

# THE SCIENCE OF REGENERATIVE MEDICINE

## SAVE THE DATE

THURSDAY, FEBRUARY 16, 2023  
THE MAR-A-LAGO CLUB

Discover how, from the lab to the  
clinic, regenerative medicine is  
revolutionizing patient care.

2:00 pm Presentations  
5:30 pm Cocktail Reception  
with Presenters

RSVP to Emily Lepore  
[elepore@thesteadmanclinic.com](mailto:elepore@thesteadmanclinic.com)

### Featured Presenters:

**Dr. Marc Philippon**  
Managing Partner,  
The Steadman Clinic, Chair, SPRI

**Dr. Johnny Huard**  
Chief Scientific Officer, SPRI



Shear family foundation



## Chairs

**Dan Drawbaugh; Marc Philippon;  
Johnny Huard**



**THE STEADMAN CLINIC**

AND

**STEADMAN PHILIPPON RESEARCH INSTITUTE**



**UNITED STATES  
OLYMPIC & PARALYMPIC  
COMMITTEE**





**Dr. Aiping Lu, MD**  
Principal Investigator and Program Director  
of Muscle Repair & Stem Cell Biology



**Dr. Xueqin Gao, MD, PhD**  
Principal Investigator and Program  
Director of Bone & Cartilage Biology  
and Tissue Engineering



**Dr. Ping Guo, PhD**  
Principal Investigator and Program  
Director of Genetic and Cellular  
Engineering



**Dr. Naoki Nakayama, PhD**  
Principal Investigator and Program  
Director of Stem Cell Engineering and  
Cartilage Regeneration



**Dr. Chelsea Bahney, PhD**  
Principal Investigator and Program  
Director of Bone Repair &  
Regenerative Therapeutics



**Dr. Sealy Hambright, PhD**  
Principal Investigator & Program Director  
of Healthy Aging & Diagnostics



**Dan Drawbaugh**  
CEO  
Steadman Philippon  
Research Institute  
The Steadman Clinic



**Dr. Marc Philippon, MD**  
Hip Arthroscopy Pioneer 30 years of Treating Athletes  
Managing Partner, The Steadman Clinic  
Co-Chair of the Board of Directors  
Steadman Philippon Research Institute



**Dr. Johnny Huard, PhD**  
Chief Scientific Officer  
Director of Center for Regenerative & Personalized Medicine  
Steadman Philippon Research Institute  
Director of Research, Proofpoint Biologics  
The Steadman Clinic  
Affiliate Faculty, Colorado State University



**Dr. Scott Tashman, PhD**  
Principal Investigator  
Director of Biomedical Engineering and Imaging



**Dr. Lauren Watkins, PhD**  
Imaging department



**Dr. Sudheer Ravuri, PhD**  
Deputy Director  
Center for Regenerative & Personalized Medicine



**Suzanne Liv Page, JD**  
VP Operations, SPRI  
Director of Grants, Regulatory & Trials



**Mr. Grant Dornan, MS**  
Director of Center for Outcomes  
Based Orthopaedic Research and  
Chief Biostatistician



**Dr. Colin R. Smith, PhD**  
Research Scientist  
Biomedical Engineering





**Marc J. Philippon, MD**  
Managing Partner, Sports Medicine, Hip Disorders, Hip Arthroscopy



**Randy W. Viola, MD**  
Hand, Wrist, Elbow & Orthopaedic Trauma Specialist



**David C. Karli, MBA, MD**  
Spine, Sports, Rehabilitation & Regenerative Medicine Specialist



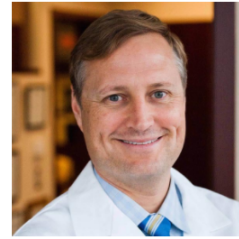
**Tom R. Hackett, MD**  
Complex Knee, Shoulder & Elbow Surgeon



**Peter J. Millett, MD, MSc**  
Shoulder, Knee, Elbow Surgery & Sports Medicine



**Thos A. Evans, MD**  
Orthopaedic Interventionalist of Spine & Joint, Regenerative Medicine Specialist & Anesthesiologist



**Matthew T. Provencher, MD**  
Complex Shoulder, Complex Knee & Sports Surgery



**Raymond H. Kim, MD**  
Adult Joint Reconstruction, Knee & Hip Arthroplasty



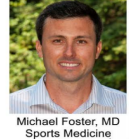
**David A. Kuppersmith, MD**  
Internal Medicine



**Joseph J. Ruzbarsky, MD**  
Shoulder, Knee, Elbow & Hip Preservation Surgery



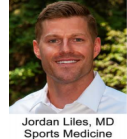
**Kent Doan, MD**  
Sports Medicine



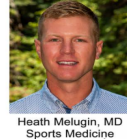
**Michael Foster, MD**  
Sports Medicine



**Toufic Jildeh, MD**  
Sports Medicine



**Jordan Liles, MD**  
Sports Medicine



**Heath Melugin, MD**  
Sports Medicine



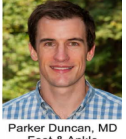
**Charles Su, MD**  
Sports Medicine



**Matthew Vopat, MD**  
Sports Medicine



**Stephen Yu, MD**  
Sports Medicine



**Parker Duncan, MD**  
Foot & Ankle



**Trevor Shelton, MD**  
Hip Preservation & Reconstruction



**DR. MICHAEL GALLIZZI, MD**  
Robotic and Endoscopic Spine Surgeon



**THE STEADMAN CLINIC**  
AND  
**STEADMAN PHILIPPON**  
RESEARCH INSTITUTE



**Dan Drawbaugh**  
CEO  
Steadman Philippon Research Institute  
The Steadman Clinic



**Dr. Marc Philippon, MD**  
Hip Arthroscopy Pioneer  
30 years of Treating Athletes  
Managing Partner, The Steadman Clinic  
Co-Chair of the Board of Directors  
Steadman Philippon Research Institute



**Dr. Johnny Huard, PhD**  
Principal Investigator  
Chief Scientific Officer  
Director of Center for Regenerative & Personalized Medicine  
Steadman Philippon Research Institute  
Director of Research, Proloport Biologics  
The Steadman Clinic  
Affiliate Faculty, Colorado State University



**U.S. OLYMPIC & PARALYMPIC**  
**NATIONAL**  
**MEDICAL CENTER**



**Dr. Tom Clanton, MD**  
Healthy Aging Physician



**Dustin Anderson, MD**  
Orthopaedic Interventionalist, Sports, Spine & Regenerative Medicine, PMQ&R and Pain Medicine



**Robert Waltz, MD**  
TSC Fellow



**Justin Ernst, MD**  
TSC Fellow



**Simon Lee, MD**  
TSC Fellow



**Hajime Utsunomiya, MD, PhD**  
International Fellow



**Yoichi Murata, MD, PhD**  
International Fellow



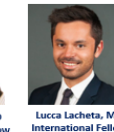
**Naomasa Fukase, MD, PhD**  
International Fellow



**Justin Arner, MD**  
TSC Fellow



**Phillip Nolte, MD**  
International Fellow



**Ingrid Stake, MD**  
International Fellow



**Luca Lacheta, MD**  
International Fellow



**Haruki Nishimura, MD, PhD**  
International Fellow



**Kohei Yamaura, MD, PhD**  
International Fellow



**Maria D. Hazra, MD**  
International Fellow



**Rony D. Hazra, MD**  
International Fellow



**Joel M. Matta, MD**  
Hip Disorders: Preservation, Replacement & Fractures



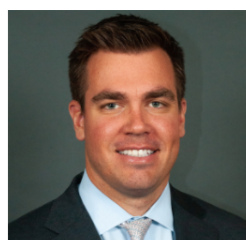
**C. Thomas Haytmanek Jr, MD**  
Foot, Ankle & Trauma Surgery



**Armando F. Vidal, MD**  
Complex Knee, Shoulder & Sports Medicine Specialist



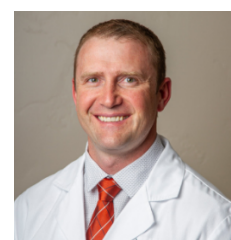
**Leslie B. Vidal, MD**  
Shoulder, Hip, Knee & Sports Medicine Specialist



**Jonathan A. Godin, MBA, MD**  
Shoulder, Knee, Hip & Sports Medicine Surgeon



**Kavi Sachar, MD**  
Hand, Wrist and Elbow Surgery



**Jared T. Lee, MD**  
Aspen Medical Director, Shoulder, Hip, Knee & Sports Medicine



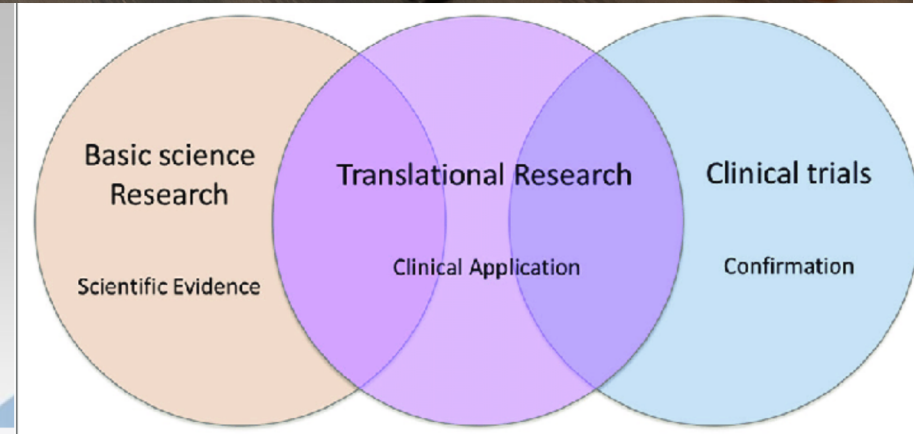
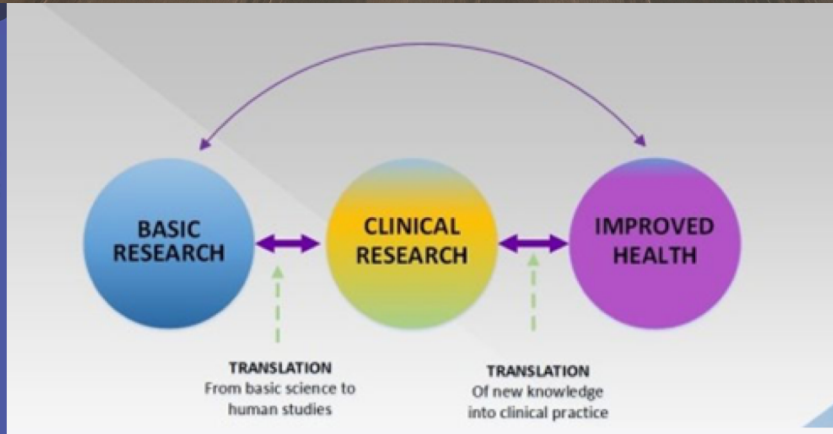
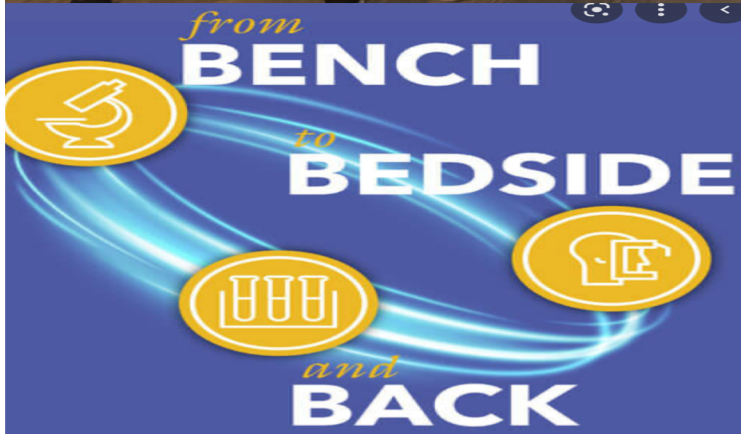
**Waqqar Khan-Farooqi, MD**  
Foot, Ankle & Trauma Surgery



**Thea Wojtkowski, MD**  
Hip Replacement & Trauma Surgery



# We are a Small team (60 members) but a Complete team for bench to bedside translation!





# SPRI Collaboration & Partnership



**Dr. Ashok Shetty**  
**Dr. Maheedhar Kodali**



**Dr. Ramesh Papanna**  
**Dr. Mikhail Kolonin**  
**Dr. Vihang Narkar**



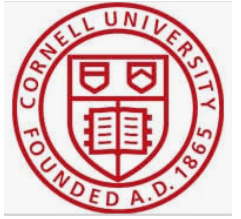
**Dr. Farshid Guilak**



**Dr. James Kirkland**  
**Dr. Chris Evans**  
**Dr. Shane Shapiro**  
**Dr. Julie Allickson**



**Dr. Patricia Hardenbergh**  
**Dr. Julie Barone**



**Dr. Yadong Wang**



Live better longer.

**Dr. Eric Verdin**  
**Dr. Herbert Kasler**  
**Dr. Akos Gerencser**



**Dr. Sylvain Cardin**



University of California  
San Francisco

**Dr. Tamara Alliston**  
**Dr. Brian Feeley**



**LINDA & MITCH HART CENTER**  
**FOR REGENERATIVE AND PERSONALIZED MEDICINE**



**Dr. Samuel Stupp**



**Dr. Michael Zuscik**



**WISCONSIN**  
UNIVERSITY OF WISCONSIN-MADISON

**Dr. William Murphy**  
**Dr. Mark Markel**



**Dr. Krishnendu Roy**



**Dr. Susan Bukata**



**Dr. Bing Wang**



**Dr. Nicole Ehrhart**  
**Dr. Lon Kendall**  
**Dr. Jeremiah Easley**  
**Dr. Kirk McGilvray**  
**Dr. Ben Gadomski**  
**Dr. Katie Sikes**  
**Dr. Stuart Tobet**  
**Dr. Kelly Santangelo**



**UNIVERSITY OF MINNESOTA**

**Dr. Paul Robbins**  
**Dr. Laura Niedernhofer**



**Dr. Bruno Peault**



**Dr. John Cooke**

UNIVERSITY OF MIAMI  
**MILLER SCHOOL**  
**of MEDICINE**

**Dr. Thomas Best**  
**Dr. Francis Hornicek**  
**Dr. Dimitrios Kouroupis**  
**Dr. Anthony Griswold**



**Dr. John Kauffman**  
**Dr. Jennifer Elliot**  
**James Miler**







# Snapshot of the SPRI footprint



**TMI-Fort  
Collins, CO**



**SPRI-Vail**



**THE STEADMAN CLINIC  
AND  
STEADMAN PHILIPPON  
RESEARCH INSTITUTE**

**Frisco  
, CO**



**Basalt/Aspen, Opening April 2022**



**THE STEADMAN CLINIC &  
STEADMAN PHILIPPON RESEARCH INSTITUTE  
BASALT**

- THREE STORIES
- 62,300 RENTABLE SQUARE FEET
- LOCATED IN WILLITS TOWN CENTER
- CONSTRUCTION OF NEW REED STREET PARK
- 80 COVERED PARKING SPACES

LEVEL 1: MRI & Parking  
LEVEL 2: Steadman Philippon Ambulatory Surgery Center  
LEVEL 3: The Steadman Clinic  
Steadman Philippon Research Institute  
Howard Head Sports Medicine



**Edwards, CO**





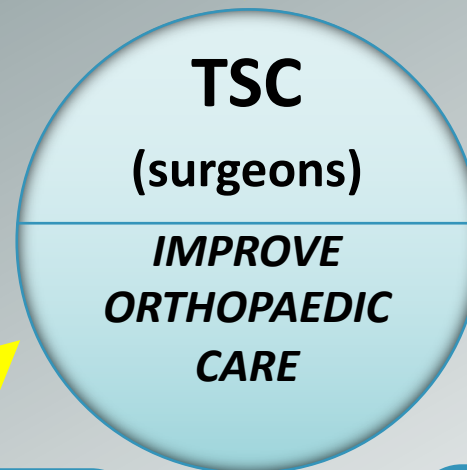
### Regenerative Medicine

- Biomarker assessment
- Strategies for advanced healing & tissue regeneration
- Blocking fibrosis
- Reducing inflammation
- Promoting angiogenesis



### Imaging/MRI

- Assessing tissue structure
- Monitoring healing and/or degeneration



### Biomotion

- Whole-body performance
- In vivo joint & tissue function

### Biomechanics/Robotics

- Understanding anatomy
- Evaluating procedures/devices

### Clinical Outcomes

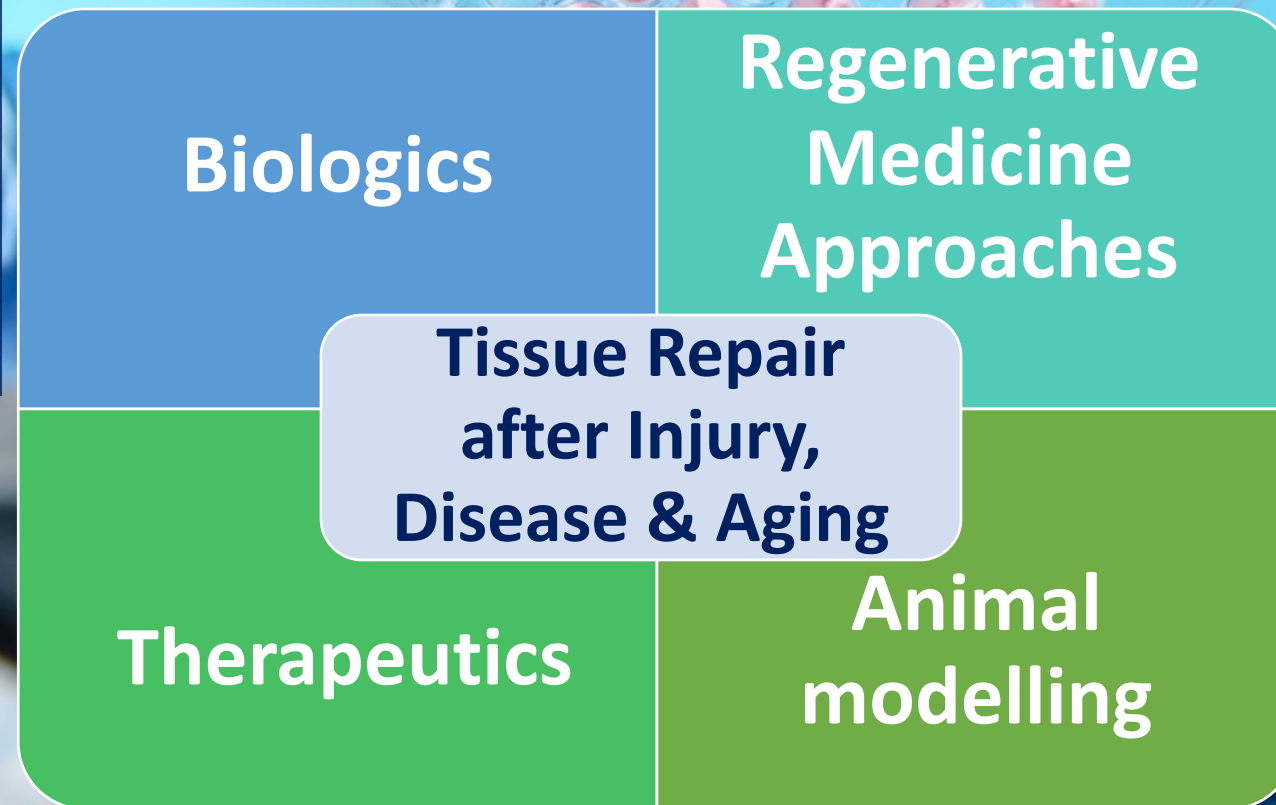
- Patient-focused outcomes assessment



# SPRI's Regenerative & Translational Medicine Program

- Adult stem cells
  - Muscle stem cells
  - Adipose stem cells
  - Bursa stem cells
  - PDGFR+ cells
  - IPS cells
- OrthoBiologics
  - Platelet-Rich Plasma
  - Bone Marrow Concentrate

- FDA-approved drugs
- Telomerase activity
- Senolytic drugs
- Senomorphic drugs
- mTOR inhibitors
  - Rapamycin
  - Metformin
- Anti-fibrotic agent
- Anti-angiogenic agent
- Epigenetic drugs



- Gene therapy
- CRISPR-CAS9 gene editing technology
- Exosomes/vesicles
- Coacervate
- Microspheres
- PA nanofibers
- Magnetic nanoparticles

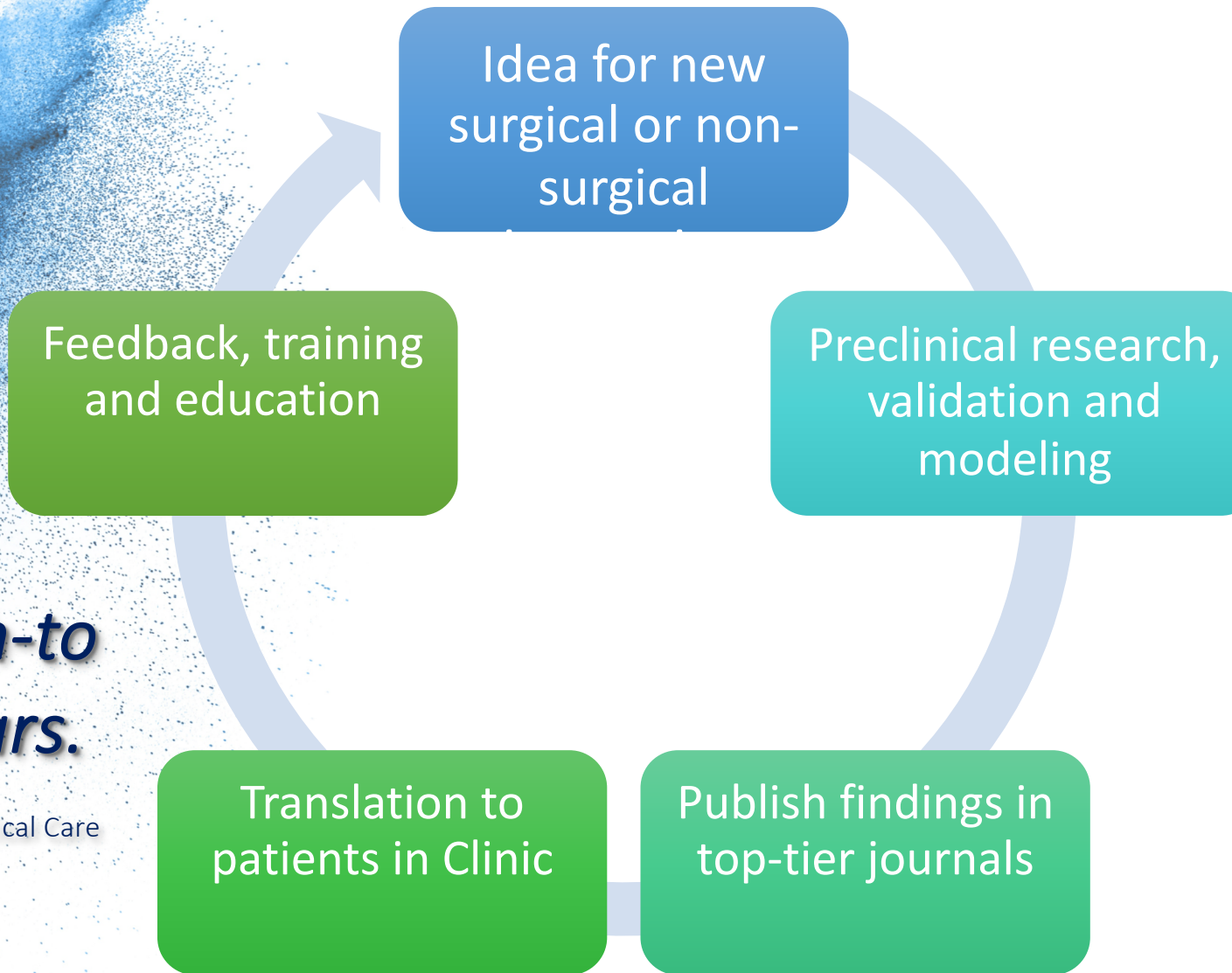
- Dystrophic mice
  - Mdx, dKO
- Progeria mice
  - Z24, ERCC mice
- Wild-type mice
- Parabiosis/Pregnancy
- Super-healer (MRL/MpJ)
- Microfracture
- Osteoarthritis model
- Ligament reconstruction



With a bench-to-bedside focus, SPRI has historically aimed to discover and validate treatments as quickly as possible

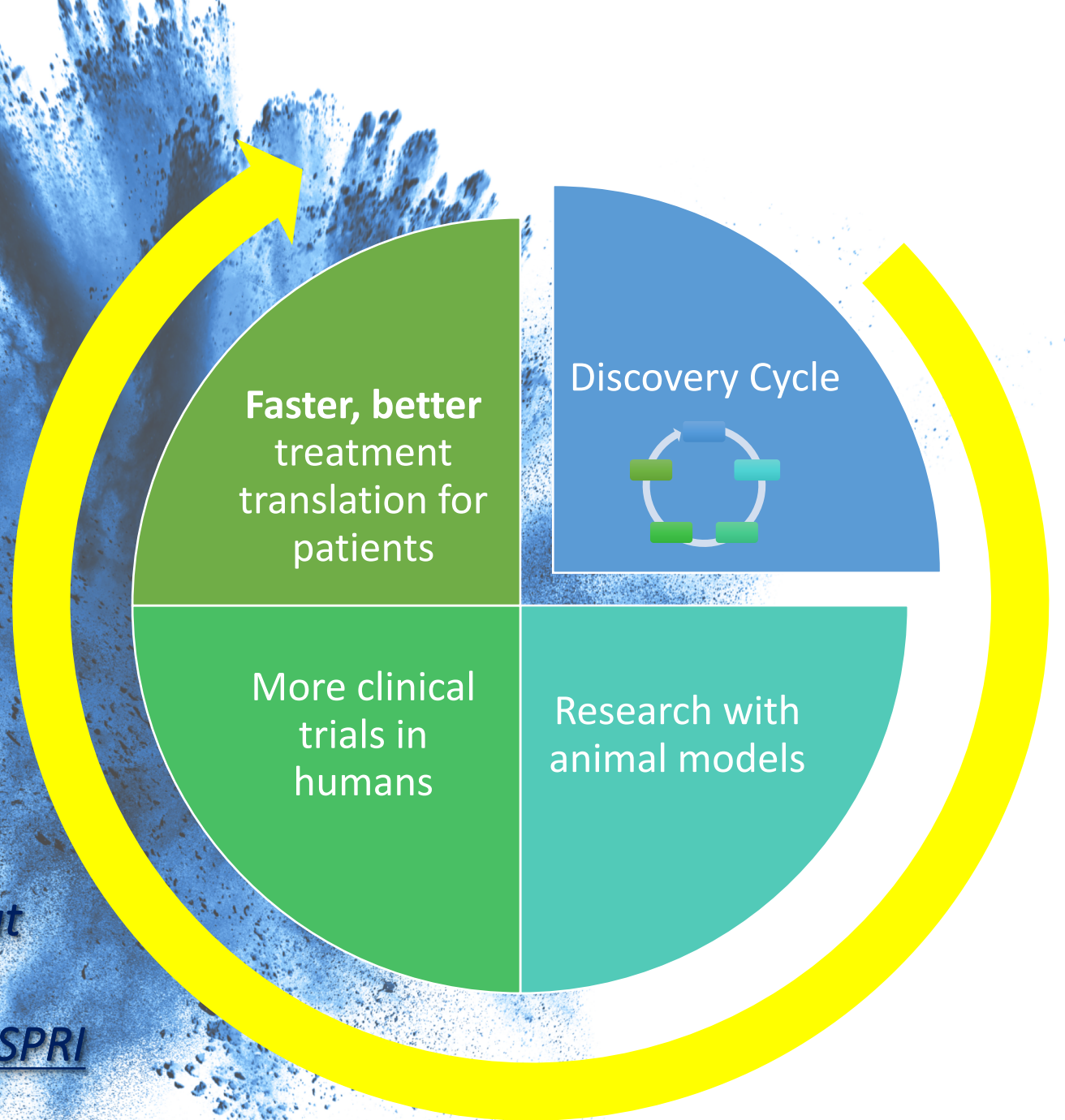
*\*Yet the average research-to practice-gap is still 17 years.*

Source: American Journal of Critical Care





But our research will be expanded and accelerated with a multidisciplinary team that include physicians and scientists working together on a daily basis!



*\*DR. Huard's Team had:*

- *3 clinical trials after 20 years of work at PITT/UPMC;*
- *5 clinical trials after 4 years of work at SPRI*



# Implications of Seed Money to Greater Results

Philanthropy

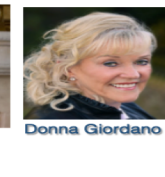
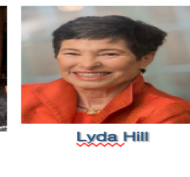
## Seed Money for New Projects



## To Obtain Federally Funded Grant Awards:



Philanthropy



**DOD # N00014-18-RFI-0014 (Huard PI) 08/08/2019 - 12/30/2022. Office of Naval Research Request for Information (RFI) # N00014-18-RFI-0014. Response to the Treatment of Poly-Traumatic Injuries Using Orthobiologics, anti-fibrotic (Losartan) and senolytic agents (Fisetin).** All the projects comprising in this proposal adapt a cross-disciplinary approach aimed at optimizing orthobiologic therapies for the treatment of joint injuries, with the ultimate goal of improving rates for return-to-duty and preserving long-term joint health and function.



**NIH 4UH3AR077748-02 (Huard PI) 08/11/2021 - 07/31/2025. The Use of Senolytic and Anti-Fibrotic Agents to Improve the Beneficial Effect of Bone Marrow Stem Cells for Osteoarthritis.**



**NIH Administrative supplement. PA-20-227. 07/01/2021 - 07/31/2022. Administrative Supplement for Research on Dietary Supplements. (Huard PI). Changes in senescent cells and SASP from bone marrow, synovial fluid, and peripheral blood after senolytic treatment.**



**DOD BAA # N00014-21-2716 (Huard PI) 08/20/2021-08/19/2024. The Use of a Senolytic Agent to Improve the Benefit of Platelet-Rich Plasma and Losartan for Treatment of Femoroacetabular Impingement and Labral Tear: A Pilot Study.** The long-term goal of this grant proposal is, therefore, to evaluate a currently available senolytic treatment for increasing the beneficial effect of PRP/losartan when used in conjunction with surgical treatment of FAI and labral tear.



**NIH 1R21 AR079075-01A1. (Huard PI, Nakayama N and Guilak F, Co-PI). 09/01/21 - 8/30/24. SMART stem cells that autonomously down-modulate TGF-β signaling for Articular Cartilage Repair has completed the first phase of peer review.**

**NIH R21 AR072870-01 (Huard PI, Guilak F, Co-PI). 02/27/2018 - 01/31/2021. Muscle Stem Cells Reprogrammed Through Genome Engineering for Autonomously Regulated Anti-Fibrotic Therapy.**



**Department of Defense (DoD) W81XWH18SBAA1 (Huard PI) 09/01/2022 - 08/31/2024.** The goal of this proposal is to develop the advanced tools for characterizing cellular senescence and its relationships to human biophysical health and performance with implications for military medicine.



**State of Colorado Collaborative Infrastructure award through the Advanced Industries Accelerator Program (Huard PI). 06/15/2022 - 05/31/2025.** The goal of this proposal is to develop the approaches to optimize stem cell banking.



Dr. Bahney is awarded her first NIH grant, **Therapeutic Application of Painless NGF to Accelerate Fracture Repair.**







## Basic & Preclinical Research

**NIH 4UH3AR07748-02:** The Use of Senolytic and Anti-Fibrotic Agents to Improve the Beneficial Effect of Bone Marrow Stem Cells for Osteoarthritis.

**DOD # N00014-18-RFI-0014:** Office of Naval Research Request for Information (RFI) # N00014-18-RFI-0014. Response to the Treatment of Poly-Traumatic Injuries Using Orthobiologics, anti-fibrotic (Losartan) and senolytic agents (Fisetin).

**DOD BAA # N00014-21-2716:** The Use of a Senolytic Agent to Improve the Benefit of Platelet-Rich Plasma and Losartan for Treatment of Femoroacetabular Impingement and Labral Tear: A Pilot Study.

**NIH 1R01AR077045-01A1:** Articular cartilage tissue engineering with human pluripotent stem cells. The goal of this project is to understand mechanisms of AC formation leading to a novel therapeutic method for joint cartilage repair.

**NIH 1R21AR075997-01:** Development of biological approaches to enhance skeletal muscle rehabilitation after anterior cruciate ligament injury.

**NIH 1R21AR074132-01A1:** Ablation of Non-Myogenic Progenitor Cells as a New Therapeutic Approach to Duchenne Muscular Dystrophy. The goal of this proposal is to test if genetic ablation of proliferating MSCs suppresses DMD progression and also to test if pharmacological ablation of adipose-derived MSCs suppresses DMD progression.

**NIH Administrative supplement. PA-20-227:** Administrative Supplement for Research on Dietary Supplements. Changes in senescent cells and SASP from bone marrow, synovial fluid, and peripheral blood after senolytic treatment. This administrative supplement is with a concurrent clinical trial (NIAMS UG3/UH3 AR077748-01 RMIP).

**NIH 1R21 AR079075-01A1:** SMART stem cells that autonomously down-modulate TFG- $\beta$  signaling for Articular Cartilage Repair.

**NIH: Therapeutic Application of Painless NGF to Accelerate Fracture Repair.**

**State of Colorado Collaborative Infrastructure award** through the Advanced Industries Accelerator Program: The goal of this proposal is to develop the approaches to optimize stem cell banking.

**Department of Defense (DoD) W81XWH18SBAA1:** The goal of this proposal is to develop the advanced tools for characterizing cellular senescence and its relationships to human biophysical health and performance with implications for military medicine.

**DOD 2019 PROJECT 1:** PROSPECTIVE EVALUATION OF PLATELET-RICH PLASMA AND BONE MARROW CONCENTRATE TREATMENT TO ACCELERATE HEALING AFTER ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION.

**RETROSPECTIVE DESIGN:** THE PURPOSE OF THE STUDY IS TO COMPARE THE QUALITY OF CARTILAGE HEALING AFTER HIP MICROFRACTURE PERFORMED DURING HIP ARTHROSCOPY SURGERY BETWEEN PATIENTS WHO TOOK LOSARTAN FOLLOWING SURGERY AND THOSE WHO DID NOT.

**DOD 2019 PROJECT 3:** SENOLYTIC DRUGS ATTENUATE OSTEOARTHRITIS-RELATED ARTICULAR CARTILAGE DEGENERATION: A CLINICAL TRIAL.

**The Use of Senolytic and Anti-Fibrotic Agents to Improve the Beneficial Effect of Bone Marrow Stem Cells for Osteoarthritis**

**DOD 2020:** THE USE OF SENOLYTIC AND ANTI-FIBROTIC AGENTS TO IMPROVE THE BENEFIT OF PLATELET-RICH PLASMA DURING HIP ARTHROSCOPY FOR TREATMENT OF FEMOROACETABULAR IMPINGEMENT & LABRAL TEAR

**DOD 2022:** THE GOAL OF THIS PROPOSAL IS TO DEVELOP THE ADVANCED TOOLS FOR CHARACTERIZING CELLULAR SENESCENCE AND ITS RELATIONSHIPS TO HUMAN BIOPHYSICAL HEALTH AND PERFORMANCE WITH IMPLICATIONS FOR MILITARY MEDICINE.

## Clinical Research & Application

**PRINCIPAL INVESTIGATORS:** JOHNNY HUARD, PHD, PETER MILLETT, MD, MATT PROVENCHER, MD, ARMANDO VIDAL, MD, LESLIE VIDAL, MD, JON GODIN, MD, SCOTT TASHMAN, PHD.

**PRINCIPAL INVESTIGATORS:** JOHNNY HUARD, PHD, MARC PHILIPPON, MD.

**PRINCIPAL INVESTIGATORS:** JOHNNY HUARD, PHD, MARC PHILIPPON, MD, PETER MILLETT, MD, MATT PROVENCHER, MD, ARMANDO VIDAL, MD, LESLIE VIDAL, MD, JON GODIN, MD, SCOTT TASHMAN, PHD.

**PRINCIPAL INVESTIGATORS:** JOHNNY HUARD, PHD, MARC PHILIPPON, MD, PETER MILLETT, MD, MATT PROVENCHER, MD, LESLIE VIDAL, MD, ARMANDO VIDAL, MD, JON GODIN, MD, SCOTT TASHMAN, PHD.

**PRINCIPAL INVESTIGATORS:** JOHNNY HUARD, PHD, MARC PHILIPPON, MD.

**PRINCIPAL INVESTIGATORS:** JOHNNY HUARD, PHD, MARC PHILIPPON, MD.



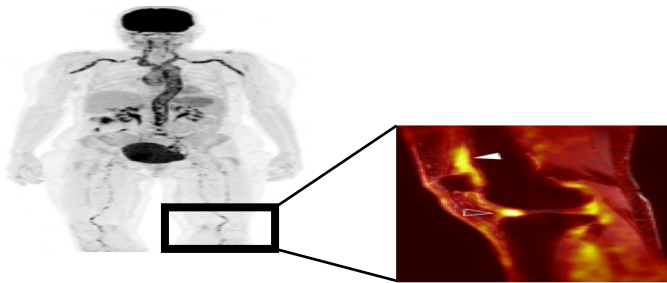


Where we have been & where we are going



# New 2023 initiatives at SPRI

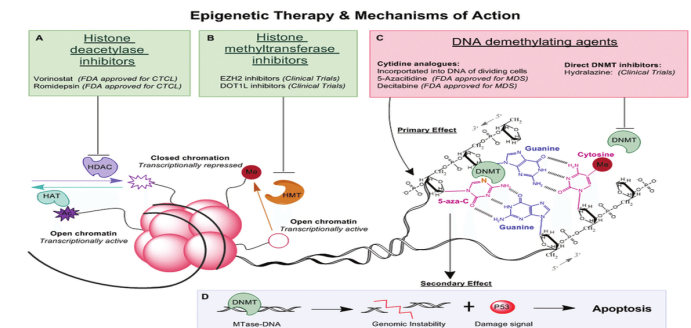
## Healthy Aging program Imaging cellular Senescence



## Stem Cell Banking Program



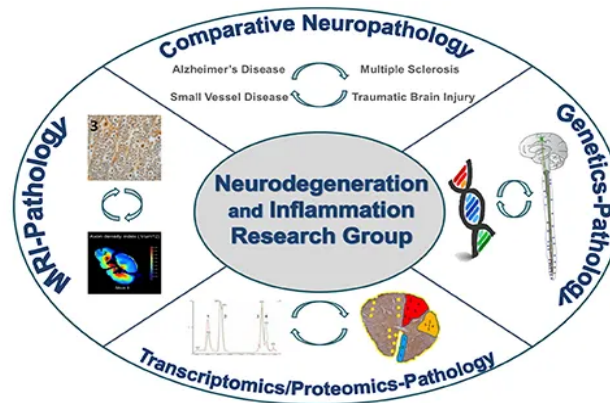
## Epigenetic Therapeutics for Healthy Aging



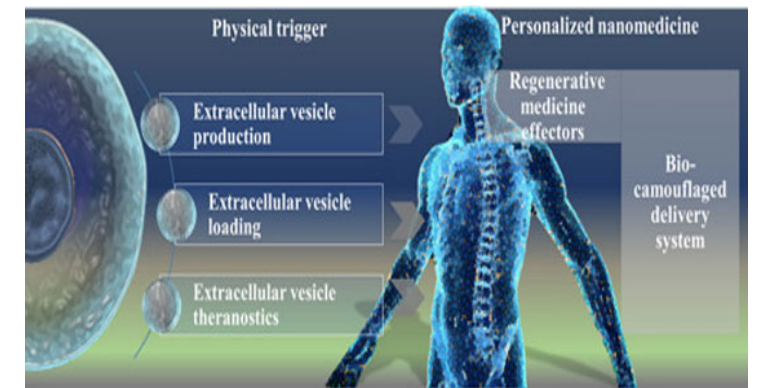
## Shaw Cancer Research



## Neurodegeneration Research



## Exosomes Therapeutics



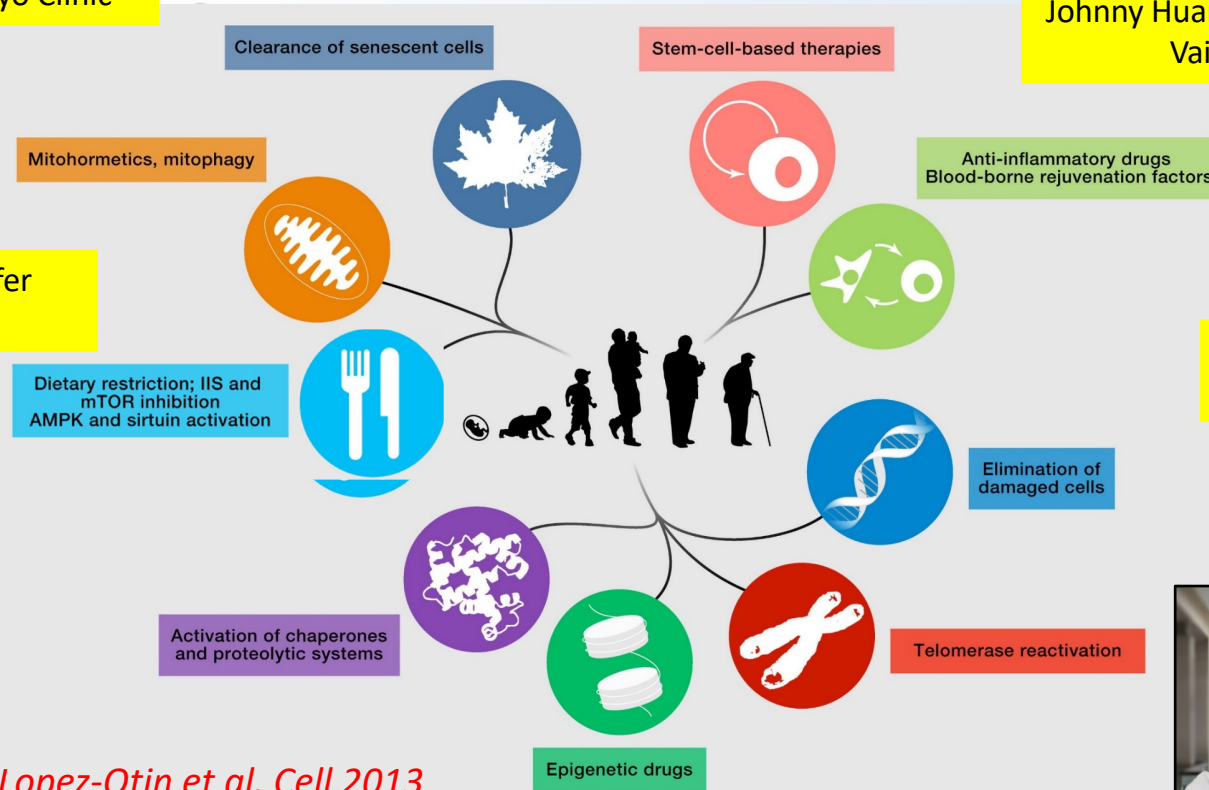




James Kirkland  
Mayo Clinic

# Healthy Aging Program

## The Hallmarks of Aging



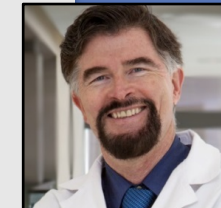
*Lopez-Otin et al. Cell 2013*



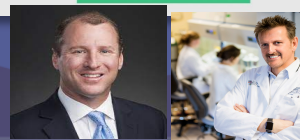
Johnny Huard & Marc Philippon  
Vail, Colorado



Paul Robbins  
U. Minnesota



John Cooke  
Methodist Inst. Houston



Peter Millett, Johnny Huard,  
Crown Family



Eric Verdin  
Buck Institute



Tamara Alliston  
UCSF



Laura Niedernhofer  
U. Minnesota

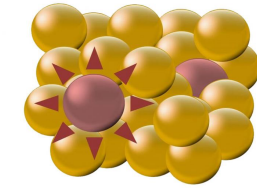
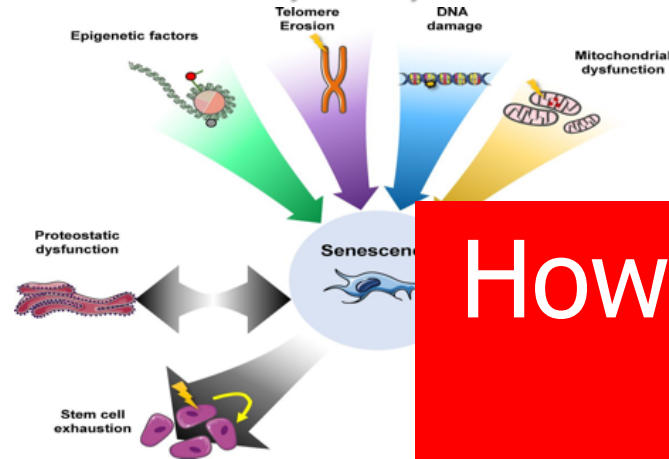




# Clearing Senescent Cells to Delay Age-Related Diseases and Conditions

- SENOLYTICS OVERVIEW -

James L. Kirkland, M.D., Ph.D.



SENOLYTICS:  
Removing  
senescent cells

How many senescent cells you have in your body?

Rapamycin

ib

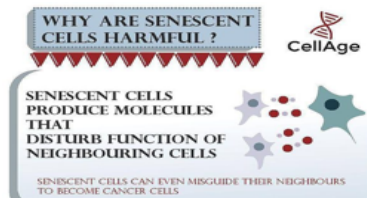
in

mycin (17-D)

in



Cancer



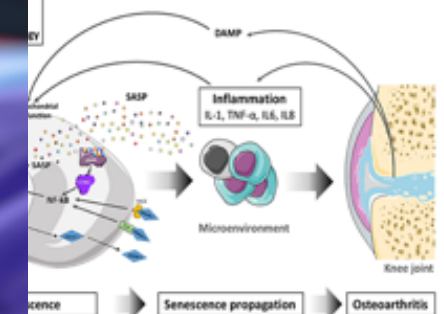
Leading Edge  
Review

Cellular Senescence in Cancer and Aging

Manuel Collado,<sup>1</sup> Maria A. Blasco,<sup>1</sup> and Manuel Serrano<sup>1\*</sup>  
<sup>1</sup>Spanish National Cancer Research Center (CNIO), Madrid, Spain  
\*Correspondence: mserrano@cnio.es  
DOI: 10.1016/j.cell.2007.07.003



Osteoarthritis



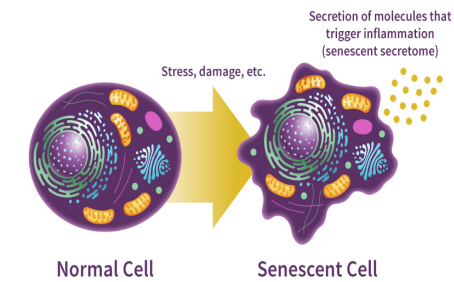
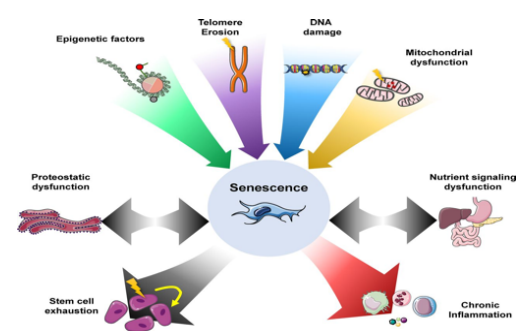
Journal of Clinical Investigation

Senescence and osteoarthritis: a painful connection

Judith Campisi, Jennifer H. Elisseeff

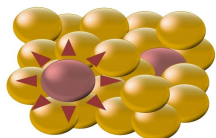
2012;123:1237. <https://doi.org/10.1172/JCI95147>.



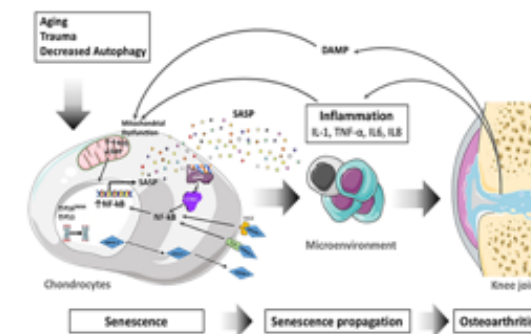


- Senescent cells (identified by C12FDG and CD87) increased with Age
  - **We have performed total 636 senescence profiling tests since 2019 to date.**
- Increased of Senescent cells correlate with increase biomarkers of inflammation, pain and osteoarthritis
- Senescent cells is significantly elevated in OA patients versus control
- Senescent cells is significantly elevated in OA patients with pain versus OA patients (asymptomatic, no pain)
- Fisetin can reduce senescent cells in all patients tested

#### - SENOLYTICS OVERVIEW -



SENOLYTICS:  
Removing  
senescent cells



## TITLE

**Detection of senescent peripheral blood mononuclear cells using C<sub>12</sub>FDG predicts chronological age and osteoarthritis**

## AUTHOR

William S. Hambright<sup>1</sup>, Victoria Duke<sup>1</sup>, Charles Huard<sup>1</sup>, Alex Goff<sup>1</sup>, Heidi Kloser<sup>1,2</sup>, Adam Goff<sup>1</sup>, Xueqin Gao<sup>1</sup>, Ping Guo<sup>1</sup>, Aiping Lu<sup>1</sup>, John Mitchell<sup>1</sup>, Michael Mullen<sup>1</sup>, Charles Su<sup>1</sup>, Tamara Tchkonja<sup>3</sup>, Jair. M. Espindola Netto<sup>3</sup>, James L. Kirkland<sup>3,4</sup>, Chelsea Bahney<sup>1,5</sup>, Marc Philippon<sup>1</sup>, and Johnny Huard<sup>1</sup>

## AFFILIATIONS

<sup>1</sup>Steadman Philippon Research Institute, Center for Regenerative Sports Medicine, 181 W. Meadow Dr., Vail, CO

<sup>2</sup>Department of Microbiology Immunology, and Pathology, Colorado State University, 225 Scott Bioengineering Building, Fort Collins, CO 80523

<sup>3</sup>Department of Physiology and Biomedical Engineering, Mayo Clinic, 200 First Street, S.W., Rochester, MN 55905

<sup>4</sup>Division of General Internal Medicine, Department of Medicine, Mayo Clinic, 200 First Street, S.W., Rochester, MN 55905

<sup>5</sup>University of California San Francisco, Orthopaedic Trauma Institute, 1500 Owens Street, San Francisco CA 94158

## \*Correspondence

Johnny Huard, PhD  
Chief Scientific Officer  
Director: Center for Regenerative Sports Medicine  
Steadman Philippon Research Institute  
Phone: 970-479-9797  
[jhuard@sprivail.org](mailto:jhuard@sprivail.org)



Research reported in this publication was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) of the National Institutes of Health (NIH) under Award Number UH3AR077748 (Huard). Major philanthropic support to the institute and this study were provided by the Shear Family Foundation



# Epigenetic, a new tool for regenerative medicine

## Reprogramming



> [Nature](#). 2020 Dec;588(7836):124-129. doi: 10.1038/s41586-020-2975-4. Epub 2020 Dec 2.

### Reprogramming to recover youthful epigenetic information and restore vision

Yuancheng Lu <sup>1</sup>, Benedikt Brommer <sup># 2 3</sup>, Xiao Tian <sup># 1</sup>, Anitha Krishnan <sup># 3 4</sup>, Margarita Meer <sup># 5 6</sup>, Chen Wang <sup>2 3</sup>, Daniel L Vera <sup>1</sup>, Qiurui Zeng <sup>1</sup>, Doudou Yu <sup>1</sup>, Michael S Bonkowski <sup>1</sup>, Jae-Hyun Yang <sup>1</sup>, Songlin Zhou <sup>2 3</sup>, Emma M Hoffmann <sup>3 4</sup>, Margarete M Karg <sup>3 4</sup>, Michael B Schultz <sup>1</sup>, Alice E Kane <sup>1</sup>, Noah Davidsohn <sup>7</sup>, Ekaterina Korobkina <sup>3 4</sup>, Karolina Chwalek <sup>1</sup>, Luis A Rajman <sup>1</sup>, George M Church <sup>7</sup>, Konrad Hochedlinger <sup>8</sup>, Vadim N Gladyshev <sup>5</sup>, Steve Horvath <sup>9</sup>, Morgan E Levine <sup>6</sup>, Meredith S Gregory-Ksander <sup>3 4</sup>, Bruce R Ksander <sup>3 4</sup>, Zhigang He <sup>2 3</sup>, David A Sinclair <sup>10 11</sup>

Affiliations + expand

PMID: 33268865 PMCID: [PMC7752134](#) DOI: [10.1038/s41586-020-2975-4](#)

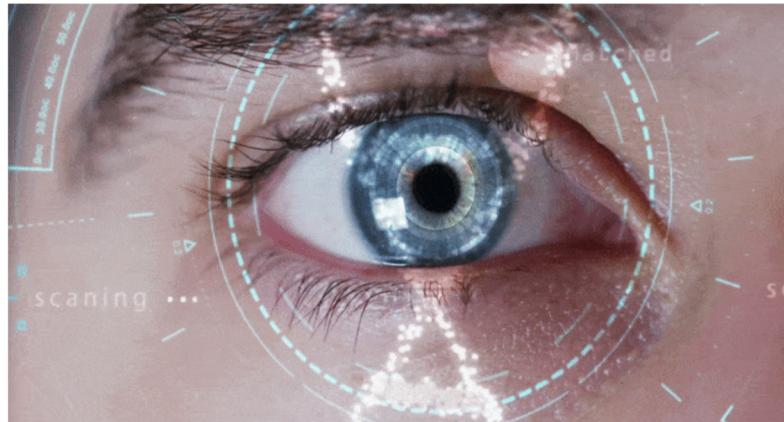
### Scientists Reverse the Aging Clock: Restore Age-Related Vision Loss Through Epigenetic Reprogramming

**TOPICS:** Aging Cell Biology Genetics Harvard Medical School Popular Vision

OPEN

Worst Habit For Memory Loss

By HARVARD MEDICAL SCHOOL DECEMBER 2, 2020



[nature](#) > [news](#) > [article](#)

NEWS | 02 December 2020

### Reversal of biological clock restores vision in old mice

'Reprogramming' approach seems to make old cells young again.

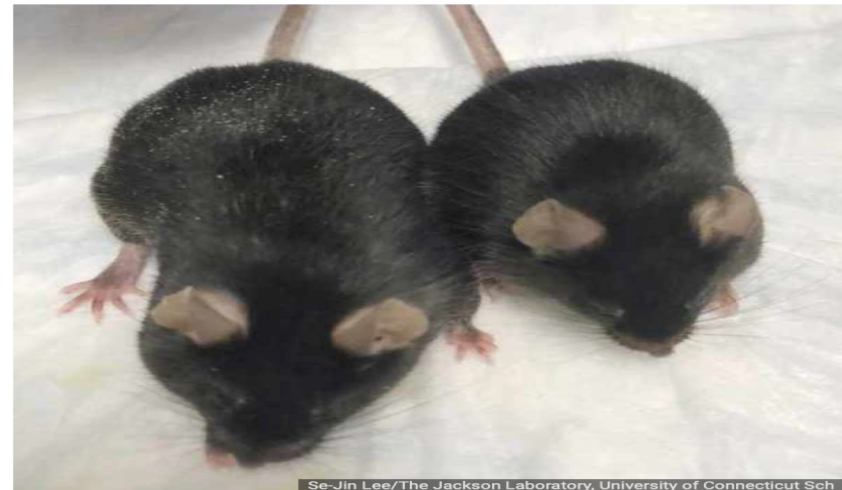
[Heidi Ledford](#)



Mice with retinal-nerve damage can have their vision restored through cell reprogramming. Credit: Qilai Shen/Bloomberg/Getty

### Reversal of Biological Clock Restores Vision in Old Mice

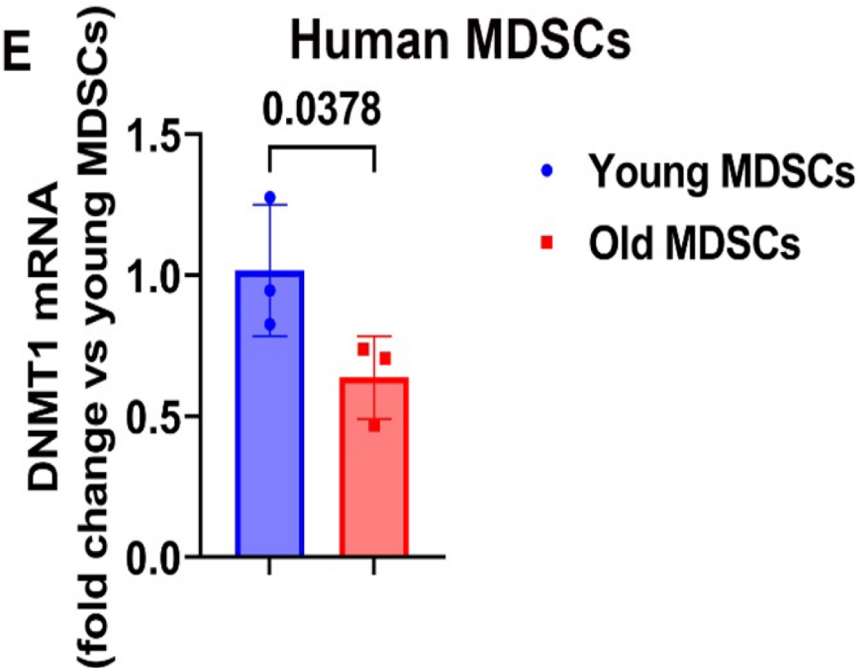
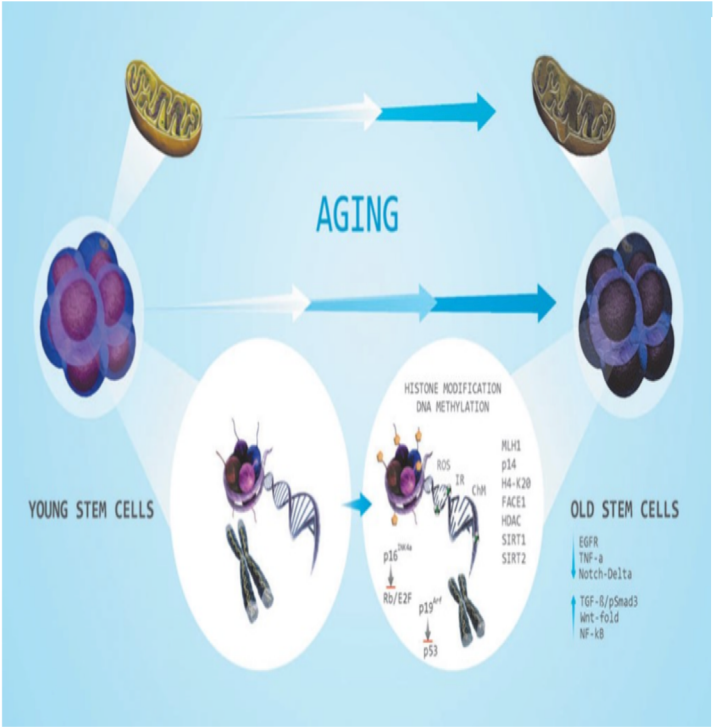
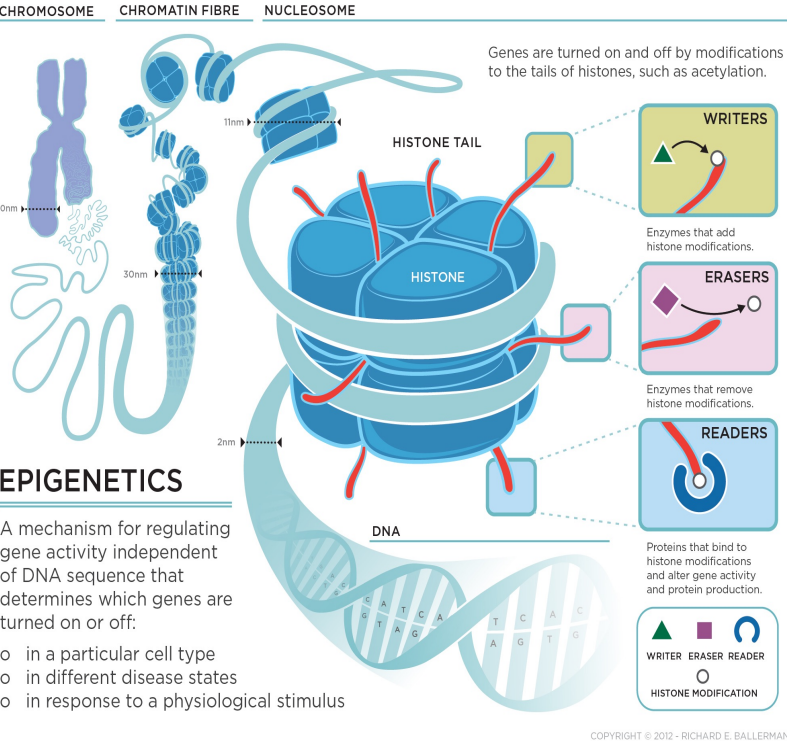
Heidi Ledford [Nature News](#) December 3, 2020



Se-Jin Lee/The Jackson Laboratory, University of Connecticut Sch

Epigenetics is the study of how your behaviors and environment can cause changes that affect the way your genes work.

Funded by the Crown Family



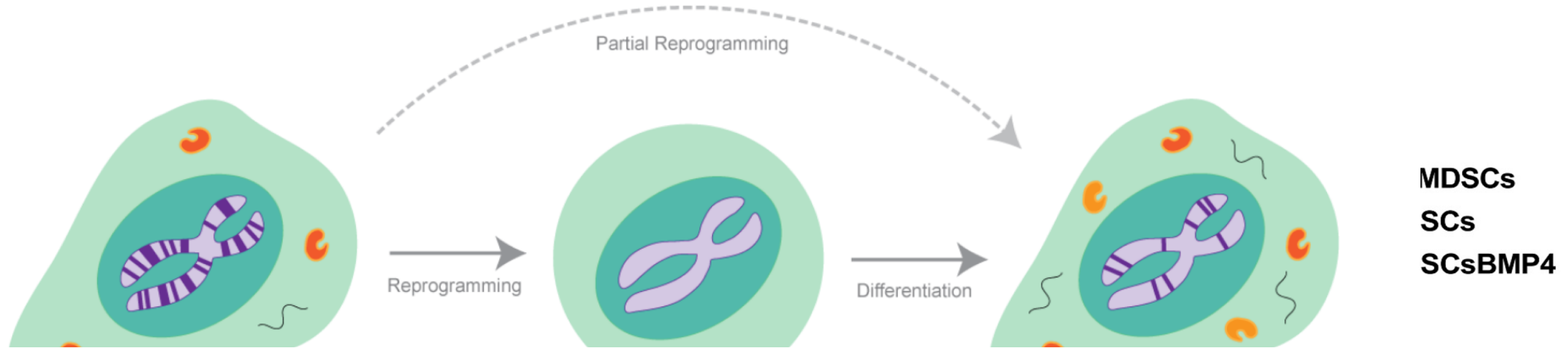
Dnmt1 is the most prevalent DNA methyltransferase that maintains genomic methylation stability and loss of Dnmt1 lead to aging



# Epigenetic drug BMP4 can reverse the loss of DnmT1 & HDAC6 and rejuvenate old stem cells

## Funded by the Crown family

(Dnmt1) is methyltransferase  
genomic methylation  
loss of Dnmt1



Epigenetic drugs to reverse cellular senescence (Azacitidine, Decitabine, Vorinostat, Romidepsin, Panobinostat, Belinostat)

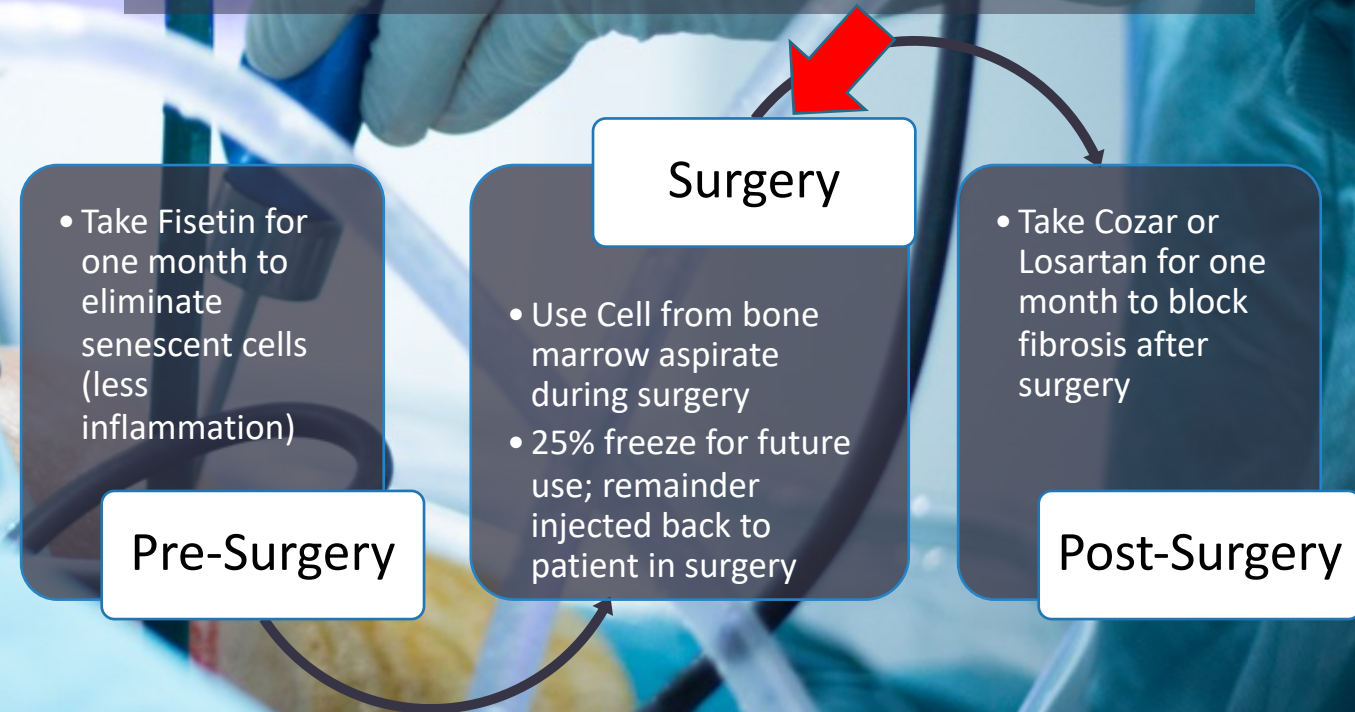


A key initiative of the regenerative medicine laboratory, in coordination with our ongoing clinical trials, is to optimize surgery

We've already begun investigating how supplements like Fisetin may enhance outcomes

Now Dr. Huard and Dr. Philippon are looking at updating protocols to further optimize surgery

## Proposed Optimization Protocol

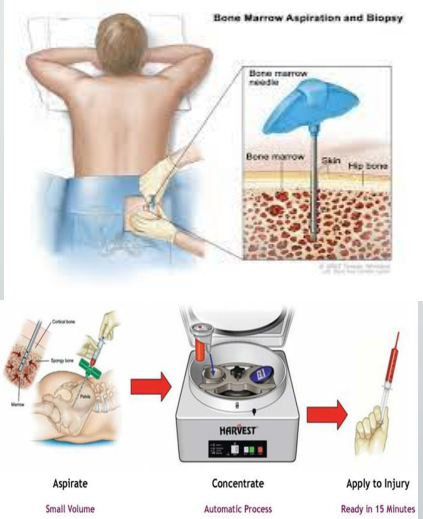




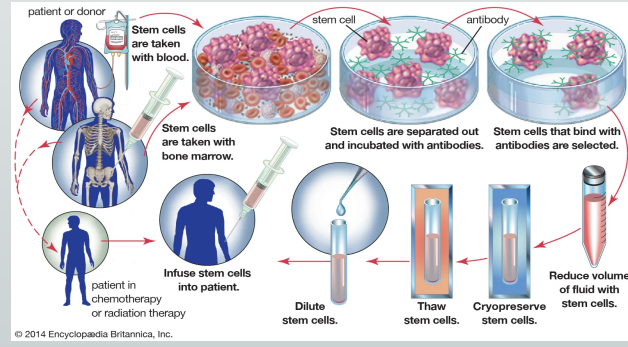
Our research team was recently awarded a \$1.5M Stem Cell Banking Project from the State of Colorado's Advanced Industries (AI) Accelerator Program Award

CO

**STEM CELL BANKING  
OR STEM CELL  
PRESERVATION**  
IS A SAFETY NET FOR YOUR  
**BABY & THE  
ENTIRE FAMILY**



120 ml of bone marrow  
is centrifugated to a  
final volume of 9-10 ml.  
**All of it is injected**



Hematopoietic stem cell injection for reconstitute the bone marrow of leukemia patients

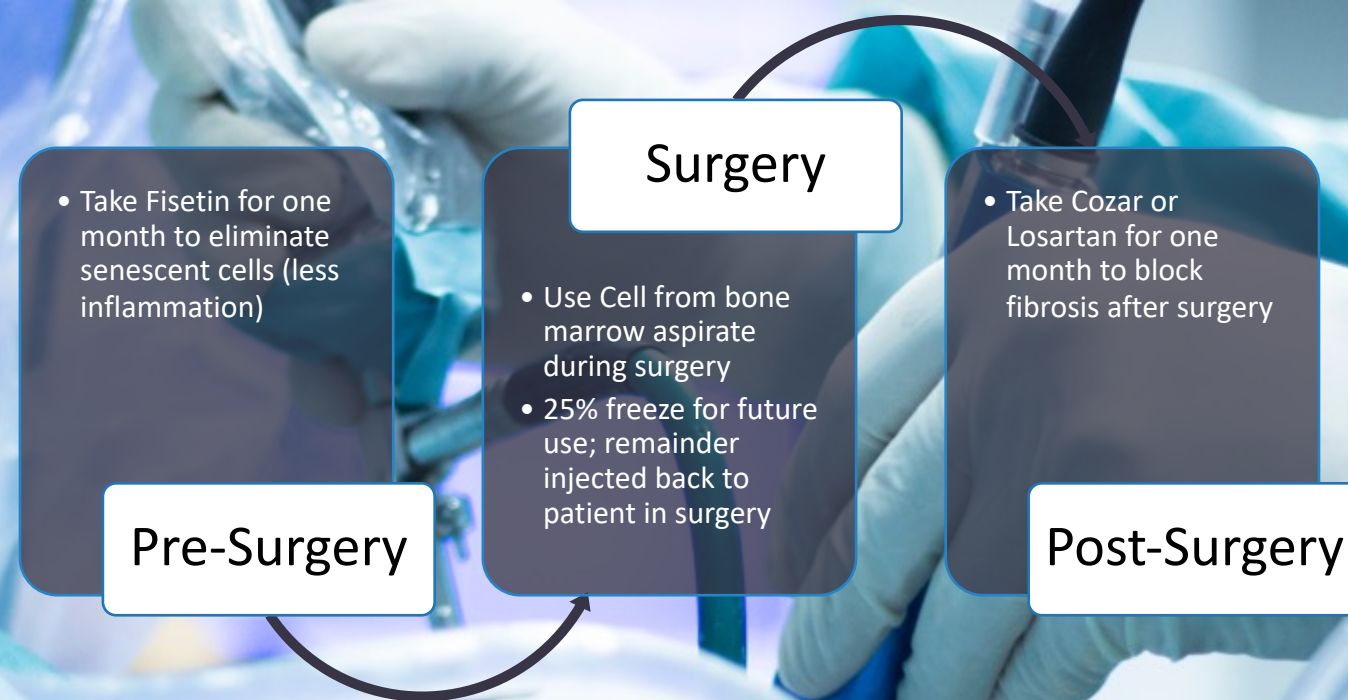
**6-20 millions cells is needed to  
reconstitute the bone marrow (1.7L) of  
leukemia patients**

***We could do over 20 injections with a single  
bone marrow harvest***

***So why not freezing a few samples for  
subsequent injections!***







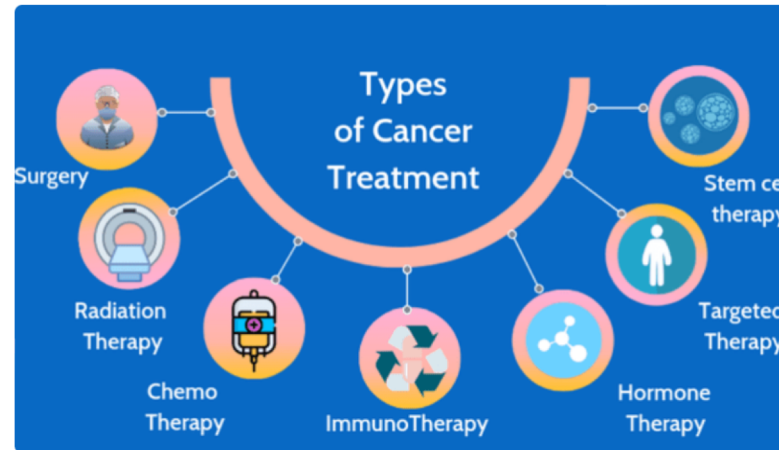
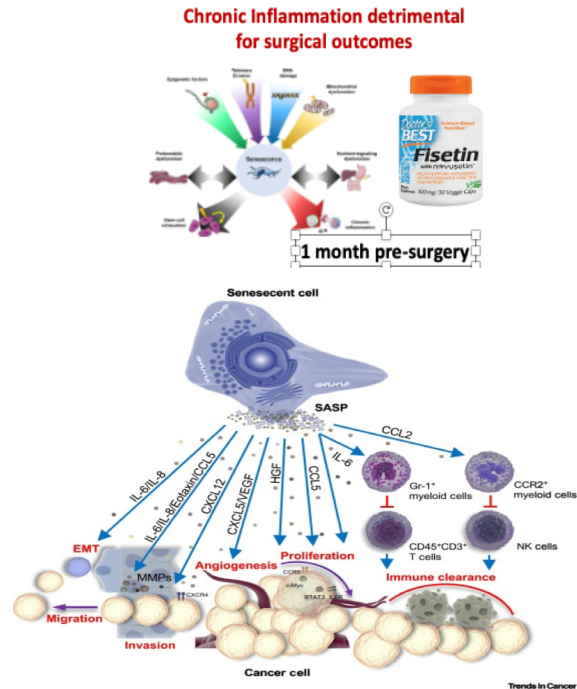
These new protocols put the patient at the center—looking at ways to provide the best possible outcomes before, during and after surgery

These new initiatives are already being studied with our Regenerative Medicine Innovation Project (RMIP) clinical trial, with plans to add the banking component in the future—a transformative approach to patient recovery

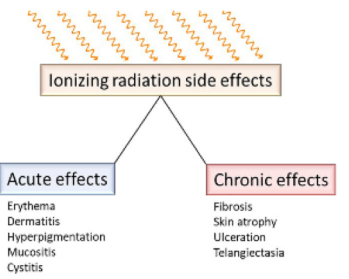


# Optimization Surgical Protocol can also Help Cancer Patients

Reducing senescent cells and inflammation prior surgery



Scar tissue, a major problem for recovery after surgery



**Fig. 1.** Acute and chronic toxic effects of radiation. Acute or short-term side effects of radiation exposure occur in skin shortly after the radiations and resolve in a relatively short duration. Late or chronic side effects appear relatively slowly, ranging from months to years post radiation exposure, and are long lasting and difficult to treat, thus exerting a treatment dose limitation effect.

## Hormesis and synergy: pathways and mechanisms of quercetin in cancer prevention and management

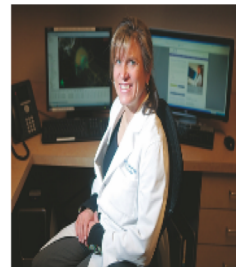
Ashley J Vargas, Randy Burd

Nutrition Reviews, Volume 68, Issue 7, 1 July 2010, Pages 418–428,  
<https://doi.org/10.1111/j.1753-4887.2010.00301.x>  
 Published: 01 July 2010

PDF Split View Cite Permissions Share

### Abstract

Quercetin is a unique dietary polyphenol because it can exert biphasic dose-responses on cells depending on its concentration. Cancer preventative effects of quercetin are observed at concentrations of approximately 1–40  $\mu$ M and are likely mediated by quercetin's antioxidant properties. Pro-oxidant effects are present at cellular concentrations of 40–100  $\mu$ M. However, at higher concentrations, many novel pathways in addition to ROS contribute to its effects. The potent bioactivity of quercetin has led to vigorous study of this compound and revealed numerous pathways that could interact synergistically to prevent or treat cancer. The effect of intake and concentration on emerging pathways and how they may interact are discussed in this review.



Patricia Hardenbergh, MD



**Dr. Patricia Hardenbergh**  
 Medical Director of  
 Shaw Cancer  
 Center



**Research collaboration between SPRI  
 and the Shaw Cancer Center**



## Radiation-induced skin fibrosis after treatment of breast cancer: profilometric analysis

J. F. Bourgeois, S. Gourgou, A. Kramar, J. M. Lagarde, Y. Gall, B. Guillot

First published: 20 January 2003 | <https://doi.org/10.1034/j.1600-0846.2003.00357.x> | Citations: 14

B Guillot  
 Service de Dermatologie  
 Hôpital Saint-Elou  
 F 34295 Montpellier Cedex 5  
 France  
 Tel: (33) 4 67 33 69 06  
 Fax: (33) 4 67 54 23 80  
 e-mail: b-guillot@chu-montpellier.fr

# Reducing senescent cells may help treat patients with brain disease & concussion

## Concussion Epidemic Is Existential Threat To Football

During the last five NFL seasons, an **average of 247 concussions** were reported per year

### Traumatic brain injury (TBI)

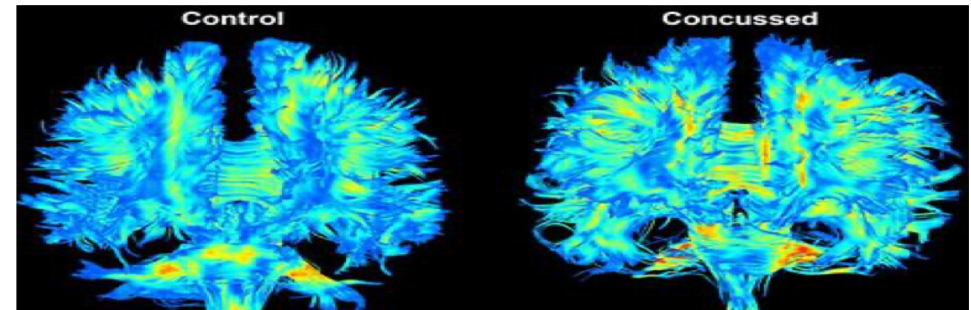
Upregulation of pro-inflammatory SASP factors in human multi-TBI cases compared to controls

Schwab et al, Acta Neuropath Comm, 2019



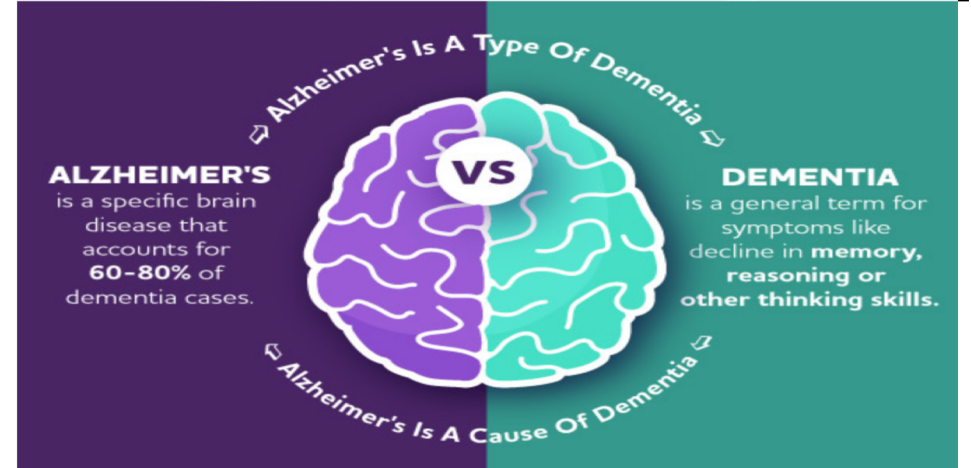
### Fisetin provides neuroprotection after TBI

- Fisetin suppressed TBI-induced oxidative stress and neuron cell death;
  - Fisetin Improved neurologic function and reduced lesion size
- (Zhang et al, Neurochem Int, 2018)



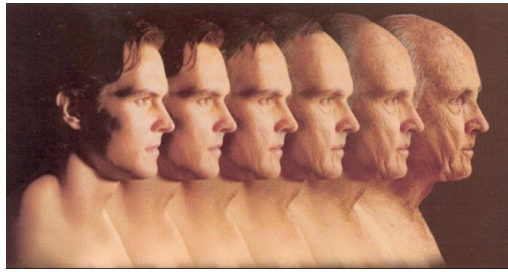
Senotherapeutics reduce Tau protein & neurofibrillary tangle (NFT) accumulation, implication for Alzheimer disease

Musi et al, Aging Cell, 2018

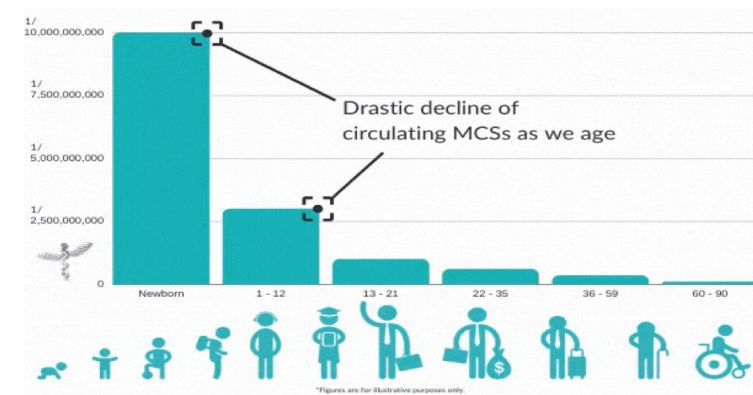
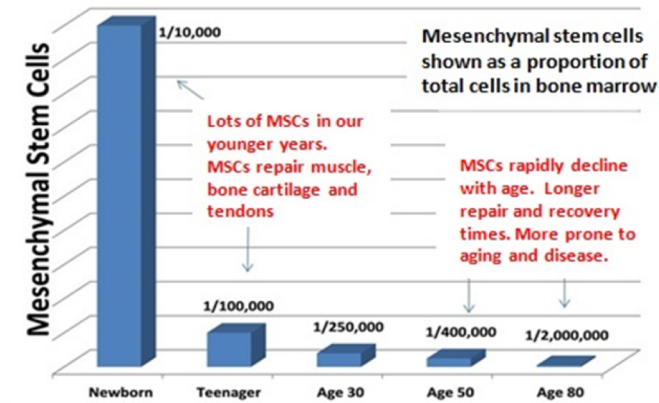




# Am I too old for stem cell therapies?



The US population ages 90 & older will quadruple between 2010 & 2050

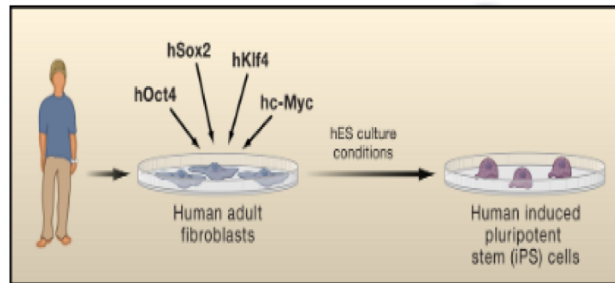


Dr. Naoki Nakayama



NIH 1R01AR077045-01A1 (Nakayama N, PI, Huard J, Co-I) 04/01/2021 - 03/31/2026.

Articular cartilage tissue engineering with human pluripotent stem cells.



iPS cells and reprogramming: turn any cell of the body into a stem cell

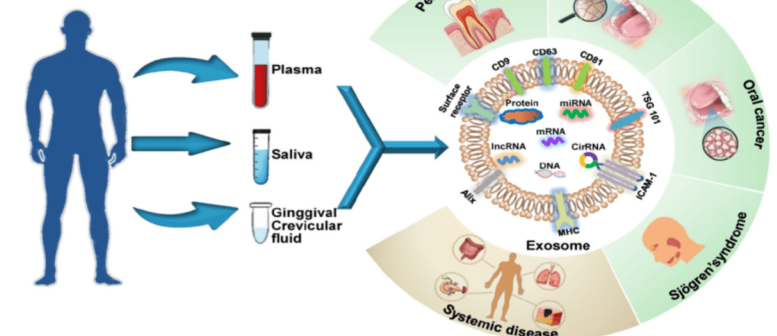
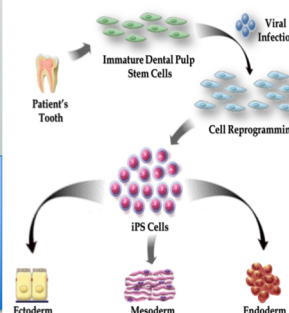
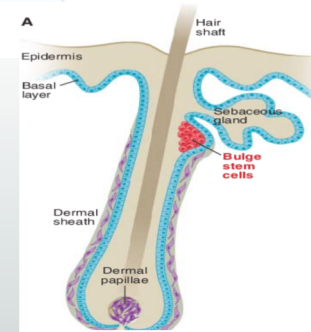
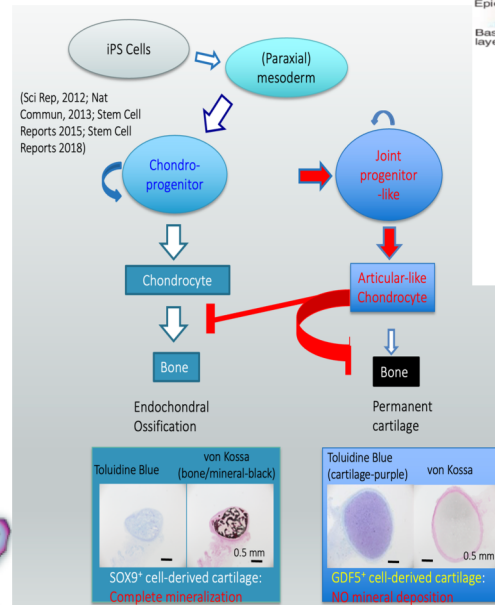
Exosomes



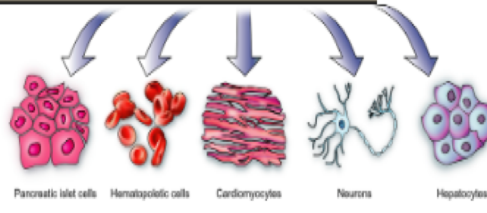
Stem Cells vs Exosomes

- Do not engraft well
- High immune response
- Paracrine effect
- Efficacy?
- Deliver regenerative cargo
- Considered likely safer
- Capable of mass production
- Efficacy?

Extracellular vesicles produced by MSCs have been recognized as a major source of pro-regenerative paracrine functions.



Rejuvenated adult cells



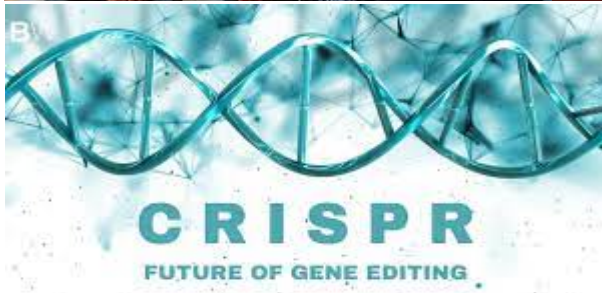
# Gene Coding: The Future of Gene Editing & Therapy

**START HERE**

## CRISPR & THE FUTURE OF GENE EDITING

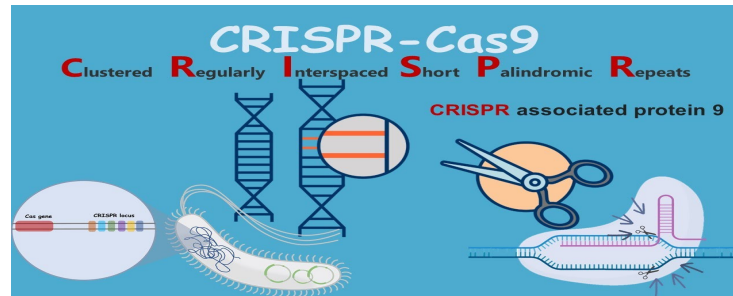
Nobel Prize 2020 in Chemistry honors CRISPR: a tool for rewriting the code of life

Emmanuelle Charpentier and Jennifer Doudna have been awarded the 2020 Nobel Prize in Chemistry for their work on CRISPR-Cas9—a method to edit DNA.

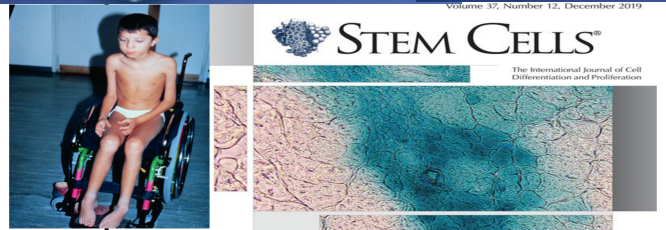


**CRISPR-Cas9: The Gene Editing Tool Changing the World**

CRISPR-Cas9 has been used by us in Vail Colorado to correct the dystrophin gene in Duchenne Muscular Dystrophy



MDX mice as an animal model for DMD      Dystrophin deficiency in DMD



> Stem Cells. 2019 Dec;37(12):1615-1628. doi: 10.1002/stem.3094. Epub 2019 Nov 18.

**CRISPR/Cas9-Based Dystrophin Restoration Reveals a Novel Role for Dystrophin in Bioenergetics and Stress Resistance of Muscle Progenitors**

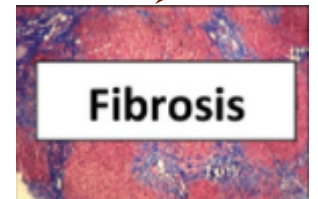
Polina R Matre <sup>1</sup>, Xiaodong Mu <sup>1, 2</sup>, Jianbo Wu <sup>1, 3</sup>, Delia Danila <sup>4</sup>, Mary A Hall <sup>1</sup>, Mikhail G Kolonin <sup>3</sup>, Radbod Darabi <sup>3</sup>, Johnny Huard <sup>1, 2, 3</sup>



Shear family foundation

Gene editing of stem cells that will improve their regenerative potential by **blocking** their sensitivity to **inflammation** and **fibrosis**

**Stem cells Modified for Autonomous Regenerative Therapy (SMART)**



In vitro analysis of genome-engineered muscle-derived stem cells for autoregulated anti-inflammatory and antifibrotic activity.

Pferdehirt L, Guo P, Lu A, Huard M, Guilak F, **Huard J**.

J Orthop Res. 2022 Mar 16. doi: 10.1002/jor.25311. Online ahead of print.

PMID: 35293626

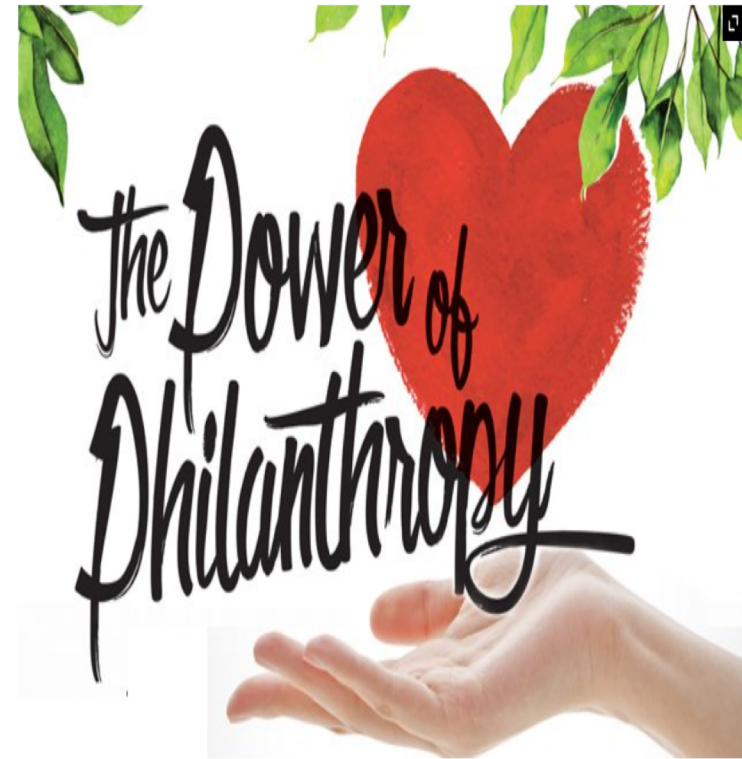
**NIH 1R21 AR079075-01A1**. (Huard PI, Nakayama N and Guilak F, Co-PI). 09/01/21 – 8/30/24. SMART stem cells that autonomously down-modulate TFG-β signaling for Articular Cartilage Repair has completed the first phase of peer review.

**NIH R21 AR072870-01** (Huard PI, Guilak F, Co-PI). 02/27/2018 – 01/31/2021

Muscle Stem Cells Reprogrammed Through Genome Engineering for Autonomously Regulated Anti- Fibrotic Therapy.



# *Thank You.*





# Dr. Patricia Harrigan Hardenbergh, MD, FASTRO

## Radiation Oncology

### 27 years



- Education: Dartmouth Medical School
- Residency : Harvard Medical School
- Faculty: Duke University Medical School, Radiation Oncology Department
- **Medical Director: Vail Health-Shaw Cancer Center**
- **American Society Clinical Oncology: Improving Cancer Award Recipient**
- **Fellow** of American Society of Therapeutic Radiation Oncology Award
- **DOD grant** for cardiac radiation avoidance in breast cancer patients
- Author: **Guidelines, Consensus papers** on the treatment of breast cancer
- **American Board of Radiology**
  - **board member** 2017-2020
  - **Examiner** : written and oral boards 2008-2020
- Design: **SAVI partial breast radiation device** treated over 10,000 patients
- **Founder Chartounds.org** : Global educational website for radiation oncologists

