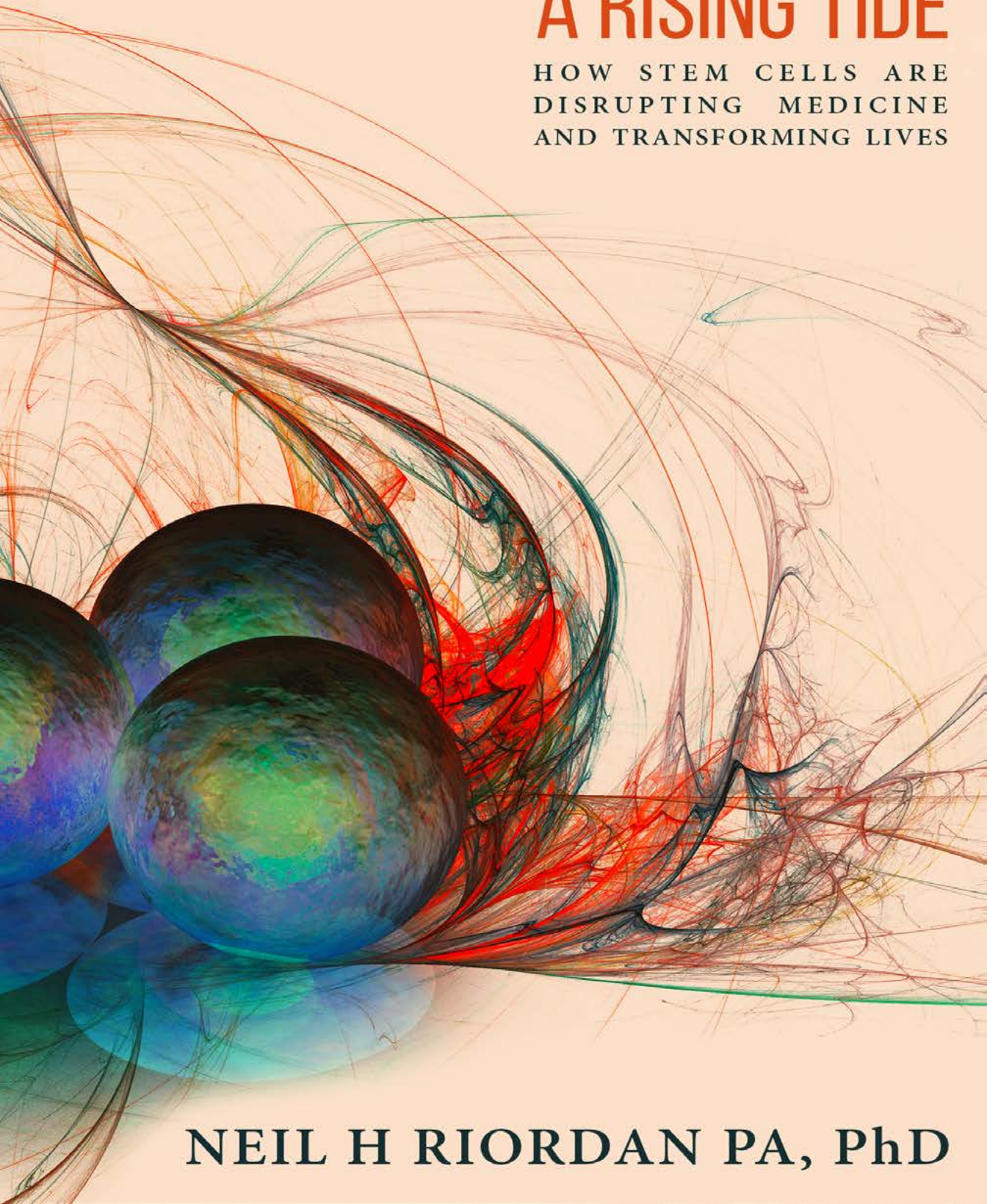


STEM CELL THERAPY

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."

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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.

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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.

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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

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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.

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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.

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Chapter Eleven

ARTHRITIS— A NEW SOLUTION



Marian D’Unger lives in a menagerie. The house she and her husband own near a creek in a suburb of Dallas sits on one and a half acres. There she tends to four cats, two love birds, two dogs, a rose-breasted cockatoo and two geese. Every night she feeds the fifty raccoons that gather on the property, including one named George, who she lets come into the house. When her fingers swelled up in November 2008 and she had trouble writing, at first she wondered if she’d gotten an insect bite or something else from one of the animals.

Marian is a real estate agent who loves her work. She sells seven days a week and shows an average of fifty to seventy-five houses a week. She always wears boots with her glitzy jeans and tailored blazers because she never

knows when she's going to have to make her way around a construction site. The night that her hand started to give her trouble, she was writing a marketing report for one of her properties. She looked down at her right hand when it started to stiffen up and saw that it had turned beet red. "I took all the pain killers in the house, the stuff we had left over from the dentist," she said.

One of her friends thought she might have gout, a chronic form of arthritis that occurs when uric acid builds up in the joints. The pain and swelling returned the next night. When Marian saw a friend of hers who is a doctor, he took a look at her hands and said he thought she had rheumatoid arthritis. He was able to diagnose that at a glance by examining Marian's fingers. From the middle joint up, her fingers were slanted toward her little finger, a characteristic of rheumatoid arthritis. The arthritis in her joints appeared to have mangled her hands.

"I had never noticed it before," she said, amazed. "Before that night I didn't have any hand pain. I'm 65 and I have aches and pains, but I thought what was going on in my hands came from something I did that day."

Arthritis is a common condition that affects nearly 30 million people in the United States, or 10 percent of the population. There are more than a hundred different kinds of arthritis, a condition of the joints that causes pain, swelling, and stiffness and limits range of motion. The cause of these difficulties is the breakdown of cartilage, the sinewy and flexible connective tissue that is not as stiff as bone and not as flexible as muscle. The cartilage helps hold your body together, keeping the bones in alignment and allowing the joints to flex and the whole body to move.

Cartilage is unique in that it is a kind of tissue that doesn't contain blood vessels. As a result, it grows and repairs more slowly. In osteoarthritis, the most widespread form of the disease, affecting 27 million people in the United States, the pain in the joints is due to the wearing away of cartilage, which leaves no protection for the joints as they move. When a sufferer bends a knee or an elbow, bone rubs on bone, causing great pain. Often with osteoarthritis, the joints wear out where the cartilage has been thinned out by overuse.

Marian's type of arthritis was rheumatoid, an autoimmune disease. The body's immune system is designed to seek and destroy invaders, particularly infections. Autoimmune diseases are those in which the body mistakenly identifies healthy tissue as a foreign substance and begins to attack its own cells. As the attack on the cartilage advances, those who suffer from rheumatoid arthritis can notice the shape of their body changing, as Marian did with her fingers. The disease can attack other joints too, resulting in swollen knees, cramped up toes, and bumpy fingers with raised nodules on the knuckles.

There is no cure for arthritis, only an array of drugs that may or may not help calm the inflammation. As Marian was about to find out, these drugs may have horrible side effects. The doctor first gave Marian methotrexate, which helped with her symptoms for a few months even though it made her feel nauseated for most of the day. When its effectiveness started to ebb, the doctor switched her to Enbrel®, which he told her to inject into her legs. That treatment only lasted two weeks because she broke out into huge rashes at the spots where she injected the drugs. "It looked like I had big red pancakes plastered on my legs," Marian said.

The next drug was Arava®, which helped with some of the pain and swelling but gave Marian terrible diarrhea two or three times a day. She was also taking Celebrex® and ten to twelve aspirin a day. Celebrex, too, stopped being effective after a while. Again she was having trouble holding a fork or a pen. When she and her husband went out to dinner, she'd just push the food around on her plate. She couldn't hold a fork well enough to maneuver food to her mouth, and she certainly wasn't going to eat with her hands. "It was impossible for me to work," Marian said. "The quality of my life was going downhill fast." She got to the point where she couldn't drive because she couldn't shift gears.

In the beginning of 2010, the doctor suggested Marian return to methotrexate, only this time to take it in an injectable form. The side effects were horrible. "It was like I was injecting myself with food poisoning every Monday evening. My hand would be shaking so badly when I tried to inject it. I was so frightened by what I knew was going to happen. The next day after the injection, I'd be lying on the floor, gagging and throwing up constantly.

I couldn't work Tuesday and Wednesday. Thursday I could go back and by Friday I'd be feeling pretty good but by Saturday I was a wreck thinking about what was coming on Monday."

How was this helping Marion battle her disease? She thought the drugs were only making things worse. She was still stiff when she got up in the morning, and the days of lying at home too sick to move contradicted the advice to stay physically active to maintain some mobility and flexibility in her joints. Worst of all, she was losing hope. No one knows the cause of rheumatoid arthritis, and all of the treatments focus on easing the symptoms, not eliminating them. In Marian's experience, none of the available drugs worked for her.

A friend of Marian's who lives in Corpus Christi said she had heard of something that might help. She knew a man there, Dusty Durrill, who had been to Panama for stem cell treatments for his osteoarthritis. He had gone down to Central America shuffling, stooped over, using a cane to support

Biologic Response Modifiers for Rheumatoid Arthritis

In recent years, a new group of drugs called biologic response modifiers, or biologics, has been approved for the treatment of rheumatoid arthritis in patients with moderate to severe forms of the disease who do not respond well to the standard drugs. These drugs are genetically-engineered proteins derived from human genes that inhibit certain components of the immune system. They can be prohibitively expensive, to the tune of \$20,000 every two months, and come with a host of side effects. For example, the disclaimer for one of these biological medications reads, "Humira® can lower your ability to fight infections including tuberculosis. Serious and sometimes fatal infections, and cancers including lymphoma, have happened, including blood, liver, and nervous system problems, serious allergic reactions, and new and worsening heart failure. Before treatment get tested for TB, tell your doctor if you've been to areas where certain fungal infections are common, and if you've had TB, hepatitis B, are prone to infections, or have flu-like symptoms or sores. Don't start Humira if you have an infection."

his weight, and unable to shake anyone's hand. He returned from treatment able to walk into the room without any assistance. He was telling everyone he knew about this miracle.

Researchers have found that the cartilage-forming cells of those who suffer with osteoarthritis don't divide as quickly as the cells of healthy individuals, so they can't replenish the cartilage tissue in a robust fashion. In experiments with animals, injections of the animals' own stem cells boosted the cartilage-forming capacity in the area of the animals' greatest suffering and pain.¹ In fact, there are veterinary services throughout the country that routinely use stem cells derived from dogs to treat animals with arthritic hips.

Dusty Durrill had a gradually worsening case of osteoarthritis that had started when he was in his fifties. He'd had perfect health for the decades when he was a Navy pilot, but by the time he reached his fifties he had trouble walking more than a block or climbing half a flight of stairs. When he reached his sixties the doctors told him he would need to have both knees replaced as well as at least one of his hips. A friend who had been married to a veterinarian told him that dog owners would bring in their pets that couldn't walk. Once they were treated with stem cells, the dogs were running and barking just as they had been when they were puppies.

"What the hell?" Dusty asked. "We can fix dogs but we can't fix humans? They've been fixing dogs for eight or ten years. There's got to be someone who can fix humans."

That's when he found our Stem Cell Institute in Panama on the Internet. He applied, described his case, and was accepted for treatment. "I went down there and got treatment, and ten days later—ten frigging days—I had no symptoms," Dusty said. "I had been suffering from this for twenty years, and they cured me with stem cells in only ten days."

I had been suffering from this for twenty years, and they cured me with stem cells in only ten days."

Dusty has a great way of explaining how the stem cells work. I like to explain it scientifically so that people understand that it makes sense medically. But because of Dusty's background in the military, he likes to use the language of war. "The best I can describe it to you, when you have something wrong with your body it's like a battlefield. When you get stem cells it's like you get a combat battalion of U.S. Marines, and they start fixing all the broken bridges and roads, and killing the enemy, attacking all the bad stuff. They don't need a road map. They just go in there and go to work," Dusty said.

A few weeks after Dusty's visit to Panama, he sent Dr. Paz an email that detailed all of the changes in his body since he'd received the stem cells. The good news was that his arthritis was in remission, but there was other

Mesenchymal Stem Cell Treatment for Osteoarthritis

Osteoarthritis (OA) is an inflammation of the joints, caused by wear and tear, which can be severe enough to impair movement and cause pain. OA is a leading cause of disability in patients over age 65² and commonly affects the hands, knees, hips, and spine. Wearing down of cartilage in the joint area may lead to the eventual need for a major replacement surgery with prosthesis. Existing treatments for OA are aimed to reduce pain, but the progression of the condition is not stopped.³

OA occurs when inflammatory and oxidative stresses progressively wear down cartilage.⁴ Mesenchymal stem cells (MSCs) have been shown to produce factors that are anti-inflammatory⁵ and that are key for tissue repair and regeneration.⁶ MSCs can also directly become new cartilage tissue.⁷ In particular, umbilical cord MSCs have been shown to have a superior potential for cartilage regeneration over other MSC sources.⁸

Animal models have shown that treatment with MSCs is effective for OA. Goats that received MSCs for knee OA had evidence of regeneration in the meniscus and less wearing down of the cartilage in the joint.⁹ Similar regenerative effects have been reported in rat,¹⁰ rabbit,¹¹ sheep,¹² and dog¹³ models, and a single dose of bone marrow MSCs has been shown to be enough to slow the progression of OA in sheep.¹⁴

good news as well. The cells had gone to work on other issues that had been troubling Dusty. The clicking and soreness in his right knee disappeared, his hair turned from white to grey, his skin cleared up and smoothed out, the folds on his lower neck disappeared, his erectile dysfunction was no longer an issue, his bladder incontinence came under control, and his office staff and son claimed that he was more alert and involved in his business than before.

The dramatic nature of his recovery turned Dusty into a stem cell evangelist. He wanted to help alleviate other people's suffering because he knew how hard their lives were and how much they hurt. He was a successful businessman and very generous. That's why he flew Dr. Paz up to Corpus Christi's Del Mar College in June of 2010 to spread the word about

Treatment with MSCs for OA has been shown also to be effective and safe in clinical settings.^{15,16,17} Recent clinical trials reported pain relief and improvements in cartilage quality in OA patients treated with bone marrow MSCs,^{18,19} as well as cartilage regeneration with MSCs derived from fat.²⁰ Another study reported improvements in walking distance and stiffness for 30 months after treatment.²¹

One very exciting breakthrough for osteoarthritis is the development of Cartistem[®], a drug manufactured from umbilical cord MSCs by Medipost, a Korean regenerative medicine company.²² Cartistem was approved for the treatment of OA in January 2012 by the South Korean equivalent of the FDA (the Ministry of Food and Drug Safety). In other words, a tier-one country's regulatory body approved an allogeneic, or off-the-shelf, stem cell product made from donor tissue. They would not have gotten approval had the product not been shown first to be safe and then secondly to be effective. As of February 2015, more than 2,000 doses had been given safely, with excellent results in a third phase (follow-up) clinical trial seven years after treatment,²³ and with a clinical trial well underway in the United States at the Cartilage Restoration Center in Chicago, IL and the Cartilage Repair Center in Chestnut Hill, MA.²⁴

There are currently several clinical trials listed on ClinicalTrials.gov to treat OA with MSCs from bone marrow, including one trial in the United States at the Regenerative Pain Center in Illinois.²⁵ Other countries also have ongoing MSC clinical trials.^{26,27,28} Our group is currently conducting a phase I/II trial to assess the safety and efficacy of intraarticular knee injection of umbilical cord MSCs.²⁹

the potential of this treatment. And Marian D'Unger was in the audience that day.

Marian was very impressed by Dusty's improvement. Even though they had different kinds of arthritis, Marian thought the stem cells might be as useful for her as they had been for Dusty. Excited by what she had heard at the seminar, she asked her doctor what he felt about adult stem cell therapy for arthritis. Her doctor was very discouraging and told her not to go to Panama for treatment. He said that she wasn't that bad yet.

"What does that mean?" Marian thought. "I have to be in a wheelchair before I should consider alternative treatments?"

The medicines she had been prescribed for her condition were taking a toll. While she was at the doctor's office, they asked her to check the lot number of the methotrexate she had injected into her system a few months earlier. The FDA had recalled some batches of the drug because they found that some of them had inadvertently contained ground glass. Marian was stunned. "This is the medicine that's supposed to be helping me, and it's approved by the FDA, yet in reality it's destroying my life," Marian thought. "I think I'm going to try the stem cells."

Marian, her husband, and her daughter all flew to Panama for the two weeks she needed to be there for treatment. They rented an apartment overlooking the Pacific Ocean and viewed the whole journey to help Marian's arthritis as a family vacation. "We cooked most of our meals in the condo because the fish in the marketplace was so fresh," she said. She even hooked up with a local real estate agent and is thinking of starting a business selling condos to retirees who want to move to Panama—all because she is feeling so much better.

Marian was injected with her own stem cells and some cells cultured from umbilical cord blood. Most mornings before treatment, she had to hold on to the furniture to move around her room. By the time she got home, she was no longer limping and sore when she got out of bed in the morning. "Within two months I was 95 percent better, virtually pain free and with no swelling," Marian said. Before the visit to our clinic, she couldn't hold a pencil in her hand. Now she can write with a pencil and use a fork when she

Mesenchymal Stem Cell Treatment for Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune condition in which otherwise healthy cells in the body are mistakenly recognized as a threat and are attacked by the immune system. In the case of RA, the lining of the joints is attacked by the immune system and becomes inflamed, leading to an eventual loss of physical function and disability. RA affects approximately 0.5 to 1 percent of the population worldwide,³⁰ with rates between 20 and 50 cases per 100,000 people in North American and Northern European countries.³¹ Persons affected by RA frequently suffer from other diseases (cardiovascular, pulmonary, and renal, for example) and show higher rates of infection.³²

RA is usually treated with anti-inflammatories to relieve pain, and with disease-modifying antirheumatic drugs (DMARDs) to stop the progression of the disease. Some of the newer DMARDs include both biologic and non-biologic medications. They work by targeting immune system cells and cytokines involved in inflammation, such as tumor necrosis factor (TNF). However, 30 to 40 percent of RA patients do not respond to DMARD treatment.³³ Additionally, DMARDs affect the performance of the rest of the immune system, leaving the body at risk for opportunistic infections and certain cancers such as lymphomas. No current treatment reverses or corrects the joint damage that has already occurred in RA.

goes out to eat. Also, she's cut the use of painkillers by 75 percent. She's gone from taking twelve aspirin a day to two. Plus, she's cut her use of Celebrex from 400 to 100 milligrams, and she doesn't take it every day. She returned to real estate and continues to work full time at age 74.

Marian's rheumatologist, after reviewing her records, told her that he couldn't believe she had experienced such dramatic results. She should have been in a wheelchair at the rate of rapid deterioration she had experienced before stem cells. In June 2016 she returned to Panama for a second treatment. "I've been very fortunate to get to go to Panama. It took four minutes to get across the room before stem cells. I had to hold on to something to be able to walk. People don't know that I have arthritis now. I am pretty active for my age. I outrun people who are 15 years younger than I am. It was the cells in Panama that did that, even my rheumatologist attests to that," Marian said.

Mesenchymal stem cells (MSCs) can modulate the immune system^{34,35,36,37} and have been used safely to treat certain inflammatory conditions^{38,39,40,41} in clinical settings. Additionally, MSCs have the ability to regenerate worn-out cartilage,⁴² with umbilical cord-derived MSCs showing greater capacity than other MSC sources.⁴³ Treatment with MSCs has been shown to be effective in animal models^{44,45,46,47} of RA, and MSCs have been effective at inhibiting production of inflammatory cytokines from cells derived from RA patients.^{48,49} MSC infusions are almost always followed by an increase in T-regulatory cells, which calm down the inflammatory T cell inflammation response common in rheumatoid arthritis. In 2010 we published a case report showing improvement in a 67-year-old RA patient, along with our proposed rationale for treatment with MSCs.⁵⁰ Additionally, we reported no major side effects in 13 RA patients given a total of 35 injections of cells from their fat in 2012.⁵¹



Angela was diagnosed with rheumatoid arthritis in 2008 after doctors misdiagnosed her with flu symptoms and joint pain. She was on the usual concoction of pharmaceuticals in addition to monthly infusions of a biologic that cost \$6,500 each month and yet only partially controlled her condition. She still had a difficult time getting up in the morning and had to take a nap each afternoon. When her brother, who was treated with umbilical cord MSCs and is a proponent of stem cell therapy, suggested she try the treatment, she was skeptical because her doctors told her it was an unproven treatment.

Angela came to our clinic in 2014 and received four stem cell infusions over the course of one week. By the second day she felt so good that she wanted to take a

“People don’t know that I have arthritis now. I am pretty active for my age. I outrun people who are 15 years younger than I am. It was the cells in Panama that did that, even my rheumatologist attests to that,” Marian said.

One particularly remarkable trial of umbilical cord MSC treatment for RA was published in 2013: 172 patients were divided into two groups; 36 received treatment with DMARDs alone (the control group) and 136 received DMARDs plus MSCs.⁵² The treatment was shown to be safe with no adverse events. Compared to the control group, those treated with DMARDs plus MSCs showed statistically significant improvements in the HAQ and DAS28—two scales used to measure the extent of RA impact on the patient. The DMARD plus MSC group also had a decrease in levels of the inflammatory markers corticotropin-releasing factor (CRF) and rheumatoid factor (RF), and an increase in T-regulatory cells (associated with clinical benefits). Patients were assessed after three-, six-, and eight-month intervals, with improvements for all three time points, but at eight months the effect was not as significant. The most exciting part of this study was the finding that a single treatment of 40 million MSCs reduced the amount of TNF- α and interleukin-6 (IL-6) in the treated patients by approximately 50 percent. TNF- α and IL-6, sentinel molecules in autoimmune disease, are the primary targets of the newer, and costly, biologic DMARDs (such as Humira® and Enbrel®). Additionally, a subset of patients who were treated a second time with the same dose of cells experienced a 25 percent further decrease of TNF- α and IL-6, for a total 75 percent reduction of TNF- α and IL-6.

walk in the mall. At the airport on her way home, she opted to walk instead of take the escalators. She followed up with her doctor the next month and found that her inflammatory markers, usually quite high, had gone down considerably. Another month later her rheumatoid arthritis was no longer detectable and she was off all of her medications. She lost the thirty pounds she had gained due to all the medications she was previously on. Her doctor was amazed.

Angela's husband had been putting off retirement because he needed his insurance to help pay for the high cost of her previous medical treatments, but after she received the stem cells, she no longer needed treatment and he could finally retire. Two years later at the time of this writing, she is still doing well after one stem cell treatment.



MSCs are therefore a potential therapy for RA that would promote the regeneration of damaged tissue and would address the underlying immunological abnormality. There are currently several clinical trials registered on ClinicalTrials.gov using MSCs to treat RA, including a nationwide trial using allogeneic (donor) cells with the participation of The University of California at Los Angeles and clinics in states including Arizona, Florida, and Maryland, among many others.⁵³ The trials are proposing umbilical cord MSCs.^{54,55} Our group in particular is conducting a phase I/II trial to assess the safety and efficacy of allogeneic umbilical cord MSCs with DMARDs to treat RA patients.⁵⁶



Janet Vaughan is a competitive ballroom dancer and orthodontist. She regularly participated in 10 to 12 American Rhythm or American Smooth style dance competitions every year, and loved every minute of it. During the final round in the 2000 U.S. National Championships American Rhythm Division, while dancing the swing, Janet heard a loud pop and felt excruciating pain in her right foot. But she refused to leave the dance floor and finished strong, winning third place with a dislocated joint. The injury left her later unable to walk, however, and she was

diagnosed with osteoarthritis and a dislocated toe that required surgery. Her doctors told her that she would never dance again. She was devastated.

She found a specialist in Houston who performed the surgery and even proved her doctors wrong—she did dance again. But not for long. She suffered a knee injury while practicing one day. Numerous injections and eventually an arthroscopic surgery failed her miserably, gave her a swollen knee, and put her on crutches. Her condition became worse with every new treatment.

Undeterred, Janet communicated with clinics all over the United States in search of the right treatment. Some clinics said her injury was too

severe to treat. Others didn't give her the confidence she needed to know the treatment would be helpful. Then she met Dusty Durrill. When she heard his story about the Stem Cell Institute, she knew stem cells were the treatment for her. She applied immediately and came down for treatment.

Janet began feeling the effects of her first stem cell treatment about six months afterward. The change was dramatic, and she felt it in all of her joints, not only her knee. She felt relief from a neck injury that had occurred twenty years earlier and from the arthritic joint pain in her hands. Since her first treatment Janet has been down a few more times for maintenance treatment, "for fighting the degenerative disease that osteoarthritis presents," she says.

Best of all, Janet is dancing again. In fact, she won the U.S. American Rhythm title with world champion Tony Dovolani, "a dream come true," she said. "Stem cell treatments, for me, were life changing. I am back to the dance floor with no pain and regaining the confidence to dance full out, not tentatively."

“Stem cell treatments, for me, were life changing. I am back to the dance floor with no pain and regaining the confidence to dance full out, not tentatively.”

References


Chapter Eleven

1. Black LL, Gaynor J, Gahring D, et al. Effect of adipose-derived mesenchymal stem and regenerative cells on lameness in dogs with chronic osteoarthritis of the coxofemoral joints: a randomized, double-blinded, multicenter, controlled trial. *Vet Ther.* 2007 Winter;8(4):272-84.
2. Theis KA, Murphy L, Hootman JM, Helmick CG, Yelin E. Prevalence and correlates of arthritis-attributable work limitation in the US population among persons ages 18-64: 2002 National Health Interview Survey Data. *Arthritis Rheum.* 2007;57(3):355-363.
3. Liu-Bryan R, Terkeltaub R. Emerging regulators of the inflammatory process in osteoarthritis. *Nat Rev Rheumatol.* 2015;11(1):35-44.doi: 10.1038/nrrheum.2014.162.
4. Goldring MB, Otero M. Inflammation in osteoarthritis. *Curr Opin Rheumatol.* 2011;23(5):471-478.doi: 10.1097/BOR.0b013e328349c2b1.
5. 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.
6. Caplan AI. Adult mesenchymal stem cells for tissue engineering versus regenerative medicine. *J Cell Physiol.* 2007;213(2):341-347.
7. Gupta PK, Das AK, Chullikana A, Majumdar AS. Mesenchymal stem cells for cartilage repair in osteoarthritis. *Stem Cell Res Ther.* 2012;3(4):25.doi: 10.1186/scrt116.
8. 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.
9. Murphy JM, Fink DJ, Hunziker EB, Barry FP. Stem cell therapy in a caprine model of osteoarthritis. *Arthritis Rheum.* 2003;48(12):3464-3474.
10. Horie M, Sekiya I, Muneta T, et al. Intra-articular injected synovial stem cells differentiate into meniscal cells directly and promote meniscal regeneration without mobilization to distant organs in rat massive meniscal defect. *Stem Cells.* 2009;27(4):878-887.doi: 10.1634/stemcells.2008-0616.
11. Grigolo B, Lisignoli G, Desando G, et al. Osteoarthritis treated with mesenchymal stem cells on hyaluronan-based scaffold in rabbit. *Tissue Eng Part C Methods.* 2009;15(4):647-658.doi: 10.1089/ten.TEC.2008.0569.
12. Al Faqeh H, Norhamdan MY, Chua KH, Chen HC, Aminuddin BS, Ruszymah BH. Cell based therapy for osteoarthritis in a sheep model: gross and histological assessment. *Med J Malaysia.* 2008;63 Suppl A:37-38.
13. Black LL, Gaynor J, Adams C, et al. Effect of intraarticular injection of autologous adipose-derived mesenchymal stem and regenerative cells on clinical signs of chronic osteoarthritis of the elbow joint in dogs. *Vet Ther.* 2008;9(3):192-200

14. Al Faqeh H, Nor Hamdan BM, Chen HC, Aminuddin BS, Ruszymah BH. The potential of intra-articular injection of chondrogenic-induced bone marrow stem cells to retard the progression of osteoarthritis in a sheep model. *Exp Gerontol.* 2012;47(6):458-464.doi: 10.1016/j.exger.2012.03.018.
15. Koh YG, Choi YJ. Infrapatellar fat pad-derived mesenchymal stem cell therapy for knee osteoarthritis. *Knee.* 2012;19(6):902-907.doi: 10.1016/j.knee.2012.04.001.
16. Davatchi F, Abdollahi BS, Mohyeddin M, Shahram F, Nikbin B. Mesenchymal stem cell therapy for knee osteoarthritis. Preliminary report of four patients. *Int J Rheum Dis.* 2011;14(2):211-215.doi: 10.1111/j.1756-185X.2011.01599.x.
17. Pers YM, Rackwitz L, Ferreira R, et al. Adipose mesenchymal stromal cell-based therapy for severe osteoarthritis of the knee: a phase I dose-escalation trial. *Stem Cells Transl Med.* 2016;5(7):847-56. doi: 10.5966/sctm.2015-0245.
18. Vega A, Martín-Ferrero MA, Del Canto F, et al. Treatment of knee osteoarthritis with allogeneic bone marrow mesenchymal stem cells: a randomized controlled trial. *Transplantation.* 2015;99(8):1681- 1690.doi: 10.1097/TP.0000000000000678.
19. Orozco L, Munar A, Soler R, et al. Treatment of knee osteoarthritis with autologous mesenchymal stem cells: a pilot study. *Transplantation.* 2013;95(12):1535-1541.doi: 10.1097/TP.0b013e318291a2da.
20. Jo CH, Lee YG, Shin WH, et al. Intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: a proof-of-concept clinical trial. *Stem Cells.* 2014;32(5):1254-1266.doi: 10.1002/stem.1634.
21. Emadedin M, Ghorbani Liastani M, Fazeli R, et al. Long-term follow-up of intra-articular injection of autologous mesenchymal stem cells in patients with knee, ankle, or hip osteoarthritis. *Arch Iran Med.* 2015;18(6):336-344.doi: 015186/AIM.003.
22. MEDIPOST | Stem Cell Drugs| Cartistem. <http://www.medi-post.com/cartistem/> Accessed October 31st, 2016.
23. Park YB, Ha CW, Lee CH, Yoon YC, Park YG, et al. Cartilage regeneration in osteoarthritic patients by a composite of allogeneic umbilical cord blood-derived mesenchymal stem cells and hyaluronate hydrogel: results from a clinical trial for safety and proof-of-concept with 7 years of extended follow-up. *Stem Cells Transl Med.* September 2016.
24. Medipost Co Ltd. Evaluation of Safety and Exploratory Efficacy of CARTISTEM®, a Cell Therapy Product for Articular Cartilage Defects. In: *ClinicalTrials.gov* [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2016 November]. Available from: <https://clinicaltrials.gov/ct2/show/NCT01733186>. NLM Identifier: NCT01733186.
25. Regenerative Pain Center, Illinois. Outcomes data of bone marrow stem cells to treat hip and knee osteoarthritis. In: *ClinicalTrials.gov* [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2016 July]. Available from: <https://clinicaltrials.gov/ct2/show/NCT01601951> NLM Identifier: NCT01601951.
26. Stempeutics Research Pvt Ltd. Allogeneic mesenchymal stem cells for osteoarthritis. In: *ClinicalTrials.gov* [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2016 July]. Available from: <https://clinicaltrials.gov/ct2/show/NCT01448434> NLM Identifier: NCT01448434.
27. International Stemcell Services Limited. Safety and efficacy of autologous bone marrow stem cells for treating osteoarthritis. In: *ClinicalTrials.gov* [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2016 July]. Available from: <https://clinicaltrials.gov/ct2/show/NCT01152125> NLM Identifier: NCT01152125

28. South China Research Center for Stem Cell and Regenerative Medicine. UCMSC transplantation in the treatment of cartilage damage. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2016 July]. Available from:<https://www.clinicaltrials.gov/ct2/show/NCT02776943> NLM Identifier: NCT02776943.
29. Translational Biosciences. Clinical Study of Umbilical Cord Tissue Mesenchymal Stem Cells (UC- MSC) for Treatment of Osteoarthritis. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2016 July]. Available from:<https://clinicaltrials.gov/ct2/show/NCT02237846> NLM Identifier: NCT02237846.
30. Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. *Semin Arthritis Rheum.* 2006;36(3):182-8.
31. Carmona L, Cross M, Williams B, Lassere M, March L. Rheumatoid arthritis. *Best Pract Res Clin Rheumatol.* 2010;24(6):733-745.
32. Michaud K, Wolfe F. Comorbidities in rheumatoid arthritis. *Best Pract Res Clin Rheumatol.* 2007;21(5):885-906.
33. Bansard C, Lequerré T, Daveau M, et al. Can rheumatoid arthritis responsiveness to methotrexate and biologics be predicted? *Rheumatology (Oxford).* 2009;48(9):1021-1028.
34. Hoogduijn MJ, Crop MJ, Peeters AM, et al. Human heart, spleen, and perirenal fat-derived mesenchymal stem cells have immunomodulatory capacities. *Stem Cells Dev.* 2007;16(4):597-604.
35. English K, Barry FP, Mahon BP. Murine mesenchymal stem cells suppress dendritic cell migration, maturation and antigen presentation. *Immunol Lett.* 2008;115(1):50-8.
36. Caplan AI. Adult mesenchymal stem cells for tissue engineering versus regenerative medicine. *J Cell Physiol.* 2007;213(2):341-347.
37. La Rocca G, Lo Iacono M, Corsello T, Corrao S, Farina F, Anzalone R. Human Wharton's jelly mesenchymal stem cells maintain the expression of key immunomodulatory molecules when subjected to osteogenic, adipogenic and chondrogenic differentiation in vitro: new perspectives for cellular therapy. *Curr Stem Cell Res Ther.* 2013;8(1):100-13.
38. Liang J, Zhang H, Hua B, et al. Allogenic mesenchymal stem cells transplantation in refractory systemic lupus erythematosus: a pilot clinical study. *Ann Rheum Dis.* 2010;69(8):1423-9.
39. Sun L, Wang D, Liang J, et al. Umbilical cord mesenchymal stem cell transplantation in severe and refractory systemic lupus erythematosus. *Arthritis Rheum.* 2010;62(8):2467-75.
40. Hu J, Yu X, Wang Z, et al. Long term effects of the implantation of Wharton's jelly-derived mesenchymal stem cells from the umbilical cord for newly-onset type 1 diabetes mellitus. *Endocr J.* 2013;60(3):347-57.
41. Connick P, Kolappan M, Crawley C, et al. Autologous mesenchymal stem cells for the treatment of secondary progressive multiple sclerosis: an open-label phase 2a proof-of-concept study. *Lancet Neurol.* 2012;11(2):150-6.
42. Gupta PK, Das AK, Chullikana A, Majumdar AS, et al. Mesenchymal stem cells for cartilage repair in osteoarthritis. *Stem Cell Res Ther.* 2012;3(4):25.
43. Arufe MC, De la Fuente A, Fuentes I, De Toro FJ, Blanco FJ, et al. Umbilical cord as a mesenchymal stem cell source for treating joint pathologies. *World J Orthop.* 2011;2(6):43-50.
44. Zhou B, Yuan J, Zhou Y, et al. Administering human adipose-derived mesenchymal stem cells to prevent and treat experimental arthritis. *Clin Immunol.* 2011;141(3):328-37.

45. Park MJ, Park HS, Cho ML, et al. Transforming growth factor beta-transduced mesenchymal stem cells ameliorate experimental autoimmune arthritis through reciprocal regulation of Treg/Th17 cells and osteoclastogenesis. *Arthritis Rheum.* 2011;63(6):1668-80.
46. González MA, Gonzalez-Rey E, Rico L, et al. Treatment of experimental arthritis by inducing immune tolerance with human adipose-derived mesenchymal stem cells. *Arthritis Rheum.* 2009;60(4):1006-19.
47. Augello A, Tasso R, Negrini SM, Cancedda R, Pennesi G, et al. Cell therapy using allogeneic bone marrow mesenchymal stem cells prevents tissue damage in collagen-induced arthritis. *Arthritis Rheum.* 2007;56(4):1175-86.
48. Wang Q, Li X, Luo J, et al. The allogeneic umbilical cord mesenchymal stem cells regulate the function of T helper 17 cells from patients with rheumatoid arthritis in an in vitro co-culture system. *BMC Musculoskelet Disord.* 2012;13:249.
49. Liu Y, Mu R, Wang S, et al. Therapeutic potential of human umbilical cord mesenchymal stem cells in the treatment of rheumatoid arthritis. *Arthritis Res Ther.* 2010;12(6):R210.
50. Ichim TE, Harman RJ, Min WP, et al. Autologous stromal vascular fraction cells: a tool for facilitating tolerance in rheumatic disease. *Cell Immunol.* 2010;264(1):7-17. doi: 10.1016/j.cellimm.2010.04.002.
51. Rodriguez JP, Murphy MP, Hong S, et al. Autologous stromal vascular fraction therapy for rheumatoid arthritis: rationale and clinical safety. *Int Arch Med.* 2012 Feb 8;5:5. doi: 10.1186/1755-7682-5-5.
52. Wang L, Wang L, Cong X, et al. Human umbilical cord mesenchymal stem cell therapy for patients with active rheumatoid arthritis: Safety and efficacy. *Stem Cells Dev.* 2013 Dec 15;22(24):3192-202. doi: 10.1089/scd.2013.0023.
53. Mesoblast, Ltd. A double-blind, randomized, placebo-controlled, dose-escalation, multi-center study a single intravenous infusion of allogeneic mesenchymal precursor cells (MPCs) in patients with rheumatoid arthritis and incomplete response to at least one TNF-alpha inhibitor. In: *ClinicalTrials.gov* [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2016 Jul 7]. Available from: <https://clinicaltrials.gov/ct2/show/NCT01851070> NLM Identifier: NCT01851070.
54. Alliancells Bioscience Corporation Limited. Safety and efficacy study of umbilical cord-derived mesenchymal stem cells for rheumatoid arthritis (RA). In: *ClinicalTrials.gov* [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2016 Jul 7]. Available from: <https://clinicaltrials.gov/ct2/show/NCT01547091> NLM Identifier: NCT01547091.
55. Shenzhen Hornetcorn Bio-technology Company, LTD. Human umbilical cord-mesenchymal stem cells for rheumatoid arthritis. In: *ClinicalTrials.gov* [Internet]. Available from: <https://clinicaltrials.gov/ct2/show/NCT02643823>. NLM Identifier: NCT02643823.
56. Translational Biosciences. Umbilical cord tissue-derived mesenchymal stem cells for rheumatoid arthritis. In: *ClinicalTrials.gov* [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2016 Jul 7]. Available from: <https://clinicaltrials.gov/ct2/show/NCT01985464> NLM Identifier: NCT01985464.



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