



Healthy Aging: Dying Young As Late As Possible

Johnny Huard, PhD

Chief Scientific Officer

Director, Linda & Mitch Hart Center for Regenerative and Personalized Medicine, Steadman Philippon Research Institute

Director of Research, ProofPoint Biologics, The Steadman Clinic

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Veterinary Medicine & Biomedical Sciences,
Colorado State University

Professor,
Duquesne University College of Osteopathic Medicine

Professor of Orthopaedic Surgery,
Miller School of Medicine, University of Miami

Professor of Orthopaedic Surgery,
University of Pittsburgh School of Medicine

Talk Outline

Who We Are & What We Do at The Steadman Clinic & Steadman Philippon Research Institute

Optimizing Patients for Surgery in 2025

Healthy Aging Program: Dying Young as Late as Possible

Skeletal Muscle Health and the Implication of Ozempic-like Drugs for Aging-Related Disease and Conditions



Match Federal Funding and Philanthropy!

NIAMS 1R21 AR072870
NIAMS 1R21 AR073509
NIAMS 1R01 AR065445
NIAMS 1R21AR075997
NIAMS 1R21AR074132
NIAMS UG3 AR077748-01 RMIP
NIAMS 1R01 AR077045
NIAMS 1R21 AR079075
NIAMS 1 RO1 AR083471
NIA 1R44AG090114
DoD N00014-18-RFI-0014
DoD N00014-21-S-B001
DOD USAMRAA "HT9425—25-1-0916"

Industry and University Research Collaboration



Colorado's Advanced Industries (AI) Accelerator Program Award



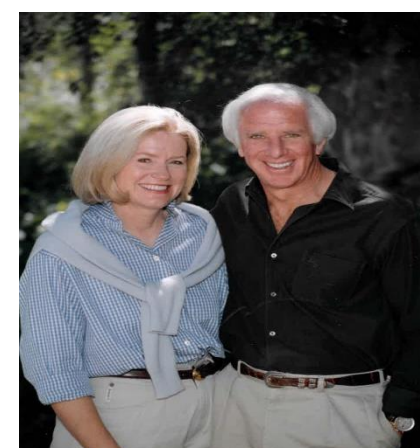
David/Elle Rubenstein



Linda/Mitch Hart



Tom Spruance family foundation



Steven/Mary Read



Mary-Sue/Mike Shannon



Borgen Family Foundation



Shear Family Foundation



Donna Giordano



Crown Family Foundation



Ann Smead & Michael Byram



Monica Sasson



George/Rose Gillett

SPRI Executive Team & Science Leadership



Marc Philippon, MD
Chairman



Dan Drawbaugh
Chief Executive Officer (CEO)



Johnny Huard, PhD
Chief Scientific Officer
Director of Center for Regenerative & Personalized Medicine



Lee Jones
Chief Operating Officer (COO)
Steadman Philippon Research Institute



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



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



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



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



Joana Roder, PhD
Clinical Trial, Biostatistician
Artificial Intelligence/Machine Learning



Anna-Laura Nelson, PhD
Bone Repair and Regenerative
Therapeutics



Greta Gohring, BS
CRPM (exosome therapeutic)



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



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



Collin Smith, PhD
Biomotion and BME



Alex Brady, MS
Manager of Robotics & Engineer



Justin Hollenbeck, MS
Biomechanical Research Engineer



Chloe Barton
Senior Trials Coordinator:
Recruitment, Protocol
Activities, Regulatory
Compliance



Sara Robinson, MS
Clinical Trials Coordinator



Marc J. Philippon, MD
Managing Partner, Sports Medicine, Hip & Knee Surgeon



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



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



Jonathon D. Backus, MD
Foot and Ankle Surgeon



Malia Cali, MD
Physical Medicine, Rehabilitation, Sports Medicine & Interventional Spine



Nathan Cafferky, MD
Total Joints, Adult Reconstruction, and Trauma



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



Jonathan A. Codin, 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



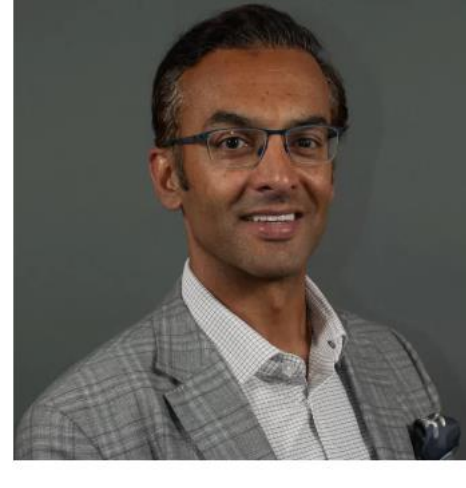
Dustin Anderson, MD
Orthopaedic Interventionalist, Sports, Spine & Regenerative Medicine, PM&R and Pain Medicine



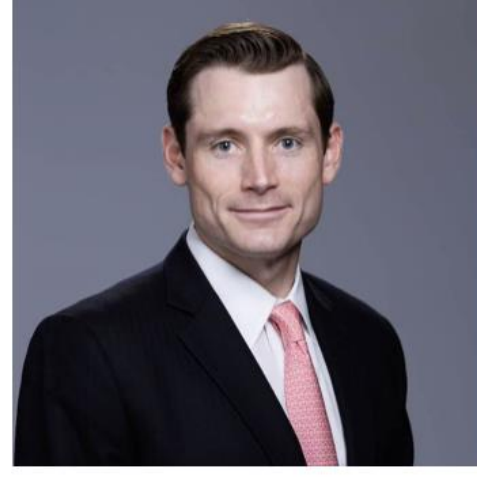
Joseph J. Ruzbarsky, MD
Shoulder, Knee, Elbow & Hip Preservation Surgery



Michael Gallizzi, MD
Robotic and Endoscopic Spine Surgeon



Sonny S. Gill, MD
Spine Surgery, Neck & Back, Minimally Invasive & Motion Preserving Surgery



Stuart D. Kinsella, MD, MSTR
Spine Surgery, Neck & Back, Robotic and Navigation-Assisted Surgery



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Bone Repair and Regenerative Therapeutics



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CRPM (exosome therapeutic)



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Director of Center for Outcomes Based Orthopaedic Research and Chief Biostatistician



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Principal Investigator
Director of Biomedical Engineering and Imaging



Collin Smith, PhD
Biomechanics and BME



Alex Brady, MS
Manager of Robotics & Engineer



Justin Hollenbeck, MS
Biomechanical Research Engineer



Chloe Barton
Senior Trials Coordinator:
Recruitment, Protocol Activities, Regulatory Compliance



Sara Robinson, MS
Clinical Trials Coordinator



Robert Waltz, MD
TSC Fellow



Justin Ernat, 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



Philip Nolte, MD
International Fellow



Ingrid Stake, MD
International Fellow



Lucca Lacheta, MD
International Fellow



Haruki Nishimura, MD, PhD
International Fellow



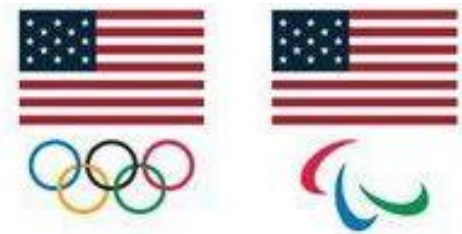
Kohei Yamaura, MD, PhD
International Fellow



Maria D. Hazra, MD
International Fellow



Rony D. Hazra, MD
International Fellow



U.S. OLYMPIC & PARALYMPIC NATIONAL MEDICAL CENTER



Ali S. Noorzad, MD
Sports Medicine, Hip Preservation & Reconstruction



Kris John Alden, MD, PhD
Total Joint & Adult Reconstructive Surgery





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

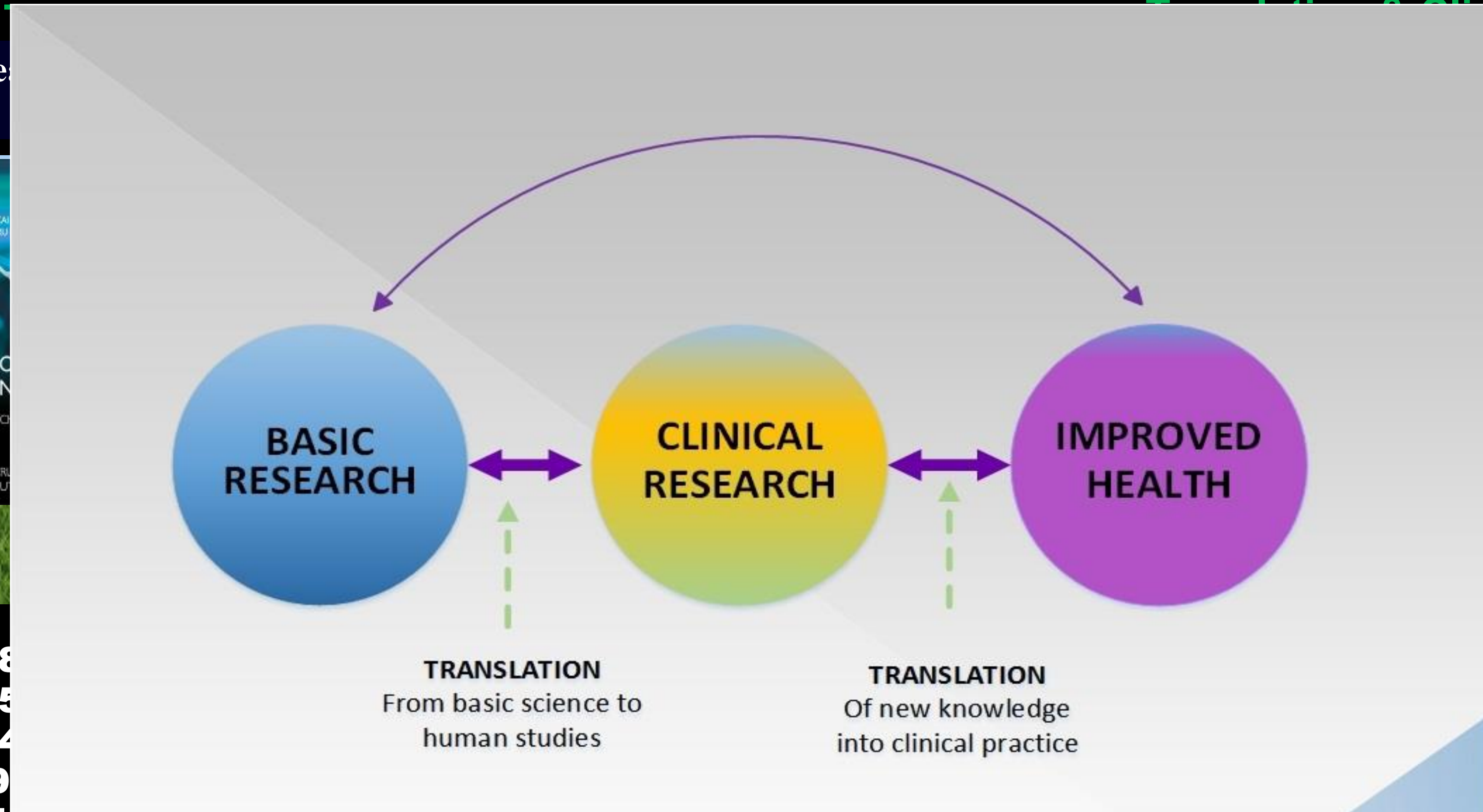


Edwards, CO

Our Vision at the Steadman Philippon Research Institute: Overcome The Academics Dilemma

Basic Science &

Translational & Clinical



Basic research

Clinical research

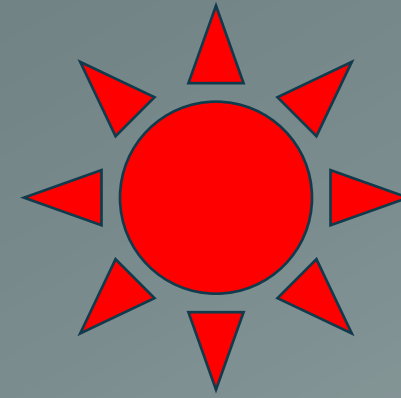
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NIAMS 1R21AR0759
NIAMS 1R21AR074132
NIAMS 1R01 AR077045
NIAMS 1R21 AR079075

AR077748-01 RMIP
DOD W81XWH-15-2-0003
DOD N00014-19-C-2052
DOD USAMRAA "HT9425—25-1-0916"



Opportunities





Regenerative Medicine

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



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. Collin Smith Ph.D
Biomotion and BME



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

Biomotion/ Imaging

- Assessing tissue structure
- Monitoring healing and/or degeneration
- Whole-body performance

Computational Imaging/movement biomechanics

- Loading effect on full body movement
- In vivo joint & tissue function
- DARI Motion analysis system

TSC (surgeons)

IMPROVE ORTHOPAEDIC CARE

Outcomes Based Orthopaedic Research

- Patient-focused outcomes assessment
- Predictive Modeling, Artificial Intelligence/Machine Learning

Clinical Trials

- Testing interventions in patients
- Institutional Review Board (IRB)
- Compliance with FDA

Biomechanics/Robotics

- Understanding anatomy
- Evaluating procedures and devices



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



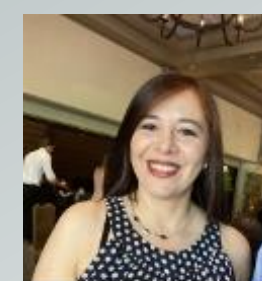
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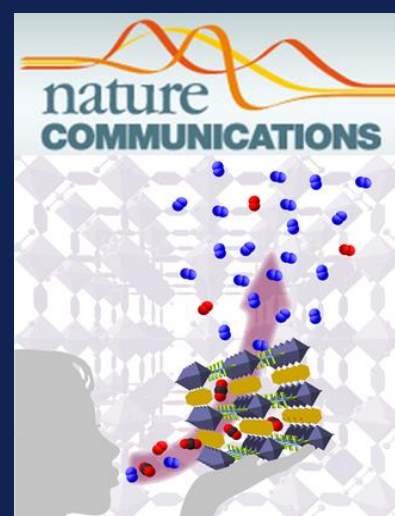
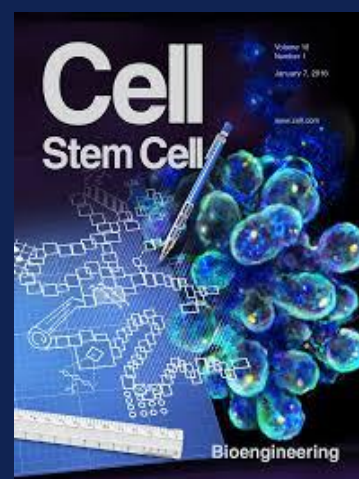
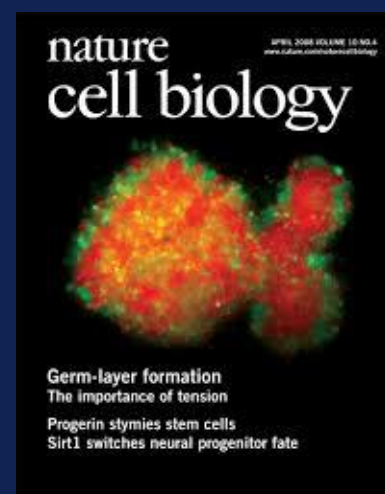
Regenerative & Translational Medicine

40 years of Research & Innovation

UQAR (1985-1988), University Laval (1989-1993), Mc Gill University (1994,1995)

University of Pittsburgh (1996-2015), UTHHealth & SPRI (2015-2019); SPRI (2019—)

Gene Therapy, Stem Cells, Tissue Engineering, Regenerative Medicine, Orthobiologics



- Chief Scientific Officer & Director of Regenerative Medicine, Steadman Philippon Research Institute
- Associate Faculty, Clinical/Biomedical Sciences, Colorado State University, Fort Collins, CO
- Professor of Orthopaedic Surgery at University of Pittsburgh, Pittsburgh, PA
- Professor of Surgery at Duquesne University, Pittsburgh, PA
- Professor of Orthopaedic Surgery at the University of Miami, Miami, FL
- Senior Fellow, Belmont University's Thomas Frist Jr, College of Medicine
- **488 manuscripts published (peer-reviewed journals)**
- 45 patent applications
- Over 1000 abstracts presented at national/international meetings
- Over 100 awards: **Kappa Delta Awards (2004, 2018), OREF Clinical Research award (2023), AOSSM: Cabaud (2000, 2019); Aircast (2003); Excellence (2019)**
- Honorary Doctorate Degree, University of Quebec, Rimouski, Canada
- Over 50 federal grants (NIH, DOD, MDA, OREF,)
- **5 current NIH grants; 3 DOD contracts**
- **6 current FDA approved & DOD/NIH sponsored clinical trials**
- Over 150 invited lectures to national and international meetings
- Johnny Huard, PhD; Google Scholar:
 - **Citations: 52399; h-index: 120; i-10-index: 417**

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/microfracture
- Anti-angiogenic agent for OA

Biologics

Regenerative Medicine Approaches

Tissue Repair after Injury, Disease & Aging

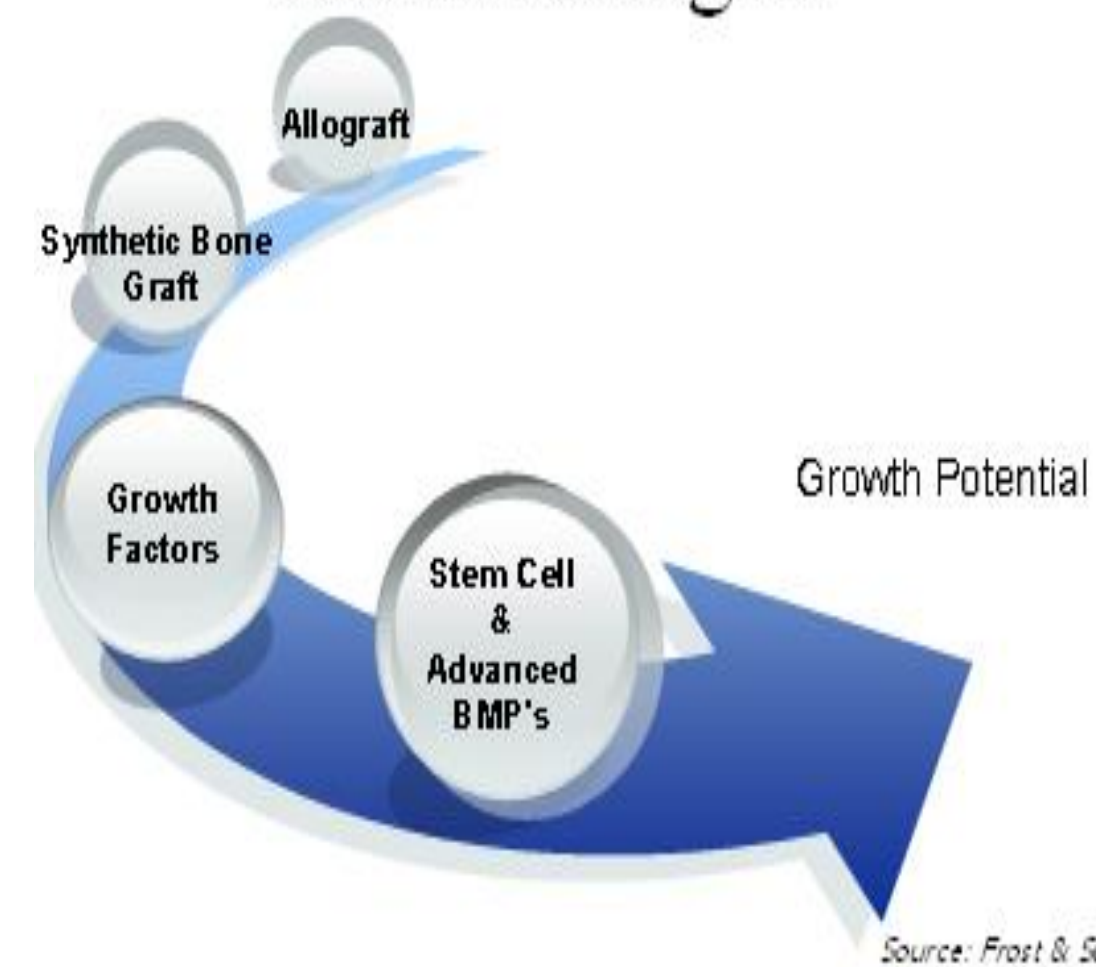
Therapeutics

Animal modelling

- 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

Orthobiologics



ORTHOBIOLOGICS MARKET

North America Orthobiologics Market, 2018



Global Orthobiologics Market (US\$ Mn), 2018 to 2026



Global Orthobiologics Market Share, By Product, 2018



- Viscosupplements
- Bone Growth Stimulators
- Synthetic Bone Substitutes
- Allograft
- Demineralised Bone Matrix
- Stem Cells
- Others

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The global orthobiologics market is expected to reach USD 6.87 Billion in 2025

Review Article

Optimizing Clinical Use of Biologics in Orthopaedic Surgery: Consensus Recommendations From the 2018 AAOS/NIH U-13 Conference

Abstract

Concern that mis

December 2013

Recommendations for development of high-quality multicenter clinical trials to strengthen the evidence behind orthobiologics!

Bone Marrow aspirates

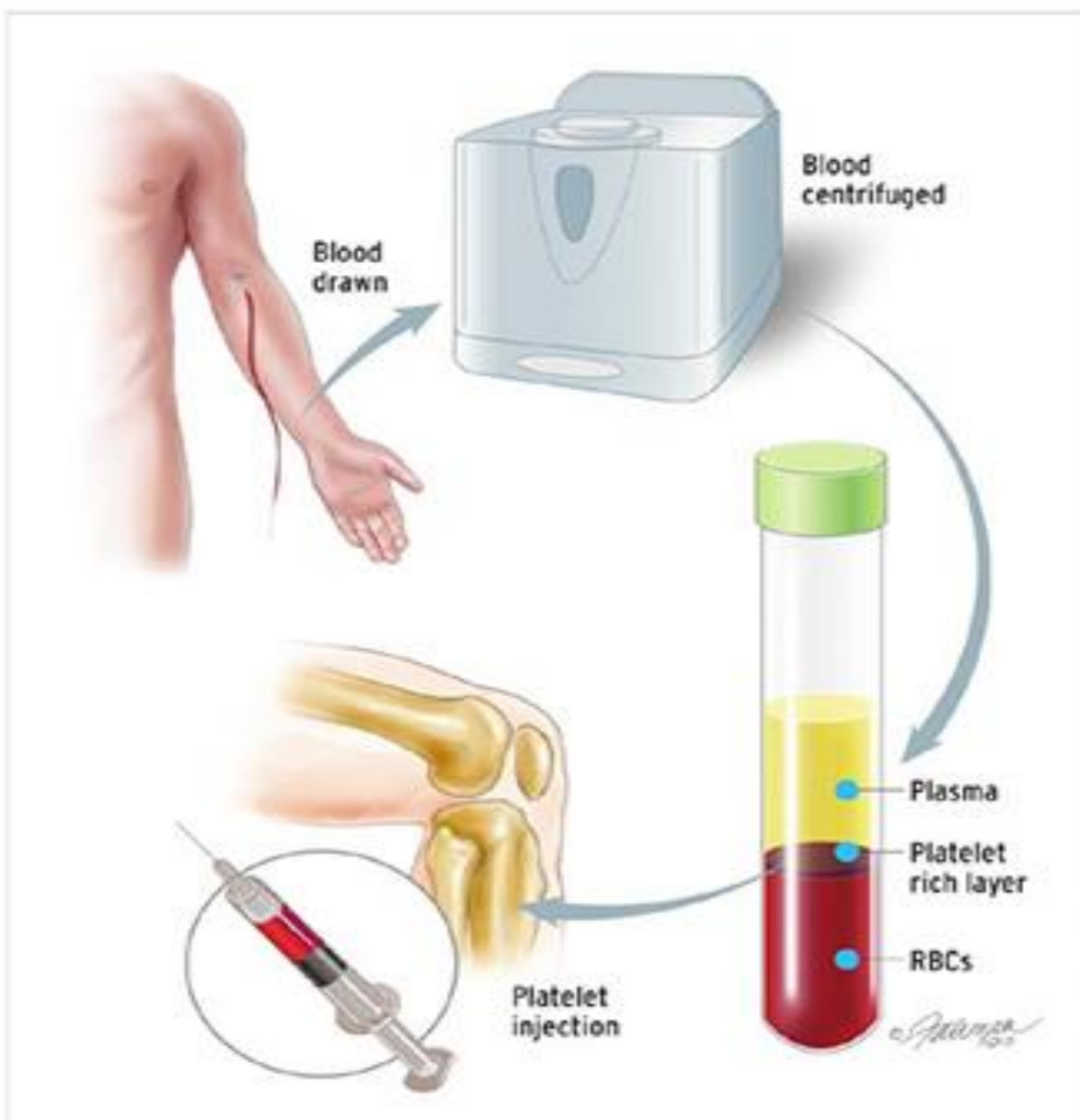


THE STEADMAN CLINIC

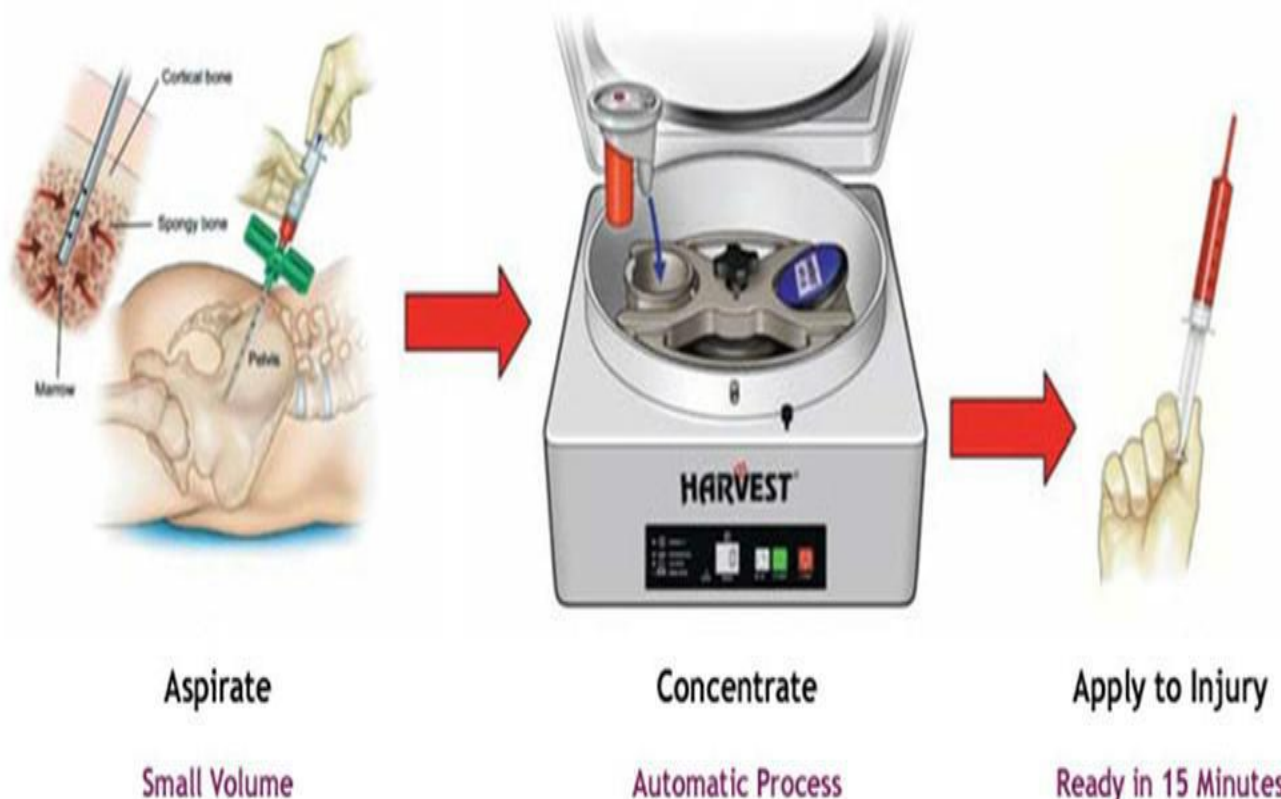
AND

STEADMAN PHILIPPON RESEARCH INSTITUTE

Platelet Rich Plasma



Preparation and administration of platelet-rich plasma



Colorado State University, Fort Collins, CO (Dr. Goodrich), the University of Texas Health Science Center, University of Texas Dental Branch, Houston, TX (Dr. Huard), the University of Pittsburgh, Pittsburgh, PA (Dr. Irrgang and Dr. Tuan), the Steadman Clinic, Vail, CO (Dr. LaPrade), the Harvard University, Cambridge, MA (Dr. Lattermann), Santa Monica Orthopaedic and Sports Medicine, Santa Monica, CA (Dr. Mandelbaum), Columbia University, New York City, NY (Dr. Mao), the Northwell Orthopaedic Partners (Dr. McIntyre), the Cleveland Clinic (Dr. Muschler, Dr. Piuze, and Dr. Spindler), the Mayo Clinic (Dr. Tokish), the Advanced Ortho Centers (Dr. Zaslav).

February 15-17, 2018 at Stanford University, Stanford California.

* Conference organizers

J Am Acad Orthop Surg 2018;00:1-14

DOI: 10.5435/JAAOS-D-18-00305

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Month 00, 2018, Vol 00, No 00

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as cell therapy and these treatments patients, and to the characterization and forward, contemporary using transcriptomics coupled with bioinformatics of standards. In a quality multicenter was that physician establishing high-quality postmarket surveillance

The clinical use of platelet-rich plasma cell-based therapies in orthopaedic complications has greatly out-

AAOS
AMERICAN ACADEMY OF
ORTHOPAEDIC SURGEONS

The Official Clinical Journal of the AAOS

- Platelet-rich Plasma in Orthopaedic Applications: Evidence-based Recommendations for Treatment
- JAAOS Plus Webinar on Platelet-rich Plasma in Orthopaedic Applications: Evidence-based Recommendations for Treatment December 10, 9 pm Eastern, orthoportal.org/jaas/
- Adhesive Capsulitis of the Hip: A Review
- Finger Tip Injuries: An Update on Management
- AAOS Appropriate Use Criteria Summary
- Optimizing the Management of Full-Thickness Rotator Cuff Tears
- Case Studies
- AAOS Appropriate Use Criteria: Optimizing the Management of Full-Thickness Rotator Cuff Tears

ProofPoint Biologics (PPB) Orthobiologics

The Steadman Clinic



- **ProofPoint Biologics (PPB)** Laboratory is CLIA and COLA accredited and **service-line of The Steadman Clinic** that is led by **Thomas A. Evans, MD** and **Johnny Huard, PhD**.
- PPB has been primarily producing safe and reliable **Platelet Rich Plasma (PRP)**, **Leukocyte Rich (LR) or Leukocyte poor (LP- PRP)**, **bone marrow concentrate (BMC)** and **Activated Fibrin Clot (AFC)** biologic products **since 2018** for **autologous treatment** of musculoskeletal disorders.
- **Supports evidenced Based clinical trials** initiated by SPRI.
- **Developing a database** of patient biologics parameters that can be correlated with patient outcomes, demographics and comorbidities.

ProofPoint Biologics: Who we are



Thos Evans MD
Medical Director



Johnny Huard PhD
Chief Scientific
Officer



Talena Williams, DMsc
VP of Clinical
Operations



Jeff Christiansen PhD
Laboratory Manager



Amanda Caruso
Technician



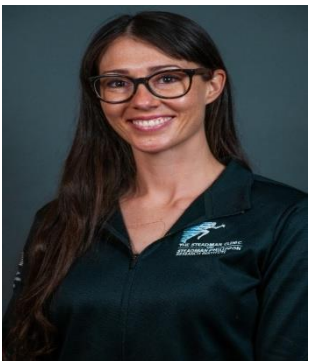
Jo Ann Baldwin
Technician



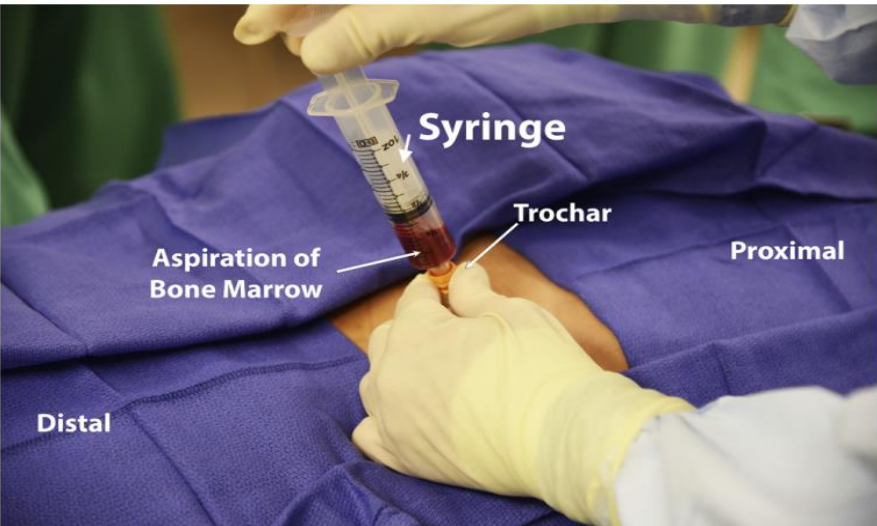
Ako Gomilla Platt
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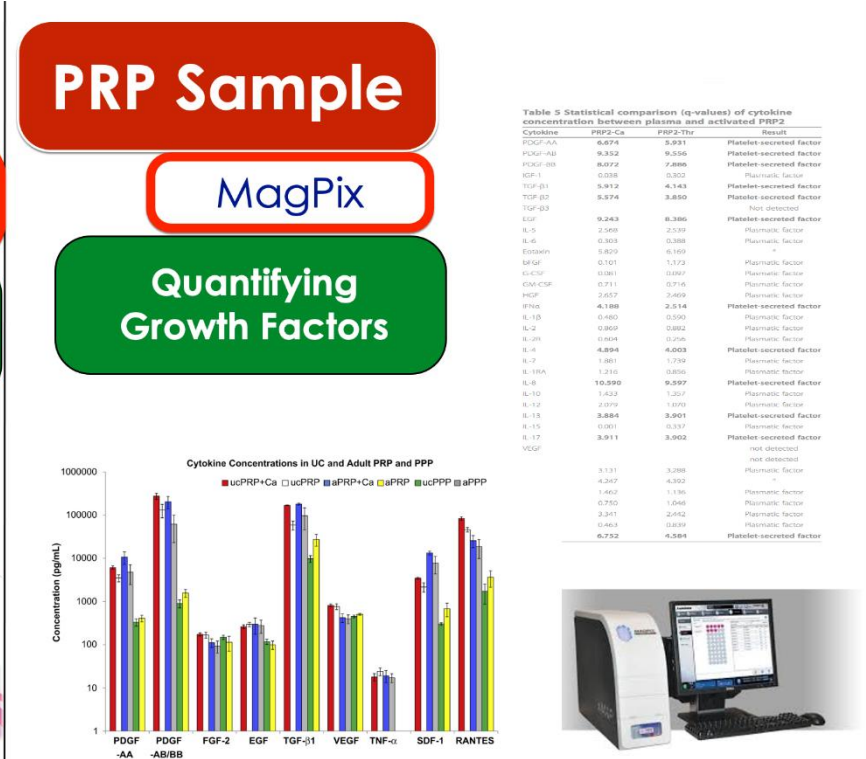
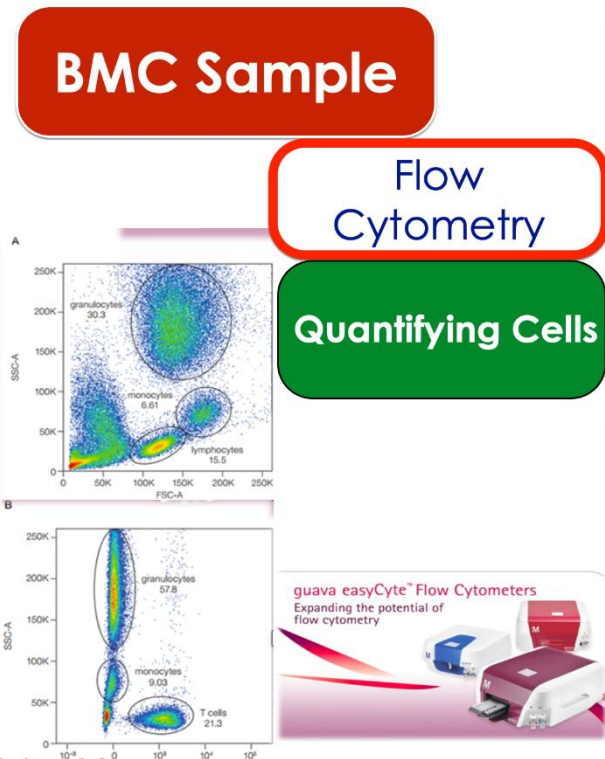
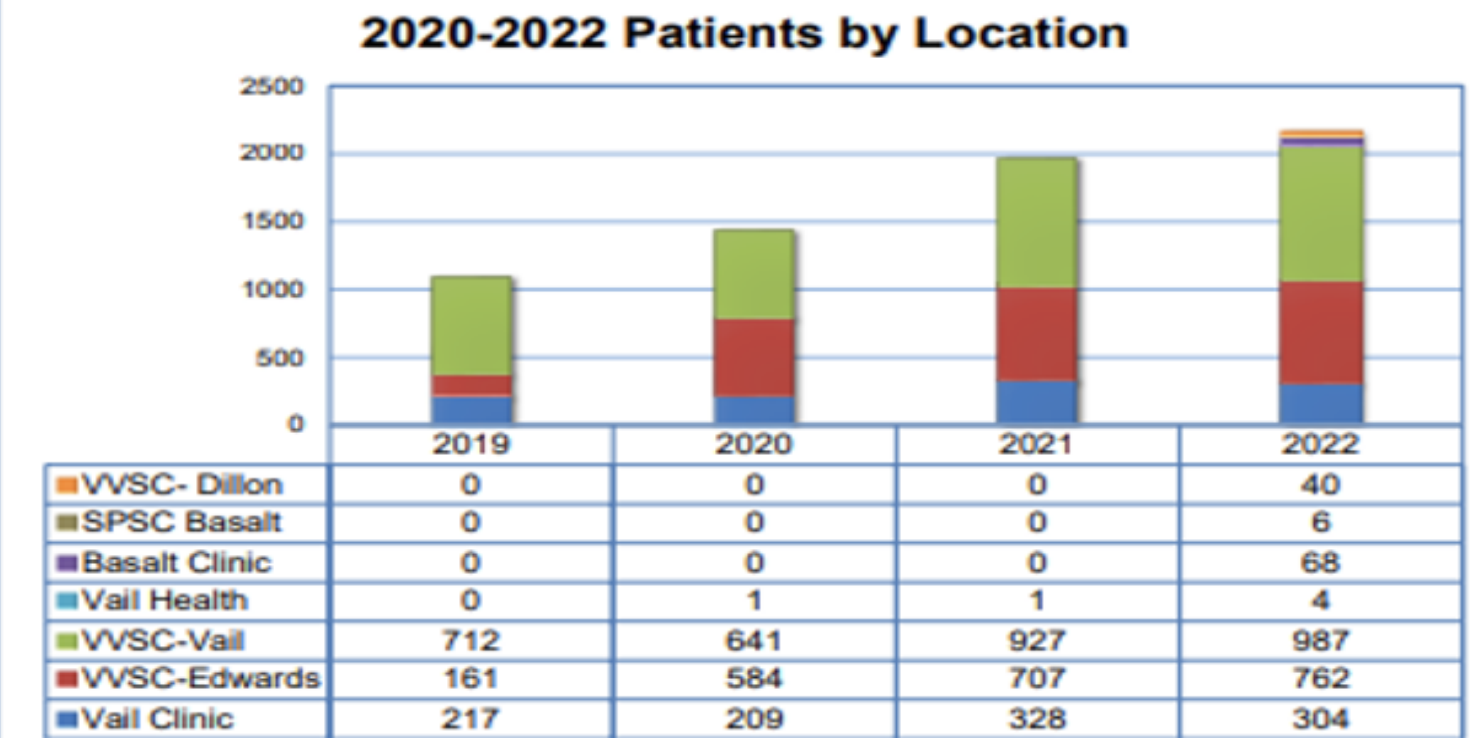
Logan Martin
Technician



Shelbi Green
Technician



3,000 orthobiologics injection in 2024 at the Steadman Clinic!. 90% PRP 10 % BMAC



Cureus

Open Access Review
Article

DOI: 10.7759/cureus.28498

Review began 07/22/2022
Review ended 08/16/2022
Published 08/28/2022

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A Review of Commercially Available Point-of-Care Devices to Concentrate Platelet-Rich Plasma

Toufic R. Jilkeh ¹, Charles A. Su ², Matthew L. Vopat ², Justin R. Brown ², Johnny Huard ³

¹. Orthopedic Surgery, Michigan State University, East Lansing, USA ². Orthopedic Surgery, The Steadman Clinic, Vail, USA ³. Biological Sciences, The Steadman Clinic, Vail, USA

Corresponding author: Toufic R. Jilkeh, touficjilkeh@gmail.com

Abstract

Platelet-rich plasma (PRP) is a promising therapy treatment option for multiple orthopedic conditions, which has demonstrated expanding clinical use. With increased clinical use of PRP, there has been a greater demand for point-of-care (POC) biologic devices. For this review, publicly available information provided by the device corporations, PubMed, Medline, and Embase databases were searched for studies related to POC device function. A scoping review study design was selected to explore the breadth of knowledge in the literature regarding PRP POC devices. ProofPoint Biologics demonstrated the highest laboratory platelet increase (5.2 ± 0.28 -fold) and the longest processing time (49 ± 1.4 minutes). Celling demonstrated the lowest laboratory platelet increase (2.7 ± 0.8 -fold), while AcCELLerated had the fastest processing time (18 ± 1.4 minutes for PurePRP® AB60 Pure (Pure Accelerated Biologics, Tequesta, FL) and 13.5 ± 2.1 minutes for AbsolutePRP® (Emcyte Corporation, Fort Myers, FL)). Celling had the lowest cost out of the various biologic devices. There is significant variability in the technical features, cost, processing time, and centrifugation parameters of the different commercially available point-of-care devices.



Clinical Research & Application

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



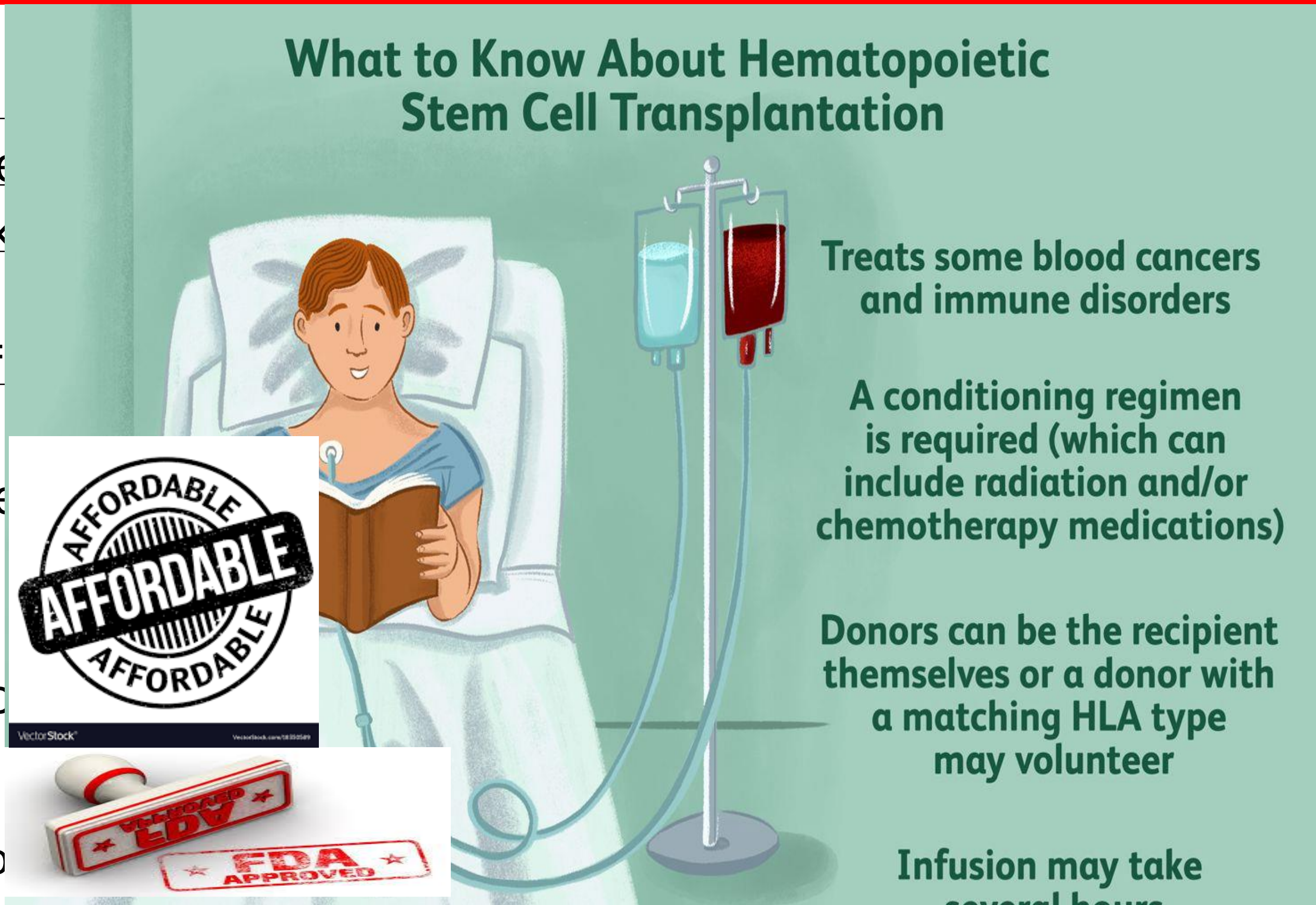
Prospective Evaluation of Platelet Rich Plasma (PRP) and Bone Marrow Aspirate Concentrate (BMAC) Treatments to Accelerate Healing After ACL R

- At 6 months after ACL led to less muscle weakness bearing in the ACLR k
- At 12 months, no diff
- No difference between measurement
- PRP and BMAC led to function after ACLR

From

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

What to Know About Hematopoietic Stem Cell Transplantation



Affordable

Treats some blood cancers and immune disorders

A conditioning regimen is required (which can include radiation and/or chemotherapy medications)

Donors can be the recipient themselves or a donor with a matching HLA type may volunteer

Infusion may take several hours

NO CELLULAR EXPANSION

Stem cell banking: Single harvest with BMAC storage for multiple injections will allow re-injection of BMAC after 6 months

ment of approaches to improve marrow stem cells banking

Johnny Huard PI

s Advanced Industries
erator Program Award



Cs from fresh and frozen Bone Marrow As-
for their function in vitro and cartilage re-

¹, Zuokui Xiao ¹, Xueqin Gao ¹, Noah Knezic ¹, Laura Chubb ², Jonathan E Layne
Huard ¹ and *

est that the freezing process does not
the function of MSCs from BMAC for
These findings support the potential
of a single harvest with BMAC storage
ons, thereby enhancing the tissue repair
AC.



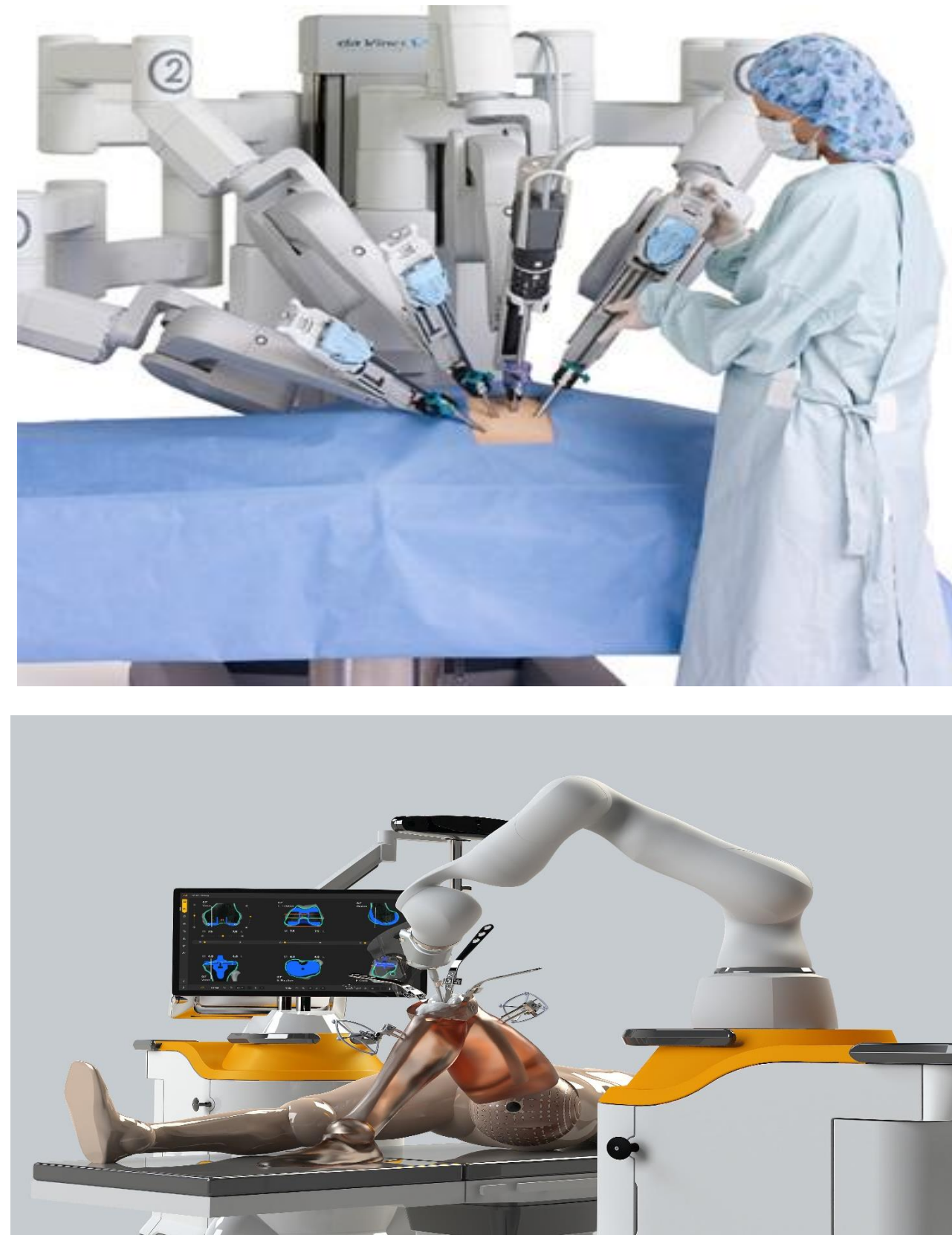
**U.S. OLYMPIC & PARALYMPIC
NATIONAL MEDICAL CENTER**

Optimizing Orthopaedic Surgical Outcomes

Optimizing surgical tools



Optimizing surgical techniques



How about optimizing your Patients?



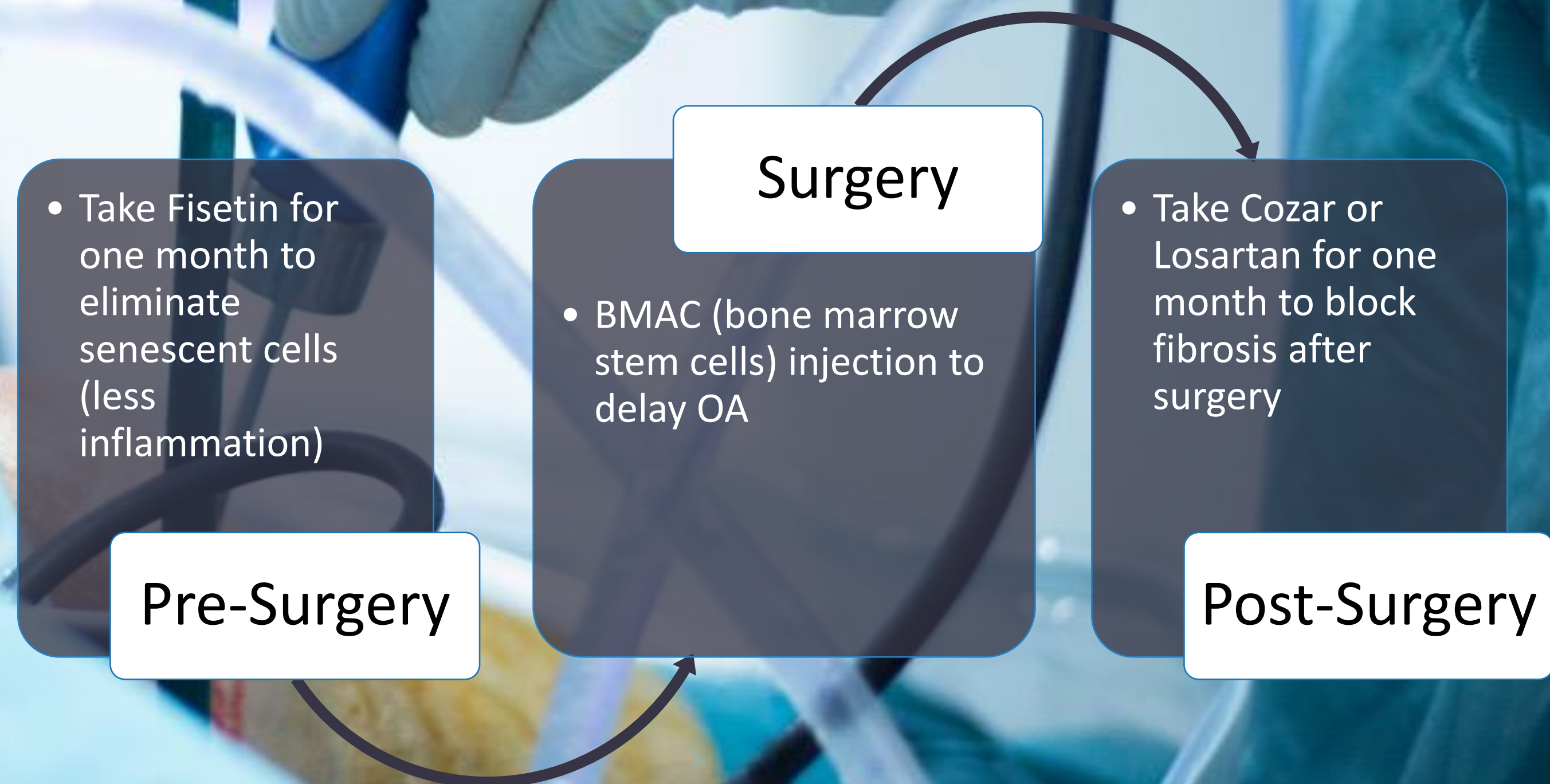
How about optimizing your Patients in 2025!

A key initiative of the regenerative medicine laboratory, in coordination with our ongoing clinical trials, is to optimize patients for **Stem Cell Transplantation**

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

Now we are looking at updating protocols to further optimize surgery

Proposed Optimization Protocol



- Take Fisetin for one month to eliminate senescent cells (less inflammation)

Pre-Surgery

- Use Stem Cells from bone marrow aspirate during surgery
- 25% freeze for future use; remainder injected back to patient during surgery
- No cellular expansion
- FDA approved
- affordable

Surgery

- Take Cozar or Losartan for one month to block fibrosis after surgery

Post-Surgery

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



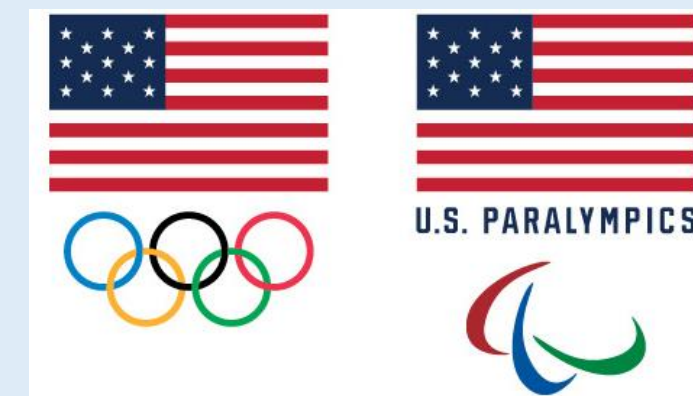
Harvesting and Banking your stem cells while you are undergoing your surgery at the Steadman Clinic!



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

Johnny Huard contact PI, Scott Tashman & Marc Philippon (Co-PIs)

NIH-RMIP: 1 UG3 AR077748-01



TREATMENTS (combined with bone marrow aspirate concentrate [BMAC]):

- Senolytic agent (Fisetin) prior to stem cell harvesting and after BMAC injection to eliminate senescent cells/inflammation
- Anti-fibrotic agent (Losartan) to reduce Fibrosis and improve the benefit of BMAC for OA patients

4 arms:

- BMAC alone (25 patients)
- BMAC + Losartan (25 patients)
- BMAC + Fisetin (25 patients)
- BMAC + Losartan+ Fisetin (25 patients)

Achieved original target enrollment of n=100 by January 11, 2023

- Target date: 4/1/2023



Key clinical trial statistics:

Approximately 80% of clinical trials are delayed or closed because of problems with recruitment.

What are the most significant technical, operation and scientific challenges that you have experienced during the trial?

Sex & Minority Recruitment

60 males and 60 females have been enrolled

Pause recruitment in the middle of the trial to enroll minority (Hispanic participants) which has increased to 31%

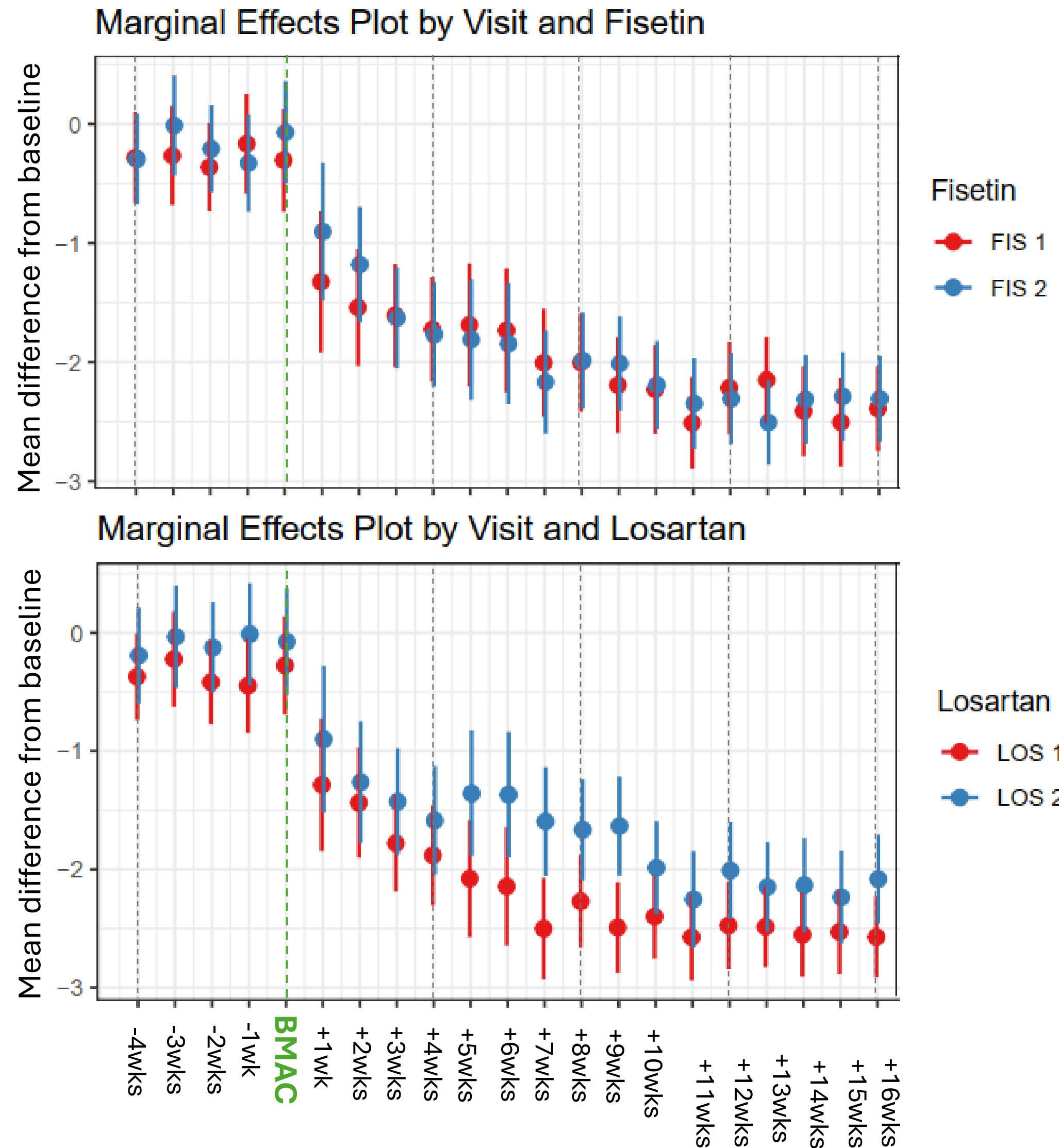
- Original target: Based on the population of Eagle County alone.

This require an integrated interdisciplinary approach with a combined effort of the DSMB, IRB, Hospital executive and etc.

Achieved Minority Recruitment Goals Using the Following Measures:

- Recruitment area was expanded beyond Eagle County
- Translated all patient facing materials into Spanish
- Retained interpreters on-site for consenting and baseline visits
- Retained permanent staff fluent in Spanish
- Recruited via radio ads, newspaper and social media, and tv spots with established local community member

NRS Average Pain IN RMIP enrolled patient – Preliminary Internal Use – data and analysis still to be verified



Reductions indicate less pain

UNBLINDED DATA

FIS 1 = subjects receiving FIS level 1

FIS 2 = subjects receiving FIS level 2

LOS 1 = subjects receiving LOS level 1

LOS 2 = subjects receiving LOS level 2

A **Numeric Pain Rating scale for pain or NRS** doesn't have a single, universally agreed-upon value; it refers to the subjective cut-off point on a [Numeric Rating Scale](#) (0–10) that separates mild from moderate or severe pain, which varies by study, clinical setting, and patient. While some guidelines use a threshold of ≥ 3 or ≥ 4 , others suggest that scores of 1–4 are mild, 5–6 are moderate, and 7–10 are severe.

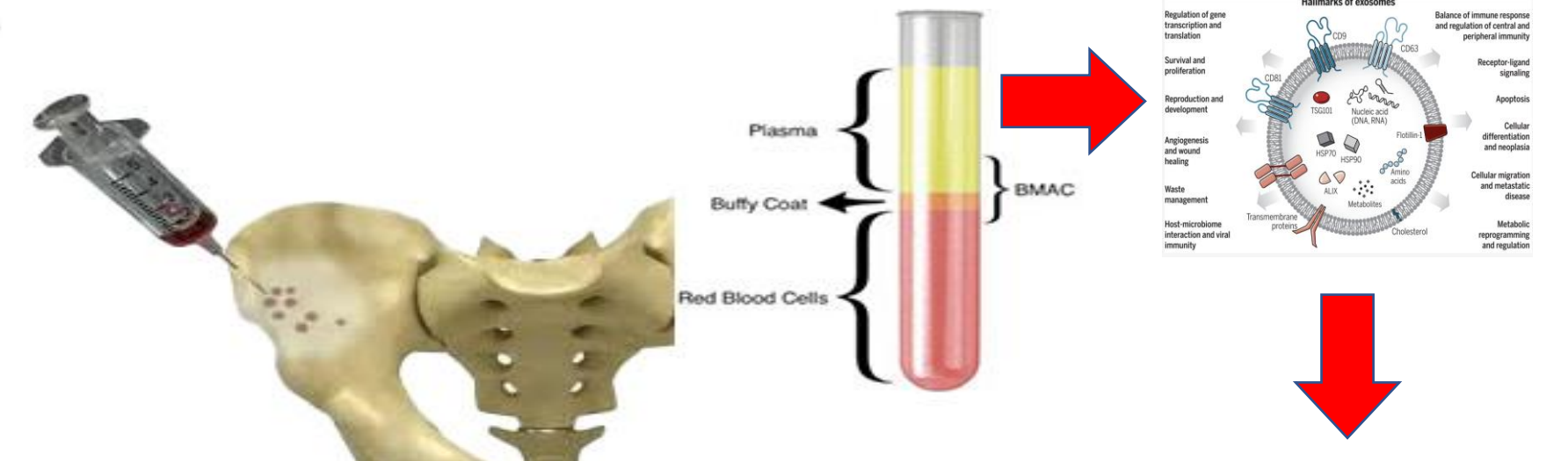
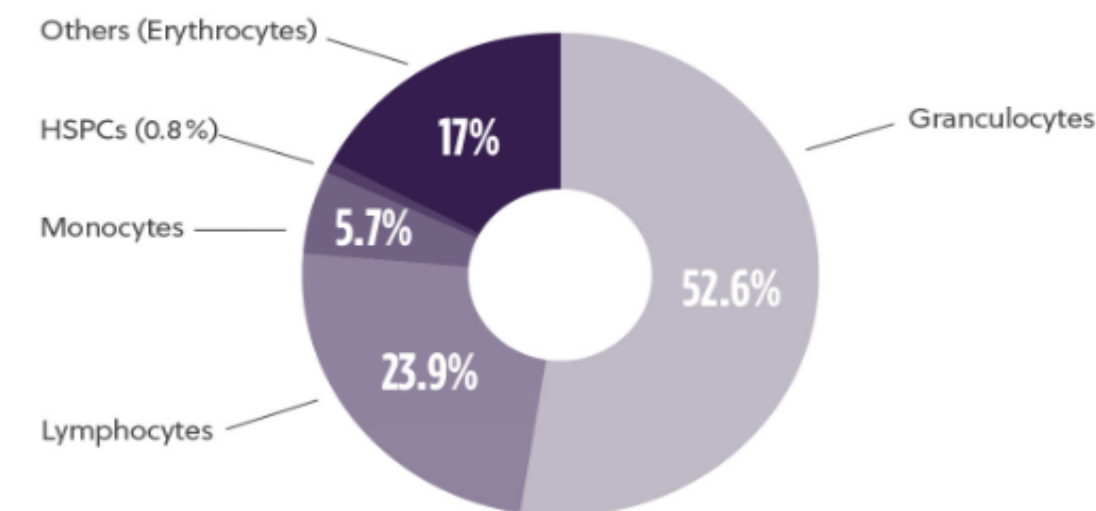
The Use of Senolytic and Anti-Fibrotic Agents to Improve the Beneficial Effect of Bone Marrow Stem Cells for Osteoarthritis

Johnny Huard contact PI, Scott Tashman & Marc Philippon (Co-PIs)

NIH-RMIP: 1 UG3 AR077748-01

What are the most significant technical, operation and scientific challenges during the trial?

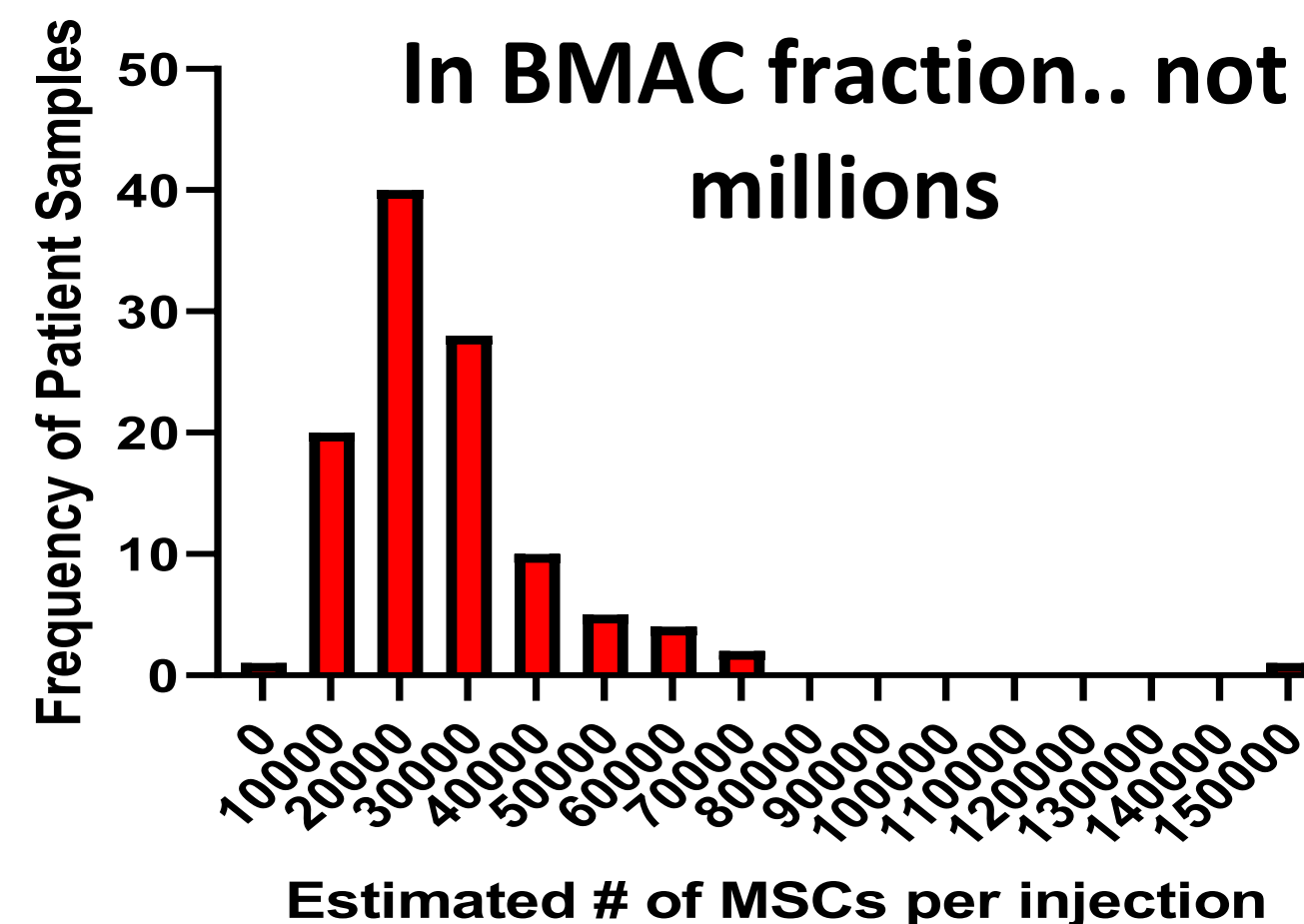
Typical Bone Marrow Aspirate Composition



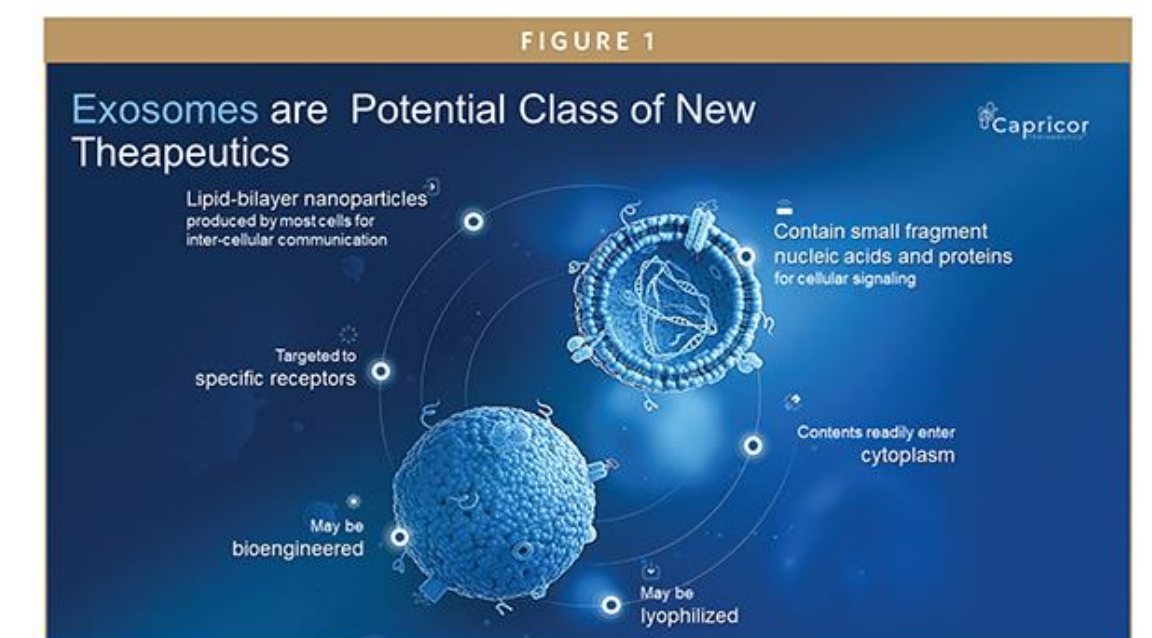
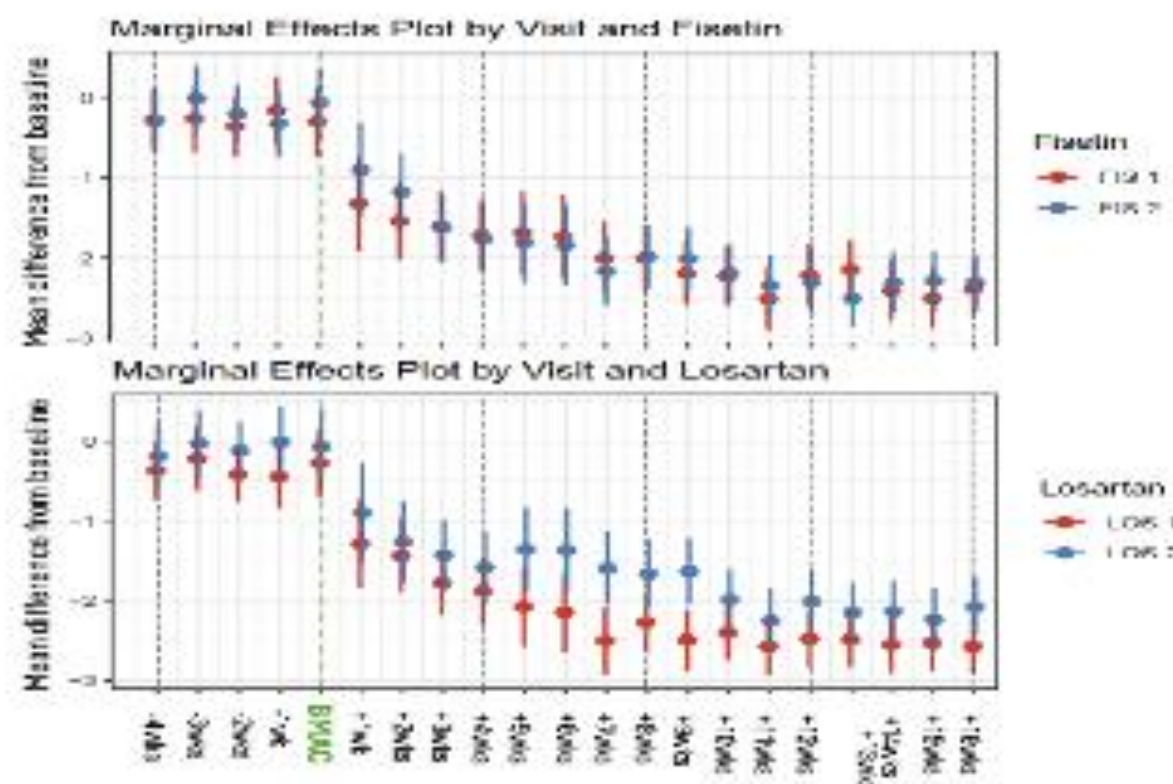
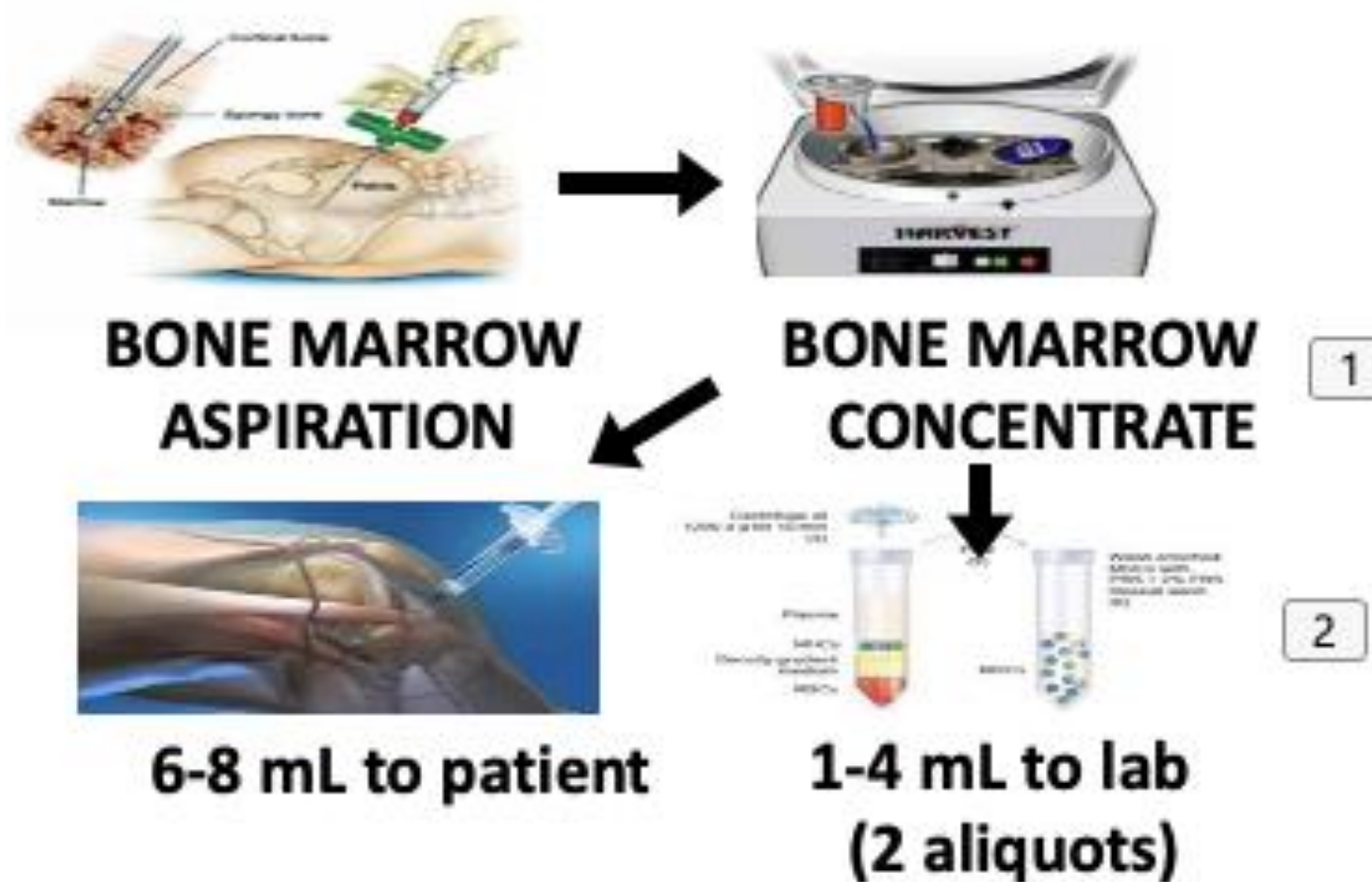
Only about 0.001-0.01% of the cells in the bone marrow are MSCs

1.56 billions exosomes (extracellular vesicles) per ml of serum

Thousands of MSCs
In BMAC fraction.. not millions



- Exosomes are naturally occurring, nano-sized biological vesicles released by cells that act as delivery vehicles for proteins, lipids, and genetic material like mRNA and microRNA to other cells.....
- This communication can influence nearby and distant cells by transferring bioactive molecules that trigger various effects, such as promoting tissue repair....



Can exosomes be used to delay osteoarthritis?

nature > bone research > review articles > all

Review Article | [Open Access](#) | Published: 19 Jul 2020

Exosomes: roles and therapeutic potential in osteoarthritis

Zhenhong Ni, Siru Zhou, Song Li, Liang Kuang, Xiaolan Du & Lin Chen

Bone Research 8, Article number: 25 (2020) |

19k Accesses | 90 Citations | 7 Altmetric |

> *Stem Cell Res Ther.* 2020 Jul 10;11(1):276. doi:

Bone marrow mesenchymal stem cell-derived exosomes protect cartilage and reduce osteoarthritis pain in a rat model

Lei He^{1,2,3}, Tianwei He^{1,2,3}, Jianghao Xing¹, Yuyong Chen^{1,2,3}, Depeng Wu^{1,2,3}, Zhenmi

Affiliations + expand

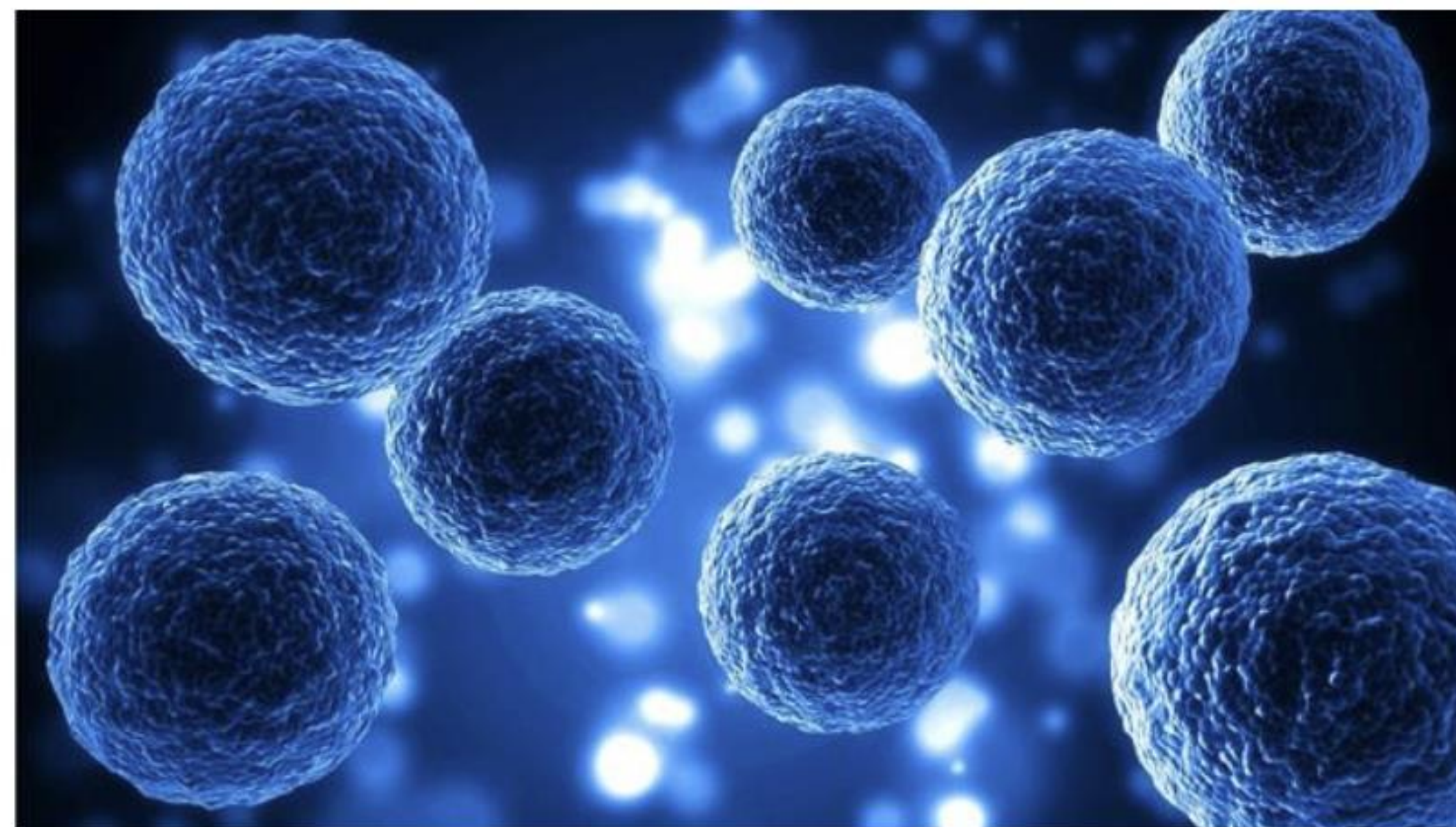
PMID: 32650828 PMCID: [PMC7350730](#) DOI: [10.1186/s13287-020-01908-1](#)

[Free PMC article](#)

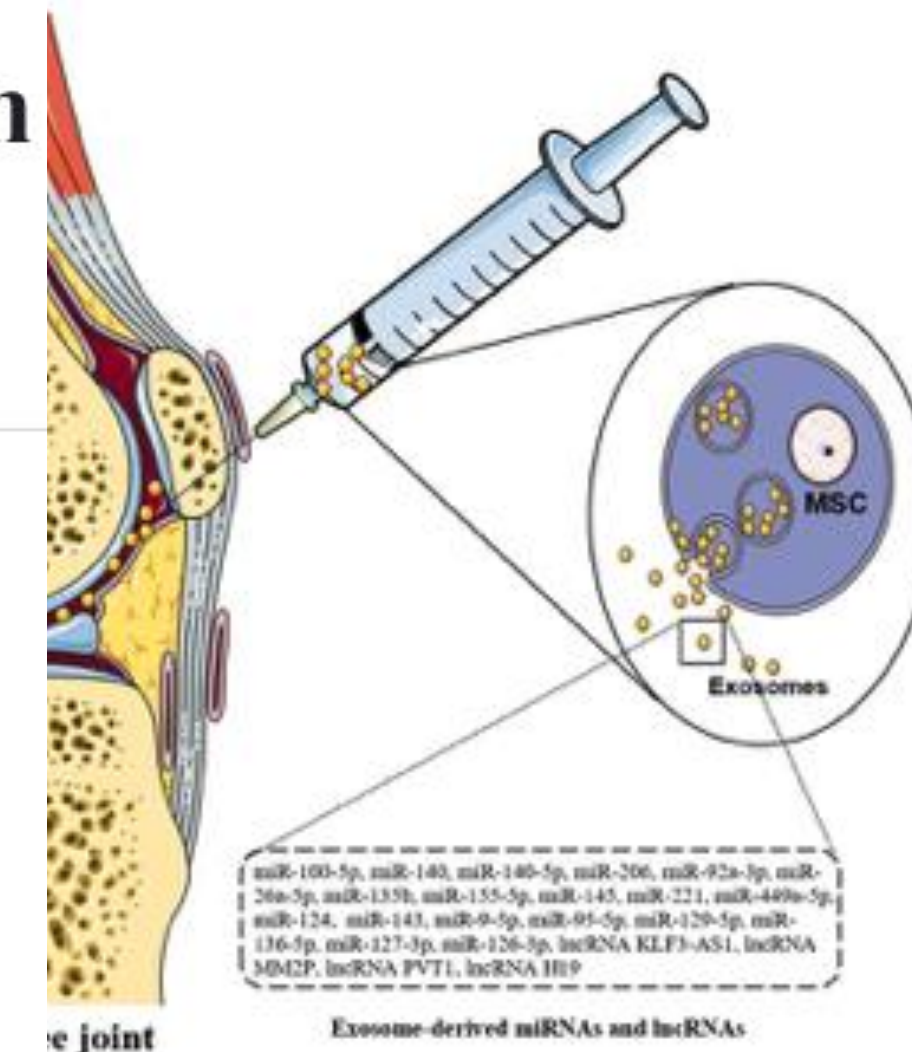
BIOLOGICS FINANCIAL SPORTS MEDICINE

Department of Defense (DoD) Awards Nearly \$1 Million to Steadman Philippon Research Institute (SPRI) for Breakthrough Study on Extracellular Vesicles Therapeutic for Joint Regeneration

by Josh Sandberg September 3, 2025



New research at SPRI's Vail and Basalt, Colo. labs will explore how microscopic messengers in the body called extracellular vesicles—often referred to as exosomes—can be enhanced to treat osteoarthritis and other musculoskeletal conditions.



Cartilage Repair: Surgical Approaches, and the Promise of Exosomes

Jonathan Layne, Greta Gohring, Jeff Christiansen, Ben Rothrauff



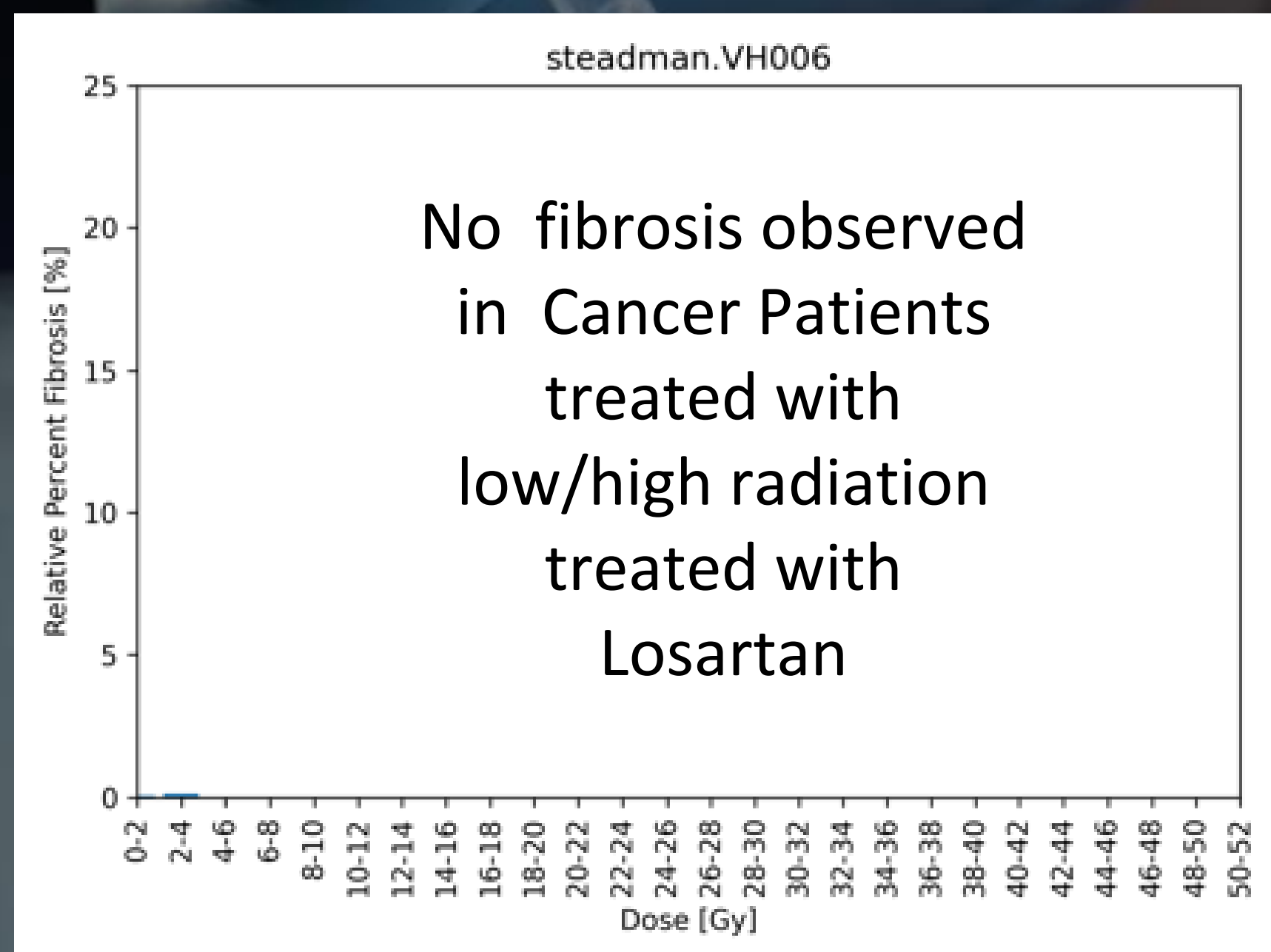
With a dedication to clinical translation, SPRI made significant progress on its 7 active clinical trials this year

- SPRI **completed enrollment ahead of schedule** for the NIH-funded Regenerative Medicine Enrollment Project and the results are being analyzed
- SPRI **completed enrollment for 3 DOD funded clinical trials** and the results are being analyzed
- SPRI launched **two new clinical trials** that began enrollment in 2024: a **new spine clinical trial with Dr. Gill** and a **total knee clinical trial with Dr. Kim**
- Additionally, SPRI is collaborating with Vail Health on 3 additional clinical trials: mental health (2) and cancer (1)

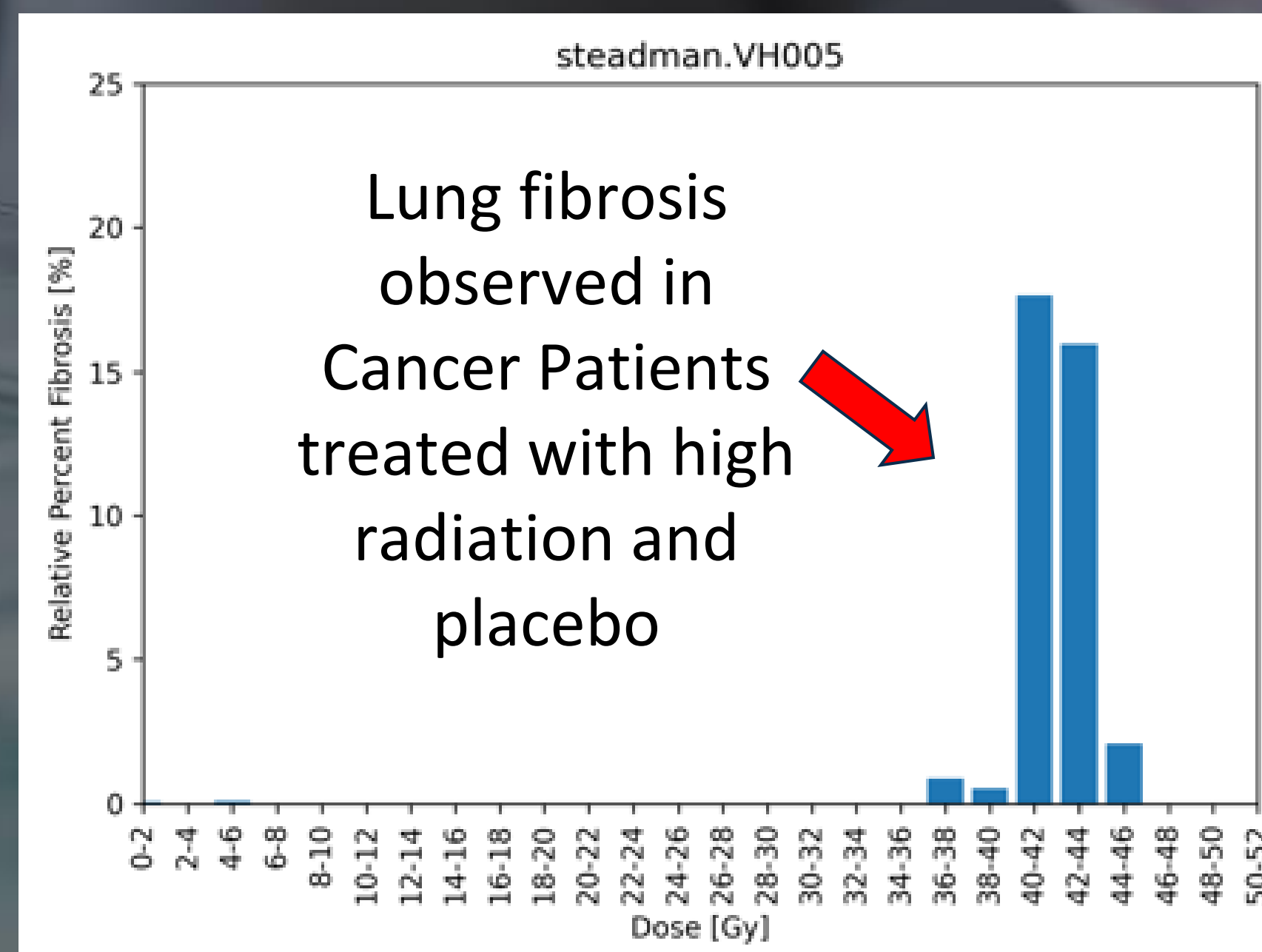
The SPRI x Shaw Cancer Center collaborative pilot program utilizing Losartan to reduce radiation-induced fibrosis in breast cancer patients has produced **remarkable results**, demonstrating **near zero fibrosis** in several patients, and has the potential to be applied to **all radiation-based oncology**

Example of Pilot Findings

Patient 6 (low ACE = Losartan)



Patient 5 (High ACE = No Losartan)



The pilot has demonstrated:

- Positive impact **returning** key biomarkers to base level
- Minimal lung fibrosis in patients treated with Losartan
- Tremendous potential for further cancer research

Optimizing Surgical Outcome Research Program



Pre-During-Post Optimizing Surgical Outcome

Before Surgery

Personalized Medicine

Biomarkers, genetic analyses
J Huard, Barry Sandler

Exercise Mimetics and Skeletal Muscle health

Aiping Lu, PhD, Program Director

Behavioral health Innovation Center, Mental Health Program

Dr. Charles Raison, Chris Lindley, Barry Sandler

Novel Imaging & Motion analyses

Scott Tashman Ph.D and Colin Smith Program Directors

Healthy Aging drugs and supplements

Xuqing Gao (MD/Ph.D)
Program Director

During Surgery

Stem Cell Banking

Aiping Lu Ph.D; Ruth McCarrick-Walmsley BS, Program Director

Crispr Cas9 SMART stem cells

Naoki Nakayama Ph,D, Program Director

Inducible Pluripotent Stem cell technology

Naoki Nakayama Ph,D, Program Director

Exosomes Therapeutics

Ping Guo (Ph.D); Greta Gohring (BS), Program Directors

mRNA Technology for musculoskeletal Repair

Xuqing Gao MD/Ph.D

After Surgery

Fibrosis chronic inflammation Research Program

Dr. Ping Guo Program Director

Computational modeling
Movement biomechanics and dynamic imaging
Dr. Tashman, Smith

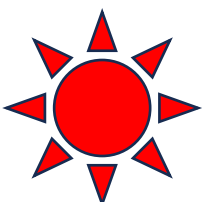
AI & ML Predictive Model for musculoskeletal Repair

Joanna Roder Ph.D, Grant Dornan MSc, Program Directors

Mental Health Research Program

Chloe Barton, Sara Robinson, Luz Thede, David Koppersmith

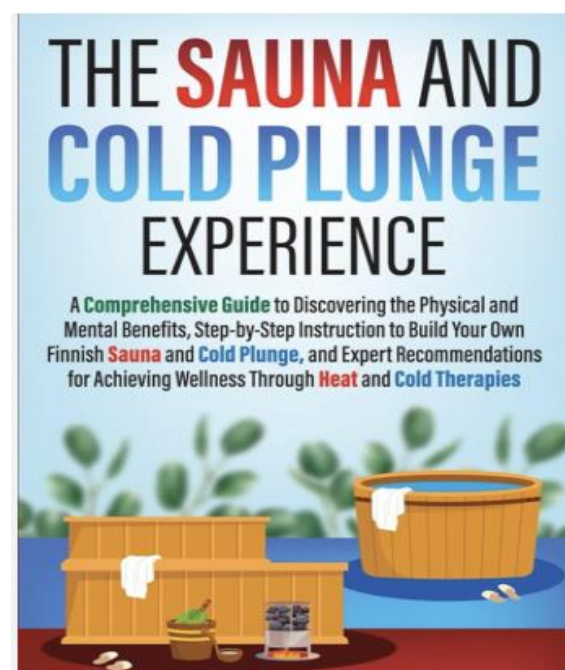
Blood Flow Restriction
Howard Head Vail Health

 **Regenerative Pre-habilitation**

Regenerative During Surgery

Regenerative Re-habilitation

Sauna and cold plunge, a practice known as contrast therapy, shows promise for treating depression and anxiety by regulating stress hormones, boosting feel-good neurotransmitters like norepinephrine and serotonin, and improving sleep and mental clarity



VH-SPRI Behavioral Health Studies

CHILL'D Study - **Approved**

Cold and Heat Investigation to Lower Levels of Depression (CHILL'D)

Program Director: Charles Raison, MD, Johnny Huard Ph.D

PI: Barry Sandler, DO

Medically healthy adults currently experiencing depressive symptoms is randomized to receive either a single Whole Body Hyperthermia (heat therapy) treatment or a Whole Body Hyperthermia treatment followed by a cold water plunge.

CRPM will perform senescence and biomarker analyses at the following timepoints:

- Baseline (pre-intervention)
- Baseline (post-intervention)
- 1 week post-intervention
- 2 weeks post-intervention



VH BHIC enrolled many participant into the CHILL'D Study on 5/30/24. The first subject completed the protocol follow-ups on 6/18/24. Now they have many patients enrolled. The SPRI CRPM lab has processed samples received for 14 subjects and has stored them for future analyses.

VH BHIC is continuing to screen individuals for study enrollment.

Which biomarkers for mental health are we using?

Interleukin-6 (IL-6) is considered a potential biomarker for depression, elevated levels of IL-6 in the blood of individuals diagnosed with Major Depressive Disorder (MDD), suggesting a link between inflammation and depressive symptoms

Short Communication

The antidepressant effect of whole-body hyperthermia is associated with the classical interleukin-6 signaling pathway

Naoise Mac Giollabhui^{a,*}, Christopher A. Lowry^b, Maren Nyer^a, Simmie L. Foster^a, Richard T. Liu^a, David G. Smith^c, Steven P. Cole^d, Ashley E. Mason^e, David Mischoulon^a, Charles L. Raison^{f,g,h}

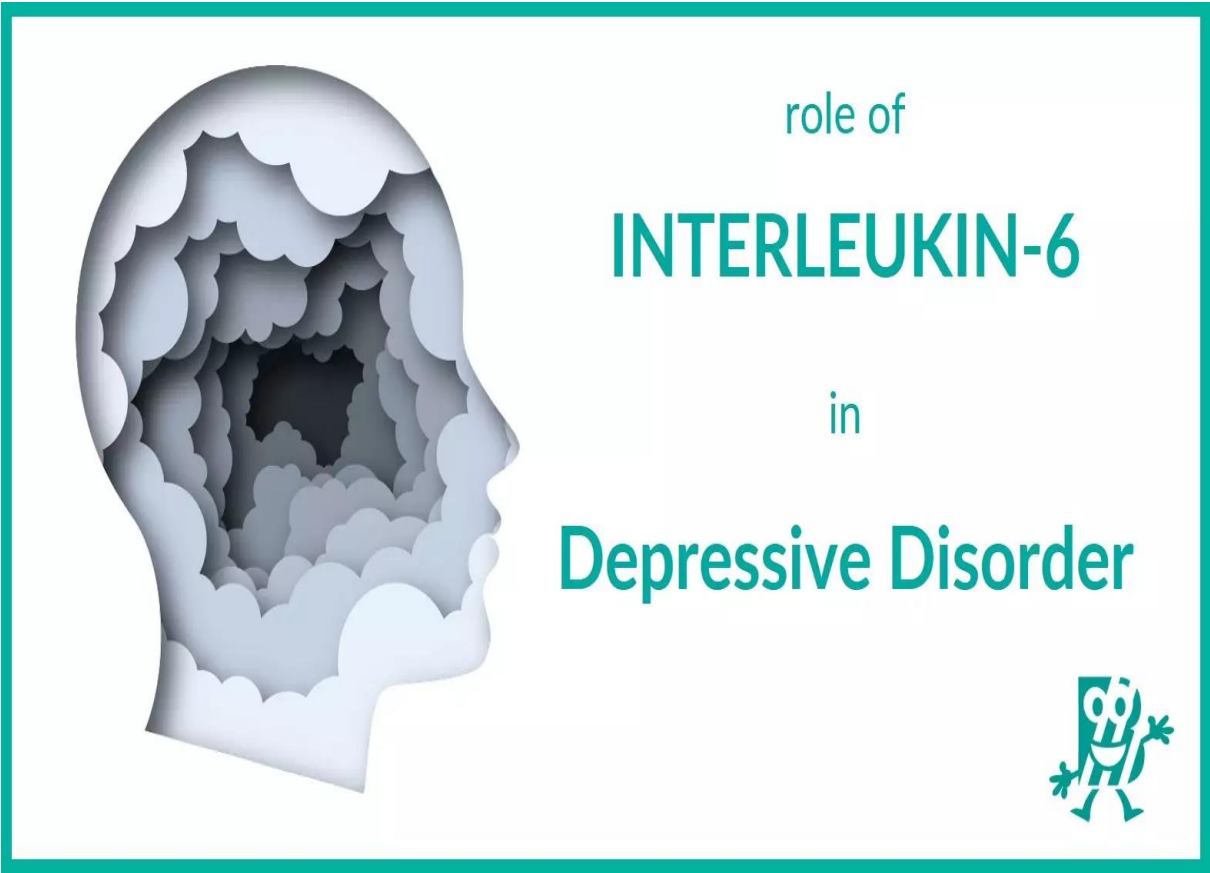
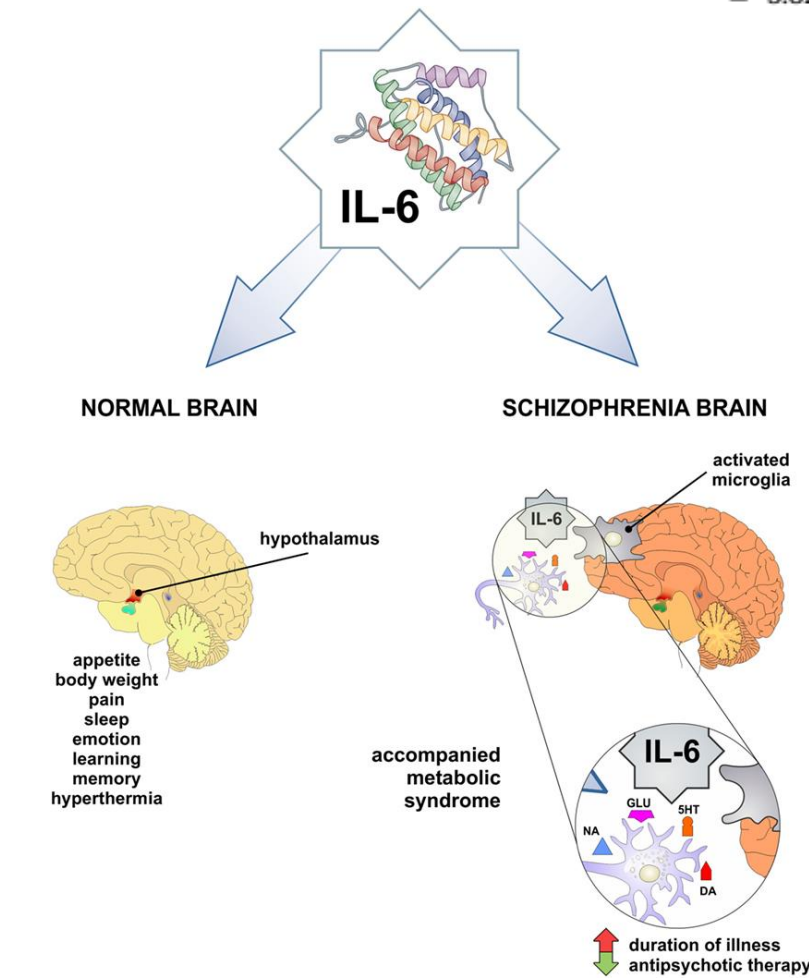
^a Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA
^b Department of Integrative Physiology, University of Colorado, Boulder, CO, USA
^c Center for Single Cell Biology, Children's Hospital of Philadelphia, Philadelphia, PA, USA
^d Research Design Associates, Yorktown Heights, NY, USA
^e Department of Psychiatry, University of California, San Francisco, CA, USA
^f Department of Psychiatry, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI, USA
^g Vail Health Behavioral Health, Edwards, CO, USA
^h Department of Spiritual Health, Woodruff Health Sciences Center, Emory University, Atlanta, GA, USA

ARTICLE INFO

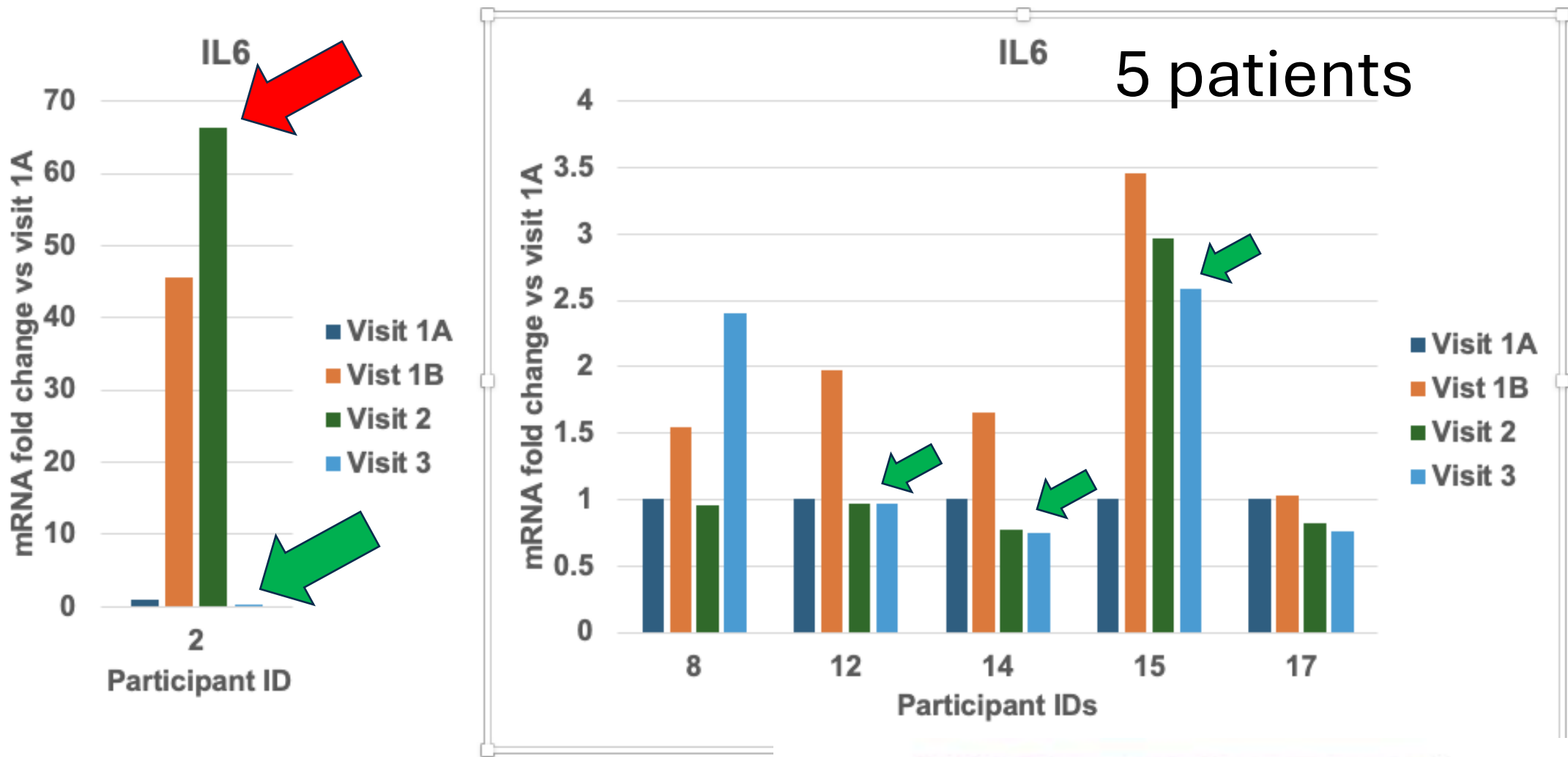
Keywords:
Depression
Randomized Clinical Trial
Whole-body Hyperthermia
Interleukin-6
Soluble Interleukin-6
Mechanism
Treatment

ABSTRACT

There is urgent need for novel antidepressant treatments that confer therapeutic benefits via engagement with identified mechanistic targets. The objective of the study was to determine whether activation of the classical anti-inflammatory interleukin-6 signaling pathways is associated with the antidepressant effects of whole-body hyperthermia. A 6-week, randomized, double-blind study compared whole-body hyperthermia with a sham condition in a university-based medical center. Medically healthy participants aged 18–65 years who met criteria for major depressive disorder, were free of psychotropic medication use, and had a baseline 17-item Hamilton Depression Rating Scale score ≥ 16 were randomized with 1-to-1 allocation in blocks of 6 to receive whole-body hyperthermia or sham. Of 338 individuals screened, 34 were randomized, 30 received interventions and 26 had ≥ 2 blood draws and depressive symptom assessments. Secondary data analysis examined change in the ratio of IL-6:soluble IL-6 receptor pre-intervention, post-intervention, and at weeks 1 and 4. Hierarchical linear modeling tested whether increased IL-6:soluble IL-6 receptor ratio post-intervention was associated with decreased depressive symptom at weeks 1, 2, 4 and 6 for those randomized to whole-body hyperthermia. Twenty-six individuals were randomized to whole-body hyperthermia [$n = 12$; 75 % female; age = 37.9 years ($SD = 15.3$) or sham [$n = 14$; 57.1 % female; age = 41.1 years ($SD = 12.5$). When compared to the sham condition, active whole-body hyperthermia only increased the IL-6:soluble IL-6 receptor ratio post-treatment [$F(3,72) = 11.73, p < .001$], but not pre-intervention or at weeks 1 and 4. Using hierarchical linear modeling, increased IL-6:sIL-6R ratio following whole-body hyperthermia moderated depressive symptoms at weeks 1, 2, 4 and 6, such that increases in the IL-6:soluble IL-6 receptor ratio were associated with decreased depressive symptoms at weeks 1, 2, 4 and 6 for those receiving the active whole-body hyperthermia compared to sham treatment ($B = -229.44, t = -3.82, p < .001$). Acute activation of classical interleukin-6 signaling might emerge as a heretofore unrecognized mechanism that could be harnessed to expand the antidepressant armamentarium.



Whole Body Hyperthermia + cold plunge influences plasma interleukin (IL-6) post-treatment in patients with major depressive disorders



AMERICAN SOCIETY FOR MICROBIOLOGY

Home / Articles / Psilocybin and Mental Health: The Magic in the Mushrooms

Psilocybin and Mental Health: The Magic in the Mushrooms

Madeline Barron, Ph.D.

Published: Feb. 10, 2023

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CBD and Anxiety and Depression FAQs

HOW DOES CBD IMPROVE MY MENTAL HEALTH ?

Studies show that CBD can help improve many mental health conditions, such as:



Preoperative depression and anxiety negatively impact surgical outcomes in female patients undergoing major surgery

- **Depression significantly worsens surgical outcomes** by increasing the risk of complications, such as infections, delirium, and readmissions, and can also prolong recovery and lead to poorer functional recovery and patient satisfaction
- **Addressing depressive symptoms** before surgery, through interventions and support, is crucial for optimizing patient recovery and improving overall surgical results.



Original Study

ANNALS OF
SURGERY OPEN

OPEN

Preoperative Depression and Anxiety Impact on Inpatient Surgery Outcomes

A Prospective Cohort Study

Roxana Geoffrion, MD,* Nicole A. Koenig, BA,* Meimuzi Zheng, MSc,* Nicholas Sinclair, BSc,* Lori A. Brotto, PhD,* Terry Lee, PhD,† and Maryse Larouche, MD MPH‡

Objectives: To determine the association of preoperative mood symptoms and postoperative adverse outcomes; to explore sex-specific differences.

Background: Depression and anxiety can increase postoperative mortality. Psychological stress is associated with a chronic inflammatory response unfavorable to postsurgical healing.

Methods: Prospective cohort study. Patients were recruited from surgical preadmission clinics at a university hospital. Preoperative depression and anxiety were measured via the Beck Depression and Beck Anxiety Inventories (BDI-II and BAI). Our primary outcome was a composite of postoperative complications, extended length of stay (ELOS) and early readmission. Associated variables included demographics, preoperative pain, pain tolerance/catastrophizing, coping mechanisms, postoperative pain, and opioid use. We adjusted for age, comorbidities, and surgical specialty.

Results: Of 1061 recruited patients (ten surgical specialties, 2015–2020), 455 males and 486 females had preoperative and postoperative data available. Mean age was 62.9 (range 20.2–96.2). At baseline, 9.3% of patients had moderate or severe depression; 7.4% had moderate or severe anxiety. Females were more likely to be moderately or severely depressed (11% vs 7%, $P = 0.036$) and moderately or severely anxious (9% vs 6%, $P = 0.034$). Females had significantly fewer reported comorbidities and lower American Society of Anesthesiologists category ($P < 0.001$). Increasing BDI-II and BAI scores significantly increased likelihood of postoperative complications, ELOS, and/or hospital readmission in females (adjusted odds ratio [aOR] = 2.57 for BDI-II 1–19 vs 0, $P = 0.041$; aOR = 4.48 for BDI-II > 19 vs 0, $P = 0.008$; aOR = 1.54 for BAI ≤ 6 vs >6, $P = 0.038$) but not in males. Mood symptoms did not influence postoperative pain or opioid use.

Conclusion: Preoperative depression and anxiety negatively impact surgical outcomes in female patients undergoing major surgery.

Pre-habilitation with (sauna/cold plunge, CBD, Psilocybin) to reduce depression & anxiety to consequently optimize surgical outcomes in patients undergoing major surgery

**Comprehensive Healthy Aging
concierge medicine**

Healthy Aging

Diet

Eat Healthy
Balanced diet
Caloric Restriction
Intermittent
Fasting

Lifestyle

Stay active
Exercise
Sleep
Reduce stress
Stay connected
No smoking
No drinking

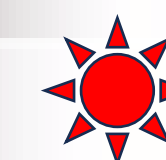


**Personalized
Medicine**
Biomarkers
Aging
Inflammatory
Fibrotic
Disease



Regenerative Medicine

Stem Cell
Banking
Stem Cell
Therapy
PRP
Exosomes



Drugs

Metformin
Rapamycin
Senolytics
Telomerase
Activity
Exercise
mimetics

Evidence Based Medicine / Patient Centered Care

Changing Lives by Keeping People **Healthy/Active**

Healthy Aging Program

Regenerative Medicine & Drugs/supplements

The Hallmarks of Aging



James Kirkland
Mayo Clinic/Cedars-Sinai Medical Center



Johnny Huard Vail, Colorado



Laura Niedernhofer
U. Minnesota



Paul Robbins
U. Minnesota



Vihang Narkar
UT Health
Houston



John Cooke
Methodist Inst. Houston



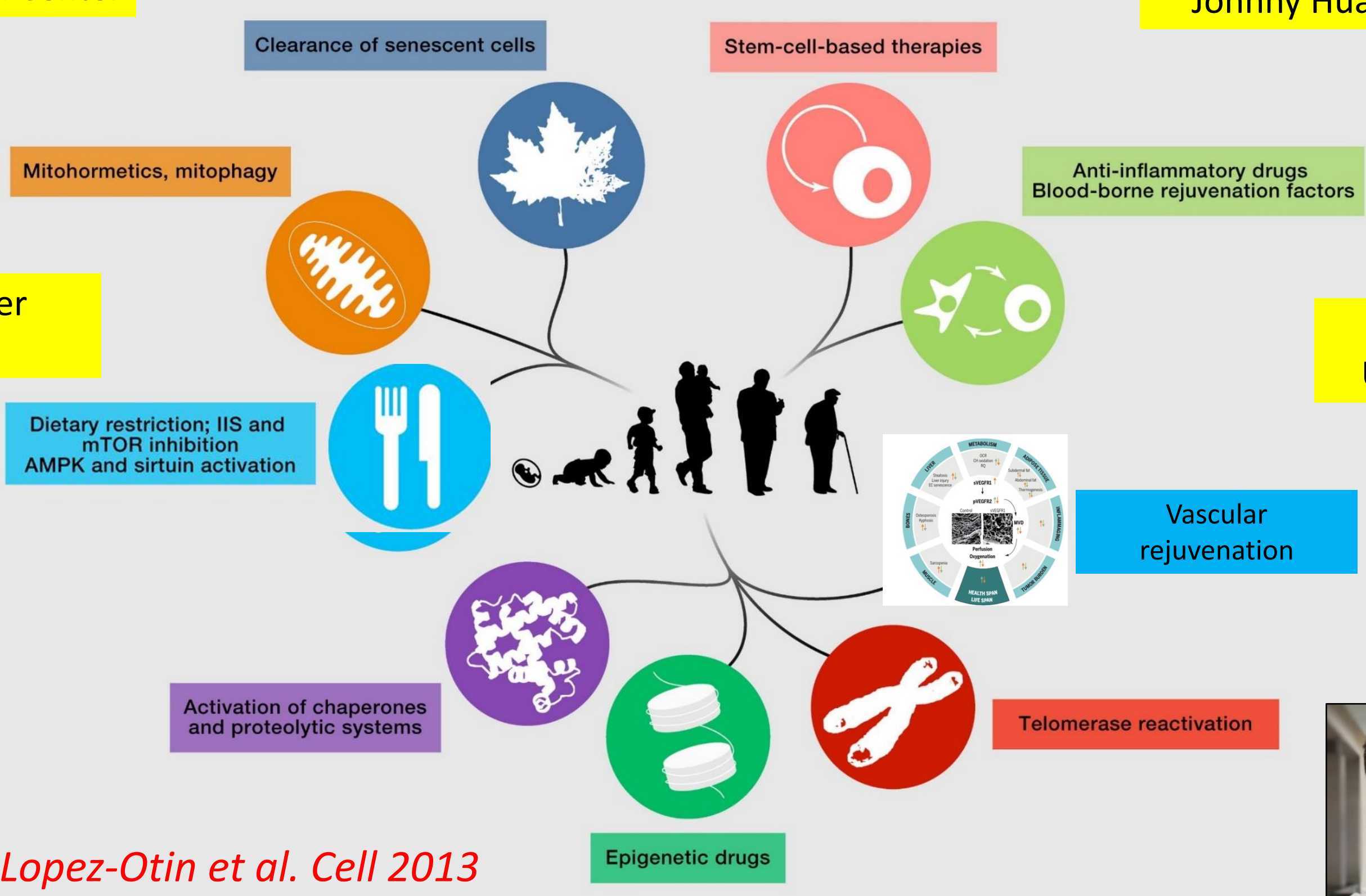
Peter Millett, Johnny Huard
Vail Colorado
Anthony Griswold
U. Miami



Tamara Alliston
UCSF



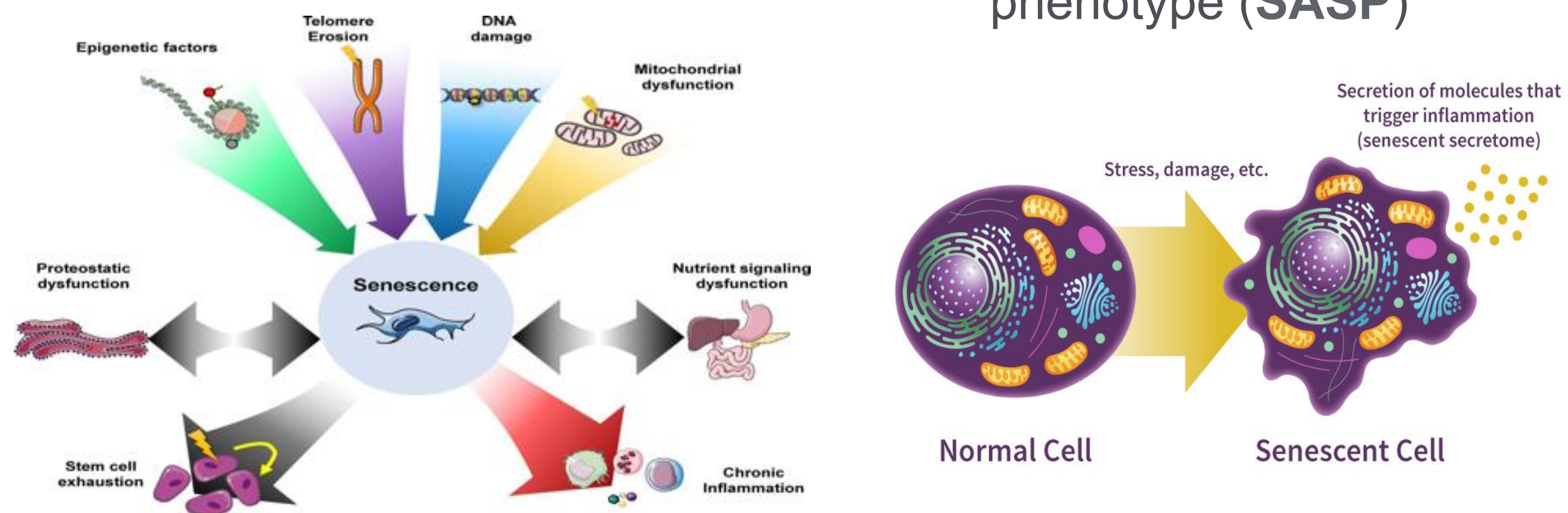
Eric Verdin
Buck Institute



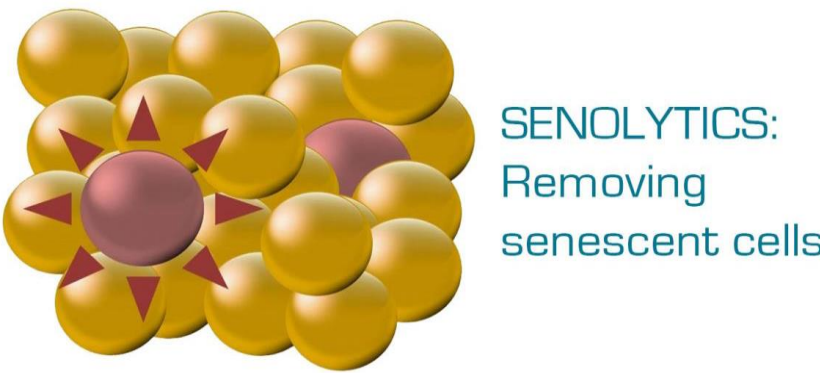
Lopez-Otin et al. Cell 2013

Killing/Clearing Senescent Cells to Delay Age-Related Diseases and Conditions

Senescence-associated secretory phenotype (SASP)



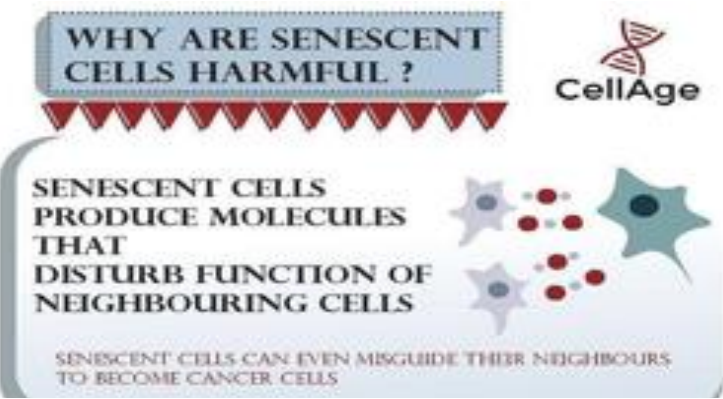
- SENOLYTICS OVERVIEW -



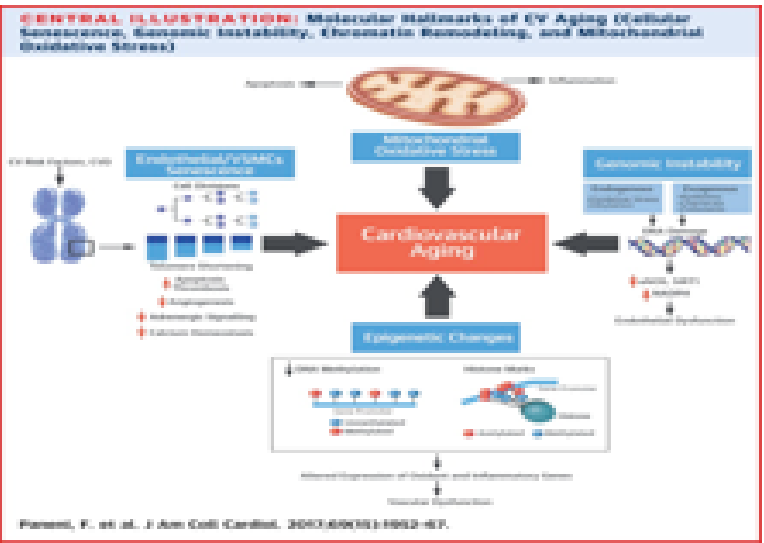
Rapamycin
Dasatinib
Quercetin
Alvespimycin (17-D)
Metformin
Fisetin



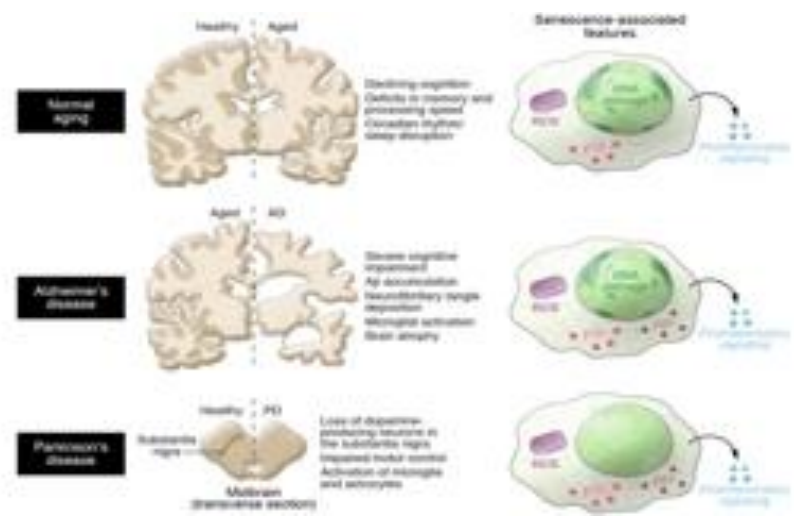
Cancer



Cardiovascular disease



Neurodegeneration



Trends in Neurosciences

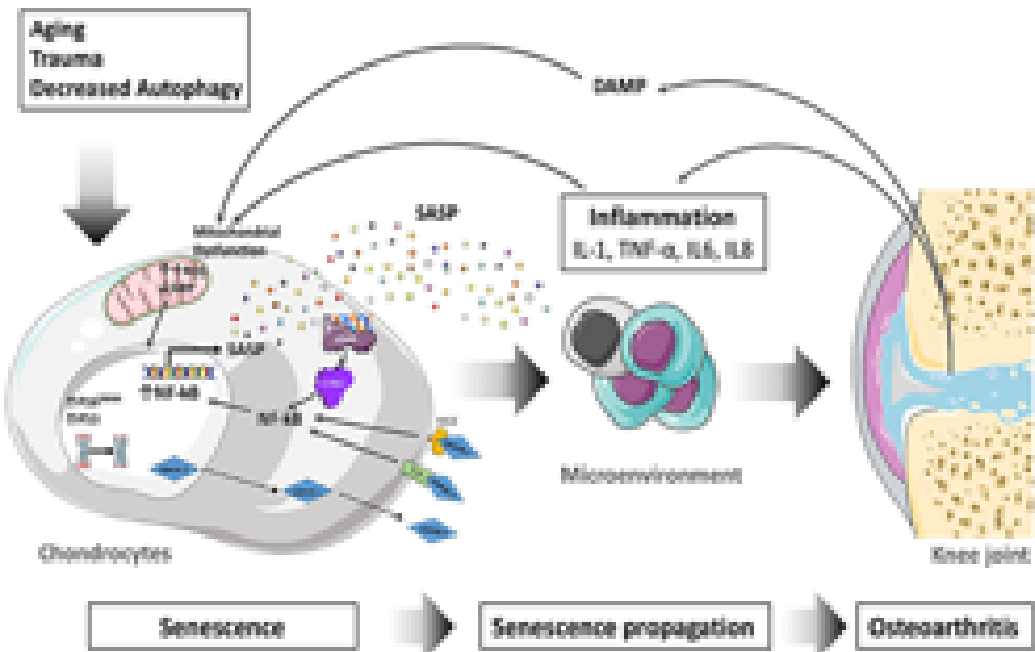
Volume 44, Issue 1
Go to Trends in Neurosciences on ScienceDirect

Feature Review
Cellular senescence at the crossroads of inflammation and Alzheimer's disease

Ana Guerrero ^{1,2}, Bart De Strooper ^{1,2,3,4}, I. Lorena Arancibia-Carcamo ^{1,2}

Show more

Osteoarthritis



JCI The Journal of Clinical Investigation

Senescent cells and osteoarthritis: a painful connection

Ok Hee Jeon, ... , Judith Campisi, Jennifer H. Elisseeff

J Clin Invest. 2018;128(4):1229-1237. <https://doi.org/10.1172/JCI95147>.

Leading Edge
Review

Cellular Senescence in Cancer and Aging

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



Ageing Research Reviews
Volume 60, July 2020, 101072

Targeting senescent cells to attenuate cardiovascular disease progression

Ping Song ¹, Qiang Zhao, Ming-Hui Zou

SPRI now has definitive scientific evidence that Fisetin reduces senescent cells and age-related serum biomarkers

Our team investigated a large cohort (175) of healthy and osteoarthritic patients to test the impact of senolytic therapeutics; **elevated cellular senescence was confirmed in osteoarthritis (OA) patients**

Through this research, the SPRI team now believes they will be able to **detect changes in blood following senolytic therapy**, which may lead to the prediction of age-related orthopaedic decline

Our team believes this research may be **clinically pertinent for quantifying cellular senescence** and determining its role in OA progression

[Aging Cell](#). 2024 May; 23(5): e14113. Published online 2024 May 6. doi: [10.1111/ace1.14113](https://doi.org/10.1111/ace1.14113)

Received: 1 May 2023 | Revised: 23 January 2024 | Accepted: 29 January 2024
DOI: 10.1111/ace1.14113

RESEARCH ARTICLE

Aging Cell WILEY

Clinical validation of C_{12} FDG as a marker associated with senescence and osteoarthritic phenotypes

William S. Hambricht¹ | Victoria R. Duke¹ | Adam D. Goff¹ | Alex W. Goff¹ | Lucas T. Minas¹ | Heidi Kloser¹ | Xueqin Gao¹ | Charles Huard¹ | Ping Guo¹ | Aiping Lu¹ | John Mitchell¹ | Michael Mullen¹ | Charles Su¹ | Tamara Tchkonja² | Jair M. Espindola Netto² | Paul D. Robbins³ | Laura J. Niedernhofer³ | James L. Kirkland^{2,4} | Chelsea S. Bahney^{1,5} | Marc Philippon¹ | Johnny Huard¹

¹Center for Regenerative Sports Medicine, Steadman Philippon Research Institute, Vail, Colorado, USA

²Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, Minnesota, USA

³Department of Biochemistry and Molecular Biology and Biophysics, Institute on the Biology of Aging and Metabolism, University of Minnesota, Minneapolis, Minnesota, USA

⁴Division of General Internal Medicine, Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA

⁵Orthopaedic Trauma Institute, University of California San Francisco, San Francisco, California, USA

Correspondence
Johnny Huard, Center for Regenerative Sports Medicine, Steadman Philippon Research Institute, 181 W. Meadow Dr., Vail, CO, USA.
Email: jhuard@sprivail.org

Funding information
National Institute of Arthritis and Musculoskeletal and Skin Diseases, Grant/Award Number: 3 UH3 AR077748-0251 and UH3AR077748; Orthopaedic Research and Education Foundation, Grant/Award Number: TAF-21-059

Abstract

Chronic conditions associated with aging have proven difficult to prevent or treat. Senescence is a cell fate defined by loss of proliferative capacity and the development of a pro-inflammatory senescence-associated secretory phenotype comprised of cytokines/chemokines, proteases, and other factors that promotes age-related diseases. Specifically, an increase in senescent peripheral blood mononuclear cells (PBMCs), including T cells, is associated with conditions like frailty, rheumatoid arthritis, and bone loss. However, it is unknown if the percentage of senescent PBMCs associated with age-associated orthopedic decline could be used for potential diagnostic or prognostic use in orthopedics. Here, we report senescent cell detection using the fluorescent compound C_{12} FDG to quantify PBMCs senescence across a large cohort of healthy and osteoarthritic patients. There is an increase in the percent of circulating C_{12} FDG⁺ PBMCs that is commensurate with increases in age and senescence-related serum biomarkers. Interestingly, C_{12} FDG⁺ PBMCs and T cells also were found to be elevated in patients with mild to moderate osteoarthritis, a progressive joint disease that is strongly associated with inflammation. The percent of C_{12} FDG⁺ PBMCs and age-related serum biomarkers were decreased in study participants taking the senolytic drug fisetin. These results demonstrate quantifiable measurements in a large group of participants that could create a composite score of healthy aging sensitive enough to detect changes following senolytic therapy and may predict age-related orthopedic decline. Detection of peripheral senescence in PBMCs and subsets using C_{12} FDG may be clinically useful for quantifying cellular senescence and determining how and if it plays a pathological role in osteoarthritic progression.



Healthy Aging Program Personalized Report



STEADMAN PHILIPPON RESEARCH INSTITUTE

HEALTHY AGING PROGRAM

Personalized Report

NAME

DATE OF REPORT

August 26, 2025

PERSONALIZED MEDICINE

An Individualized Approach

Personalized medicine uses data from your genetic, lifestyle, and environmental characteristics to tailor a treatment plan to you.

Precision medicine uses data from your genetic, lifestyle, and environmental characteristics to tailor a treatment plan to you.

NEXT STEPS

What do these results mean for you?

These results are not intended as a diagnostic tool but should serve as a guide for focusing on adopting healthy habits and positive lifestyle choices. This includes maintaining a balanced diet, engaging in regular physical activity, staying mentally active, and prioritizing social and emotional well-being — all of which help positively influence your cellular senescence results. Additionally, you may find it beneficial to consult with your healthcare provider regarding the incorporation of supplements, such as Fisetin, Quercetin, and others, which may help reduce cellular senescence.*

Senescence testing can be repeated, ideally on an annual basis, to monitor any changes relative to your baseline results.

The aim of our Healthy Aging Program is to integrate various tests — such as cellular senescence, inflammatory biomarkers, and telomere length — to more accurately assess your aging status. Our testing protocols are continually refined as we collect data from more individuals, improving the precision of your percentile estimation within your age group.

For further insight, the following publications provide more information regarding our testing and the implications of cellular senescence during the aging process:

[Hambricht WS, Duke VR, Goff AD, et al. Clinical validation of C12FDG as a marker associated with senescence and osteoarthritic phenotypes. Aging Cell. 2024;23\(5\):e141113. doi:10.1111/acel.14113](#)

[Di Micco R, Krizhanovsky V, Baker D, d'Adda di Fagagna F. Cellular senescence in ageing: from mechanisms to therapeutic opportunities. Nat Rev Mol Cell Biol. 2021;22\(2\):75-95. doi:10.1038/s41580-020-00314-w](#)



STEADMAN PHILIPPON RESEARCH INSTITUTE

01

Testing of baseline cellular senescence

02

Review results with healthcare provider

03

Incorporate changes to improve cellular senescence

04

Repeat testing annually to monitor changes in cellular senescence

05

Explore additional tests to assess aging status

*Please note that these results should be reviewed with a healthcare provider in the context of your overall health before making any changes to your lifestyle, medications, or supplements. These results have been generated within a research context and should not be used for diagnostic purposes or for making decisions without medical oversight.

HEALTHY AGING | PAGE 6



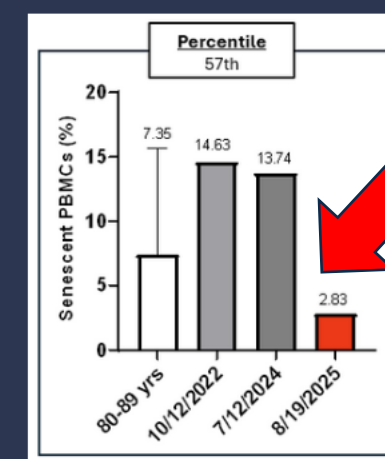
STEADMAN PHILIPPON RESEARCH INSTITUTE

SUMMARY OF SENESENCE TESTING RESULTS

Date of Testing: 08/19/2025

SPRI's methodology of detecting senescent (aging) cells in blood uses a technique called flow cytometry. We look at a specific type of blood cells called Peripheral Blood Mononuclear Cells (PBMCs), which are good indicators of aging or the senescent state in the blood.

We utilize a special stain that highlights senescent cells. When we analyze the stained PBMCs via flow cytometry, we see distinct groups of cells that glow brightly. This brightness occurs because of the fluorescent marker that we use, which only glows when it reacts with an enzyme that increases during cell aging (senescence). Cells with higher brightness have more of this enzyme, which suggests that they are in a later stage of aging.



*Results are based upon your average data compared to the average collected data of individuals in the same age bracket

Please note that these results cannot be used for diagnostic purposes. Results obtained from SPRI's patent-pending technology based on flow cytometry technique may vary based upon optimization and validation methodologies used to identify and measure senescent PBMCs.

HEALTHY AGING | PAGE 5

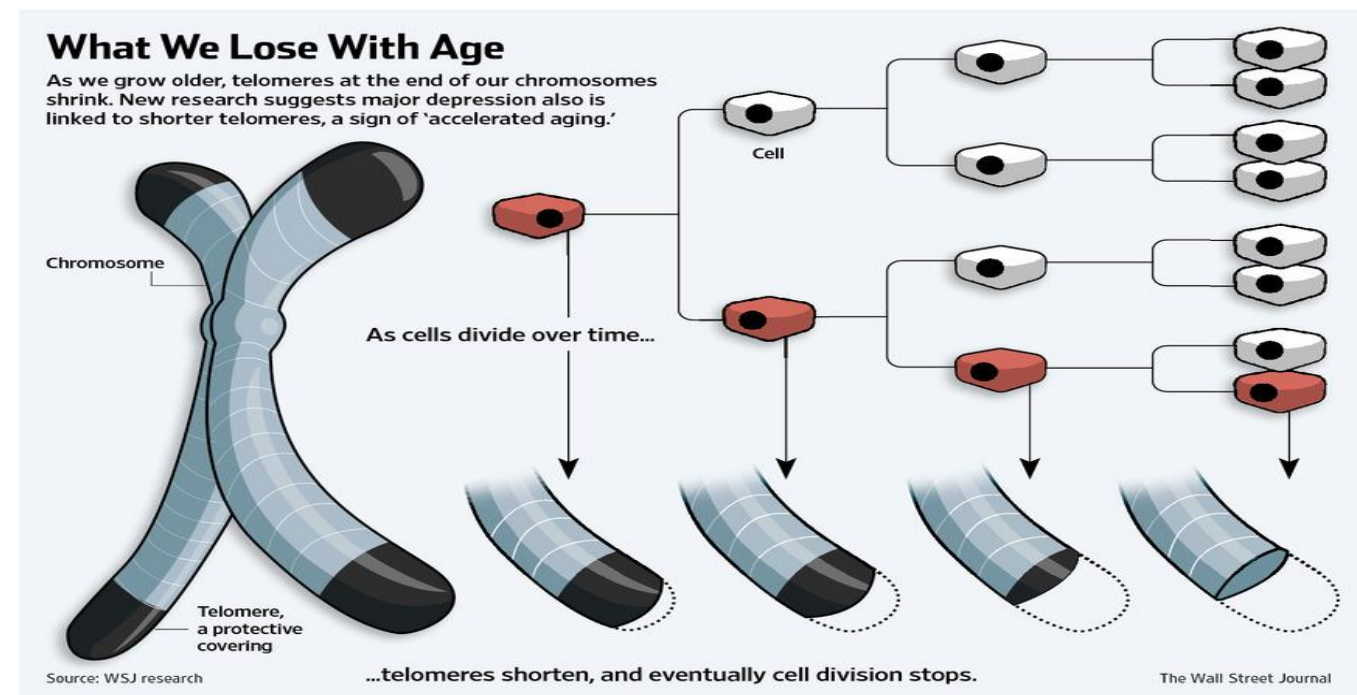


After fisetin treatment

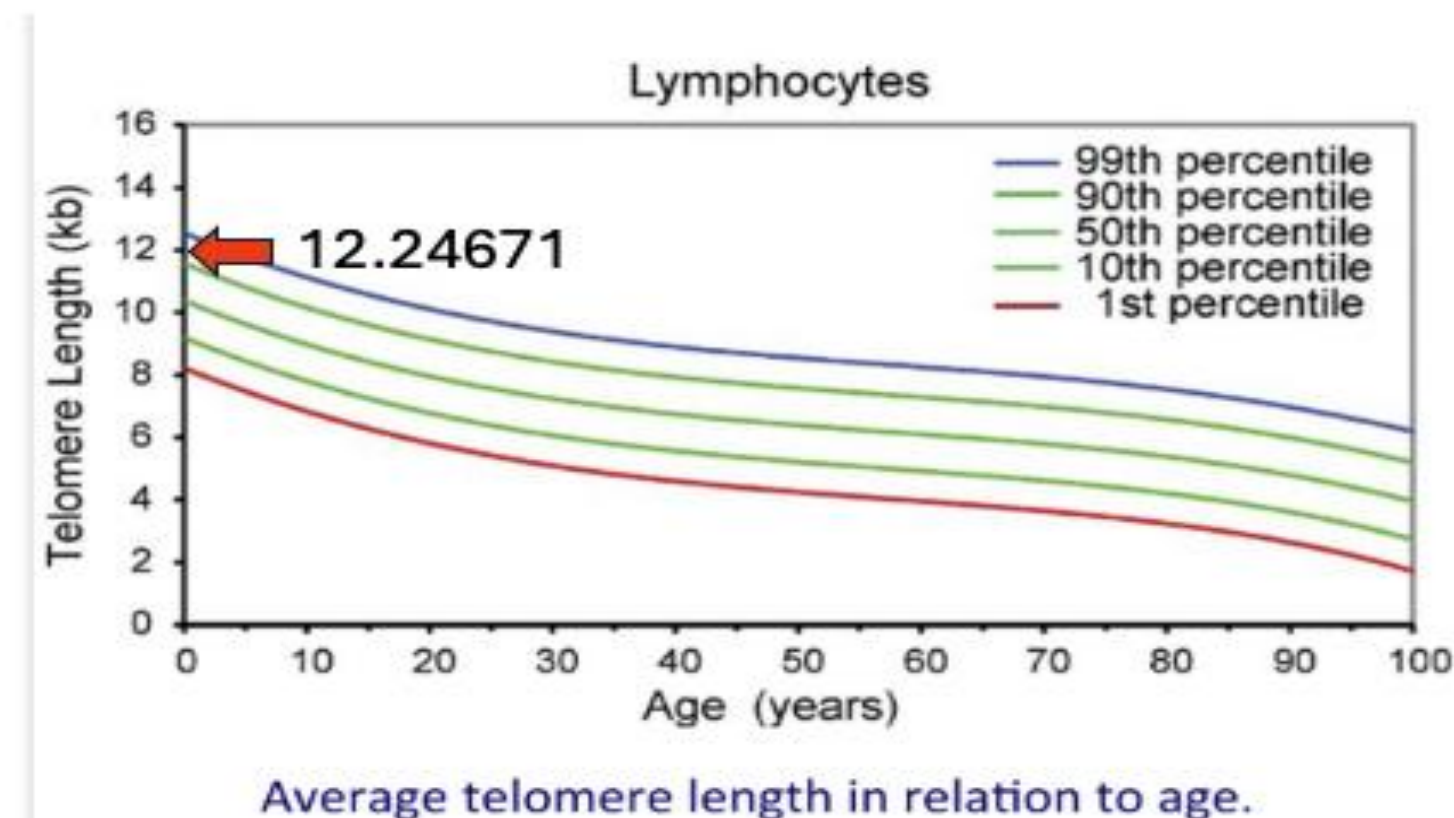
Telomere Length

Telomere is a region of repetitive DNA sequences at the end of a chromosome. Each time a cell divides, the telomeres become slightly shorter.

Telomere length is a potential biomarker of aging, as it shortens with age and is linked to aging-related conditions.



LH-PBMC: 12.24671 ±0.896101 (Kilo base pair)



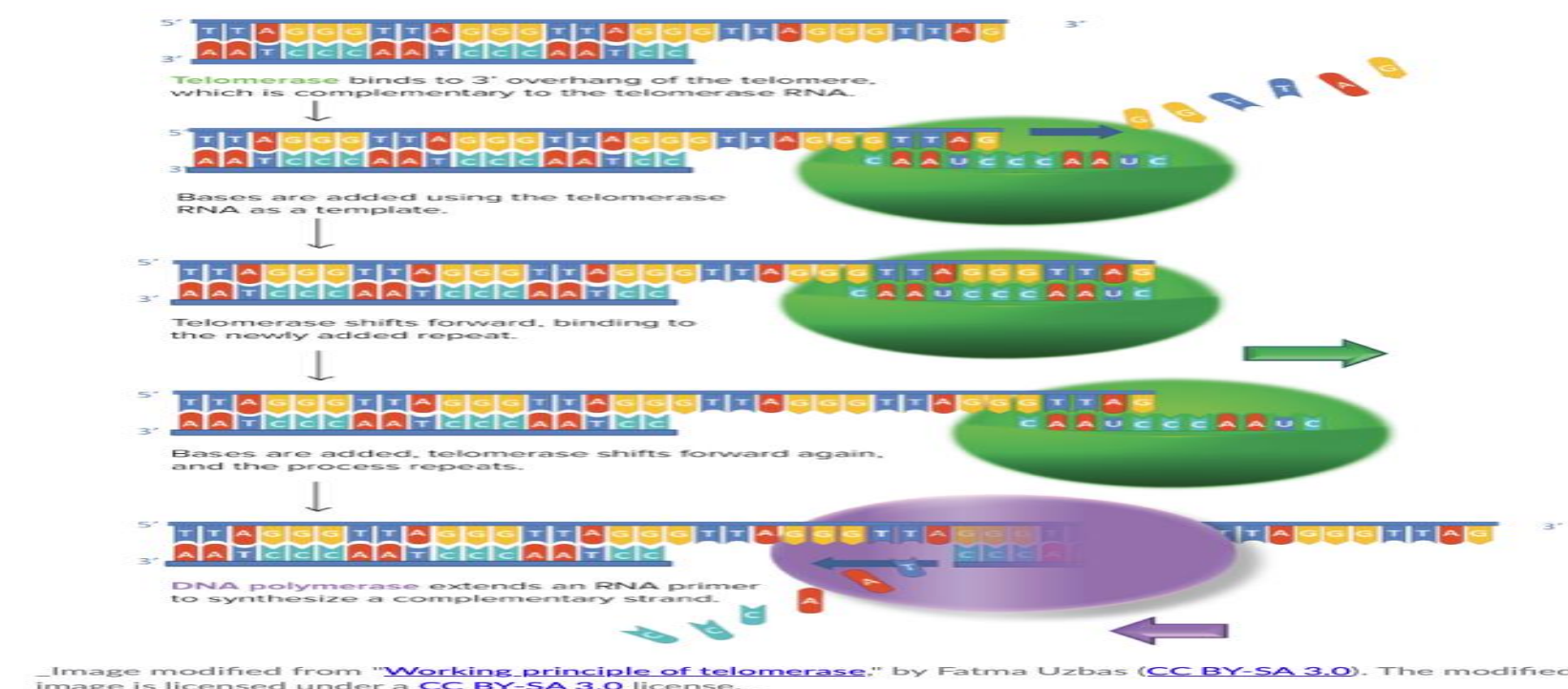
LAB: 12.24671 KB 99TH PERCENTILE FOR AGE GROUP
DNA Telomere length Results: OUTSTANDING

These values are above 99th percentile for age group. 99% of people of the same age as shorter telomere and lower telomerase activity!

Telomerase

Telomerase is an enzyme that increases the length of telomeres, the protective caps at the end of chromosomes.

Longer telomeres are considered a strong indicator of high telomerase activity, as telomerase is the enzyme primarily responsible for lengthening telomeres,



L.H. Plasma Telomerase by ELISA

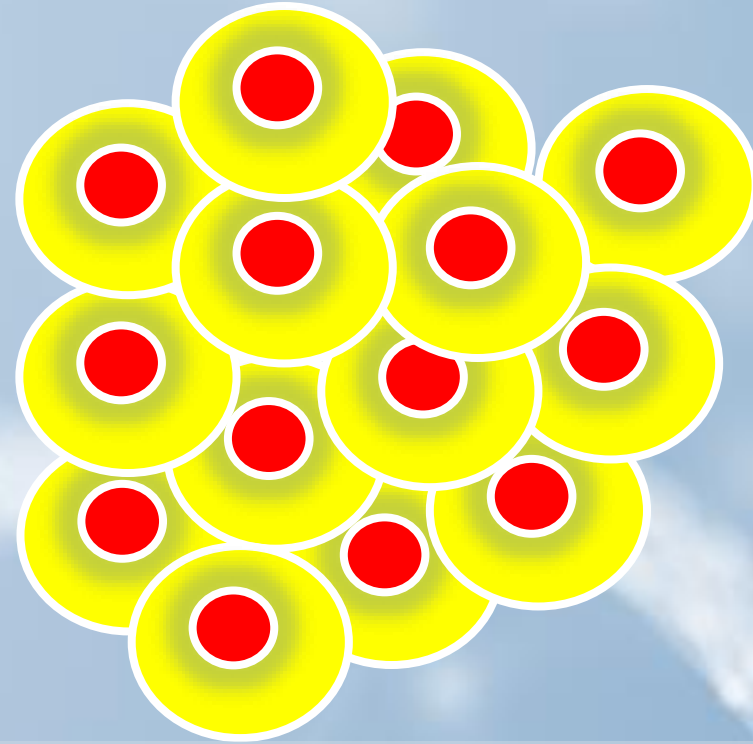
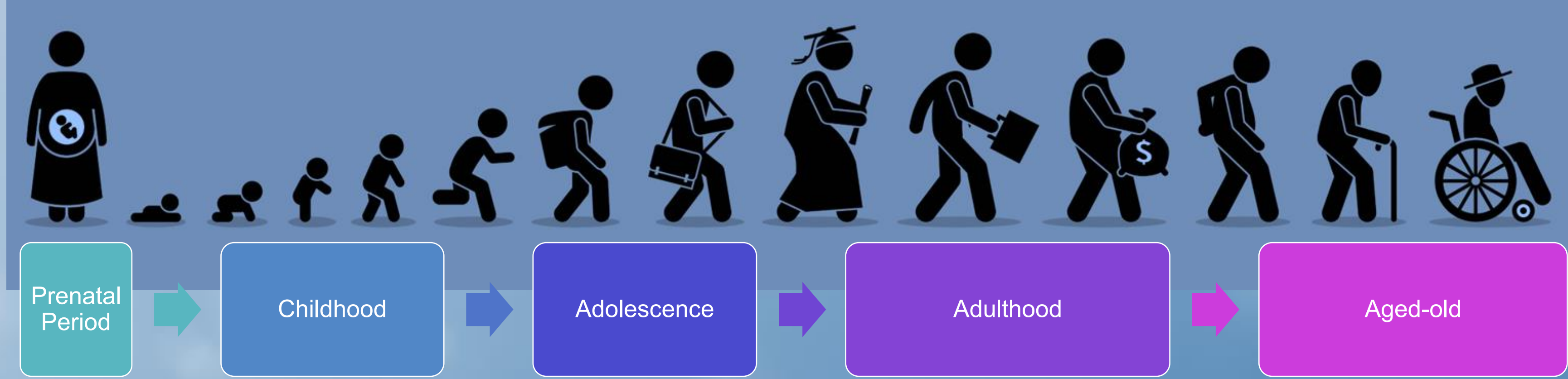
LH plasma Average
Telomerase: 2.15218ng/ml

Kits provided Normal range:

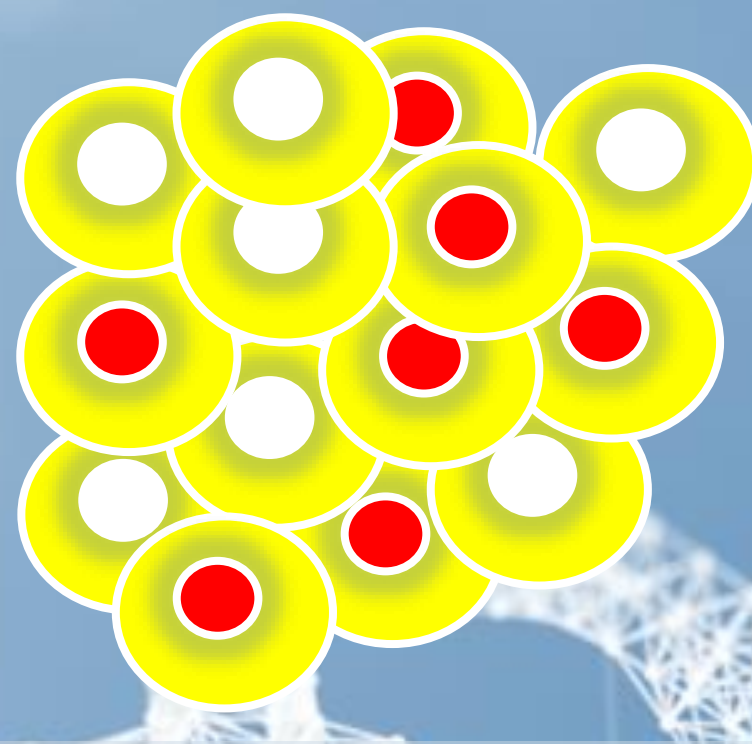
Human Plasma:0.24-
1.3ng/ml, Average 0.52 ng/ml.

Telomerase level is 4 times more elevated
than normal level

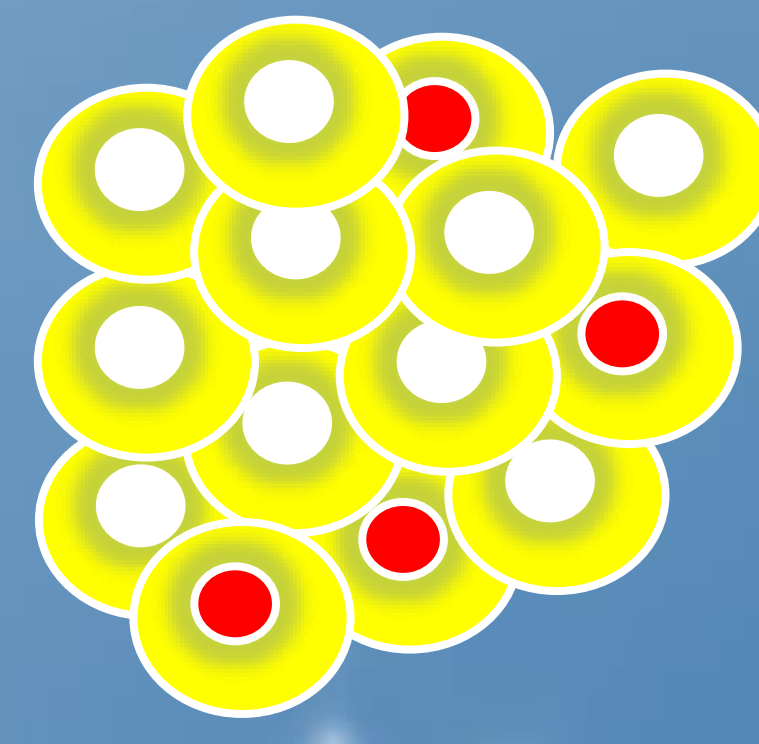
Stem cells depletion/ exhaustion during the aging process



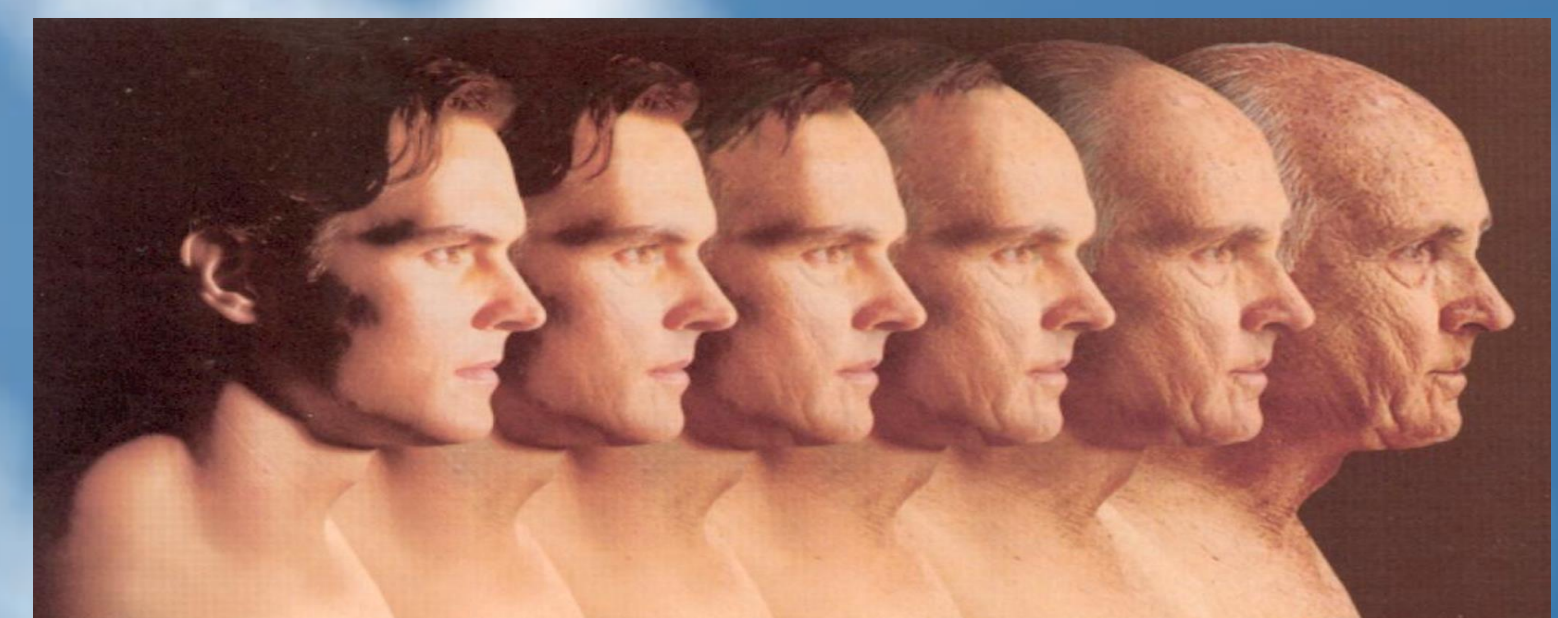
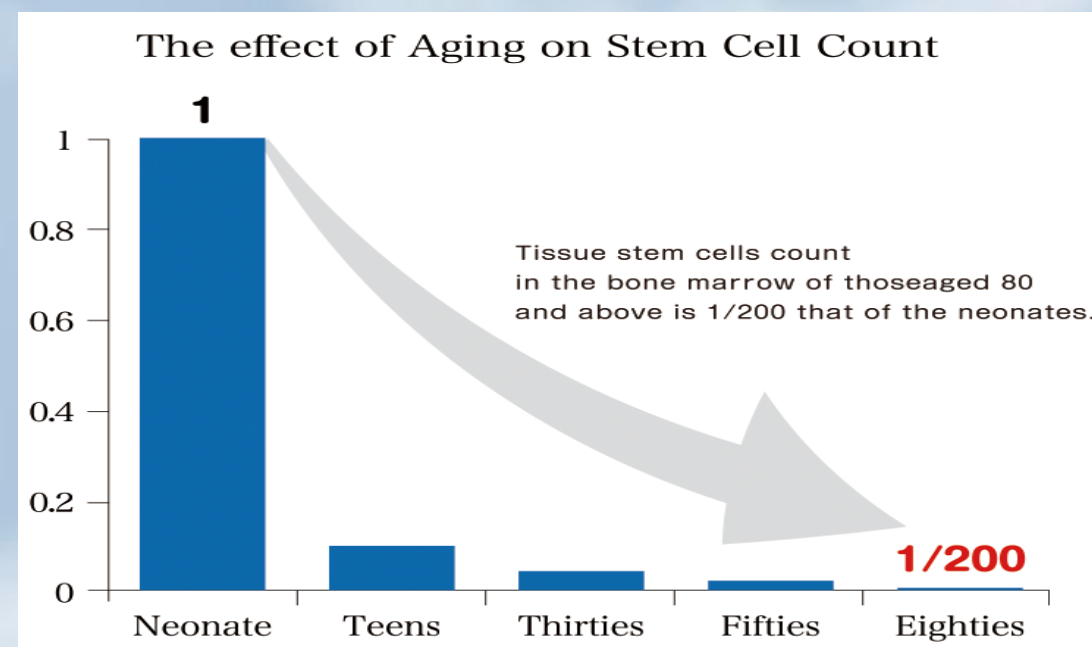
At birth 100% of cells are good with rejuvenation/ regenerative potential



In adults 50% of cells are good with rejuvenation/ regenerative potential



At older age, 75% of cells become senescent and lose rejuvenation potential



20 years of work at the University of Pittsburgh

UTHealth & SPRI: 2015 - present

Isolation of muscle-derived stem cells (MDSCs)

Late 1990s – early 2000s

Regenerative medicine with MDSCs

Mid 2000s

Isolation of human MDSCs & clinical trials with human MDSCs

2006-present

Origin of MDSCs, mechanisms of actions

2007-2009

Promoting angiogenesis for tissue repair

2011-2014

Blocking angiogenesis is required for the repair of non-vascularized tissues

2012-2014

Stem cell depletion during aging

2011-2015

Parabiotic pairing between normal and old or diseased mice

2014-2017

Pregnancy as a natural form of parabiotic pairing

2014-2018



Paul Robbins

Laura Niedernhofer



Progeria mice



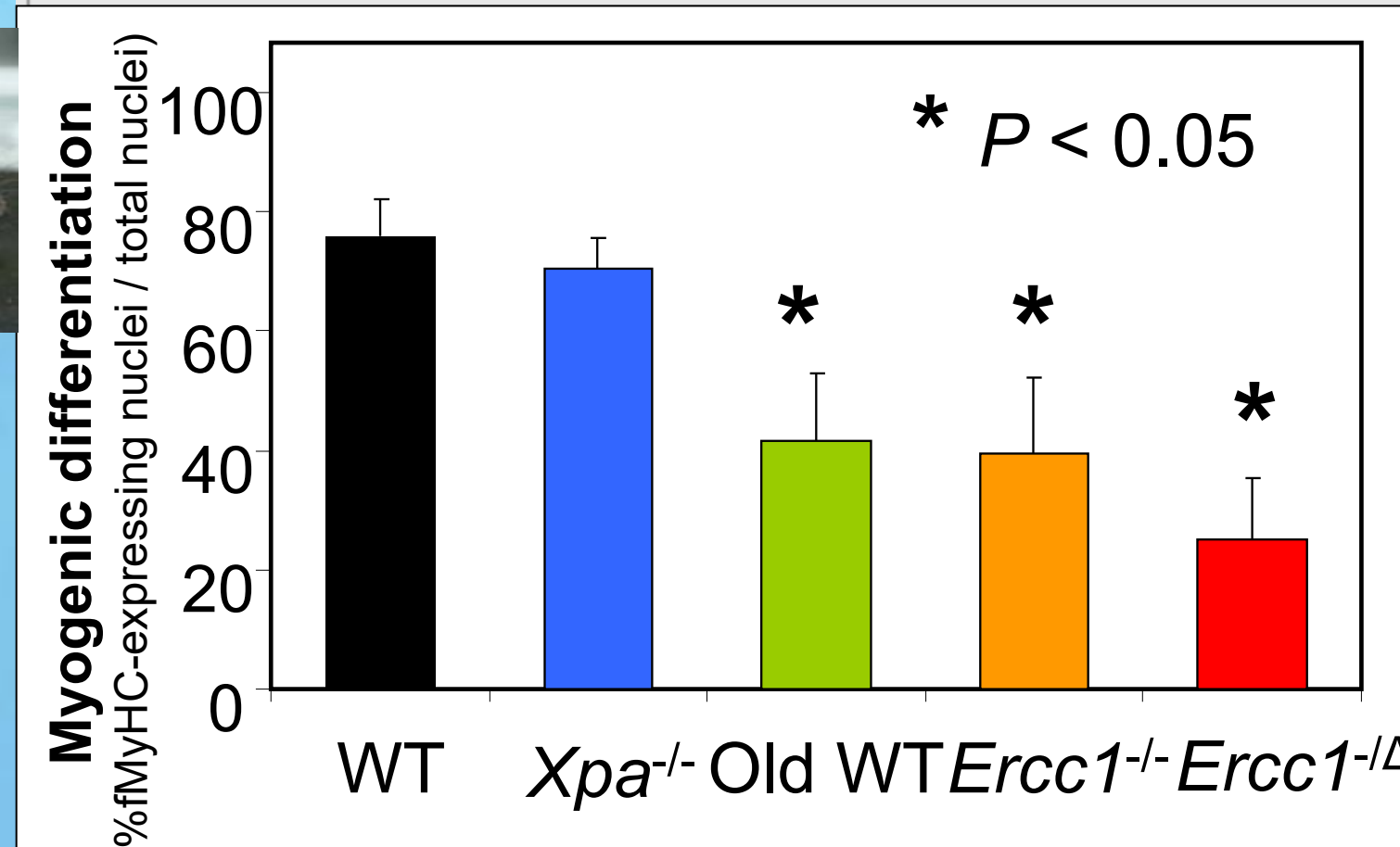
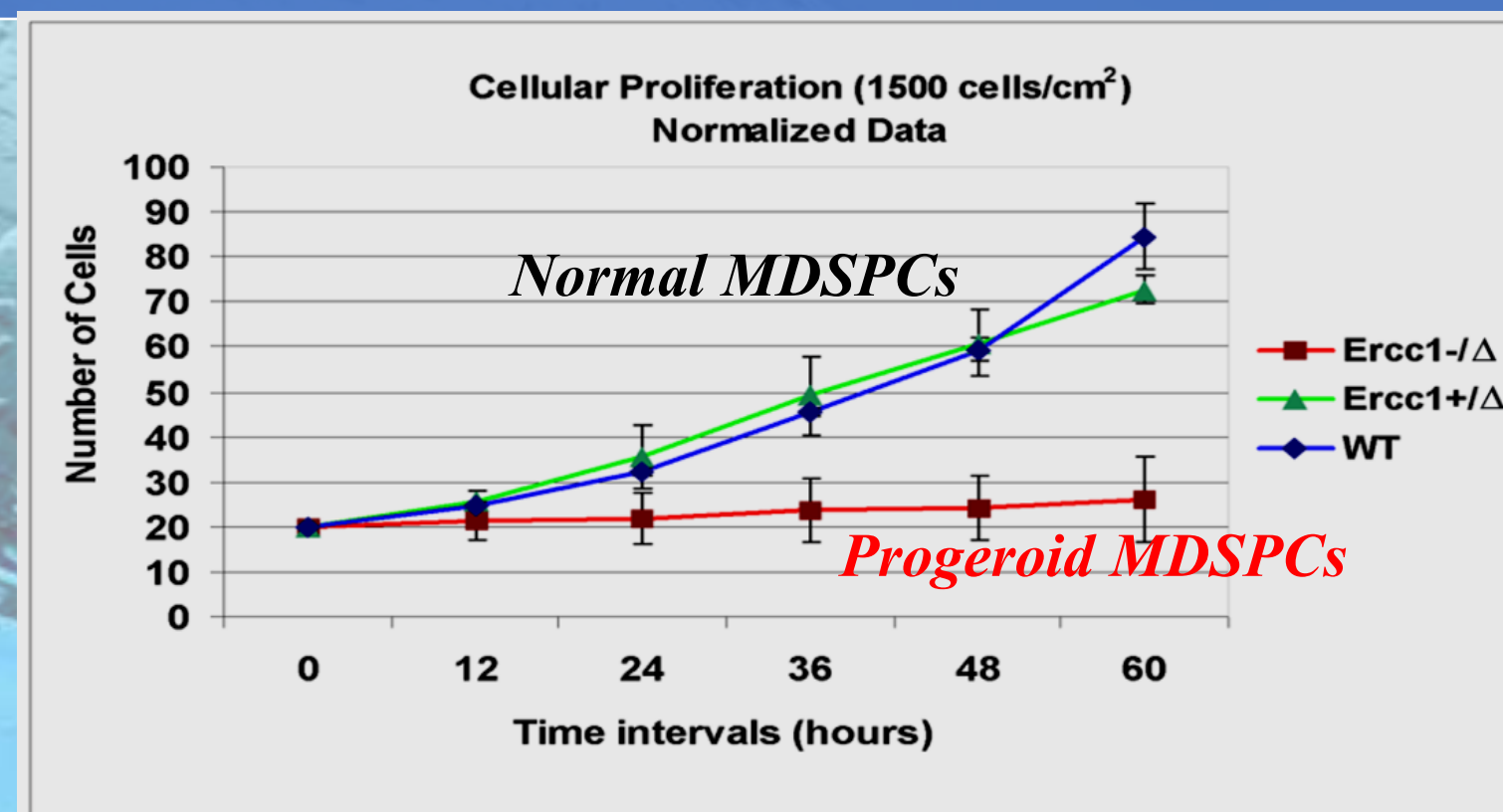
ERCC-/- mice

ERCC1-XPF is a DNA repair endonuclease

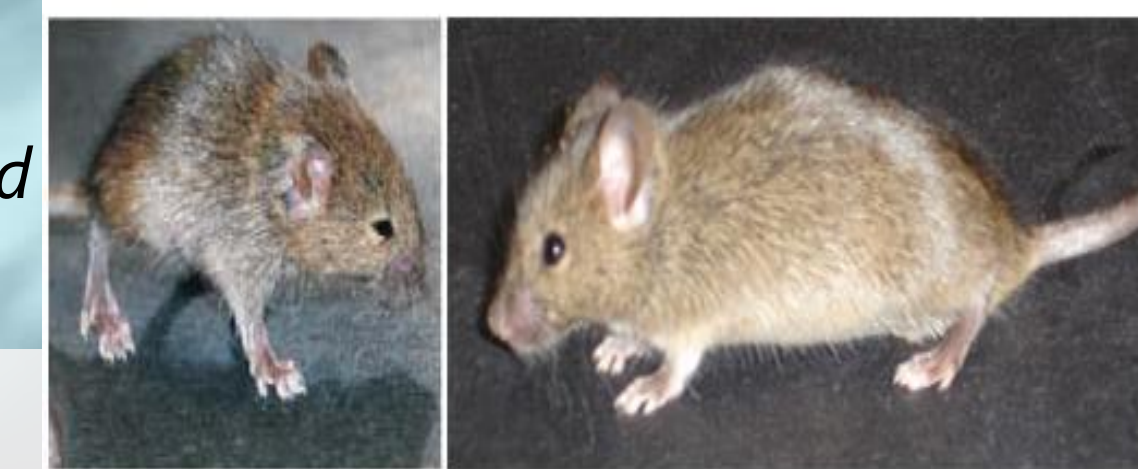
- Nucleotide excision repair
- Interstrand crosslink repair
- Double-strand break repair

Deficiency in humans causes progeria

Niedernhofer LJ et al. Nature (2006) 444; 1038-43

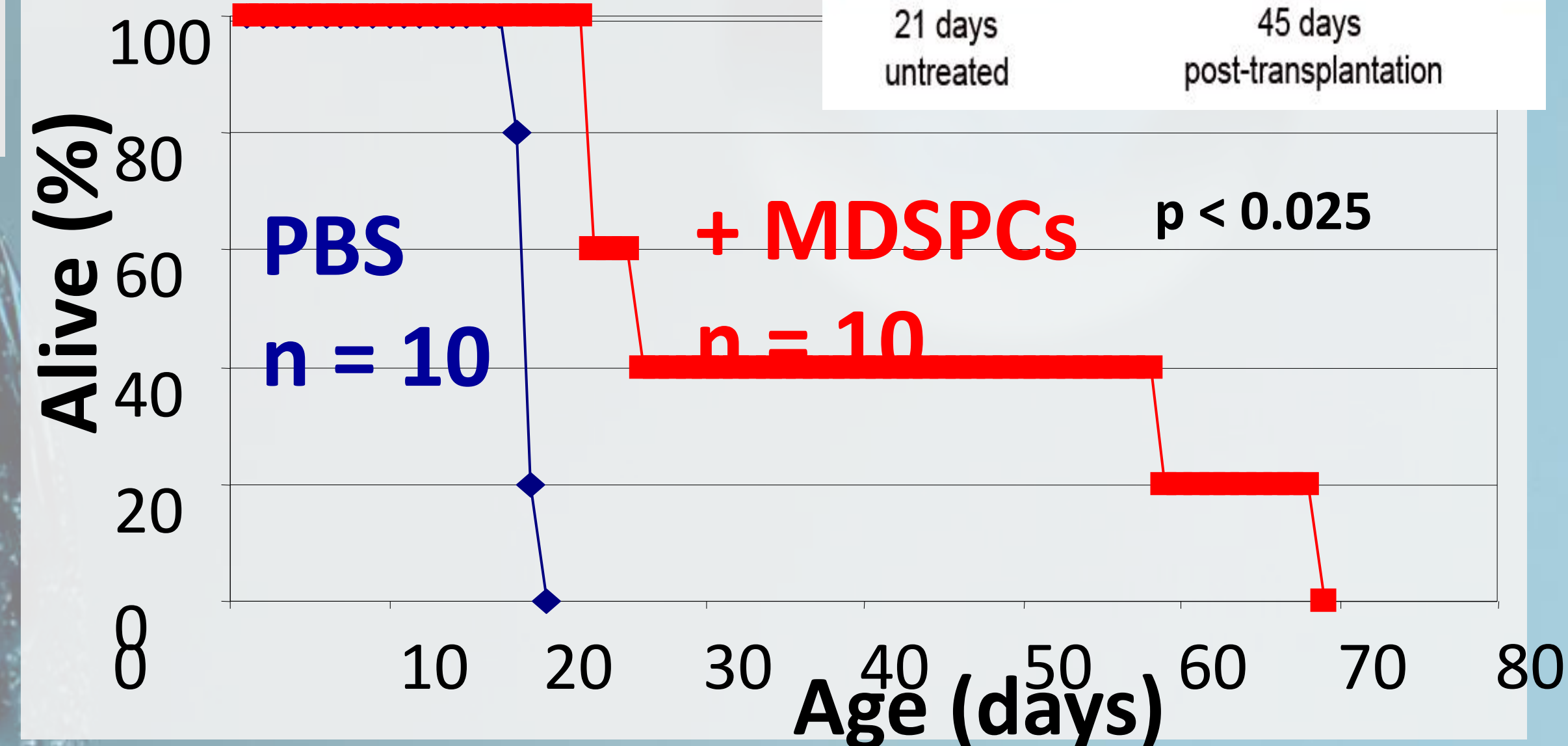


5x10⁵ young stem cells injected into 17-day-old progeroid mice



21 days untreated

45 days post-transplantation



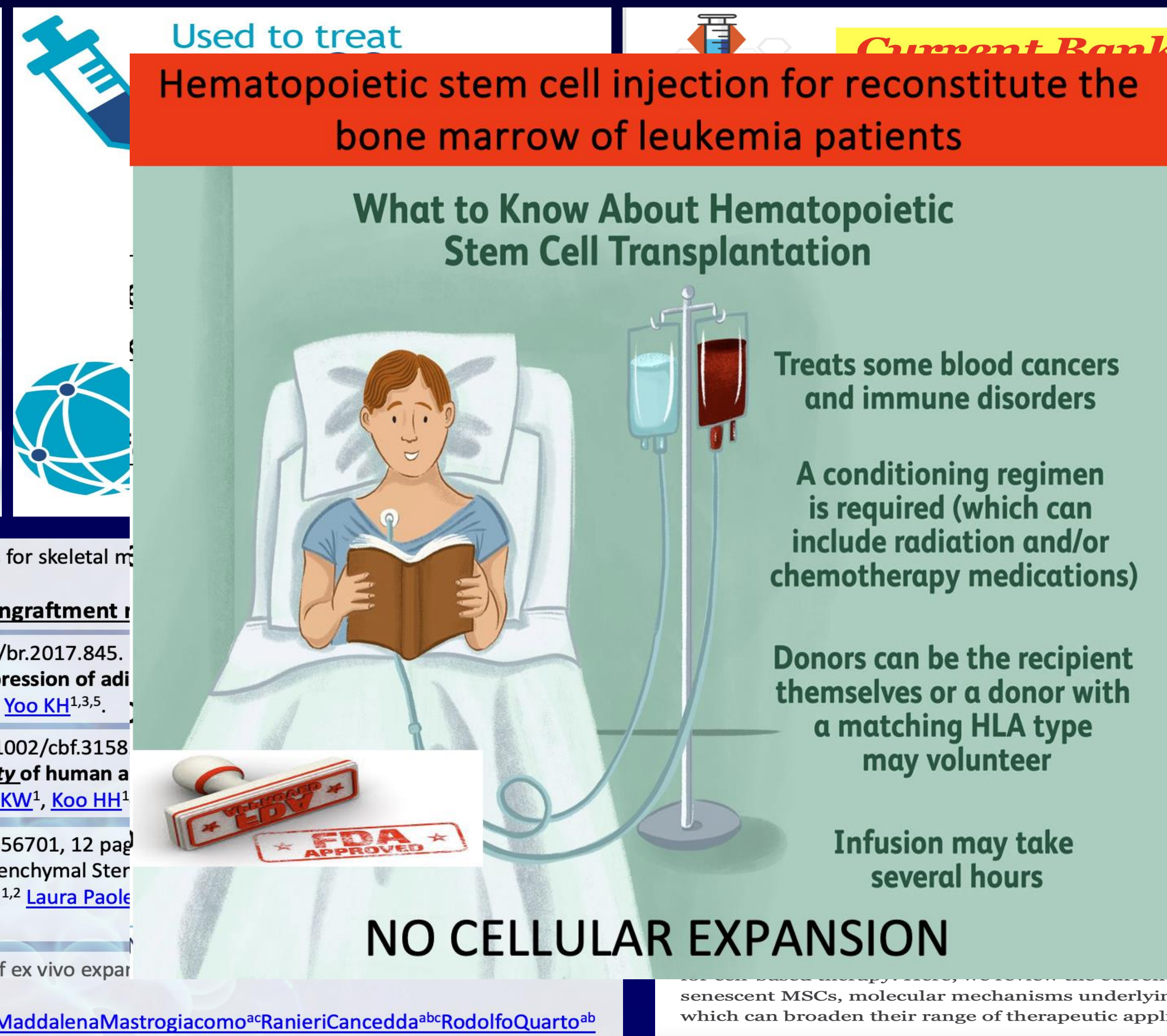
Lavasani M. et al. Nature Commun. 2012, Jan 3, 3;608 Song M et al. Stem Cell Res. & Therapy 4:33; 2013

The development of novel stem cell banking modalities: Limitations (stem cell expansion- cost- not FDA approved)



cordlife
one chance, one choice.

HOW MUCH
BENEFICIAL IS
THE STEM CELL
PRESERVATION



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

What to Know About Hematopoietic
Stem Cell Transplantation

Treats some blood cancers
and immune disorders

A conditioning regimen
is required (which can
include radiation and/or
chemotherapy medications)

Donors can be the recipient
themselves or a donor with
a matching HLA type
may volunteer

Infusion may take
several hours

NO CELLULAR EXPANSION



Current Banking
Methods

Collection of stem cells

Cryopreservation

Stem cell therapy

decades later

-150°C

Aseptic processing and
secure storage in
a liquid nitrogen tank at -150°C

Treatment of disease and
rejuvenation with the use
of young stem cells

Monterras D et al. Direct isolation of satellite cells for skeletal m
2005

Expansion of muscle cells in culture before engraftment r

Biomed Rep. 2017 Mar;6(3):300-306. doi: 10.3892/br.2017.845.
Cell culture density **affects the stemness** gene expression of adi
Kim DS¹, Lee MW¹, Lee TH², Sung KW¹, Koo HH^{1,3,4}, Yoo KH^{1,3,5}.

Cell Biochem Funct. 2016 Jan;34(1):16-24. doi: 10.1002/cbf.3158
Cell culture density **affects the proliferation activity** of human a
Kim DS¹, Lee MW¹, Ko YJ¹, Chun YH², Kim HJ², Sung KW¹, Koo HH¹

Stem Cells International Volume 2016, Article ID 5656701, 12 pag
The Effect of Culture on Human Bone Marrow Mesenchymal Ster
Angela Bentivegna^{1,2}, Gaia Roversi^{1,3}, Gabriele Riva^{1,2}, Laura Paole
Miloso¹, Giovanni Tredici¹ and Leda Dalprà¹.

Proliferation kinetics and differentiation potential of ex vivo expan
Implications for their use in cell therapy
panel [Andrea Banfi](#)^{abc} [Anita Muraglia](#)^a [Beatrice Dozin](#)^{ab} [Maddalena Mastrogiacomo](#)^{ac} [Ranieri Cancedda](#)^{abc} [Rodolfo Quarto](#)^{ab}

2020.00258

Check for updates

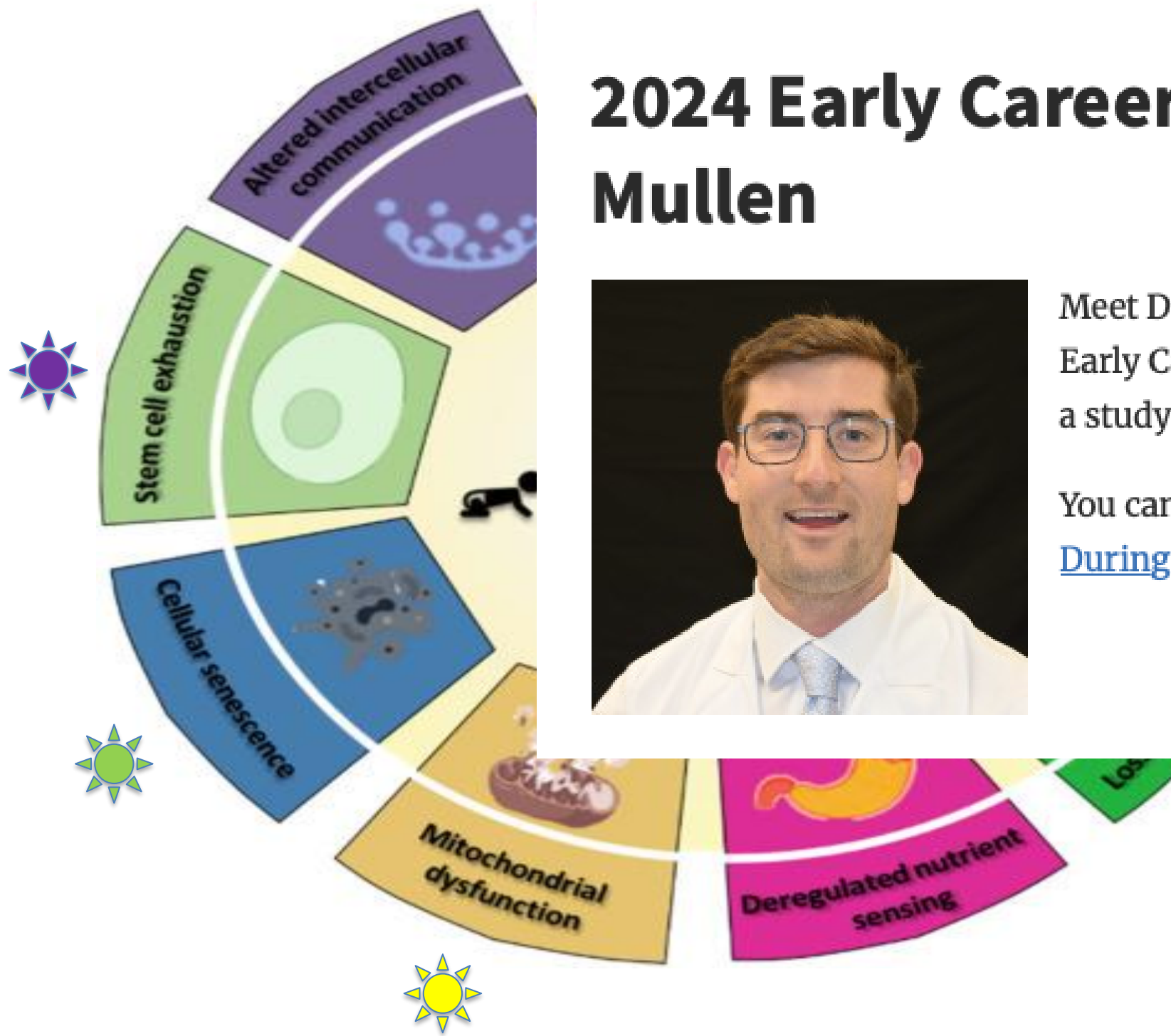
Myeloid Stem Cells: Functional Mechanisms, and Rejuvenation

Xiaoting Liang^{1,4*}

al, School of Medicine, Tongji University, Shanghai, China
ongji University School of Medicine, Shanghai, China
and Military Medical University, Shanghai, China
ol of Life Sciences and Technology, Tongji University, Shanghai, China

cells capable of self-renewal and differentiation. There is
s in various clinical situations, however, these cells gradually
accompanying increase in cellular dysfunction. Stem cell aging and

number of population doublings before becoming senescent. This
cultures must be expanded to obtain a sufficient number of cells
knowledge of the phenotypic and functional characteristics of
senescent MSCs, molecular mechanisms underlying MSCs aging, and strategies to rejuvenate senescent MSCs,
which can broaden their range of therapeutic applications.

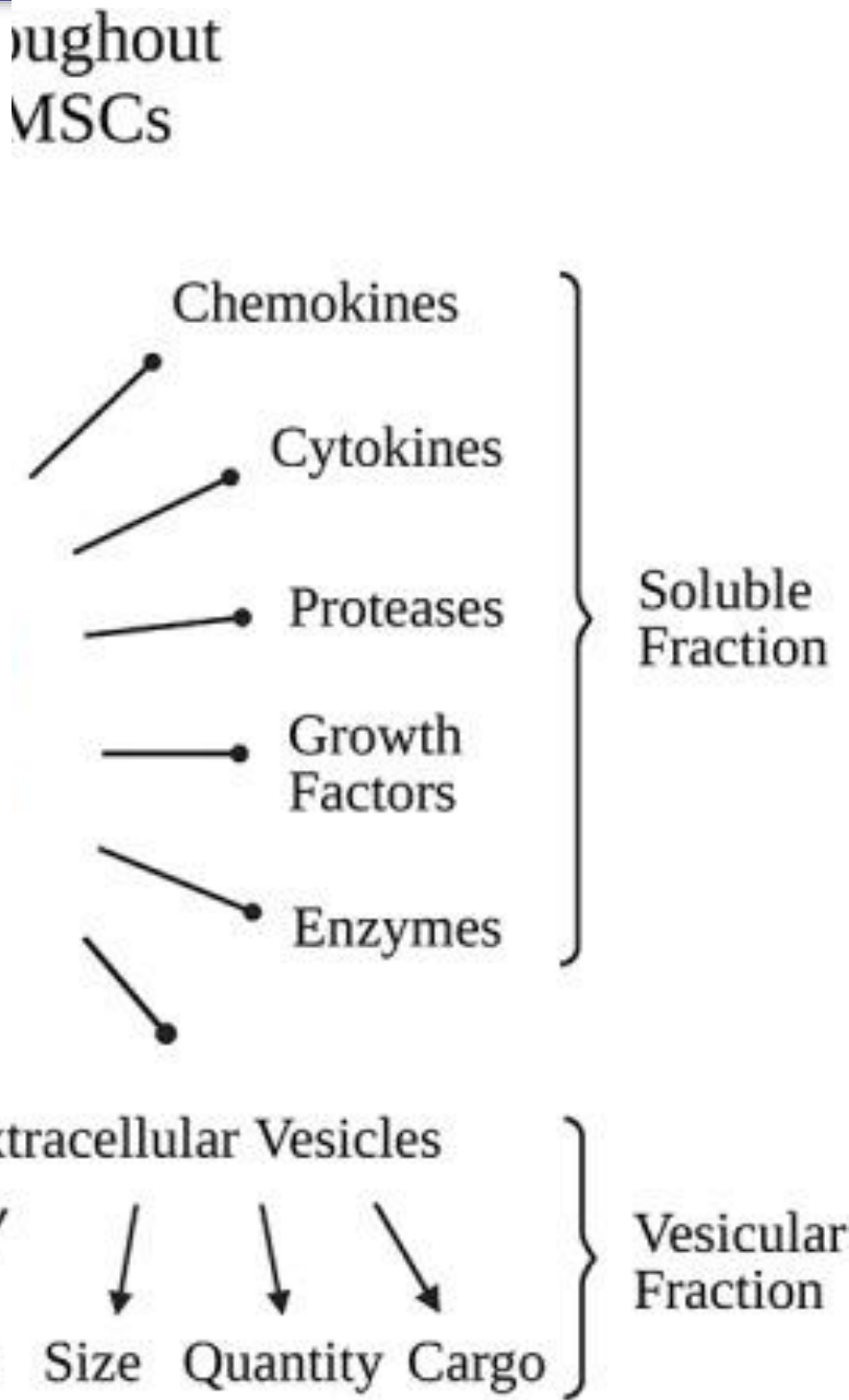
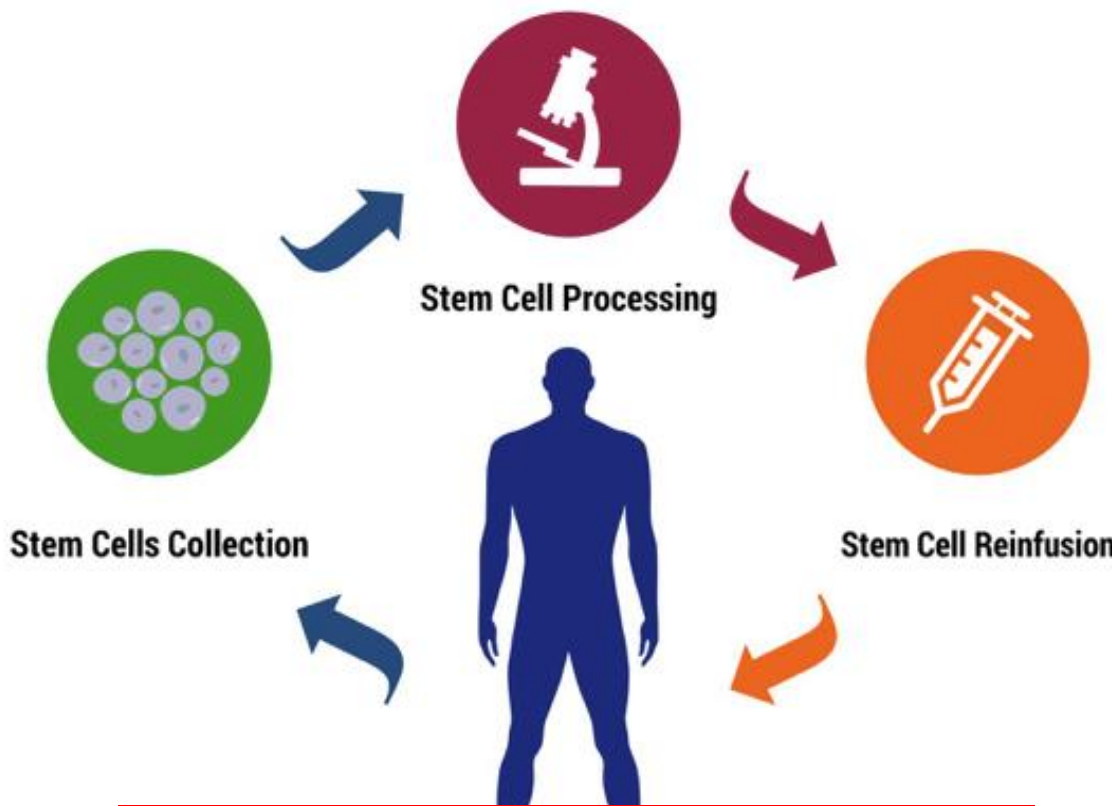


2024 Early Career Investigator Award Recipient: Dr. Michael Mullen



Meet Dr. Michael Mullen – winner of the 2024 *STEM CELLS* Early Career Investigator Award. The Early Career Investigator Award is a prize granted annually to an early career scientist publishing a study with *STEM CELLS* that is deemed to be of global significance.

You can read the winning paper here: [Fisetin Attenuates Cellular Senescence Accumulation During Culture Expansion of Human Adipose-Derived Stem Cells](#)



Received: 26 July 2022 | Revised: 14 November 2022 | Accepted: 2 December 2022
DOI: 10.1111/accel.13759

REVIEW ARTICLE

Cellular expansion of MSCs: Shifting the regenerative

Katherine Miclau^{1,2}  | William S. Hambright¹ | Johnny Huard¹ | Martin
Chelsea S. Bahney^{1,3}

Aging 

Treat your patients with
senolytics (fisetin,
quercetin...) Before
harvesting stem cells!

3 Jul 14;41(7):698-710. doi: 10.1093/stmcls/sxad036.

Fisetin Attenuates Cellular Senescence Accumulation During Culture Expansion of Human Adipose-Derived Stem Cells

Mullen¹, Anna Laura Nelson¹, Alexander Goff¹, Jake Billings¹, Heidi Kloser¹,
Huard¹, John Mitchell¹, William Sealy Hambright¹, Sudheer Ravuri¹, Johnny Huard¹

Why Stem cells become dysfunctional during the aging process?

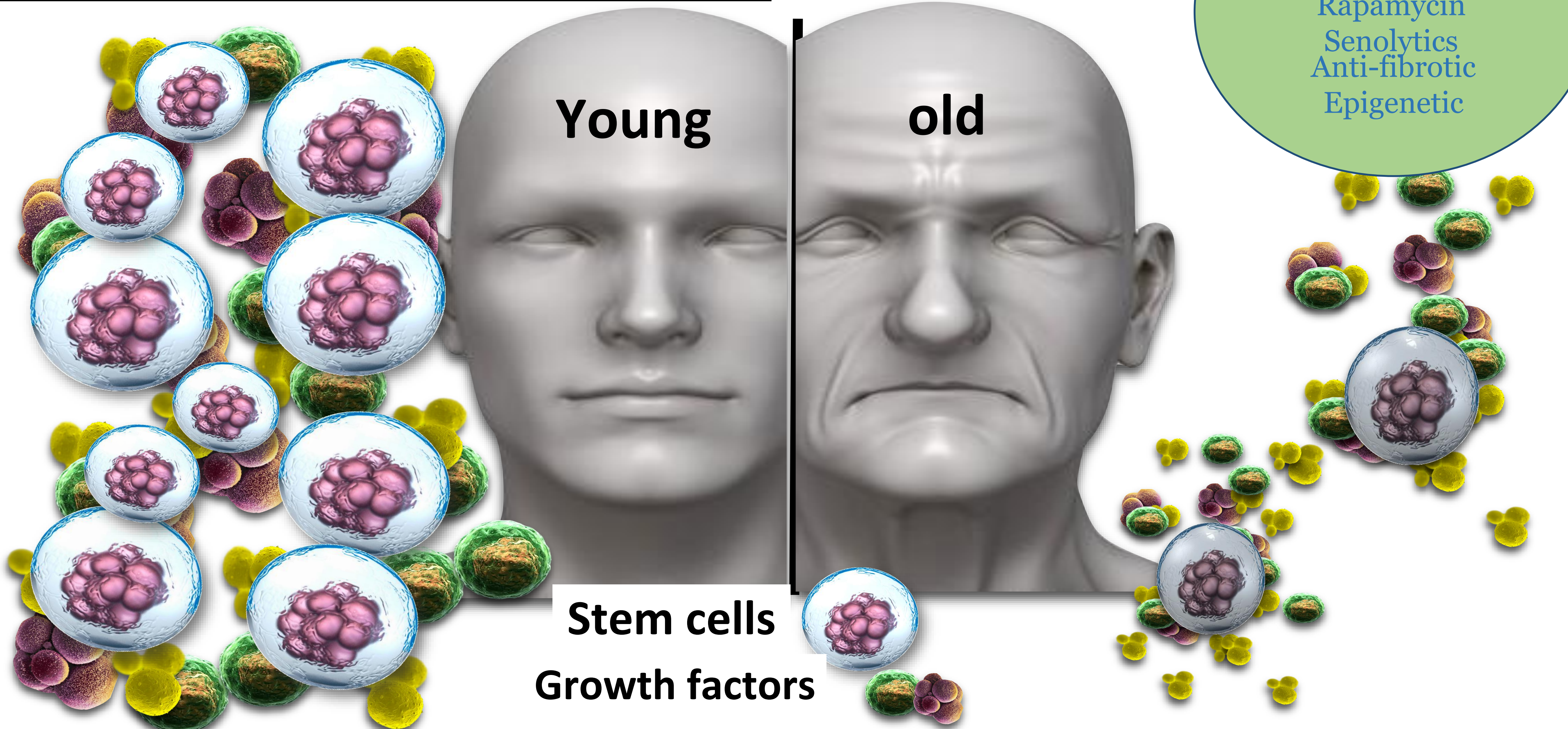
Drugs

Metformin
Rapamycin
Senolytics
Anti-fibrotic
Epigenetic

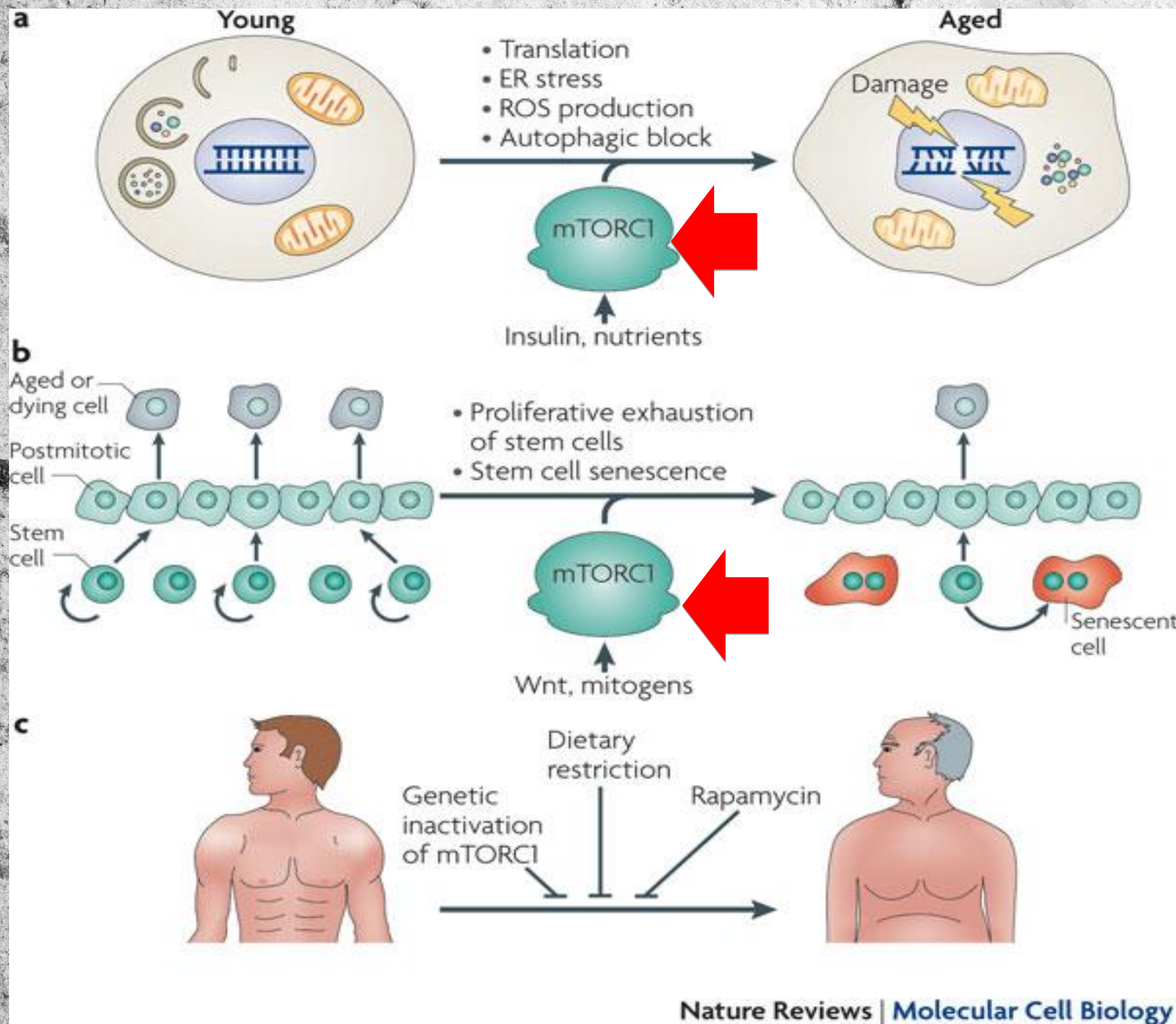
Young

old

Stem cells
Growth factors



Why Stem Cells get exhausted/depleted with Aging



> [J Orthop Res.](#) 2017 Jul;35(7):1375-1382. doi: 10.1002/jor.23409. Epub 2016 Sep 22.

mTOR signaling plays a critical role in the defects observed in muscle-derived stem/progenitor cells isolated from a murine model of accelerated aging

Koji Takayama^{1 2 3}, Yohei Kawakami^{1 2 3}, Mitra Lavasani^{1 2}, Xiaodong Mu^{1 2 4 5}, James H Cummins^{1 2 4}, Takashi Yurube¹, Ryosuke Kuroda³, Masahiro Kurosaka³, Freddie H Fu¹, Paul D Robbins⁶, Laura J Niedernhofer⁶, Johnny Huard^{1 2 4 5}

> [Stem Cell Res Ther.](#) 2013 Mar 25;4(2):33. doi: 10.1186/scrt183.

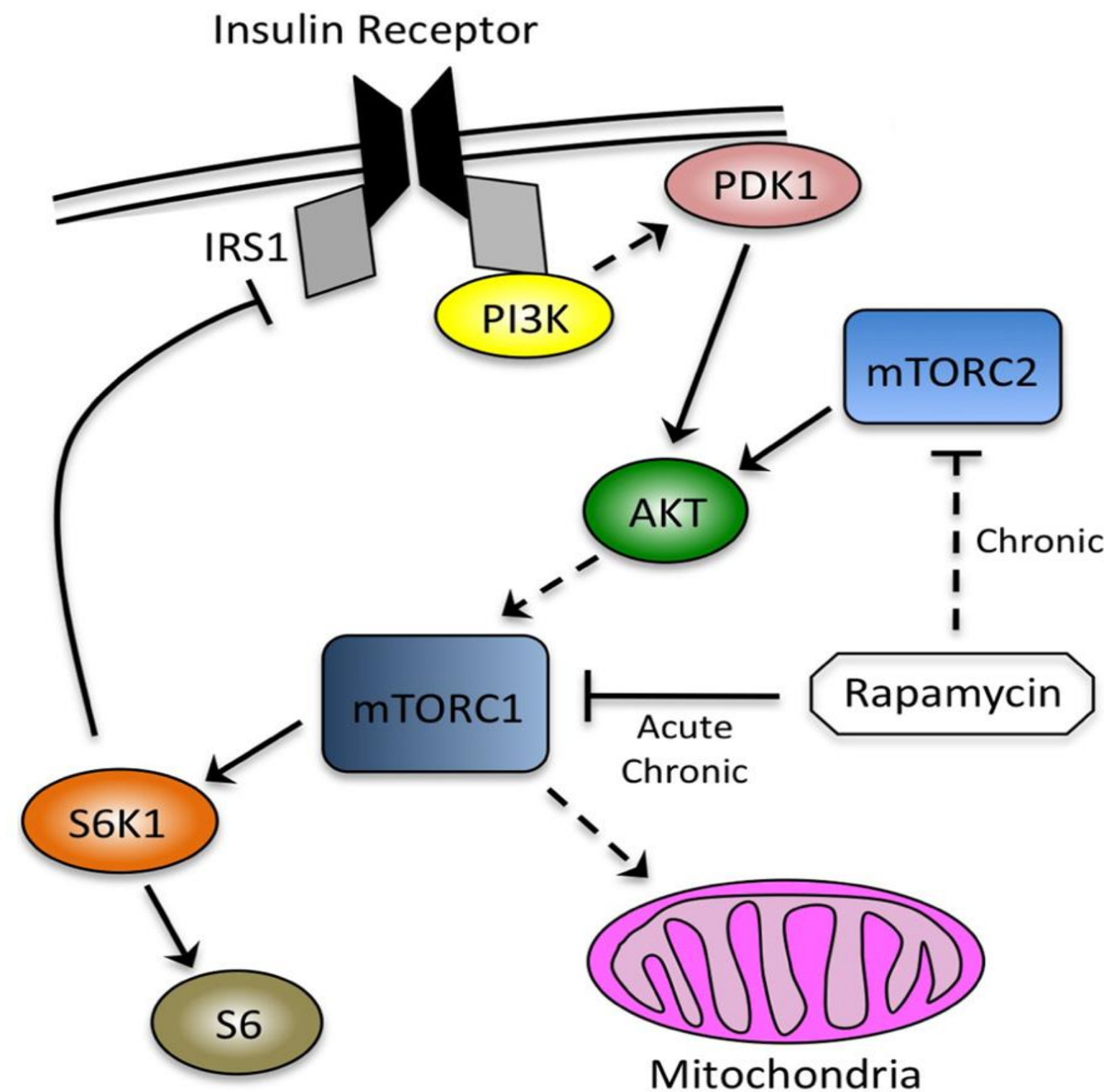
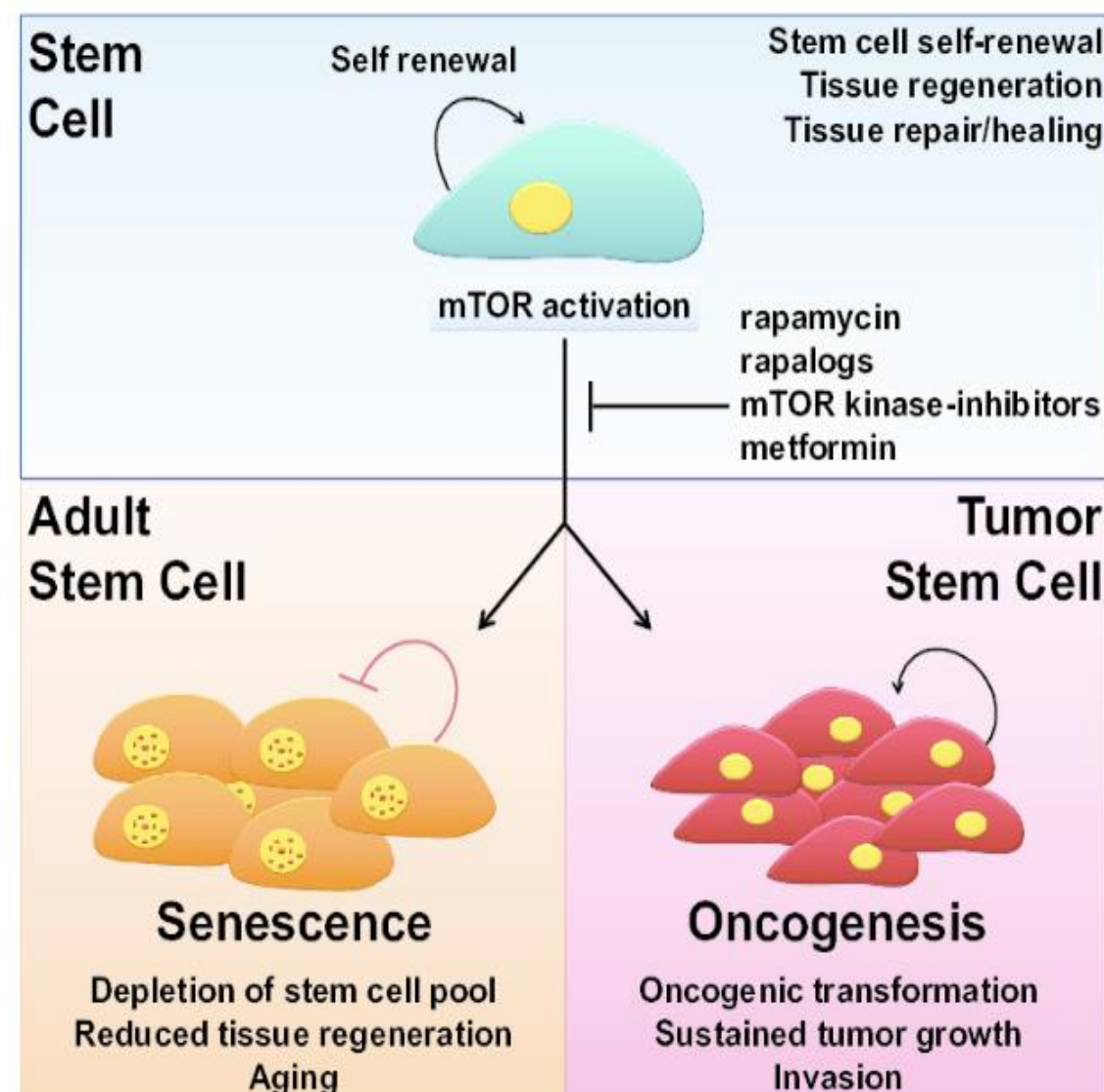
Muscle-derived stem/progenitor cell dysfunction in Zmpste24-deficient progeroid mice limits muscle regeneration

Minjung Song, Mitra Lavasani, Seth D Thompson, Aiping Lu, Bahar Ahani, Johnny Huard

PMID: 23531345 PMCID: [PMC3706820](#) DOI: [10.1186/scrt183](#)

[Free PMC article](#)

mTOR inhibitors (Rapamycin & Metformin) rescue stem cells from exhaustion/depletion



Review > [Cell Metab.](#) 2020 Jul 7;32(1):15-30. doi: 10.1016/j.cmet.2020.04.001.
Epub 2020 Apr 24.

Benefits of Metformin in Attenuating the Hallmarks of Aging

[Ameya S Kulkarni](#)¹, [Sriram Gubbi](#)², [Nir Barzilai](#)³

Affiliations + expand
PMID: 32333835 PMCID: [PMC7347426](#) DOI: [10.1016/j.cmet.2020.04.001](#)
[Free PMC article](#)

Editorial > [Aging \(Albany NY\)](#). 2020 Aug 4;12(15):15184-15185. doi: 10.18632/aging.103816.
Epub 2020 Aug 4.

Rapamycin for aging stem cells

[William S Hambright](#)¹, [Marc J Philippon](#)^{1 2}, [Johnny Huard](#)^{1 2}

Affiliations + expand
PMID: 32756013 PMCID: [PMC7467370](#) DOI: [10.18632/aging.103816](#)
[Free PMC article](#)

> [Mol Ther Methods Clin Dev](#). 2019 May 30;14:64-76. doi: 10.1016/j.omtm.2019.05.011.
eCollection 2019 Sep 13.

Rapamycin Rescues Age-Related Changes in Muscle-Derived Stem/Progenitor Cells from Progeroid Mice

[Yohei Kawakami](#)^{1 2}, [William S Hambright](#)^{3 4}, [Koji Takayama](#)^{1 2}, [Xiaodong Mu](#)^{1 3 4},
[Aiping Lu](#)^{1 3 4}, [James H Cummins](#)¹, [Tomoyuki Matsumoto](#)², [Takashi Yurube](#)²,
[Ryosuke Kuroda](#)², [Masahiro Kurosaka](#)², [Freddie H Fu](#)¹, [Paul D Robbins](#)⁵,
[Laura J Niedernhofer](#)⁵, [Johnny Huard](#)⁴

Affiliations + expand
PMID: 31312666 PMCID: [PMC6610712](#) DOI: [10.1016/j.omtm.2019.05.011](#)
[Free PMC article](#)

[Aging Cell](#) [Open Access](#) [ANATOMICAL SOCIETY](#)

[Aging Cell](#). 2018 Aug; 17(4): e12765.
Published online 2018 Apr 16. doi: [10.1111/ace.12765](#)

PMCID: [PMC6052468](#)
PMID: [29659168](#)

Metformin alleviates human cellular aging by upregulating the endoplasmic reticulum glutathione peroxidase 7

[Jingqi Fang](#)^{1,2,†}, [Jiping Yang](#)^{1,2,†}, [Xun Wu](#)^{1,2,†}, [Gangming Zhang](#)^{1,2}, [Tao Li](#)^{1,2}, [Xi'e Wang](#)¹, [Hong Zhang](#)^{1,2},
[Chih-chen Wang](#)^{1,2}, [Guang-Hui Liu](#)^{1,2,3} and [Lei Wang](#)^{1,2}

> [Author information](#) > [Article notes](#) > [Copyright and License information](#) [PMC Disclaimer](#)

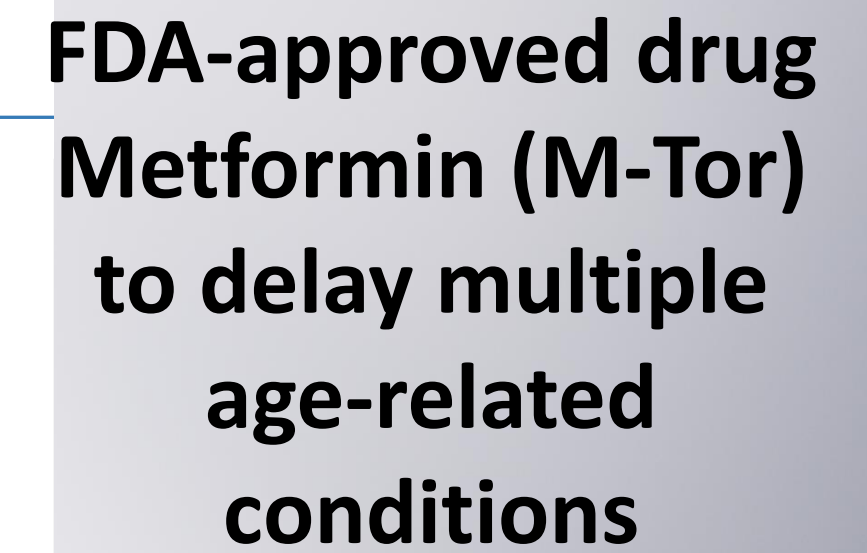
- **Transient rapamycin treatment can increase lifespan and healthspan in middle-aged mice.** Elife. 2016 Aug 23;5. pii: e16351. Bitto A1 et al.

Nature. 2009 Jul 16;460(7253):392-5. [Harrison](#) DE et al

Affiliations & Notes Article Info

- Metformin prevents brain atrophy, elevating cognitive function in aged male primates
- Metformin slows the pace of aging across diverse male primate tissues
- Metformin counteracts neuronal aging, delivering geroprotection via Nrf2 in male primates

In a rigorous 40-month study, we evaluated the geroprotective effects of metformin on adult male cynomolgus monkeys, addressing a gap in primate aging research. The study encompassed a comprehensive suite of physiological, imaging, histological, and molecular evaluations, substantiating metformin's influence on delaying age-related phenotypes at the organismal level. Specifically, we leveraged pan-tissue transcriptomics, DNA methylomics, plasma proteomics, and metabolomics to develop innovative monkey aging clocks and applied these to gauge metformin's effects on aging. The results highlighted a significant slowing of aging indicators, notably a roughly 6-year regression in brain aging. Metformin exerts a substantial neuroprotective effect, preserving brain structure and enhancing cognitive ability. The geroprotective effects on primate neurons were partially mediated by the activation of Nrf2, a transcription factor with anti-oxidative capabilities. Our research pioneers the systemic reduction of multi-dimensional biological age in primates through metformin, paving the way for advancing pharmaceutical strategies against human aging.



**medication that
costs 6 cents a pill
could be a key to
living longer**

TheScientist
EXPLORING LIFE, INSPIRING INNOVATION

[Home](#) / [Archive](#) / [March 2018](#) / [Notebook](#)

From extending lifespan to bolstering the immune system, the drug's effects are only just beginning to be understood.

Mar 1, 2018
ANNE N. CONNOR



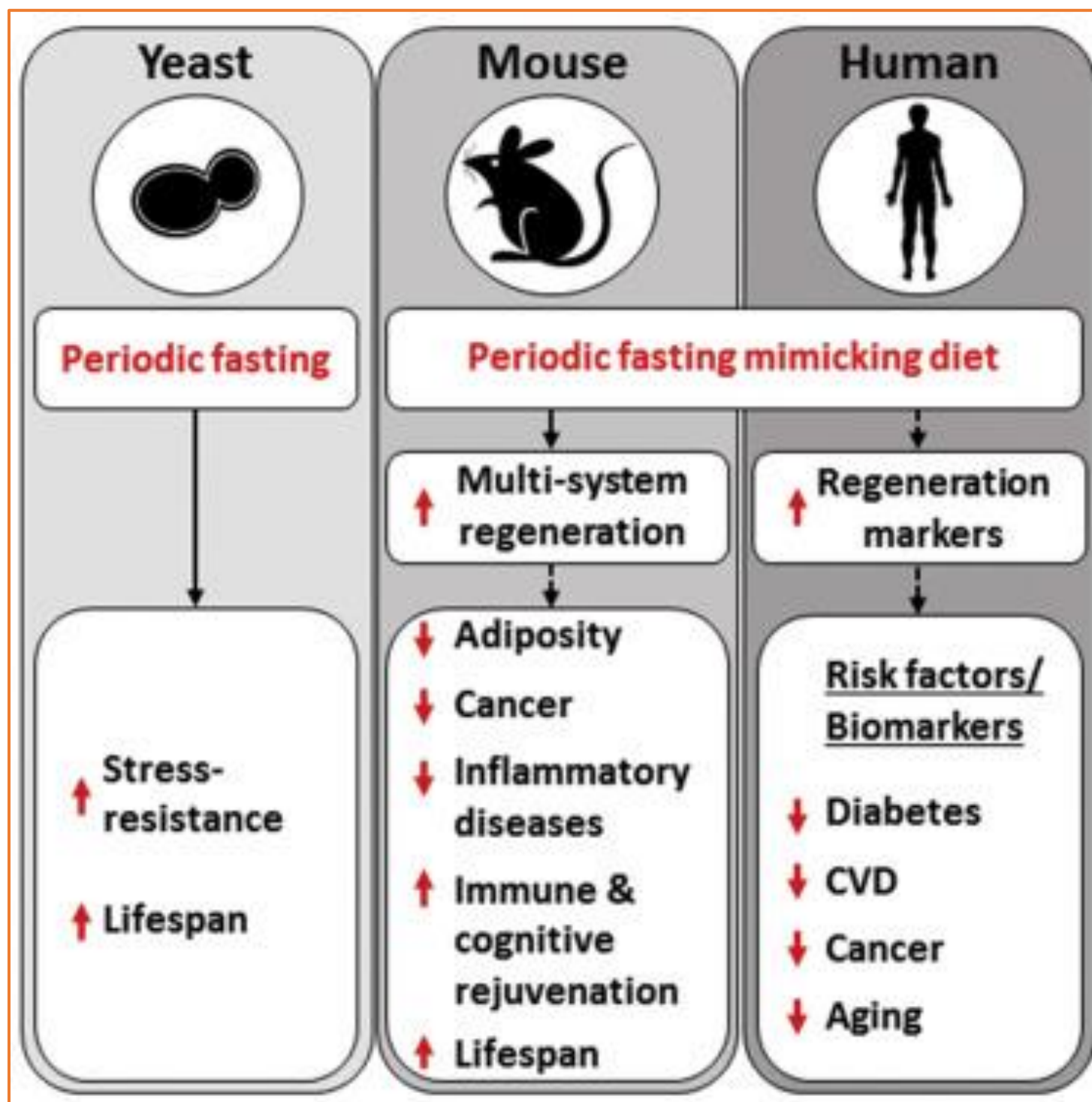
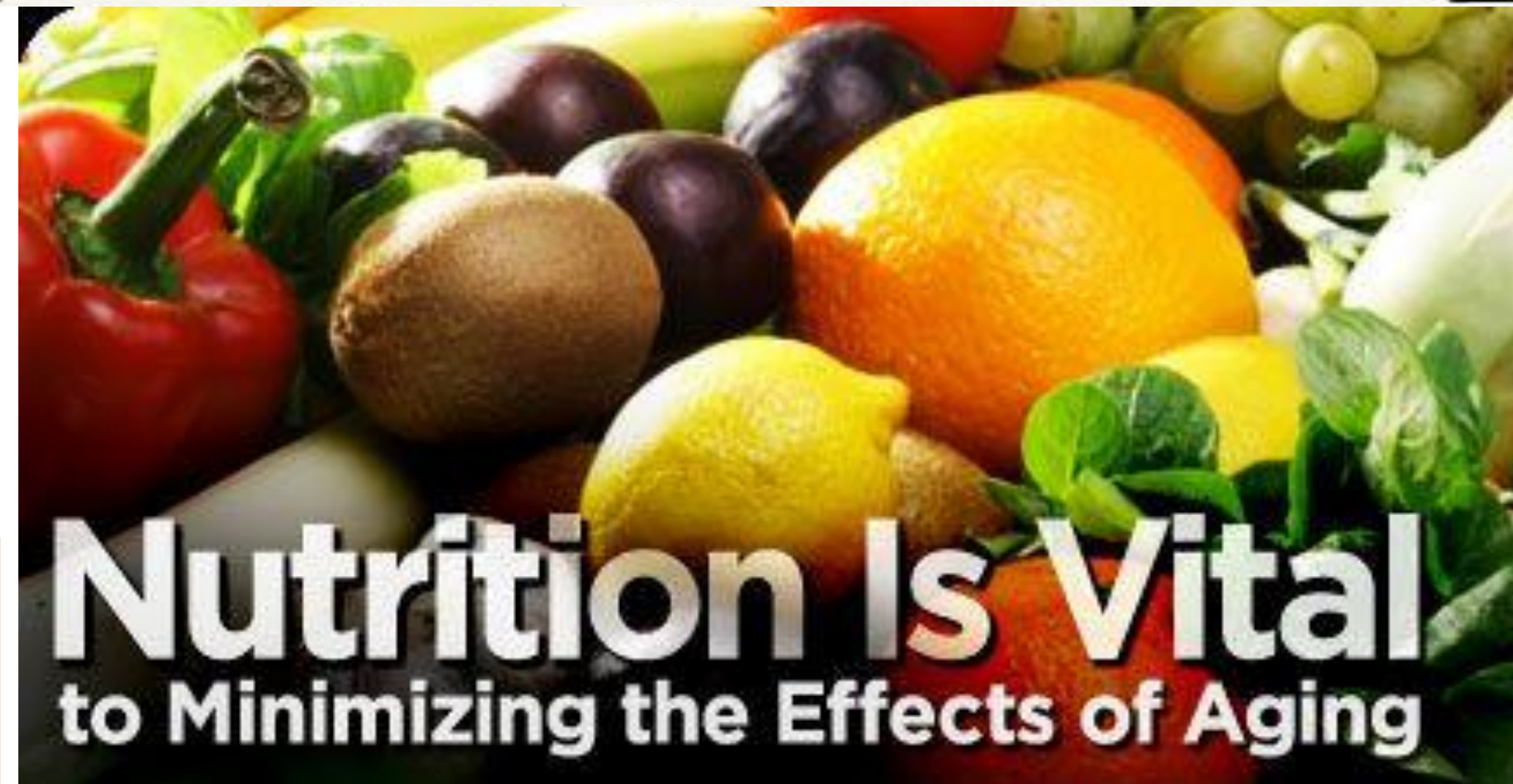
In the 1990s, pharmacologist [Dave Sharp](#) of the University of Texas's Barshop Institute for Longevity and Aging Studies in San Antonio was studying mice with pituitary dwarfism—a condition in which the pituitary gland fails to make enough growth hormone for normal development. The puzzle, Sharp explains, was that research had shown that these hormone-deficient dwarf mice lived longer than normal mice. “I wondered, why is being small connected with longer life?” he says.

Diet

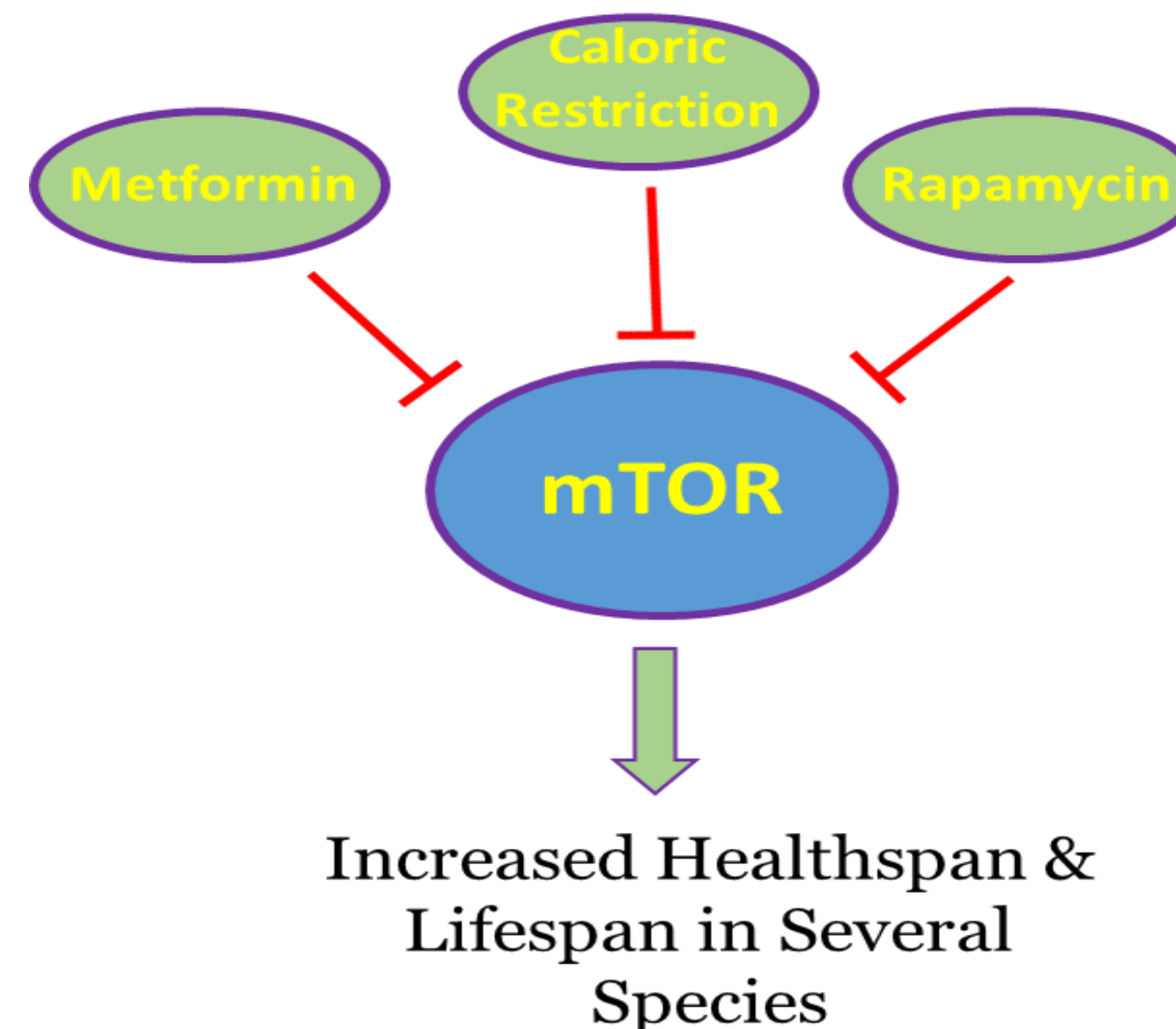
Caloric Restriction
Intermittent Fasting
Ketogenic Diet

Healthy Eating is Healthy Living

Eat right and stay healthy to ensure your body is getting enough of the following nutrients:



Longo et al. Cell Met. 2015



mTOR inhibitors (diet)
rescue your stem cells
and make you live
longer and healthier...

A combinatorial approach to provide Personalized Healthy-Aging Therapy

Diet

Caloric Restriction
Intermittent Fasting
Mediterranean diet



Lifestyle(LS)

Aerobic Exercise
Angiogenesis
Sleep



Ischemic Heart Disease



Arthritis



Diabetes



Arthritis



Depression



Alzheimer's Disease



Chronic Kidney Disease



Alzheimer's Disease

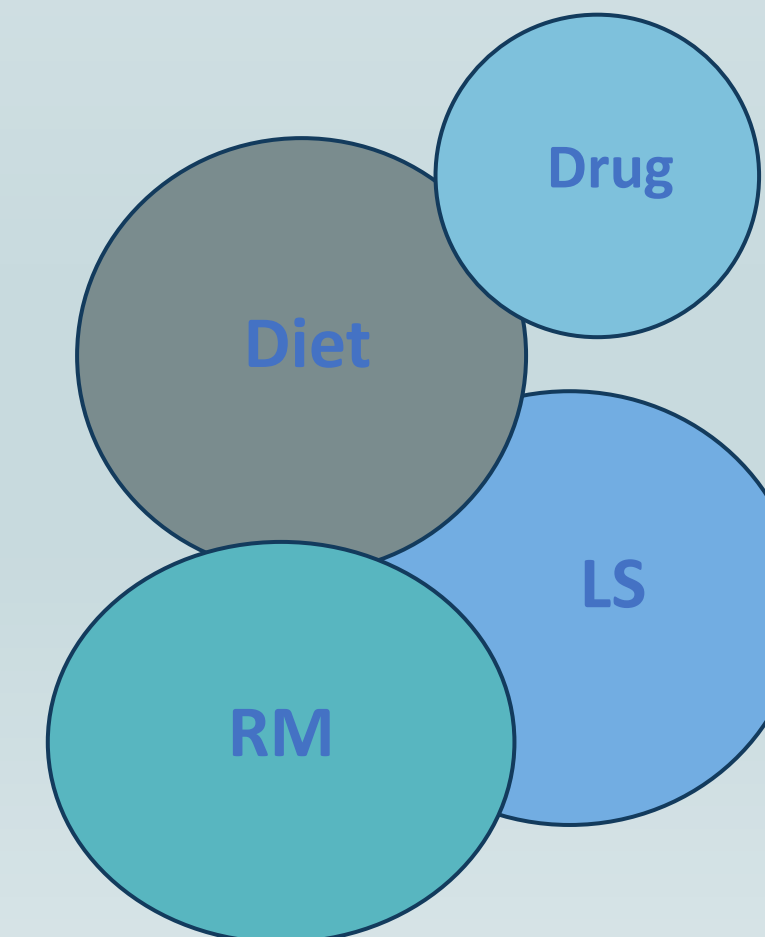
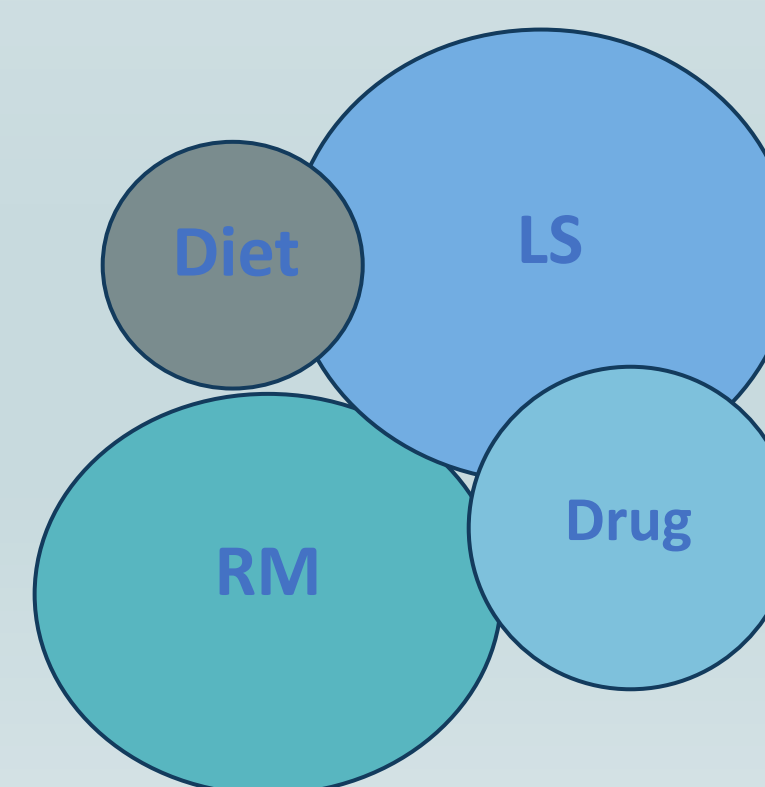
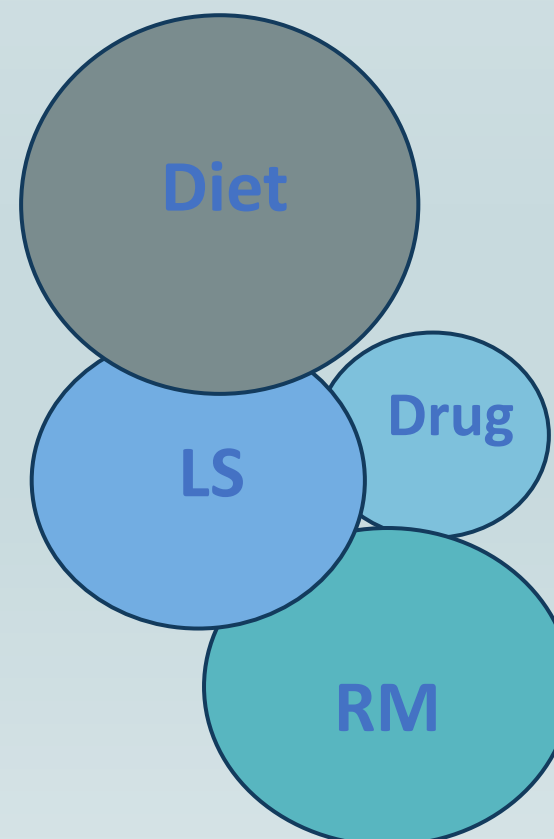


Diabetes

It is estimated that about 25 percent of the variation in human life span is determined by **genetics**, but which genes, and how they contribute to longevity, are not well understood

Regenerative Medicine (RM)

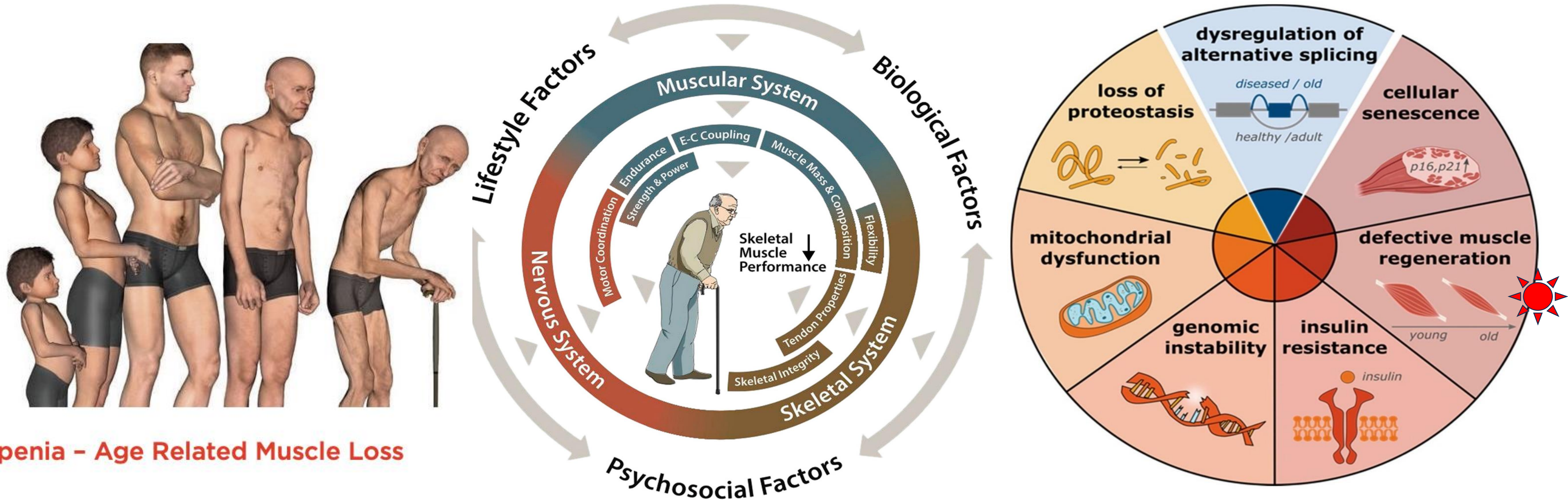
Stem Cell Banking
Stem Cell Therapy
PRP
Exosomes



Drugs Supplements

Metformin
Rapamycin
Senolytics
Losartan

Skeletal muscle health significantly declines with age, a process known as sarcopenia, characterized by a loss of skeletal muscle mass, strength, and physical function

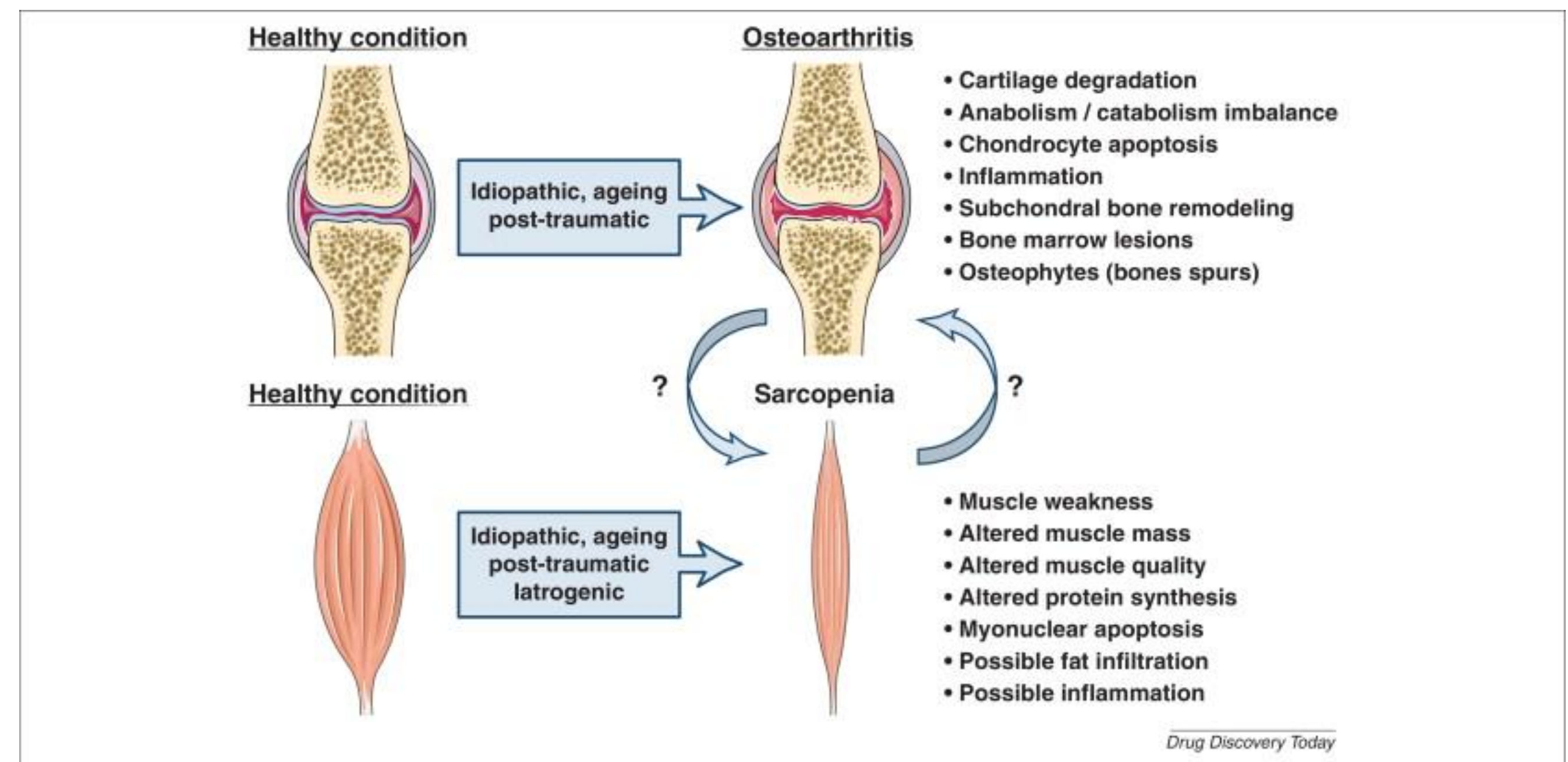
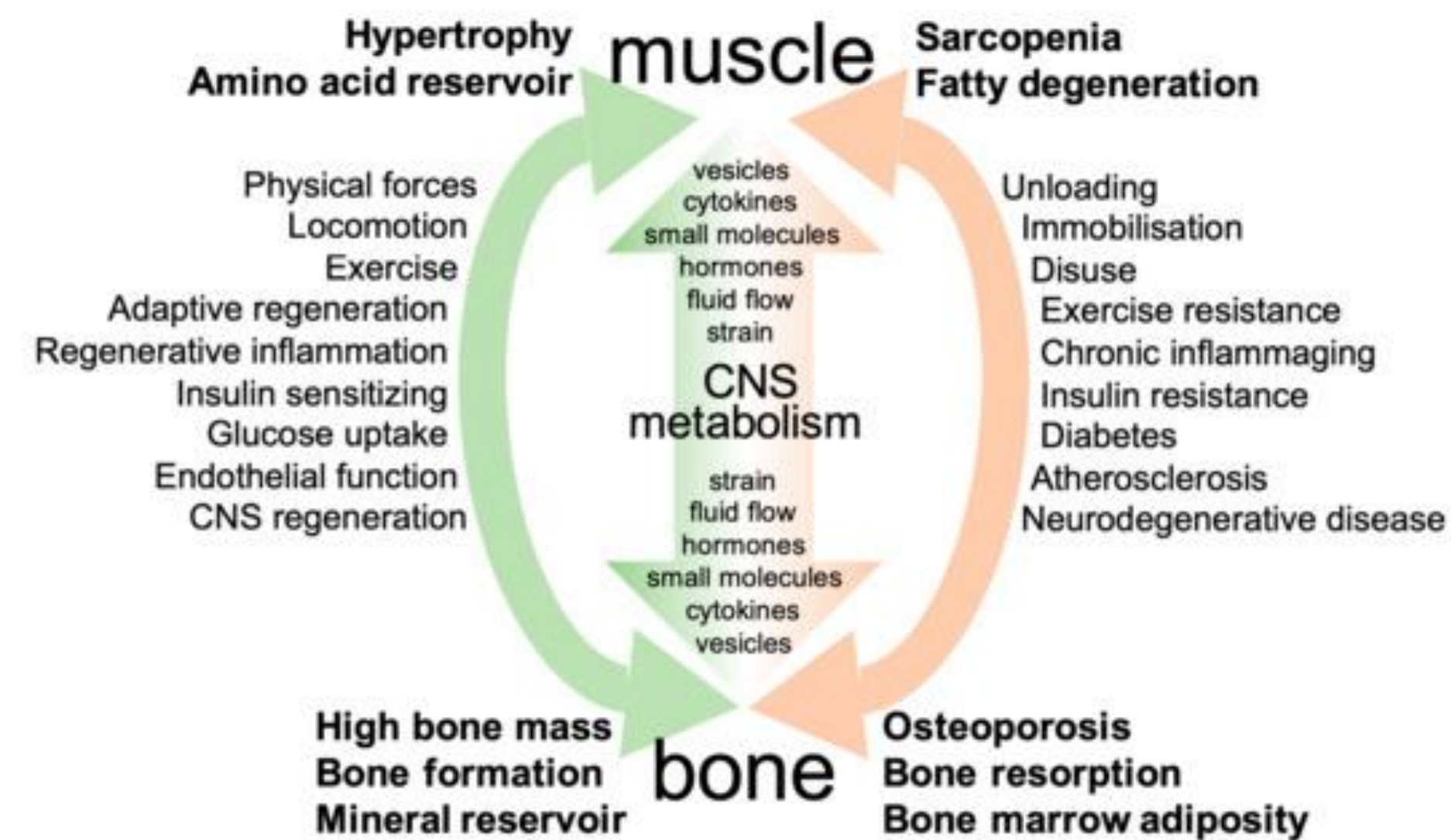


Maintaining skeletal muscle health through exercise is crucial for healthy aging and preventing disability

Skeletal muscle and bone/Joint Health

Skeletal muscles and bones are interconnected tissues, with muscles exerting mechanical forces on bones to allow movement and also impacting bone health through endocrine activity.

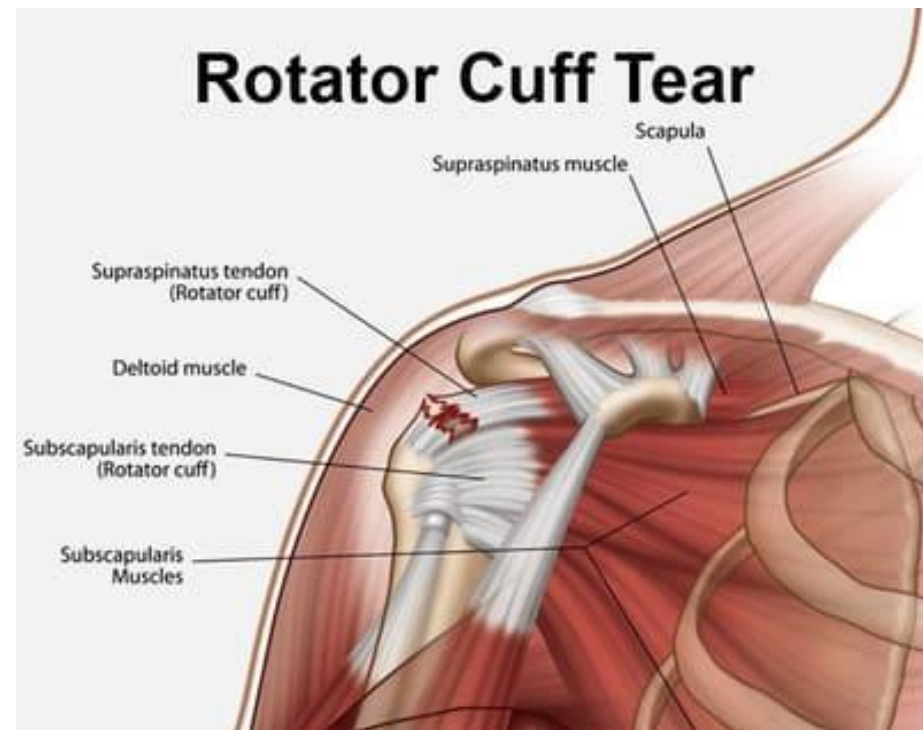
Cartilage, a connective tissue in joints, is also affected by skeletal muscle activity and can contribute to joint health.



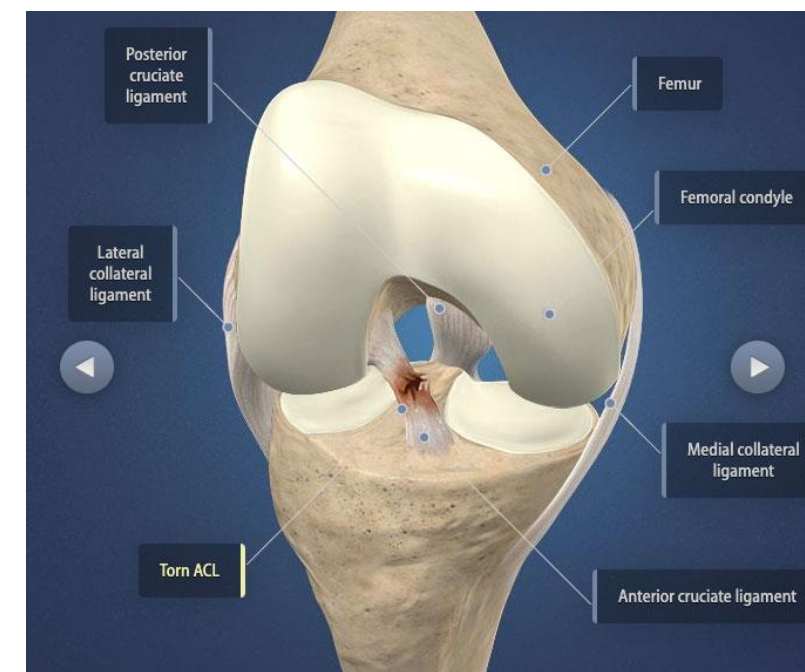
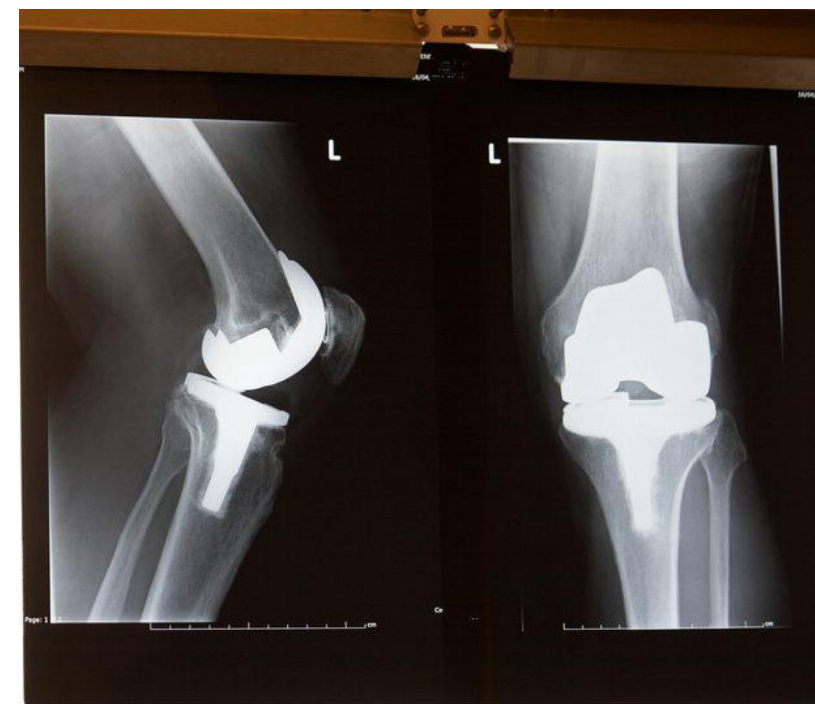
Developing Therapeutic for Osteoporosis/Osteoarthritis through improving skeletal muscle health!

Skeletal muscle health, particularly muscle strength and muscle mass, is a significant predictor of outcomes in orthopaedic surgeries. Specifically, sarcopenia, the loss of skeletal muscle mass, is linked to poorer outcomes, including prolonged recovery and increased complications

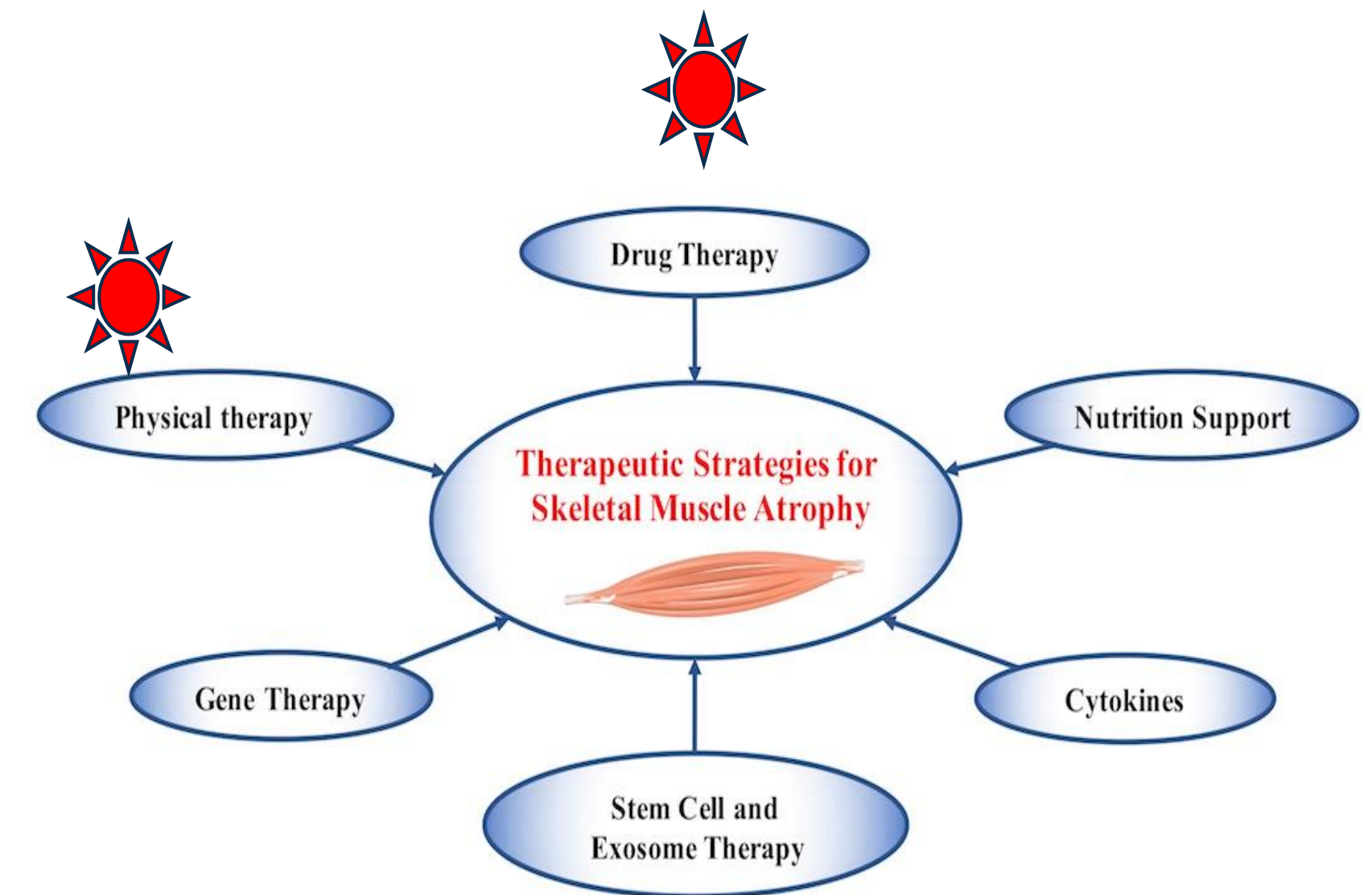
Skeletal muscle health, particularly before knee replacement surgery, is a strong predictor of surgical outcomes



While several factors influence the success of rotator cuff surgery, muscle health, particularly strength and absence of fatty infiltration, is considered a key predictor of outcomes



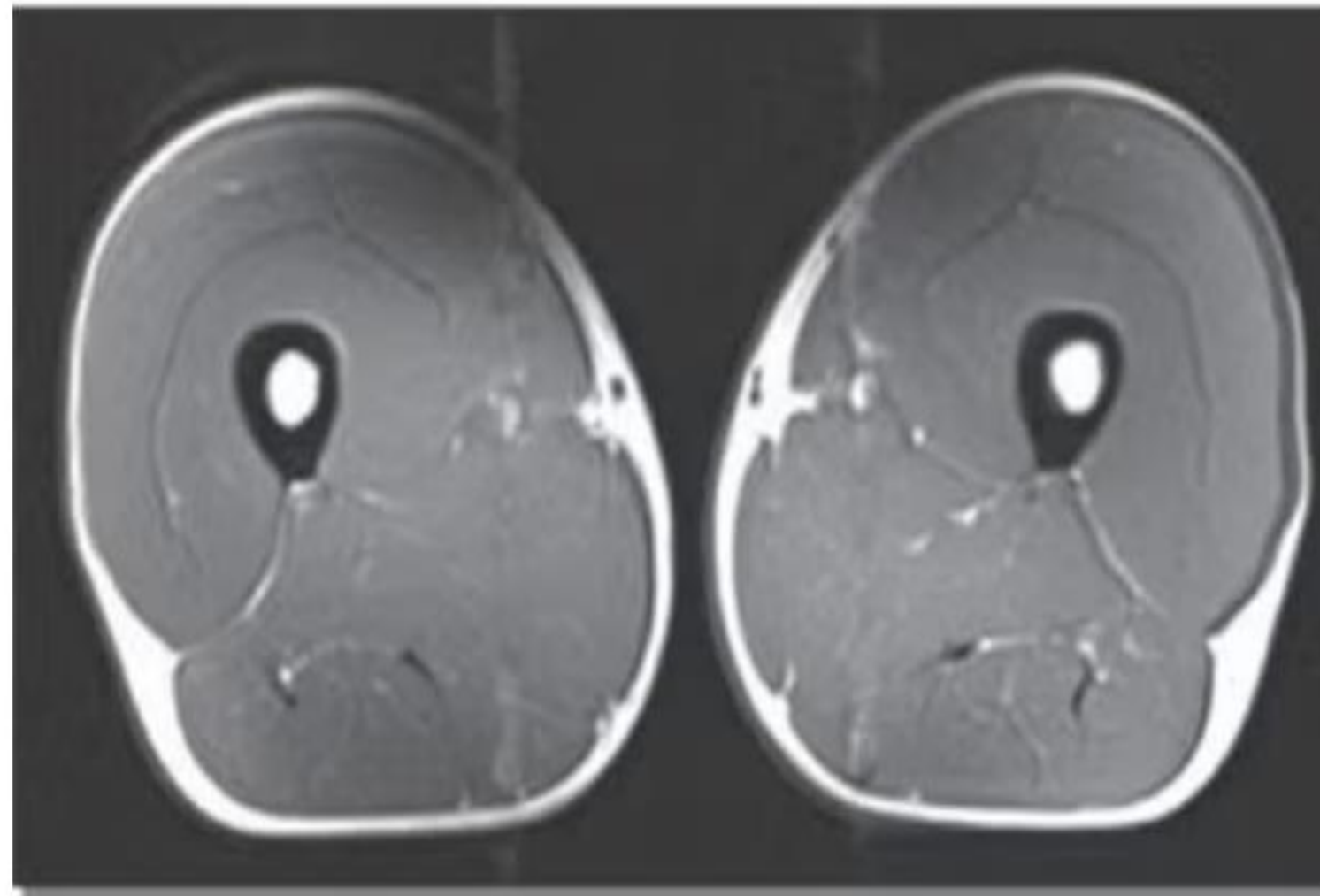
Skeletal muscle health is a significant predictor of anterior cruciate ligament (ACL) reconstruction outcomes. Quadriceps strength, in particular, is a strong indicator of patient-reported function and return-to-sport success.



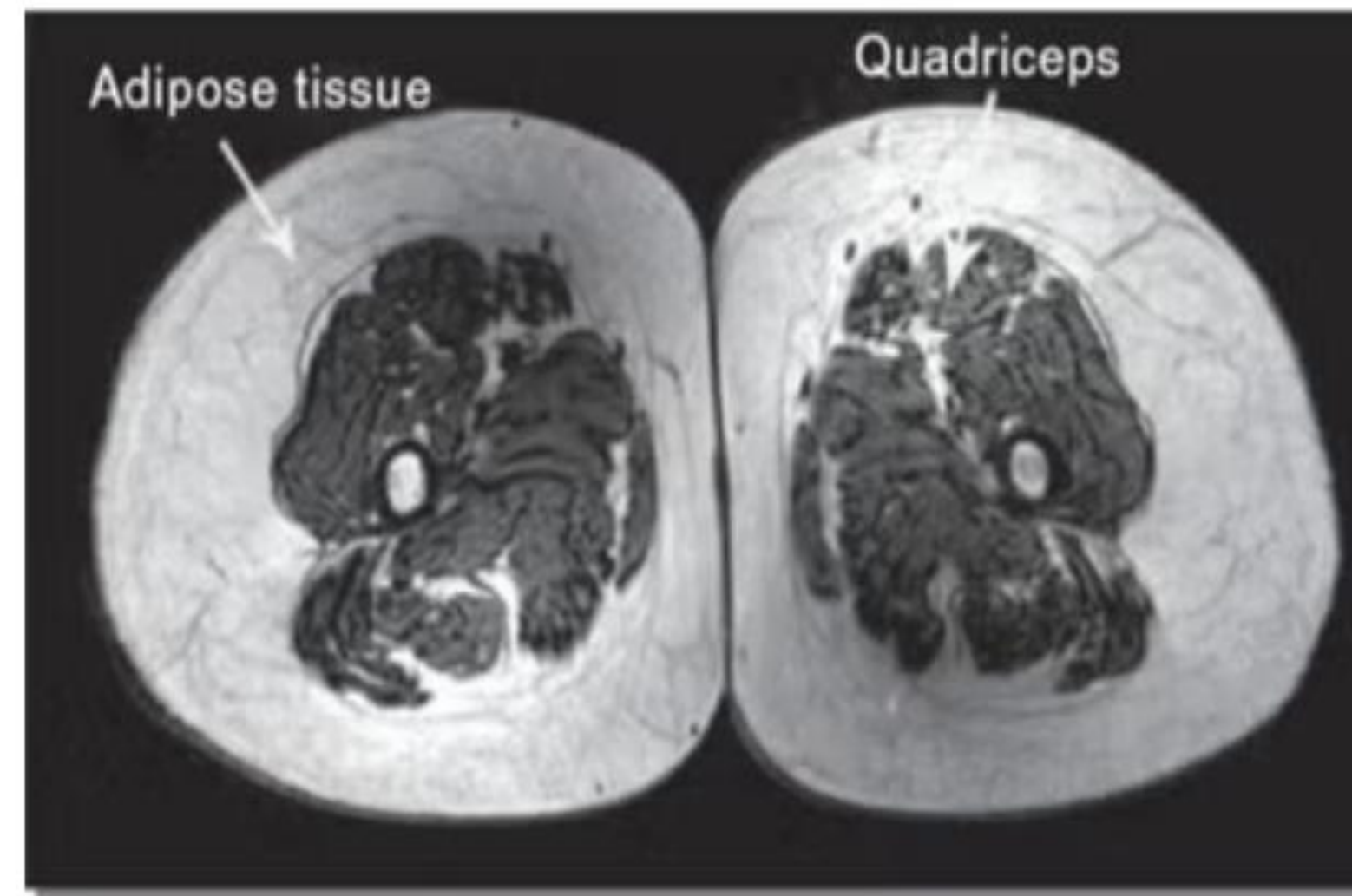
Maybe it is time to look at exercise and drugs that improve skeletal muscle. Pre-habilitation Program to improve skeletal muscle health BEFORE orthopaedic surgery

Chronic Exercise Preserves Lean Muscle Mass in Masters Athletes

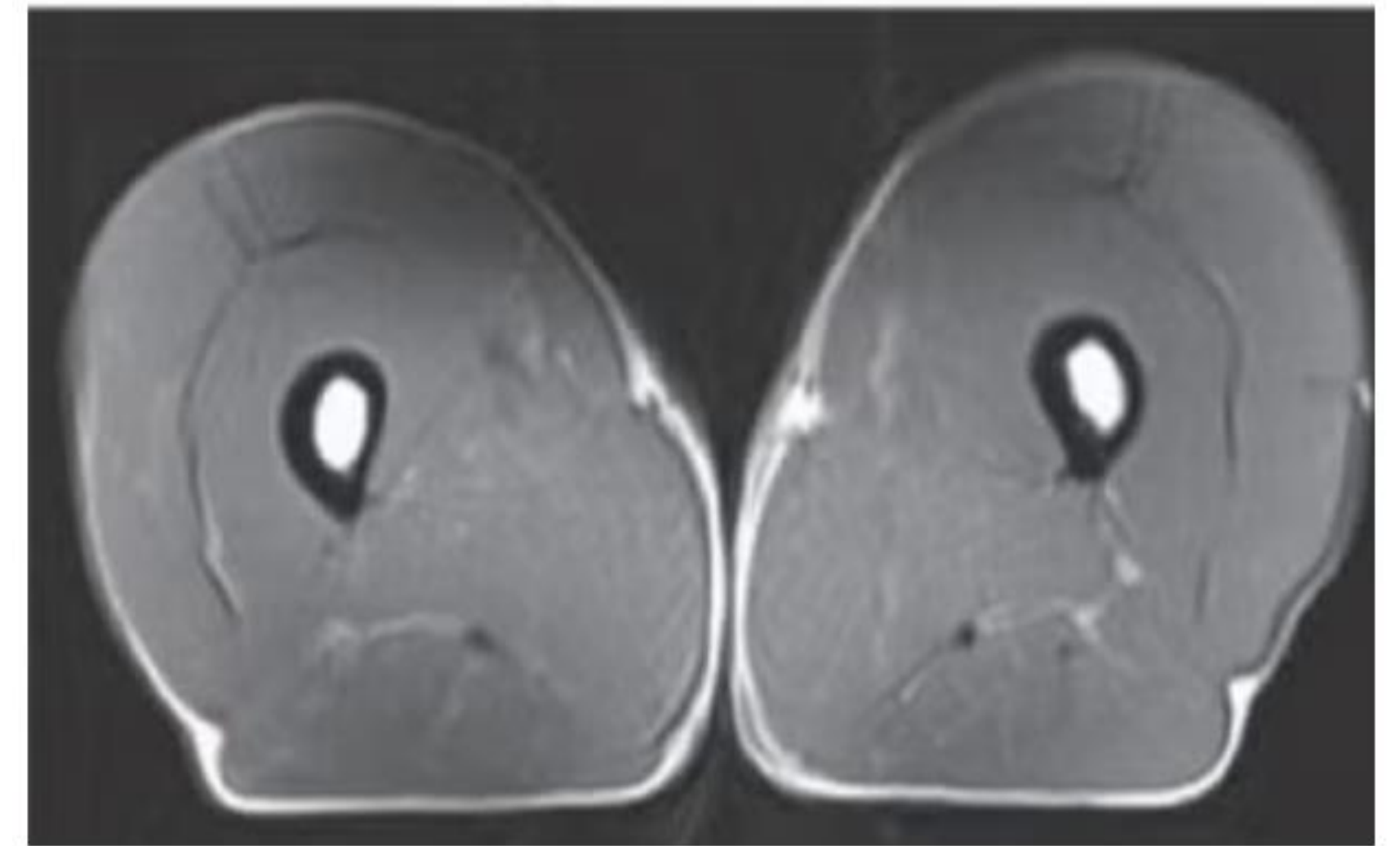
40-year-old triathlete



74-year-old sedentary man



70-year-old triathlete



Dr. Vonda Wright

**MUSCLE STRENGTH IN
MENOPAUSE:
KEY TESTS & LIFESTYLE
MEASURES**



featuring
Dr. Vonda Wright

Wroblewski AP, Amati F, Smiley MA, Goodpaster B, Wright V.

Chronic exercise preserves lean muscle mass in masters athletes. Phys Sportsmed. 2011

Sep;39(3):172-8. doi: 10.3810/psm.2011.09.1933. PMID: 22030953.

**Pre-habilitation program to preserves lean muscle mass and
optimize surgical outcome**

Consideration: To date, therapeutic OA clinical trials have largely been unsuccessful

Currently **4,323 interventional OA clinical trials** listed on clinicaltrials.gov

- **2,882** have been completed
- **680** are currently recruiting
- **138** trials funded by NIH
- **98** trials funded by other agencies, like DoD

Many trials focus on **symptomatic relief** rather than slowing or reversing disease progression

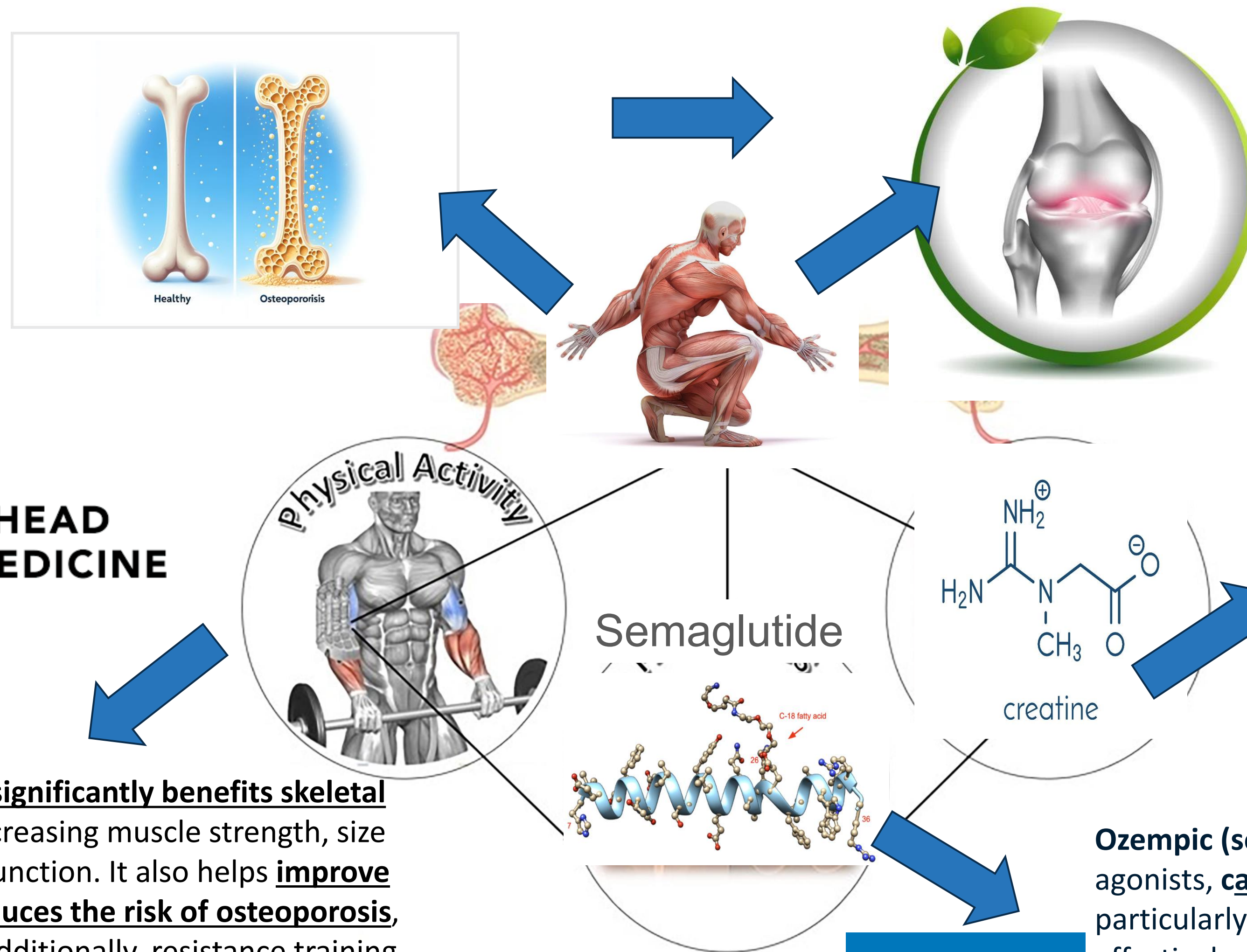
Few treatments have proven more effective than common analgesics/NSAIDs

No disease-modifying osteoarthritis drugs (DMOADs) have demonstrated clinical trial efficacy or achieved FDA approval

Many clinical trials for osteoarthritis (OA) have focused on drugs that target the joint directly, particularly for pain management. These include treatments like intra-articular injections of corticosteroids and hyaluronic acid, as well as NSAIDs targeting joint inflammation

Most clinical trials have been performed to identify drugs to delay osteoarthritis with NO SUCCESS.
All of these drugs target the joint! Maybe it is time to look at drugs that target other musculoskeletal tissues

Improving Skeletal Muscle Health to Improve Bone & Joint Health



THE STEADMAN CLINIC
AND
STEADMAN PHILIPPON RESEARCH INSTITUTE

Creatine supplementation can be beneficial for skeletal muscle health, particularly when combined with resistance training, and may help in muscle growth, strength, and recovery. It can also be beneficial for older adults, helping to maintain muscle mass and function as they age and reduce sarcopenia

Resistance training significantly benefits skeletal muscle health by increasing muscle strength, size (hypertrophy), and function. It also helps improve bone density and reduces the risk of osteoporosis, falls, and fractures. Additionally, resistance training can improve metabolic health and assist in weight management.

Ozempic (semaglutide), which are GLP-1 receptor agonists, can lead to a reduction in muscle mass, particularly during rapid weight loss. While they effectively reduce fat, they can also cause a decline in lean body mass, including muscle, potentially leading to sarcopenia (loss of muscle mass), strength, and function.

VAIL HEALTH

Ozempic (semaglutide), while effective for weight loss and managing type 2 diabetes, can lead to muscle loss as a side effect, particularly with rapid weight reduction. This is because Ozempic can reduce appetite, leading to decreased calorie intake and potential loss of muscle mass alongside fat. While not directly causing muscle loss, the rapid weight loss it induces can contribute to this side effect

Comment

<https://doi.org/10.1038/s41574-025-01160-6>

Balancing weight and muscle loss in GLP1 receptor agonist therapy

Fabian Sanchis-Gomar, Ian J. Neeland & Carl J. Lavie

 Check for updates

Rapid weight loss with GLP1 receptor agonists can come at the cost of skeletal muscle, potentially undermining metabolic and functional outcomes. This Comment highlights emerging evidence and advocates for clinical strategies that prioritize muscle preservation to ensure the long-term success and safety of pharmacological weight management.

use⁴. However, without muscle-specific tissue analysis, such inferences remain speculative. In fact, preclinical evidence suggests potential protective effects of GLP1 receptor agonists on muscle, including studies in rodent models demonstrating reduced muscle atrophy by modulating both anabolic and proteolytic pathways^{5,6}. These findings emphasize the need for mechanistic studies in human skeletal muscle to clarify these effects.

Targeting the myostatin-activin A pathway is a promising muscle preservation strategy. These ligands suppress muscle growth via activin type II receptors (ActRII). Inhibition of ActRII has been shown to induce hypertrophy and reduce adipose tissue mass in both animal models and preliminary human studies. A 2024 study⁷ combined semaglutide with



Ozempic prescriptions for non-diabetic individuals increasing by 700% from 2019 to 2023.
One-third of Ozempic prescriptions today go to non-diabetic individuals

Reducing skeletal muscle mass will predispose to osteoporosis and osteoarthritis!

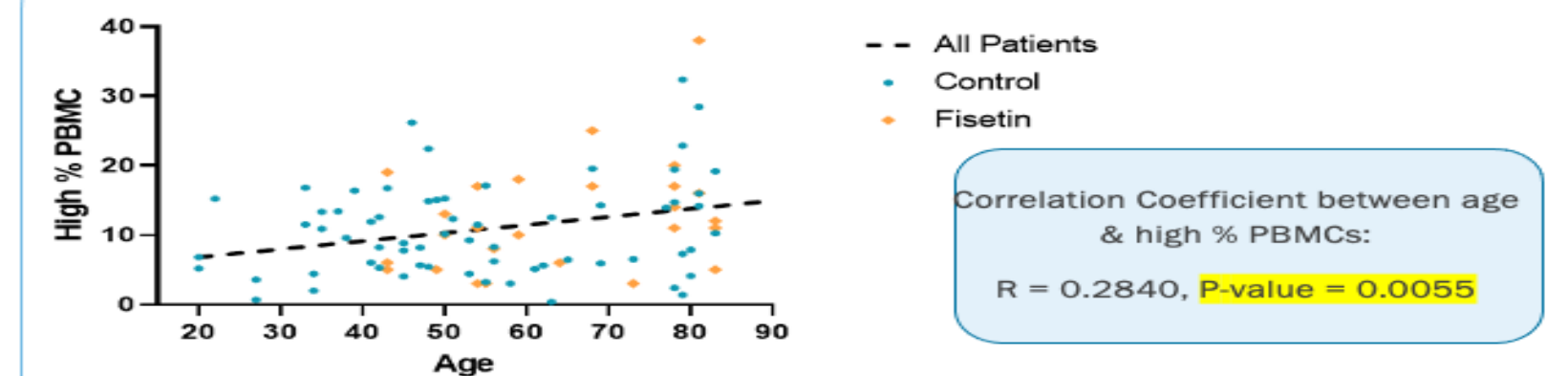
Adding exercise and creatine to Ozempic may help preserve muscle mass, which is a key component of a safer and more effective weight loss journey

CAN WE MEASURE BIOMARKERS OF AGING

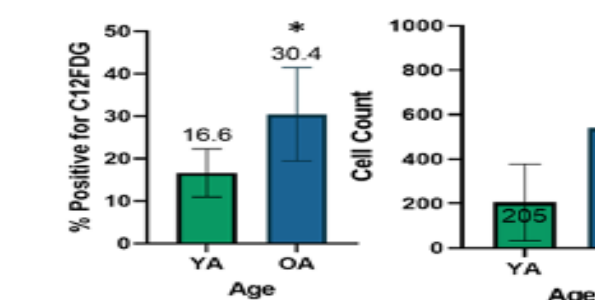
YES



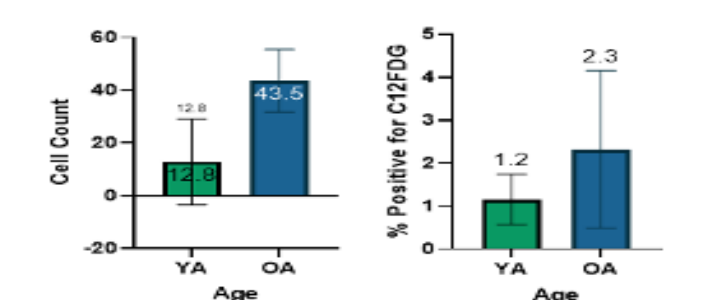
SENESCENCE IN PBMCS SIGNIFICANTLY INCREASES WITH AGE



PBMCS Flow Data

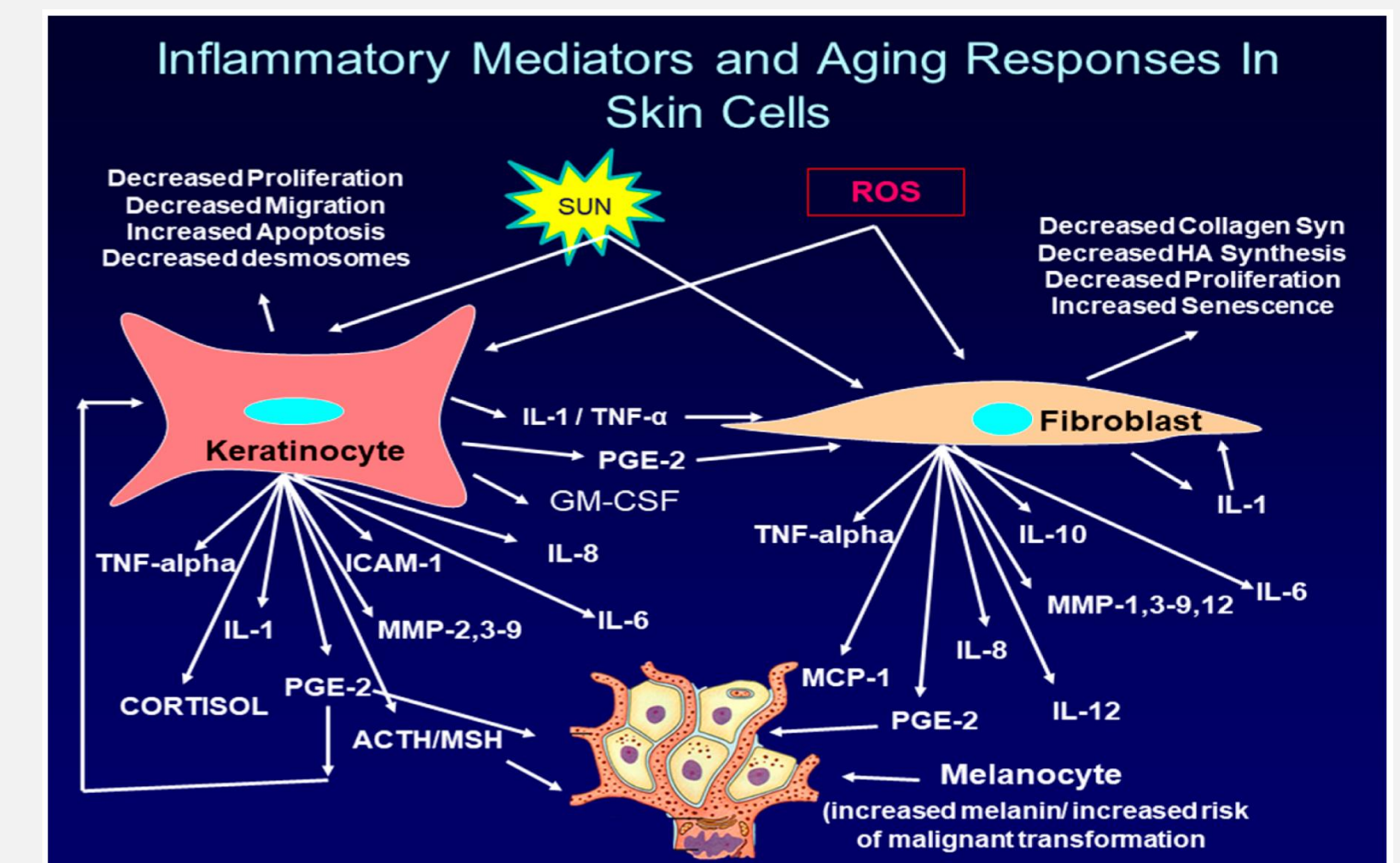


CD3+ T-Cells Flow Data

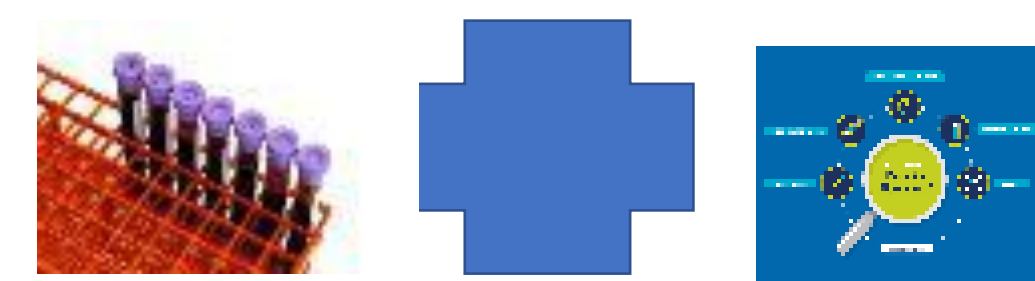


PBMCS show a direct correlation between age and percent senescence while T-cells do not

Biological Aging	Biomarkers
Genomic Instability	Plasma cf-DNA, SNP variations, mtDNA copy number, post-irradiation DNA damage/repair, g-H2A.X, PARP1
Telomere Attrition	Blood leukocyte telomere length, Telomerase RNA
Epigenetic	Epigenetic clocks, DNA methylation patterns, Line-1 DNA methylation, H4K16 acetylation
Proteostasis	Proteomics; Autophagy (p62, p62 mRNA, LC3I +II), N-glycan profile, Carbonyls, Amyloid-b-derived diffusible ligands
Nutrient Sensing	Insulin-like growth factor-I (IGF-I), insulin signaling, metabolomics
Mitochondrial	Mitochondrial respiration, Mitochondrial number, DNA copy number, and protein levels
Cellular Senescence	p16 ^{INK4a} , SA-βGal, p53, p21, g-H2A.X, cytokines, chemokines, MMPs, TIMPs
Stem Cell Exhaustion	Clonal composition, lineage (SLAM/CD50), self-renewal capacity, proliferative response to cytokines, cell senescence
Cell Communication & Inflammation	Circulating Factors, e.g. IL-6, TNF-α, IL-1Ra, IL-1β, TGF-β, PAI-I, CCL11/eotaxin, VEGF, β2 microglobulin



Personalized medicine for Healthy Aging!



Sarcopenia Markers:

Myostatin, Myokine (Irisin), Plasma transthyretin (TTR), N-terminal procollagen peptides, Myostatin, Agrin fragment, GDF-15 - IGF-1 - Follistatin - Activin A – Myostatin, Ferritin, eHsp72, CRP, Cathepsin D, Alarmin S100A8, Fragments of Aldolase A, IL-6, SPARC, MIF, C-reactive protein, Interleukin 6, Tumor Necrosis Factor-α

Osteoporosis Markers:

BTM (bone turnover marker), CTX (C-terminal telopeptide of type I collagen), NTX (N-terminal telopeptide of type I collagen), ICTP (C-terminal cross-linked telopeptide of type I collagen), PYD (pyridinoline), DPD (deoxy-pyridinoline), PINP (N-terminal propeptide of type 1 collagen), PICP (C-terminal propeptide of type 1 collagen), TRAP (Tartrate-resistant acid phosphatase), PTH (Parathyroid hormone), PLOD1 (Procollagen-lysine,2-oxoglutarate 5-dioxygenase 1), ALPI (Alkaline phosphatase, intestinal), ALPL (Alkaline phosphatase, liver/bone/kidney), ALPP (Alkaline phosphatase, placental), ALPPL2 (Alkaline phosphatase, placental like 2)

Osteoarthritis (OA) Markers:

MMPs, CRPM, C3M, sCOMP, HA, PIIANP, Col2-3/4, uCTX-II, MMP-3, uCol2-1 NO2, sHA, sCTX-II, sMMP-3, sPIINP

Senescence associated secretory phenotype (SASP) factors

p53, p21, p16, Bmi-1, GM-CSF, IL-1β, IL-6, IL-8, IL-10, IFNγ, CRAMP, EF-1α, 4-HNE, Malondialdehyde (MDA), 3- nitro-tyrosine (3-NT), TNF-α , NF-kappaB, C/EBP beta

ReCODE Tests

Target Values

GENETICS		
	ApoE	Negative for ApoE4
BLOOD TESTS		
	<u>Inflammation vs cellular protection</u>	
	CRP	< .9 mg/dL
	Homocysteine	< 7 mcmol/L
	Vitamin B6	60-100 mcg/L
	Vitamin B12	500-1500 pg/ml
	Folate	10-25 ng/ml
	Vitamin C	1.3-2.5 mg/dL
	Vitamin D3	50-80 ng/ml
	Vitamin E	12-20 mcg/ml
	Omega-6 to 3 ratio	.5-3.0
	A/G ratio (albumin:globulin)	>=1.8
	Albumin	> 4.5 g/dL
	Fasting insulin	<=4.5 microIU/ml
	Fasting glucose	70-90 mg/dL
	HgbA1c	< 5.6%
	Body Mass Index	18-25

LDL-p		700-1000 nmol/L	Estradiol : progesterone ratio	10-100
sdLDL		< 20 mg/dL	Pregnenolone	50-100 ng/dL
oxidized LDL		< 60 U/l	Cortisol	10-18 mcg/dL
Cholesterol		> 150 mg/dL	DHEA sulfate (f)	350-430 mcg/dL
HDL		> 50 mg/dL	Total testosterone	500-1000 ng/dL
Triglycerides		< 150 mg/dL	Free testosterone	6.5-15 ng/dL
Glutathione		5.0-5.5 micromolar	Free T3	3.2-4.2 pg/ml
Serum thiamine		20-30 nmol/l	Free T4	1.3-1.8 ng/dL
RBC thiamine pyrophosphate		100-150 ng/ml	Reverse T3	< 20 ng/dL
Leaky gut	Cyrex Array 2 - Negative		TSH	< 2.0 microIU/ml
Leaky blood-brain barrier	Cyrex Array 20 - Negative		Free T3x100 : Rev T3 ratio	> 20
Gluten sensitivity		Tissue transglutaminase antibodies - negative OR Cyrex Array3 and Cyrex Array 4 -	<u>Toxin Related</u>	
			Mercury	< 5 mcg/L
Autoantibodies		Cyrex Array 5 - negative	Lead	< 2 mcg/dL
			Arsenic	< 7 mcg/L
<u>Trophic Support</u>			Cadmium	< 2.5 mcg/L
Vitamin D3		50-80 ng/ml	Copper : zinc ratio	0.8-1.2
Estradiol		50-250 pg/ml	C4a	< 2830 ng/ml
Progesterone		1-20 ng/ml	TGF-beta 1	< 2380 pg/ml

MSH	35-81 pg/ml
HLA-DR/DQ	Benign
<u>Metals</u>	
RBC-magnesium	5.2-6.5 mg/dL
Copper	90-110 mcg/dL
Zinc	90-110 mcg/dL
Serum Selenium	110-150 ng/ml
Potassium	4.5-5.5 mmol/L
Calcium	8.5-10.5 mg/dL
URINE TESTS	
Trichothecenes	Negative
Ochratoxin A	Negative
Aflatoxin	Negative
Gliotoxin derivative	Negative
COGNITIVE PERFORMANCE	
CNS vital signs, Brain HQ or equivalent	> 50th percentile for age, improving with practice
IMAGING	
MRI with volumetrics	Hippocampal, cortical volume percentiles steady (or increasing)

Beyond senescent cells testing!

1. **Flow cytometry immunophenotyping including senescent T-Cell detection:**

Rationale: Senescent cell burden has been shown to strongly correlate with age-related orthopaedic conditions. Furthermore, targeting and eliminating senescent cells has been shown to mitigate age-related musculoskeletal decline. Thus, the ability to accurately detect senescent cells and their associated SASP factors will dramatically improve our understanding of individual patients response to treatment and potentially assist in deciding interventional strategies in the clinic.

2. Luminex multiplexing or SASP profiling: Cell Senescence is a natural aspect of life. Understanding the various mechanisms that cause the progressive decline of cellular and tissue function may aid in developing therapies to delay or treat age-related conditions and diseases. Luminex technology is a multifunctional liquid phase analysis platform that can detect key targets of cell senescence signaling pathway. **Advantages of cell senescence signaling pathway detection:**

3. Telomere Length: Length of telomeres correlate with overall health and aging. They can be considered a measure of 'biological age.' When telomeres get too short and cells can no longer divide, they become 'senescent' and lead to a cascade of events that accelerate aging. Telomerase is an enzyme that repairs telomeres and maintains their length. Preliminary studies indicate that you can influence telomerase and telomere length with diet, lifestyle, and bioactive botanicals. There are several companies with different testing methods available. Example:

4. Full Genome Sequencing: Companies like Veritas sequences the genetic material ([https://www . veritasgeneti cs. com/myGenome](https://www.veritasgenetics.com/myGenome)). This is a tremendous amount of data, but as our knowledge grows and we better understand genetic drivers and we can always access this gene sequence information. Veritas provides reports and key genes of interest such as ApoE, NOS3, FOXO3, MTHFR, COMT, DAO, PEMT. This test can be ordered with an alias for anyone who does not want their test results connected to them for medicolegal or insurance reasons.

5. Microbiome testing: Research on the microbiome is exploding. The microbes that live inside us impact every almost every aspect of health. This can be very valuable information, especially for people with otherwise medically unexplained symptoms. It's also an important part of optimal health. Presence or absence of certain strains of bacteria have been highly correlated with health outcomes AND can be modulated by diet, exercise, and supplement (pro-biotics and pre-biotics).

<https://www.viome.com/>

[https://www . onegevity. com/products/gutbio](https://www.onegevity.com/products/gutbio)

6. Oura Ring Apple Watch: This tracks a person's steps, calorie burn, heart rate and heart rate variability, details about sleep, meditation sessions, body temperature, and overall readiness. This vital information not only allows us to see how much a person is really sleeping, exercising, and meditating, but also how their body is responding to changes in diet and lifestyle. For example, cutting out alcohol and food intake for 3 hours before bedtime results in measurable improvements in sleep and heart rate variability metrics. ([https:// ourari ng. co m/how-o ura-wo rks/](https://ouraring.com/how-oura-works/))

DO WE HAVE HEALTHY AGING DRUGS & SUPPLEMENTS FOR HEALTHY AGING?

YES



de

Emerging research suggests that lithium have anti-aging effects by influencing key biological processes and offering neuroprotective benefits



Creatine may have several anti-aging effects by enhancing cellular energy, protecting against oxidative stress, and improving physical and cognitive function in older adults

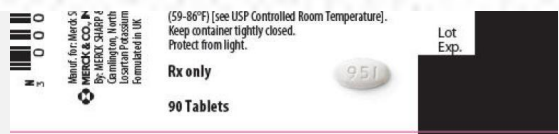


Bioidentical hormone therapy (BHRT) as an anti-aging strategy because it uses hormones structurally identical to the body's own to potentially counteract age-related hormonal declines, reducing risks for age-related conditions such as osteoporosis and cognitive decline.



Let's make the best pills cocktail

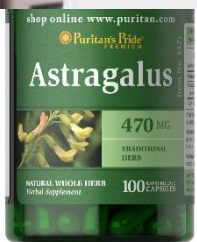
Talk to your doctor



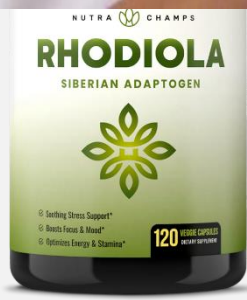
curcumin



Garlic



Astralagus



Rhodiola



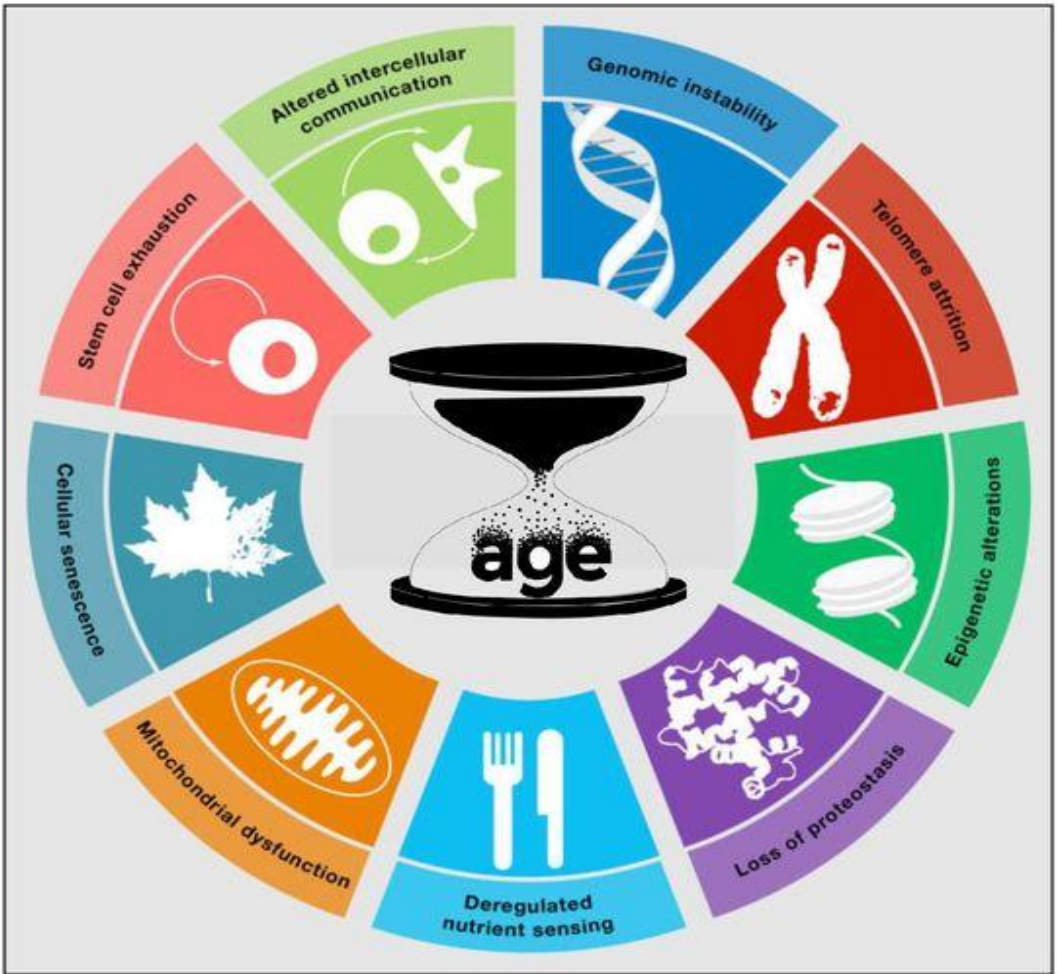
L-Theanine

Aging is Multi-Factorial

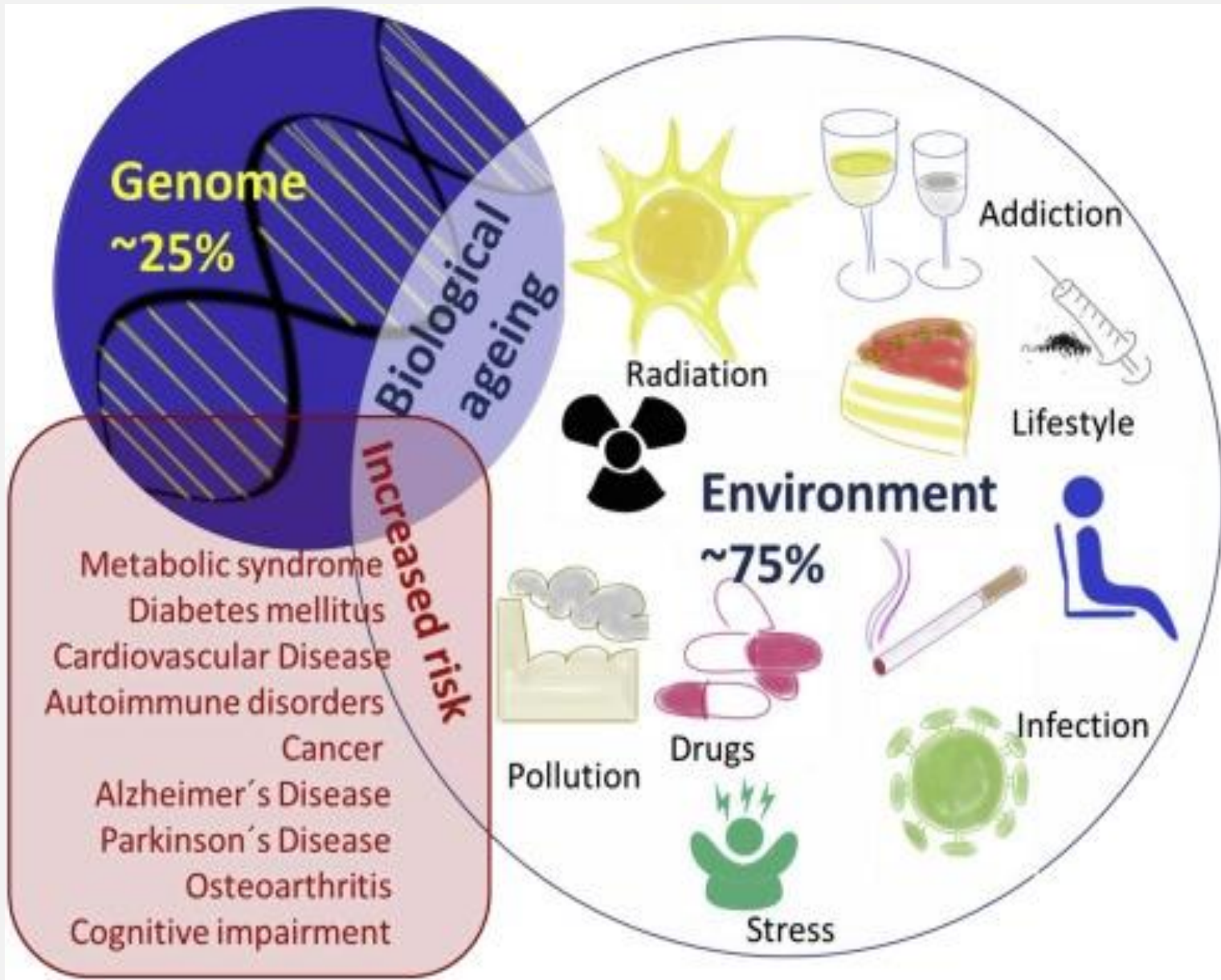
Geroscience

Hallmarks of Biological Aging

- Genomic Instability
- Telomere Attrition
- Epigenetic
- Proteostasis
- Nutrient Sensing
- Mitochondrial
- Cellular Senescence
- Stem Cell Exhaustion
- Cell Communication & Inflammation



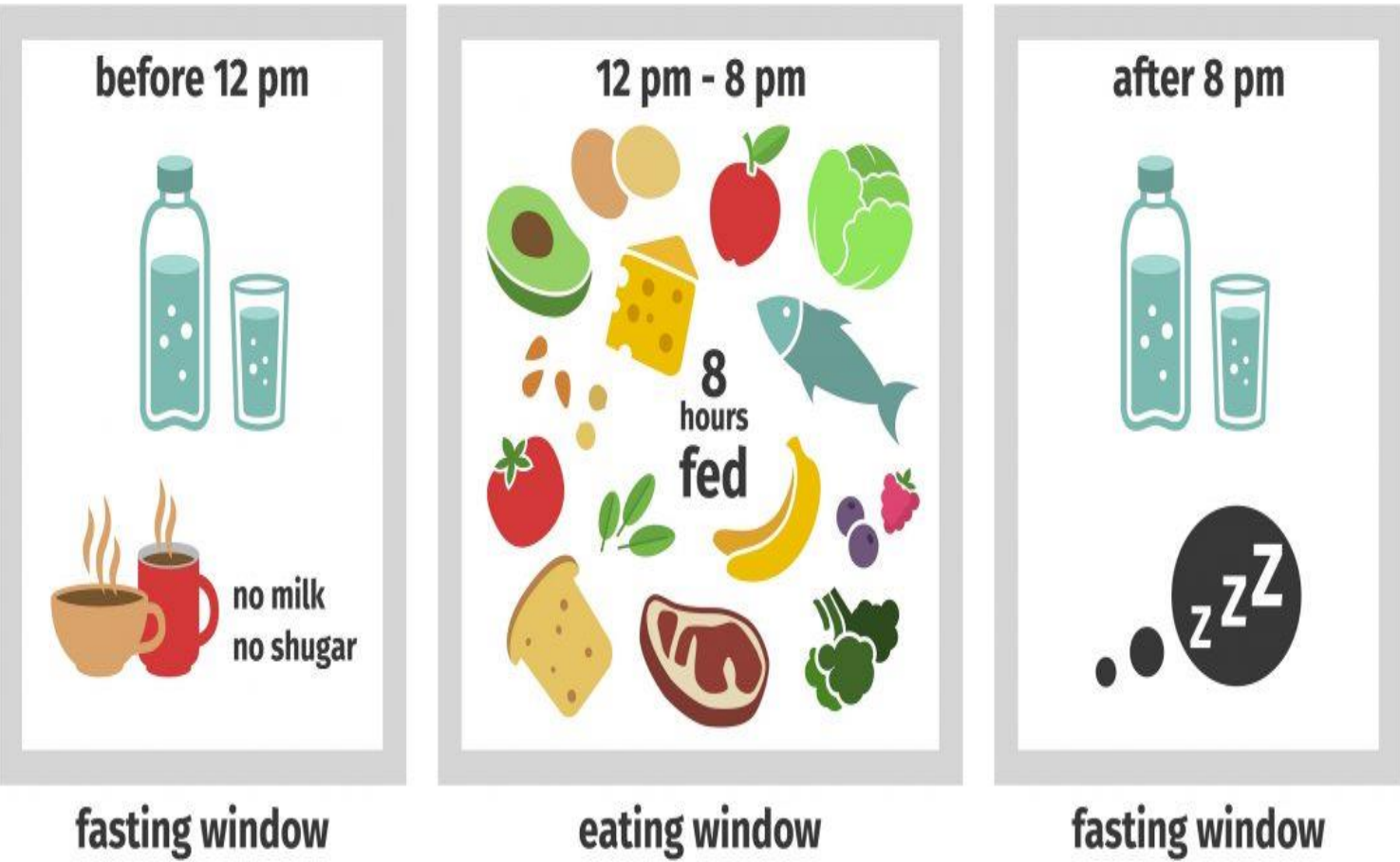
Lopez-Otin et al. Cell, 2013.



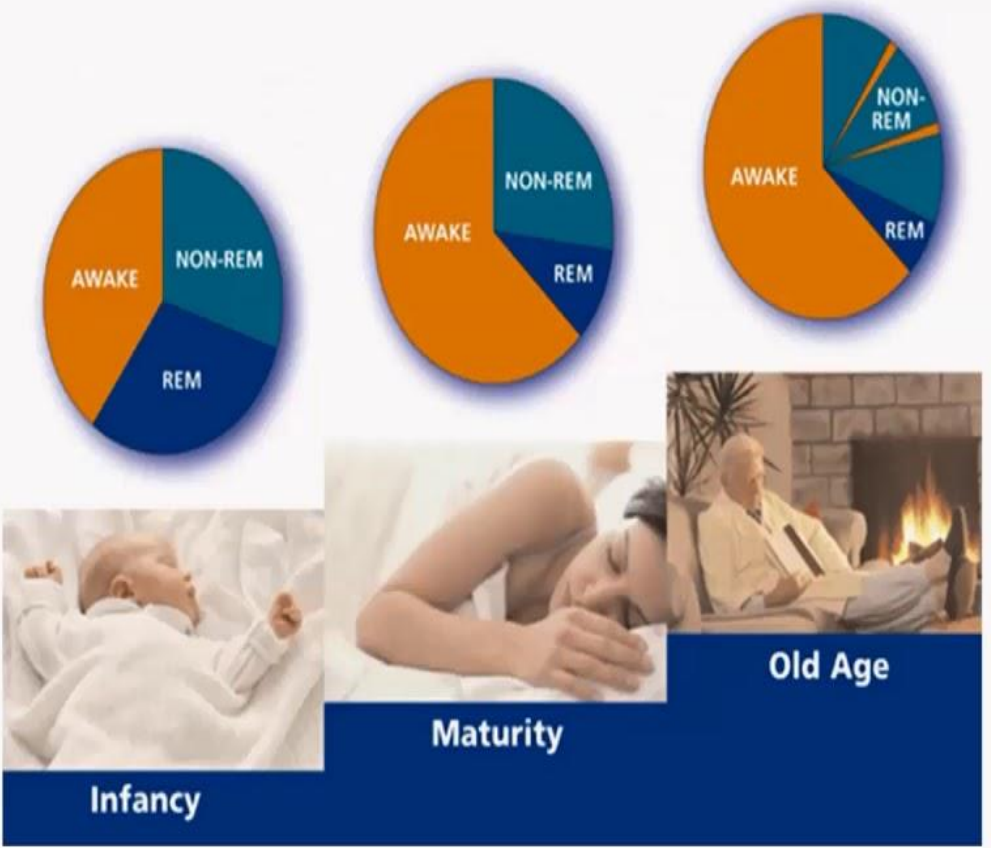
NUTRITION IS ESSENTIAL FOR HEALTH AND WELL-BEING AT EVERY STAGE OF LIFE



Intermittent FASTING



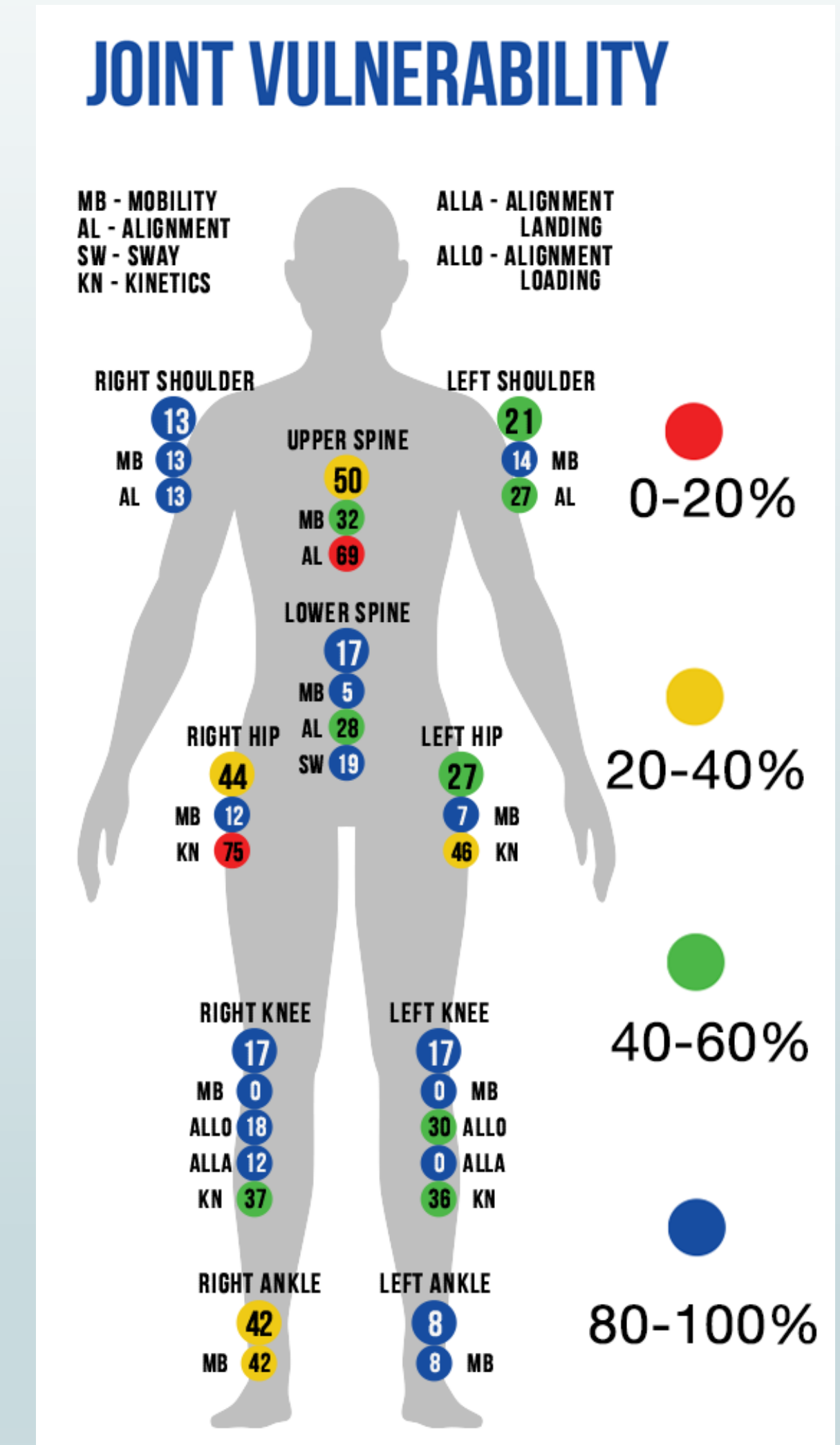
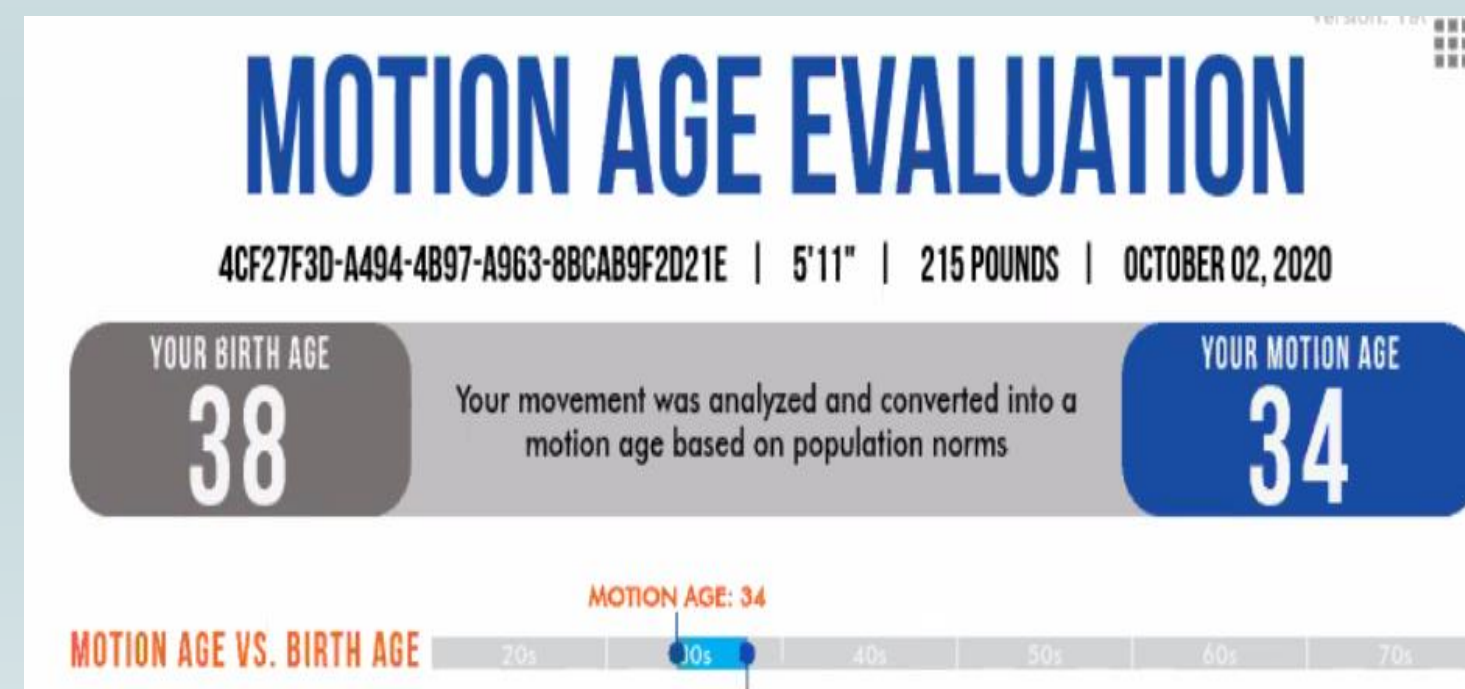
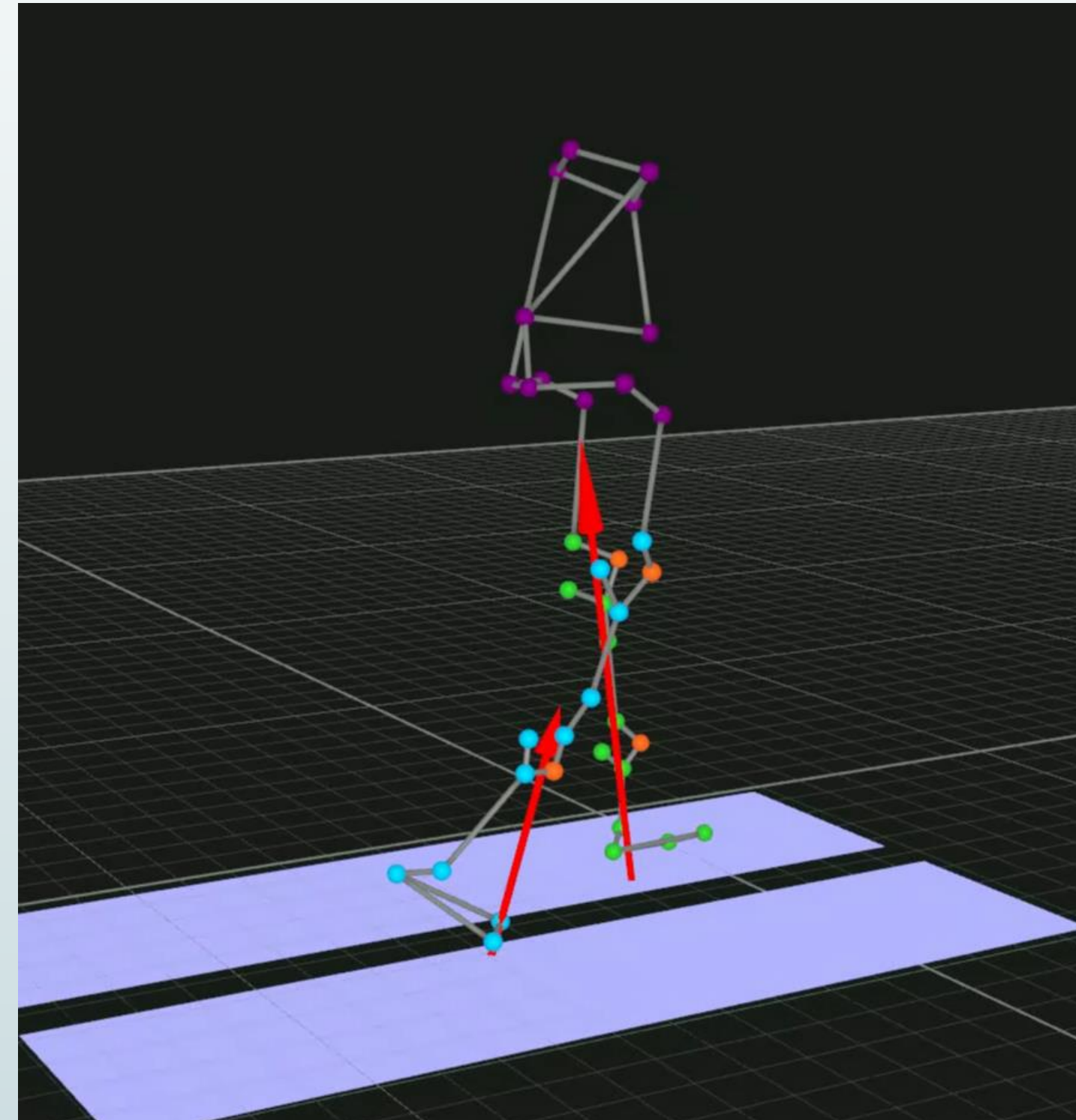
Normal Sleep and Normal Aging: Less deep sleep as we age



Beyond Senescent Cells Testing

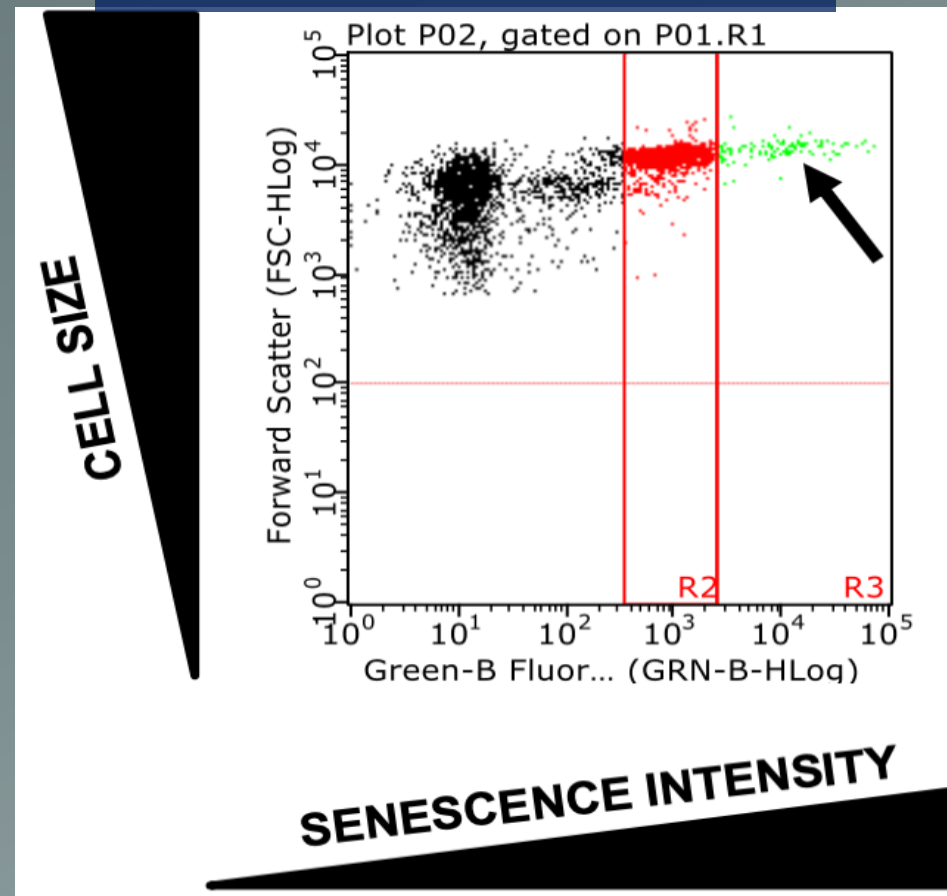
Brain Health Assessment: This testing aims at a comprehensive 360-degree-approach to optimal brain health to know individual's brain's risk factors so that those factors can be addressed as soon as possible. This assay could identify what the patient should be taking for optimal physical and mental wellness and explore which types of exercise are best for the brain health. This test could help to plan for healthy meals that is nourishment to mind, body AND brain.

- NeuroQuant MRI scanning
- **Estimated around \$50K per year**
- PET scanning for amyloid: Detecting amyloid in brain is now possible. In those with typical late onset Alzheimer's, amyloid starts accumulating decades before symptoms occur. Early detection could be vital to early intervention.
- This test combined with the NeuroQuant MRI scan ability would be an incredible thing to offer people.



Healthy Aging Program moving toward a comprehensive concierge medicine

Senolytics Proteomics



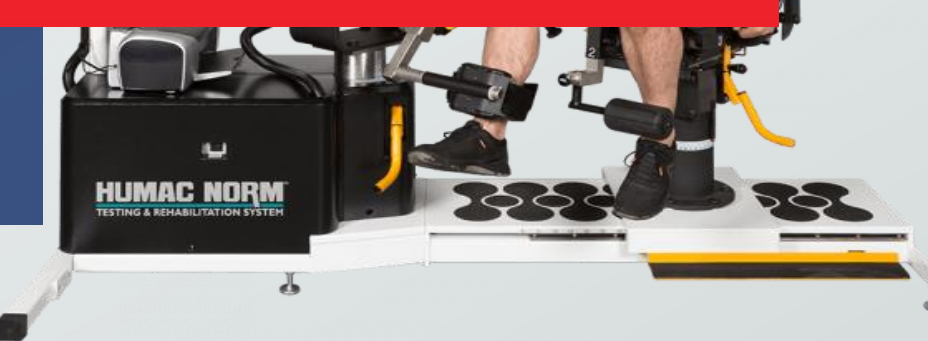
Biological Aging	Biomarkers
Genomic Instability	Plasma/urinary DNA damage, mtDNA copy number, post-translational DNA damage/repair, g-H2A.X, PARP1
Telomere Attrition	Telomere length, Telomerase RNA
Epigenetic Alterations	Methylation patterns, Line-1 DNA methylation, H4K16 acetylation
Protein Alterations	p62 mRNA, LC3I +II), N-glycan profile, cell-surface derived diffusible ligands
Metabolic Alterations	IGF-I), insulin signaling, metabolic hormones
Cellular Senescence	Respiration, mitochondrial DNA copy number, and protein levels of p21, p27, g-H2A.X, cytokines, chemokines, MMPs, TIMPs
Stem Cell Alterations	Stem cell composition, lineage (SLAM/CD50), self-renewal capacity, proliferative response to cytokines, cell senescence
Circulating Factors	Circulating Factors, e.g. IL-6, TNF- α , IL-1Ra, IL-1 β , TGF- β , PAI-1, CCL11/eotaxin, VEGF, β 2 microglobulin

Disease risk

Outcomes Prediction

Recommendations for Healthy Aging

Biomechanics & Strength





Linda Hart practicing her golf swing after few weeks after shoulder surgery with Dr. Millett

Working out every day for
the last 40 plus years
Play Golf, ski
Eat very healthy
(3 meals per day)
Dinner-breakfast 12-14 hours (fasting)
Sleep well (Melatonin)
Very social life
Works 5 days per week (start at 8:30 am-5 pm)



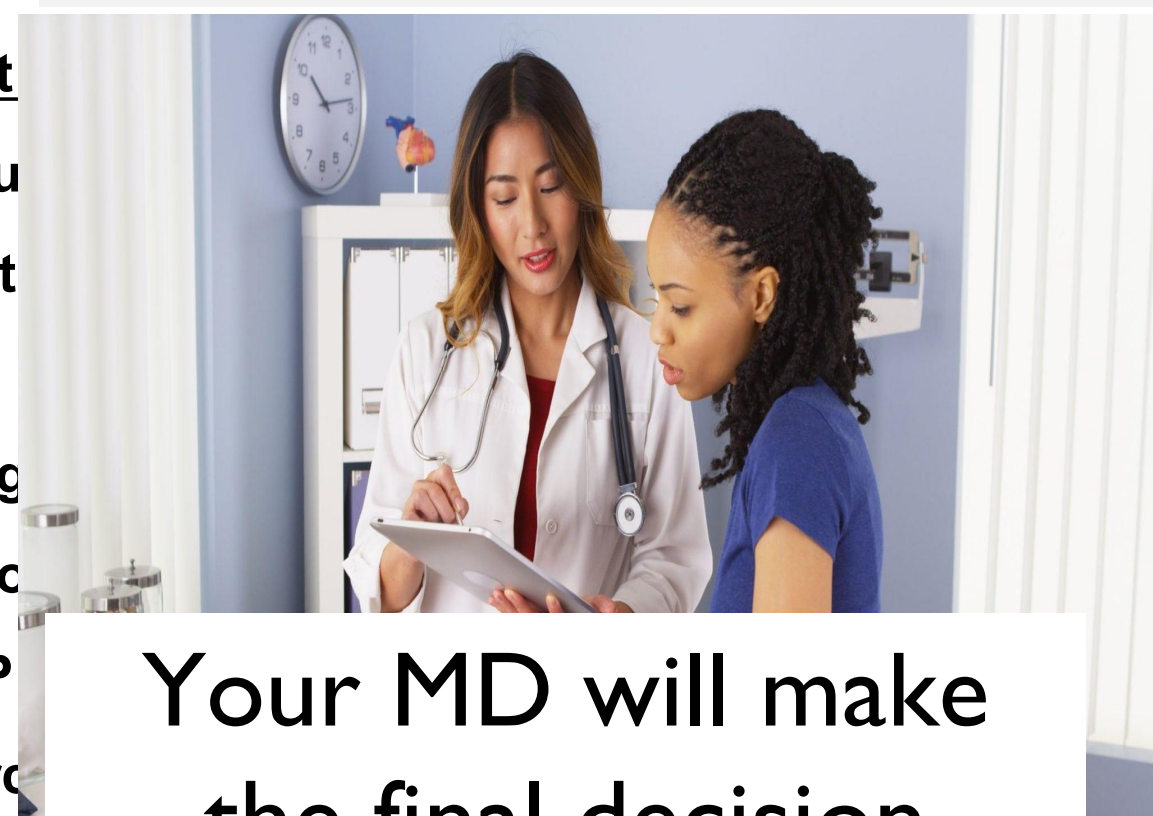
Me
Ch
De
NM
Pro
Qu
Sa
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TR
1/2
/Pr
10mg)

Fisetin
Flax Seed Oil (2)
Ginko-Combo
Glutathione (1,000mg)

85-year-old woman
Senescent cells result 1 percentile: 99% of people of



Let's make the best
pill cocktail



Your MD will make
the final decision

Night
Lithiu
5-Met
MSM
Omeg
Ostec
P-5-P
Querc
Rapam

Resveratrol (1,000mg)
Taurine (1000mg 1-2xday)
Turmeric Curcumin w. Bioperine
1/2 Bioidentical Hormone (Estrogen 4mg
/Progesterone100mg
/Testosterone10mg)
1 Troche (0.125mg CJC 1295; 0.125
Ipamorelin) *Collagen-producing
peptides

Health is Better than Wealth

Wealth management and health management are distinct fields, with **wealth management focusing on financial assets** and **health management on physical and mental well-being**.

However, these two areas are **deeply interconnected**, as financial stability can significantly improve health outcomes by enabling better nutrition, healthcare and reduced stress; poor health can financially devastate an individual by increasing medical costs and reducing productivity.

Therefore, the goal for many is not a "versus" scenario but a holistic approach that integrates **both—financial health supports physical health and vice versa**, creating a cycle of wellness.



Key Takeaways

At SPRI, we are focused on aging research, and the **goal is to delay aging-related diseases**, including osteoarthritis, osteoporosis, neurodegeneration and cancer

Optimizing Patients for Surgery by using anti-inflammatory/fibrotic and mental health care **will impact** the clinical outcome of your patients

Dying Young As Late As Possible is **achievable** through a balanced nutrition, exercise, and drugs/supplement to delay the aging process

Skeletal Muscle Health is **paramount** for the aging process and Ozempic-like drugs should be used with caution, as their effects on skeletal muscle health may predispose individuals for accelerated aging

THANK YOU!!!



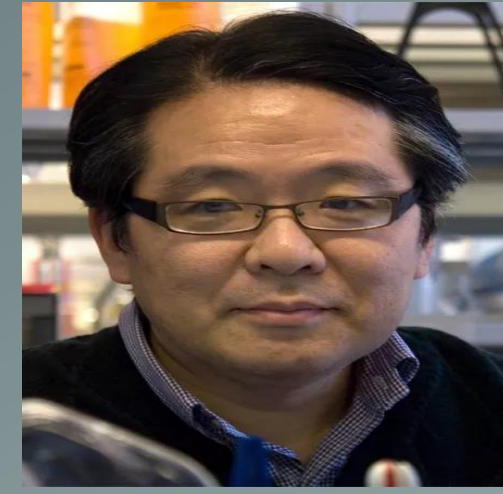
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Kristin Morgan



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Karen Briggs, MPH



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Alexa Dietrich



Greta Gohring



Matthieu Huard



Keegan Leach



Shivani Rao



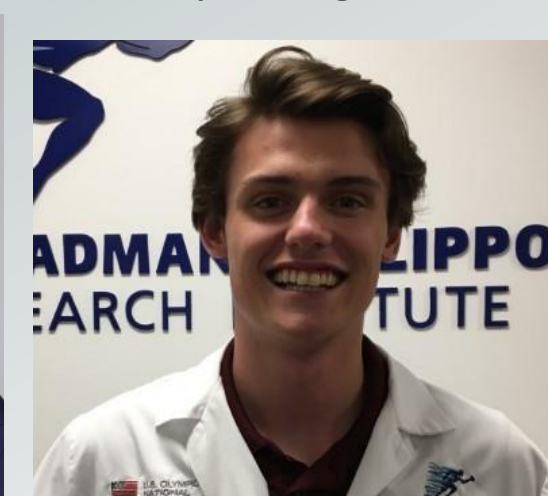
Alex Alessi



Britney Force



Marcos Rascon



Charles Huard



SPRI Collaboration & Partnership



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Dr. Mikhail Kolonin
Dr. Vihang Narkar



Dr. Farshid Guilak



Dr. James Kirkland
Dr. Chris Evans



Dr. Patricia Hardenbergh
Dr. Julie Barone



Dr. Charles Raison
Chris Lindley MPH,MS,MBA



Live better longer.

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

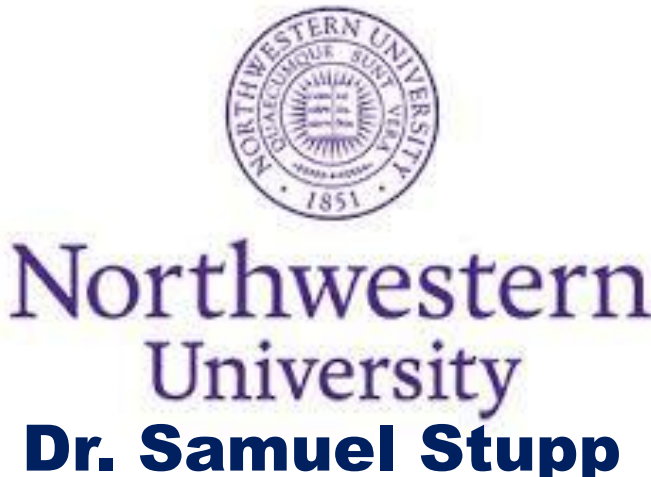


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Dr. Mark Markel



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Dr. Krishnendu Roy



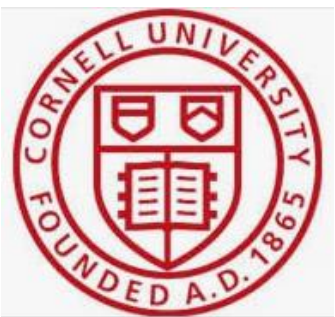
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Dr. Bing Wang



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Dr. Ben Gadomski
Dr. Katie Sikes
Dr. Stuart Tobet
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University of California, Los Angeles
Dr. Bruno Peault



UNIVERSITY OF MINNESOTA

Dr. Paul Robbins
Dr. Laura Niedernhofer



Dr. John Cooke



UNIVERSITY OF MIAMI
MILLER SCHOOL
of MEDICINE



Establishment of the Vail Scientific Summit, world-renowned scientists to fortify collaborations (2015)

2024 9th Annual Vail Scientific Summit

Scientists-Surgeons-Philanthropists-Hospital executive officials-family members-NIH-DOD-ORS-OREF executive officials
Dr. Lindsey Criswell director of NIAMS, NIH

SPRI NEWS

VAIL SCIENTIFIC SUMMIT 2024



STEADMAN PHILIPPON RESEARCH INSTITUTE

SPECIAL ISSUE:

VAIL SCIENTIFIC SUMMIT

WORLD-RENOWNED EXPERTS RETURN TO VAIL TO SHARE
THE LATEST IN REGENERATIVE MEDICINE

Each August, scientists, physicians and researchers join Steadman Philippon Research Institute (SPRI) in Vail for the annual Vail Scientific Summit. Now in its ninth year, the summit has become an essential event for experts in regenerative medicine—scientists not only share their latest research, but also have the opportunity to collaborate and meet with other scientists in the field.



Thank You

“The idea is to die young
as late as possible.”

—Ashley Montagu
anthropologist

