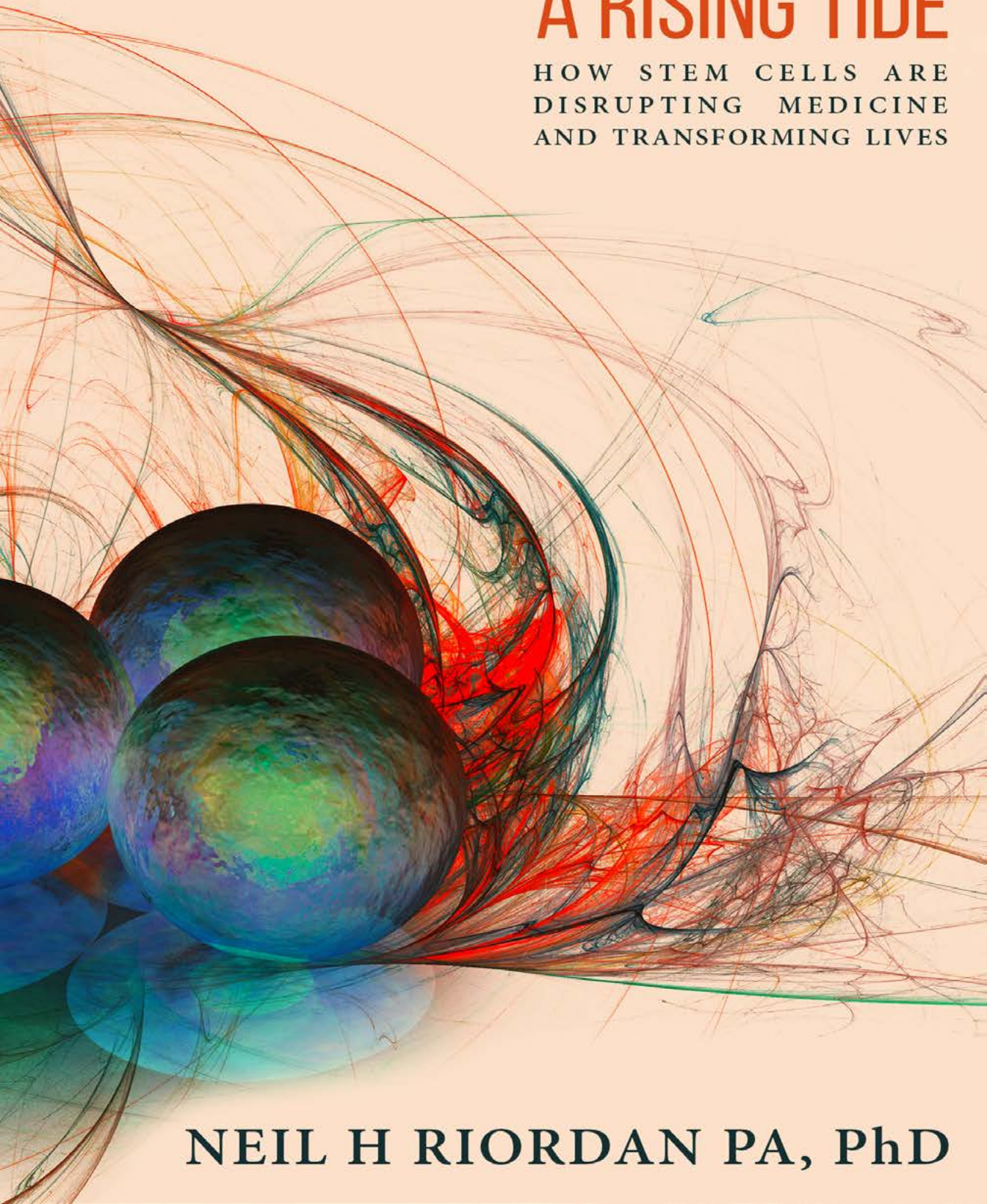


STEM CELL THERAPY

A RISING TIDE

HOW STEM CELLS ARE
DISRUPTING MEDICINE
AND TRANSFORMING LIVES



NEIL H RIORDAN PA, PhD

"Neil takes readers on a riveting journey through the past, present and future of stem cell therapy. His well-researched, educational and entertaining book could change your life. I highly recommend it."

Tony Robbins, NY Times #1 Bestselling Author

"100 years old will soon become the new 60. Stem cells are a key therapeutic to enable this future. Dr. Riordan's book is your guide to why this is true and how you will benefit. A must read for anyone who cares about extending their healthy lifespan."

Peter H. Diamandis, MD; Founder, XPRIZE & Singularity University; Co-Founder, Human Longevity, Inc.; Author of NY Times Best Sellers *Abundance* and *Bold*

Stem cells are the repair cells of your body. When there aren't enough of them, or they aren't working properly, chronic diseases can manifest and persist.

From industry leaders, sport stars, and Hollywood icons to thousands of everyday, ordinary people, stem cell therapy has helped when standard medicine failed. Many of them had lost hope. These are their stories.

Neil H Riordan, author of *MSC: Clinical Evidence Leading Medicine's Next Frontier*, the definitive textbook on clinical stem cell therapy, brings you an easy-to-read book about how and why stem cells work, and why they're the wave of the future.

"I'm the luckiest guy in the world. Stem cells have given me my life back."

Sam Harrell – Football coach and Multiple Sclerosis patient

"I never want to go back to autism before stem cells."

Marty Kelly – Parent of a child with autism



NEIL H RIORDAN, PA, PhD

Neil H Riordan is an accomplished scientist and developer of regenerative medicine therapeutics, with more than 70 peer reviewed publications and more than 40 patents and patent applications to his credit. He is the author of *MSC: Clinical Evidence Leading Medicine's Next Frontier*, a groundbreaking compilation of stem cell studies for more than 30 medical conditions, with over 800 references to peer-reviewed articles. Dr. Riordan founded Medistem Panama, a leading stem cell laboratory and research facility that is ISO 9001 certified and fully licensed by the Panamanian Ministry of Health. He also founded the Stem Cell Institute in Panama, where his mesenchymal stem cell technologies continue to be implemented in patients, now numbering in the thousands, with autoimmune and degenerative diseases and injuries.

Stem Cell Therapy A Rising Tide

**How Stem Cells are
Disrupting Medicine and
Transforming Lives**

Neil H. Riordan

Stem Cell Therapy: A Rising Tide
How Stem Cells are Disrupting Medicine and Transforming Lives

Copyright 2017 by Neil Riordan, PA, PhD
All rights reserved.
www.cellmedicine.com
info@neilriordanbooks.com

No part of this book may be used or reproduced in any manner whatsoever without written permission from Neil Riordan, except as provided by the United States of America copyright law or in the case of brief quotations embodied in articles and reviews.

This book is not intended as a substitute for the medical advice of physicians. The information provided in this book is designed solely to provide helpful information on the subjects discussed. The reader should regularly consult a physician in matters relating to their health and particularly with respect to any symptoms that may require diagnosis or medical attention. While all the stories in this book are true, some names and identifying details have been changed to protect the privacy of the people involved.

Layout design by www.iPublicidades.com

Illustrations by
Blake Swanson – Innercyte: Medical Art Studios
Steve Lewis – Blausen Medical
Stem Cell Institute & Riordan Medical Institute

Cover art design by n23art

Printed in the United States of America.
First Printing: 2017
ISBN: 978-0-9990453-0-5

TABLE OF CONTENTS

Foreword	v
Introduction	vii
CHAPTER ONE: The Seed Is Planted—Hope for Muscular Dystrophy	1
CHAPTER TWO: The Body’s Innate Healing Ability— Cancer Spelled Backwards	11
CHAPTER THREE: Redirecting the Immune System— Cancer Exposed	21
CHAPTER FOUR: Getting Started with Stem Cells	31
CHAPTER FIVE: Stem Cells in Action	45
<i>Arnold Caplan Interview</i>	49
<i>Robert Hariri Interview</i>	67
CHAPTER SIX: Spinal Cord Injury—The Ultimate Repair	77
CHAPTER SEVEN: Multiple Sclerosis— Calming the Immune System	91
<i>Bob Harman Interview</i>	98
CHAPTER EIGHT: Heart Failure Turnarounds— A New Approach	113

CHAPTER NINE: Frailty of Aging—Reversing the Inevitable	125
CHAPTER TEN: Respiratory Disorders—A Fresh Breath.....	141
CHAPTER ELEVEN: Arthritis—A New Solution	149
CHAPTER TWELVE: Biologics in Orthopedics— The Riordan Medical Institute	163
CHAPTER THIRTEEN: Autism—Progress, Not Regression	185
CHAPTER FOURTEEN: Ulcerative Colitis— Autoimmunity in the Gut.....	201
CHAPTER FIFTEEN: Diabetes—A Paradigm Shift	205
CHAPTER SIXTEEN: Lupus—An Opportunity in Autoimmune Health	211
CHAPTER SEVENTEEN: Magic Juice—The Elixir of Life?	215
CHAPTER EIGHTEEN: Lifestyle Choices— How to Protect Your Health	221
CHAPTER NINETEEN: Controversy and Legality	231
Conclusion	243
Epilogue	249
References	255
Acknowledgments	287

Foreword

As I read this book, I became very emotional. I had to go back about 28 years ago when my wife and I sat in a doctor's office and listened to a neurologist list in grim detail how our beautiful three-year-old son Ryan would spend his next 20 years. The doctor told us there was nothing that they could do at that time. He suggested that we do everything we could to keep Ryan active in order to maintain the strength he had as long as possible. And hopefully in the next 20 years they might find a cure for muscular dystrophy. The prognosis changed our lives forever. It was a very painful time for all of us.

As I continued to read about all of the patients who have been treated by Dr. Riordan, I realized that we all had one thing in common: traditional medicine had given up on us. There was nothing that could be done. Our own government, founded on the premise of life, liberty, and the pursuit of happiness, had evolved into overreaching bureaucracy that would attempt to prevent us from seeking lifesaving alternative treatments.

But once again, we all had something else in common. We found a man who was willing to do everything in his power to offer us options and give us hope for the future of our loved ones. Dr. Riordan has truly dedicated himself to his profession as a medical pioneer. He has sacrificed everything he has to give those who have been told there are no options a fighting chance and real hope for the future.

Dr. Riordan has never wavered in the face of scrutiny. It takes true courage to stand up to the often judgmental “traditional” medical community—those who act offended when you suggest that there might be a different way.

Fortunately for all of us, Dr. Riordan had the foresight to look beyond the walls of traditional medicine and fight the fight for us. I encourage you to read this book, and not just the chapters related to your condition. As a whole, the book lays out Dr. Riordan’s courageous and successful journey through his stories and the stories of his patients.

Thank you, Dr. Riordan, for all that you have done for us and our families. You truly are a hero!

George Benton, Ryan’s father

Introduction

BY ARNOLD CAPLAN, PHD

Neil Riordan, PhD, PA is a pioneer of the highest order, in some ways like John Glenn or Neil Armstrong. Neil has ventured where the routes were uncharted and the dangers huge. His rocket of cell therapy was launched on a rickety platform filled with hopes and dreams, and powered by an engine of money. This pioneer has hacked his way through the jungle of naysayers and has produced miracles of enormous proportions. He has taken our scientific dreams and translated them into a high-caliber medical facility that does good by offering exposure to cell therapy treatments that we working scientists only dream about.

Although there are those in my professional realm who would say that Neil is a medical “cowboy” who “experiments” with human subjects, I would say that he is providing access to therapies that are no more experimental than one sees every single day in the surgical suites of major medical centers. In such situations, the surgeon is “forced” to improvise because of the complexity of the wound field. Such improvisation sometimes involves using materials that are not approved but that the surgeon “feels” will work well in the situation he faces. For example, human decellularized skin from dead people was approved for topical applications for ulcerated wounds in diabetic patients. But these “membranes” are fabulous for closing abdominal surgical wounds in hernia repair operations and have changed the way such closures are done. This surgical improvisation, originally performed by a “cowboy” surgeon, is now the standard of care. We move forward in medicine by the skill and insightful work of pioneers—some with IRB approval and some not. Riordan’s procedures with MSCs currently have IRB approvals.

In a sense of transparency, let me say that I have accepted honoraria from Neil Riordan and gifts of hotel rooms, meals, and, indeed, infusions of MSCs. These all have monetary value, but none influences my opinion. The monetary success of Neil's enterprises evoke jealousy in some entrepreneurs, but Neil's continual reinvestment of money into his next medically successful enterprise displays his true motives—the advancement of a medically necessary science despite great obstacles. The key to his success is in the enormously high quality of his facilities; the people, doctors, nurses, receptionist, PR team, etc. are *all* highly principled and care about the patients they serve. These people care about what they do because Neil recruits them for their skills and attitude. He does not discuss this in this book, but they are present on every page. He talks about Dr. Paz, but he does not tell you of his long medical experience and his reputation in the United States and in Panama for caring and experienced medical judgements. In all of Neil's clinics, quality control labs, hotels for patients, and restaurants where they eat, the staff behind the scenes are dedicated to providing the highest quality medical care possible. Some clinics and hospitals in the United States could take lessons from the Riordan gang. That said, the cell-based therapies Neil's clinics provide have not all been approved and tested by double-blind, placebo control and rigorously monitored clinical trials, although such trials are currently underway. But, like innovative surgeons, these open-label uses have proven effective, as hopefully we will see in published peer-reviewed reports of his studies.

Each chapter of this book recounts the personal stories of how Neil's unwavering confidence that cell-based therapies with MSC preparations from fat, marrow, or umbilical cords can make a medical difference. Neil made medical tourism work, and what he has done is highly laudable, not only because of the patients he has helped, but because of the laws that have been written to support cell-based therapies in Panama. This book is not what I pleaded with Neil to write, however. I have, for many years, begged him to give us outcome reports of his many patients: what they have as clinical problems, what they walk in with, and the longitudinal outcomes after the cell infusions. Hopefully these will be forthcoming, but they are not in this book. What is here in these pages is, none-the-less, amazing.

I first learned about Neil's clinic in Costa Rica and thought his procedures and therapies were brilliant. And these were crude compared to those currently underway in Panama. The Panama GMP-production facilities, his offices and treatment rooms, and the products including MSCs from umbilical tissue are of the highest quality. These are the vehicles and the platform that allow him to write this treatise of the therapies they provide. It is a shame that we have to fly to Panama to have access to these therapies instead of having them available in the United States. How long will it take for such therapies to be available to the patients covered by Medicaid or Medicare instead of those from Beverly Hills or Long Island who can afford to travel to Panama?

Almost daily I receive emails from people who want access to "stem cell" treatments. I tell them that I am just a PhD researcher and cannot suggest an avenue of treatment for medical issues. If you have this book in hand, read the chapters. They are honest, open, and spellbinding. While Neil is not a medical doctor, his clinical experience as a physician assistant along with his research background have prepared him for the serious medical issues for which Neil has organized cell therapy treatments, often with quite significant outcomes. Neil is certainly a student of the medical arts and an expert using innovative treatments. I have talked to patients of Neil's clinics and their family members about their treatments; the stories told in this book are just the tip of the iceberg. This is an interesting book and an interesting and gutsy journey of Neil Riordan. His physician father would be proud to recognize Neil's passion and medical achievements.

Arnold I. Caplan, PhD
Skeletal Research Center
Department of Biology
Case Western Reserve University
10600 Euclid Avenue
Cleveland, Ohio 44106
January 15, 2017

Chapter Twelve

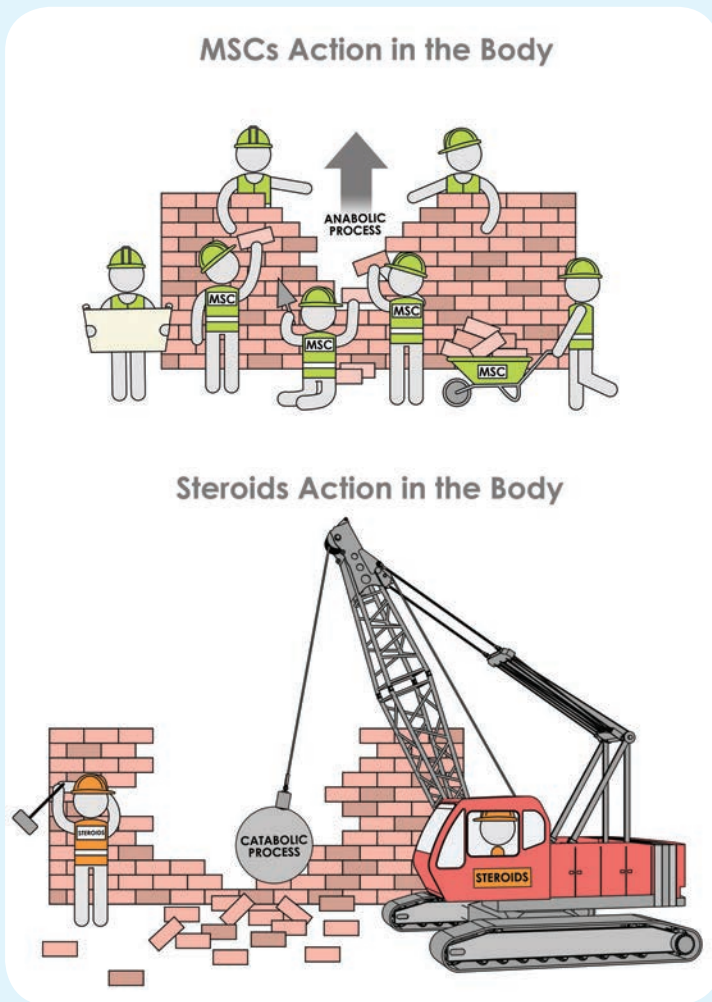
BIOLOGICS IN ORTHOPEDICS—THE RIORDAN MEDICAL INSTITUTE

Over the years, I've followed the adoption of biologics in orthopedic surgery practice among my colleagues. Biologics are medical products derived from living sources; stem cells are a type of biologic. Many physicians started out by using the only biologic available to orthopedic doctors in the United States at the time: platelet-rich plasma (PRP). PRP is essentially made up of the growth factors from whole blood - in orthopedics, PRP is actually a mixture of white blood cells and platelet-rich plasma. PRP is used to augment the healing response in soft tissue injuries such as tendon and muscle tears. Before biologics came into use, patients were usually given steroid injections to ease pain from soft tissue injuries.

Steroids make the injury feel better short term, but in the long run, they actually tear up the tissue, breaking down proteins and sometimes worsening the injury rather than healing it. They do nothing to address the underlying problem, which is how to regenerate damaged or degenerated tissue. Eventually, the patient may need surgery due to the damage.

Do Steroid Injections Help or Harm?

Inflammation of the joints can be treated with a combination of a local anesthetic and corticosteroids to reduce pain. However, this treatment can induce death in cartilage cells,^{1,2} especially at higher doses,³ raising questions about the benefit when used for osteoarthritis. Animal models, particularly in horses, show a detrimental effect of corticosteroids on cartilage:⁴ treatment with corticosteroids alters cartilage and collagen production not just in the treated joint(s) but also in untreated joints, an effect that may spread to the rest of the body.⁵ Similar negative effects to cartilage tissue have also been observed in dog models *in vivo*, and *in vitro*.^{6,7}



Steroids are associated with damage to cartilage cells and with avascular necrosis of the joints, along with other negative effects on the body:

- Decrease overall immunity
- Toxic to stem cells
- Destroy body's capacity to repair tendons

The progression of osteoarthritis was shown to continue regardless of corticosteroid treatment as early as 1993: the knees of steroid-treated patients showed more degeneration (78.6 percent) than the knees of those who did not receive treatment (52.4 percent).⁸ More recently, the use of corticosteroids has been shown to have fewer long-term benefits for lateral epicondylitis, more commonly known as tennis elbow—an inflammation in the elbow region with damage to the tendons and muscles in the joint area. Despite positive short-term effects, injections with corticosteroids have been found to be no better in the long term than injections with a placebo,^{9,10,11,12} with higher recurrence rates after a year.¹³

Interestingly, steroids are naturally secreted in the body by the adrenal cortices in response to stress only in the absence of sufficient vitamin C. The adrenal cortices have the highest concentration of vitamin C of any tissue in the body. When the body is under stress, vitamin C is secreted from the adrenals first, having a potent anti-inflammatory effect in the body. We routinely put our orthopedic patients on oral vitamin C, and we give a vitamin C IV after every surgery to replenish the body's and the adrenals' supply.

It makes sense evolutionarily that if the building blocks of repair are not available to heal a wound, the wound will remain in a chronically inflamed state. Vitamin C is crucial for collagen production and therefore wound healing. If the adrenals are out of vitamin C, the secreted corticosteroids may have an anti-inflammatory effect, but their catabolic action is inferior to the vitamin C they are replacing.

Early on, orthopedic specialists used PRP to treat a variety of inflammatory conditions like infrapatellar tendonitis, also known as jumper's knee. They knew that surgery would likely make this condition worse in many patients, especially in athletes. Reports were coming in of patients being treated with PRP for a variety of tendon conditions, without needing surgery. Very few doctors were using PRP treatments, but then

Arthroscopy for Orthopedic Injuries

Arthroscopy is a surgical procedure performed with the aid of an arthroscope, a small camera-like optical instrument that allows the surgeon to see the interior of an affected joint. This procedure usually requires two small incisions, one for the arthroscope and the other for the surgical instrument, making it a minimally invasive intervention under local, regional, or general anesthesia. Arthroscopy may be used in cases of ankle, wrist, shoulder, or elbow damage, but is most commonly used for the knee in meniscal tears or anterior cruciate ligament (ACL) reconstructions.

While recovery time is not as long as it would be with arthrotomy (fully opening the joint), arthroscopy patients still experience swelling and pain, and necessitate physical rehabilitation to be able to bear weight in the joint. There is great interest in augmentation in arthroscopic surgery—in particular, the use of biologics to speed recovery time and to promote healing in the affected area. Therapy with platelet-rich plasma (PRP) containing high levels of growth factors has shown promising results; studies summarizing multiple clinical trials report pain reduction and a decreased risk of reinjury after PRP treatment for certain conditions.^{14,15,16}

again, their options were limited. PRP turned out to be a good choice for infrapatellar tendonitis. Patients did much better with PRP than they would have with arthroscopy, the most common surgical procedure for that condition.

Without the growth factors from PRP, a tendon has little chance to heal due to the low blood supply—much like cartilage in people with arthritis. Platelets are designed to heal a wound and stop bleeding as well as recruit cells from the bloodstream and bone marrow to induce healing. When PRP is injected, it sends the message, “this tissue is injured” to the body so that the body responds accordingly. With a minimally invasive procedure taking fewer than 30 minutes, athletes could now be back on the field in six weeks, playing with no pain.



As PRP technology matured, physicians moved from pulling growth factors out of blood to pulling growth factors out of bone marrow, as well as stem cell concentrate. Whole blood contains very few stem cells, but bone marrow is a rich source of these cells. It is particularly rich in stem cells that promote angiogenesis, or the development of new blood vessels, which helps to bring needed nutrients to the site of injury. When working with tissues that naturally have less blood supply, growth of new blood vessels to the area can make a big difference.

Also during this time, orthopedic surgeons performed microfracture surgeries, the standard of care for patients with damaged knee cartilage. The procedure involves drilling holes into the knee that go just deep enough to let bone marrow leak out. In microfracture, the bone marrow is key to prompting healing of the cartilage. Stem cells and other growth factors from bone marrow home to the area of damage and promote healing of the cartilage. Whether or not the procedure is successful is largely dependent on how robust the stem cells are. The problem is, many patients who undergo this procedure do not recover from the injury, or they only recover for a couple years because they were not able to heal the cartilage well enough. Unfortunately, this procedure has poorer outcomes than other cartilage repair techniques,¹⁸ and a paper that reviews 20 years of data in 28 studies has found that there is insufficient data available on its long-term effects.¹⁹ As it turns out, the protective covering that grows back to heal the cartilage after a microfracture procedure is not hyaline, the type of cartilage we are born with, but fibrocartilage, which is inherently less stable than hyaline within joints. Fibrocartilage breaks down more easily than hyaline, which is why so many microfracture procedures fail.

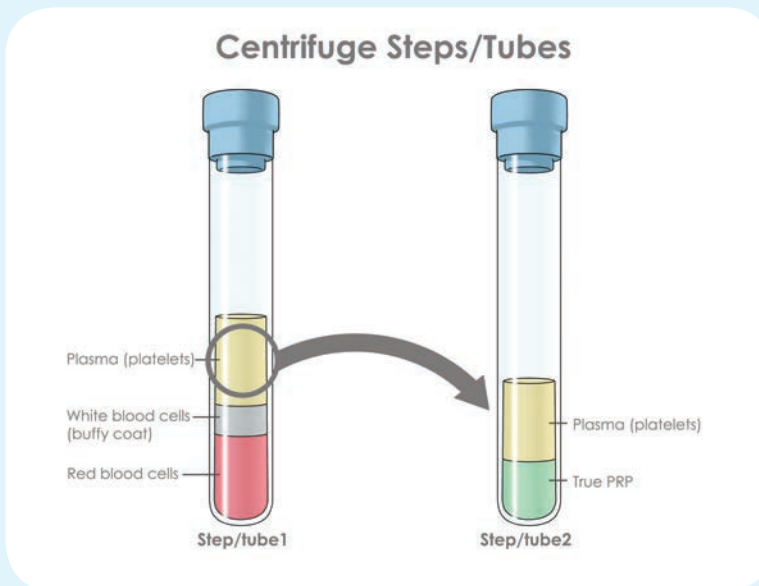
The relatively poor success rate of microfracture surgery spurred doctors to look for a better alternative and some began adding a concentrated bone marrow aspirate to help heal the knee better than the few drops that are extracted during microfracture. The problem was, at the time, the procedure involved extracting bone marrow with a tool called a Jamshidi™, a long nail-like needle that is driven into the hip bone using a mallet. The old Jamshidi procedure was painful, required the patient to be put under anesthesia, and involved multiple bone marrow draws to get a good sample. Jamshidi design improved over the years and nowadays, an experienced doctor can use a

Platelet-Rich Plasma (PRP)

Treatment with platelet rich plasma (PRP) is a technique to enhance the healing process after injury. Blood is drawn, generally from the patient's arm vein, and is then centrifuged to obtain platelets and cytokines in higher concentrations than in circulating blood. This process separates the PRP product into three distinct layers: 1) red blood cells at the bottom; 2) white blood cells and inflammatory cytokines (the buffy coat) in the middle; and 3) plasma (the liquid part of the blood), containing platelets and growth factors at the top.

There are actually two products that are commonly referred to as PRP. One of them is pure PRP. This classical, or true, PRP is made by centrifuging the tube gently so that the platelets remain suspended in the plasma. The plasma is then transferred to another tube, which is centrifuged harder so that the platelets separate to the bottom.

In the field of orthopedics, PRP is not only PRP—it also includes the white blood cells (from the buffy coat). Most machines that automate this process will also include the white blood cells (commonly known as the PBMCs, or peripheral blood mononuclear cells). So, in the literature there are many articles that refer to PRP when in fact they are describing PRP with PBMCs. Preferably, you would want the white blood cells in the PRP mixture if the goal is to heal the wound, because it includes cellular components that aid in healing.



Once the platelets are activated inside the body, they release more growth factors, which promotes blood vessel formation. This newly formed blood vessel network allows nutrients and other cells to be delivered to the area, resulting in a faster recovery with less pain and reduced scarring of the injured tissue. Treatment with PRP is especially useful in orthopedics and in sports medicine, with notable successes in arthroscopy (anterior cruciate ligament and meniscal repairs), muscle tears, Achilles tendon injury, and tennis elbow, among many other injuries.¹⁷

PRP plus PBMCs can be described as “bone marrow lite.” The bone marrow is a very rich environment of stem cells, including CD34+ cells, which are the precursors to all blood cells, and endothelial progenitor cells (EPCs), which are very important for inducing new blood vessel growth. EPCs and CD34+ cells both contribute to new blood vessel formation. The bone marrow also contains MSCs, which also can enhance new blood vessel growth as well as secrete many trophic factors that stimulate regeneration and decrease inflammation.

specially designed Jamshidi to quickly harvest bone marrow with minimal discomfort for the patient. Processing the bone marrow aspirate in a vertical axis centrifuge enables doctors at RMI to maximize the concentration of extracted mononuclear cells, which includes stem cells, compared to older machines like the Magellan.

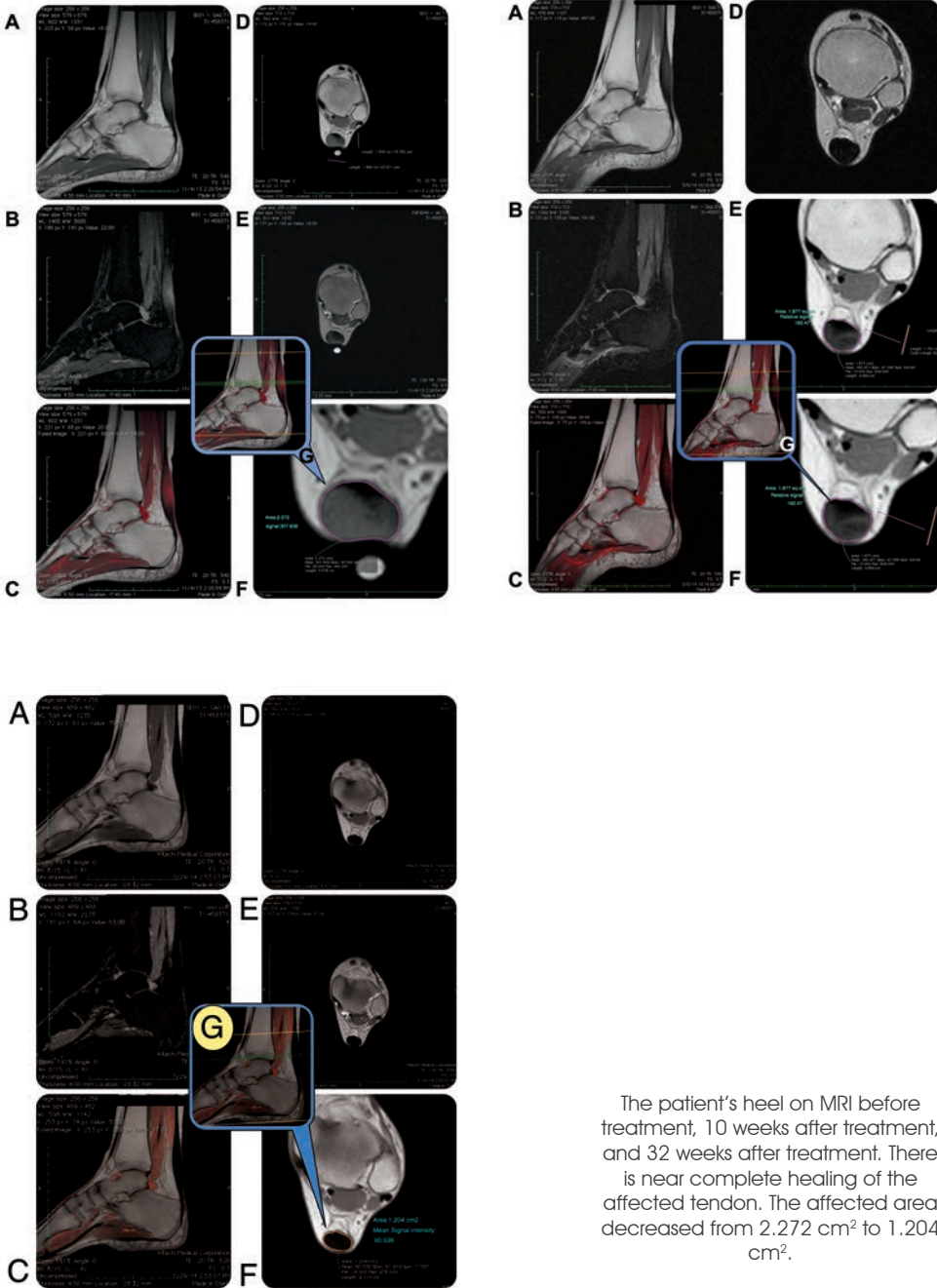
Given the current regulatory environment in the United States, one of the very few stem cell options available to us is bone marrow aspirate concentrate (BMAC). Even though it is available in the United States, it is rarely paid for by insurance. I believe that soon, that is all going to change.

Stem cells from bone marrow aspirate have been compared to almost every graft with more success found in the treatment groups receiving bone marrow. What many orthopedic surgeons did not understand in the past was that bone marrow aspirate is not only useful for healing bone, but also for other tissues. We published a paper about our treatment with bone marrow aspirate concentrate of a 56-year-old woman with Achilles tendonopathy and a partially torn Achilles tendon that limited her ability to participate in daily activities that involved walking or wearing shoes other than sandals.⁴⁷ To our knowledge, she was the first Achilles tendonopathy patient treated with bone marrow aspirate. Previously an active tennis player, she hadn't been

on the court in ten years due to her injury. She had seen multiple physicians over the years and followed standard conservative treatment involving stretching and anti-inflammatory medications. She had opted out of steroid injections and the standard surgery for the injury, but when presented with the possibility of an ultrasound-guided bone marrow aspirate concentrate injection of her own bone marrow, a non-invasive procedure that takes fewer than 60 minutes, she was interested.

Just six weeks after the procedure, the patient reported significantly less pain upon rest and while walking. The knot in her Achilles tendon decreased to 50 percent of its original size and was no longer tender to the touch. She was finally able to put on heels and walk over uneven surfaces without pain. And best of all, she returned to the court to play tennis for the first time in years. An MRI done ten weeks after the procedure showed that her heel looked almost indistinguishable from her other heel, which was not injured. A regeneration of tissue health such as this is not seen with other treatment types. Recovery time for the standard surgical procedure for her injury would have taken at least six months, but would not have restored her tendon as the bone marrow aspirate did, as evidenced by the MRI. Recovery like this simply doesn't happen with surgery.

Our rationale for treating this woman's Achilles tendonopathy came from our success with using bone marrow concentrate with Achilles tendon grafts in ACL (anterior cruciate ligament) tear repairs of the knee. ACL injuries are one of the most common injuries and often involve removing part of the patient's own tendon from below the kneecap to replace the ACL. This repair takes 369 days to heal, at which point it looks normal on an MRI. Unfortunately, the tendon that is removed from below the kneecap often does not heal properly, sometimes resulting in tendonitis or a shortening of the tendon, both of which affect the placement of the kneecap and can lead to arthritis. Orthopedic surgeons at RMI use a sterilized graft of an Achilles heel taken from a cadaver, which can be better tailored to the size of the new ACL without needing to remove the patient's own tendon. They inject bone marrow concentrate at the site of the injury, and healing time is fewer than 24 weeks, which is about half the time of the conventional treatment. Patients are able to avoid the complications of conventional treatment and get back to their normal lives sooner.



The patient's heel on MRI before treatment, 10 weeks after treatment, and 32 weeks after treatment. There is near complete healing of the affected tendon. The affected area decreased from 2.272 cm² to 1.204 cm².

Hyaline vs. Fibrocartilage

Cartilage is a connective tissue formed by cells called chondrocytes that are stacked within a collagen-based matrix. There are no blood vessels in this structure; nutrients are absorbed via the matrix, resulting in a limited capacity for regeneration. Cartilage may be classified into three types: hyaline cartilage, fibrocartilage, and elastic cartilage.²⁰

Elastic cartilage is found in the ear and throat and is the most pliable of the three types. Fibrocartilage is designed to bear tension and compression, and as such it is a strong type of cartilage present in the vertebral discs of the spine, in the meniscus, at the end of tendons, and in the callus structure of the bones. Hyaline cartilage may be found in the rib area and in the more mobile articular joints (wrists, elbows, shoulders, hips, knees, etc.) where synovial fluid reduces friction in the space between the bones. The matrix of hyaline



Teresa Hamrick is a registered nurse from Tallahassee, FL. In 1983 she was injured in a bike accident but brushed off the injury and continued to walk around as normally as possible for as long as possible. Knee pain eventually brought her to the doctor two years later, where she was told that she had degenerative joint disease and needed to have both knees replaced. The cartilage in her knees was non-existent, and her femur heads were worn after being ground away by bone chips. Her doctors recommended that she find a new line of work that allowed her to sit. She went back to school and got a degree in management. Her orthopedic surgeon told her that if she proceeded with total knee replacement, she would need to repeat the surgeries about seven years later due to the wear and tear of her usual rate of activity. She opted out of the surgery and was soon bound to a motorized scooter.

Twelve years later, at age 50, Teresa experienced her first heart attack. She recovered and slowly began working out with a trainer to help prevent further heart problems. But in July 2011 she had a massive heart attack and was forced to retire due to the state of her heart. She was left with not much hope at that point. Her medical background spurred her interest in finding

cartilage is formed by collagen type II, whereas fibrocartilage is made up of collagen type I. There are fewer chondrocytes in fibrocartilage than in hyaline cartilage, as well as fewer proteoglycans and glycoproteins. Under the microscope, cells in hyaline cartilage are rounded and cluster in small groups as they are scattered within the matrix, encased by the perichondrium, a supporting structure. Cells in fibrocartilage lie in rows and are surrounded by bundles of collagen fibers that give it an array-like appearance.

A particular concern^{21,22} when treating cartilage defects in the joints is that the tissue that regrows might contain fibrocartilage instead of hyaline cartilage, leading to stiffness in a previously mobile joint and a loss of normal function. In some cases, hyaline-like tissue does form successfully, but fibrocartilage²³ and type I collagen²⁴ can appear in up to 40 percent of cases.²⁵

a solution. She read scientific articles and clinical trials about her condition and possible options. She eventually decided to try autologous bone marrow stem cell therapy for her heart. After treatment her ejection fraction went from 12 to 30 percent in three months.

Fast forward to early September 2013. Her heart was in good shape—ejection fraction was 40 percent, and she was up to walking, albeit with some trouble, a mile and a half a day. One day she was walking down a hill and she felt a rip on the side of her knee. That injury put her back in the motorized scooter, only able to walk up to ten or fifteen feet on her own. She saw an orthopedic surgeon who recommended total knee replacement of both knees. Not a big fan of surgery or drugs, she went online to find out if anyone was doing stem cell treatments for knees. She learned about the International Stem Cell Symposium to be held in the Bahamas in September 2014. A year before, I had met an orthopedic surgeon at a conference in Florida organized by the same group. At the Bahamas symposium, he was scheduled to present his results on treating patients in his orthopedic practice. Teresa booked a ticket to the Bahamas to learn more about his work. She was impressed with his presentation and met him after his talk. They arranged for her to come back to Texas for treatment. In March, the orthopedic surgeon evaluated her knees and determined that she still

needed a total knee replacement for the left knee, but only a partial for the right. He performed the surgery along with BMAC and amnion injections. Amnion is a human amniotic membrane product, derived from the lining of the amniotic sac from a healthy, live birth.

With age, the number of stem cells inside bone marrow steadily declines. By the time a human reaches skeletal maturity, the number of mesenchymal stem cells in bone marrow has declined by 90 percent. The doubling time of cells, which is an indication of their robustness, also declines with age. In older patients with chronic orthopedic conditions, the Riordan Medical Institute augments bone marrow concentrate with amnion. When exposed to the amnion, the cells of the bone marrow concentrate actually alter in such a way that makes them appear and behave like bone marrow concentrate cells from a younger individual.

Four weeks later, Teresa was able to fly home. The following September she came back for a right partial knee replacement and more BMAC and amnion injections. “No one ever thought I would get back to my current functional status after scootering and limping for 30 years and then being in a wheelchair for six months. I have been working out with a trainer again. I have been walking one to three miles every day. On X-ray my knees are perfectly aligned and there is a nice uniform spacing between the bones. My treatments were extremely successful. I am thriving. I am over-the-moon happy with my outcome. I have my life back.”



Jennifer Ziegler is an active 50-year old woman who injured the ACL of her knee during a skiing accident in January 2015. “I dove out of the way of another skier, heard a pop in my knee, and limped back down the mountain,” she said. ACL injury is common, and like Jennifer, many people are stubborn

“No one ever thought I would get back to my current functional status after scootering and limping for 30 years and then being in a wheelchair for six months. I have my life back.”

and try to muscle through the injury. A few months later, in June, Jennifer reinjured the knee while gardening. “I felt the pain all over again. Getting in and out of the car was difficult. Walking my dogs was interesting. I never knew when my knee was going to give out.”

After her husband convinced her to get an MRI, she visited her orthopedic doctor. He recommended the traditional autotransplant surgery, which involves the removal of part of the infrapatellar tendon at the front of the knee to replace the missing ACL. This type of procedure creates yet another injury and takes up to a year to heal, if it even heals at all. The idea of going through such a surgery made Jennifer uncomfortable. That’s when she contacted me. I referred her to our clinic.

A few days later, she was on a plane to Texas. After examination, our surgeon recommended arthroscopy and injection of BMAC and amnion. Some of her ACL remained intact so he didn’t feel she needed a more extensive procedure. She went through with the treatment, and six weeks later Jennifer was hiking and biking on vacation in Colorado. By January she was skiing again. “I wish everyone had the opportunity to choose a less invasive treatment. It should be covered by insurance. It should be something that everyone in the United States has the option to do,” she said.



Jim Morello is a 70-year-old marathon runner who was experiencing what he called “bone on bone pain” in his knees while running. A friend of his had received stem cell treatment in Colorado and was happy with it, which prompted Jim to research different clinics. After speaking with our orthopedic surgeon, he decided to undergo stem cell treatment along with arthroscopy on both knees.

“The experience was very positive,” he said. “The staff there is awesome.” The procedure occurred on Monday with a follow-up on Thursday, after which he

“I wanted my knees to be in good shape to stay active with my grandkids—that was my biggest impetus.”

Bone Marrow Aspirate Concentrate (BMAC)

Bone marrow aspirate concentrate (BMAC) is the preferred source of stem cells for orthopedic injuries due to the improved focus of the stem cells toward skeletal healing. One peptide secreted by these cells, known as sox-9, is useful in the formation of cartilage. The high concentration of CD34+ stem cells in bone marrow concentrate is another reason why it's the stem cell source of choice. The CD34+ cells are focused on angiogenesis, or growth of new blood vessels, which are essential for healing orthopedic injuries that are already at a blood supply disadvantage. The bone marrow concentrate secretes what the body already knew it needed in order to heal.

Bone marrow aspiration is a procedure that extracts a small amount of bone marrow in liquid form. Well-tested harvesting techniques allow a simple and safe aspiration to be performed within the clinic under local anesthesia. Bone marrow may be obtained from bones in the leg or arm, or from the iliac crest (hip area). The extracted liquid (between 60 and 120 cc) is then concentrated down to 5 cc. This bone marrow aspirate concentrate is rich in mesenchymal stem cells (MSCs), endothelial progenitor cells (EPCs), and other proteins and factors secreted by these cells, such as CD133+ and CD34+.

As discussed elsewhere, MSCs have anti-inflammatory properties, promote blood vessel growth, and are able to modulate the immune system.²⁶ It has recently been shown that the secretions stimulated by MSCs are responsible for their therapeutic potential,²⁷ including for cartilage repair.²⁸ In particular, vascular endothelial growth factor (VEGF) stimulates blood-forming cells (endothelial progenitor cells, or EPCs) to grow new blood vessels in the injured or inflamed area. This process provides nutrients more efficiently and promotes faster healing.

BMAC treatment has been safely used in animal models. Goats that received BMAC showed significant improvements in the damaged joints, with almost complete recovery of the cartilage.²⁹ Similarly, when treatment was enhanced with BMAC, the cartilage of horses showed greater healing.³⁰ Horses that received bone marrow-derived MSCs after meniscal damage arthroscopy showed an improvement in ability to return to work compared to those receiving surgery alone.³¹ Similarly, rats receiving human bone marrow-derived MSCs as a complement to rotator cuff repair surgery showed early improvements.³²

BMAC has also been used in clinical settings with no adverse effects³³ and with positive results. Patients who received BMAC after knee surgery showed higher improvement in all

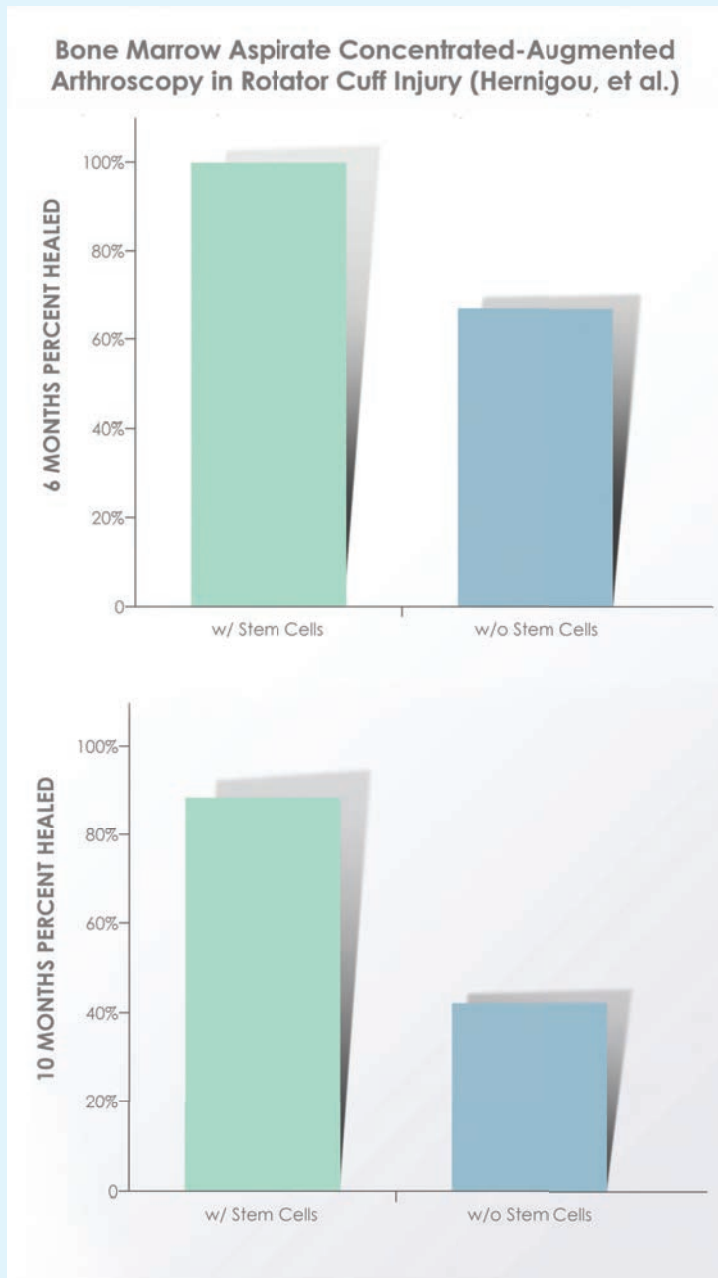
measured scores, with healthy cartilage covering the injured areas in a two-year follow-up.³⁴ BMAC was also shown to be beneficial in the treatment of bone defects,³⁵ bone grafts,³⁶ tendon injuries,^{37,38} and arterial disease in the lower limbs.³⁹ A recent review reports excellent overall outcomes with the use of BMAC for osteoarthritis and cartilage injuries.⁴⁰

PRP and BMAC have been used together to treat a football athlete following complications of a hip arthroscopy, with significant improvements in physical activity as well as in the appearance of tendons under magnetic resonance imaging (MRI).⁴¹ Treatment with BMAC to complement rotator cuff arthroscopy was shown to be safe and to enhance tissue quality in affected tendons after a one-year follow-up.⁴²

Probably the most compelling argument for the use of BMAC in orthopedics, both from a patient-centric perspective and also from an economic perspective, is a 2014 article by Hernigou, et al.⁴³ It documented the results of ten-year study—a follow-up of rotator cuff repair in two groups of patients, one that received BMAC and another that did not. The group receiving BMAC had a 100 percent healing rate at six months, compared to 67 percent in the non-BMAC group. Ten years later only 13 percent of the patients who received BMAC had failure in their rotator cuff compared to 66 percent of the patients who did not. Given the high costs of rotator cuff repair surgery for an insurance company, it becomes readily apparent that paying for a single BMAC procedure would be more cost effective for insurance companies, as well as patients.

returned home to Tulsa. “I was able to start running a little bit over time. I ran a race, carefully, three months later. I had some MRIs done, which showed new growth between the bones—good news after spending the money.” One year after treatment he ran a race that qualified him to be up front in the next Tulsa Run. “I wanted my knees to be in good shape to stay active with my grandkids—that was my biggest impetus,” Jim said. “The stem cell outcome was very positive. I’ve recommended a number of people to go.”





Adapted from data in Hernigou P et al. Biologic augmentation of rotator cuff repair with mesenchymal stem cells during arthroscopy improves healing and prevents further tears: A case-controlled study. *Int Orthop*. 2014 Sep;38(9):1811-8.

There are currently several clinical trials registered on ClinicalTrials.gov to investigate the effects of treatment with MSCs as an aid to arthroscopic procedures, such as umbilical cord MSCs for ACL (anterior cruciate ligament) arthroscopy,⁴⁴ BMAC for rotator cuff arthroscopy,⁴⁵ and BMAC for ankle arthroscopy.⁴⁶

David Crumpton, DDS happens to be the dentist for one of our former physician's family. One day David reached over to lift an object, and with nothing more than a slight amount of pressure, his bicep detached from the bone and tore some of the tendon. He came to Southlake for treatment. Our orthopedic surgeon reattached the bicep and injected BMAC and amnion to help it heal. "The way I think about it is, something tore in my arm so that I could learn how to fix my back," he said. While his bicep was healing, the pressure he put on his left arm to compensate for his right bicep aggravated an old back injury. As a dentist, Dr. Crumpton is always bent at the waist, which left him with a chronic backache, especially after his bicep injury. He had pinched and injured discs in his lumbar spine that caused a lot of discomfort. Our doctor first referred him to another physician to try epidurals, but when those didn't work, he recommended a discogram to determine which discs were affected, and then injected BMAC and amnion into three discs. The procedure was done on a Thursday; he experienced some soreness on Friday and Saturday and was back to work on Monday. "Immediately after the surgery the pain went away, and over the next six months it continued to improve week by week. Today I am probably the best I have ever been in 30 years. I feel so great about what I did."

Today I am probably the best I have ever been in 30 years."



Elizabeth Fortado, a twenty-one-year-old Division 1 volleyball player for the University of Arkansas, tore all the ligaments in her ankle playing the sport in Europe during her sophomore year. She visited two prominent orthopedic specialists who both told her she needed surgery and that the recovery would be at least eight months. That meant she would not be able to play volleyball that year. Elizabeth's father was familiar with our

surgeon, being a sales representative for orthopedic devices, so he brought Elizabeth in for a consultation. "We would lose two months undergoing this treatment, but we were already going to lose her entire season if she had to have surgery."

They decided to go ahead with the procedure and Elizabeth was injected with BMAC and amnion in 2015. Eight weeks later she started training again. "I immediately noticed the difference with my ankle," she said. "It felt so much stronger than it did before. It was amazing. Before the procedure I had so much popping in the ankle that was extremely painful. I have no popping anymore." Ten weeks later she started her first volleyball game, achieving her highest hitting percentage ever. Then, in her second game, she experienced her all-time career high. "As a high-level athlete trying to get back into the game, to come back and compete at a stronger position than she ever had, it made such an unbelievable difference," her father added. "Everyone was skeptical about the procedure—her orthopedic surgeons at the school, her trainers— everyone handled her with kid gloves. It blew everyone's mind that

"I immediately noticed the difference with my ankle," she said. "It felt so much stronger than it did before. It was amazing."

she could come back from such a severe injury. They see those injuries in volleyball and never see people return like that.” Elizabeth experienced a strengthening and improvement in range of motion in her ankle that surpassed even her uninjured ankle. She later returned for another injection of BMAC and amnion to continue to fortify her ankle. “Now my bad ankle at the time is my good ankle, and my good ankle is my bad ankle,” she said.



Billy Minick is a 77-year-old bull rider from Texas. One of the world’s top four professional bull riders in his youth, he has spent his life riding bulls, roping steer, and running Billy Bob’s Texas, a bull riding arena and country club in Fort Worth that he eventually purchased along with three friends. He married his wife, Pam, in 1983 and ran the company with her until 2013 when they both retired. Pam is extremely active with a number of charities and is well known throughout Fort Worth, Texas.

While roping a calf one day, Billy’s arm went limp. “His arm turned blue,” Pam said. He put off a doctor’s visit for a few days, in true cowboy style, but his pain pushed him to consult an orthopedic specialist who recommended a reverse rotator cuff arthroplasty, the most drastic surgery for this type of injury. Billy had seen Pam suffer tremendously for eight months from a lesser surgery two years prior for her own rotator cuff tear. “It was months before I didn’t call my doctor a four-letter word,” she said. Billy was reluctant to undergo a major surgery because he didn’t want to suffer as Pam had, so he sought a second opinion. The next doctor recommended a much more conservative treatment—physical therapy alone.

“My colleagues tend to be at extreme ends of the spectrum,” said a surgeon at RMI. “Mr. Minnick had been told that his shoulder was so chronically injured that he was no longer a candidate for a traditional shoulder replacement, but that he would need a reverse arthroplasty—where they reverse the cup and ball because of the lack of rotator cuff—due to the significant and chronic nature of his tear. At the other end of the spectrum, the second doctor told Mr. Minnick that there was nothing that could be done other than physical therapy to try to get back some deltoid function. I didn’t think either was the best option for Mr. Minnick. Reverse arthroplasty is the

most significant shoulder intervention that can be accomplished surgically. The problem with this surgery is that there are no good fallback procedures—if it doesn't work out, nothing can be done. It basically burns your bridges. There is nowhere to go after that. The surgery is fairly new, and for patients like Mr. Minick, who do not have significant humeral arthritis, its popularity is beginning to wane.”

Billy's close friend had been treated with BMAC and amnion with excellent results, and recommended that Billy visit the clinic. Billy had no strength or use of his right arm at the time. Moving his arm was painful and difficult. He decided to pay us a visit. “Mr. Minick had significant weakness of the upper extremity and couldn't really raise his arm to get his elbow to the level of his chest,” said our doctor. “He had no significant rotator cuff tissue left. He had a complete retraction of the most important muscle of his rotator cuff. His shoulder was basically dislocated—we call it cephalad migration—the bone of his humerus was riding up underneath the bones of his shoulder blade because he had no muscle or tendon of the rotator cuff to keep it in place.”

“After significant discussion of what I thought were his options, I did not think he was a good candidate for stem cell therapy alone. I also did not think he was a good candidate for a total reverse shoulder arthroplasty. I recommended a combination of cell therapy, using injections of his own BMAC along with amnion, and a minimally invasive partial arthroplasty of the shoulder.” After some consideration, Mr. Minick decided to proceed with our surgeon's recommendations. The doctor was able to clean up the loose pieces and debris in his shoulder with arthroscopy, remove the bone spurs, and insert a partial shoulder that would reduce pain and help improve range of motion. The cell therapy would help increase cellular volume to increase the strength of his deltoid muscle.

Billy's pain after the procedure was so minimal that he took only one pain pill. “I never had any pain amount to anything other than soreness,” he said. Within several weeks Billy was out of his arm sling and working on range of motion with physical therapy.

“What amazed me,” said the surgeon, “was that even at 77 years old and with little function in his arm at the time of his exam, Mr. Minick was

anxious to get back to roping. I told him that our goal was to see how much function, strength, range of motion, and pain relief we could get for him. Even getting a wallet out of his pocket or putting on a seatbelt was difficult at the time. But sure enough, eight months after the procedure, Mr. Minick was roping again.”

“It wasn’t pretty, but I got him,” Billy said. “The strength part has been a slow process, but I am more than satisfied. It is getting better and better every week. The pain relief was the greatest thing.” Between Pam and some of Billy’s friends who had undergone similar surgeries without cell therapy, their recoveries took much longer than Billy’s. “I credit the stem cells personally,” he said.

“Without cell therapy, this type of surgery—even though it’s minimally invasive—in this age group can still result in significant pain relief but doesn’t really result in improvements of range of motion or strength,” said the surgeon. “With cell therapy, within two months he was able to fully elevate his shoulder. Repopulating the areas of atrophy, the cellularity is restored and the patient heals and has less pain and more function.”

Our goal is to use BMAC and amnion to turn big surgeries into small surgeries and small surgeries into simple injections. In-office injections are currently used for conditions such as osteoarthritic or inflamed joints, partial and full thickness tears, and chronic, painful, partial tearing. Minimally-invasive surgeries are augmented with BMAC and amnion.

I have computed the savings to insurance companies, extrapolated from published data,⁴⁸ of the inclusion of autologous BMAC to rotator cuff injury surgery. Assuming a surgical cost of \$25,000 and a bone marrow kit cost of \$2,500, roughly \$4.8 billion would be saved by insurance companies annually due to surgical failures and revision surgeries for shoulders alone. That number does not include any of the lost time at work, or the increased aftercare due to follow-up surgeries that would be saved by employers and employees.

A notable effect of bone marrow concentrate treatment is that patients who undergo orthopedic surgeries may experience a lower infection rate when they receive bone marrow concentrate than they would without

it. At least one surgeon has been able to dramatically lower infection in surgeries that typically have around a three to five percent infection rate. One explanation for this is likely due to the highly antimicrobial peptide known as LL-37, secreted by mesenchymal stem cells found in bone marrow concentrate. Another explanation for reduced infection is the faster healing rate of the wound due to greater mobility of the patient, which increases blood flow to the wound site and reduces swelling.

References

BY CHAPTER

Chapter One

1. Vieira NM, Valadares M, Zucconi E, et al. Human adipose-derived mesenchymal stromal cells injected systemically into GRMD dogs without immunosuppression are able to reach the host muscle and express human dystrophin. *Cell Transplant*. 2012;21(7):1407-17. doi: 10.3727/096368911X.
2. Muntoni F, Torelli S, Ferlini A. Dystrophin and mutations: one gene, several proteins, multiple phenotypes. *Lancet Neurol*. 2003;2(12):731-740.
3. Spuler S, Engel AG. Unexpected sarcolemmal complement membrane attack complex deposits on nonnecrotic muscle fibers in muscular dystrophies. *Neurology*. 1998;50(1):41-46.
4. Skuk D, Vilquin JT, Tremblay JP. Experimental and therapeutic approaches to muscular dystrophies. *Curr Opin Neurol*. 2002;15(5):563-569.
5. Balaban B, Matthews DJ, Clayton GH, Carry T. Corticosteroid treatment and functional improvement in Duchenne muscular dystrophy: long-term effect. *Am J Phys Med Rehabil*. 2005;84(11):843-850.
6. Ricotti V, Ridout DA, Scott E, et al. Long-term benefits and adverse effects of intermittent versus daily glucocorticoids in boys with Duchenne muscular dystrophy. *J Neurol Neurosurg Psychiatry*. 2013;84(6):698-705.
7. Ginn SL, Alexander IE, Edelstein ML, Abedi MR, Wixon J. Gene therapy clinical trials worldwide to 2012 - an update. *J Gene Med*. 2013;15(2):65-77.
8. Aggarwal S, Pittenger MF. Human mesenchymal stem cells modulate allogeneic immune cell responses. *Blood*. 2005;105(4):1815-1822.
9. Caplan AI. Adult mesenchymal stem cells for tissue engineering versus regenerative medicine. *J Cell Physiol*. 2007;213(2):341-347.
10. Chamberlain G, Fox J, Ashton B, Middleton J. Concise review: mesenchymal stem cells: their phenotype, differentiation capacity, immunological features, and potential for homing. *Stem Cells*. 2007;25(11):2739-2749.
11. Bachrach E, Perez AL, Choi YH, et al. Muscle engraftment of myogenic progenitor cells following intraarterial transplantation. *Muscle Nerve*. 2006;34(1):44-52.
12. Bailo M, Soncini M, Vertua E, et al. Engraftment potential of human amnion and chorion cells derived from term placenta. *Transplantation*. 2004;78(10):1439-1448.
13. Pelatti MV, Gomes JP, Vieira NM, et al. Transplantation of human adipose mesenchymal stem cells in non-immunosuppressed GRMD dogs is a safe procedure. *Stem Cell Rev*. 2016;12(4):448-53. doi: 10.1007/s12015-016-9659-3.

Chapter Twelve

1. Nakazawa F, Matsuno H, Yudoh K, Watanabe Y, Katayama R, Kimura T. Corticosteroid treatment induces chondrocyte apoptosis in an experimental arthritis model and in chondrocyte cultures. *Clin Exp Rheumatol*. 2002;20(6):773-781.
2. Farkas B, Kvell K, Czömpöly T, Illés T, Bárdos T. Increased chondrocyte death after steroid and local anesthetic combination. *Clin Orthop Relat Res*. 2010;468(11):3112-3120.doi: 10.1007/s11999-010-1443-0.
3. Wernecke C, Braun HJ, Drago J. The effect of intra-articular corticosteroids on articular cartilage: a systematic review. *Orthop J Sports Med*. 2015;3(5):2325967115581163.doi: 10.1177/2325967115581163. eCollection 2015.
4. Fubini SL, Todhunter RJ, Burton-Wurster N, Vernier-Singer M, MacLeod JN. Corticosteroids alter the differentiated phenotype of articular chondrocytes. *J Orthop Res*. 2001;19(4):688-695.
5. Céleste C, Ionescu M, Robin Poole A, Laverty S. Repeated intraarticular injections of triamcinolone acetone alter cartilage matrix metabolism measured by biomarkers in synovial fluid. *J Orthop Res*. 2005;23(3):602-610.
6. Sherman SL, James C, Stoker AM, et al. In vivo toxicity of local anesthetics and corticosteroids on chondrocyte and synoviocyte viability and metabolism. *Cartilage*. Apr 2015;6(2):106-112.doi: 10.1177/1947603515571001.
7. Sherman SL, Khazai RS, James CH, Stoker AM, Flood DL, Cook JL. In vitro toxicity of local anesthetics and corticosteroids on chondrocyte and synoviocyte viability and metabolism. *Cartilage*. 2015;6(4):233-240.doi: 10.1177/1947603515594453.
8. Wada J, Koshino T, Morii T, Sugimoto K. Natural course of osteoarthritis of the knee treated with or without intraarticular corticosteroid injections. *Bull Hosp Jt Dis*. 1993;53(2):45-48.
9. Lewis M, Hay EM, Paterson SM, Croft P. Local steroid injections for tennis elbow: does the pain get worse before it gets better?: Results from a randomized controlled trial. *Clin J Pain*. 2005;21(4):330-334.
10. Olaussen M, Holmedal Ø, Mdala I, Brage S, Lindbæk M. Corticosteroid or placebo injection combined with deep transverse friction massage, Mills manipulation, stretching and eccentric exercise for acute lateral epicondylitis: a randomised, controlled trial. *BMC Musculoskelet Disord*. 2015;16:122.doi: 10.1186/s12891-015-0582-6.
11. Sayegh ET, Strauch RJ. Does nonsurgical treatment improve longitudinal outcomes of lateral epicondylitis over no treatment? A meta-analysis. *Clin Orthop Relat Res*. 2015;473(3):1093-1107. doi: 10.1007/s11999-014-4022-y.
12. Smidt N, Assendelft WJ, van der Windt DA, Hay EM, Buchbinder R, Bouter LM. Corticosteroid injections for lateral epicondylitis: a systematic review. *Pain*. 2002;96(1-2):23-40.
13. Smidt N, van der Windt DA, Assendelft WJ, Devillé WL, Korthals-de Bos IB, Bouter LM. Corticosteroid injections, physiotherapy, or a wait-and-see policy for lateral epicondylitis: a randomised controlled trial. *Lancet*. 2002;359(9307):657-662.
14. Rafols C, Monckeberg JE, Numair J, Botello J, Rosales J. Platelet-rich plasma augmentation of arthroscopic hip surgery for femoroacetabular impingement: a prospective study with 24-month follow-up. *Arthroscopy*. 2015;31(10):1886-1892.doi: 10.1016/j.arthro.2015.03.025.
15. Zhang Q, Ge H, Zhou J, Cheng B. Are platelet-rich products necessary during the arthroscopic repair of full-thickness rotator cuff tears: a meta-analysis. *PLoS ONE*. 2013;8(7):e69731.doi: 10.1371/journal.pone.0069731.

16. Duif C, Vogel T, Topcuoglu F, Spryou G, von Schulze Pellengahr C, Lahner M. Does intraoperative application of leukocyte-poor platelet-rich plasma during arthroscopy for knee degeneration affect postoperative pain, function and quality of life? A 12-month randomized controlled double-blind trial. *Arch Orthop Trauma Surg.* 2015;135(7):971–977.doi: 10.1007/s00402-015-2227-5.
17. Lopez-Vidriero E, Goulding KA, Simon DA, Sanchez M, Johnson DH. The use of platelet-rich plasma in arthroscopy and sports medicine: optimizing the healing environment. *Arthroscopy.* 2010;26(2):269-78. doi: 10.1016/j.arthro.2009.11.015.
18. DiBartola AC, Everhart JS, Magnussen RA, et al. Correlation between histological outcome and surgical cartilage repair technique in the knee: A meta-analysis. *Knee.* 2016;23(3):344–9. doi: 10.1016/j.knee.2016.01.017.
19. Mithoefer K, McAdams T, Williams RJ, Kreuz PC, Mandelbaum BR. Clinical efficacy of the microfracture technique for articular cartilage repair in the knee: an evidence-based systematic analysis. *Am J Sports Med.* 2009;37(10):2053-63.doi: 10.1177/0363546508328414.
20. Sophia Fox AJ, Bedi A, and Rodeo SA. The basic science of articular cartilage: structure, composition, and function. *Sports Health.* 2009;1(6):461-468. doi:10.1177/1941738109350438.
21. Fricker J, “Cartilage transplantation: an end to creaky knees?” *Lancet.* 1998;352(9135):1202.
22. Hattori K, Takakura Y, Ohgushi H, Habata, T, Uematsu K, Ikeuchi K. Novel ultrasonic evaluation of tissue-engineered cartilage for large osteochondral defects—non-invasive judgment of tissue-engineered cartilage. *J Orthop Res.* 2005;23(5):1179-83.
23. Briggs TW, Mahroof S, David LA, Flannelly J, Pringle J, Bayliss M. Histological evaluation of chondral defects after autologous chondrocyte implantation of the knee. *J Bone Joint Surg Br.* 2003; 85(7):1077-83.
24. Peterson L, Brittberg M, Kiviranta I, Akerlund EL, Lindahl A. Autologous chondrocyte transplantation. Biomechanics and long-term durability. *Am J Sports Med.* 2002; 30(1):2-12.
25. Henderson I, Tuy B, Oakes B. Reoperation after autologous chondrocyte implantation. Indications and findings. *J Bone Joint Surg Br.* 2004; 86(2):205-11.
26. Caplan AI. Adult mesenchymal stem cells for tissue engineering versus regenerative medicine. *J Cell Physiol.* 2007;213(2):341-347.
27. Madrigal M, Rao KS, Riordan NH. A review of therapeutic effects of mesenchymal stem cell secretions and induction of secretory modification by different culture methods. *J Transl Med.* 2014;12(1):260.doi: 10.1186/s12967-014-0260-8.
28. Arufe MC, De la Fuente A, Fuentes I, De Toro FJ, Blanco FJ. Umbilical cord as a mesenchymal stem cell source for treating joint pathologies. *World J Orthop.* 2011;2(6):43-50.doi: 10.5312/wjo.v2.i6.43.
29. Saw KY, Hussin P, Loke SC, et al. Articular cartilage regeneration with autologous marrow aspirate and hyaluronic Acid: an experimental study in a goat model. *Arthroscopy.* 2009;25(12):1391-1400. doi: 10.1016/j.arthro.2009.07.011.
30. Fortier LA, Potter HG, Rickey EJ, et al. Concentrated bone marrow aspirate improves full-thickness cartilage repair compared with microfracture in the equine model. *J Bone Joint Surg Am.* 2010;92(10):1927-1937.doi: 10.2106/JBJS.I.01284.
31. Ferris DJ, Frisbie DD, Kisiday JD, et al. Clinical outcome after intra-articular administration of bone marrow derived mesenchymal stem cells in 33 horses with stifle injury. *Vet Surg.* 2014;43(3):255–265.doi: 10.1111/j.1532-950X.2014.12100.x.
32. Degen RM, Carbone A, Carballo C, et al. The effect of purified human bone marrow-derived mesenchymal stem cells on rotator cuff tendon healing in an athymic rat. *Arthroscopy.* June 2016. [Epub ahead of print.]

References

33. Hendrich C, Franz E, Waertel G, Krebs R, Jäger M. Safety of autologous bone marrow aspiration concentrate transplantation: initial experiences in 101 patients. *Orthop Rev.* 2009;1(2):e32.doi: 10.4081/or.2009.e32.
34. Gobbi A, Karnatzikos G, Scotti C, Mahajan V, Mazzucco L, Grigolo B. One-step cartilage repair with bone marrow aspirate concentrated cells and collagen matrix in full-thickness knee cartilage lesions: results at 2-year follow-up. *Cartilage.* 2011;2(3):286-299.doi: 10.1177/1947603510392023.
35. Jäger M, Jelinek EM, Wess KM, et al. Bone marrow concentrate: a novel strategy for bone defect treatment. *Curr Stem Cell Res Ther.* 2009;4(1):34-43.
36. Pasquali PJ, Teixeira ML, de Oliveira TA, de Macedo LG, Aloise AC, Pelegrine AA. Maxillary sinus augmentation combining bio-oss with the bone marrow aspirate concentrate: a histomorphometric study in humans. *Int J Biomater.* 2015;2015:121286.doi: 10.1155/2015/121286.
37. Campbell KJ, Boykin RE, Wijdicks CA, Erik Giphart J, LaPrade RF, Philippon MJ. Treatment of a hip capsular injury in a professional soccer player with platelet-rich plasma and bone marrow aspirate concentrate therapy. *Knee Surg Sports Traumatol Arthrosc.* 2013;21(7):1684-1688.doi: 10.1007/s00167-012-2232-y.
38. Stein BE, Stroh DA, Schon LC. Outcomes of acute Achilles tendon rupture repair with bone marrow aspirate concentrate augmentation. *Int Orthop.* 2015;39(5):901-905.doi: 10.1007/s00264-015-2725-7.
39. Iafrati MD, Hallett JW, Geils G, et al. Early results and lessons learned from a multicenter, randomized, double-blind trial of bone marrow aspirate concentrate in critical limb ischemia. *J Vasc Surg.* 2011;54(6):1650-1658.doi: 10.1016/j.jvs.2011.06.118.
40. Chahla J, Dean CS, Moatshe G, Pascual-Garrido C, Serra Cruz R, LaPrade RF. Concentrated bone marrow aspirate for the treatment of chondral injuries and osteoarthritis of the knee: a systematic review of outcomes. *Orthop J Sports Med.* 2016;4(1):2325967115625481.doi: 10.1177/2325967115625481. eCollection 2016.
41. Campbell KJ, Boykin RE, Wijdicks CA, Erik Giphart J, LaPrade RF, Philippon MJ. Treatment of a hip capsular injury in a professional soccer player with platelet-rich plasma and bone marrow aspirate concentrate therapy. *Knee Surg Sports Traumatol Arthrosc.* 2013;21(7):1684-1688.doi: 10.1007/s00167-012-2232-y.
42. Ellera Gomes JL, da Silva RC, R Silla, LM, Abreu MR, Pellanda R. Conventional rotator cuff repair complemented by the aid of mononuclear autologous stem cells. *Knee Surg Sports Traumatol Arthrosc.* 2011;20(2):373-377.doi: 10.1007/s00167-011-1607-9
43. Hernigou P, Flouzat Lachaniette CH, Delambre J, et al. Biologic augmentation of rotator cuff repair with mesenchymal stem cells during arthroscopy improves healing and prevents further tears: A case-controlled study. *Int Orthop.* 2014 Sep;38(9):1811-8. doi: 10.1007/s00264-014-2391-1.
44. Samsung Medical Center. Development of novel strategy for treatment of anterior cruciate ligament (ACL) injury using stem cell. In: *ClinicalTrials.gov* [Internet]. Bethesda (MD): National Library of Medicine (US). 2000-[cited 2016 July] Available from: <https://clinicaltrials.gov/ct2/show/NCT02755376> NLM Identifier: NCT02755376.
45. Rush University Medical Center. Mesenchymal stem cell augmentation in patients undergoing arthroscopic rotator cuff repair. In: *ClinicalTrials.gov* [Internet]. Bethesda (MD): National Library of Medicine (US). 2000-[cited 2016 July] Available from: <https://clinicaltrials.gov/ct2/show/NCT02484950> NLM Identifier: NCT02484950.
46. Duke University. Bone marrow aspirate concentrate (BMAC) supplementation for osteochondral lesions (BMAC). In: *ClinicalTrials.gov* [Internet]. Bethesda (MD): National Library of Medicine (US). 2000-[cited 2016 July] Available from: <https://clinicaltrials.gov/ct2/show/NCT02011295> NLM Identifier: NCT02011295.

47. McKenna RW, Riordan HN. Minimally invasive autologous bone marrow concentrate stem cells in the treatment of the chronically injured Achilles tendon: A case report. *CellR4*. 2014;2(4):e1100.
48. Hernigou P, Flouzat Lachaniette CH, Delambre J, et al. Biologic augmentation of rotator cuff repair with mesenchymal stem cells during arthroscopy improves healing and prevents further tears: A case-controlled study. *Int Orthop*. 2014 Sep;38(9):1811-8. doi: 10.1007/s00264-014-2391-1.

Additional References

- Bark S, Piontek T, Behrens P, Mkalaluh S, Varoga D, Gille J. Enhanced microfracture techniques in cartilage knee surgery: Fact or fiction? *World Journal of Orthopedics*. Sep 18 2014;5(4):444-449.
- Bert JM. Abandoning microfracture of the knee: has the time come? *Arthroscopy*. Mar 2015;31(3):501-505.
- DiBartola AC, Everhart JS, Magnussen RA, et al. Correlation between histological outcome and surgical cartilage repair technique in the knee: A meta-analysis. *The Knee*. Jun 2016;23(3):344-349.
- Goyal D, Keyhani S, Lee EH, Hui JH. Evidence-based status of microfracture technique: a systematic review of level I and II studies. *Arthroscopy*. Sep 2013;29(9):1579-1588.
- Kon E, Filardo G, Berruto M, et al. Articular cartilage treatment in high-level male soccer players: a prospective comparative study of arthroscopic second-generation autologous chondrocyte implantation versus microfracture. *The American Journal of Sports Medicine*. Dec 2011;39(12):2549-2557.
- McCormick F, Harris JD, Abrams GD, et al. Trends in the surgical treatment of articular cartilage lesions in the United States: an analysis of a large private-payer database over a period of 8 years. *Arthroscopy*. Feb 2014;30(2):222-226.
- Oussedik S, Tsitskaris K, Parker D. Treatment of articular cartilage lesions of the knee by microfracture or autologous chondrocyte implantation: a systematic review. *Arthroscopy*. Apr 2015;31(4):732-744.

Chapter Thirteen

1. Vargas DL, Nascimbene C, Krishnan C, Zimmerman AW, Pardo CA. Neuroglial activation and neuroinflammation in the brain of patients with autism. *Ann Neurol*. 2005;57(1):67-81.
2. Stubbs G. Interferonemia and autism. *J Autism Dev Disord*. 1995;25(1):71-3.
3. Sweeten TL, Posey DJ, Shankar S, McDougale CJ. High nitric oxide production in autistic disorder: a possible role for interferon-gamma. *Biol Psychiatry*. 2004;55(4):434-7.
4. Ichim TE, Solano F, Glenn E, et al. Stem cell therapy for autism. *J Transl Med*. 2007;5:30.doi: 10.1186/1479-5876-5-30.
5. Ashwood P, Anthony A, Torrente F, Wakefield AJ. Spontaneous mucosal lymphocyte cytokine profiles in children with autism and gastrointestinal symptoms: mucosal immune activation and reduced counter regulatory interleukin-10. *J Clin Immunol*. 2004;24(6):664-73.
6. Okada K, Hashimoto K, Iwata Y, Nakamura K, Tsujii M, Tsuchiya KJ, et al. Decreased serum levels of transforming growth factor-beta1 in patients with autism. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31(1):187-90.
7. Neuhaus E, Beauchaine TP, Bernier R. Neurobiological correlates of social functioning in autism. *Clinical psychology review*. 2010;30(6):733-748.doi: 10.1016/j.cpr.2010.05.007.