



GROUNDBREAKING RESEARCH CONTINUES AT STEADMAN PHILIPPON RESEARCH INSTITUTE AMIDST COVID-19 OUTBREAK

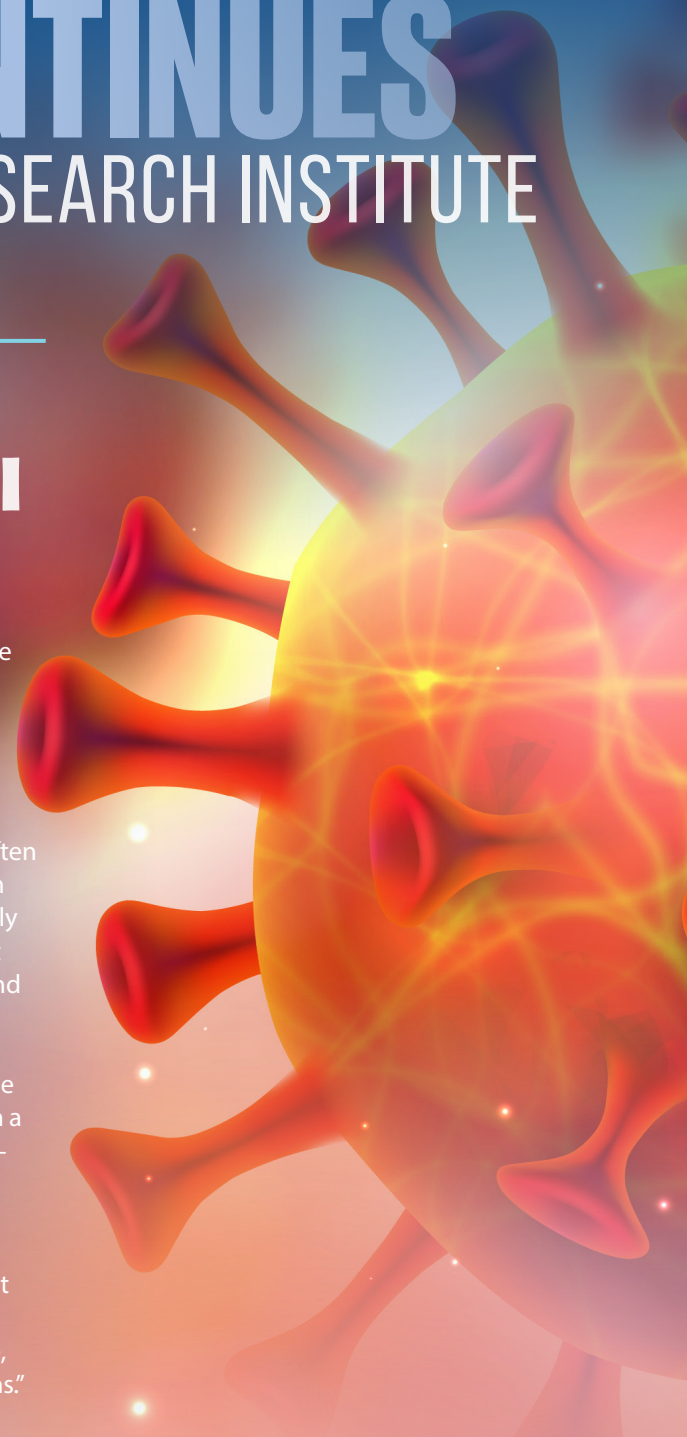
Senescence Research: A Differentiator at SPRI

When Steadman Philippon Research Institute (SPRI) founded the Center for Regenerative Sports Medicine (CRSM) in 2015 and recruited Chief Scientific Officer and CRSM Director Johnny Huard, PhD, SPRI expanded its research, focusing on science at the cellular and molecular level. This includes extensive research into stem cells and other orthobiologics, and how these therapies can be harnessed to advance healing following injury or surgery.

Since joining SPRI, Dr. Huard and his team of scientists and researchers have launched the Regenerative Medicine Program on Healthy Aging, which explores the way musculoskeletal and orthopaedic conditions are often age-related disorders. Through these investigations, Dr. Huard and his team have focused on the concept of senescence—the aging of cells—to not only explore its effect on musculoskeletal conditions like osteoarthritis (OA), but also diseases like Duchenne Muscular Dystrophy (DMD) and even cancer and cardiovascular disease.

“Of all my years of research, and we’re talking about thirty years of science, the most groundbreaking work is in senescent cells,” said Dr. Huard. Coming from a two-time Kappa Delta award winner who discovered the presence of muscle-derived stem cells (MDSCs) in adult muscle tissue, that’s a big statement.

“We started looking at aging, how senescent cells impact the patient as they age,” said Dr. Huard. “For example, patients with osteoarthritis have senescent cells that damage their cartilage, so we are looking at ways to fix that. And now we have a direct link from this research to cancer, cardiovascular disease, neurodegeneration—the senescent cell is at the root of all of these conditions.”



Taking Senescence Research to the Patient

Exemplary of the bench-to-bedside science model, CRSM began with tests in the lab, exploring senescence at a cellular level. From there, the research went to preclinical trials, which centered around an animal model with OA. Treating the mice with senolytic supplements (therapeutics designed to kill senescent cells), the researchers discovered that OA could be delayed in mice. The next step, funded by the Department of Defense (DoD), is a clinical trial in humans, utilizing these same supplements to not only delay cartilage degeneration, but also to potentially improve existing, damaged cartilage. If the clinical trial is successful, this could lead to a new therapeutic treatment for patients with OA.

In addition to this clinical trial, which is currently underway at SPRI and The Steadman Clinic, Dr. Huard and his team are exploring the development of a test for senescence. This blood test could advise a patient about their level of senescence, informing his or her physician if a senolytic supplement could be beneficial.



Johnny Huard, PhD, Chief Scientific Officer at SPRI and Director of the Center for Regenerative Sports Medicine

A New Test with Tremendous Potential Impact

The team began their work with 60 patient volunteers who had an initial blood draw and their cells tested. If the patient had a high percentage of senescent cells in their blood, they were given a supplement to attempt to reduce their levels. Most of the test subjects were in a similar range, but a few outliers triggered a research question: why were their levels so high? Dr. Huard sent these volunteers to have full blood work completed in Denver. Most of these patients have chronic health concerns, which Dr. Huard hypothesizes is the reason for an increased senescent cell count.

The effect of this finding is multifaceted. First, the senescent cell counts were like a red flag, triggering the need for a more thorough investigation. Now, in addition to using senolytic agents to try to reduce their counts, these patients can work with their physicians to treat their other conditions. Additionally, it's given Dr. Huard and his team a future approach with this new test:

"The future for us is to start with testing senescent cells, attempt to reduce them with the supplement, and retest after different time periods. For most, their senescent cells will reduce. And for those that are not reducing, we know they need a full work up. Then we test again." Dr. Huard indicated that the purpose of reducing the senescent cells can be different for distinct patients, but in the context of orthopaedic conditions, it could be the difference between a patient needing a surgical intervention or not. If surgery is inevitable, the patient will now be in a healthier position, and will likely have a better recovery.

"At the most basic level, we're optimizing your surgery before you have it."

Senescence: Orthopaedics and Beyond

Dr. Huard shared that the benefits of senescent testing do not stop with orthopaedic conditions and musculoskeletal diseases. While that initial lens helped to guide these projects, it has opened up greater potential in other fields as well.

"We're already into clinical trials in orthopaedics," Dr. Huard said. "So now we think about, what else?" For Dr. Huard, this includes looking into Duchenne Muscular Dystrophy (DMD), a topic he has spent 30 years investigating. Dr. Huard is currently looking to target treating senescent cells in DMD patients, looking to compare the effect of standard steroid treatments with an alternative treatment: senolytic agents. Given the side effects of the steroids, Dr. Huard is hopeful that using senolytic agents instead would improve the patients' quality of life.

"We are going to begin a clinical trial in partnership with leaders in the field. We have 25 DMD patients from Québec City, and the trial will compare steroid versus senolytic agents. DMD is a genetic disease, but stem cells are also deficient in these patients. Life expectancy has increased with steroids, but the side effects are so bad for the patient. They live longer than before, but they are in tremendous pain. We need to see if using senolytic agents will extend their life without the detrimental effects of steroids."

In addition to DMD, Dr. Huard is looking into a cancer case study. In collaborating with the patient's physician, Dr. Huard encouraged the stage 4 cancer patient to begin using senolytic agents. Since using the supplements, the patient is healthier, and her scans showed that her tumor is no longer present. "Now her physician wants to do a biopsy from where the tumor was. This is just one case, but if senolytic agents could help cancer patients, imagine the potential," said Dr. Huard.

Dr. Huard has been talking to oncologists in Vail, considering a collaborative effort to determine the role of senescent cells in cancer. More importantly, alongside the oncologists, he plans to look into whether eliminating senescent cells can be an alternative treatment for cancer patients.

Senescence and COVID-19?

Since the outbreak of COVID-19 in early March, Dr. Huard and the CRSM team have explored COVID-19 as a potential research topic. "As an orthopaedic institute, we don't typically study viruses, infections," Dr. Huard said. "But we do thorough cellular analysis. Why couldn't we analyze COVID-19 patients for senescent cells? If we discovered high counts, senolytic agents could be a meaningful therapy."

Dr. Huard and his team have put together study proposals on COVID-19, using CRSM's expertise in senescence.

"If we could determine that senolytic agents help people to recover, or help people to prevent becoming sick, that would be a huge impact," Dr. Huard said.

"Of course, right now we are in an interesting place locally in Vail," he said. "Right now, we don't have a lot of active COVID-19 cases, and isn't that a great thing? But that also means that COVID-19 investigations like ours, which require patients, would need to wait."

But the research topic has stayed on his mind. "I think there's something there," said Dr. Huard. "I mean, we started this, and we were just thinking about osteoarthritis. Then we realized the potential impact in DMD, in cancer, other areas like neurodegeneration...as a career scientist, I'm always looking for connections, and why couldn't there be a connection to COVID-19 too?"

Senescence at SPRI

Currently, the CRSM team is working on five distinct projects involving senescence, including clinical trials and bench research. The institute also has an additional five senescence projects under full patent processing. The ultimate goal of these projects is to develop therapeutic approaches to a variety of conditions, both as treatment and preventative therapies.

"There is so much potential here," explained Dr. Huard. "I am a scientist, so of course I get enthusiastic about my research," he said. "But this work—with senescent cells—this is one of the most exciting topics I've ever investigated."

CURRENT SENESCENCE RESEARCH AT SPRI

| PROJECT TITLE | POTENTIAL IMPACT |
|---|--|
| 1. IMPROVE MUSCULOSKELETAL REGENERATION THROUGH PRE-CLINICAL AND CLINICAL TRIALS OF SENOLYTIC THERAPIES | This study will represent the first preclinical and clinical evidence testing therapeutic efficacy of a senolytic compound on preventing age-related bone and cartilage loss |
| 2. OPTIMIZE REGENERATIVE THERAPIES THROUGH PRESERVATION OF STEM CELL NICHE | This study will represent the first preclinical study testing the hypothesis that preserving the stem cell niche without expanding the cells can improve regenerative outcomes compared to expanded adipose stem cells |
| 3. DEVELOP STEM-CELL-DERIVED EXOSOME THERAPIES TO PROMOTE REGENERATION | Therapeutic exosomes have significant potential in clinical applications. These therapies will allow our scientists to test their efficacy as compared to stem cell therapies, which are much more highly regulated |
| 4. THE USE OF SENOLYTIC AND ANTI-FIBROTIC AGENTS TO IMPROVE THE BENEFICIAL EFFECT OF BONE MARROW STEM CELLS FOR OSTEOARTHRITIS | Funded by the National Institutes of Health (NIH), these clinical trials have the potential to dramatically improve osteoarthritis patient outcomes following Bone Marrow Stem Cell treatment |
| 5. DETERMINE THE EFFICACY OF SENOLYTIC TREATMENTS ON STEM CELLS | The data from this study will allow SPRI scientists to optimize the effective dose of senolytic agents for clinical trials |

SPRI AWARDED PRESTIGIOUS REGENERATIVE MEDICINE INNOVATION PROJECT GRANT FROM NATIONAL INSTITUTES OF HEALTH

Team Science and Medicine an Integral Part of Historic Grant

Since its founding, SPRI has been committed to team science and medicine, which is exemplified in the synergistic relationship between SPRI and The Steadman Clinic. This extends throughout the institute, where the distinct departments—the Center for Regenerative Sports Medicine, Department of Biomedical Engineering, Center for Outcomes-Based Orthopaedic Research and Department of Imaging Research—collaborate on many research projects every day. The institute’s clinical trials are made possible by the clinical teams and physicians at The Steadman Clinic, alongside each unique department at SPRI.

Just this May, SPRI learned that it had been awarded a prestigious grant from the National Institutes of Health (NIH). The Regenerative Medicine Innovation Project (RMIP) is a five-year, multi-million-dollar matching grant that will total \$5.8M for this research—\$2.9M from the NIH, and SPRI is required to match \$2.9M through philanthropy. A generous SPRI benefactor committed to fund a year of the match, and SPRI is hopeful that with the NIH matching the funds, more philanthropists will be inspired to become involved in this groundbreaking project.

This grant funds a multi-step clinical trial that builds from SPRI’s pioneering therapeutic and biologic research and expands upon the clinical trials currently underway from the Department of Defense. Johnny Huard, PhD, acts as the contact principal investigator and Marc J. Philippon, MD, and Scott Tashman, PhD, serve as co-principal investigators on the grant. The clinical trial will include the collaborative efforts of all of SPRI’s teams and The Steadman Clinic.

This clinical trial is designed to determine whether senolytic and/or antifibrotic agents will improve the beneficial effect of Bone Marrow Stem Cells (BMSC) for the treatment of symptomatic knee osteoarthritis (OA). The trial will include four groups, totaling 100 patients, to investigate the team’s hypotheses that the use of these agents will improve patient outcomes.

The RMIP award is a true milestone for SPRI; not only because of its size, but also because the NIH does not fund human regenerative medicine clinical trials often. It is a unique opportunity for SPRI, and receiving it validates the incredible work the institute has already achieved in bench-to-bedside research.

SPRI anticipates receiving the NIH RMIP award this summer, and the study is scheduled to begin in Fall 2020.

IF YOU ARE INTERESTED IN LEARNING MORE ABOUT THIS UNIQUE PHILANTHROPIC MATCHING GRANT, PLEASE CONTACT VP OF DEVELOPMENT LEE JONES AT LJONES@SPRIVAIL.ORG

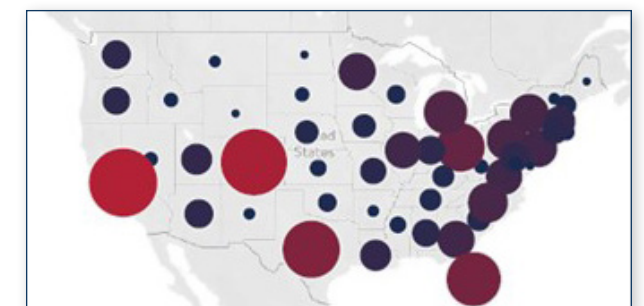
SPRI and United States Olympic and Paralympic Committee Host First-Ever Virtual Injury Prevention Symposium

4TH ANNUAL IPS REACHES 4,880 PARTICIPANTS ACROSS THE GLOBE

With the COVID-19 outbreak, SPRI and its partner, the United States Olympic and Paralympic Committee (USOPC) canceled the annual in-person conference in Vail, scheduled to be held at the end of April 2020. But soon after this cancellation, SPRI and the USOPC recognized that there was still tremendous interest in the annual conference, and SPRI quickly pivoted to create the first all-virtual web conference in under two weeks, hosted at the USOPC campus in Colorado Springs, Colorado.

SPRI’s team, including its media production department and key researchers from the Center for Outcomes-Based Orthopaedic Research (COOR), helped to assemble an outstanding conference with greater reach than they originally thought was possible. Initially hoping for 500 registrants in its first web conference, SPRI soon learned about the true level of interest in its conference—5,700 people registered for the event, with 4,880 people tuning into the all-day web conference on April 29, 2020. That’s more than an 85% participation rate from those that registered, which demonstrates the power of science and research happening in Injury Prevention today.

As in previous years, the conference featured topics on Injury Prevention and included speakers from all over the world—scientists, physicians and other experts in the space. Although SPRI was initially disappointed to not be able to host the event in-person in Vail as it has done in previous years, the institute was able to reach more people, sharing the latest in science and technology advancements in Injury Prevention Research on a global scale. Participants in this year’s digital conference spanned six continents and included at least 36 countries, as well as all 50 of the United States.



(TOP) Global heat map: The 4,880 attendees spanned six continents and at least 36 distinct nations

(BOTTOM) USA heat map: All fifty U.S. states attended the first all-virtual Injury Prevention Symposium

(BELOW) Broadcasting from the USOPC campus in Colorado Springs, the SPRI onsite team included researchers and members of the digital media and production team



A BUSY SUMMER OF TESTING KICKS OFF IN THE BIOMOTION LAB

Testing Resumed in Early June with Safer Lab Protocols

With the outbreak of COVID-19 in early March, it may have been expected that SPRI would pause most of its research; instead the institute proved that its science was essential, continuing to conduct research from its regenerative medicine and robotics labs with physical distancing and mask wearing, as well as remote data analysis from the COOR, BME and Imaging Research teams. With a ramp up in volumes at The Steadman Clinic, the Biomotion Lab has resumed its onsite testing, using new protocols to ensure that its scientists and research subjects remain safe.

New Protocols in Biomotion Lab

In order to safely continue its research projects, the Biomotion team has begun working with extra precautions including:

- Limiting the number of staff in the lab to the minimum number necessary to effectively run instrumentation
- Limiting physical contact with research participants to only one researcher
- Maintaining six feet (or more) of distance between staff and participants whenever feasible; the exception is when a researcher is required to put on or take off sensors
- Mandatory mask use for everyone in the lab, including the research participant
- Increased cleaning and sanitation measures

The team is confident that these precautions will not impact their productivity and is looking forward to a busy summer of testing in the lab. The increase in patients to The Steadman Clinic has indicated a greater need for testing this summer.

Testing for Major Projects

As testing resumes in the Biomotion Lab, the team is focused on major projects from the institute's Department of Defense (DoD) award, including testing osteoarthritis patients and those who have had an ACL repair to evaluate the efficacy of senolytic agents and biologic therapies for restoring functional movement. The team will also start the next phase of the Mobile Platform for Optimizing Warfighter Rehabilitation (MPOWR) study—a project designed to develop protocols to help return active duty personnel to duty following injury. In addition to resuming these key projects, the Biomotion Lab will test all participants of the RMIP study (page 4).

Although new testing protocols represent a change for the Biomotion team, the researchers are optimistic about a productive summer of testing and analysis for the Biomedical Engineering department.

SPRI IS CURRENTLY ENROLLING VOLUNTEERS FOR ITS CLINICAL TRIALS

For more information, please visit www.sprivail.org/about-us/clinical-trials or email clinicaltrials@sprivail.org



Taking Research Outside

In addition to its in-lab testing, the Biomotion team will continue testing subjects on the outdoor obstacle course for the MPOWR study. Testing outside will allow researchers to maintain distance and research participants will not be required to wear masks while on the course.

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REGISTRATION DEADLINE: THURSDAY, SEPTEMBER 10, 2020

FOR MORE INFORMATION CONTACT:

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