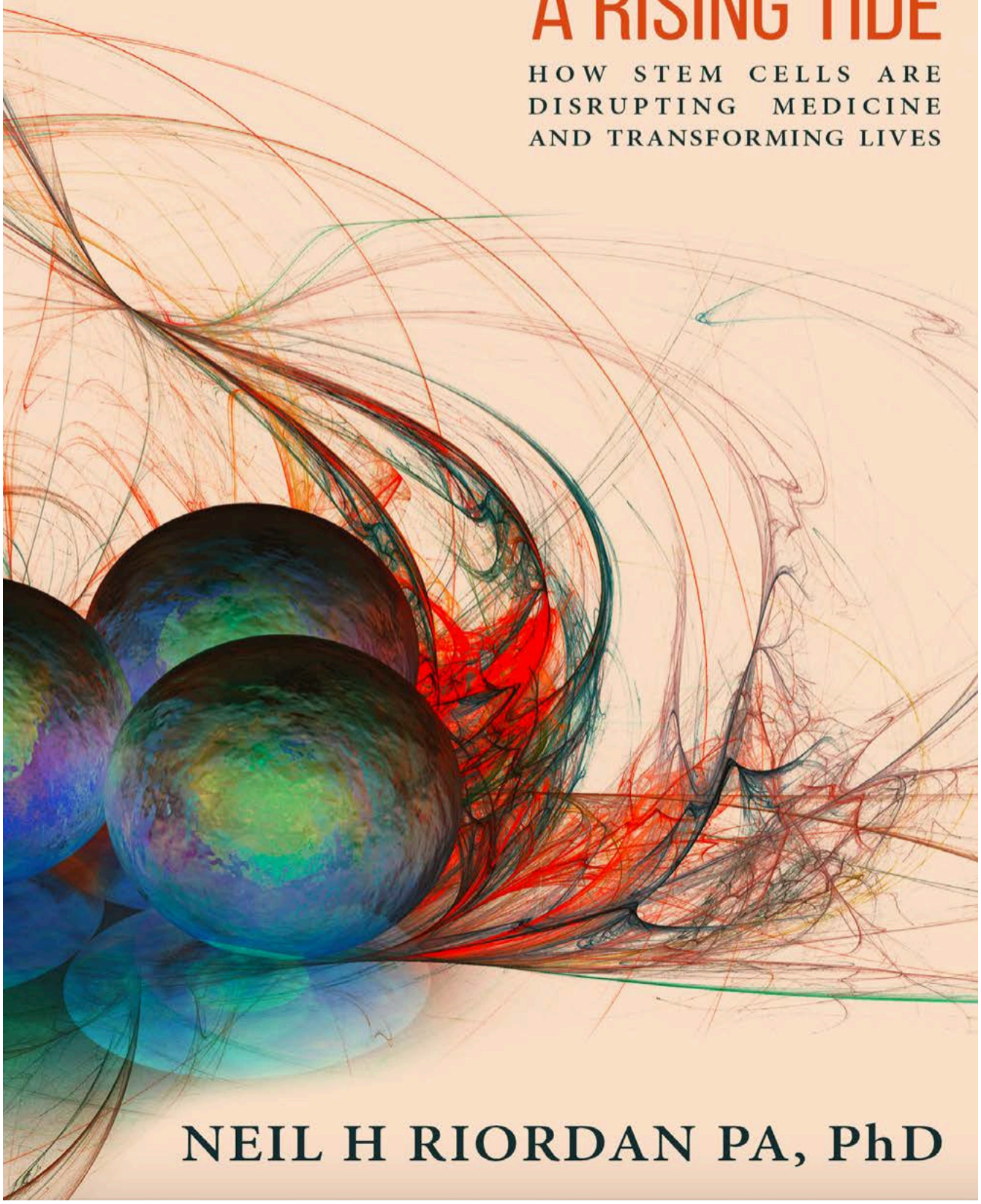
STEM CELL THERAPY

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

www.cellmedicine.com
info@neilriordanbooks.com

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

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 improvision, 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

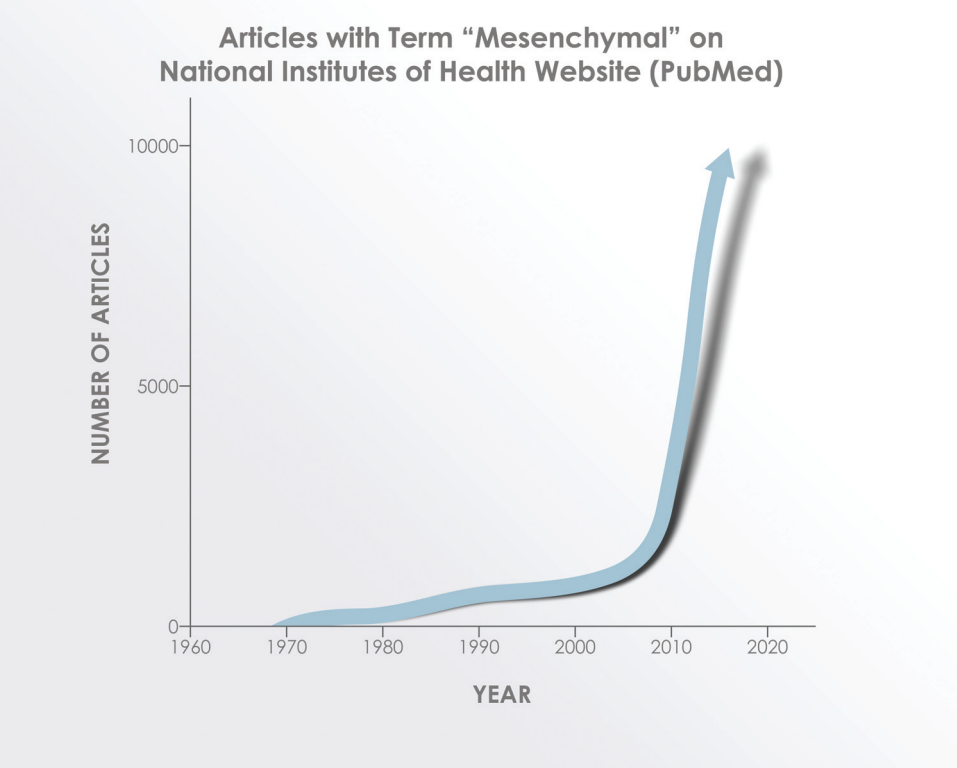
January 15, 2017

Chapter Five

STEM CELLS IN ACTION

I began my work with stem cells using CD34+ cells, but shortly after establishing the clinic in Costa Rica, we began using mesenchymal stem cells (MSCs). I was inspired by the work of Osiris Therapeutics, a company based on stem cell technology discovered by researchers at Case Western Reserve University led by Arnold Caplan, PhD. Osiris was the first company to ever treat a patient with an autologous (self-derived) stem cell product in 1998, and then the first to treat a patient with an allogeneic (donor) stem cell product two years later. By 2007, they had launched a phase III clinical trial with MSCs for patients suffering from graft versus host disease (GvHD), and successfully brought the world's first approved stem cell drug to market in Canada and New Zealand for the treatment of GvHD. They were doing great work that made me feel comfortable using MSCs with our patients.

Not a lot was known about MSCs before 2004, but since then there has been a meteoric rise in interest, a trend that doesn't appear to be slowing down any time soon. We began using MSCs in 2006, and by 2009 every patient was getting MSCs, either exclusively or in combination with CD34+ cells. Today, and for the past few years, we only use CD34+ cells for a few conditions, and always in conjunction with MSCs.



MSCs address immune imbalance and inflammation in ways that CD34+ cells cannot. CD34+ cells do not elicit a T cell response by the immune system, but MSCs take it one step further—they actually suppress immune response, an important safety factor when using cells from a donor. All doctors are taught in medical school that the presence of a foreign cell from another organism will always trigger a strong T cell immune response against the "invading" donor cell. But MSCs do not elicit this response. They are immunologically immature. In other words, MSCs are not antigenic, so they are tolerated by the immune system and do not require immune-suppressive drugs as part of their treatment. They are also non-tumorigenic because they do not differentiate into any cell, as do embryonic stem cells. Additionally, the safety profile of MSCs is excellent, making them the most-suited cell therapy for the conditions we treat.

Over time we have been able to carefully refine our cell selection and expansion process such that the cells we now use are more robust and effective than ever before. Most of all, we see equal or better treatment results

in patients who receive MSCs as were seen using CD34+ cells. For all these reasons, MSCs are our cell therapy of choice.

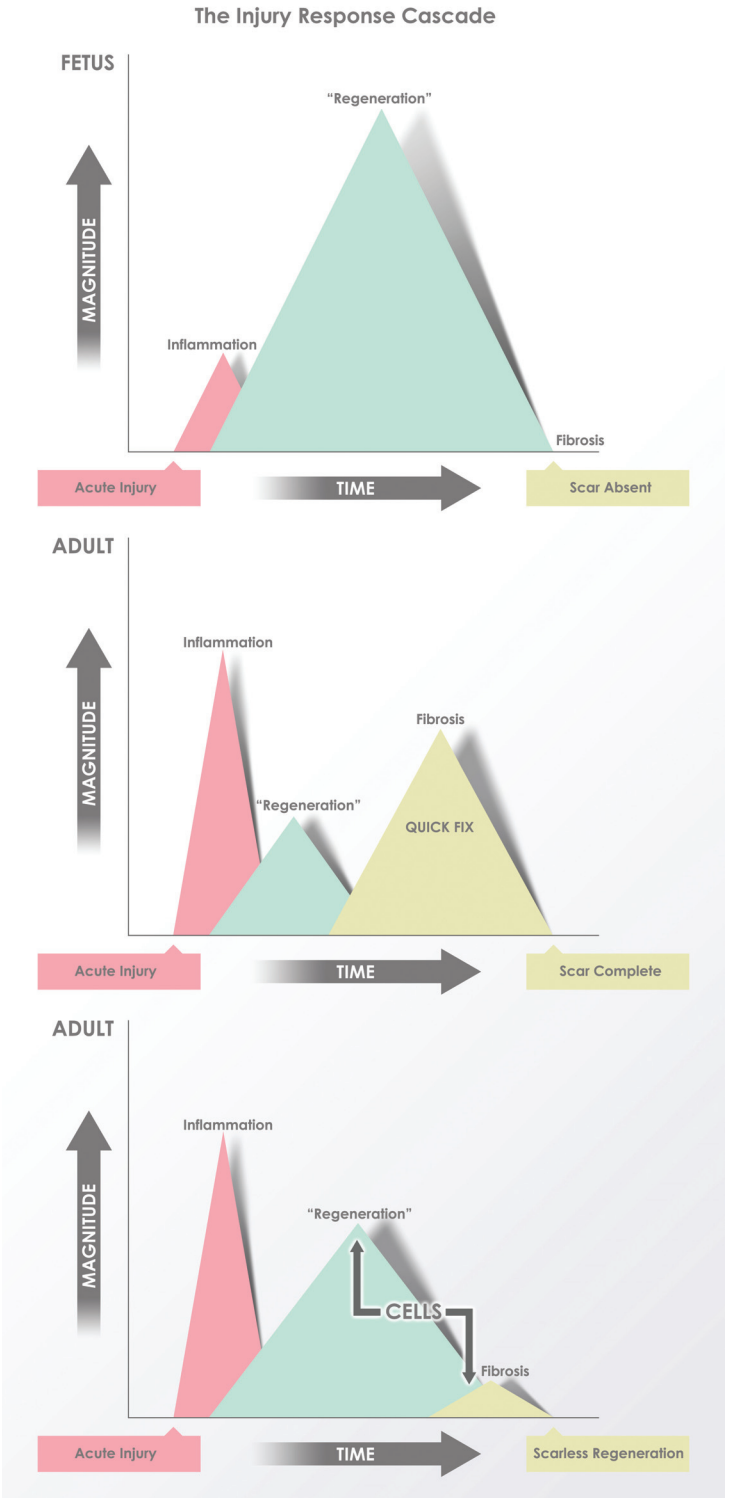
Mesenchymal stem cells work in four main ways. They:

- Control inflammation
- Modulate the immune system
- Stimulate regeneration
- Reduce scarring

MSCs secrete a curtain of bioactive molecules, or trophic factors, that help to dampen inflammation where appropriate. At a site of injury, the cells release trophic factors that tell the immune system to stop overreacting to the injury, which is the immune system's natural response—to get to the site of injury and produce inflammatory molecules to help remove the damage. This inflammatory response often gets out of hand. MSCs don't completely shut down the body's inflammatory response, however. Rather, they shut it down when it appears to be excessive or inappropriate. More accurately, they work to modulate immune response, tuning it to an appropriate level.

MSCs tell the immune system to calm down while also sending the body signals to regenerate healthy tissue and heal. MSCs are masters of producing the right trophic factors at the right time and in the right place so that the body can restore its natural structure and function. As a result, less scar tissue is formed. If you have ever had a scar, you know that it looks and feels different than normal skin. Scars also form inside the body at sites of injury. Scar tissue is fibrotic and can get in the way of the normal functioning of the body. Patients in our clinics and I personally have experienced scar healing unrelated to the condition being treated with MSCs. Recently, a patient being treated for rheumatoid arthritis reported that her permanent makeup tattoos, which are made of scar tissue, disappeared. Similarly, I experienced the complete disappearance of a three-year-old burn scar on my arm after my first MSC injection.

Importantly, the ability of an MSC to regenerate tissue within the body lies not in the cell's capacity to replicate itself and create another cell but, rather, in its stimulatory effect on the body to naturally regenerate its *own*



In a fetus, inflammation in response to injury is minimized while regeneration is maximized. Scar tissue is not formed.[1] In an adult, inflammation in response to injury is heightened, regeneration is stunted, and scar formation is emphasized. MSCs increase the regeneration phase of healing while decreasing inflammation and scar formation. Adapted from correspondence with Dr. Arnold Caplan.

cells. In study after study, MSCs do not become new cells themselves unless manipulated by a human to specifically do so. In fact, Arnold Caplan, considered the father of the MSC because he originally named it *mesenchymal stem cell*,[2] actually wants to rename the MSC as *medicinal signaling cell* because the most important functions of the MSC lie in its secretome, or the totality of secreted bioactive molecules from the cell, rather than in its ability to become another type of tissue.

"MSCs are multifactorial site-specific sensors with genetically wired molecular responses," states Caplan. "MSCs see a signal and they respond in a very controlled way. The management of innate regenerative potential is what they do. The MSC story will change the way medicine is practiced. Management of the patient's innate regenerative resources will be the new treatment."

Interview with Arnold Caplan, PhD, Professor of Biology and Director, Skeletal Research Center at Case Western Reserve University

Neil Riordan: I've known of Dr. Caplan's work for years. He named the mesenchymal stem cell, although he has some thoughts on changing that name. His work, patents, and intellectual property was the basis for the founding of Osiris, the second company in the world that was able to get a cell-based product approved in Canada and New Zealand for the treatment of acute graft-versus-host disease in children. Since then the product has also been approved for use in Japan. Can you talk a little bit about the regulatory landscape, your interpretation of the Japan law, and what that's led to?

Arnold Caplan: Japan passed legislation that simplified the clinical entry of cell-based products for a variety of conditions by requiring corporations or entities to show that the cell-based product was safe and that there was some reason to believe there was efficacy. The legislation allowed that the product could be provisionally approved. Within five years, enough clinical outcome information would be amassed by the company or investigators so that a proper review for efficacy could be entertained by the Japanese regulatory authority. At that time, the company or individual would petition for full approval of the product. If

In fact, MSCs only survive for about four to eight months in the body. They are initially tolerated by the immune system because they lack a molecule that says to the body, "I'm not you." But they eventually start producing that molecule, which triggers the immune system to engulf the cell and gently remove it from the body. This is a key point to their safety and a major differentiator between MSCs and other stem cells, particularly embryonic stem cells. They do not stick around, implanting in the body and growing into other tissue types or tumors.

So when you cut yourself, when you have a heart attack, or when you break your leg, the injury will mobilize these cells to repair it by secreting trophic factors that we also call cell survival molecules. They stimulate the molecules that are already there to repair the tissue. Essentially, MSCs help

there were adverse events, these would be immediately reported to the regulatory agency and the agency could withdraw provisional approval at any time.

This unique and game-changing legislation takes away the need for massive and hugely expensive phase III clinical trials, because provisional approval with paid products allows the company to conduct post-marketing analysis and provide substantial data to prove to the regulators that the product is efficacious. We don't have that provision in the United States and so very costly, time-consuming phase III trials must be entertained by every company. This further keeps these products out of clinical use until there is full approval, which can take two to four years past the phase II clinical trials. Many companies from the United States, Australia, and Europe have either out-licensed to Japanese companies or set up shop in Japan to take advantage of this new legislation. If a product is approved in Japan, it can make approval easier in Europe and the United States.

NR: What is the difference, in number of years and amount of money, between the current model in Japan and that in the United States to get a product moving down the road?

AC: The big difference is in the phase III trial, the submission of appropriate forms, and the deliberation of the FDA. Japan's model can save anywhere from two to five years and many tens of millions of dollars of investment money when compared to the process in the United States. At the time of this interview, there are current proponents of this accelerated pathway in the United States, and attempts by two or three groups to

maintain the status quo in the body. My belief is that the vast majority of chronic diseases are due to a lack or dysfunction of mesenchymal stem cells, and to a lesser degree, other stem cells.

One way in which MSCs stimulate regeneration is via angiogenesis, the process whereby new blood vessels are grown from the existing vascular network. In the case of injured or inflamed tissue, this newly formed blood supply facilitates the delivery of

My belief is that the vast majority of chronic diseases are due to a lack or dysfunction of mesenchymal stem cells, and to a lesser degree, other stem cells.

provide such legislation through Congress. Certainly, in 2017 there will be legislative changes in the United States, but the exact content of those changes on the federal level are completely unknown. Meanwhile, as you well know, there are a number of lobbies attempting to get state legislators to pass laws that would make it easier for patients to get access to cell-based therapies. For example, the governor in California recently signed a bill for patients who are suffering from terminal disease, particularly cancer, on a compassionate use basis. These people can have access to life-saving drugs, even if they're still being tested in clinical trials.

NR: That's a right-to-try law?

AC: Yes, that's the short term for it. It lowers the liability risk considerably for pharmaceutical companies to provide these drugs to patients who are not on their clinical trial protocols.

NR: Switching from politics to science, one of the more compelling sets of slides in your talks is in the injury response cascade (see page 48). I was wondering if you could talk about how MSCs can affect the injury response and how that relates to chronic injuries and chronic inflammation?

AC: It turns out that MSCs exist in the body on every single blood vessel. When a blood vessel is broken, inflamed, or involved in a chronic wound, those perivascular (surrounding a blood vessel) cells come off and differentiate into what I call MSCs. An MSC in this context is a cell that makes drugs or molecules that are specific to the site where the injury has

oxygen, nutrients, and molecules critical for the healing process. Without reestablishment of the blood supply after an injury, healing will not occur.

When you are born, you have a huge number of MSCs, and they are found everywhere in your body. As mentioned in Chapter 4, MSCs exist in dormant form as pericyte cells on capillaries throughout the body. The MSCs on your capillaries are your body's own pharmacy. Capillary density, or the amount of capillaries a person has, decreases as you get older. Therefore, your pharmacy disappears with age. Ask any surgeon if they would rather do surgery on a 24-year-old or an 84-year-old. They will all pick the younger patient. Complete wound healing requires revascularization, which is much easier to achieve with a higher capillary density and the higher number of MSCs housed on those capillaries, as found in younger

occurred. For example, the MSCs in brains of patients with stroke, or in hearts of patients with heart attack, though they're similar, will make different cascades of molecules. These cells naturally function to protect sites of injury from an over-aggressive immune system that is always trying to survey and interrogate injured tissues, looking for invasive components. And so, your natural immune response brings these very aggressive immune cells into the injury field. The MSCs slow them down and tell them to go away because they are not needed. They let the body know that the injury can take care of itself, and that it's not a huge infection.

These MSCs are sentinels for injury. Not only do they put up a local curtain on their front side, which stops these aggressive immune cells, but from the backside, these MSCs also produce molecules that allow the injured tissue to slowly heal without scarring. This is real tissue regeneration—not simply plugging the hole with a scar, but with more tissue, which takes time. The MSCs set up an environment in which real regeneration can take place.

The problem is that, as adults age, we lose blood vessels, and therefore we lose these very important regenerative cells. Very often, we need a booster shot of more MSCs. There are two ways to do that: You can isolate the MSCs from your own body and get them back to the injury site; or you can use cells from someone else. Because of the curtain of molecules produced by the MSCs, which is directed against immune cells, the MSC is sort of hidden from the immune system. Your MSCs in my body would temporarily not be seen by my

individuals. When your capillary density decreases, the MSCs have nowhere to live, so they die. Even by the time you reach skeletal maturity, during the teenage years, 90 percent of your MSC bone marrow reserve, which is utilized for injury, is gone. That means that you are living on that 10 percent for the rest of your life.

Mesenchymal stem cells are intimately involved in the process of new blood vessel growth. The more vasculature or new blood vessel growth, the better the wound will heal and the stronger it will heal. The addition of MSCs along with their secretions to an injured site can speed up the healing. MSCs release secretions that promote angiogenesis, particularly vascular endothelial growth factor (VEGF). Endothelial precursor cells (EPC) and endothelial cells (EC) have CD34 and CD133 markers on their cellular

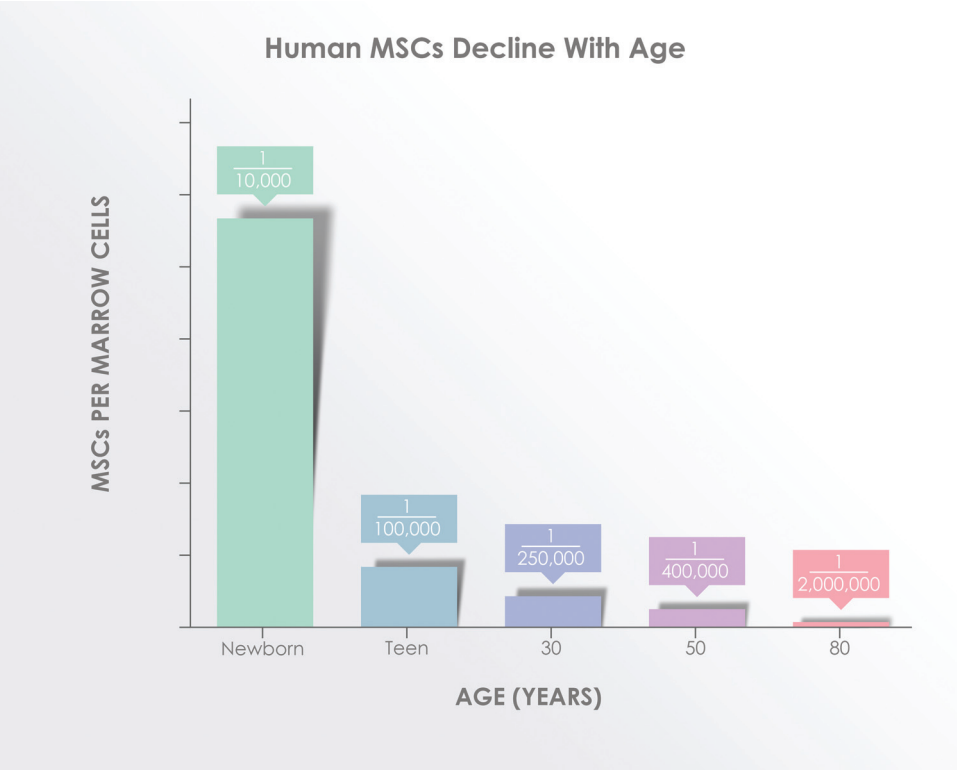
immune system. Some people call this immune-privileged, but that's not the case—the immune system eventually catches up with them. But for the short term, MSCs pour out molecules so the immune system can't see them. In essence, they are camouflaged. We call this immuno-evasion: MSCs evade the immune system.

In older people who don't have enough local MSCs, in particular for heart attack, you can inject MSCs from somebody else into the blood stream. The allogeneic MSCs will dock at the injury site and supplement the local MSCs, producing therapeutic effects. There's a gigantic number of clinical trials now in play using MSCs both from the patient and from an unrelated donor. So umbilical MSCs, which come from discarded tissue, are just as good as your own MSCs. In fact, when they are put in culture and caused to divide, they are actually more plentiful than your own MSCs as an adult.

There are a variety of ways in which you can propagate MSCs and get them to expand, and a variety of ways to get them to sites of injury. Direct to the injury site (e.g. into the knee cavity) is one way; and systemic delivery into the blood stream is another way to introduce MSCs from outside the body. MSCs put up this curtain of molecules, which protects the injured tissue from immune surveillance. In people who have a defective curtain, destruction of tissue by the immune system occurs. We call this autoimmune disease. Multiple sclerosis (MS) is an autoimmune disease in which the immune system attacks nerve coverings, destroying myelin. Therefore, the myelin insulation gets attacked by the immune system, short-circuiting those nerves. That's the basic clinical cause of MS. So even if you give

surface and a receptor for VEGF.[3] When VEGF is present, signals are sent for EPC and EC to move to the area, and to start differentiating into tissue that will construct the new blood vessels.[4]

During treatment with MSCs, angiogenesis in the affected area helps the healing process. A recent review summarizes the substantial evidence of their role in blood vessel formation and their therapeutic effect for many different conditions, particularly for cardiovascular diseases (ischemia, myocardial infarction, etc.), diabetes ulcers, burns, and wound healing.[5]



Adapted from data in Caplan AI. Why are MSCs therapeutic? New data: new insight.J Pathol. 2009;217(2):318-24.

Not only does the number of your MSCs decline with age,[6] but so does their robustness.[7] MSC robustness is determined by a few main factors: the rate at which the cells multiply, or double;[8] the amount of trophic factors they produce; and cell senescence, or deterioration.[9] MSCs in older individuals

do not multiply, or double, as quickly, nor do they produce as many healing trophic factors as do the cells in younger individuals. This explains why umbilical cord MSCs are so potent—they come from a very young, healthy human being. We have found that umbilical cord MSCs are the most potent when compared to bone marrow, fat, and menstrual cell MSCs, all of which we have used and extensively tested.

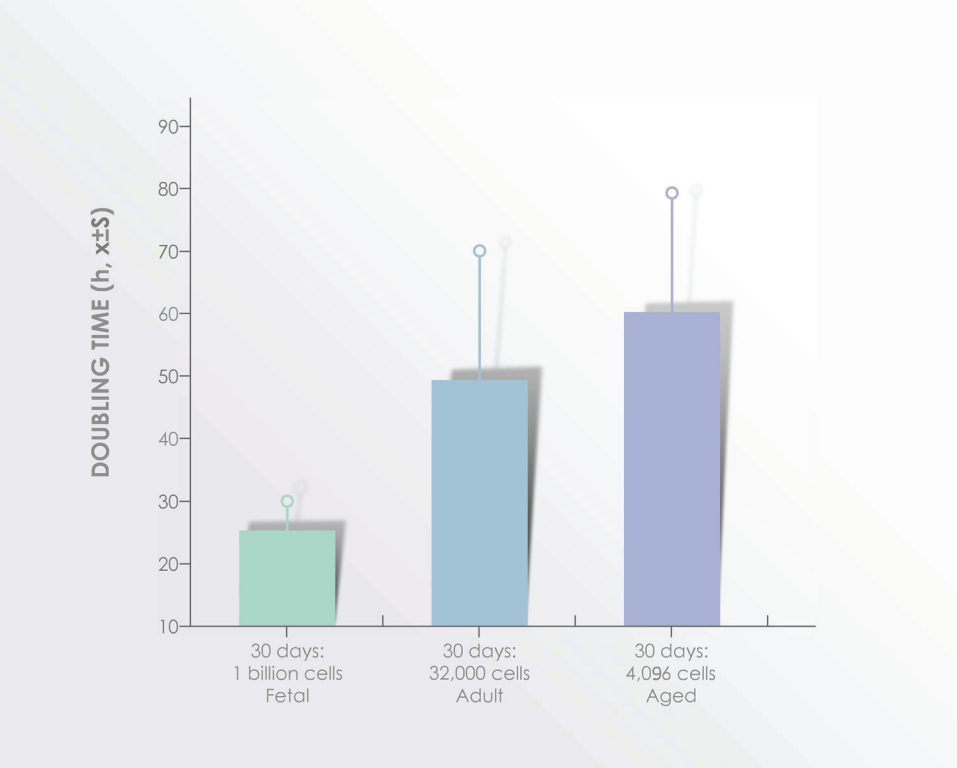
somebody back their own MSCs, they may be defective. In people with autoimmune disease, it is probably better to deliver someone else's MSCs from normal, healthy donors who don't have autoimmune diseases. The choice between autologous (from yourself) versus allogeneic (someone else's) is a medical decision that needs to be made depending on the disease that these cells are introduced for treatment. This is subtlety. There is no question in my mind that some individuals will have MSCs with defects, and that's going to be the reason for certain autoimmune diseases.

NR: In the last couple years, Dr. Sun in Nanjing, China has done a bunch of work on lupus. He has identified the actual defect in the MSCs of people with lupus, and it's led to a lot of clinical trials, one very recently published.

AC: We are going to sponsor an investigator-initiated trial for rheumatoid arthritis (RA), which is quite similar to lupus in lots of ways. But the important aspect of the trial we're going to conduct here in Cleveland, is that we are going to use newly diagnosed rheumatoid patients. The FDA has allowed some companies to conduct clinical trials using MSCs in patients with refractory RA—patients who have tried every standard treatment but still continue to worsen. From our standpoint, a newly diagnosed patient would be perfect because all the downstream horrible effects of RA haven't happened yet. These patients' immune systems are overreacting to certain tissues at joints. We are going to take those allogeneic MSC preparations and optimize the cells for their response to these kinds of inflammatory situations at joints. We've developed an assay for picking a donor who will provide us with MSCs with the maximum response to inflammation, therefore having a better chance of curing the patients of their RA.

NR: That's a great idea. Like a surrogate assay?

AC: It's very simple. We have eight or nine donors from whom we've gotten bone marrow. We've isolated their MSCs and then exposed them to, for example IL-1. We pick a donor who gives us the best muting of that IL-1 response.



How long it takes for MSCs to duplicate in fetal, adult and aged bodies.

Adapted from data in Chang HX, Yang L, Li Z, Chen G, Dai G. Age-related biological characterization of mesenchymal progenitor cells in human articular cartilage. Orthopedics. 2011;34(8):e382-8.

NR: We're doing similar things. We take an immortalized monocyte line, expose it to lipopolysaccharide, co-culture it with the MSCs, and look at their secretions. We look for the maximum suppression of TNF-alpha and IL-6.

AC: Yeah, that's similar to what we are looking at. We've developed another potency assay for the ability of MSCs to make antibiotic proteins, and to optimize the immune system for taking care of massive infections. So for kids with cystic fibrosis, because of the secretion problems they have, they get massive lung infections. We will take kids 18 or older with cystic fibrosis, who have been through every antibiotic known to man to quell their lung infections, and we give them allogeneic MSCs, donor MSCs that have been put in culture with *Pseudomonas* or *Staphylococcus* bacteria. We've identified a donor spectacular in his

The MSCs we use in our Panama clinic have a similar doubling time as the cells from a fetus in the chart above: 20 to 24 hours. In an adult, the cell doubling time is roughly two days. In a 65-year-old, doubling time is only every 60 hours. This may appear to be a linear increase in doubling time, but with synchronous doubling, the difference in the total number of cells produced over time is exponential: in a fetus, 1 billion cells are grown from one cell in 30 days; in an adult, 32,000 cells are created in 30 days; in a 65-year-old, 200 cells are created in 30 days.

Why is cell robustness so important? We have found a high correlation between cell robustness and treatment effect at our clinics over the years. We became very aware of this when we were using MSCs derived from fat tissue. We were the first in the world to use MSCs from fat tissue in human beings, which we administered as stromal vascular fraction (SVF), a portion of fat tissue containing a mixture of pericytes, MSCs, and T-regulatory cells.[10] In a study we did with Indiana University, we found injection of SVF in the vein and joint to be safe and feasible for 13 rheumatoid arthritis patients

killing activity. We look at the immune response and the bacterial carcasses, which cause an endotoxin effect. We want a special macrophage to come in and clean them up. We have a donor who is particularly gifted at producing cells that carry away the carcasses. We want to specifically tune the cells to the disease state we're using them for.

NR: Wow, that's very interesting. It is mind blowing that these cells produce drugs that kill microbes. When was that discovered?

AC: We were partially responsible for discovering that. These molecules are called *defensins*, and they've been studied by dentists for twenty to thirty years. Defensins are naturally secreted in your mouth—it's how you control the bacteria loads that go to your gastrointestinal tract. These molecules have not only been studied as proteins, but their genes have been cloned. It turns out the MSCs have these same sequences in their genome, and if they bump into a bacterium, they produce defensins. If there are no bacteria around, these molecules have no adverse effects on any other cells. As a matter of fact, young women who have monthly bleeds never get sepsis. They have broken blood vessels, and when a pericyte comes off and differentiates into an MSC, if a bacterium is present and bumps into it, goodbye bacterium.

after one-, three-, six-, and 13-month follow-ups.[11,12] In the beginning, some patients did not respond as well to their own fat cell MSCs. When we tested their cells, we learned that their cells had a reduced robustness. There was a high correlation of MSC robustness and treatment effect. After learning this, we tested the robustness of the fat tissue-derived MSCs in all patients. For those patients with lackluster MSC robustness, we augmented their treatment with umbilical cord MSCs. Over time, the production of umbilical cord MSCs became so efficient, and the cell selection process so improved, that we discontinued using patient-derived fat cells altogether. As a result, we are able to treat our patients more efficiently. For example, we treat our multiple sclerosis patients in three days now compared to a two- to four-week treatment in the past.

NR: Can we visit the safety issue of using cells from another person—allogeneic MSCs? You mentioned that there are a lot of trials using allogeneic cells. Many people fear the use of stem cells for the treatment of cancer, because they are afraid of getting non-malignant tumors from MSCs. The fact that allogeneic umbilical cord MSCs have temporary immune privilege worries some people. Can you explain the mechanism by which allogeneic MSCs are allowed to be used clinically? And what is the mechanism in the body from the cells that makes them safe?

AC: These cells have been introduced into 30,000 to 50,000 people worldwide, and we don't know of any adverse events. The fear that these cells will cause cancer is a misnomer, and it's my fault because I named them *mesenchymal stem cells*. Everything I've just said about their abilities has nothing to do with a stem cell. If you have a heart attack, MSCs trigger the body's production of new cells, not new heart muscles. Calling them mesenchymal stem cells is inappropriate for what they do in the body, which is different than what they do in a petri dish. It's correct in that I can make MSCs "dance" on a petri dish, but back in the body they don't do that dance. They make drugs, naturally. I've written a paper to rename them to *medicinal signaling cells*—still *MSCs*. They make medicines that signal the tissue to regenerate itself. In a simplistic sense, they manage the patient's own capacity to regenerate tissues. We are always regenerating tissues, which is one of the most important aspects of life in general. In all of your tissues—every single tissue in your body—cells drop dead and are perfectly replaced. For example, every single second, 15 million blood

cells drop dead and are perfectly replaced. They are perfectly replaced because in your bone marrow is a stem cell that gives its own stem cells. Your liver, heart, kidney, and skin also have their own stem cells. Every single day millions of cells are dropping dead and being replaced. That replacement is how we stay alive. If you can't regenerate that tissue, you won't be around very long.

That, indeed, is what the MSC manages. It manages your innate capacity to regenerate every single tissue of your body where the MSC resides—your liver, your fat, your skin, etc. The important aspect of MSCs put back in the body is to understand that they don't form tissues and so won't form cancers. One of the problems right from the beginning of MSC therapies is that cancers with a solid tumor in your body have what we call leaky blood vessels. If you put an MSC into your body and you already have a tumor growing, it will go to that tumor, see it as injured tissue, and pervert it to get larger. So there are experiments that are now being done where people are putting powerful suicide genes in MSCs and giving them to patients with tumors to trigger the tumor to commit suicide. But by themselves the MSCs will not form tumors. Again, 30,000 to 50,000 patients with no adverse events. When we have given MSCs to a couple million patients, we'll find complications, and we'll deal with them.

An important aspect missing from our regulatory process is transparency. We need a public website to register the clinical conditions of people who are getting MSCs. When they come for regular checkups, their conditions and outcome results can be monitored and put on the website. Those of us who are interested will see any problems immediately and be able to deal with them. To put this into modern context, consider the drug Vioxx, a non-steroidal anti-inflammatory drug that has since been taken off the market because it led to death in people with cardiac problems. If information from those patients had been on a publicly accessible, real-time website, those deaths could have been prevented. We would have ranted and raved to stop the medication from being used in cardiac patients. [The manufacturer] Merck allowed a hundred people to die. Then to save their name, they withdrew the drug from the market, which is itself a crime because it's a useful drug. Transparency in reporting is one of the most important aspects of using new technologies.

MSCs produce these curtains of molecules that mute the response of the immune system, allowing the MSCs to evade the immune surveillance. Therefore, allogeneic MSCs can be used. In the end, this is one of the cheapest ways to provide suitable therapies for a large variety of diseases.

Safety

In May of 2016, the prominent *British Medical Journal* released a study that reported medical error to be the third leading cause of death in the United States.[13] That means you are more likely to die of a medical error made by your doctor or medical practitioner than you are of all but two other conditions—heart disease or cancer.

Before I started to use umbilical cord MSCs, there was only one published trial on their use. I had to have a high degree of comfort that the cells were safe. In addition to the work already done by Arnold Caplan and Osiris, I looked to microchimerism. When a woman has a baby, she will retain cells—some of which are MSCs—from that baby in her body for up

NR: I want to talk to you about vascular density with age. Do you have a reference for vascular density from skeletal maturity to old age? Is there a reference for that?

AC: They're not published, and no one's done a systematic study. It's hugely labor intensive to standardize the histological preparations for you to get quantitative information. But the best data available has to do with skin. If you take a skin biopsy from younger patients, you see variegations at the junction of the dermis and epidermis—they're called *rete ridges*. Underneath the dermis are huge loops of capillaries, which are what make baby skin the softest and most wonderful skin to touch—it's so highly vascularized because of these deep ridges. You can tell the age of somebody by these ridges. If you look at my skin biopsy, I don't have any ridges anymore.

NR: So if you're just looking at the skin, if you start with a baby at 100 in vascular density, at your age it would be what?

AC: I would say I'm at a two.

NR: Essentially, the homes for the MSCs—capillaries—disappear with age, so the MSCs also disappear with age because they die when the blood vessels diminish, is that correct?

AC: Yeah. With these skin biopsies, I can also tell whether a patient has diabetes or not because diabetics have half the blood vessel density of an age-matched control. That's why you see diabetic foot ulcers as such a difficult malady to treat, because their standard blood vessel density is so low.

NR: So they have fewer resources to repair.

AC: Right, so when they get a bleed, the number of MSCs that come in from the surrounding area is likewise diminished.

NR: Could you talk about the vascular density of liver tissue versus other tissues? And why the regenerative capacity of the liver is so good?

AC: The liver is organized like this: Arteries come in, then you have a bunch of liver cells, and then you have drain veins. Around every single arterial capillary in the liver, there are liver stem cells. Those stem cells divide, and their progeny begin differentiating into liver cells. The most differentiated liver cells, the hepatocytes, are sitting next to the vein. If you cut through a piece of liver in the just the right way, you can see the whole differentiation pattern from the stem cell to the most differentiated cell next to the vein. So blood comes in through the artery and gets detoxified as it goes to the vein. All of those cells, from the most primitive, newly differentiated hepatocyte all the way to the most highly differentiated hepatocyte has a certain capacity to detoxify the blood. What's interesting is that, when you cut off a hunk of liver, if you're going to survive, that liver needs lots of arteries and blood vessels. Sitting next to every one of those surviving arteries is a liver stem cell. They divide like wildfire, and they produce in rapid time the newly regenerated liver.

Sitting next to every single liver stem cell is an MSC pericyte, and that pericyte is obligatory for the expansion and differentiation of those liver stem cells. Those cells—the MSC pericytes that are sitting next to those stem cells—have a special name (hepatic stellate cells), have been studied extensively, and are highly unusual perivascular cells.

Every tissue in your body regenerates to some extent. You have a neural stem cell, a cardiac stem cell, a liver stem cell, etc. In all those stem cells there is a universal site that you could describe for every single stem cell, and the way to picture it in your mind is: that stem cell is sitting on top of a blood vessel's vascular endothelial cell. Sitting right next to it is an MSC pericyte. So both the stem cell and the pericyte are in contact with the endothelial cell. That's the universal stem cell niche, whether it's in your brain, your liver, or your heart, there is an MSC pericyte. Therefore, every time one of your tissues gets injured, the MSC pericyte is activated, which then activates the tissue-specific stem cell.

NR: I know there are not complete data on this, but if you look at the spinal cord—the vasculature of the spinal cord itself and the vascular density—there are data showing that the white matter, which is the majority of the cord, has one-fifth the vascular density of the gray matter. What would you think overall is the differential? The cord does have innate regenerative capacity but relative to the liver it is lacking. What would be the percentage?

to 30 years.[14] Those cells are 50 percent genetically distinct from the mother's cells, and yet her immune system allows them to remain. Again, this flies in face of what doctors learn in medical school—that foreign cells cannot remain in the body without the immune system mounting a strong, and sometimes fatal, response. And yet mothers house these foreign cells in their bodies for decades. In one report, a woman with hepatitis who had stopped taking medication despite her doctor's orders actually saw an improvement in her condition. An analysis of her liver cells found that her liver contained 400 male liver cells per square centimeter.[15] This woman was not a twin, had never received a blood transfusion and had therefore no reason to have male

AC: There's no way of doing that, but I would state the following: If you cut somebody's spinal cord and squirted in some MSCs from the outside, one of the things all MSCs do—all of them—is they inhibit scar formation. We know that, even in cut spinal cords, those nerves can regenerate, but they can't regenerate if scar tissue moves across the cut site. So therefore, in animals it's shown that if you cut the spinal cord in half and squirt in MSCs and no scars form, eventually the nerves will regenerate down the tracks that are already there.

It's the same with stroke. The important thing with strokes is you get this big blood clot, and that kills some of the axons, the nerves that are carrying information. If you make sure that no scar forms, those nerves can regenerate down the tracks that are there. That is how you can get coordinate function back—the tracks are still there. That has been shown in animal models and is one of the reasons why MSCs have a chance of being really useful for stroke patients. We normally teach stroke patients how to make new routings for their nerves. If you inhibit scar formation, the normal axons regenerate.

NR: One more question. What do you think of our facilities in Panama?

AC: As I tell people, I've gloved and gowned and gone into the GMP facility, which is as good as any GMP facility that I know in the United States. The fact that you have a way of selecting efficacious cells makes this an unusual facility. My mantra every time I talk to you is the same: publish, publish, publish. Because we need outcome data. That goes for every clinic in the United States and elsewhere.

NR: Our MS study data are complete, and I would love for you to look at it.

AC: Happy to do it.

cells in her liver. Follow-up studies revealed that a probable source for those male liver cells was likely a pregnancy between 17 and 19 years earlier. The male cells were morphologically indistinguishable from the surrounding liver tissue. It is possible that fetal cells that are transferred to the mother have the capacity to differentiate to various tissues and potentially home to a site of injury: once there, they may essentially "blend" with the mother's cells to aid recovery.[16]

It was once thought that mothers have a higher incidence of autoimmune disease, especially systemic sclerosis, but a prospective study in 2004 actually found a reduced risk for systemic sclerosis in women who had been pregnant compared with women who had not.[17] Additionally, a study of women with rheumatoid arthritis, another common autoimmune condition, found no correlation between the risk of developing the disease and whether or not the women had given birth, and how many times.[18] In women who had given birth, there was actually a lower risk of rheumatoid arthritis, such that the researchers concluded, "HLA-disparate fetal microchimerism can persist many years after birth and could confer temporary protection against rheumatoid arthritis." In fact, the life span of mothers increases linearly by about one-third of a year per each additional child up to 14 children,[19] further evidence that microchimerism—or the presence of non-self cells within the body—is not a danger and may even confer a health benefit.

For every stem cell type that we have used in the clinic, I was always patient number one. The first time we used bone marrow MSCs, menstrual blood MSCs, fat-derived MSCs, or umbilical cord MSCs, I was the first patient to undergo treatment. Since patient number one, we have successfully performed over 5,000 treatments for a range of chronic health conditions with no serious adverse events.

When considering the safety of stem cells, tumor growth is a top concern. Because embryonic stem cells, and in some cases fetal stem cells, are potentially tumorigenic, meaning they develop into tumors, regulators tend to be wary of the safety of any stem cells. In order to be approved by the FDA for investigational new drug (IND) use of stem cells for our Duchenne muscular dystrophy patient Ryan Benton, the FDA wanted to

Allogeneic Stem Cell Clinical Trials

Today, there are many clinical trials currently evaluating the use of allogeneic (donor) stem cells for a range of chronic diseases.

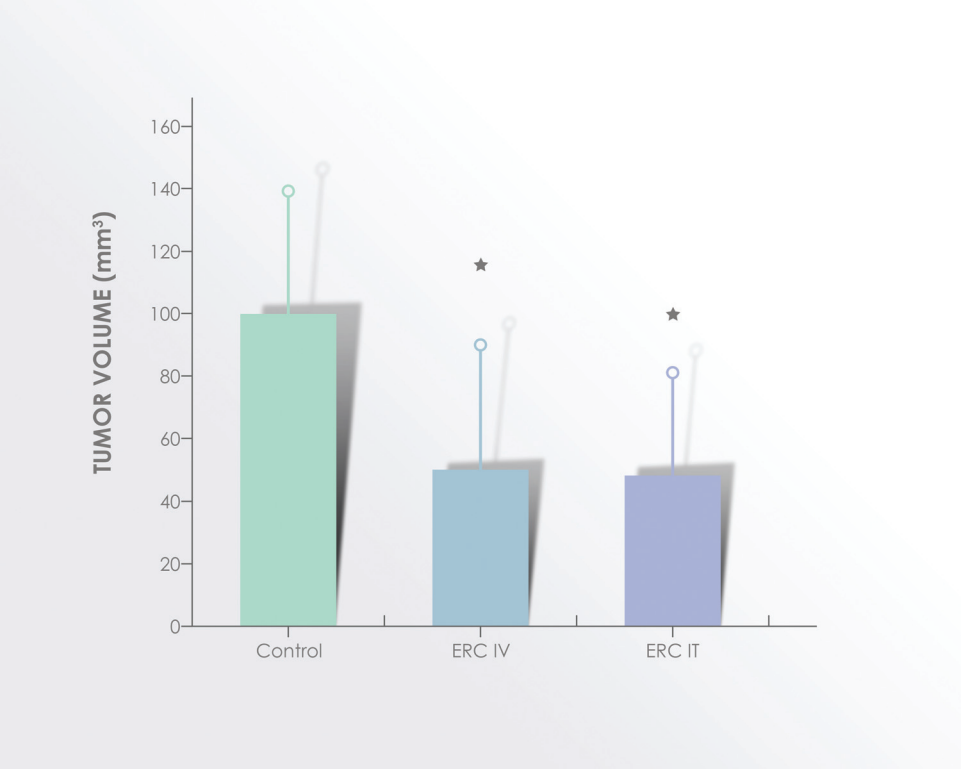
Condition	Number of Clinical Trials
Multiple sclerosis	5
Type I diabetes	10
Lupus	5
Rheumatoid arthritis	4
Sjögren's syndrome	1
Autoimmune hepatitis	1
Crohn's disease	5
Primary biliary cirrhosis	2

In addition to these, we are currently conducting seven National Bioethics Committee-approved clinical trials for multiple sclerosis, rheumatoid arthritis, autism, spinal cord injuries, asthma, and osteoarthritis. We do and have collaborated with doctors and scientists at major universities in the United States, Canada, and Costa Rica including the University of California San Diego, University of Utah, University of Western Ontario, Indiana University, and the University of Costa Rica.

see safety data that our stem cells do not enhance tumor growth. While some studies using MSCs from older donors have been found to enhance tumor growth, the vast majority of studies actually show the opposite—that they kill tumor cells.

We injected MSCs intravenously or intratumorally (into the tumor) into rats with glioma, a brain tumor. By both modes of administration, the tumors shrank by 50 percent, which satisfied the FDA's concerns.[20]

In a second study by researchers at Kansas State University, MSCs were injected either directly into tumors or intravenously. The tumors in both MSC-treated animal groups disappeared and did not reappear.[21]

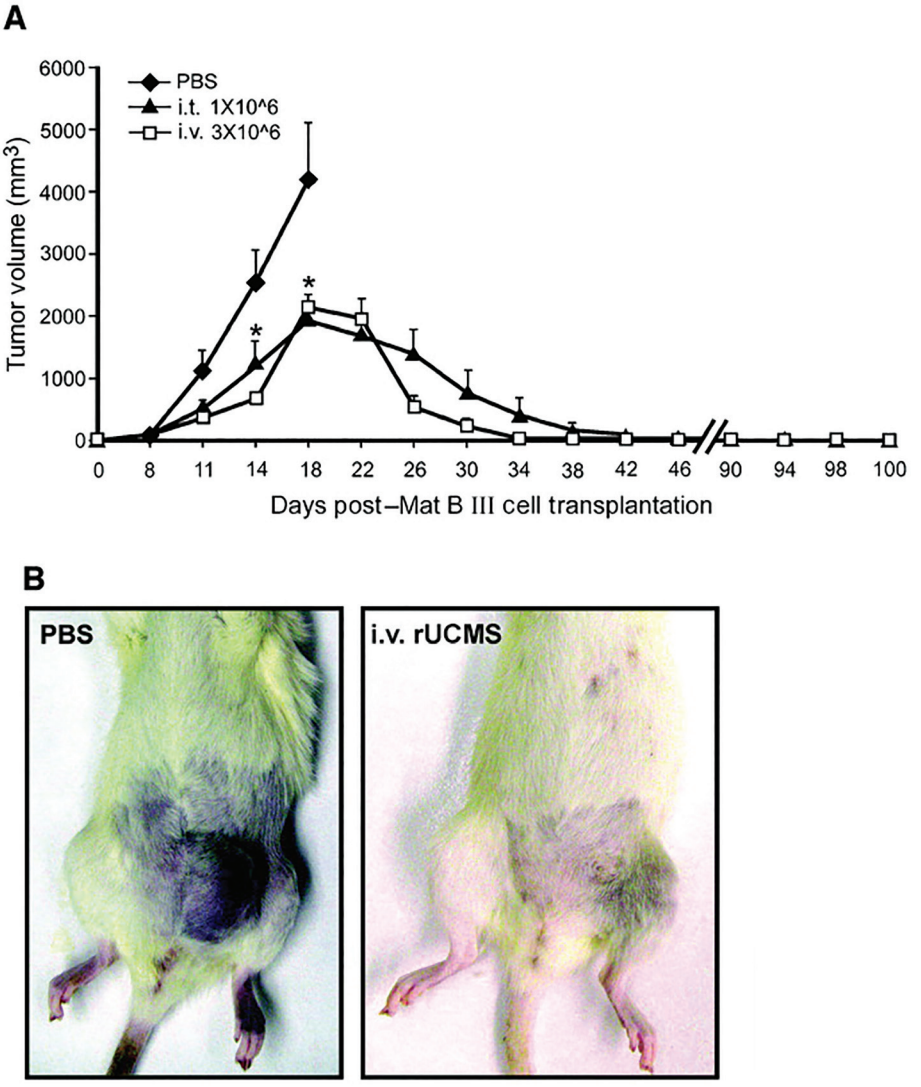


ERCs are mesenchymal-like cells derived from menstrual blood. Tumor cells were implanted into the brains of rats in three groups: 1) the control group (untreated), 2) a group receiving ERC into their veins, and 3) a group receiving ERC into the tumor. The size of the tumor was measured after 14 days.

Adapted from Han X, Riordan N., et al. Inhibition of intracranial glioma growth by endometrial regenerative cells. Cell Cycle. 2009;8(4):606-10.

As I mentioned in Chapter 2, my belief is that most solid tumors are caused by a dysfunction or lack of MSCs—cancer is a last-ditch effort to heal a non-healing wound. Replenishing the body's supply of MSCs has a healing effect and, as these studies show, has beneficial effects on suppression of tumor growth. In some studies complete eradication of all tumors in the body leads to the conclusion that MSCs can either kill directly or induce the death of the cancer stem cells themselves. See Chapter 3 for more about the anti-tumor effects of umbilical MSCs and their cell products.

Rat Umbilical Cord MSCs eliminate tumors with no recurrence.



Cells from the Wharton jelly of rat umbilical cord (rUCMS) completely eliminate the tumors with no recurrence. The curve represents the growth of the tumor with time. Rats received either a placebo solution or rUCMS, representative examples after treatment are shown in the picture.

Reproduced with permission from Ganta C, et al. Rat umbilical cord stem cells completely abolish rat mammary carcinomas with no evidence of metastasis or recurrence 100 days post-tumor cell inoculation.Cancer Res. 2009;69(5):1815-20.

Interview with Robert Hariri, MD, PhD, Co-Founder and President, Human Longevity Cellular Therapeutics, and Founder, Chief Scientific Officer, Celgene Cellular Therapeutics

Neil Riordan: Dr. Hariri, you are one of the true pioneers in cell therapy and a personal hero of mine. I've literally read every word of every patent you've written—and you've written many—in the field of regenerative medicine, in particular for isolating and making drugs out of mesenchymal-like cells from placenta. You founded a company called Anthrogenesis, which you later sold to Celgene and became the CEO of Celgene's Cellular Therapeutics division, correct?

Robert Hariri: That's exactly right Neil. You and I are members of a mutual fan club.

NR: I am interested in your thoughts on the genesis of this research, where we are now, and where you think it's going to go.

RH: You and I have spent the last two decades believing that cellular medicine has the potential to transform how we deliver care for serious and life-threatening diseases. Much of our work has been based on trying to harness the regenerative power of these cells, and directing it to restore functionality in organs and tissues affected by either disease or injury. I think we both can admit that in the past 15 to 20 years, we've learned a tremendous amount. These cells are not simply replacement parts—they are master orchestrators of processes in the organs and tissues that restart functional renovation and regeneration of those tissues.

In 2012 a meta-analysis was conducted that included eight randomized controlled trials of patients receiving MSC treatment for a range of disease conditions.[22] The only adverse reaction the analysis detected was transient fever. They found no evidence of cancer, immune reaction, organ system complications, toxicity, infection, or death. Over 40 studies published on the use of MSCs in a wide range of chronic and acute health conditions have been found to have no serious adverse reactions. In particular, there have been no adverse events reported with the use of umbilical cord MSCs, which

That's an important concept to keep in mind. As our friend and colleague, Arnie Caplan, who is credited with naming the mesenchymal stem cell, initially described these cells for their differentiation behavior, he is now very focused—as are we—on the synthetic and secretory behavior of these cells. That's how we all feel about how these cells exert much of their biological activity. That has been an important evolution in our thinking.

I've personally spent quite a bit of time focused on what I've always felt to be the most reliable, abundant, economical, and scalable resource for deriving these types of cells—that is, the leftovers of birth. As you know, 20 years ago when the world was focused on stem cells derived from embryonic or fetal material, we went and explored the placenta as a source of these cells and found it was an incredibly rich harbor for pluripotent cells and more specialized stem and regenerative populations, which could be recovered in very, very high quantities with very, very high quality, and allowed us to procure under very rigorous control.

As we've all been laboring to turn these living cells into medicines, we have faced the challenge of doing so in a way that meets the high quality standards necessary to satisfy the regulatory and clinical communities, as opinion leaders who are comfortable with delivering therapeutics in the form of discreet chemicals or biologic products.

That said, I think we're on the threshold now of tremendous progress in using these products as therapeutics for two basic reasons: 1) because our understanding has grown

appear to have the highest safety profile among the four most commonly used MSC types: bone marrow, fat tissue, menstrual blood, or umbilical cord. For this reason, umbilical cord MSCs are the primary cells we use in our treatments.

Cell Selection Process

Our laboratory, Medistem Panama, Inc., is the only lab in the Western Hemisphere fully licensed by the government to isolate, manufacture, store, and use for treatment bone marrow, fat, and umbilical cord stem cells. We are licensed by the Panama Ministry of Health. Our 8,000 square foot laboratory utilizes state-of-the-art ISO-certified equipment and follows

so much and we can begin to select clinical indications on the basis of that understanding; and 2) because cellular medicine has developed a fairly extensive clinical safety database. There are literally tens of thousands of recipients of cellular products, and that fundamental safety profile of living stem and progenerative cells administered as therapeutics is giving our colleagues in the regulatory community great comfort in knowing that these products can be deployed with a high level of confidence that they're not going to do any damage. We can begin to focus our lens on what they do beneficially, and begin to make decisions about how to use them, for what indications, at what dose and frequency, etc. I am very optimistic that we're entering into an era of a much more receptive community on the regulatory and clinical side, and we're going to see these products gain ever-increasing numbers of approvals and commercial authorizations so that we can begin to really build a much stronger clinical database to support their use in treating diseases.

NR: What indications has Celgene been pursuing with their cell products?

RH: We first focused on one specific attribute of cells from a placenta, which was linked to a unique biologic property of the organ that we found to be extremely intriguing and important—that's the unique immunobiology of the product. The placenta is very unique in that it's nature's professional allograph, meaning that it's designed to be transplanted across highly discordant HLA barriers without the need to change the immunology of the recipient. The placenta is an allograph that the mother accepts for nine months without

current Good Manufacturing Practices (GMPs), meeting the standards of the best laboratories in the United States.

Over the years of treating patients with chronic diseases, we noticed that certain patients experienced benefits above and beyond those of other patients. Miraculous recoveries were occurring on a regular basis. Other patients were improving after treatment, but the recovery of some patients astonished us. By this time, we had treated enough patients that we could take a good look at the activity of our cells to determine whether some cells were performing better than others.

We retrospectively analyzed cells used in highly successful cases, which we discovered were almost entirely limited to six particular cell lines. We then compared those cells to six cell lines of moderately successful cases

rejecting. That particular unique relationship is even more evident in the case of surrogate pregnancy, whereby a woman carries a totally unrelated fetus and its placenta for nine months without rejecting it. That unique biological and immunological relationship is also conserved in the cells derived from the placenta.

We have treated hundreds of patients with placental cells without matching those cells between recipient and donor, and we've never seen a negative immunologic consequence from doing so. That, in its own right, is suggestive that the placenta has the ability to modulate the immune system of a recipient in a beneficial way. Our early work was to take these cells to treat autoimmune disease, in which an individual's aberrant immune response targets her own tissues. We observed, in clinical conditions, that the placental progenitor and stem cells could downregulate a host's immune system and suppress or control that autoimmune disease and, in some cases, put patients into full remission. That is obviously something we are very excited about and intend to pursue aggressively at Cellularity.

We have treated hundreds of patients with placental cells without matching those cells between recipient and donor, and we've never seen a negative immunologic consequence from doing so.

and six fibroblast cell lines, which have no activity at all. We then screened those cells, using high throughput screening, for the secretion of over 1,100 molecules.

What emerged was a molecular signature that was significantly different in the cells from the six lines given to highly successful cases compared with the other two groups. I call these highly effective cells Riordan Golden Cells.

This screening process took two and a half years because we first grew the cells in two dimensions, or on flat surfaces with the cells multiplying side by side. While this is the industry standard, it's a space- and medium-

NR: Can you talk about Cellularity? You and others are putting together a regenerative medicine company.

RH: For the last 15 years, I have been proud to lead an excellent group at Celgene, but I've always felt that this industry could benefit greatly from a broader, more diversified collaboration across businesses and academic centers whereby we operate from a position of strength—technological strength, intellectual property strength, and clinical development strength—and pool our resources in order to accomplish a great deal more that can be accomplished by an individual entrant into the field. The timing is right for leaders in the field to begin to align and consolidate our efforts in order to deliver these products to the clinical community—to the patients—at a much faster pace. That's been my dream for the last half a decade, and we're making a lot of progress in that direction.

NR: You and I were at a meeting a couple weeks ago and you were talking about the potential for modulating the life span of a mammal with these cells. Can you talk about that?

RH: Years ago our community was paying attention to stem cells in very specific clinical indications. While at Celgene, a leading biopharmaceutical company focused on oncology and hematology, I became interested in observations that the bone marrow, which is one of the body's most abundant reservoirs of stem cells, changes as a consequence of age. I learned, through data shared by Arnie Caplan, that bone marrow, as a source of blood and blood-forming cells, functions less efficiently over time and is less resistant to disease as the total number of stem cells in that tissue decline with age. There is a significant decline in the total number of available stem cells necessary to continually remodel and renovate tissue.

dependent process that we have been working to improve. The cells are anchorage dependent, so they require a huge surface area to grow. We have since grown the cells in bioreactors that allow the cells to multiply in three dimensions, a cutting-edge technology that allows us to grow more cells in less medium, with just the right density. We went through well over one year of screening to ensure that the Riordan Golden Cell molecular signature is preserved in cells grown in three dimensions. It is preserved. In fact, it's even pronounced.

At Human Longevity, the company I founded with Craig Venter and Peter Diamandis, over the last several years we did a comprehensive study in collaboration with Evan Snyder, looking at the change in stem cell compartments in tissues of animals as a function of age. Sure enough, we found these changes weren't limited to bone marrow, but occurred in other tissues. We then, based on the hypothesis that age-related degenerative changes are driven by a loss of the total number and quality of stem cells, attempted to modulate that loss with cells recovered from the placenta over the life span of the subjects; and looked at what that did to the stem cell compartments and, more importantly, to the quality and functionality of the tissues. We found that we could actually restore a more youthful functionality in tissues like muscles by giving back stem cells as these animals aged.

These studies are very supportive of the theory that one way to delay, reverse, or arrest degenerative disease associated with aging is to simply pay attention to the reservoir of stem cells in the tissues necessary to remodel and renovate them. We have at our fingertips a great tool—isolated, expanded cryopreserved stem cells that are coming from this newborn source. I believe this will be a very easy way to help maintain our tissues and organs as we age and potentially offset and reverse degenerative changes that I believe are a consequence of the loss of that regenerative engine. That technology is taking a center stage as we build a focus on placenta to address some of these degenerative diseases. I am very optimistic that we have a reasonable clinical rationale and a strong scientific rationale for using these products that way.

This is the first time in history that anyone has been able to retrospectively analyze which MSCs have more benefit. I like to say that an MSC is not an MSC. They are not all created equal. If you are picking a basketball team, would you want me on your team or LeBron James, possibly the best basketball player of all time? We are both humans, but our abilities on the court are not equal. It's the same with MSCs. Some perform better than others. That's why we've been working to select the best cells for use in patients with chronic disease. Now we can retrospectively analyze existing data of outcomes. We are the only stem cell company with the data to do that.

This new technology allows for us to continue to grow stem cells more efficiently, a crucial factor for the eventual large-scale use of MSCs for patients. With dosage costs of thousands of dollars, MSCs are not yet able

NR: One chapter in this book is about what we call "magic juice," or the secretions of these cells. Can you speak to the non-cellular products made from the expanded postnatal cells, that could be potentially useful?

RH: I've been a big proponent of what you've done. In fact, if you look at some talks I've given, including my TED talk on the role of stem cells and aging, I speak extensively about exactly what you're doing. My work has taught me that a stem cell is really a repository of the most intact, uncorrupted genomic information that we ever have in our lifetime. As our body is exposed to various environmental factors and other injurious stimuli, the DNA in our stem cell populations become, in many cases, subtly damaged and corrupted. The net result of that corruption in the software of our cells is that the synthetic repertoires of our cells are capable of generating a slow decline in quality or quantity.

> ***The healthier and more intact the stem cell population you have, and the healthier and more normal the extracellular secreted product concentrations are, the more likely you are to maintain a healthy, youthful phenotype.***

I speak about the fact that aging echoes stem cell depreciation and accumulation of these subtle genomic problems that lead to an even more limited synthetic repertoire that I believe is essential to health and a youthful phenotype. It's clear to me that when you have cells from a youthful source—from newborn placental material—under cultivation conditions that produce and secrete factors into the supernate, as they would in the serum or the extracellular milieu, those factors are vitally important to cells that constitute the main structural and biological component of our organs and tissues.

to serve the large number of patients who need such treatment. We are the first stem cell manufacturer to grow these cells in three dimensions and are making major strides toward eventually reaching a wider population.

If we can replace those factors, which become deficient as we age, we can get many of the same biological benefits that we can by restoring the quality of those stem cell reservoirs. I believe the two clinical approaches are perfectly married: one is delivering very specific products in the form of soluble factors to patients; and the other is delivering specific living cells that take up residence either permanently or transiently, delivering factors that are lost or diminished in quantity in the aging individual.

The healthier and more intact the stem cell population you have, and the healthier and more normal the extracellular secreted product concentrations are, the more likely you are to maintain a healthy, youthful phenotype.

NR: Because of the embryonic world, and embryonic stem cells producing cancer, can you speak to the safety vis-à-vis the cancer perception with postnatal MSCs?

RH: Absolutely. Over the last twenty years we have recognized that the stem cells derived from healthy adult bone marrow or from healthy newborns can be delivered to recipients with essentially no significant risk of any adverse effects. These cells are incredibly stable, do not behave in an aberrant way, take up temporary residence in many cases, respond to local signaling, and secrete factors and products that have a selective advantage to the recipient.

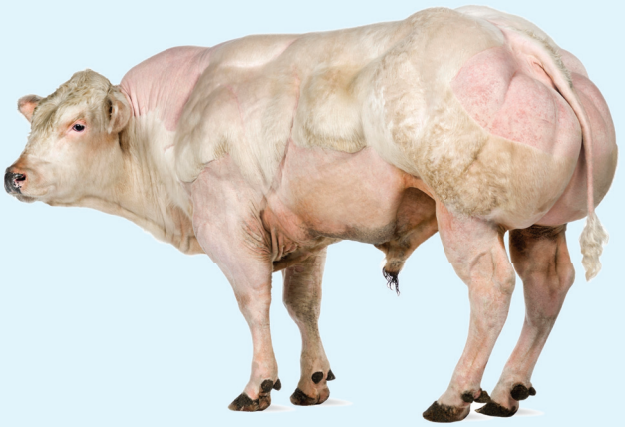
I believe that some of the work done by our colleagues who are treating inherited metabolic disorders is, in essence, replacing a defective biological software system with one that can produce and secrete the appropriate factors, which can restore health or reverse or alter the natural history of a disease. That, to me, is very clear evidence that these products behave in an adaptive way to the environment they find themselves in, and they don't behave in an aberrant manner that puts the recipient at risk.

NR: Anything you want to close with?

RH: I am thrilled to be working with you in any way, shape, or form, and I believe our industry can really benefit from all of us finding pathways forward to meet the high standards that we want for these products, and from continually evaluating the combination of our clinical experience with the data so that it grows in size and quality. We are finally on the threshold of the decade of cellular medicine. I am happy to be working on it with you and our other colleagues.

Follistatin—Repair and Rebuild

One of the molecules secreted in higher amounts by the Riordan Golden Cells is the molecule follistatin. Follistatin is involved in tissue repair and rebuilding and is known to have anti-inflammatory effects. It is currently being investigated for its muscle growth ability. Follistatin is a natural inhibitor of myostatin, which inhibits muscle growth. The Blue Belgian Bull, bred to have decreased levels of myostatin, provides a visual for how the suppression of myostatin can increase muscle growth to impressive levels.



Licensed from Gettyimages by NH Riordan.

Now that our laboratory has established what makes an MSC a Riordan Golden Cell, we test the cells we receive to ensure that we only use those cells with the best molecular signature. Out of 100 umbilical cords that we receive, we now only use cells from fewer than ten.

Patient Selection Process

At the Stem Cell Institute we treat a handful of conditions for which we have developed institutional review board (IRB)-approved clinical protocols that are carefully followed. These conditions include rheumatoid arthritis, osteoarthritis, degenerative joint disease, multiple sclerosis, spinal cord injury, autism, cerebral palsy, and heart failure. We often receive requests

to treat people with conditions that we are not currently taking patients for. These include amyotrophic lateral sclerosis (ALS), Alzheimer's, Duchenne muscular dystrophy, Parkinson's, and stroke. While we do believe that stem cells offer hope for a wide range of chronic diseases, offering stem cell treatment for any and all patients with simply the means to pay for it is not our practice. We are involved in cutting-edge medicine and are avidly collecting data so that we can continue to apply this treatment to the appropriate conditions and patients.

Our patient selection process involves a thorough review of medical history and a strict selection process so that we can be sure our patients get the most out of their treatment. For example, we generally treat only secondary progressive and relapsing remitting multiple sclerosis; spinal cord injury patients who were injured within the last ten years (the more recent, the better) and who are medically stable; autism and cerebral palsy patients under the age of 18; and heart failure patients with an ejection fraction of 10 or higher. Patients must be cancer free for at least five years and cannot have an active infection or open wounds. These criteria help us to identify the patients who will most benefit from treatment.

Chapter Five

[1] Stelnicki EJ, Chin GS, Gittes GK, Longaker MT. Fetal wound repair: where do we go from here? Semin Pediatr Surg. 1999;8(3):124-30.

[2] Caplan AI. Mesenchymal stem cells. J Orthop Res. 1991 Sep;9(5):641-50.

[3] Hristov M, Erl W, Weber PC. Endothelial progenitor cells: mobilization, differentiation, and homing. Arterioscler Thromb Vasc Biol. 2003;23(7):1185-9.

[4] Urbich C, Dimmeler S. Endothelial progenitor cells: characterization and role in vascular biology. Circ Res. 2004;95:343-353.

[5] Watt SM, Gullo F, van der Garde M, et al. The angiogenic properties of mesenchymal stem/stromal cells and their therapeutic potential. Br Med Bull. 2013;108:25-53. doi: 10.1093/bmb/ldt031.

[6] Caplan AI. Why are MSCs therapeutic? New data: new insight. J Pathol. 2009;217(2):318-24. doi: 10.1002/path.2469.

[7] Alt EU, Senst C, Murthy SN, et al. Aging alters tissue resident mesenchymal stem cell properties. Stem Cell Res. 2012 Mar;8(2):215-25. doi: 10.1016/j.scr.2011.11.002.

[8] Chang HX, Yang L, Li Z, Chen G, Dai G. Age-related biological characterization of mesenchymal progenitor cells in human articular cartilage. Orthopedics. 2011;34(8):e382-8. doi: 10.3928/01477447-20110627-06.

[9] Stolzing A, Jones E, McGonagle D, Scutt A. Age-related changes in human bone marrow-derived mesenchymal stem cells: consequences for cell therapies. Mech Ageing Dev. 2008;129(3):163-73. doi: 10.1016/j.mad.2007.12.002.

[10] Riordan NH, Ichim TE, Min WP, et al. Non-expanded adipose stromal vascular fraction cell therapy for multiple sclerosis. J Transl Med. 2009;7:29. doi: 10.1186/1479-5876-7-29.

[11] Rodriguez JP, Murphy MP, Hong S, et al. Autologous stromal vascular fraction therapy for rheumatoid arthritis: rationale and clinical safety. Int Arch Med. 2012;5:5. doi: 10.1186/1755-7682-5-5.

[12] 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.

[13] Makary MA and Daniel M. Medical error—the third leading cause of death in the US. BMJ. 2016;353:i2139. doi: 10.1136/bmj.i2139.

[14] O'Donoghue K, Chan J, de la Fuente J, et al. Microchimerism in female bone marrow and bone decades after fetal mesenchymal stem-cell trafficking in pregnancy. Lancet. 2004;364(9429):179-82.

[15] Johnson, KL, Samura O, Nelson JL, McDonnel M d WM, Bianchi DW. Significant fetal cell microchimerism in a nontransfused woman with hepatitis C: Evidence of long-term survival and expansion. Hepatology. 2002 Nov;36(5):1295-7.

[16] Khosrotehrani K and Bianchi DW. Multi-lineage potential of fetal cells in maternal tissue: a legacy in reverse. J Cell Sci. 2005 15;118(Pt 8):1559-63.

[17] Turco AE, Bambara LM. Pregnancy, microchimerism and autoimmunity: an update. Lupus. 2004;13(9):659-60.

[18] Guthrie KA, Dugowson CE, Voigt LF, Koepsell TD, Nelson JL. Does pregnancy provide vaccine-like protection against rheumatoid arthritis? Arthritis Rheum. 2010;62(7):1842-8. doi: 10.1002/art.27459.

[19] McArdle PF, Pollin TI, O'Connell JR, et al. Does having children extend life span? A genealogical study of parity and longevity in the Amish. J Gerontol A Biol Sci Med Sci. 2006;61(2):190-5.

[20] Han X, Meng X, Yin Z, et al. Inhibition of intracranial glioma growth by endometrial regenerative cells. Cell Cycle. 2009;8(4):606-10.

[21] Ganta C, Chiyo D, Ayuzawa R, et al. Rat umbilical cord stem cells completely abolish rat mammary carcinomas with no evidence of metastasis or recurrence 100 days post-tumor cell inoculation. Cancer Res. 2009;69(5):1815-20. doi: 10.1158/0008-5472.CAN-08-2750.

[22] Lalu MM, McIntyre L, Pugliese C, et al. Safety of cell therapy with mesenchymal stromal cells (SafeCell): a systematic review and meta-analysis of clinical trials. PLoS One. 2012;7(10):e47559. doi: 10.1371/journal.pone.0047559.

Chapter Six

1. Grayson J. Microcirculation: Blood-vessel interactions systems in special tissues 1. Oxygen Supply to the Spinal Cord and Its Autoregulation. Erdmann W et al. Springer Science & Business Media; 2012;13.5
2. Purves MJ. The physiology of the cerebral circulation. CUP Archive; May 25, 1972.
3. Fausto N, Campbell JS, Riehle KJ. Liver regeneration. Hepatology. 2006 Feb;43(2 Suppl 1): S45-53.
4. Michalopoulos GK. Liver regeneration: alternative epithelial pathways. Int J Biochem Cell Biol. 2011 Feb;43(2):173-9. doi: 10.1016/j.biocel.2009.09.014.
5. Thron AK. Vascular anatomy of the spinal cord: Radioanatomy as the key to diagnosis and treatment. Springer;2016.
6. Hagg T, Oudega M. Degenerative and spontaneous regenerative processes after spinal cord injury. Journal of neurotrauma. 2006;23(3-4):264-280.
7. Simpson LA, Eng JJ, Hsieh JT, et al. Spinal Cord Injury Rehabilitation Evidence Scire Research T. The health and life priorities of individuals with spinal cord injury: a systematic review. JNeurotrauma. 2012;29(8):1548-1555.
8. Kang KS, Kim SW, Oh YH, et al. A 37-year-old spinal cord-injured female patient, transplanted of multipotent stem cells from human UC blood, with improved sensory perception and mobility, both functionally and morphologically: a case study. Cytotherapy. 2005;7(4):368–373
9. Li HJ, Liu HY, Zhao ZM, et al. [Transplantation of human umbilical cord stem cells improves neurological function recovery after spinal cord injury in rats]. Zhongguo Yixue Kexueyuan Xuebao. Acta Academiae Medicinae Sinicae. 2004;26(1):38–42.
10. Zhao ZM, Li HJ, Liu HY, et al. Intraspinal transplantation of CD34+ human umbilical cord blood cells after spinal cord hemisection injury improves functional recovery in adult rats. Cell Transplant. 2004;13(2):113-22.
11. Nishio Y, Koda M, Kamada T, et al. The use of hemopoietic stem cells derived from human umbilical cord blood to promote restoration of spinal cord tissue and recovery of hindlimb function in adult rats. Journal of neurosurgery. J Neurosurg Spine. 2006 Nov;5(5):424-33.
12. Cízková D, Rosocha J, Vanický I, Jergová S, Cízek M. Transplants of human mesenchymal stem cells improve functional recovery after spinal cord injury in the rat. Cell Mol Neurobiol. 2006 Oct-Nov;26(7-8):1167-80.
13. Saito F, Nakatani T, Iwase M, et al. Spinal cord injury treatment with intrathecal autologous bone marrow stromal cell transplantation: the first clinical trial case report. J Trauma. 2008 Jan;64(1):53-9. doi: 10.1097/TA.0b013e31815b847d.

Take the first step. It's time to stop feeling powerless and embrace the opportunity to potentially change your life.

Apply Today!

https://www.cellmedicine.com/treatment-application