STEADMAN PHILIPPON RESEARCH INSTITUTE

ORTHOPAEDIC RESEARCH JOURNAL

2021-2022

STEADMAN PHILIPPON RESEARCH INSTITUTE

BUILDING ON OUR LEGACY OF EXCELLENCE

IN ORTHOPAEDIC SPORTS MEDICINE,

STEADMAN PHILIPPON RESEARCH INSTITUTE

IS UNLOCKING THE SECRETS OF HEALING,

FINDING CURES AND ENHANCING LIVES

THROUGH GLOBAL LEADERSHIP IN

REGENERATIVE MEDICINE, SCIENTIFIC

RESEARCH, INNOVATION AND EDUCATION.

DEAR FRIENDS,

We are pleased to share the fifth edition of the Steadman Philippon Research Institute (SPRI) *Orthopaedic Research Journal* with you. This publication is a celebration of the cutting-edge science being performed at our institution, and we are thrilled to share these updates with you.

This year's edition picks up where our fourth edition left off, presenting key scientific and research updates from August 2021–July 2022. Each department at SPRI—the Linda & Mitch Hart Center for Regenerative and Personalized Medicine, Department of Biomedical Engineering, Center for Outcomes-Based Orthopaedic Research and Department of Education—has selected their top highlights from the past year to share with you.

As SPRI has continued to grow, advancing in its clinical trials and broadening into new focus areas, its commitment to conducting bench-to-bedside research, accelerating clinical translation and getting discoveries to patients faster and safer remains a constant. As SPRI works with physician partners from The Steadman Clinic in its federally funded clinical trials, the organizations are able to translate clinical advancements in real time.

SPRI is home to a motivated, passionate and innovative team of scientists and researchers who conduct high-impact science in pursuit of SPRI's mission to find cures and enhance lives. Their dedication ensures that patients all over the world will benefit from SPRI's discoveries.

Thank you for your support of SPRI—our research partners, community and friends are imperative in helping SPRI achieve its success in research and clinical science. We speak on behalf of the entire SPRI team when we thank you again for your support.

Respectfully yours,

MARC J. PHILIPPON, MD
Chair

JOHNNY HUARD, PHD
Chief Scientific Officer

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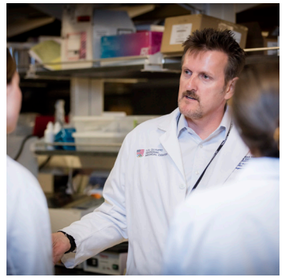



Linda & Mitch Hart Center for Regenerative and Personalized Medicine (CRPM): The CRPM team is focused on the basic science of regenerative medicine. CRPM's team of scientists, researchers and technicians conduct research designed to translate discoveries into practical treatments, including integral participation in each of SPRI's clinical trials.

Department of Biomedical Engineering (BME): SPRI's BME team enhances patient care by focusing on injury and re-injury mechanisms and prevention, develops and validates novel surgical treatments and rehabilitation techniques and teaches advanced research protocols using state-of-the-art biomedical research techniques and technologies. The department includes a Robotics Laboratory, Biomotion Laboratory and advanced imaging utilizing 3-Tesla magnetic resonance imaging (MRI).

Center for Outcomes-Based Orthopaedic Research (COOR): SPRI's robust outcomes database is now tracking over 46,000 surgeries. The center conducts evidence- and outcomes-based research using actual clinical data, which helps both physicians and patients in making better and more informed treatment decisions.

Department of Education: The education team administers and coordinates the clinical fellowships and international scholars programs, hosts conferences and international academic meetings, produces and distributes publications and educational media and organizes outreach programs with local Colorado students.

AN UPDATE ON SPRI'S CLINICAL TRIALS

IN THE MOST RECENT EDITION OF SPRI'S *ORTHOPAEDIC RESEARCH JOURNAL,* WE SHARED THAT SPRI HAD ACCELERATED ITS BENCH-TO-BEDSIDE RESEARCH BY LAUNCHING SEVERAL FEDERALLY FUNDED CLINICAL TRIALS, SUPPORTED BY THE DEPARTMENT OF DEFENSE (DOD) AND NATIONAL INSTITUTES OF HEALTH (NIH). THESE CLINICAL TRIALS HAVE BECOME A KEY ELEMENT OF SPRI'S RESEARCH PROGRAM, EMBLEMATIC OF THE ORGANIZATION'S FOCUS ON TRANSLATIONAL SCIENCE.

DEPARTMENT OF DEFENSE PROJECTS

SPRI's DoD projects include four clinical trials and a clinical study that are currently in progress. The investigative team includes SPRI Chief Scientific Officer Dr. Johnny Huard; SPRI Chair and The Steadman Clinic Managing Partner Dr. Marc Philippon; The Steadman Clinic's Dr. Matthew T. Provencher, a retired U.S. Navy Captain; and SPRI Chief Medical Officer and The Steadman Clinic surgeon Dr. Peter Millett. The studies also include the support of The Steadman Clinic's Dr. Thos Evans; SPRI's Director of Biomedical Engineering Dr. Scott Tashman; Grant Dornan, Director of SPRI's Center for Outcomes-Based Orthopaedic Research; SPRI's VP of Operations Suzanne Liv Page and collaborator Dr. James Kirkland, of Mayo Clinic.

Each of the clinical trials are focused on optimizing patient outcomes from orthopaedic surgery, including through the use of biologics—Bone Marrow Cell Concentrate (BMCC) and Platelet-Rich Plasma (PRP)—and therapeutics—anti-fibrotic medication or senolytic supplements. These trials are made possible through close collaboration between SPRI's science team and The Steadman Clinic's physicians. The clinical study is focused on enhancing return-to-duty protocols through the use of real-world situations, versus standard controlled physical testing.

- **Project 1:** The first DoD clinical trial involves Drs. Peter Millett, Thomas Hackett, Matthew Provencher, Armando Vidal, Leslie Vidal and Jonathan Godin from The Steadman Clinic. The goal of the project is to investigate if the intervention of PRP, BMCC, or Placebo during an ACL repair improves the treatment. Currently 24 of 60 participants in the trial have been treated.

- **Project 2:** With a retrospective design, the second clinical trial compares the quality of cartilage healing after hip microfracture treatment during arthroscopy, examining the differences between patients who took an anti-fibrotic medication after surgery, and those who did not. Led by Dr. Marc Philippon, 21 on-site exams have been completed and 289 hips (274 unique patients) are being examined via patient-reported outcomes with the Center for Outcomes-Based Orthopaedic Research (COOR).

- **Project 3:** The third DoD clinical trial investigates the use of a senolytic supplement v. a placebo for treating mild to moderate osteoarthritis. With The Steadman Clinic collaborating physicians Drs. Thos Evans, Raymond Kim, Armando Vidal, Leslie Vidal and Jonathan Godin, this project has completed its enrollment of 64 patients and has begun follow-up visits with patients.

- **Project 4:** This clinical study has enrolled 57 participants to date. It is focused on optimizing return-to-duty protocols through improved physical testing to ensure warfighters are healthy before returning to active service. After a COVID shutdown, the team completed a study redesign including a new location at lower altitude with more consistent terrain and revised activities that are repeatable and reproducible at military sites.

- **Project 5:** In SPRI's second DoD contract, Dr. Philippon's clinical trial investigates the effect of a senolytic supplement v. placebo taken pre- and post-hip surgery for femoroacetabular impingement (FAI) and labral tear. Enrollment is currently underway.

REGENERATIVE MEDICINE INNOVATION PROJECT UPDATE

The National Institutes of Health (NIH) Regenerative Medicine Innovation Project (RMIP) is a five-year clinical trial. The RMIP was established by the 21st Century Cures Act, focused on accelerating progress in the field of regenerative medicine by supporting clinical research on adult stem cells. SPRI's RMIP is entitled, "The Use of Senolytic and Anti-Fibrotic Agents to Improve the Beneficial Effect of Bone Marrow Stem Cells for Osteoarthritis," and includes Drs. Marc Philippon, Johnny Huard and Scott Tashman as Principal Investigators. Clinical Investigators include The Steadman Clinic's Drs. Leslie Vidal, Thos Evans, Armando Vidal and Jonathan Godin.

The goal of this trial is to treat patients with senolytic agents prior to harvesting bone marrow to improve the benefit of bone marrow cell concentrate treatment in patients experiencing osteoarthritis in the knee. The study will include 100 patients who will participate as follows:

- **25 patients** will receive Bone Marrow Cell Concentrate Treatment and a Placebo
- **25 patients** will receive Bone Marrow Cell Concentrate Treatment and Losartan (anti-fibrotic medication)
- **25 patients** will receive Bone Marrow Cell Concentrate Treatment and Fisetin (senolytic supplement)
- **25 patients** will receive Bone Marrow Cell Concentrate, Losartan and Fisetin

AWARD MILESTONES

The original enrollment goal set May 1, 2022 for 50% participant enrollment, but the enthusiasm for the clinical trial enabled the team to achieve this goal a full month early. The team had enrolled 66 participants by April 6, 2022 and anticipates reaching the 75% milestone by November 1, 2022, and will achieve 100% by April 1, 2023.

In addition to recruitment progress on the trial, SPRI received additional awards from the NIH in support of this project:

- A supplemental award to allow SPRI to further explore peripheral blood, bone marrow and synovial fluid in the regenerative medicine lab

- An award for Year Two of the trial in recognition of SPRI achieving its milestones

With the success of the RMIP, the NIH created an Innovation Catalyst that includes the University of Maryland and Georgia Tech to conduct additional advanced assays on the human specimens collected as part of the RMIP, at no cost to SPRI. The Catalyst will conduct sophisticated assays like mRNA single sequencing and proteomics, utilizing equipment that SPRI does not have in its regenerative medicine lab. Access to these technologies will position SPRI for future funding opportunities.

A REFLECTION BY

DAN DRAWBAUGH, CEO OF SPRI AND THE STEADMAN CLINIC

A DESTINATION FOR SCIENCE

I joined SPRI as CEO in 2015. We had just decided to open the Center for Regenerative Sports Medicine—now the Linda & Mitch Hart Center for Regenerative and Personalized Medicine (CRPM)—and had three part-time PhDs employed at SPRI: Drs. Johnny Huard, Scott Tashman and Sudheer Ravuri.

Today, there are ten PhDs and two MDs employed by SPRI—nine of these professional scientists work for SPRI's CRPM and Clinical Trials team and three work in the Department of Biomedical Engineering. These scientists and physicians account for 20% of SPRI's total workforce, and represent a 700% growth in scientists from when I joined the organization in 2015. More than half of the SPRI scientists are international, giving our small institute a real global feel.

This growth and cultivation of research talent not only means the SPRI team is producing innovative science at the highest level, but it also means that SPRI has become a destination for professional scientists and researchers. There is a tremendous sense of purpose in our laboratories—that the work conducted here will have a global impact. At the time of this publication, SPRI is underway on seven clinical trials in partnership with The Steadman Clinic, and is working on seven active National Institutes of Health (NIH) grants and six research projects funded through two Department of Defense (DoD) contracts, in addition to industry, foundation and philanthropic projects.

When I joined the organization in 2015, I knew there was tremendous potential in this small scientific research institute in Vail. I did not know that just seven years later our team would be represented by a dozen professional scientists from all over the world, producing top-level science and making an enduring impact on clinical translation research.

This change did not happen by accident—SPRI's success today is a result of the vision and leadership of SPRI Chair Dr. Marc Philippon and Chief Scientific Officer Dr. Johnny Huard, and the commitment and diligence of SPRI's team of scientists, researchers and physicians.

As CEO, it has been an honor to see the evolution and growth at SPRI, all while maintaining a commitment to our mission to enhance people's lives through our leading-edge research.

THE STEADMAN CLINIC SURGEONS AND PHYSICIANS

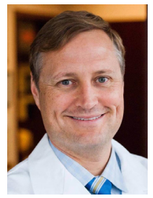
MARC J. PHILIPPON, MD
Managing Partner
Sports Medicine, Hip Disorders, Hip Arthroscopy
Chair, Steadman Philippon Research Institute

THOS A. EVANS, MD
Orthopaedic Interventionalist of Spine & Joint, Regenerative Medicine Specialist & Anesthesiologist

C. THOMAS HAYTMANEK JR., MD
Foot, Ankle & Trauma Surgery

JARED T. LEE, MD
Aspen Medical Director
Shoulder, Hip, Knee & Sports Medicine

RANDALL W. VIOLA, MD
Hand, Wrist, Elbow & Orthopaedic Trauma Specialist



MATTHEW T. PROVENCHER, MD, MBA
Complex Shoulder, Complex Knee & Sports Surgery

ARMANDO F. VIDAL, MD
Complex Knee, Shoulder & Sports Medicine Specialist

WAQQAR KHAN-FAROOQI, MD
Foot, Ankle & Trauma Surgery

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DUSTIN ANDERSON, MD
Orthopaedic Interventionalist, Sports, Spine & Regenerative Medicine, PM&R, Pain Medicine

THOMAS R. HACKETT, MD
Complex Knee, Shoulder & Elbow Surgeon

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Internal Medicine

JONATHAN A. GODIN, MBA, MD
Shoulder, Knee, Hip & Sports Medicine Surgeon

JOSEPH J. RUZBARSKY, MD
Shoulder, Knee, Elbow & Hip Preservation Surgery

PETER J. MILLETT, MD, MSC
Shoulder, Knee, Elbow Surgery & Sports Medicine

JOEL M. MATTA, MD
Hip Disorders: Preservation, Replacement & Fractures

KAVI SACHAR, MD
Hand, Wrist & Elbow Surgery

MICHAEL GALLIZZI, MD
Robotic and Endoscopic Spine Surgery

Dr. Michael Gallizzi celebrated his 100th career robotic spine surgery on April 19, 2022.

WELCOME TO THE STEADMAN CLINIC

DR. MICHAEL GALLIZZI JOINED THE STEADMAN CLINIC IN MARCH 2022 FROM THE GREATER DENVER AREA

A Michigan native, Dr. Gallizzi specializes in minimally invasive, robotic and endoscopic adult spinal surgery. He is a graduate of the University of Michigan and the Rosalind Franklin University of Medicine and Science/Chicago Medical School. Dr. Gallizzi completed his residency training in orthopaedics at the University of Missouri and also served as a clinical instructor in orthopaedic adult spinal surgery as a fellow at Duke University.

On April 19, 2022, Dr. Gallizzi performed his 100th robotic spinal surgery, just one month after joining The Steadman Clinic team. In 2019, Dr. Gallizzi became the first surgeon in the state of Colorado to perform a robotic spinal surgery. Just three years later, his completion of his 100th case placed him amongst just a handful of spinal surgeons worldwide who have completed 100 or more robotic spinal surgeries.

Robotic spinal surgery allows for shorter time for the patient in the operating room, precision hardware placement, tracking and improved accuracy. Dr. Gallizzi utilizes the Globus Excelsius robotic system.

The addition of robotic spine surgery to The Steadman Clinic's offerings continues the practice's commitment to innovation and using the latest in cutting-edge technology to enhance patient care.

SPRI OPENS NEW LABORATORY IN BASALT, COLORADO

In April 2022, The Steadman Clinic opened a new clinic in Basalt, Colorado, located 20 miles from Aspen.

ABOVE: The Steadman Clinic, SPRI, Orthopedic Care Partners, Aspen Valley Hospital and Vail Health celebrated the grand opening of Steadman Philippon Basalt.

BELOW: The SPRI laboratory is located within The Steadman Clinic.

Emblematic of SPRI and The Steadman Clinic's symbiotic relationship, the new clinic features a SPRI regenerative medicine laboratory located within the clinic space. A large glass window allows patients and visitors to see into the laboratory, watching SPRI's cutting-edge science as it happens.

NEW LAB TO GROW SPRI'S CLINICAL TRIALS AND EXPAND RESEARCH

A major focus of SPRI's Basalt laboratory is to expand its clinical trials to the region. Participants from Aspen and the Roaring Fork Valley will participate in some of SPRI's federally funded clinical trials, broadening the reach of the research. This includes a Department of Defense (DoD)-funded clinical trial involving femoroacetabular impingement (FAI) and labral tears of the hip, led by SPRI Chair and The Steadman Clinic Managing Partner Dr. Marc Philippon and Dr. Johnny Huard. This trial will have patient representation from both the new Basalt lab and SPRI's Vail location. In addition to clinical trials, SPRI's Basalt lab will also analyze patient samples as part of its Healthy Aging Program.

Steadman Philippon Basalt also includes an ambulatory surgery center and rehabilitation services alongside The Steadman Clinic and SPRI. The building is a partnership with The Steadman Clinic, Orthopedic Care Partners, Aspen Valley Hospital and Vail Health.

LINDA & MITCH HART CENTER FOR REGENERATIVE AND PERSONALIZED MEDICINE

FACULTY AND STAFF

JOHNNY HUARD, PHD
Director
Chief Scientific Officer

SUDHEER RAVURI, PHD
Deputy Director

CHELSEA S. BAHNEY, PHD
Principal Investigator
Program Director of Fracture Repair and Regenerative Therapeutics

XUEQIN GAO, MD, PHD
Principal Investigator
Program Director of Bone and Cartilage Repair and Stem Cell Biology

PING GUO, PHD
Principal Investigator
Program Director of Genetic and Cellular Engineering

WILLIAM S. HAMBRIGHT, PHD
Principal Investigator
Program Director of Healthy Aging Diagnostics

AIPING LU, MD
Principal Investigator
Program Director of Muscle Repair and Stem Cell Biology

NAOKI NAKAYAMA, PHD
Principal Investigator
Program Director of Stem Cell Engineering and Cartilage Regeneration

ANNA LAURA NELSON, MS
PhD Graduate Student

KAITIE WHITNEY
Clinical Translation Research Coordinator

MICHAEL MULLEN
Research Associate

KELSEY O'HARA
Research Associate

VERENA OBERLOHR
Research Associate

MOLLY CZACHOR
Research Technician

VICTORIA DUKE
Research Technician

MATTHIEU HUARD
Research Technician

SARAH EASTON
Research Assistant

ALEX GOFF
Research Assistant

ADAM GOFF
Research Assistant

CHARLES HUARD
Research Assistant

HEIDI KLOSER
Research Assistant

RAYVEN NAIRN
Research Assistant

MARC PHILIPPON, JR.
Research Assistant

CLINICAL TRIALS TEAM

SUZANNE LIV PAGE, JD
Vice President, Operations

LUZ THEDE, MD
Clinical Trials Clinician

MICHAEL BEGG, DMSC, PA-C, ATC
Clinical Trials Physician Assistant

SARA ROBINSON
Clinical Trials Data Coordinator

CHLOE BARTON
Clinical Trials Coordinator

THE LINDA & MITCH CENTER FOR REGENERATIVE AND PERSONALIZED MEDICINE (CRPM) WAS LAUNCHED IN 2015 AS THE CENTER FOR REGENERATIVE SPORTS MEDICINE. IN 2021, THE TEAM'S NAME WAS BROADENED, ACKNOWLEDGING THE ARRAY OF SCIENCE BEING CONDUCTED IN THE LAB.

> Scientists and researchers at CRPM are underway on several research projects, including SPRI's federally funded clinical trials, preclinical projects and research programs sponsored by philanthropy. CRPM is conducting research supported by the National Institutes of Health (NIH), Department of Defense (DoD), industry and foundation grants and awards. The team employs seven full-time PhDs and two full-time MDs, six of whom are principal investigators and program directors for CRPM's research categories. The team is led by Johnny Huard, PhD, who also serves as SPRI's Chief Scientific Officer.

CRPM's scientific programs investigate cellular science and regenerative medicine techniques and therapies. Each program is led by a Principal Investigator, who is a subject matter expert in their program. These programs are:

- **Fracture Repair and Regenerative Therapeutics**
- **Muscle Repair and Stem Cell Biology**
- **Bone and Cartilage Repair and Stem Cell Biology**
- **Genetic and Cellular Engineering**
- **Stem Cell Engineering and Cartilage Regeneration**
- **Health Aging Diagnostics**

The CRPM team is committed to conducting high-impact science and earns major funding awards each year. In addition to its federal funding and industry grants, CRPM receives significant philanthropic funding each year, which is used to launch vital pilot studies and research programs, many of which include major university collaborators. The findings made from CRPM's pilot studies are often used to develop major grant applications, including numerous trials awarded by federal agencies.

Alongside the other SPRI teams, CRPM is committed to conducting the highest impact team science, leveraging the expertise of the orthopaedic physicians at The Steadman Clinic and the strengths of the institute's other scientific departments. CRPM's key area of focus is to accelerate clinical translation and help scientific discoveries and proven treatments get to patients faster.

FEDERAL AND STATE FUNDING AWARDS

NATIONAL INSTITUTES OF HEALTH (NIH)

- **4** Primary Grants
- **3** Subaward Grants
- **1** Regenerative Medicine Innovation Project (RMIP) Clinical Trial

DEPARTMENT OF DEFENSE (DOD)

- **1** Contract: **3** Clinical Trials, **1** Clinical Study
- **1** Grant: **1** Clinical Trial

STATE OF COLORADO

- **1** Grant

DR. JOHNNY HUARD, CHIEF SCIENTIFIC OFFICER

Dr. Johnny Huard is the Director of CRPM and SPRI's Chief Scientific Officer. He is a Principal Investigator on five National Institutes of Health (NIH) grants and four Department of Defense (DoD) grants at SPRI and has been successful in bringing in philanthropic funding to support SPRI's regenerative medicine program. Philanthropic gifts support research projects that fill the pipeline of federally funded grants and awards.

Dr. Huard has extensive knowledge in the areas of gene therapy, tissue engineering and regenerative medicine applications based on the use of muscle-derived stem/progenitor cells (MDSCs). Dr. Huard and his team have published over 420 peer-reviewed papers, over 90 reviews/book chapters, and have had over 900 abstracts accepted for presentation at national and international conferences (Citations 43286; h-index:111, i10-index: 365). Dr. Huard and his team's current major research interests include:

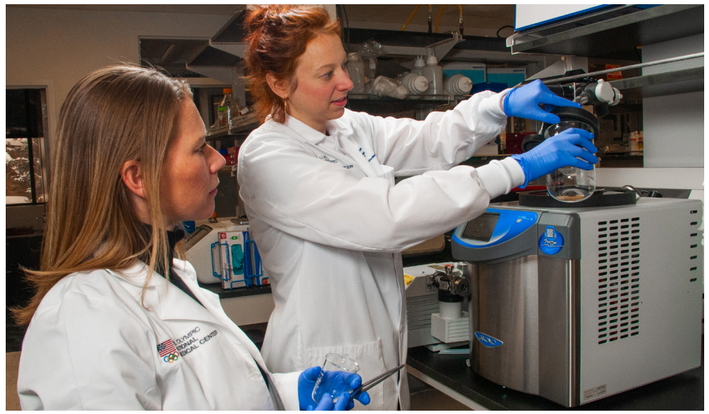
- **Muscle stem cells isolation and characterization**
- **Bone and articular cartilage regeneration and repair**
- **Senotherapeutics in musculoskeletal repair, cardiac and skeletal muscle injury repair, regeneration and fibrosis prevention**
- **Peripheral nerve regeneration**
- **Healthy aging and the use of adult stem cells as a source for paracrine factors to alleviate the phenotypic changes associated with natural and accelerated aging**

The focus of Dr. Huard's laboratory is to develop biological medicine approaches to improve musculoskeletal tissue repair after injury, disease and aging. His team of scientists uses a variety of technologies that falls into four different categories including:

- **BIOLOGICS**
  - Adult stem cells, including muscle-derived stem cells and adipose-derived stem cells
  - Bone Marrow Cell Concentrate
  - Platelet-Rich Plasma
- **REGENERATIVE MEDICINE APPROACHES**
  - Gene therapy approaches
  - CRISPR-Cas9
  - Protein delivery like coacervate, microspheres, PA-nanofibers and magnetic nanoparticles
- **THERAPEUTICS**
  - FDA-approved drugs such as anti-fibrotic agents and pro-angiogenic agents
  - Telomerase activity (hTERT)
  - Senotherapeutics like senolytic and senomorphic drugs
- **ANIMAL MODELING**
  - Dystrophic and progeria mice models
  - Super healer mice (MRL/MpJ)
  - Osteoarthritis model/microfracture
  - Tibia fracture
  - Calvarial defect
  - Ovariectomy

CRPM Scientists Share Program Updates

CRPM'S SCIENTISTS WORK COLLABORATIVELY ACROSS THEIR PROGRAMS TO SUPPORT THE EFFORTS OF SPRI'S CLINICAL TRIALS AND THE DEPARTMENT'S GRANTS AND PHILANTHROPICALLY FUNDED STUDIES. EACH SCIENTIST REVIEWED THEIR PAST YEAR OF RESEARCH (JULY 2021–JUNE 2022) FOR INCLUSION IN THIS EDITION OF THE *ORTHOPAEDIC RESEARCH JOURNAL.*



Dr. Chelsea Bahney works with PhD student Anna-Laura Nelson in the CRPM lab.

CHELSEA S. BAHNEY, PHD – PRINCIPAL INVESTIGATOR

DR. CHELSEA BAHNEY IS THE PROGRAM DIRECTOR OF FRACTURE REPAIR AND REGENERATIVE THERAPEUTICS IN CRPM. THIS YEAR, DR. BAHNEY COMPLETED SEVERAL MAJOR RESEARCH MILESTONES, INCLUDING:

PUBLICATIONS

Manuscripts: Three published, one reprint article, three manuscripts in revision

1. Mullen, MM, William K, LaRocca T, Duke V, Hambright WS, Ravuri S, **Bahney CS***, Ehrhart N*, Huard. "Mechanical Strain Drives Exosome Production, Function, and miRNA Cargo in C2C12 Muscle Progenitor Cells." *Co-Submitting *Journal of Orthopaedic Research* (Accepted)

2. Hambright WS, Xiaodong Mu, Yohei Kawakami, John Mitchell, Michael Mullen, Anna-Laura Nelson, **Bahney CS**, Xueqin Gao, Justin Hellwinkel, Andrew Eck, and Johnny Huard. "The senolytic drug fisetin attenuates bone degeneration in the Zmpste24-/- progeria mouse model." *J. of Osteoporosis.* (2022)

3. Working ZM, Peterson D, Lawson M, O'Hara KM, Coghlan RF, Provencher MT, Friess DM, Johnstone B, Miclau T, **Bahney CS.** "Collagen X Longitudinal Fracture Biomarker Suggests Staged Fixation in Tibial Plateau Fractures Delays Rate of Endochondral Repair." *Journal of Orthopaedic Trauma* (2022)

PREPRINT: Rivera KO, Cuylear DL, Duke V, O'Hara KM, Kharbikar BN, Kryger AN, Miclau T, **Bahney CS**, Desai TA. "Localized delivery of β-NGF via injectable microrods accelerates endochondral fracture repair."

PRESENTATIONS

Dr. Bahney had 17 abstracts accepted for podium or presentation and moderated and organized five symposiums. She would like to highlight the following significant presentations from this year:

- **ORS Spotlight Speaker:** April 2022, Tampa Bay, Fl. "Transforming Fracture Healing: Engineering Accelerated Endochondral Repair."

- **Invited Speaker: International San Francisco Orthopaedic Trauma Course**
  October 2021, San Francisco, CA. "Stem Cell Therapies in Orthopaedic Trauma."

- **Invited Seminar: University of Illinois, Chicago (UIC) Regenerative Sciences Seminar Series**
  July 2021. "Design and validation of bioactive materials to promote neuronal-mediated tissue regeneration."

AWARDS

- Elected Fellow of International Orthopaedic Research
- ORS 2022 Spotlight Speaker
- Appointed AO Foundation R&D Commission

GRANT SUBMISSIONS

- Dr. Bahney's research is currently funded by two NIH R01s and three foundation grants from the Orthopaedic Trauma Association (OTA), the Orthopaedic Research Education Foundation (OREF) Aircast Foundation Award, and the SPRI-UCSF-Buck Tri-Institutional Pilot Award.
- Dr. Bahney continues to submit additional NIH and DoD grant applications including two currently under review.

YEAR IN REVIEW

2021–2022 was a successful year for the Program of Fracture Repair and Regenerative Therapeutics. The team was fortunate to receive national recognition for its program in the form of two NIH R01s and three foundational grants. Progress on research was disseminated through 17 abstracts at scientific meetings. Dr. Bahney was recognized for her career accomplishments as an ORS 2022 Spotlight Speaker and elected as a Fellow of International Orthopaedic Research. She was also excited to support PhD Candidate Anna-Laura Nelson in winning the 2022 International Society of Fracture Repair Poster Award and Staff Research Assistant Victoria Duke in winning the 2022 ORS Three-Minute Research Pitch Competition for their research on fracture repair.

LOOKING AHEAD

In the upcoming year the Program of Fracture Repair and Regenerative Therapeutics looks forward to advancing its NIH- and foundation-funded research program, which aims to test and develop novel strategies to accelerate fracture repair. Specifically, the team is focusing on developing an injectable biomaterial platform that can prevent infection and activate osteogenic programs that will promote fracture repair. The team will collaborate closely with Drs. Huard and Hambright's Healthy Aging program to understanding the role that senescent cells play in delaying fracture repair with aging. In July 2022, a number of talented employees that were contributing to this project left CRPM to advance their training through PhD and MD programs. Two talented PhD students continue to work on the Regenerative Therapeutics Platform and the team is excited to welcome a new Bioengineering Research Assistant and is interviewing for a talented Post-Doctoral Fellow to join the team.

XUEQIN GAO, MD, PHD – PRINCIPAL INVESTIGATOR

DR. XUEQIN GAO IS THE PROGRAM DIRECTOR OF BONE AND CARTILAGE REPAIR AND STEM CELL BIOLOGY AT CRPM. OVER THE PAST YEAR, DR. GAO HAS SUPPORTED THE DEPARTMENT'S CLINICAL TRIALS AND BENCH RESEARCH PROJECTS.

PUBLICATIONS

*# co-first authors, * corresponding authors*

1. Deng Z#, **Gao X**#*, Utsunomiya H, Arner JW, Ruzbarsky JJ, Huard M, Ravuri S, Philippon MJ, Huard J*. "Effects of oral losartan administration on homeostasis of articular cartilage and bone in a rabbit model." *Bone Rep*. 2022 Mar 28;16:101526.

2. Gao Z, Lu A, Daquinag AC, Yu Y, Huard M, Tseng C, **Gao X**, Huard J*, Kolonin MG*. "Partial Ablation of Non-Myogenic Progenitor Cells as a Therapeutic Approach to Duchenne Muscular Dystrophy." *Biomolecules*. 2021 Oct 15;11(10):1519.

3. **Gao X**, Patwa AN, Deng Z, Utsunomiya H, Grinstaff MW, Ruzbarsky JJ, Snyder BD, Ravuri S, Philippon MJ, Huard J*. "Influence of fixation on CA4+ contrast enhanced microCT of articular cartilage and subsequent feasibility for histological evaluation." *Am J Transl Res.* 2021 Aug 15;13(8):8921-8937.

4. **Gao X**, Cheng H, Sun X, Lu A, Ruzbarsky JJ, Wang B, Huard J*. "Comparison of Autologous Blood Clots with Fibrin Sealant as Scaffolds for Promoting Human Muscle-Derived Stem Cell-Mediated Bone Regeneration." *Biomedicines.* 2021 Aug 9;9(8):983.

5. Logan CA#, **Gao X#**, Utsunomiya H#, Scibetta AC, Talwar M, Ravuri SK, Ruzbarsky JJ, Arner JW, Zhu D, Lowe WR, Philippon MJ, Huard J. "The Beneficial Effect of an Intra-articular Injection of Losartan on Microfracture-Mediated Cartilage Repair Is Dose Dependent." *Am J Sports Med*. 2021 Jul;49(9):2509-2521.

ABSTRACTS AND PRESENTATIONS:

*# Co-first authors, *Corresponding authors*

1. **Xueqin Gao**, Xuying Sun, Haizi Cheng, Michael Mullen, Matthieu Huard, Johnny Huard*. "Super Healer Mice Resist Age and Ovariectomy Induced Bone Loss and Mechanisms." ASBMR2021 Virtual meeting, Oct 1-4, 2021, **Poster presentation**.

2. **Xueqin Gao***; Mintai Hwang; Aiping Lu; Matthieu Huard; Joseph Ruzbarsky; Yadong Wang; Johnny Huard*. "Transplantation Of Culture Expanded Human Muscle-derived Stem Cells Containing High Percentage Of Senescent Cells Adversely Affect Bone Regeneration Mediated By BMP2," ORS 2022, **Poster presentation.**

3. **Xueqin Gao**; Mintai Hwang; Matthieu Huard; Aiping Lu; Joseph Ruzbarsky; Sudheer Ravuri; Yadong Wang*; Johnny Huard*. "The Use Of Coacervate Sustained Release System To Identify Most Potent Bmp For Bone Regeneration In Critical Size Calvarial Bone Defect Model." **Poster Presentation.**

4. Matthieu Huard; **Xueqin Gao*;** Naomasa Fukase; Johnny Huard*. "Effect Of Oral Fisetin On Uninjured Skeletal Muscle Homeostasis." ORS2022, Feb 4-8, 2022, **Poster presentation**.

5. Naomasa Fukase#, **Xueqin Gao#**, William S. Hambright, Kaitlyn E. Whitney, Matthieu Huard, Yoichi Murata, Philip Nolte, Ingrid K. Stake, Charles Huard, Sudheer K. Ravuri, Marc J. Philippon*, Johnny Huard*. "Cartilage Healing with Microfracture Augmented with Fisetin & Bone Marrow Aspirate Concentrate." ORS 2022, Feb 4-8. **Poster presentation.**

KEY RESEARCH UPDATES

- Dr. Gao is actively participating in five clinical trials directed by Dr. Huard and clinical directors by running Biomarker detections using ELISA assays and Q-PCR and data analysis.
- Dr. Gao submitted seven grants to the NIH and DoD as co-investigator.
- Dr. Gao is currently working on the development of new strategies to improve bone health of Duchenne Muscular Dystrophy (DMD) using Dystrophin/Utrophin double knockout mice model.
- Dr. Gao uses biomaterials, gene therapies and cell therapies to develop new approaches for enhancing bone repair using critical size calvarial defect model and tibia defect model.
- Dr. Gao utilizes different strategies to enhance cartilage repair using microfracture and osteoarthritis model.

PING GUO, PHD – PRINCIPAL INVESTIGATOR

DR. PING GUO IS THE PROGRAM DIRECTOR OF GENETIC AND CELLULAR ENGINEERING AT SPRI'S CRPM. FOR THE PAST YEAR, DR. GUO HAS FOCUSED HIS RESEARCH ON OSTEOARTHRITIS.

PUBLICATIONS

1. Jae Sung Lee, **Ping Guo,** Katarina Klett, MacGregor Hall, Krishna Sinha, Sudheer Ravuri, Johnny Huard and William L. Murphy, "VEGF-attenuated platelet-rich plasma improves therapeutic effect on cartilage repair," *Biomater. Sci*, 2022; May 4; 10(9):2172-2181.

2. **Ping Guo,** Lara Pferdehirt, Aiping Lu, Mathew Huard, Farshid Guilak, Johnny Huard, "In vitro analysis of genome-engineered muscle-derived stem cells for autoregulated anti-inflammatory and antifibrotic activity," *J. Orthop Res,* 2022; Mar 16, Online ahead of print.

PRESENTATIONS

- TIPE2 Treatment Attenuates the Histopathology of Osteoarthritis in An Accelerate Aging Mouse Model, **Poster presentation: ORS 2022.**

AWARDS

- NIH R01 AR077045-01A1(PI: Dr. Huard), 04/1/2021-3/31/2026, **SMART stem cells that autonomously down-modulate TFG-β signaling for Articular Cartilage Repair**

KEY RESEARCH UPDATES

1. Primary focus on TIPE2 gene therapy for OA using Z24 mouse model. There is a new finding in the Z24 mice knee that senescent cells were found in the five-month-old cartilage and TIPE2 gene-therapy-reduced senescent cells in the knee of Z24 mice. Collected data, wrote a grant application and a manuscript has been written.

2. Dr. Guo submitted three NIH grants as a co-investigator.

3. Worked on NIH- and DoD-funded clinical trial projects. Mainly performed multiplex assay for patient samples.

4. Involved in other PI's projects, performed *in vitro* and *in vivo* experiments.

LOOKING AHEAD

Dr. Guo plans to work on osteoarthritis and therapy and perform excellent research in stem cell therapies for skeletomuscular diseases. Dr. Guo will continue to work on the NIH-funded project SMART stem cells that autonomously down-modulate TFG-β signaling for Articular Cartilage Repair (1R21AR079075) and Articular Cartilage Tissue Engineering with Human Pluripotent Stem Cells (NIH 5R01AR077045). Dr. Guo is revising and will resubmit the R21 grant submitted 10-16-2021.

WILLIAM S. HAMBRIGHT, PHD – PRINCIPAL INVESTIGATOR

DR. WILLIAM "SEALY" HAMBRIGHT IS THE PROGRAM DIRECTOR OF HEALTHY AGING DIAGNOSTICS IN SPRI'S CRPM.

PUBLICATIONS:

1. Michael Mullen, **William S. Hambright,** John Mitchell, Heidi Kloser, Sudheer Ravuri, Johnny Huard. "Fisetin Attenuates Senescence in Culture Expanded and Banked Adipose Derived Stem Cells" *Stem Cells* 2022. **Submitted*

2. Liu Lei, **Hambright WS,** Matre Polina, Feng Qi, Cui Yan, Zhong Ling, Wang Zhihui, Robbins Paul, Huard Johnny, Mu Xiaodong "Reduction of senescent FAPs in premature aged muscle by senolytics rescues the function of muscle stem cells." *Front. In Cell and Developmental Biology*. 2022. **Under Review*

3. Liu Lei, Xianlin Yue, Zewwei Sun, Jianming Wei, **Hambright WS,** Cui Yan, Huard Johnny, Mu Xiaodong "Suppression of SUN2 protects against senescent cells from mechanical stress-induced nuclear damage." *Journ. Cell Biol*. 2022. **Under Review*

4. Liu Lei, Feng Qi, **Hambright WS,** Cui Yan, Mu Yanling, Wang Zhihui, Huard Johnny, Mu Xiaodong "VDAC1 oligomerization-mediated activation of mitophagy and cGAS-Sting promote the aging of skeletal muscle fibers." *Autophagy.* 2022. **Under Review*

5. Mullen M, Williams K, Duke V, Ravuri S, **Hambright WS,** Bahney C, Ehrhart N, Huard J. "Mechanical Stimulus Drives Exosome Production and Function in C2C12 Myoblast Cells" *Journal of Orthopaedic Research*. 2022. **Under Review*

6. **Hambright WS,** Xiaodong Mu, Yohei Kawakami, John Mitchell, Michael Mullen, Anna-Laura Nelson, Xueqin Gao, Justin Hellwinkel, Andrew Eck, and Johnny Huard. "Senolytic drugs attenuate age-related cartilage and bone degeneration in the Zmpste24$^{-/-}$ progeria mouse model." *J. of Osteoporosis*. 2022. **In Press*

7. Naomasa Fukase, Ingrid K. Stake, Yoichi Murata, **William S. Hambright,** Sudheer Ravuri, Marc J. Philippon, Johnny Huard. "Interventional Strategies to Delay Aging-Related Dysfunction of the Musculoskeletal System." *Intech Open*. 2021.

8. **Hambright WS*,** Yeargan A*, Whitney K, Montgomery B, Philippon M, Evans T, Hellwinkel J, Buckwalter J, Peault B & Huard J. "Potential Disease-Modifying Treatment Strategies in the Setting of Osteoarthritis." *OROAJ.* 2021.

PRESENTATIONS

Dr. Hambright had 18 presentations in 2021–22, including podium and poster presentations. His highlighted presentations are:

1. **William S Hambright,** Alex Goff, Victoria Duke, Heidi Kloser, Chelsea Bahney, Johnny Huard. "Senescent CD3+ T-Cells: A Potentially Novel Biomarker for Mild to Moderate Osteoarthritis of the Knee." **Podium Presentation**: ICRS 2022, Berlin Germany ***ON/ICRS Education Award Winner**

2. Victoria Duke, Naomasa Fukase, Marc Philippon Jr., Matt Huard, Anna-Laura Nelson, **William S. Hambright*** and Chelsea Bahney*. "An Accelerated Model for Aged Fracture Repair." **Podium Presentation:** EORS 2021, Rome Italy *Co-Submitting Author

3. Victoria Duke, Kelsey O'Hara, Michael Mullen, Verena Oberlohr, Kaitie Whitney, Xueqin Gao, William S. Hambright* and Johnny Huard*. "Multimodal Assessment of Aging Indices & The Reduction of Senescence in Patients Taking Fisetin." **Poster Presentation**: ORS 2022 *Co-Submitting Author

AWARDS (SINCE 2020)

- 2022: ON/ICRS Education Grant Recipient
- 2020: New Investigator Recognition Award (NIRA) Finalist, ORS Annual Meeting
- 2020: Travel Award Recipient from ORS to attend Annual Meeting

PATENTS

Senescent T-cell detection from peripheral blood mononuclear cells using C_{12}FDG. **Role: Co-inventor**, patent filed (US20210046123A1)

GRANT SUBMISSIONS

Dr. Hambright has submitted eight grants in 2021/2022 as Principal Investigator. Below are **funded** grants with Co-Investigator or PI status that support Dr. Hambright's work:

1. *UCSF/Buck Institute/SPRI Tri-Institutional Musculoskeletal Performance Research Program, PI(s) W.S. Hambright and C. Bahney, 4/1/22-4/1/23* "Impact of Cellular Senescence on the Fracture Phenotype." **Role: Co-PI, design, implementation, and co-direct** tri-institute collaboration to understand senescence during delayed fracture repair in preclinical murine models.

2. *Lyda Hill Philanthropies, PIs (Johnny Huard & WS Hambright), 2yrs, 3/1/2022-3/1/2024 (FDA/IND Pending)* "Investigation of fisetin to reduce systemic senescence indices: A randomized controlled dosing study." **Role: Co-PI, design, implementation, and co-direct** sample analysis of the dosing trial at multiple SPRI sites (Vail, Basalt.)

3. *Department of Defense, Office of Naval Research, Contract #N00014-19-C-2052, Sponsor/PI (Johnny Huard), 8/1/19-7/31/22*

   Overall project title: Response to the Treatment of Poly-Traumatic Injuries Using PRP and Bone Marrow Concentrate. Dr. Hambright directly supports three clinical trials within this contract.

   - **Clinical Trial #1:** "Prospective Evaluation of Platelet-Rich Plasma and Bone Marrow Concentrate Treatment to Accelerate Healing After Anterior Cruciate Ligament Reconstruction." NCT04205656
     Role: Key Personnel, established key techniques to assess senescence in different biologics including blood, bone marrow and platelet-rich plasma. Directed the Healthy Aging team in the collection and evaluation of data.
   - **Clinical Trial #2:** "Senolytic Drugs Attenuate Osteoarthritis-Related Articular Cartilage Degeneration: A Clinical Trial." NCT04210986, IND#144317
     Role: Key Personnel, Investigator, established key techniques to assess senescence in whole blood peripheral mononuclear cells. Directed the Healthy Aging team in the collection and evaluation of data.
   - **Clinical Trial #3:** "Senolytic Agents to Improve the Benefit of Platelet-Rich Plasma and Losartan for Treatment of Femoroacetabular Impingement and Labral Tear." NCT05025956
     Role: Key Personnel Investigator, established key techniques to assess senescence in whole blood peripheral mononuclear cells. Directed the Healthy Aging team in the collection and evaluation of data.

4. *National Institutes of Health, NIAMS, 1-UG3 AR077748-01, Sponsor/PI (Johnny Huard), 5/1/20-4/30/25* NCT04815902, "The Use of Senolytic and Anti-Fibrotic Agents to Improve the Beneficial Effect of Bone Marrow Stem Cells for Osteoarthritis."
   Role: Co-Investigator, completion of key techniques to assess senescence in BMAC and peripheral blood following investigational drug treatment.

RESEARCH INTERESTS

At SPRI, Dr. Hambright's focus is to develop strategies that target fundamental properties of aging including senescent (aged) cell accumulation, telomere erosion and inflammation to improve orthoregenerative medicine therapies. He investigates interventions that encompass four primary pillars: exercise, diet, stem cell-based therapies, and anti-aging compounds including senolytic drugs. He coordinates basic science projects in CRPM and helps design and initiate clinical studies targeting age-related conditions such as osteoarthritis, osteoporosis and delayed fracture repair. In this role, he helps translate aging-related pre-clinical findings to the clinic by negotiating the regulatory and scientific challenges that exist between. His overarching goal is to provide a combinatorial treatment approach targeting these pillars to improve healthy aging and restore active living.

Dr. Hambright has recently moved to the new SPRI laboratory in Basalt, Colorado. Here he will continue to direct efforts for ongoing clinical studies, and also implement new studies measuring the effects of senotherapies on peripheral senescence and investigating the relationship between senescence and cognitive decline with advancing age. Working with The Steadman Clinic physicians in Basalt, Dr. Hambright will play a key role in the execution of SPRI's Stem Cell Banking Program and study ways to improve the efficacy of stem cell therapies and other biologic therapies in the context of age-related orthopaedic decline. He is enthused and honored to help extend SPRI's research excellence and commitment to evidence-based medicine to the Roaring Fork Valley.

AIPING LU, MD – PRINCIPAL INVESTIGATOR

DR. AIPING LU IS THE PROGRAM DIRECTOR OF MUSCLE REPAIR AND STEM CELL BIOLOGY AT SPRI'S CRPM.

PUBLICATIONS

1. Lara Pferdehirt, Ping Guo, **Aiping Lu,** Mathew Huard, Farshid Guilak, Johnny Huard. "In vitro analysis of genome-engineered muscle-derived stem cells for autoregulated anti-inflammatory and antifibrotic activity." *J Orthop Res*. 2022 Mar 16.

2. Zhanguo Gao, **Aiping Lu,** Alexes C Daquinag, Yongmei Yu, Matthieu Huard, Chieh Tseng, Xueqin Gao, Johnny Huard, Mikhail G Kolonin. "Partial Ablation of Non-Myogenic Progenitor Cells as a Therapeutic Approach to Duchenne Muscular Dystrophy." *Biomolecules.* 2021 Oct 15;11(10):1519.

3. Xueqin Gao, Haizi Cheng, Xuying Sun, **Aiping Lu,** Joseph J Ruzbarsky, Bing Wang, Johnny Huard. "Comparison of Autologous Blood Clots with Fibrin Sealant as Scaffolds for Promoting Human Muscle-Derived Stem Cell-Mediated Bone Regeneration." *Biomedicines.* 2021 Aug 9;9(8):983.

ABSTRACTS

1. Aiping Lu, Ping Guo, Matthieu Huard, Xueqin Gao, Scott Tashman, Vihang A. Narkar, Johnny Huard. "Muscle ERRγ overexpression mitigates the muscle atrophy after ACL injury." *ORS Annual Meeting 2022. Accepted for **poster presentation.**

GRANT SUBMISSIONS:

Dr. Lu submitted four grants to the NIH and DoD this year as co-investigator.

CURRENT RESEARCH PROJECTS

Project #1: Ablation of Non-Myogenic Progenitor Cells as a New Therapeutic Approach to Duchenne Muscular Dystrophy (NIH R21 AR074132-01A1).
This proposal will investigate mesenchymal stromal cells (MSCs), the non-myogenic progenitor cells that form fibrotic lesions, promote fatty infiltration and disable myogenic progenitors during Duchenne muscular dystrophy (DMD) progression.

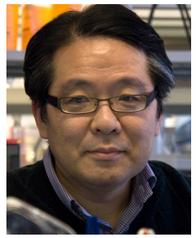
Project #2: Development of biological approaches to enhance skeletal muscle rehabilitation after anterior cruciate ligament injury (NIH R21AR075997-01).
This grant will potentially reveal the cellular and molecular mechanism linking muscle weakness, MPCs depletion/FAPs activation with muscle vascularity after ACL injury and could consequently lead to the development of more effective novel therapeutic approaches and rehabilitation strategies for delaying/reversing muscle weakness after ACL injury.

RESEARCH PROJECTS FOR COMING YEAR:

1. **Reducing Fatty Infiltration and Fibrosis after Rotator Cuff Injury to Preserve Musculoskeletal Function (3030 Salah Study of RC Disease).**
   Rotator cuff (RC) pathology is a common, age-related degenerative musculoskeletal disorder, leading to pain and dysfunction that is exacerbated by degenerative changes in the RC muscles, including atrophy, fatty infiltration and fibrosis, that typically cannot be reversed by exercise alone. We propose to investigate a new therapeutic pathway for preserving or improving muscle function by increasing blood vessels (angiogenesis), using a unique mouse model. The results of this study could lead to the development of drugs that can preserve muscle and improve outcomes after rotator cuff injury as well as facilitating more effective surgical repairs.

2. **Can Aged FAPs be Utilized to Promote Muscle Regeneration Through Improved Mitochondrial Biogenesis?**
   This study is a mechanistic evaluation of how ß-adrenergic stimulation of intramuscular fibroadipoprogenitors (FAPs) can amplify the endogenous process of mitochondrial biogenesis and activity to improve myoblast differentiation and muscle function in the setting of aging.

   Dr. Lu will also continue her support of the RMIP and DoD clinical trials.



NAOKI NAKAYAMA, PHD – PRINCIPAL INVESTIGATOR

DR. NAOKI NAKAYAMA IS THE PROGRAM DIRECTOR OF STEM CELL ENGINEERING AND CARTILAGE REGENERATION IN SPRI'S CRPM.

PUBLICATIONS

1. Pothiawala, A., Sahbazoglu, B.E., Ang, B.K., Matthias, N., Pei, G., Yang, Q., Huard, J., Zhao, Z., and **Nakayama, N.** (2022) "GDF5^{+} chondroprogenitors derived from human pluripotent stem cells preferentially form permanent chondrocytes." *Development. *In Press*

2. **Nakayama, N.,** Ravuri, S., and Huard, J. (2021) "Rejuvenated stem/progenitor cells for cartilage repair using the pluripotent stem cell technology." *Bioengineering.* (Basel) *8*

ABSTRACTS

1. Easton, S.M., Sahbazoglu, B.E., Pei, G., Pothiawala, A., Matthias, N., Ang, B.K., Huard, J., Zhao, Z., and **Nakayama, N.** (2022) "Human pluripotent stem cell-derived chondroprogenitors committed to form distinct types of chondrocytes for the future cartilage tissue engineering." **AOSSM Annual Meeting Abstract**

2. Easton, S.M., Pei, G., Pothiawala, A., Sahbazoglu, B.E., Matthias, N., Ang, B.K., Huard, J., Zhao, Z., and **Nakayama, N.** (2022) "Human GDF5^{+} tendon/ligament precursor-like mesodermal cells preferentially generate permanent cartilage through a cell non-autonomous mechanism." **20th ISSCR Annual Meeting Abstract**

3. Easton, S.M., Pei, G., Pothiawala, A., Sahbazoglu, B.E., Matthias, N., Ang, B.K., Huard, J., Zhao, Z., and **Nakayama, N.** (2022) "Human GDF5^{+} mesodermal cells show gene expression profile resembling tendon/ligament precursors and preferentially generate permanent cartilage through a cell non-autonomous mechanism." **The 74th ORS Annual Meeting Abstract**

PRESENTATIONS

1. **The Regenerative Medicine Lecture Series, Western Michigan University School of Medicine** "What in vitro embryology using human pluripotent stem cells can do for cartilage tissue engineering." (April 2022)

2. **The 74th Orthopaedic Research Society Annual Meeting**, Tampa Convention Center, Tampa, FL "Human GDF5^{+} Mesodermal Cells Show Gene Expression Profile Resembling Tendon/Ligament Precursors and Preferentially Generate Permanent Cartilage Through a Cell Non-autonomous Mechanism." (February 2022)

3. **The 6th Vail Scientific Summit,** Steadman Philippon Research Institute, Vail, CO "Cellular rejuvenation using the iPS technology for cartilage repair." (August 2021)

RESEARCH SUPPORT:

1. **R21AR079075**, Nakayama, N. (mPI), (Huard, J. cPI, Guilak, F. mPI) 3/01/22-2/29/24
   NIAMS, National Institutes of Health (PA20-195) "SMART Stem Cells that Autonomously Down-modulate TGF-β signaling for Articular Cartilage Repair."
   This project aims to test the novel technical concept of autonomous inhibition of extracellular (i.e., TGF-β) signaling for cartilage repair.

2. **R01AR077045**, Nakayama, N. (PI) 04/01/21-03/31/26
   NIAMS, National Institutes of Health (PA19-056) "Articular Cartilage Tissue Engineering with Human Pluripotent Stem Cells."
   This study seeks to develop and characterize the GDF5^{+} permanent cartilage-forming cells from human pluripotent stem cell.

ACHIEVEMENTS

1. Dr. Nakayama finished moving his lab from UTHealth, purchasing necessary lab equipment and reagent, and hiring student intern, Ms. Sarah Easton.

2. Dr. Nakayama gained access to CSU's animal facility and FACS core facility.

3. Dr. Nakayama's major research activity was funded by NIH (R01) as PI (2021, applied earlier in 2020).

4. His second NIH grant (R21) was also funded (2022, applied 6.2021).

5. Dr. Nakayama published a review article in the Journal *Bioengineering* with Drs. Huard and Ravuri.

6. Dr. Nakayama published a research article in the Journal "Development" that was originated in IMM UTHealth, by adding more experimental results.

7. He was invited to talk at VSS 2021 and 2022 ORS Annual Meeting, and gave lectures for the University of Texas Medical School's Stem Cell course and Western Michigan University Medical School's Regenerative Medicine course.

KEY RESEARCH/LAB UPDATES

The key outcomes of this year's efforts are first, to start Dr. Nakayama's own group in a new place, and second, to provide more evidence for satisfying reviewer's questions leading to completion of his manuscript published in April 2022. Dr. Nakayama is one of the SPRI scientists moving from Fort Collins to the Vail laboratory.

FOCUS FOR COMING YEAR:

This coming year, Dr. Nakayama's group will focus on making progress on his R01 grant project by hiring a postdoc. He plans to initiate the program for his R21 grant this year. Dr. Nakayama plans to submit another research grant with Dr. Huard, aiming to elucidate molecular basis of the tissue "super-healing" activity observed with a specialized mouse line called MRL/MpJ mice.

SUDHEER RAVURI, PHD – DEPUTY DIRECTOR, CRPM

DR. SUDHEER RAVURI WORKS CLOSELY WITH CRPM DIRECTOR AND CHIEF SCIENTIFIC OFFICER DR. JOHNNY HUARD AND LEADS AND MANAGES MULTI-DISCIPLINARY RESEARCH PROJECTS AT CRPM, INVOLVING BASIC SCIENCE STUDIES AND CLINICAL TRANSLATION.

Dr. Ravuri's main areas of research focus each year are the study of adipose-derived stem cell biology and applications, biomaterials, characterization of orthobiologics, senotherapeutics and technology development with implications for healthy aging and active living.

Dr. Ravuri is an investigator on NIH, DoD, state and philanthropy-funded research projects and is actively involved in translational studies under Dr. Huard's supervision. He is also serving as reviewer and editorial board member of several research journals, member of research societies, member of leadership committees, and co-chair of research conferences.

Dr. Ravuri has played a significant role in expanding the CRPM laboratory to different locations in Colorado, including leading the team's move from Fort Collins to Vail and into the new regenerative medicine laboratory in Basalt, Colorado.

SPRI'S CLINICAL TRIALS TEAM ADVANCES CLINICAL TRANSLATION

In 2018, SPRI received its first primary National Institutes of Health (NIH) Grant, and since that first award, the research team has steadily increased its number of awards, including clinical trials and studies supported by federal agencies. SPRI's Clinical Trials Team works collaboratively with SPRI and The Steadman Clinic to facilitate and support the ongoing clinical science efforts.

Co-located with CRPM, the team is led by SPRI's VP of Operations Suzanne Liv Page and includes Dr. Luz Thede, Clinical Trials Clinician; Michael Begg, Clinical Trials Physician Assistant; Sara Robinson, Clinical Trials Data Coordinator and Chloe Barton, Clinical Trials Coordinator.

DEPARTMENT OF BIOMEDICAL ENGINEERING

FACULTY AND STAFF

SCOTT TASHMAN, PHD
Director

LAUREN WATKINS, PHD
Research Scientist

COLIN SMITH, PHD
Research Scientist

ALEX BRADY, MS
Senior Robotics Engineer

JUSTIN HOLLENBECK
Research Engineer

STEVE ATHERTON
Director, SPRI Golf Sports Medicine Program

ADAM BRADSHAW
Research Engineer

AUSTIN CARCIA
Research Engineer

BEN BERNARDING
Research Assistant

JUSTIN BROWN
Research Assistant

BRAD FOSSUM
Research Assistant

ALEX GARCIA
Research Assistant

SPRI'S DEPARTMENT OF BIOMEDICAL ENGINEERING IS A COLLECTION OF MULTIDISCIPLINARY LABORATORIES INCLUDING BIOMOTION, ROBOTICS AND ADVANCED IMAGING. THE TEAM IS COMPRISED OF SCIENTISTS AND RESEARCHERS THAT APPLY QUANTITATIVE, ANALYTICAL AND INTEGRATIVE METHODS TO THE FIELD OF ORTHOPAEDIC MEDICINE.

In 2021, the Department of Imaging Research officially joined the Department of Biomedical Engineering (BME), further integrating the labs and research projects. The team employs three full-time PhD researchers in Director Dr. Scott Tashman and Research Scientists Drs. Lauren Watkins and Colin Smith.

The BME team focuses on the role of mechanics and movement on injury and re-injury prevention as well as assessment of surgical and nonsurgical treatments for restoring musculoskeletal function. The team is dedicated to integrating clinical care, research and education, combining SPRI's engineering expertise with the resources of renowned orthopaedic surgeons from The Steadman Clinic, with the ultimate goal of improving treatment of musculoskeletal diseases and orthopaedic injuries. Biomechanics, motion analysis, advanced biomedical imaging, computational modeling and orthopaedic engineering are at the center of the department's research approach.

BME continues to collaborate closely with physicians, maintaining the imperative clinical lens that keeps its focus on high-impact research. BME's research portfolio has expanded significantly to include an essential role in nearly all of SPRI's clinical trials, providing advanced biomechanical and quantitative imaging assessments to evaluate the effectiveness of regenerative medicine treatments for restoring tissue health and function.

The department is home to a state-of-the-art Biomotion Laboratory for assessing human movement and function that includes video-motion analysis, an instrumented treadmill, force plates, a wireless EMG system, wearable IMU sensors, insole pressure sensors and a unique Dynamic Stereo X-ray system, utilizing cutting-edge technology designed by Dr. Scott Tashman, BME Director. Studies of musculoskeletal anatomy and new orthopaedic procedures are conducted in the department's Robotics Laboratory, which is one of the most advanced facilities of its kind in the world. This includes a custom robotic-arm that can recreate physiological joint motion, and video-motion analysis and 3D laser scanning technologies to capture musculoskeletal geometry and function. The BME team also conducts advanced imaging with its leading-edge 3.0 Tesla Siemens MAGNETOM Skyra and Canon Vantage Galan magnetic resonance imaging (MRI) scanners in Vail, Frisco and Basalt, Colorado, while applying imaging tools to improve patient outcomes.

The SPRI Golf Sports Medicine Program operates under the Department of Biomedical Engineering, integrating a high-tech simulator system within the Biomotion Laboratory. This unique combination of technologies enables the SPRI to perform one of the most advanced biomechanical analyses of golf swings in the world, leading to a faster return to play after orthopaedic treatments, reduced injuries, and improved performance.

KEY HIGHLIGHTS

- Integrating Imaging Research within the Department of Biomedical Engineering has led to greater synergy within the department, other SPRI teams and The Steadman Clinic's physicians. Researchers in Biomedical Engineering contribute across laboratories, leading to comprehensive research projects spanning a range of biomedical engineering science.

- Since the last *Orthopaedic Research Journal* was published, the team hired two full-time PhDs—Dr. Lauren Watkins, who specializes in advanced imaging, and Dr. Colin Smith, who specializes in computational modeling and biomechanical experiments in the Biomotion and Robotics Laboratories.

- SPRI's BME team had ten podium presentations accepted to the 2022 World Biomechanics Congress, the most prestigious biomechanics conference globally, held once every four years.

- Expanding the team's imaging research footprint, a new Canon 3T MRI was installed at the new Steadman Philippon building in Basalt. In addition to serving orthopaedic patients at The Steadman Clinic in Aspen and the Roaring Fork Valley, this highly capable system will be a cornerstone of the clinical research planned for the Basalt clinic.

- The BME team continues to play a critical role in nearly all of SPRI's clinical trials, using biomechanical testing and imaging to test the efficacy of treatments and therapies. Director Dr. Scott Tashman continues to submit grants to the NIH and other organizations as Co-Principal Investigator alongside CRPM Director Dr. Johnny Huard.

INTRODUCING THE TEAM'S NEWEST SCIENTISTS

LAUREN WATKINS, PHD

Dr. Lauren Watkins is a Biomedical Engineer and Research Scientist in the Biomedical Engineering and Imaging Research department. She received her BS and MS in Biomedical Engineering at Purdue University, where she focused on tissue engineering for bone regeneration. She then completed her PhD training in Bioengineering at Stanford University. As a PhD student, she worked with Feliks Kogan, Marc Levenston, and Garry Gold to develop new strategies for imaging of joint structure and function in knee osteoarthritis. Her research interests are focused on quantitative MRI and PET imaging techniques to identify changes in bone and cartilage related to osteoarthritis onset and progression.

At SPRI, Dr. Watkin's goal is to leverage her expertise in bone and cartilage imaging to monitor therapies and treatments that restore or maintain musculoskeletal function. She plans to integrate imaging with biomechanics and regenerative medicine for comprehensive assessments of orthopaedic disorders and treatments. She helps design, initiate and investigate imaging outcomes of federally funded and industry-sponsored clinical studies.

HONORS AND AWARDS

- 2020: Summa Cum Laude Merit Award, International Society for Magnetic Resonance in Medicine
- 2020: Top-Scoring Musculoskeletal Abstract, International Society for Magnetic Resonance in Medicine
- 2018–2020: Travel Award, International Society for Magnetic Resonance in Medicine
- 2019–2020: Travel Award, Stanford Bio-X
- 2019: Poster Award, Stanford Bio-X Interdisciplinary Initiates Seeds Grands Symposium
- 2016–2019: William K. Bowes Jr. Graduate Fellow, Stanford Vice Provost for Graduate Education
- 2015: Mark and Pamela Lamp Graduate Scholar, Purdue University
- 2011–2015: Trustees Scholar, Purdue University

SELECTED PUBLICATIONS

1. L Watkins, J MacKay, B Haddock, V Mazzoli, S Uhlrich, G Gold, F Kogan. "Assessment of quantitative [18F] Sodium fluoride PET measures of knee subchondral bone perfusion and mineralization in osteoarthritic and healthy subjects," *Osteoarthritis and Cartilage* 29 (6), 849-858.
2. JW MacKay, L Watkins, G Gold, F Kogan. "[18F] NaF PET-MRI provides direct in-vivo evidence of the association between bone metabolic activity and adjacent synovitis in knee osteoarthritis: a cross-sectional study," *Osteoarthritis and Cartilage* 29 (8), 1155-1162.
3. LE Watkins, EB Rubin, V Mazzoli, SD Uhlrich, AD Desai, M Black, GK Ho, SL Delp, ME Levenston, GS Beaupre, GE Gold, F Kogan. "Rapid volumetric gagCEST imaging of knee articular cartilage at 3T: evaluation of improved dynamic range and an osteoarthritic population," *NMR in Biomedicine* 33 (8), e4310.

COLIN SMITH, PHD

Dr. Colin Smith is a Research Scientist in the Biomedical Engineering Department who brings expertise in computational modeling, movement biomechanics and dynamic imaging. His research investigates the role of loading in the musculoskeletal system during full body movements on the causes and successful treatment of orthopaedic pathologies. He received his B.S. from Clemson University, and M.S. and Ph.D. from the University of Wisconsin-Madison in Mechanical Engineering. He was previously a visiting scholar to the National Center for Simulation in Rehabilitation Research at Stanford University and the Human Movement Biomechanics Lab at Katholieke Universiteit (KU) Leuven, Belgium. Prior to joining SPRI, Dr. Smith was a research fellow in the Laboratory for Movement Biomechanics at ETH Zurich, Switzerland, where he led two research teams focused on computational simulation of knee loading and developing an implantable sensor to measure tendon strain.

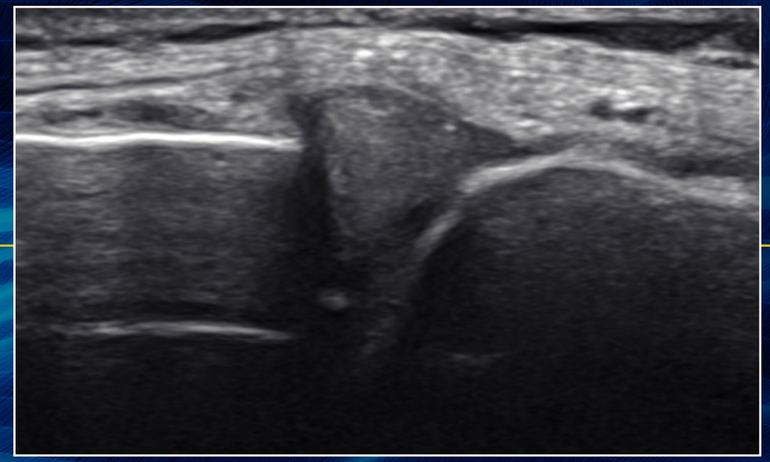
Dr. Smith's research program leverages novel sensing, imaging and simulation technologies in the SPRI Biomotion and Robotic laboratories to investigate the movement of musculoskeletal joints (hip, knee, shoulder, etc.) and loading of soft tissues (muscles, ligaments, cartilage) during functional movements. His research focuses on the role of mechanical loading in the development and progression of osteoarthritis and improving orthopaedic surgical techniques and rehabilitation protocols. He is the developer of OpenSim-JAM (Joint and Articular Mechanics), an award-winning open-source software framework for predicting the effect of orthopaedic treatments on musculoskeletal joint loading and function.

HONORS AND AWARDS

- S.M. Perren Research Award (2022)
  27th Congress of the European Society of Biomechanics, Porto, Portugal
- Mimics Innovation Award: Americas Region (2019)
- American Society of Biomechanics Young Scientist Pre-doctoral Award (2017)
  41st Annual Meeting American Society of Biomechanics, Boulder, CO, USA
- Andrzej Komor New Investigator Award (2017)
  16th International Symposium on Computer Simulation in Biomechanics, Gold Coast, Australia
- McCaig Institute First Prize for Trainee Presentation (2015)
  13th International Symposium Computer Methods in Biomechanics and Biomedical Engineering, Montreal, Canada
- Andrzej Komor New Investigator Award (2015)
  15th International Symposium on Computer Simulation in Biomechanics, Edinburgh, Scotland

INTEGRATION BECOMES HALLMARK OF BME PROGRAM

ONE OF THE KEY HIGHLIGHTS FOR SPRI'S DEPARTMENT OF BIOMEDICAL ENGINEERING (BME) THIS PAST YEAR WAS INTEGRATING THE DEPARTMENT OF IMAGING RESEARCH WITHIN THE TEAM—FOR YEARS, THE TWO DEPARTMENTS WORKED CLOSELY, BUT THE FORMAL INTEGRATION ENABLED FOR MORE SYNERGY ACROSS THE TEAM'S LABORATORIES.



Researchers are looking at how the meniscus moves under load and at different knee angles to learn more about how it behaves during activities of daily life. This ultrasound image shows the meniscus (triangle shape) squishing out a healthy knee when the person is standing, a behavior that can't be seen on a typical knee MRI because the patient is lying down.

Scientists are able to work cross-disciplinarily, moving between Biomotion, Robotics and Advanced Imaging to provide a comprehensive lens to its research. Research Scientist Lauren Watkins, PhD, leads the imaging research efforts at SPRI, with a focus on harnessing advanced imaging technology not only as a diagnostic tool, but also in validating treatments and therapies across SPRI's research departments.

ULTRASOUND AS A RESEARCH TOOL

The integration of advanced imaging within the BME team has led to several focused studies utilizing a state-of-the-art clinical ultrasound machine, including in robotics, biomotion and regenerative medicine projects. The use of this technology across BME's labs and with the regenerative medicine team is exemplary of successful integration of imaging at SPRI.

The BME team utilizes ultrasound technology to investigate meniscus behavior under load. In the Robotics Laboratory, researchers use ultrasound imaging to measure how far the meniscus protrudes under load in cadaveric specimens, both in the healthy meniscus and in cases of meniscus tears and repairs. In a similar study in the Biomotion Laboratory, ultrasound combined with video-motion analysis technology is used to look at meniscus behavior under load and different positions to help link findings with what occurs in healthy human volunteers. Ultrasound imaging of the knee in motion offers a different perspective than what is seen on magnetic resonance imaging (MRI), which is typically used to look at meniscal damage in a stationary and unloaded position.

FROM BIOMEDICAL ENGINEERING TO REGENERATIVE MEDICINE

The BME team also has two shoulder studies underway that use ultrasound to examine the rotator cuff. Ultrasound measurements of the stiffness and flexibility of the rotator cuff tendons and muscles may help a surgeon determine if a torn rotator cuff can be repaired before a patient goes into surgery. Ultrasound is also being used to measure blood flow in the shoulder after rotator cuff tears and repairs, which may provide new information about healing.

These ultrasound tools may be useful in future work, adapting to the regenerative medicine team's preclinical trials as well as in SPRI's clinical trials—using ultrasound to non-invasively assess the efficacy of regenerative medicine therapies. Because novel ultrasound technologies can image tiny vasculature and stiffness in muscles and tendons, this technology could have a role in monitoring healing and recovery for patients.

THE ROLE OF THE DELTOID LIGAMENT IN ANKLE INSTABILITY

The BME Robotics Laboratory has recently completed a research project focused on the deltoid ligament—a central ligament within the ankle joint—and how deltoid injuries correlate to ankle instability.

WHAT ARE DELTOID INJURIES?

The deltoid ligament is frequently ruptured during an ankle fracture or severe sprain, but surgical repair is not the current practice due to the belief that the non-weightbearing period required for fracture recovery allows for adequate ligament healing. However, this conservative management has shown poor outcomes—both acutely, and over time with the development of arthritis. The robotics team investigated the role of the native anterior and posterior deltoid ligament in ankle stability to determine the efficacy of simple suture vs. repair of each bundle.

DELTOID INJURIES AND ANKLE STABILITY

In a controlled laboratory study, the team investigated ten cadaveric ankles. The specimens underwent biomechanical testing in eight sequential states, with three tests each. The most important finding of this study is that a complete deltoid tear causes major ankle instability. Therefore, it is strongly recommended to surgically repair the deltoid ligament—an improvement to the current standard of care. Because of this finding, this study has important implications and clinical impact for the treatment of deltoid tears in ankle injuries.

NEXT STEPS

This study was accepted for presentation at the World Congress of Biomechanics—the most prestigious conference for biomedical engineering, held once every four years—with a focus on the robotic testing methodology. It was also accepted at the American Orthopaedic Society for Sports Medicine's (AOSSM) annual meeting in 2022, with a focus on the clinical findings. The manuscript for this project is currently being reviewed by a premier peer-reviewed journal.

The Steadman Clinic Foot and Ankle Surgeon Dr. Tommy Haytmanek in the Operating Room.

Improving Orthopaedic Treatments through Computational Medicine

By constructing computational models of the musculoskeletal system, SPRI research scientist Dr. Colin Smith aims to develop virtual tools to aid in patient diagnostics and orthopaedic treatments. This innovative interdisciplinary research leverages the full capabilities of the Department of Biomedical Engineering's imaging, robotics and biomotion facilities to predict the mechanical loading in musculoskeletal tissues and investigate the role loading plays in pathology and surgical outcomes.

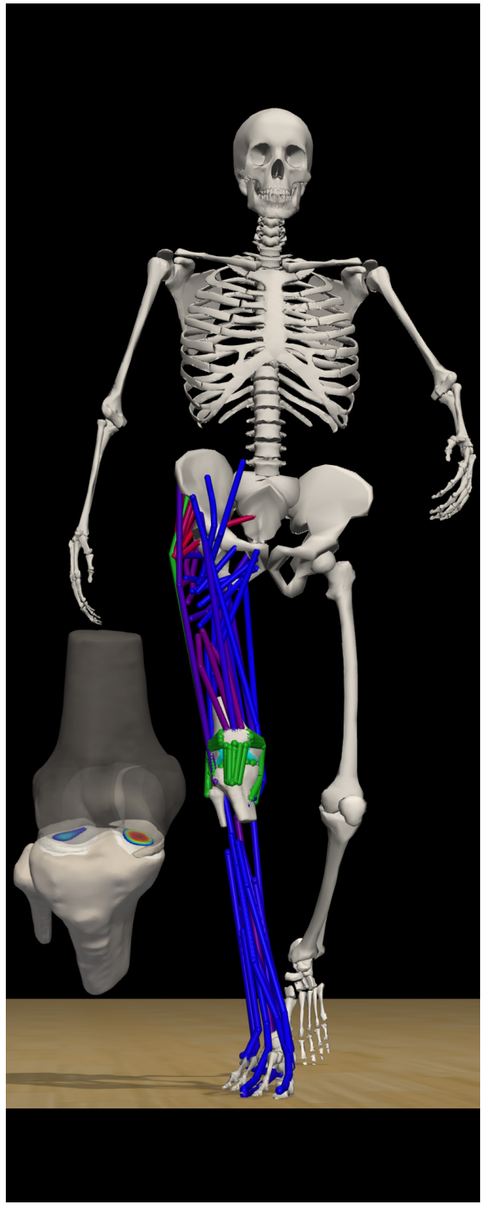
CALCULATION OF KNEE LOADING IN ATHLETES AND OSTEOARTHRITIS PATIENTS

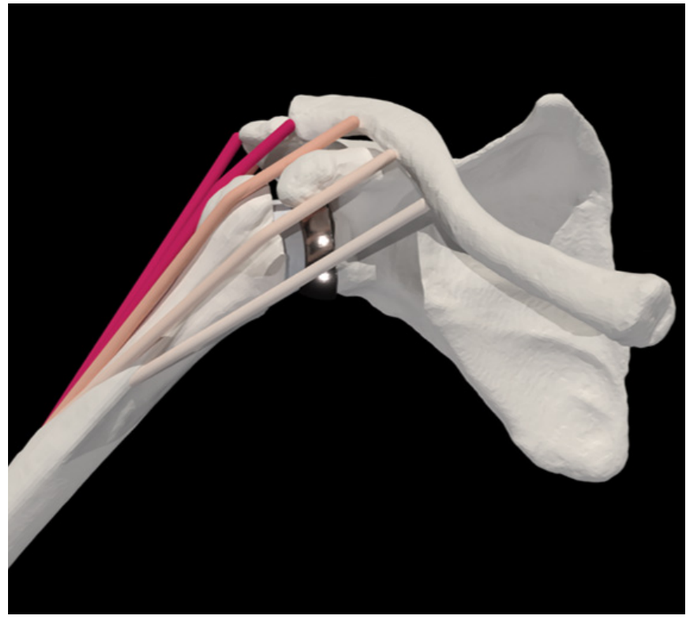
SPRI's ongoing clinical trials to improve treatments for anterior cruciate ligament (ACL) injury and knee osteoarthritis include two key measurements: MRIs to assess the cartilage morphology and biomotion assessments to measure joint angles during daily activities in the biomotion lab. Dr. Smith has developed a novel computational musculoskeletal modeling approach that integrates these MRI and biomotion measurements to predict muscle, ligament and cartilage loading during full body movements. This revolutionary technology provides a non-invasive means to assess *in vivo* tissue loading and thus can provide important insights into the biomechanical factors involved in joint degeneration.

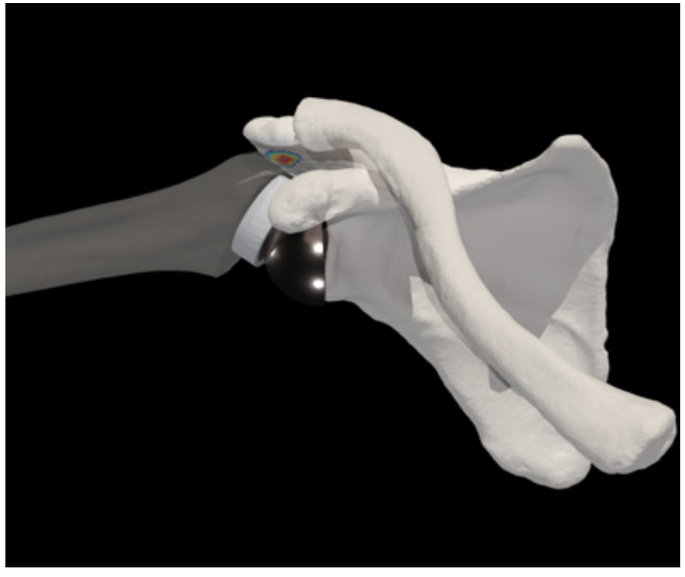
SURGICAL PLANNING FOR TOTAL SHOULDER REPLACEMENT

Reverse total shoulder arthroplasty (RTSA) is a common surgical procedure to treat shoulder osteoarthritis and rotator cuff tears. State-of-the-art implant designs offer an enormous variety of sizes and shapes for surgeons to choose from and patient-specific instruments enable surgeons to precisely perform their planned procedures. However, a critical aspect of optimizing patient outcomes after RTSA is selecting the best implant design and alignment for a given patient.

By creating a digital twin of each patient based on CT scans, musculoskeletal modeling can provide important insights into RTSA surgical planning. Two key metrics of a successful RTSA are improved post-operative range of motion and shoulder muscle function. With novel physics-based predictive modeling techniques, Dr. Smith has developed a computational tool to virtually predict the effect of implant design and positioning on these measures of post-operative function. By leveraging super-computing to perform thousands of virtual surgeries on a patient's digital twin and determining the best predicted outcome, this approach can construct highly personalized surgical plans. Ongoing research is using the SPRI Surgical Skills and Robotics Labs to validate this technology in cadavers, and the Biomotion Lab to demonstrate its predictive capacity in patients using the DSX imaging system.







LEFT: Motion analysis measurements from the Biomotion Lab are used as inputs to muscle-driven simulations to calculate the loading in the knee joint articular cartilage in research studies on osteoarthritis.

TOP RIGHT: Musculoskeletal simulations are used to predict the effect of reverse total shoulder arthroplasty implant design and alignment on the deltoid muscle function.

BOTTOM RIGHT: Novel computational modeling techniques enable the range of motion of a virtual reverse total shoulder arthroplasty surgical plan to be predicted.

THE IMPACT OF PAIN, SHOULDER ARTHROPLASTY AND ROTATOR CUFF SURGERY ON GOLF SWING MECHANICS

LAST SUMMER, SPRI LAUNCHED ITS NEW GOLF SPORTS MEDICINE PROGRAM, WHICH INTEGRATED A STATE-OF-THE-ART GOLF SIMULATOR WITHIN SPRI'S BIOMOTION LAB. A DEFINING CHARACTERISTIC OF THIS PROGRAM IS THAT IT LEVERAGES THE BIOMOTION LAB'S CUTTING-EDGE VIDEO MOTION CAPTURE SYSTEM ALONGSIDE RESEARCH-GRADE FORCE PLATES AND WEARABLE SENSORS, ENHANCING THE CAPABILITIES OF TRADITIONAL GOLF SIMULATORS. THE PROGRAM OFFERS BIOMECHANICAL ASSESSMENTS FOR THE GOLF SWING, ALONGSIDE LESSONS AND UNIQUE BIOMOTION RESEARCH STUDIES.

INITIATION OF GOLF-SPECIFIC RESEARCH STUDIES

One of the research studies underway in the Biomotion Lab investigates the effects of pain, shoulder arthroplasty (replacement) and rotator cuff surgery on golf swing biomechanics and performance. As golf is an immensely popular recreational sport, particularly in the aging population, investigating how golfers may maintain or restore playing ability after musculoskeletal injury or disorder is important, not only for an individual's golf game, but also for their overall health and wellbeing.

IMPACT ON THE GOLF SWING

Golfers with glenohumeral arthritis and rotator cuff disease often complain of pain and decreased range of motion, which interferes with the natural movements of the golf swing—this ultimately affects their ability to play. While golf is traditionally considered to be a low-impact sport, the extreme peak positions of the golf swing involve placing the shoulder joint in maximum abduction and adduction positions, which can provoke impingement and even a form of posterior shoulder instability.

All of these contributing factors can cause pain, impair a golfer's swing, and ultimately reduce functional activity and quality of life. The SPRI team is investigating how pain and shoulder surgery impact shoulder kinematics and kinetics, range of motion and performance during the golf swing, as compared to an age-matched asymptomatic group. This research will provide a data-driven approach to train golfers with shoulder pathologies towards healthier swings and better performance.

ABOVE: PGA Master Professional Steve Atherton oversees a participant in the lab.

BELOW: BME Research Engineers apply wearable sensors to a Golf Sports Medicine participant.

RETURN TO GOLF

To date, there have been few retrospective studies on shoulder surgery in relation to return to golf and performance, and there is not a defined consensus about the recommendation on safety and when to return to golf. This study will help researchers better identify when golfers are best positioned to return to play safely—which is exemplary of SPRI's injury and re-injury prevention efforts.

CENTER FOR OUTCOMES-BASED ORTHOPAEDIC RESEARCH

FACULTY AND STAFF

GRANT DORNAN, MS
Director

KAREN BRIGGS, MBA, MPH
Director of Hip Research

HEATHER GILMAN, PA-C
Hip Research Manager

MARILEE HORAN, MPH
Upper Extremity Research Coordinator

ASHLEY PERRIGAUD
Data Collection Coordinator

SPENCER COMFORT
Research Assistant 2020–2022

ANNALISE PEEBLES
Research Assistant 2020–2022

HANNAH DAY
Research Assistant 2021–2022

JARED HANSON
Research Assistant 2021–2022

CHRISTIE RUTLEDGE
Research Assistant 2021–2023

JARROD BROWN
Research Assistant 2022–2023

RYAN WHALEN
Research Assistant 2022–2023

THE CENTER FOR OUTCOMES-BASED ORTHOPAEDIC RESEARCH (COOR) IS THE LONGEST STANDING DEPARTMENT AT SPRI. THE TEAM HAS BEEN TRACKING AND STUDYING PATIENT OUTCOMES FOR OVER THIRTY YEARS, AND IS NOW TRACKING OVER 46,000 SURGERIES IN THE COOR DATABASE. THE TEAM HAS COLLECTED OVER 186,000 SUBJECTIVE PATIENT QUESTIONNAIRES AND HAS OVER 150,000 UNIQUE PATIENTS INCLUDED IN THE DATABASE.

> COOR tracks patient outcomes following their orthopaedic treatments. In studying these outcomes, the team is able to validate the efficacy of surgical techniques, therapies and other medical treatments. COOR partners closely with The Steadman Clinic physicians, who use the database to aid in diagnosis and treatment selection. Patients also benefit from the database, as physicians can offer recovery expectations based in concrete data. One of COOR's primary responsibilities is producing long-term outcomes studies, including studies on the pioneering techniques of SPRI's Founder, Dr. J. Richard Steadman and Chair, Dr. Marc J. Philippon.

COOR is involved in each of SPRI's clinical trials and is integral in the publication of SPRI's papers. The outcomes data in COOR's database supports The Steadman Clinic's mission of practicing evidence-based medicine—treatments and techniques that are backed by research. Physicians from all over the world look to COOR's evidence-based medicine research to inform their clinical decision making.

As a partner to the U.S. Olympic & Paralympic Committee (USOPC), COOR has been instrumental in organizing the past six Injury Prevention Symposium events. The annual event connects leading scientists, researchers and clinicians from all over the world to engage on topics related to injury prevention and protecting the health of athletes.

46,432	186,248	106,248	19,779	155,118
SURGERIES BEING TRACKED	SUBJECTIVE PATIENT QUESTIONNAIRES RECORDED	OBJECTIVE CLINICAL EXAMS	MRIS INTERPRETED	UNIQUE PATIENTS INCLUDED IN DATABASE

PUBLICATIONS

- **45** COOR primary publications since July 2021
- **28** publications utilizing Patient Outcomes Database
  - 10 publications in the *American Journal of Sports Medicine*
  - 6 publications in *Arthroscopy*
  - 5 published in *Journal of Shoulder and Elbow Surgery* or *Journal of Shoulder and Elbow Surgery International*
  - 1 published in *The Journal of Bone and Joint Surgery*
  - 6 published in other journals
- **71%** of SPRI's publications since 2021 included a COOR author
- **96%** of COOR primary publications were performed in conjunction with the Clinical Fellows and/or International Scholars

KEY HIGHLIGHTS

- COOR was instrumental in submitting the International Olympic Committee (IOC) Center for Excellence application. Currently, SPRI and its partners within the U.S. Coalition for the Prevention of Illness and Injury in Sport represent the United States as one of 11 countries with the IOC research center designation.
- Building on its launch of the Climbing-Related Injury Monitoring and Prevention (CRIMP) program, SPRI expanded this injury surveillance project, rolling out the program to additional teams and extending the program.
- COOR's Snow-sport Lower extremity Injury Prevention (SLIP) program continued with athletes within Vail Ski & Snowboard Club in the 2021–22 winter seasons, with the athletes taking the warmup exercises on themselves (a goal of all injury prevention programs). An abstract and manuscript were written about this program.
- The COOR team was an integral part of the planning and execution of the 6th Annual Injury Prevention Symposium, co-hosted with the U.S. Olympic & Paralympic Committee.
- COOR continued its support of SPRI's clinical trials, including database support and beginning a retrospective study involving hip microfracture treatment for a Department of Defense (DoD)-funded clinical trial.

THANK YOU, KAREN BRIGGS

In 2021, Karen Briggs retired after spending 28 years of her career at SPRI. Karen built the outcomes database, and spent her career publishing high-impact outcomes research on the groundbreaking work of SPRI Founder Dr. J. Richard Steadman, SPRI Chair Dr. Marc J. Philippon and other physicians from The Steadman Clinic. After her retirement, Karen has continued to collaborate on select projects at SPRI. Thank you to Karen for her incredible contributions to SPRI and her commitment to patient outcomes and evidence-based medicine.

MAKING A GLOBAL IMPACT WITH COOR

AS A PARTNER TO THE U.S. OLYMPIC & PARALYMPIC COMMITTEE (USOPC), SPRI AND THE STEADMAN CLINIC HAVE BEEN SUPPORTING TEAM USA ATHLETES THROUGH MEDICAL TREATMENT, INJURY PREVENTION RESEARCH AND INJURY SURVEILLANCE PROGRAMS. THE STEADMAN CLINIC IS ONE OF ONLY THREE USOPC-DESIGNATED NATIONAL MEDICAL CENTERS IN THE NATION, AND HAS TREATED NEARLY 400 TEAM USA ATHLETES SINCE 2017 (AS OF MAY 1, 2022).

SPRI and The Steadman Clinic work closely with Team USA athletes, including Track & Field athlete Colleen Quigley, who was filmed during a SPRI shoot at the USOPC training center.

With the University of Utah, SPRI and the USOPC form the U.S. Coalition for the Prevention of Illness and Injury and Sport, which was designated by the International Olympic Committee (IOC) as one of 11 research centers worldwide, focused on injury prevention and the protection of athlete health. In this capacity, SPRI's research not only has an impact on the United States, but also globally. With the Olympic spirit in mind, these centers form an international network of connected scientists and clinicians—experts who share their discoveries and findings to help athletes worldwide.

THE UNITED STATES AS A CENTER FOR EXCELLENCE

In the Summer of 2022, SPRI—alongside its U.S. Coalition partners—submitted an application to the IOC to continue its status as an IOC Research Centre of Excellence for the coming 2023–2026 Olympic cycle. This application highlighted SPRI's educational conferences, fellowship and residency programs, international research scholarships, laboratories, and distinctive research programs focused on injury prevention.

These research programs include several COOR-focused initiatives including Injury Surveillance in elite climbers (CRIMP Program), Injury Prevention in youth alpine ski racers (SLIP Program) and athlete screening ("Hip at Risk" Program). The application also highlighted The Steadman Clinic's National Medical Network Care for Olympic and Paralympic Athletes, including treating nearly 100 Team USA athletes in 2021 alone.

SPRI'S FOCUS ON RE-INJURY PREVENTION

As a part of the U.S. Coalition, SPRI's research strengths are found in secondary injury prevention, more commonly known as re-injury prevention. By harnessing COOR's outcomes database and analyzing patient data from Team USA and other athletes, SPRI develops programs to assess when it is safe for athletes to return to play without risk of re-injury, helping to prolong an athlete's career. Prioritizing secondary injury prevention is an important part of a comprehensive athlete health program, as elite athletes often need to return to their sports soon following injury and treatment.

CONNECTING WITH SCIENTISTS AND CLINICIANS

Representative of SPRI's U.S. Coalition partnership, SPRI co-hosts the Injury Prevention Symposium with the U.S. Olympic & Paralympic Committee each year. Now a virtual event, there have been six meetings, featuring international scientists, researchers and clinicians, who gather at the event to share their latest research on injury prevention and athlete health.

ELITE BALLET DANCERS PARTICIPATE IN SPRI ATHLETE SCREENING

Athlete screening has been a staple of programming in SPRI's COOR for several years, with a special focus on the "hip at risk." Many sports, ranging ice hockey to ballet, are prone to the development of femoroacetabular impingement (FAI) and other hip injuries in athletes due to the specific movements and force the body experiences while in action. These injuries are most often diagnosed once the injury has become painful and symptomatic, requiring medical intervention. Athlete screening over a period of years helps to identify these conditions in an early stage of development.

CLINICAL EVALUATION

Led by SPRI Chair Dr. Marc Philippon, COOR launched a screening program with an elite regional dance company, focusing on pre-professional dancers aged 13–20. The screening program is structured as a five-year program that will include an annual screening using a clinical ultrasound system and physical exam. Through this annual screen, Dr. Philippon and his clinical team—including Physician Assistant Heather Gilman and Athletic Trainer Hannah Mundy—will track the dancers and record data from their exams. Thirty dancers participated in the first screen of the program this year. As many dancers were under 18, their parents consented their participation in the program.

As FAI commonly occurs in youth athletes, special attention will be dedicated to the potential development of this condition before the dancers experience any symptoms. The ultrasound system is used to examine the hip joint, allowing clinicians to notice any shape changes and early signs of impingement before the dancer experiences pain or discomfort. This early detection not only helps clinicians and researchers identify what athletes are at risk, but it also helps identify what may be causing the risk, leading athletes and their coaches to modify their activities to diminish their risk and prolong their athletic careers.

PROGRESSING THE PROGRAM

SPRI will continue to enroll new athletes with the dance company each year. Because this screening program is focused on preventing or reducing injury risk, the athletes and their parents are enthusiastic about their participation in the program. Athlete screening programs like this one are a critical step in injury prevention efforts because the screens allow clinicians and researchers to better support athletes in their sport through reducing their injury risk, which ultimately prolongs their careers as elite athletes.

Dr. Marc Philippon performs hip arthroscopy in the operating room.

CLINICAL TRIALS AND THE IMPORTANCE OF OUTCOMES DATA

With over thirty years of tracking patient outcomes in COOR, SPRI has a strong foundation in collecting and analyzing patient data. At the end of 2020, COOR completed its largest database upgrade since 2011, implementing state-of-the-art data science tools and improving the technology that supports data capture and clinical research. This upgrade, paired with the department's study design and statistical analysis, has enabled COOR to be a key contributor to the success of SPRI's federally funded clinical trials.

COOR's expertise with data and contribution to SPRI's clinical trials is exemplified in SPRI's Regenerative Medicine Innovation Project (RMIP), for which COOR has led development and ongoing management of a clinical trial database used to collect, analyze and report on patient data. This five-year clinical trial includes 100 participants who undergo a variety of treatments and assessments over the course of the trial. Successful data capture and reporting are imperative to the success of the trial. SPRI anticipates that the RMIP database will contain 500,000 unique data points by the completion of the trial.

Outcomes Enhance Current Clinical Trial

While much of SPRI's clinical trials focus on current patients undergoing treatments and therapies, the team found a unique opportunity in a DoD-funded trial focused on hip microfracture treatment. This trial investigates whether or not anti-fibrotic agents improve the effects of microfracture in the hip—and COOR's database may unlock additional data to bolster the trial's findings.

COOR is analyzing data from 289 patients treated with hip microfracture since 2011. Because Dr. Philippon began prescribing anti-fibrotic medication in 2015, researchers can look at the outcomes of patients before 2015 alongside patients who received treatment *after* 2015. By looking back at these patients, the team may be able to identify whether or not the anti-fibrotic treatment not only reduced fibrosis, but also if it improved the quality of the cartilage after microfracture treatment. This, paired with the current research in the active clinical trial, could lead to a new clinical standard of care for this treatment.

Database as a Differentiator

With SPRI's robust outcomes database, the institute's clinical trials are supported not only with excellent data capture, analysis and reporting, but also with the distinctive ability to analyze patient outcomes. COOR's participation in these trials exemplifies how team science across the institute helps bolster the success of the research performed.

DEPARTMENT OF EDUCATION

FACULTY AND STAFF

MARC J. PHILIPPON, MD
Chair, Steadman Philippon Research Institute
Co-Director, Sports Medicine Fellowship;
Co-Director, Hip Preservation & Reconstruction Fellowship

MATTHEW T. PROVENCHER, MD, MBA
Co-Director, Sports Medicine Fellowship

JOEL M. MATTA, MD
Co-Director, Hip Preservation & Reconstruction Fellowship

C. THOMAS HAYTMANEK JR, MD
Director, Foot & Ankle Fellowship

THOMAS R. HACKETT, MD
Faculty, Sports Medicine Fellowship

PETER J. MILLET, MD, MSc
Faculty, Sports Medicine Fellowship

ARMANDO F. VIDAL, MD
Faculty, Sports Medicine Fellowship

LESLIE B. VIDAL, MD
Faculty, Sports Medicine Fellowship

JONATHAN A. GODIN, MBA, MD
Faculty, Sports Medicine Fellowship

ERICA LUPIEN
Fellowship Program Coordinator

ALEX BRADY, MS
Education and Public Outreach Program Co-Manager

PATRICIA MCNAMARA
Education and Public Outreach Program Co-Manager

EDUCATING TOMORROW'S ORTHOPAEDIC AND SPORTS MEDICINE LEADERS

CLINICAL FELLOWSHIPS

SPRI's Department of Education is focused on educating top orthopaedic surgeons following their residency. Each year, SPRI hosts these surgeons for a one-year intensive at SPRI and The Steadman Clinic. These programs include the ACGME-accredited Sports Medicine Fellowship, Foot & Ankle Fellowship and Hip Preservation & Reconstruction Fellowship. Over the past year, SPRI has hosted eight sports medicine fellows, one foot & ankle fellow and one hip preservation & reconstruction fellow. These physicians work with attending faculty from The Steadman Clinic and each of SPRI's research teams to have a comprehensive clinical fellowship that is based in research and the practice of evidence-based medicine.

The clinical fellowship alumni network now includes nearly 250 surgeons practicing in communities around the world. These alumni often hold academic positions at leading universities, maintain chief positions at hospitals and work at elite practices. Several of the programs' former fellows have been recruited back to The Steadman Clinic as physicians, including Drs. Randall W. Viola, Peter J. Millett, C. Thomas Haytmanek, Jr, Jonathan A. Godin, Jared T. Lee and Joseph J. Ruzbarsky. Three of these former fellows now serve on the faculty for these clinical fellowships—Drs. Millett, Haytmanek and Godin.

INTERNATIONAL SCHOLARSHIPS

SPRI is proud to host international physicians and scientists each year to participate in research and learn from SPRI's renowned scientists. As practicing surgeons in their native countries, these scholars focus on research while at SPRI and observe The Steadman Clinic's attending physicians. This year, SPRI hosted seven international scholars from Japan, Thailand, Germany and Switzerland.

The goal of both the fellowships and scholarships is to provide a comprehensive, immersive education experience for surgeons during their time in Vail. They are able to participate in research in their areas of interest, from biomechanics and biologics to clinical outcomes research. Fellows and scholars work closely with surgeons and scientists, refining their orthopaedic skills in the Surgical Skills Laboratory. They investigate the causes, prevention and cures of degenerative diseases alongside the treatment and prevention of joint injuries. When they complete their time in Vail, these fellows and scholars go on to practice orthopaedic and sports medicine care that is backed in research, ensuring that patients around the world have the opportunity to receive the best evidence-based medical care for their needs.

2021–2022 SPORTS MEDICINE FELLOWS

KENT C. DOAN, MD
Undergraduate: University of Missouri, Kansas City
Medical School: University of Missouri, Kansas City
Residency: University of Colorado

CHARLES A. SU, MD, PHD
Undergraduate: Case Western Reserve University
Medical School: Case Western Reserve University
Doctorate: Case Western Reserve University; Cleveland Clinic
Residency: University Hospitals/Case Western

MICHAEL J. FOSTER, MD
Undergraduate: Mount St. Mary's University
Medical School: University of Maryland School of Medicine
Residency: University of Maryland

MATTHEW LOUIS GEORGE VOPAT, MD
Undergraduate: University of Kansas
Medical School: University of Kansas
Residency: University of Kansas School of Medicine–Wichita

TOUFIC R. JILDEH, MD
Undergraduate: Michigan State University
Medical School: Wayne State University School of Medicine
Residency: Henry Ford Health System

STEPHEN W. YU, MD
Undergraduate: University of Michigan
Medical School: Wayne State University School of Medicine
Residency: NYU Langone

JORDAN L. LILES, MD
Undergraduate: Western Illinois University
Medical School: Loyola University Chicago
Residency: Duke University

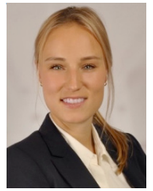
2021–2022 FOOT & ANKLE FELLOW

PARKER P. DUNCAN, MD
Undergraduate: University of Memphis
Medical School: University of Tennessee Health Science Center College of Medicine
Residency: Campbell Clinic

HEATH P. MELUGIN, MD
Undergraduate: Missouri State University
Medical School: University of Kansas
Residency: Mayo Clinic

2021–2022 HIP PRESERVATION & RECONSTRUCTION FELLOW

TREVOR J. SHELTON, MD, MS
Undergraduate: University of Utah
Medical School: University of Utah School of Medicine
Residency: University of California, Davis
Sports Medicine Fellowship: Southern California Orthopedic Institute



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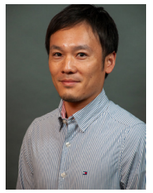

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Medical School: Medical School Charité University Berlin, Germany
Orthopaedic Surgery & Traumatology Residency: University of Heidelberg
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YOUTH EDUCATION SPARKS PASSION FOR SCIENCE AND MEDICINE

AS EDUCATION IS INTERTWINED WITH SPRI'S MISSION, THE ORGANIZATION IS PROUD TO OFFER PROGRAMS TO LOCAL COLORADO STUDENTS.

Since 2011, SPRI has offered fifth grade science tours through SPRI's state-of-the-art laboratories—Biomotion, Regenerative Medicine, Robotics and Surgical Skills—interactive sessions at local middle school and science fair judging and immersive experiences for high school students.

SPRI offers a year-long program for local high school students in which juniors and seniors perform hands-on research alongside SPRI scientists and researchers. In addition to the science club, SPRI hosts a week-long summer course called the Summer Scholars Program, in which dozens of high school students participate in an immersive STEM course. All of SPRI's youth education programs are made possible by SPRI researchers, engineers and scientists, who volunteer their time to work with local students.

This year, SPRI resumed the Summer Scholars program after a hiatus due to COVID-19. Fourteen SPRI mentors across SPRI's departments worked with the students from Eagle and Summit Counties in Colorado.

EVENTS

Dr. Johnny Huard welcomes guests to the 6th Annual Vail Scientific Summit.

Dr. Marc Philippon presents at the Vail Scientific Summit.

SPRI'S EVENTS CONNECT SCIENTISTS, CLINICIANS AND RESEARCHERS

SPRI'S COMMITMENT TO COLLABORATION EXTENDS BEYOND THE TEAM SCIENCE PERFORMED AT THE INSTITUTE—FROM ESTABLISHING RESEARCH NETWORKS TO HOSTING AND CO-HOSTING MAJOR ACADEMIC MEETINGS, SPRI IS DEDICATED TO PARTICIPATING IN IMPORTANT CONVERSATIONS IN ORTHOPAEDIC AND SPORTS MEDICINE SCIENCE AND RESEARCH. THESE EVENTS WELCOME CLINICIANS, SCIENTISTS AND RESEARCHERS FROM ALL OVER THE WORLD TO JOIN IN KEY DISCUSSIONS AROUND TOPICS LIKE REGENERATIVE MEDICINE, THERAPEUTICS, INJURY PREVENTION AND MORE.

VAIL SCIENTIFIC SUMMIT

The 6th Annual Vail Scientific Summit was held August 19–22, 2021 at the Vail Marriott Mountain Resort. The theme of the meeting was "Advances in Regenerative Medicine," and the presenting sponsor of the event was Avanos.

The conference included a keynote on Healthy Aging by Dr. Vonda Wright and SPRI's Dr. Johnny Huard called "Precision Longevity: Rethinking what it means to Live Long and Prosper." The four-day event included sessions ranging "Sports and Military Performance," interventional strategies for healthy aging, innovative technologies for musculoskeletal repair, bone and articular cartilage regeneration and repair, and more.

As in past years, the summit included presentations from world-renowned physicians, scientists and researchers. Some of these presenters included Dr. Tamara Alliston of the University of California, San Francisco; Dr. John Cooke of Houston Methodist Research Institute; Dr. Farshid Guilak of Washington University in St. Louis; Dr. James Kirkland of the Mayo Clinic; Drs. William Murphy and Mark Markel of the University of Wisconsin; Dr. Linda Sandell of Washington University School of Medicine; Dr. Samuel Stupp of Northwestern

University; and many other esteemed scientists and clinicians. Several of The Steadman Clinic's physicians—Drs. Philippon, Provencher, A. Vidal, L. Vidal, Godin and Anderson—and SPRI's scientists—Drs. Huard, Bahney, Hambright, Fukase, Ravuri, Lu, Nakayama and Tashman also presented at the Summit.

The 7th Annual Vail Scientific Summit will be held August 20–24, 2022 at The Hythe Resort in Vail, and will feature updates on the latest musculoskeletal innovations including basic science and clinical applications, amongst other topics.

INJURY PREVENTION SYMPOSIUM

The 6th Annual Injury Prevention Symposium was presented via live webinar April 27–29, 2022, following great success from the previous years' virtual formats. Hosted by SPRI and its partner the U.S. Olympic & Paralympic Committee (USOPC), the Injury Prevention Symposium was broadcast from the USOPC Headquarters in Colorado Springs, Colorado.

The event included a keynote address from Dr. Evert Verhagen from the Amsterdam Collaboration on Health and Safety in Sports. The focus of his address was on the importance of visionary leadership in medical team efforts to prevent injuries in sport and athletic performance. The symposium featured U.S. Olympic and Paralympic skiers Tommy Ford and Tyler Carter in the final panel of the event.

SPRI's onsite team included members of the Media and Production Department, Events and the Center for Outcomes-Based Orthopaedic Research (COOR), who collaborated with the USOPC team in Colorado Springs to produces another successful conference.

The 6th Annual Injury Prevention Symposium was broadcast from the USOPC headquarters in Colorado Springs, Colorado.

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