while the PCB and PG horses received no IA placebo. Thus, comparison between groups should take this fact into consideration, although the authors have not noted significant effects when this type of placebo (saline and amikacin) has been utilized in previous studies and do not believe this is a significant confounding factor. Further, it should be noted that a group of horses treated IA with PG had beneficial effects while the PPG (data presented in the current study) had some negative outcomes.[5] Given both had amikacin in the OA affected joints the authors feel that the presence of amikacin was unlikely to be an explanation in the disparate result; however, interaction between the PG and amikacin cannot be ruled out.

Thus, given the current level of information the IV administration of this formulation can not be recommended over an IA route.

References

1. Rossdale P.D., Hopes R., Digby N.J., et al. Epidemiological study of wastage among racehorses 1982 and 1983. Vet Rec 1985;116:66-69.

2. NAHMS. Part 1: Baseline reference of 1998 equine health and management. National Animal Health Monitoring System. Fort Collins: USDA APHIS, Veterinary Services-Centers for Epidemiology and Animal Health 1998. http://www.aphis.usda.gov/animal_health/nahms/equine/downloads/equine98/Equine98_dr_Partl.pdf. Accessed May 29, 2013.

3. NAHMS. Lameness and laminitis in US Horses. National Animal Health Monitoring System. Fort Collins: USDA APHIS, Veterinary Services-Centers for Epidemiology and Animal Health, 2000. http://www.aphis.usda.gov/animal_health/nahms/equine/downloads/equine98/Equine98_dr_Lameness.pdf. Accessed May 29, 2013.

4. Todhunter R., Lust G. Pathophysiology of synovitis: Clinical signs and examination in horses. Comp Cont Educ Pract 1990;12:980-992.

5. Frisbie DD, Kawcak CE, Werpy NM, et al. Evaluation of polysulfated glycosaminoglycan or sodium hyaluronan administered intra-articularly for treatment of horses with experimentally induced osteoarthritis. Am J Vet Res 2009;70: 203-209.

6. Ferris DJ, Frisbie DD, McIlwraith CW, et al. Current joint therapy usage in equine practice: A survey of veterinarians 2009. Equine Vet J 2011;43:530-535.

7. Frisbie DD, McIlwraith CW, Kawcak CE, et al. Evaluation of intra-articular hyaluronan, sodium chondroitin sulfate and N-acetyl-d-glucosamine combination versus saline (0.9% NaCl) for osteoarthritis using an equine model. Vet J 2013;197:824-829.

An optimized injection technique of the navicular bursa that avoids the deep digital flexor tendon

This is a summary of a paper published in the Equine Veterinary Journal by A. Daniel, L. Goodrich, M. Barrett, N. Werpy, P. Morley and W. McIlwraith in 2014. doi: 10.1111/evj.12402.

Take home message

Palmar foot pain represents a major cause of poor performance and lost time from exercise in horses. Diagnostic imaging of this region is most commonly performed using radiographs[1–3] and magnetic resonance imaging (MRI).[4–11] Following diagnostic imaging, injection of the navicular bursa may be indicated. Clinicians can use this optimised approach to the navicular bursa to aspirate synovial fluid or medicate the bursa with minimal risk of puncturing the DDFT.

Introduction

The purpose of this study was to report an optimised radiographic guided injection technique of the navicular bursa from the lateral aspect that consistently avoids the DDFT. Furthermore, we aimed to determine the risk of penetration of the DIP joint and DFTS in normal limbs and compare this to those with distension of the bursa, DIP joint and DFTS. We hypothesised that the lateral technique would consistently avoid the DDFT and that distension of the DIP joint and DFTS would be associated with increased risk of needle penetration compared to normal limbs.

Materials and Methods

Cadaver limbs (n=40) were placed in a stand to simulate weight bearing. Each clinical case limb (n=31) was positioned on blocks to allow subsequent lateromedial radiographs for the technique. In cadaver and clinical limbs, contrast was injected and the needle position assessed with radiographs. Post imaging MRI analysis was performed on all cadaver limbs to confirm correct location of the needle within the bursa and to determine any penetration of the needle through the DIP joint capsule, the DFTS and/or the DDFT. If the needle passed through the synovial lining of either the DIP or the DFTS this was classified as entering that structure; however, to be classified as within the navicular bursa the needle had to be located within the navicular bursal fluid.

Results

Successful navicular bursal injection was achieved in all limbs (n = 71). Based on the previously described zoning scheme (Fig 3, Table 1), if the needle was positioned in Zone B or Zone C it was determined to be within the navicular bursa in 44 (98%) and 26 (96%)

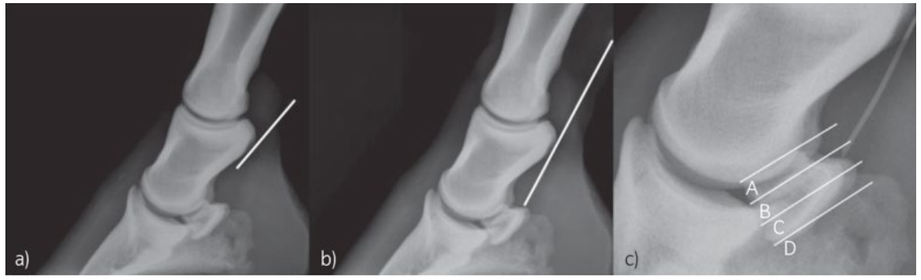


Fig. 1: (A) Needle angle showing incorrect trajectory towards the palmar recess of the distal interphalangeal joint. (B) Adjusted needle placement after moving the needle tip palmar. Subsequent contrast injection confirmed accurate needle location. Contrast injection confirmed accurate needle location. (C) Zoning analysis of image in (B) showing zones A, B, C and D.

Zone	Bursa	DIP	Palmar to DDFT
A	0	4	0
B	44	1	0
C	26	0	1
D	0	0	3

Table 1: Summary of needle tip location in combined cadaver and clinical limbs immediately prior to contrast injection. DIP, distal interphalangeal joint; DDFT, deep digital flexor tendon; Bursa, navicular bursa.

limbs, respectively (Table 1). When placed in Zone A or D it was determined to be either in the DIP joint (Zone A) or palmar to the DDFT (zone D) in 4 limbs (100%) or 3 limbs (100%), respectively. In all cases the needle was then repositioned into the bursa prior to MRI examination.

Discussion

Navicular bursal injection was achieved in all limbs and the needle only penetrated the dorsal margin of the DDFT in one of 40 cadaver limbs (2.5%) based on MRI examination. The technique used for the clinical and cadaver limbs was considered identical despite the lack of axial load on the cadaver limbs.[12]

Our hypothesis for this study was proven in that the results reveal that this optimised lateral technique avoids the DDFT and important surrounding soft tissue structures associated with the navicular bursa. Our objective of determining the risk of puncture through the distended DIP joint and/or DFTS was met, and we proved that synovial puncture is high when each respective structure is distended.

References

1. Dyson, S. (2011) Radiological interpretation of the navicular bone.Equine Vet. Educ. 23, 73-87.

2. Verschooten, F., Roels, J., Lampo, P., Desmet, P., De Moor, A. and Picavet, T. (1989) Radiographic measurement from the lateromedial projection of the equine foot with navicular disease.Res. Vet.Sci.46,15-21.

3. Turner, T.A., Kneller, S.K., Badertscher, R.R. and Stowater, J.L. (1986) Radiographic changes in the navicular bones of normal horses. Proc. Am.Ass. Equine Practnrs. 32, 309-314.

4. Holowinski, M.E., Solano, M., Maranda, L. and García-López, J.M. (2012) Magnetic resonance imaging of navicular bursa adhesions.Vet.Radiol.Ultrasound 53,566-572.

5. Gutierrez-Nibeyro, S., Werpy, N. and White, N. II (2012) Standing low-field magnetic resonance imaging in horses with chronic foot pain. Aust. Vet. J. 90, 75-83.

6. Maher, M.C., Werpy, N.M., Goodrich, L.R. and McIlwraith, C.W. (2011) Positive contrast magnetic resonance bursography for assessment of the navicular bursa and surrounding soft tissues. Vet. Radiol. Ultrasound 52, 385-393.

7. Biggi, M. and Dyson, S. (2011) High-field magnetic resonance imaging investigation of distal border fragments of the navicular bone in horses with foot pain. Equine Vet. J. 43, 302-308.

8. Dyson, S. and Murray, R. (2007) Magnetic resonance imaging evaluation of 264 horses with foot pain: the podotrochlear apparatus, deep digital flexor tendon and collateral ligaments of the distal interphalangeal joint. Equine Vet. J. 39, 340-343.

9. Murray, R.C., Schramme, M.C., Dyson, S.J., Branch, M.V. and Blunden, T.S. (2006) Magnetic resonance imaging characteristics of the foot in horses with palmar foot pain and control horses. Vet. Radiol. Ultrasound 47, 1-16.

10. Busoni, V., Heimann, M., Trenteseaux, J., Snaps, F. and Dondelinger, R.F. (2005) Magnetic resonance imaging findings in the equine deep digital flexor tendon and distal sesamoid bone in advanced navicular disease–an ex vivo study. Vet. Radiol. Ultrasound 46, 279-286.

11. Dyson, S., Blunden, T. and Murray, R. (2012) Comparison between magnetic resonance imaging and histological findings in the navicular bone of horses with foot pain. Equine Vet. J. 44, 692-698.

12. Swanstrom, M.D., Stover, S.M., Hubbard, M. and Hawkins, D.A. (2004) Determination of passive mechanical properties of the superficial and deep digital flexor muscle-ligament-tendon complexes in the forelimbs of horses. Am. J. Vet. Res. 65, 188- 197.

Comparison of intraarticular polysulfated glycosaminoglycan (PSGAG) and triamcinolone acetonide (TA) with intraarticular polysulfated glycosaminoglycan alone or placebo for treatment of osteoarthritis using an equine experimental model

This was a study performed by Drs. D. Frisbie, C. Kawcak, W. McIlwraith and N. Werpy.

Take home message

Neither PSGAG nor PSGAG + TA demonstrated lameness that was significantly different compared to placebo. This study continues to support the use of IA PSGAG but suggests significant caution when 5 mg TA per horse is co-administered with PSGAG.

Introduction

Numerous medications are routinely used to treat osteoarthritis (OA) in horses and include non-steroidal anti-inflammatory drugs, corticosteroids, polysulfated glycosaminoglycan (PSGAG) and hyaluronan.[1-5] Beneficial effects of PSGAG have been demonstrated in vitro, although not all effects have been realized when evaluated in vivo.

The aim of the blinded controlled study reported here was to evaluate the clinical signs and disease modifying effects of PSGAG plus TA (PSGAG + TA) compared to placebo (PCB) and PSGAG treatments alone in an established experimentally induced model of equine OA.[5-11]

Methods

As previously described,[12] 24 horses had OA induced in one randomly selected middle carpal joint while the opposite joint served as a control. One joint was designated as the OA affected joint and the other referred to as the control joint.

Beginning on day 15 post OA induction, horses were exercised on a high speed treadmill 5 days each week until the end of the study.

Treatment in the OA limb began on day 14 and was repeated on study days 21, 28, 35 and 42. Horses treated with PSGAG + TA were administered 250 mg PSGAG, 5 mg TA and 125 mg amikacin sulfate injection (Amikacin, Sicor Pharmaceuticals) IA (n = 8). Horses treated with PSGAG received 250 mg PSGAG and 125 mg amikacin sulphate injection (n = 8). PCB horses received 2 mL 0.9% NaCl and 125 mg amikacin sulphate IA (n = 8). All horses received 2 mL 0.9% NaCl in the control joint on similar study days.

Clinical outcomes measured consisted of lameness exams, carpal flexion, joint effusion, radiographic evaluation, synovial fluid total protein, white blood cell count and differential, synovial fluid biomarkers PGE2 and GAG concentration, gross pathologic observation of joints, histologic examination, articular cartilage proteoglycan content and total articular cartilage GAG content and cartilage matrix metabolism.

Results

On average significantly greater improvement in lameness was observed in the OA affected limb treated with PSGAG when compared to PSGAG + TA (Fig. 1).

Radiographically, significantly less pathology was seen in PSGAG + TA treated OA joints (-1.38 ± 0.42) when compared to PCB (-3.00 ± 0.42).

OA joints treated with PSGAG had the most improvement in synovial fluid TP levels, significantly greater

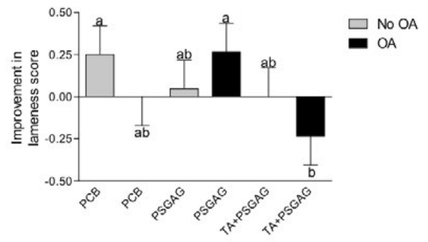


Fig. 1: Improvement in lameness score (raw day 14 value – raw value) averaged over the treatment period. Values are mean ± standard error of the mean for all graphs. Different letters indicate a statistical difference (P < 0.05).

than both OA joints in the PCB or PSGAG + TA groups (Fig. 2). Throughout the study greater GAG concentrations were noted in the OA joints of PSGAG horses compared to both the OA joints of PCB or PSGAG +TA.

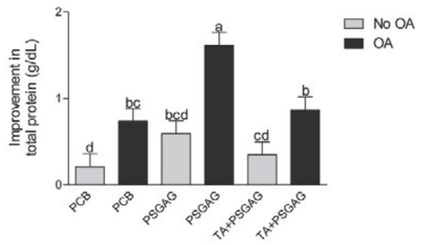


Fig. 2: Improvement in synovial fluid total protein levels (g/dL) (raw day 14 value – raw value). Different letters indicate statistically significant differences (P < 0.05).

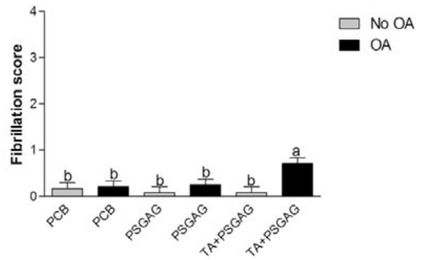


Fig. 3: Graph showing histologic fibrillation score among treatment groups. Different letters indicate statistically significant differences (P < 0.05).

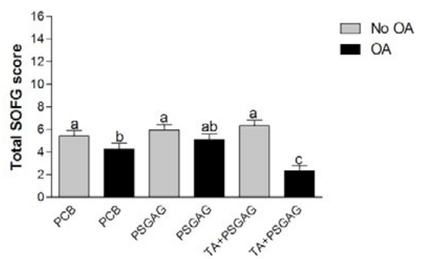


Fig. 4: Graph showing total safranin O fast green (SOFG) score among treatment groups. Different letters indicate statistically significant differences (P < 0.05).

When individual parameters were assessed, only an increase in fibrillation was noted in OA joints treated with PSGAG + TA compared to PSGAG or PCB OA joints (Fig. 3).

Evaluation of articular cartilage for SOFG staining demonstrated a significant reduction with the induction of OA, as well as a more significant reduction with treatment of PSGAG + TA in the OA joints when compared to the PCB OA joints (Fig. 4).

Discussion

The main aim of this study was to compare IA PSGAG + TA to IA PSGAG alone using an established model. The degree of lameness improved significantly more with PSGAG when compared to PSGAG + TA; however, PSGAG nor PSGAG + TA were significantly different than PCB which was unexpected.

It has been suggested that the addition of TA to PSGAG may decrease joint 'flares' compared to when PSGAG is administered alone. However, based on the results of this study, the authors continue to support the use of IA PSGAG alone, but suggest significant caution in co-administration of TA.

References

1. Rossdale, P.D., Hopes, R., Digby, N.J., Offord, K., 1985. Epidemiological study of wastage among racehorses 1982 and 1983. Veterinary Record 116, 66-69.

2. Todhunter, R. and Lust, G., 1990. Pathophysiology of synovitis: Clinical signs and examination in horses. Compendium on Continuing Education for the Practicing Veterinarian 12, 980-992.

3. NAHMS, 1998. Part 1: Baseline reference of 1998 equine health and management. National Animal Health Monitoring System. Fort Collins: USDA APHIS, Veterinary Services-Centers for Epidemiology and Animal Health. http://www.aphis.usda.gov/animal_health/nahms/equine/downloads/equine98/Equine98_dr_PartI.pdf (accessed 29 May 2013).

4. NAHMS, 2000. Lameness and laminitis in US Horses. National Animal Health Monitoring System. Fort Collins: USDA APHIS, Veterinary Services-Centers for Epidemiology and Animal Health. http://www.aphis.usda.gov/animal_health/nahms/equine/downloads/equine98/Equine98_dr_Lameness.pdf (accessed 29 May 2013).

5. Frisbie, D.D., Kawcak, C.E., Werpy, N.M., McIlwraith, C.W., 2009. Evaluation of polysulfated glycosaminoglycan or sodium hyaluronan administered intra-articularly for treatment of horses with experimentally induced osteoarthritis. American Journal of Veterinary Research 70, 203-209.

6. Foland, J.W., McIlwraith, C.W., Trotter, G.W., Powers, B.E., Lamar, C.H., 1994. Effect of betamethasone and exercise on equine carpal joints with osteochondral fragments. Veterinary Surgery 23, 369-379.

7. Frisbie, D.D., Kawcak, C.E., Trotter, G.W., Powers, B.E., Walton, R.M., McIlwraith, C.W., 1997. The effects of triamcinolone acetate on an in vivo equine osteochondral fragment exercise model. Equine Veterinary Journal 29, 349-359.

8. Kawcak, C.E., Frisbie, D.D., McIlwraith, C.W., Trotter, G.W., Gillette, S., Powers, B.E., Walton, R., 1997. The effect of intravenous administration of sodium hyaluronate on carpal joints in exercising horses after arthroscopic surgery and osteochondral fragmentation. American Journal of Veterinary Research 58, 1132-1140.

9. Frisbie, D.D., Kawcak, C.E., Baxter, G.M., Trotter, G.W., Powers, B.E., Lassen, E.D., McIlwraith, C.W., 1998. Effects of 6α-methylprednisolone acetate on an in vivo equine osteochondral fragment exercise model. American Journal of Veterinary Research 59, 1619-1628.

10. Frisbie, D.D., Kawcak, C.E., Werpy, N.M., Park, R.D., McIlwraith, C.W., 2007. Clinical, biochemical, and histologic effects of intra-articular administration of autologous conditioned serum in horses with experimentally induced osteoarthritis. American Journal of Veterinary Research 68, 290-296.

11. Frisbie, D.D., Kawcak, C.E., McIlwraith, C.W., 2009. Evaluation of the effect of extracorporeal shock wave treatment on experimentally induced osteoarthritis in middle carpal joints of horses. American Journal of Veterinary Research 70, 449-454.

12. Frisbie, D.D., Ghivizzani, S.C., Robbins, P.D., Evans, C.H., Trotter, G.W., McIlwraith, C.W., 2002. Treatment of experimental equine osteoarthritis by in vivo delivery of the equine interleukin-1 receptor antagonist gene. Gene Therapy 9, 12-20.

Clinical Outcome After Intra-Articular Administration of Bone Marrow Derived Mesenchymal Stem Cells in 33 Horses With Stifle Injury

This paper has been published in Veterinary Surgery by Drs. D. Ferris, D. Frisbie, J. Kisiday, C. McIlwraith, B. Hague, M. Major, R. Schneider, C. Zubrod, C. Kawcak and L. Goodrich in 2014. Vet Surg 2014;43:255-265. doi: 10.1111/j.1532-950X.2014.12100.x.

Take Home Message

Intra-articular administration of bone marrow derived stem cells (BMSCs) post-arthroscopic surgery for stifle lesions causes improvement in the ability to return to work compared to arthroscopic surgery alone in horses with stifle injury. There was a significant increase in success with Grade 3 meniscal tears compared to arthroscopic surgery alone.

Introduction

Musculoskeletal injuries involving joint soft tissues, specifically articular cartilage, ligament and/or meniscus, in horses and human athletes, have a suboptimal prognosis for return to athletic function when treated with conventional means, including arthroscopic debridement and rest.[1-4] In particular severe injuries to the meniscus have been reported to have a poor prognosis.[2] Despite increased clinical use of stem cells in horses in the US, no peer-reviewed follow up studies focusing on clinical case series treated intra-articularly (IA) with BMSCs has been published. Based on our experience of perceived and proved outcomes after intra-articular therapy using BMSCs and the controlled study performed by Murphy, at el.[32] we began a prospective study treating clinical cases undergoing arthroscopic confirmation of disease severity with the goal of obtaining follow up at 2 time points: at 6 months and 2 years after treatment (the current study).[27] These data were then compared to published reports with surgery alone as the first step of assessing the potential for BMSCs to augment treatment in joint disease.

Methods

Inclusion criteria included horses that had lameness localized to the stifle by diagnostic anesthesia, arthroscopic surgery of the femorotibial joint and subsequent intra-articular administration of autologous BMSCs. Case details and follow up were gathered from medical records, owner, trainer or veterinarian. Outcome was defined as returned to previous level of work, returned to work, or failed to return to work. The outcome of horses in our study were compared to 2 published, peer-reviewed studies that describe return to function after routine stifle arthroscopy and treatment.[1,2] Horses in our study classified as 'returned to previous level of work' were compared to those in Cohen et al. classified as 'returned to previous use' in Walmsley et al. classified as 'sound' and 'returned to full use'.[1,2] Horses in the current study classified as 'returned to work' were compared to Cohen et al. horses classified as 'becoming sound' and 'improved' (though Cohen et al. make no claim that these horses were working) and Walmsley et al. horses classified as 'light work only'.[1,2] Horses in our study classified as 'no return' were compared to the remaining horses in Cohen et al. and the horses in Walmsley et al. classified as 'lame'.[1,2]

Results

Thirty-nine horses were treated with BMSCs for a stifle injury during the study period and outcome was available for 33 horses. In most horses (n=30), bone marrow was aspirated at the time of the arthroscopic procedure and sent for expansion. BMSCs were injected IA~3-4 weeks after surgery. The other 3 horses had BMSCs injected at the time of surgery. All cases received a single injection. Overall, 14 (42%) horses returned to or exceeded their previous level of work, over 11 (33%) returned to work, and 8 (24%) failed to return to work. For 16 horses with follow up >2years, 5 horses (31%) returned to and maintained their previous level of work, 6 (38%) returned to work, and 5 (31%) failed to return to work. Western performance horses (n=21) were the most common performance type treated (reining, cutting, working cow horse).

In 20 unilaterally affected cases, the medial femorotibial (MFT) joint of the affected leg was the only joint treated with BMSC. In 2 unilaterally affected cases, the lateral femorotibial (LFT) joint was treated alone with the MFT of the same stifle. In 10 bilaterally affected cases, bilateral MFT joints were treated, and in 1 bilateral case, 1 MFT and the contralateral LFT were treated.

Some degree of articular cartilage damage was present in all 33 cases; 26 horses had fibrillation or small areas of damage, which were mechanically debridement during arthroscopy. Nine of 26 (35%) returned to previous level of work, 10/26 (38%) returned to work, and 7/26 (27%) failed to return. Seven horses had more severe cartilage damage or eburnation and were treated by microfracture of the lesions. Five of these returned to the previous level of function (71%), 1 returned to work (14%) and 1 (14%) failed to return to work. The meniscal injury scoring system of Walmsley, et al.[1] was used to score the meniscal injuries in our horses. Twenty-four horses had meniscal damage recorded: 9 with a grade 1 score, 7 with a grade 2 score, and 8 with a grade 3 score. Of 9 horses given a meniscal score of 1, 5 (56%) returned to previous level, 4 (44%) returned to work. Of the 7 horses with a meniscal score of 2, 2 (29%) returned to previous level, 2 (29%) returned to work, and 3 horses (42%) failed to return. Of the 8 horses with a grade 3 meniscal score, 2 returned to previous level of work (25%), 3 (37%) returned to work, and 3 (37%) failed to return. This resulted in 62% of horses with a grade 3 meniscal tear being able to return to some level of work after treatment with BMSCs and surgical debridement.

Horses with meniscal lesions from our study were compared to horses reported with meniscal lesions from Cohen et al. and Walmsley at al.[1,2] There was a significant difference in the clinical proportion of horses able to return to work in the 3 studies (P=.038) hen examining all horses with meniscal injury irrespective of injury grade. Walmsley et al. (40%) and Cohen et al. (36.4%) reported a greater percentage of horses 'failed to return to work' compared to our study (25%).[1,2] Overall, a higher percentage of horses in our study were able to return to some level of work (75%) compared to Walmsley et al. (60%) and Cohen et al. (64%).[1,2] It is worth noting that the effect of concomitant injuries or the exclusion of horses with other injuries was not specifically addressed by Cohen et al. or Walmsley et al. nor was it stated whether horses in the 'became sound' or 'improved' groups of Cohen et al. were working or not.[1,2]

Discussion

In our study participating surgeons were instructed to enroll horses with severe injury or injuries that had failed other treatments. Joint flare occurred in 3 (9%) horses and there was no record in those cases of NSAIDs being administered before the BMSC injection (we recommend it). Particular note is that with grade 3 tears of the meniscus, 2/8 of the horses in our study returned to work, 0/4 in Cohen et al. study returned to work and 1/17 (6%) in the Walmsley et al. study returned to work.

References

1. Walmsley J.P.: Meniscal tears in horses: an evaluation of clinical signs and arthroscopic treatment of 80 cases. Equine vet J 2003;35:402–406

2. Cohen J.M., Richardson D.W., McKnight A.L., et al: Long-term outcome in 44 horses with stifle lameness after arthroscopic exploration and debridement. Vet Surg 2009;38:543–551

3. Mithoefer K., Williams R.J. III, Warren R.F., et al: High-impact athletics after knee articular cartilage repair. Am J Sports Med 2006;34:1413–1418 Veterinary Surgery 43 (2014) 255–265 © Copyright 2014 by The American College of Veterinary Surgeons 263 Ferris et al. Intra-Articular Administered Bone Marrow Derived Mesenchymal Stem Cells

4. Cerynik D.L., Lewullis G.E., Joves B.C., et al: Outcomes of microfracture in professional basketball players. Knee Surg Sports Traumatol Arthrosc 2009;17:1135–1139

5. Caplan A.: New era of cell-based orthopedic therapies. Tiss Eng 2009;15:195–200

6. Ribitsch I., Burk J., Delling U., et al: Basic science and clinical application of stem cells in veterinary medicine. Adv Biochem Eng/Biothechnol 2010;123:219–263

7. Christoforakis J., Pradhan F.R., Sanchez-Ballester J., et al: Is there association between articular cartilage changes and degenerative meniscus tears? Arthroscopy 2005;21:1366–1369

8. Kawamura S., Lotito K., Rodeo S.A.: Biomechanics and healing response of the meniscus. Oper Tech Sports Med 2003;11:68–76

9. Izuta Y., Ochi M., Adachi N., et al: Meniscal repair using bone marrow-derived mesenchymal stem cells: experimental study using green fluorescent protein transgenic rats. Knee 2005;12:217–223

10. Peretti G.M., Gill T.J., Xu J., et al: Cell-based therapy for meniscal repair: a large animal study. Am J Sports Med 2004;32:146–158

11. Angele P., Johnstone B., Kujat R., et al: Stem cell based tissue engineering for meniscus repair. J Biomed Mater Res A 2008;85A:445–455

12. Kon E., Chiari C., Marcacci M., et al: Tissue engineering for total meniscal substitution: animal study in sheep model. Tissue Eng 2007;14-A:1067–1080

13. Centeno C.J., Busse D., Kisiday J.A., et al: Regeneration of meniscus cartilage in a knee treated with percutaneously implanted autologous mesenchymal stem cells. Med Hypotheses 2008;71:900–908

14. Schramme M.C., Jones R.M., May S.A., et al: Comparison of radiographic, ultrasonographic and arthroscopic findings in 29 horses with meniscal tears. Proceedings of 12th Annual Congress of the European Society of Veterinary Orthopaedics and Traumatology, Munich, Germany, 2004, p 186

15. Coudry V., Denoix J.M.: Ultrasonography of the femorotibial collateral ligaments of the horse. Equine Vet Educ 2005;17:275–279

16. Werpy N.M.: Imaging of the stifle and tarsus. Proceedings of Focus on Lameness and Imaging, American Association of Equine Practitioners, Fort Collins, CO, 2007, pp 135–141

17. Barrett M.F., Frisbie D.D., McIlwraith C.W., et al: The arthroscopic and ultrasonographic boundaries of the equine femorotibial joints. Equine Vet J 2012;44:57–63

18. Watts A.E., Nixon A.J.: Comparison of arthroscopic approaches and accessible anatomic structures during arthroscopy of the caudal pouches of equine femorotibial joints. Vet Surg 2006;35:219–226

19. Muurlink T., Walmsley J., Young D., et al: A cranial intercondylar arthroscopic approach to the caudal medial femorotibial joint of the horse. Equine Vet J 2009;41:5–10

20. Howard R.D., McIlwraith C.W., Trotter G.W.: Arthroscopic surgery for subchondral cystic lesions of the medial femoral condyle in horses: 41 cases (1988–1991). J Am Vet Med Assoc 1995;206:842–850

21. Kold S.E., Hickman J.: An experimental study of the healing process of equine chondral and osteochondral defects. Equine Vet J 1986;18:18–24

22. Jackson W.A., Stick J.A., Arnoczky S.P., et al: The effect of compacted cancellous bone grafting on the healing of subchondral bone defects of the medial femoral condyle in horses. Vet Surg 2000;29:8–16

23. Bodo G., Hangody L., Modis L., et al: Autologous osteochondral grafting (mosaic arthroplasty) for treatment of subchondral cystic lesions in the equine stifle and fetlock joints. Vet Surg 2004;33:588–596

24. Fortier L.A., Nixon A.J.: New surgical treatments for osteochondritis dissecans and subchondral bone cysts. Vet Clin Equine 2005;21:673–690

25. Wallis T.W., Goodrich L.R., McIlwraith C.W., et al: Arthroscopic injection of corticosteroids into the fibrous tissue of subchondral cystic lesions of the medial femoral condyle in horses: a retrospective study of 52 cases (2001–2006). Equine Vet J 2008;40:461–467

26. Ortved K.F., Nixon A.J., Mohammed H.O., et al: Treatment of subchondral cystic lesions of the medial femoral condyle of mature horses with growth factor enhanced chondrocyte grafts: a retrospective study of 49 cases. Equine Vet J 2012;44:606–613

27. Frisbie D.D., Hauge B.A., Kisiday J.D.: Stem cells as a treatment for osteoarthritis. Proceedings of American College of Veterinary Surgeons Surgical Summit, San Diego, CA, 2007, pp 39–42

28. Kisiday J.A., Kopesky P.W., Evans CH, et al: Evaluation of adult equine bone marrow and adipose-derived progenitor cell chondrogenesis in hydrogel cultures. J Orthop Res 2008;26:322– 331

29. Vidal M.A., Robinson S.O., Lopez M.J., et al: Comparison of chondrogenic potential in equine mesenchymal stromal cells derived from adipose tissue and bone marrow. Vet Surg 2008;37:713–724

30. Berg L.C., Koch T.G., Heerkens T., et al: Chondrogenic potential of mesenchymal stromal cells derived from equine bone marrow and umbilical cord blood. Vet Comp Orthop Traumatol 2009;22:363–370

31. Frisbie D.D., Kisiday J.D., Kawcak C.E., et al: Evaluation of adiposederived stromal vascular fraction or bone marrow-derived mesenchymal stem cells for treatment of osteoarthritis. J Orthop Res 2009;27:1675–1680

32. Murphy J.M., Fink D.J., Hunziker E.B., et al: Stem cell therapy in a caprine model of osteoarthritis. Arthritis Rheum 2003;48:3464–3474

33. Fortier L.A., Potter H.G., Rickey E.J., et al: Concentrated bone marrow aspirate improves full-thickness cartilage repair compared with microfracture in the equine model. J Bone Joint Surg Am 2010;92-A:1927–1937

34. McIlwraith C.W., Frisbie D.D., Rodkey W.G., et al: Evaluation of intra-articular mesenchymal stem cells to augment healing of microfractured chondral defects. Arthroscopy 2011;27:1552–1561

35. Frisbie D.D., Kawcak C.E., Werpy N.M., et al: Evaluation of bone marrow derived stem cells and adipose derived stromal vascular fraction for treatment of osteoarthritis using an equine experimental model. Proc Am Assoc Equine Pract 2006;52:420–421

36. Nixon A.J., Begum L., Mohammed H.O., et al: Autologous chondrocyte implantation drives early chondrogenesis and organized repair in extensive full and partial-thickness cartilage defects in an equine model. J Orthop Res 2011;29:1121–1130

37. Frisbie D.D., Stewart M.C.: Cell-based therapies for equine joint disease. Vet Clin Equine 2011;27:335–349 264 Veterinary Surgery 43 (2014) 255–265 © Copyright 2014 by The American College of Veterinary Surgeons Intra-Articular Administered Bone Marrow Derived Mesenchymal Stem Cells Ferris et al.

38. Smith R.K.: Mesenchymal stem cell therapy for equine tendinopathy. Disabil Rehabil 2008;30:1752–1758

39. Godwin E.E., Young N.J., Dudhia J., et al: Implantation of bone marrow-derived mesenchymal stem cells demostrates improved outcome in horses with overstrain injury of the superficial digital flexor tendon. Equine Vet J 2011;44:25–32

40. Burk J., Brehm W.: Stem cell therapy of tendon injuries—clinical outcome in 98 cases. Pferdeheilkunde 2011;27:153–161

41. Smith M.A., Walmsley J.P., Phillips T.J., et al: Effect of age at presentation on outcome following arthroscopic debridement of subchondral cystic lesions of the medial femoral condyle: 85 horses (1993–2003). Equine Vet J 2005;37:175–180

42. Frisbie DD, Smith RK: Clinical update on the use of mesenchymal stem cells in equine orthopaedics. Equine Vet J 2010;42:86–89

43. Welch R.D., DeBowes R.M., Liepold H.W.: Evaluation of the effects of intra-articular injection of dimethylsulfoxide on normal equine articular tissues. Am J Vet Res 1989;50:1180–1182

44. Bohannon L., Walker N., Burges J., et al: Effects of mixing pharmaceuticals with equine stem cells for the treatment of orthopedic injuries. Proc Am Assoc Equine Pract 2011;57:78

45. Homandberg G.A., Ummadi V., Kang H., et al: Hyaluronan enhances cartilage repair through low grade tissue remodeling involving cytokines and matrix metalloproteinases. Inflamm Res 2004;53:534–543

46. Hegewald A.A., Ringe J., Bartel J., et al: Hyaluronic acid and autologous synovial fluid induce chondrocyte differentiation of equine mesenchymal stem cells: a preliminary study. Tissue Cell 2004;36:431–438

47. Seitz B., Hayashi S., Wee W.R., et al: In vitro effects of aminoglycosides and fluoroquinolones on keratocytes. Invest Ophthalmol Vis Sci 1996;37:656–665

48. Watts A.E., Nixon A.J.: Distribution and homing of stem cells after intra-articular injection to normal and arthritic joints. Proc Am Assoc Equine Pract 2011;57:79

Back Problems

This is a summary of a book chapter written by K. Haussler and L. Jeffcott and published in 2014. Back and pelvis. In: Equine Sports Medicine and Surgery, 2nd edition, (K. Hinchliff, A. Kaneps, A. Goer, editors), Elesvier, pp. 419-456.

Take Home Message

Back problems in horses cause a considerable degree of wastage and lost performance in almost all athletic horses. Definitive diagnosis is often difficult due to vague clinical signs and the lack of good diagnostic imaging coupled with pathological reports.[1,2] This has inevitably resulted in widespread controversy engendering many unsubstantiated opinions about the incidence and clinical significance of back problems, which only increase the state of confusion. Much of this controversy has resulted from the general dearth of knowledge of the functional aspects of the equine thoracolumbar spine and scientific studies on the pathogenesis of back problems in horses. It is also clear that many horses perform poorly without an underlying back problem and many other horses perform surprisingly well in spite of one. In recent years there has been an encouraging progression of studies and biomechanical research to improve this situation.[3-8] There is also much more willingness for those involved with traditional methods of clinical medicine to work closely alongside those involved with spinal manipulative therapy and complementary medicine.[9] The purpose of this chapter is to try and combine all these aspects for the benefit and treatment of suspected cases of back pain.

Back problems – A syndrome

The general description of a horse having 'back problems' is not particularly useful from either a diagnostic or therapeutic perspective. Affected horses could have differing combinations, severity, chronicity, distribution, and locations of soft tissue, articular, neurologic or even behavioral issues related to chronic pain and discomfort. From this perspective, a horse could also be described as having 'lameness' or 'colic', which signifies that a potential disease process is present but it is does not specify in any way the pathophysiology or affected tissues, which is often a prerequisite for providing a definitive diagnosis and focused treatment.

A proposed approach for describing the vague and sometimes complex clinical features associated with back problems in horses is to define back problems as a syndrome. A syndrome is typically defined as a collection of clinically recognizable features that often occur together and the presence of one of these features should alert the practitioner to the possibility of the presence of other findings. Within a syndrome, the reason that the clinical signs occur together typically has not yet been discovered (i.e., pathophysiology). The majority of musculoskeletal injuries are characterized by signs of acute inflammation, which include heat, swelling, pain, altered function, and in some cases redness. Chronic musculoskeletal injures are also characterized by altered function and chronic pain (i.e., lameness) and swelling most likely due to effusion, fibrosis or osteophytosis. Therefore, the syndrome of acute back problems includes signs of heat, pain and altered function (e.g., stiffness, muscle hypertonicity) and occasional swelling due to the deep location of most spinal structures. All of these signs are clearly observable and measurable with existing objective outcome measures such as infrared thermography, pressure algometry, myotonometry, goniometry or other measures of spinal range of motion. Chronic back problems are characterized by signs of stiffness and chronic pain, which may include behavioral issues in some horses. The presence of any one of these clinical signs within the axial skeleton should then alert the examiner to the possibility of the existence of other related signs of back problems or spinal dysfunction.

Relationship of back pain to lameness

Lameness is not a typical feature of horses suffering primary back problems. However, secondary back pain is often associated with lameness as the underlying condition causing poor performance. Most primary back cases exhibit only low-grade hind limb lameness, which is often bilateral and most commonly associated with hock injury. A study in which back

pain was induced using lactic acid injections into the longissimus muscles did not produce any signs of hind limb lameness.[10] However, in other studies that evaluated naturally-occurring clinical cases of thoracolumbar or sacroiliac pain, the prevalence of limb lameness varied from 35% up to 74-85%.[11-13] Conversely, in horses presented for primary limb lameness the prevalence of back problems varied between 23-32%.[12,13] Therefore, it appears that a large percentage of horses with back pain have concurrent lameness versus a smaller proportion of horses with lameness also have back pain. The clinical significance of this is that practitioners that focus solely on back problems (e.g., equine chiropractors) are likely not addressing concurrent lameness issues if they are not collaborating with limb lameness specialists. Conversely, practitioners that focus solely on limb lameness without considering the potential adverse effects on spinal function are likely not providing comprehensive treatment of musculoskeletal pain and poor performance.

Saddle fit

A frequent cause of back discomfort can be due to either an inappropriate saddle being used or the saddle not fitting properly. Most poorly fitting saddles produce pressure or pinching over the caudal withers region hence the appearance of white hairs in the midline. Horses change shape, particularly the contour of the back, when they are out of work (i.e., deconditioned) or if they have an increase in body weight. Many saddle-fitting techniques provide a static assessment of the fit of the saddle to the shape and contour of the withers and back. Unfortunately, saddles do not come in a wide variety of standardized sizes for individual fit and comfort, like clothes or shoes for humans. Most horses have to conform to only a few different tree widths and saddle types. Ideally, the saddle should fit comfortably and provide as large an area of contact to help to distribute the rider's weight across the withers and back musculature. Computerized pressure pads help to provide both a static and dynamic assessment of saddle fit, pad thickness and placement, rider influences and changes in pressure associated with different gaits.

Medical management

The basic principles of medical management are to reduce pain and muscle spasms to permit better healing, followed by a program of rehabilitation and measures to prevent further injury or stress to the back. It is therefore necessary in many cases to use a combination of medications (e.g., NSAID, muscle relaxants, corticosteroids, local irritants, or analgesics) in addition to physiotherapy or manipulative therapies.

Conclusion

The focus of the physical examination of the vertebral column is to identify if a back problem exists and to localize the injury to either soft tissue, osseous, or neurologic structures. Traditional orthopedic and neurologic evaluations are important adjunctive assessments used to rule out other, more common, causes of lameness and neurological disorders. The spinal examination also helps to determine if the back problem is acute or chronic and if the vertebral dysfunction is segmental and localized or regional and diffuse.

References

1. Jeffcott L.B. Back problems in the horse - a look at past, present and future progress. Equine Veterinary Journal 1979;11:129-136.
2. Cauvin E. Assessment of back pain in horses. In Practice 1997;19:522-533.
3. Licka T., Peham C. An objective method for evaluating the flexibility of the back of standing horses. Equine Veterinary Journal 1998;30:412-415.
4. Pourcelot P., Audigie F., Degueurce C., et al. Kinematics of the equine back: a method to study the thoracolumbar flexion-extension movements at the trot. Vet Res 1998;29:519-525.
5. Audigié F., Pourcelot P., Degueurce C., et al. Kinematics of the equine back: flexion-extension movements in sound trotting horses. Equine Vet J Suppl 1999;30:210-213.
6. Denoix J.M. Spinal biomechanics and functional anatomy. Vet Clin North Am Equine Pract 1999;15:27-60.
7. Licka T., Peham C., Zohmann E. Range of back movement at trot in horses without back pain. Equine Vet J Suppl 2001:150-153
8. Faber M., Johnston C., Schamhardt H.C., et al. Three-dimensional kinematics of the equine spine during canter. Equine Vet J Suppl 2001:145-149.
9. Haussler K.K., Bertram J.E.A., Gellman K. In-vivo segmental kinematics of the thoracolumbar spinal region in horses and effects of chiropractic manipulations. Proc Amer Assoc Equine Practitioners 1999;45:327-329.
10. Jeffcott L.B., Dalin G., Drevemo S., et al. Effect of induced back pain on gait and performance of trotting horses. Equine Veterinary Journal 1982;14:129-133.
11. Steckel R.R., Kraus-Hansen A.E., Fackelman G.E., et al. Scintigraphic diagnosis of thoracolumbar spinal disease in horses: A review of 50 cases. Proc Amer Assoc Equine Practitioners 1991;37:583-591.
12. Landman M.A., de Blaauw J.A., van Weeren P.R., et al. Field study of the prevalence of lameness in horses with back problems. Vet Rec 2004;155:165-168.
13. Dyson S. The interrelationships between back pain and lameness: a diagnostic challenge. Proc Congr Brit Equine Vet Assoc 2005;44:137-138.

RESEARCH | FOCUS 5 -Validation of Rehabilitation and Physical Therapy Techniques for Musculoskeletal Disease

Physiologic effects of long-term immobilization of the equine distal limb

This study was done by Drs. H. Stewart, N. Werpy, W. McIlwraith and C. Kawcak and has been submitted to Equine Veterinary Journal.

Take home message

Casting of the distal limb of the horse (below the knee and encasing the foot) can lead to significant changes in the tissues of the fetlock joint. In particular, subchondral bone can lose significant density and articular cartilage and tendons and ligaments can lose strength leading to osteoarthritis and tendinosis within those tissues. The results of this study will lead to future studies focused on rehabilitation strategies that can overcome the negative influences of lower limb casting.

Introduction

Lower limb casts in horses are often necessary to manage injuries. In some cases they are needed to supplement internal fixation of complex fractures. Two previous studies have demonstrated the negative influence of joint immobilization on subchondral bone and articular cartilage; however, a complete study of all the tissues was needed. The goal of this study was to evaluate the effects of lower limb immobilization on all tissues around the fetlock joint in the horse.

Materials and Methods

Sixteen, 3-5 year-old horses were used for this study. All horses were clinically normal at the beginning of this study based on x-rays, CT, MRI and clinical evaluation. After baseline data were obtained a lower limb cast was applied to one randomly selected forelimb in each horse for six weeks. After six weeks, the limbs were again evaluated, the case was removed and the horses began a gradual increase in exercise. Clinical data were obtained at that time and eight weeks later. Imaging data included radiography, CT (Figure 1), nuclear scintigraphy and MRI (Figure 2, 3). Serum biomarkers of bone metabolism were also acquired. Synovial fluid biomarkers of inflammation were also measured throughout the study.

Results

Horses were significantly lamer in the casted limb throughout the study than the uncasted limb. Clinical parameters of joint disease, which included joint capsule thickening, synovial effusion and pain on flexion were also significantly higher in the casted limb of each horse. Radiographic and MRI parameters of joint disease were also significantly higher in the casted limb compared to the control limb and on CT examinations there was a significant loss in bone density at the time of cast removal. There was also significant soft tissue changes as detected on MRI. In particular, there was degenerative changes present in the deep digital flexor tendon in the area of the fetlock joint in casted limbs.

CTX1, a serum biomarker of bone resorption was significantly higher during the casted period in all horses indicating active bone resorption occurred during that time.

PGE2, a marker of joint inflammation was significantly higher in synovial fluid from fetlock joints of the casted limb compared to those of the uncasted limb.

Discussion

This is the first study to show the effects of lower limb immobilization on all tissues in and around the fetlock joint of horses. There was significant decrease in bone density, which was not a surprise; however, the changes seen in the surrounding tissues have not been thoroughly described. The fact that there were significantly higher changes indicative of OA in the casted limb is a concern. These included the development of osteophytes, fragmentation, cartilage thinning and edema within the tissues. In addition, the lesions seen within the deep digital flexor tendon of casted limbs is also a concern. Lower limb immobilization has been shown for quite some time now to lead to significant reduction in density based on the fact that the stimulus for maintaining bone strength is taken away. Although these changes are known to occur in other musculoskeletal tissues such as tendon, ligament and articular cartilage, the severity of changes were not expected for a six-week immobilization period. Therefore, methods to reduce these degenerative changes that occur as a consequence to lower limb immobilization need to be addressed in order to optimize tissue healing and maintenance of uninjured tissues in that area.

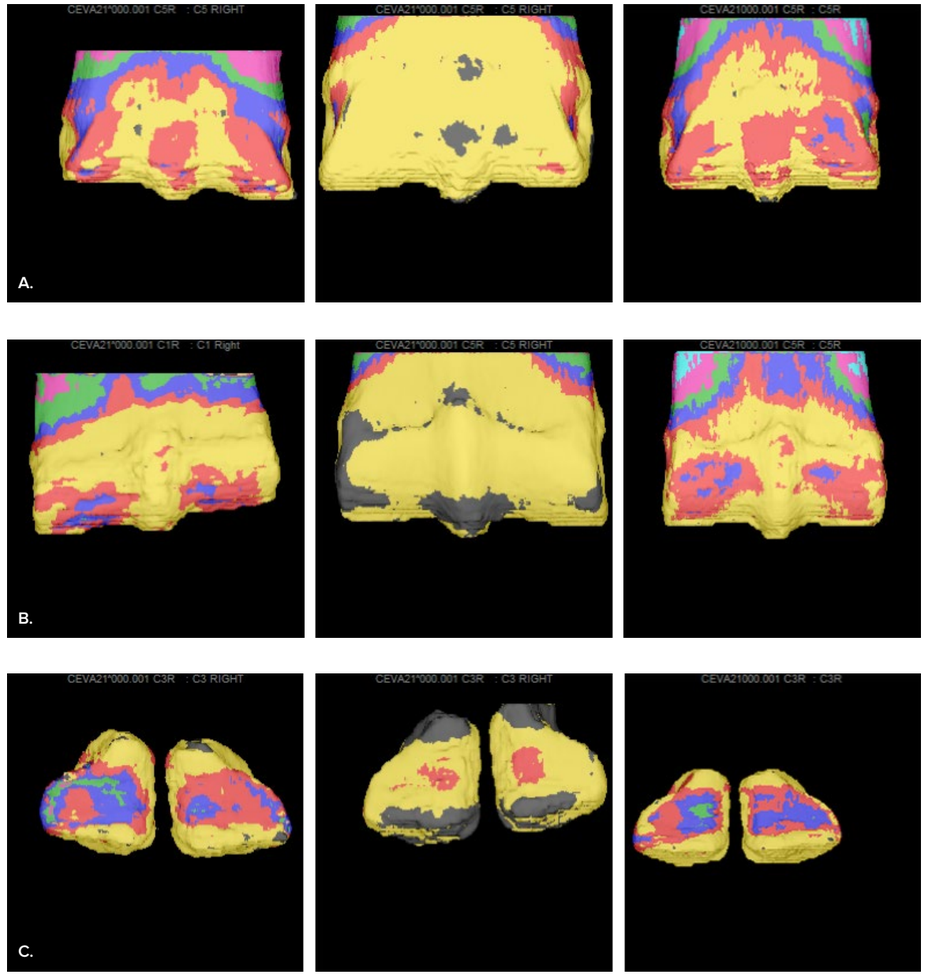


Fig. 1: Examples of volumetric computed tomographic images of bones of the metacarpophalangeal (MCP) joint in the casted forelimb. Row (A) Dorsal third metacarpal bone, (B) palmar third metacarpal bone, and (C) proximal sesamoid bones.

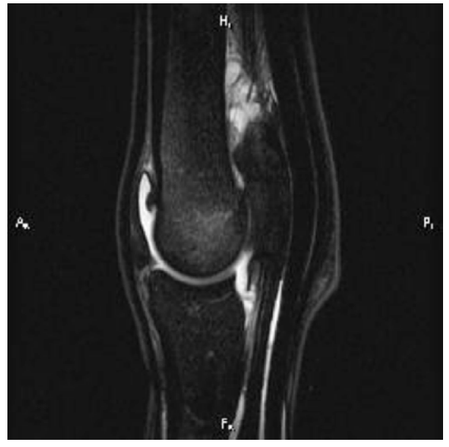


Fig. 2: Sagittal plane STIR MR image of the metacarpophalangeal (MCP) joint. There is osseous fluid in the casted limb (indicated by the arrow). The increased signal intensity (light gray to white area) indicates the presence of diffuse trabecular bone fluid. Synovitis is also present, characterized by joint effusion.

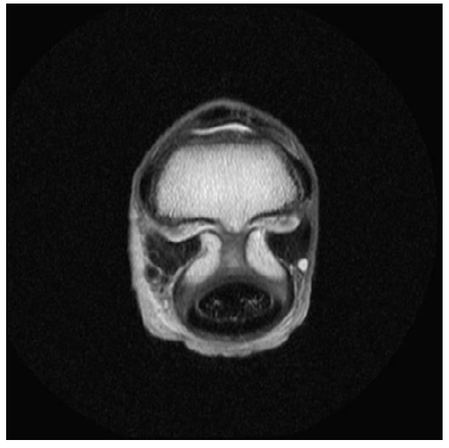


Fig. 3: Transverse PD TSE image at the level of the proximal sesamoid bones. There is increased signal intensity in the palmar aspect of the deep digital flexor tendon which was present on T2 weighted FSE and STIR images which correlates with a tendinopathy.

Chiropractic treatment for athletic horses

This is a summary of a book chapter written by Dr. K. Haussler and published in 2014. Equine rehabilitation: Chiropractic treatment for athletic horses. In: Equine Sports Medicine and Surgery, 2nd edition, (Hinchcliff K.W., Kaneps A.J., Geor R., editors), 2014, Elsevier. pp. 1225-1229

Take Home Message

A thorough physical examination, coupled with orthopaedic and neurologic evaluation, is used to identify common causes of lameness or neurological disorders. A detailed spinal examination helps to identify compensatory or concurrent musculoskeletal issues not readily diagnosed or treated with traditional medical or surgical approaches. The spinal evaluation focuses on evaluating and localizing segmental vertebral dysfunction, which is characterized by localized pain, muscle hypertonicity, and reduced joint motion. The challenge, as with any musculoskeletal injury, is to identify the specific musculoskeletal structures affected and quantify the associated disability or altered function present.

Introduction

Chiropractic is a form of manual therapy that is characterized by the use of high-velocity, low-amplitude thrusts typically applied to regions of stiffness, pain or muscle hypertonicity within the axial skeleton.[1] In humans, chiropractic care has primarily demonstrated clinical efficacy in treating acute and chronic neck and back pain.[2-4] Due to human applications and perceived therapeutic efficacy in treating musculoskeletal issues, chiropractic techniques have subsequently been applied to horses.[5] Equine chiropractic techniques within the United States were primarily developed and taught by Dr. Sharon Willoughby beginning in 1985. Since then, numerous veterinary chiropractic certification programs have been established world-wide. Currently, chiropractic evaluation and treatment techniques have been applied to sport horses for issues mostly related to poor performance and overt signs of back pain.[6,7]

Mechanism of action

The goal of chiropractic treatment is to restore normal joint motion, stimulate neurologic reflexes, and to reduce pain and muscle hypertonicity.[5] Multiple theories have been proposed and tested over the years to explain the pathophysiology of vertebral segment dysfunction and its interactions and influences on the neuromusculoskeletal system.[8,9] Chiropractic treatment is thought to affect mechanoreceptors (i.e., Golgi tendon organ and muscle spindles) to induce reflex inhibition of pain, reflex muscle relaxation, and to correct abnormal movement patterns.[10,11] The literature suggests that any stimulus that activates high-threshold receptors within the periarticular tissues has the potential to initiate unique neurologic reflexes associated with joint manipulation.[12] Alterations in articular neurophysiology from mechanical or chemical injuries can affect both mechanoreceptor and nociceptor function via increased joint capsule tension and nerve ending hypersensitivity.[13] Mechanoreceptor stimulation induces reflex paraspinal musculature hypertonicity and altered local and systemic neurologic reflexes. Nociceptor stimulation results in a lowered pain threshold, sustained afferent stimulation (i.e., facilitation), reflex paraspinal musculature hypertonicity, and abnormal neurologic reflexes.

It is likely that specific manual therapy techniques are inherently more effective than others in addressing each of these local, regional or systemic components.[14] The challenge is in choosing the most appropriate form of manual therapy or combination of techniques that will be efficacious for an individual patient with specific musculoskeletal disabilities. If soft tissue restriction and pain are identified as the primary components of a musculoskeletal injury, then massage, stretching and soft tissue mobilization techniques are indicated for increasing tissue extensibility.[15,16] However, if the musculoskeletal dysfunction is localized to articular structures, then stretching, joint mobilization and manipulation are the most indicated manual therapy techniques for restoring joint range of motion and reducing pain.[17,18]

Indications

A thorough diagnostic workup is required to identify soft tissue and osseous pathology, neurologic disorders, or other lameness conditions that may not be responsive to manual therapy. Clinical signs indicative of a primary spinal disorder include localized musculoskeletal pain, muscle hypertonicity and restricted joint motion. This triad of clinical signs can also be found in a variety of lower limb disorders; however, they are most evident in horses with neck or back problems. Clinical signs indicative of chronic or secondary spinal disorders include regional or diffuse pain, generalized stiffness, and widespread muscle hypertonicity. In these cases, further diagnostic evaluation or imaging should be done to identify the primary cause of lameness or poor performance. Chiropractic may help in the management of muscular, articular and neurologic components of select musculoskeletal injuries in performance horses. Musculoskeletal conditions that are chronic or recurring, not readily diagnosed, or are not responding to conventional veterinary care may be indicators that manual therapy evaluation and treatment is needed. Chiropractic treatment is usually more effective in the early clinical stages of disease processes versus end-stage disease where reparative processes have been exhausted. Joint manipulation is usually contraindicated in the acute stages of soft tissue injury; however, mobilization is safer than manipulation and has been shown to have short-term benefits for acute neck or back pain in humans.[19] Manipulation is probably more effective than mobilization for chronic neck or back pain and has the potential to help restore normal joint motion, thus limiting the risk of reinjury.[20]

Contraindications

Chiropractic is not a is not a 'cure all' for all joint or back problems and is generally contraindicated in the presence of fractures, acute inflammatory or infectious joint disease, osteomyelitis, joint ankylosis, bleeding disorders, progressive neurological signs, and primary or metastatic tumors.[21] Contraindications are often based on clinical judgment and are related to the technique applied and skill or experience of the practitioner.[21] Acute episodes of osteoarthritis, impinged dorsal spinous processes, and severe articular instability are often contraindications for manipulation. Inadequate physical or spinal examination and poorly developed manipulative skills are also contraindications for applying manual therapy.[22] All horses with neurologic diseases should be evaluated fully to assess the potential risks or benefits of joint mobilization or manipulation. Cervical vertebral myelopathy occurs because of both structural and functional disorders.[23] Static compression caused by vertebral malformation and dynamic lesions caused by vertebral segment hypermobility are contraindications for cervical manipulation; however, adjacent regions of hypomobile vertebrae may benefit from mobilization or manipulation to help restore joint motion and reduce biomechanical stresses in the affected vertebral segments. Serious diseases requiring immediate medical or surgical care need to be ruled out and treated by conventional veterinary medicine before any routine manual therapy is initiated, although manual techniques may contribute to the rehabilitation of most post-surgical cases or severe musculoskeletal injuries by helping to restore normal joint motion and function. Horses that have concurrent hock pain (e.g., osteoarthritis) and a stiff, painful thoracolumbar or lumbosacral vertebral region are best managed by addressing all areas of musculoskeletal dysfunction.

Future Research

Further research is needed to assess the effectiveness of specific chiropractic techniques or combined treatments for pain management and select lameness conditions. Currently there is no validated equine model for studying the effects of manual therapies which would allow characterization of the anatomic, biomechanical, neurophysiologic, pathophysiologic, cellular or biochemical changes associated with soft tissue and joint mobilization or high-velocity thrusts.[12,18] Further understanding of the local and systemic effects of mobilization and manipulation on pain reduction and tissue healing is also needed. Additional studies are needed to determine the duration of the clinical effects of chiropractic treatment. Controlled trials using different forms of spinal manipulation (e.g., manual thrusts versus instrument-assisted thrusts versus manipulation under anesthesia) need to be done to determine which method is most effective for addressing specific disease processes. Studies are also needed to identify which specific clinical measures of back pain or performance are likely to benefit from the various forms of manual therapy, either individually or in combination. New methods of objectively measuring musculoskeletal dysfunction and further studies into the pathophysiology of chronic pain syndromes are needed to help assess the effectiveness of manual therapies on reducing morbidity and improving overall performance in equine athletes.

References

1. Haussler K.K. Review of manual therapy techniques in equine practice. J Equine Vet Sci 2009;29:849-869.
2. Walker B.F., French S.D., Grant W., et al. A Cochrane review of combined chiropractic interventions for low-back pain. Spine (Phila Pa 1976) 2011;36:230-242.
3. Bronfort G., Haas M., Evans R., et al. Effectiveness of manual therapies: the UK evidence report. Chiropr Osteopat 2010;18:3.
4. Globe G.A., Morris C.E., Whalen W.M., et al. Chiropractic management of low back disorders: report from a consensus process. J Manipulative Physiol Ther 2008;31:651-658.
5. Haussler K.K. Chiropractic evaluation and management. Vet Clin North Am Equine Pract 1999;15:195-209.
6. Haussler K.K. Current status of integrative medicine techniques used in equine practice. J Equine Vet Sci 2009;29:639-641.
7. Haussler K.K. The role of manual therapies in equine pain management. Veterinary Clinics of North America: Equine Practice 2010;26:579-601.
8. Leach R.A. Soft outcome measures of dysfunction. The chiropractic theories: Principles and clinical applications. 3rd ed. Baltimore, MD: Williams & Wilkins, 1994;55-71.
9. Haldeman S. The evolution and importance of spinal and chiropractic research. J Manipulative Physiol Ther 1992;15:31-35.
10. Gatterman M.I. Foundations of chiropractic. St. Louis: Mosby-Year Book, Inc., 1995.
11. Cassidy J.D., Lopes A.A., Yong-Hing K. The immediate effect of manipulation versus mobilization on pain and range of motion in the cervical spine: a randomized controlled trial. J Manipulative Physiol Ther 1992;15:570-575.
12. Pickar J.G., Bolton P.S. Spinal manipulative therapy and somatosensory activation. J Electromyogr Kinesiol 2012.
13. Cameron M.H. Physical agents in rehabilitation. Philadelphia: W.B. Saunders Company, 1999.
14. Triano J. The theoretical basis for spinal manipulation In: Haldeman S, ed. Principles and practice of chiropractic. 3rd ed. New York: McGraw-Hill, 2005;361-381.
15. Lederman E. The biomechanical response. Fundamentals of manual therapy: physiology, neurology and psychology. St. Louis: Churchill Livingstone, 1997;23-37.
16. Liptan G.L. Fascia: A missing link in our understanding of the pathology of fibromyalgia. J Bodyw Mov Ther 2010;14:3-12.
17. Bronfort G., Haas M., Evans R.L., et al. Efficacy of spinal manipulation and mobilization for low back pain and neck pain: a systematic review and best evidence synthesis. Spine J 2004;4:335-356.
18. Simmonds N., Miller P., Gemmell H. A theoretical framework for the role of fascia in manual therapy. J Bodyw Mov Ther 2012;16:83-93.
19. Hurwitz E.L., Aker P.D., Adams A.H., et al. Manipulation and mobilization of the cervical spine. A systematic review of the literature. Spine (Phila Pa 1976) 1996;21:1746-1759; discussion 1759-1760.
20. Liebenson C. Rehabilitation of the spine. 1st ed. Baltimore, MD: Williams & Wilkins, 1996.
21. Scaringe J., Kawaoka C. Mobilization techniques In: Haldeman S, ed. Principles and practice of chiropractic. 3rd ed. New York: McGraw-Hill, 2005;767-785.

22. West D.T., Mathews R.S., Miller M.R., et al. Effective management of spinal pain in one hundred seventy-seven patients evaluated for manipulation under anesthesia. J Manipulative Physiol Ther 1999;22:299-308.

23. Levine J.M., Adam E., MacKay R.J., et al. Confirmed and presumptive cervical vertebral compressive myelopathy in older horses: a retrospective study (1992-2004). J Vet Intern Med 2007;21:812-819.

Effect of underwater treadmill exercise in experimental osteoarthritis in the horse

This is a summary of findings in a study by Drs. M. King, K. Haussler, C. Kawcak, W. McIlwraith and R. Reiser, 'Effect of underwater treadmill exercise in postural sway in horses with experimentally induced carpal joint osteoarthritis. MJ Vet Res, 2013; 74:971-982. doi: 10.2460/ajvr.74.7.971 (reference 13 below).

Take Home Message

Aquatic rehabilitation programs that focus on reducing pain, maintaining or improving proprioceptive acuity and strength, and enhancing joint stability through neuromuscular training have the potential to improve function and alter the progression of osteoarthritis in horses.

Introduction

Physical rehabilitation is an effective treatment option for managing primary musculoskeletal injuries, as well as reducing or limiting harmful compensatory gait abnormalities in humans.[1] Rehabilitation programs designed to address osteoarthritis and musculoskeletal injuries often incorporate some form of aquatic exercise. Exercising in water provides an effective medium for increasing joint mobility, promoting normal motor patterns, increasing muscle activation and reducing the incidence of secondary musculoskeletal injuries due to primary joint pathology.[2] Humans with lower extremity osteoarthritis show a significant increase in limb-loading parameters, improved joint range of motion and a significant reduction in the severity of balance deficits following aquatic exercise.[3] The enhancements in muscle strength and function associated with aquatic exercise also significantly improve proprioceptive deficits, poor motor control and abnormal locomotor characteristics typically found in osteoarthritic adults.[4] While aquatic therapy is widely used in rehabilitation programs, there are few investigations into the benefits of this form of exercise for equine patients. Equine investigations involving aquatic therapy focus mainly on the horse's physiologic responses to exercising in water.[5-7] Swim training programs provide improvements in cardiovascular function, reductions in musculoskeletal injury (e.g., tendonitis) and increases in fast-twitch, high-oxidative muscle fibers, which reflect improved aerobic capacity.[8,9] Fine-wire electromyography has been used to measure increased muscle activation of the thoracic limb musculature during pool swimming exercise, compared to overground walking.[10] More recently, changes in stride parameters have been assessed while horses walked in various depths of water.[11] Underwater treadmill exercise with water at the level of the ulna produced increased stride lengths and reduced stride frequencies, compared to walking in water at the level of the pastern joint.[11] A similar study assessed the influence of water depth on distal limb joint range of motion.[12] The varied depths of water (from <1 cm water height to the level of the stifle joint) significantly influenced the fetlock, carpal and tarsal joint range of motion.[12] Results of this study demonstrate that water at varying depths promotes joint specific increases in ranges of motion, therefore providing the ability to adapt therapeutic protocols to target certain joints. A study assessing the efficacy of underwater treadmill exercise to diminish the progression of experimentally induced carpal osteoarthritis was completed at the Colorado State University, Equine Orthopaedic Research Center.[13] This project was established to provide an objective assessment of the pathologic characteristics associated with osteoarthritis and the potential clinical and disease-modifying effects allied with aquatic therapy.

Materials and Methods

An osteochondral fragment (OCF) was induced arthroscopically on day 0 in one middle carpal joint of all 16 horses. Beginning on study day 15, horses were assigned to either over-ground or underwater treadmill exercise (UWT) at the same speed, frequency and duration. Over-ground thoracic and pelvic limb ground reaction forces (GRF), thoracic limb kinematics and electromyography (EMG) of select thoracic limb muscles acting on the carpi were collected at study days -7, 14, 42, and 70. Weekly evaluations included clinical assessments of lameness, response to carpal flexion, passive range of motion (PROM) of thoracic limb ar-

ticulations, middle carpal joint intra-articular pressure (IAP) and synovial fluid analysis. At study conclusion gross pathologic and histologic examinations of articular cartilage and synovial membrane from the middle carpal joints were performed.

Results

Underwater treadmill exercise was able to re-establish baseline levels of passive carpal flexion, returning the carpal joint to full range of motion. In addition, horses exercised in the underwater treadmill demonstrated evenly distributed thoracic limb axial loading, symmetrical timing of select thoracic limb musculature, and significant improvements in static balance control under various stance conditions. The improvement in clinical signs of osteoarthritis in the aquatic therapy group was further supported by evidence of disease-modifying effects at the histologic level. Underwater treadmill exercise reduced joint capsule fibrosis and decreased the degree of inflammatory infiltrate present in the synovial membrane. Results from this study indicate that underwater treadmill exercise is a viable therapeutic option in managing osteoarthritis in horses, which is fundamental to providing evidence-based support for equine aquatic therapy.

Discussion

Aquatic therapy incorporates several different mechanisms of action, all of which have particular benefit in the management of equine musculoskeletal disorders. The current human and veterinary literature suggests that aquatic therapy has beneficial effects on several osteoarthritis-related morbidities, such as pain reduction and increased joint range of motion. Well-designed, controlled, clinical trials using aquatic therapy are needed in horses to determine dosages effects (e.g., water level, duration and speed) and to assess clinical changes in soft tissue swelling, joint stability and motor control patterns associated with adaptive and maladaptive compensatory gait alterations. The diverse physical characteristics of aquatic therapy provide unique approaches to individualized rehabilitation of osteoarthritis and secondary musculoskeletal issues in horses.

References

1. Hurley M. The effects of joint damage on muscle function, proprioception and rehabilitation. Manual Therapy 1997;2.
2. Prins J., Cutner D. Aquatic therapy in the rehabilitation of athletic injuries. Clinics in Sports Medicine 1999;18:447-461.
3. Miyoshi T., Shirota T., Yamamoto S.I., et al. Effect of the walking speed to the lower limb joint angular displacements, joint moments and ground reaction forces during walking in water. Disability and Rehabilitation 2004;26.
4. Messier S., Royer T., Craven T., et al. Long-term exercise and its effect on balance in older, osteoarthritic adults: results from the Fitness, Arthritis, and Seniors Trial (FAST). J Am Geriatr Soc 2000;48:131-138.
5. Voss B., Mohr E., Krzywanek H. Effects of aqua-treadmill exercise on selected blood parameters and on heart-rate variability of horses. J Vet Med A Physiol Pathol Clin Med 2002;49:137-143.
6. Hobo S., Yosjida K., Yoshihara T. Characteristics of respiratory function during swimming exercise in Thoroughbreds. J Vet Med Sci 1998;60:687-689.
7. Nankervis K.J., Williams R.J. Heart rate responses during acclimation of horses to water treadmill exercise. Equine Vet J Suppl 2006:110-112.
8. Misumi K., Sakamoto H., Shimizu R. Changes in skeletal muscle composition in response to swimming training for young horses. J Vet Med Sci 1995;57:959-961.
9. Misumi K., Sakamoto H., Shimizu R. The validity of swimming training for two-year-old thoroughbreds. J Vet Med Sci 1994;56:217-222.
10. Tokuriki M., Ohtsuki R., Kai M., et al. EMG activity of the muscles of the neck and forelimbs during different forms of locomotion. Equine Vet J Suppl 1999;30:231-234.
11. Scott R., Nankervis K., Stringer C., et al. The effect of water height on stride frequency, stride length and heart rate during water treadmill exercise. Equine Vet J Suppl 2010:662-664.
12. Mendez-Angulo J.L., Firshman A.M., Groschen D.M., et al. Effect of water depth on amount of flexion and extension of joints of the distal aspects of the limbs in healthy horses walking on an underwater treadmill. Amer J Vet Research 2013;74:557-566.
13. King M., Haussler K., Kawcak C., et al. Effect of underwater treadmill exercise on postural sway in horses with experimentally induced carpal osteoarthritis. Amer J Vet Research 2013;74:971-982.

2014 ORC
FACULTY AND STAFF

ORTHOPAEDIC RESEARCH CENTER