IN THE DISTRICT COURT OF DOUGLAS COUNTY, NEBRASKA

STATE OF NEBRASKA, ex rel. DOUGLAS J. PETERSON, ATTORNEY GENERAL, Plaintiff, **v.** **OMAHA STEM CELLS, LLC, a corporation,** **REGENERATIVE MEDICINE AND ANTI-AGING INSTITUTES OF OMAHA, LLC, a corporation,** **STEM CELL CENTERS, LLC, a/k/a STEM CELL CENTERS OF ALASKA, LLC, a corporation,** **TRAVIS AUTOR, individually, and** **EMILY AUTOR, individually.** Defendants.	CI 20-_____ **COMPLAINT**

COMES NOW the State of Nebraska, by and through its Attorney General, Douglas J. Peterson, and Assistant Attorneys General Shereece Dendy-Sanders and Meghan Stoppel (hereinafter collectively referred to as, "the State of Nebraska"), and brings this action against Defendants Omaha Stem Cells, LLC, Regenerative Medicine and Anti-Aging Institutes of Omaha, LLC, Stem Cell Centers, LLC a/k/a Stem Cell Centers of Alaska, LLC, Travis Autor and Emily Autor ("Defendants") to obtain injunctive relief, the refund of monies paid, civil penalties, and

other equitable relief for Defendants' violations of the Consumer Protection Act, Neb. Rev. Stat. § 59-1601 et seq. ("CPA") and the Uniform Deceptive Trade Practices Act, Neb. Rev. Stat. § 87-301 et seq. ("UDTPA"), in connection with the advertising, marketing, distribution, and sale of stem cell products, treatments and services, including but not limited to, exosomes injections (hereinafter "stem cell therapy") to treat, cure, and mitigate various diseases and health conditions.

INTRODUCTION

1. The Nebraska Attorney General is responsible for enforcement of the CPA, UDTPA, and other state and federal laws that affect Nebraska consumers. Pursuant to Neb. Rev. Stat. § 59-1608, the Attorney General may bring an action in the name of the State against any person to restrain and prevent the doing of any act prohibited by the CPA.

2. In addition, pursuant to Neb. Rev. Stat. § 87-303.05, the Attorney General may apply for and obtain, in an action in any district court of Nebraska, a temporary restraining order, or injunction, or both, prohibiting a person from engaging in deceptive trade practices or doing any act in furtherance thereof.

3. The Attorney General has cause to believe that Defendants have violated the CPA and the UDTPA and brings this action in the public interest because Defendants have deceived, misled, and caused financial harm to hundreds of consumers from Nebraska and other states.

PARTIES

4. Plaintiff is the State of Nebraska, ex rel. Nebraska Attorney General Douglas J. Peterson. Pursuant to the CPA and UDTPA, the Attorney General may initiate civil law enforcement proceedings in the name of the State to enjoin violations of the CPA and UDTPA and secure such equitable and other relief as may be appropriate in each case.

5. Defendant Omaha Stem Cells, LLC ("OSC") d/b/a Stem Cell Centers is a Nebraska

corporation with its principal place of business at 9839 South 168th Avenue, Suite 2E, Omaha, NE 68136. OSC transacts or has transacted business in this state. At all times material to this Complaint, acting alone or in concert with others, OSC has advertised, marketed, or sold stem cell therapy to treat, cure, and mitigate various diseases and health conditions to consumers throughout Nebraska and other states. Defendant OSC was administratively dissolved by the Nebraska Secretary of State on June 29, 2019.

6. Defendant Regenerative Medicine and Anti-Aging Institutes of Omaha, LLC ("RMAAI") a/k/a Stem Cell Centers is a Nebraska corporation with its principal place of business at 9839 South 168th Avenue, Suite 2E, Omaha, NE 68136. Defendant RMAAI is a successor in interest to Defendant OSC and assumed the operations of OSC upon OSC's dissolution. Defendant RMAAI transacts or has transacted business in this state. At all times material to this Complaint, acting alone or in concert with others, Defendant RMAAI has advertised, marketed, or sold stem cell therapy to treat, cure, and mitigate various diseases and health conditions to consumers throughout Nebraska and other states.

7. Defendant Stem Cell Centers, LLC a/k/a Stem Cell Centers of Alaska, LLC ("SCC") is an Alaska corporation with its principal place of business at 1231 West Northern Lights Boulevard, # 911, Anchorage, AK 99503. Defendant SCC transacts or has transacted business in Nebraska and is the sole member of Defendant RMAAI and Defendant OSC. At all times material to this Complaint, acting alone or in concert with others, Defendant SCC has advertised, marketed, or sold stem cell therapy to treat, cure, and mitigate various diseases and health conditions to consumers throughout Nebraska and other states.

8. Defendant Travis Autor f/k/a Travis Broughton is a principal and owner of OSC, RMAAI, and SCC. At all times material to this Complaint, acting alone or in concert with others, Defendant

Travis Autor was responsible for directing and controlling the operations of OSC, RMAAI and SCC, including the representations made in the advertising, marketing, and sale of stem cell therapy to treat, cure, and mitigate various diseases and health conditions to consumers throughout Nebraska and other states.

9. Defendant Emily Autor is a principal and owner of OSC, RMAAI, and SCC and is married to Defendant Travis Autor. At all times material to this Complaint, acting alone or in concert with others, Defendant Emily Autor was responsible for directing and controlling the operations of OSC, RMAAI and SCC, including the representations made in the advertising, marketing, and sale of stem cell therapy to treat, cure, and mitigate various diseases and health conditions to consumers throughout Nebraska and other states.

10. Defendants OSC, RMAAI, SCC (collectively "the Corporate Defendants") and Defendants Travis and Emily Autor have operated as a common enterprise while engaging in the deceptive acts and practices alleged below. The Defendants have conducted the business practices described below, with a common pecuniary interest, through interrelated companies that have common ownership, officers, managers, business functions, employees, and office locations. Because these Defendants have operated as a common enterprise, each of them is jointly and severally liable for the acts and practices alleged below.

JURISDICTION AND VENUE

11. The District Court of Douglas County has jurisdiction over Defendants and the subject matter of this action pursuant to Neb. Rev. Stat. § 59-1608 and Neb. Rev. Stat. § 87-303.05(1) because Defendants have transacted business within the State of Nebraska at all times relevant to this Complaint.

12. Venue for this action properly lies in the District Court of Douglas County pursuant to Neb. Rev. Stat. § 59-1608.01 and Neb. Rev. Stat. § 87-303.05(1) because Defendants have transacted business in Douglas County, Nebraska.

BACKGROUND ON STEM CELLS

13. In the United States, the Food and Drug Administration ("FDA") "has the authority to regulate stem cell products."[1]

14. Stem cells are "the cells that develop into blood, brain, bones, and all of the body's organs."[2]

15. According to the FDA, stem cells "have the potential to repair, restore, replace and regenerate cells," and in the future "could *possibly* be used to treat many medical conditions and diseases."[3]

16. However, stem cell use for most medical conditions remains unproven and, therefore, unapproved by the FDA with few exceptions.

17. Currently, the only stem cell-based products approved by the FDA "consist of blood-forming stem cells (hematopoietic progenitor cells) derived from cord blood."[4]

18. The FDA has approved these products only for "limited use in patients with disorders that affect the body system that is involved in the production of blood (called the 'hematopoietic' system)."[5]

19. According to the FDA, the unapproved use of stem cell treatments can be "particularly unsafe,"[6] and may lead to adverse reactions, such as cells changing into inappropriate cell types

[1] FDA Warns About Stem Cell Therapies," https://www.fda.gov/consumers/consumer-updates/fda-warns-about-stem-cell-therapies, last visited April 22, 2020, attached hereto as Exhibit A.
[2] *Id*.
[3] *Id* (Emphasis in original).
[4] *Id*.
[5] *Id*.
[6] *Id*.

or multiplying, the failure of cells to function as expected, and tumor growth.

20. As noted by former FDA Commissioner Scott Gottlieb in November 2017:

> "[T]he rapid growth and promise of this field has increasingly sowed the ground for the entry of some unscrupulous actors, who have opportunistically seized on the clinical potential of regenerative medicine to make deceptive claims to patients about unproven and, in some cases, dangerous products."[7]

21. "The Food and Drug Administration (FDA) [has] inform[ed] the public, especially patients, health care practitioners, and clinics, of multiple recent reports of serious adverse events experienced by patients in Nebraska who were treated with unapproved [stem cell] products marketed as containing exosomes."[8]

DEFENDANTS' BUSINESS ACTIVITIES

22. Defendants Travis and Emily Autor (collectively "the Individual Defendants") operate a network of limited liability companies across the country that advertise and ultimately sell stem cell therapy directly to consumers.

23. In addition to the Corporate Defendants named herein, the Individual Defendants are associated with the following corporations, many of which bear similar names to the Defendants named herein:

a. Stem Cell Centers Montana, LLC d/b/a Regenerative Medicine and Anti-Aging Institutes of Montana is a Montana corporation with its principal place of business at 711 North Garry Drive, Liberty Lake, Washington;

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[7] "Statement from FDA Commissioner Scott Gottlieb, M.D. on FDA's Comprehensive New Policy Approach to Facilitating the Development of Innovative Regenerative Medicine Products to Improve Human Health," https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-fdas-comprehensive-new-policy-approach-facilitating, last visited April 22, 2020, attached hereto as Exhibit B.

[8] Public Safety Notification on Exosome Products," https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/public-safety-notification-exosome-products, last visited April 15, 2020, attached hereto as Exhibit C.

b. Stem Cell Centers of Vermont, LLC is a Vermont corporation with its principal place of business at 145 Pine Haven Shores, STE 1000A, Shelburne, Vermont;

c. Stem Cell Centers of Virginia, LLC is a Virginia corporation with its principal place of business at 711 North Garry Drive, Liberty Lake, Washington;

d. Stem Cell Centers, LLC is a Washington corporation with its principal place of business at 711 North Garry Drive, Liberty Lake, Washington;

e. Arizona Health Clinics is an Arizona corporation with its principal place of business at 10084 Terrastone Drive, Las Vegas, Nevada;

f. Stem Cell Centers, LLC d/b/a NW Regenerative Medicine and Anti-Aging Institutes of Post Falls is an Idaho corporation with its principal place of business at 4751 West Selway Avenue, Post Falls, Idaho; and

g. Stem Cell Centers of Florida, LLC is a Florida corporation with its principal place of business at 3030 N. Rocky Point Drive, Ste. 150A, Tampa, Florida.

24. Since at least April 2018, Defendants have advertised, offered for sale, sold, and distributed stem cell therapy using stem cells derived from amniotic fluid, Wharton's Jelly, cord blood, bone marrow, exosomes, and platelet-rich plasma therapy (PRP) in Nebraska and to Nebraska consumers.

25. Defendants administer stem cell therapy through a variety of procedures including, but not limited to, injection, intravenous administration, and/or through inhalation using a nebulizer.

26. At all times relevant to this Complaint, Defendants purchased stem cell products, including its exosome products, from EuCyt Laboratories LLC in Las Vegas, Nevada.

27. Exosomes are extracellular vesicles released from cell.[9]

28. "[…] exosomes used to treat diseases and conditions in humans are regulated as drugs and biological products under the Public Health Service Act and the Federal Food Drug and Cosmetic Act and are subject to premarket review and approval requirements."[10]

29. Similar to most stem cell products, "there are currently no FDA-approved exosome products."[11]

30. On June 4 2020, EuCyt Laboratories received a Warning Letter from the FDA pertaining to an inspection of EuCyt's facilities initiated by FDA in November 2019. In its letter, the FDA confirms that it issued its Public Safety Notification on Exosome Products (see Exhibit C) "following multiple reports of serious adverse events experienced by patients who were treated with XOsomes™ [exosome product]."[12]

31. Based on invoices provided by Defendants, Defendants spent hundreds of thousands of dollars purchasing stem cell therapy related products, including but not limited to, Wharton's Jelly and XOsomes™ from EuCyt between May 2018 and September 2019.

32. Defendants have advertised, and continue to advertise, their stem cell therapy through newspapers, direct mailings, and social media. Examples of Defendants' promotional materials are referenced below as Figures 1, 2 and 3, and attached hereto as Exhibits F, G and H, respectively.

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[9]Edgar, James R., *Q&A: What are exosomes, exactly?*. 14 BMC Biology 46, (June 13, 2016). https://doi.org/10.1186/s12915-016-0268-z, attached hereto as Exhibit D.

[10] Public Safety Notification on Exosome Products," https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/public-safety-notification-exosome-products, last visited April 15, 2020, attached hereto as Exhibit C.

[11] *Id*.

[12] Warning Letter from Karlton T. Watson, Program Division Director, FDA, to Travis H. Bird, CEO, EuCyt Laboratories, LLC, 2 (Jun. 4, 2020). https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/EuCyt-laboratories-llc-607182-06042020, attached hereto as Exhibit E.

FIGURE 1:

ISN'T IT TIME YOU FOUND A REAL SOLUTION FOR YOUR PAIN?

Joint & Back Pain • Neuropathy • COPD • Anti-Aging

Are you still suffering from joint pain or other debilitating medical condition? You are not alone! Millions of Americans just like you are still suffering because the current healthcare system hasn't provided viable solutions. Prescription opioids, pain pills or risky surgery may only mask symptoms without providing potential real solutions.

If you or a family member is still suffering from one of the conditions, this revolutionary treatment may be a life-changing solution for you!

There is a revolutionary new way!
Enjoy a complimentary dinner while you learn more about these new treatment options at our upcoming free educational seminar:
"Stem Cell Therapy: A New Path to a Better Quality of Life"

What is Stem Cell Therapy?
Regenerative medicine is the practice of using the body's fundamental natural systems for repair and healing. Stem cells are the body's essential regenerative building blocks of life. They divide, multiply, renew and regenerate – all of which can potentially help heal and repair damaged tissue throughout your body. Treating the root cause of your condition in this way can reduce pain and inflammation, which could provide you with a higher quality of life.

In fact, according to a recent U.S. Government Accountability Office (GAO) report:
"Virtually any disease that results from malfunctioning, damaged or failing tissues may be potentially cured through regenerative medicine treatments."

Why Choose Regenerative Medicine & Anti-Aging Institute for Stem Cell Therapy?
As an innovative leader in regenerative medicine and stem cell therapy, we have successfully treated thousands of patients suffering from chronic joint pain and other conditions, allowing them to enjoy a better quality of life.

Are You Suffering from These Conditions?
Attend one of our upcoming free educational seminars and learn how this revolutionary new therapy could make a significant improvement in the quality of life for you and your loved ones.

What We'll Share with You:
- Information about our mission and treatment team
- The past, present and future of stem cell therapy
- How stem cell therapy can work to treat and heal the body
- Our innovative treatment options for specific conditions
- Success stories from actual patients
- Answers to any remaining questions you may have

Can't make the event? Call (855) 845-7422 for your private consultation

Now is the time for you to consider options for treating your healthcare needs. Come learn about the revolutionary stem cell therapy by attending a free educational seminar near you. Please select the date and time which best suits your schedule. Space is limited - reserve your seat today!

MONDAY	TUESDAY	WEDNESDAY	THURSDAY
September 23rd	September 24th	September 25th	September 26th
4:30 pm	4:30 pm	4:30 pm	11:30 am or 4:30 pm
Fleming's Prime Steakhouse & Wine Bar	**Sullivan's Steakhouse**	**Piedmont Bistro by Venue**	**Venue Restaurant & Lounge**
140 Regency Pkwy	222 S 15th St	1265 S Cotner Blvd Ste 38	4111 Pioneer Woods Dr Ste 100
Omaha, NE 68114	Ste 100	Lincoln, NE 68510	Lincoln, NE 68506
	Omaha, NE 68102		

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Stem Cell Centers
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8639 S 168th Ave
Suite 22
Omaha, NE 68136

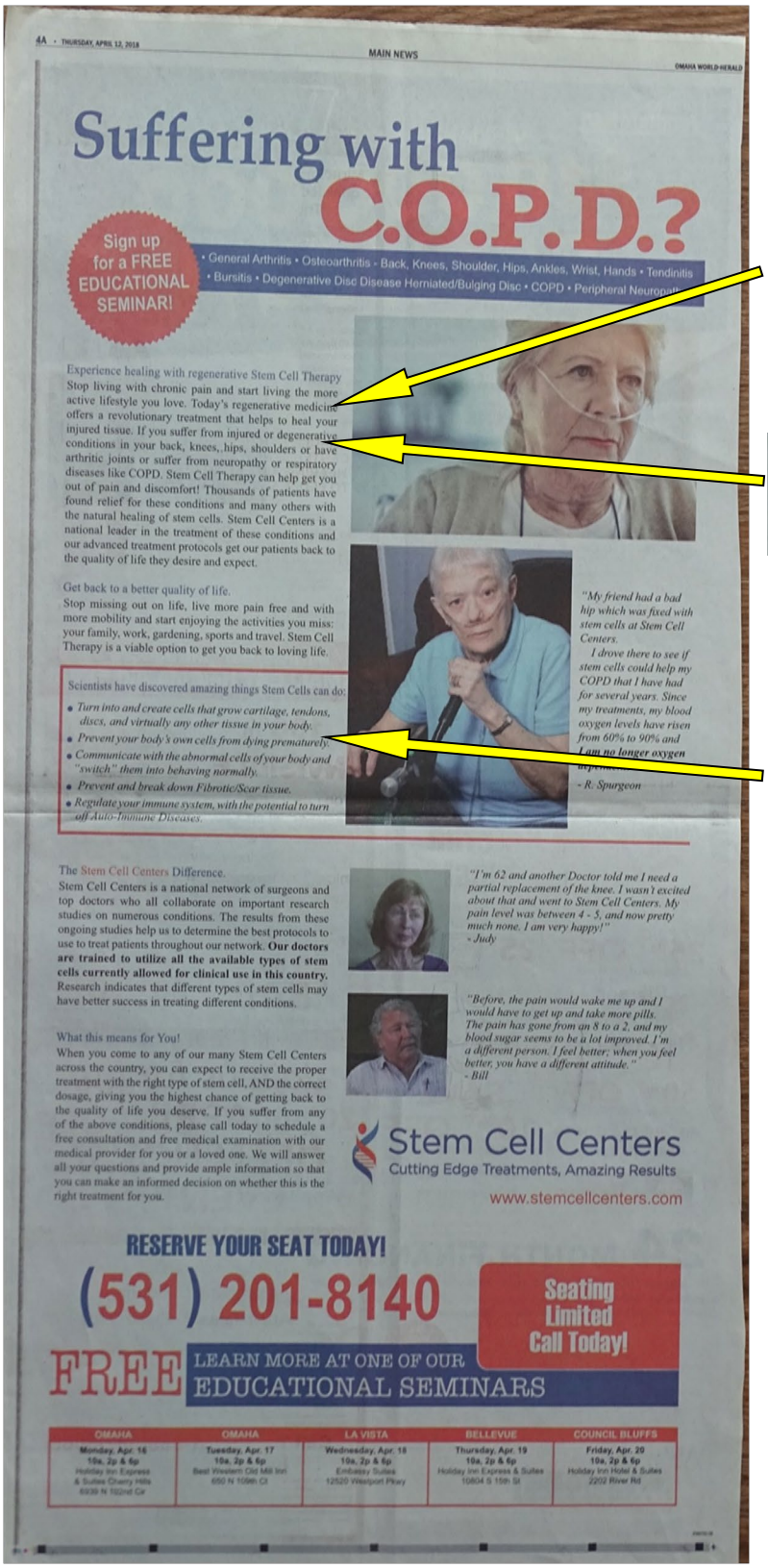
Reserve Your Seats (800) 898-3572
Your Personal RSVP Code is **395612**
or register online at **seminar.rsvpyes.com/395612**

- Stem cell therapy is considered experimental. These statements have not been evaluated by the Food and Drug Administration.
- Not everyone responds in the same way stem cell therapy. However, a significant percentage of patients do respond favorably and are satisfied with their results, demonstrating that this is a viable treatment option for conditions we treat.
- Adverse reactions are rare but may include flushing, drop in blood sugar levels, hives, rash and inflammation at injections site.

*2019 LeadingResponse

Why Choose Regenerative Medicine & Anti-Aging Institute for Stem Cell Therapy?
As an innovative leader in regenerative medicine and stem cell therapy, we have successfully treated thousands of patients suffering from chronic joint pain and other conditions, allowing them to enjoy a better quality of life.

FIGURE 2:



4A • THURSDAY, APRIL 12, 2018 MAIN NEWS OMAHA WORLD-HERALD

Suffering with C.O.P.D.?

Sign up for a FREE EDUCATIONAL SEMINAR!

• General Arthritis • Osteoarthritis - Back, Knees, Shoulder, Hips, Ankles, Wrist, Hands • Tendinitis • Bursitis • Degenerative Disc Disease Herniated/Bulging Disc • COPD • Peripheral Neuropath

Experience healing with regenerative Stem Cell Therapy

Stop living with chronic pain and start living the more active lifestyle you love. Today's regenerative medicine offers a revolutionary treatment that helps to heal your injured tissue. If you suffer from injured or degenerative conditions in your back, knees, hips, shoulders or have arthritic joints or suffer from neuropathy or respiratory diseases like COPD. Stem Cell Therapy can help get you out of pain and discomfort! Thousands of patients have found relief for these conditions and many others with the natural healing of stem cells. Stem Cell Centers is a national leader in the treatment of these conditions and our advanced treatment protocols get our patients back to the quality of life they desire and expect.

Get back to a better quality of life.

Stop missing out on life, live more pain free and with more mobility and start enjoying the activities you miss: your family, work, gardening, sports and travel. Stem Cell Therapy is a viable option to get you back to loving life.

Scientists have discovered amazing things Stem Cells can do:

- *Turn into and create cells that grow cartilage, tendons, discs, and virtually any other tissue in your body.*
- *Prevent your body's own cells from dying prematurely.*
- *Communicate with the abnormal cells of your body and "switch" them into behaving normally.*
- *Prevent and break down Fibrotic/Scar tissue.*
- *Regulate your immune system, with the potential to turn off Auto-Immune Diseases.*

"My friend had a bad hip which was fixed with stem cells at Stem Cell Centers.
I drove there to see if stem cells could help my COPD that I have had for several years. Since my treatments, my blood oxygen levels have risen from 60% to 90% and I am no longer oxygen
- R. Spurgeon

The Stem Cell Centers Difference.

Stem Cell Centers is a national network of surgeons and top doctors who all collaborate on important research studies on numerous conditions. The results from these ongoing studies help us to determine the best protocols to use to treat patients throughout our network. **Our doctors are trained to utilize all the available types of stem cells currently allowed for clinical use in this country.** Research indicates that different types of stem cells may have better success in treating different conditions.

What this means for You!

When you come to any of our many Stem Cell Centers across the country, you can expect to receive the proper treatment with the right type of stem cell, AND the correct dosage, giving you the highest chance of getting back to the quality of life you deserve. If you suffer from any of the above conditions, please call today to schedule a free consultation and free medical examination with our medical provider for you or a loved one. We will answer all your questions and provide ample information so that you can make an informed decision on whether this is the right treatment for you.

"I'm 62 and another Doctor told me I need a partial replacement of the knee. I wasn't excited about that and went to Stem Cell Centers. My pain level was between 4 - 5, and now pretty much none. I am very happy!"
- Judy

"Before, the pain would wake me up and I would have to get up and take more pills. The pain has gone from an 8 to a 2, and my blood sugar seems to be a lot improved. I'm a different person. I feel better; when you feel better, you have a different attitude."
- Bill

Stem Cell Centers
Cutting Edge Treatments, Amazing Results
www.stemcellcenters.com

RESERVE YOUR SEAT TODAY!

(531) 201-8140

Seating Limited Call Today!

FREE LEARN MORE AT ONE OF OUR EDUCATIONAL SEMINARS

OMAHA	OMAHA	LA VISTA	BELLEVUE	COUNCIL BLUFFS
Monday, Apr. 16 10a, 2p & 6p Holiday Inn Express & Suites Cherry Hills 6939 N 102nd Cir	Tuesday, Apr. 17 10a, 2p & 6p Best Western Old Mill Inn 650 N 109th Ct	Wednesday, Apr. 18 10a, 2p & 6p Embassy Suites 12520 Westport Pkwy	Thursday, Apr. 19 10a, 2p & 6p Holiday Inn Express & Suites 10804 S 15th St	Friday, Apr. 20 10a, 2p & 6p Holiday Inn Hotel & Suites 2202 River Rd

Today's regenerative medicine offers a revolutionary treatment that helps to heal your injured tissue.

If you suffer from injured or degenerative conditions in your back, knees, hips, shoulders or have arthritic joints or suffer from neuropathy or respiratory diseases like COPD. Stem Cell Therapy can help get you out of pain and discomfort!

- *Prevent your body's own cells from dying prematurely.*

FIGURE 3:


Gain the knowledge at one of our FREE
STEM CELL THERAPY SEMINARS
Learn How You Can Benefit
from the most significant medical breakthrough in natural medicine this century
Do you suffer from...
Knee Pain
Back Pain
Joint Pain
Neuropathy
COPD
Osteoarthritis
Seating is limited. Call NOW to reserve!
402.881.8044
Join us...
Monday, December 3rd
12:00 – 2:00pm or 6:00 – 8:00pm
Holiday Inn Express & Suites Cherry Hills
6939 N 102nd Circle
Omaha, NE 68122
Tuesday, December 4th
12:00 – 2:00pm or 6:00 – 8:00pm
Home 2 Suites by Hilton Omaha West, NE
17889 Chicago St
Omaha, NE 68118
Wednesday, December 5th
12:00 – 2:00pm or 6:00 – 8:00pm
Omaha Marriott
10220 Regency Circle
Omaha, NE 68114
Thursday, December 6th
12:00 – 2:00pm or 6:00 – 8:00pm
Holiday Inn Express & Suites
Council Bluffs-2211 South 32nd Street
Norman Way
Council Bluffs, IA 51501
Friday, December 7th
12:00 – 2:00pm or 6:00 – 8:00pm
Best Western Plus Kelly Inn
4706 S 108th St
Omaha, NE 68137
Stem Cell Centers
Cutting Edge Treatments. Amazing Results
DISCOVER A LIFE FREE OF PAIN!

Regenerative treatments can repair tissues in your body that are damaged due to age, disease and defects.

33. Defendants also market and sell their stem cell therapy through websites owned by RMAAI including, but not limited to, www.stemcellcenters.com and www.rmaiomaha.com. Examples of statements appearing on Defendants' websites are referenced below at Figures 4 and 5, attached hereto at Exhibits I and J, respectively.

FIGURE 4:

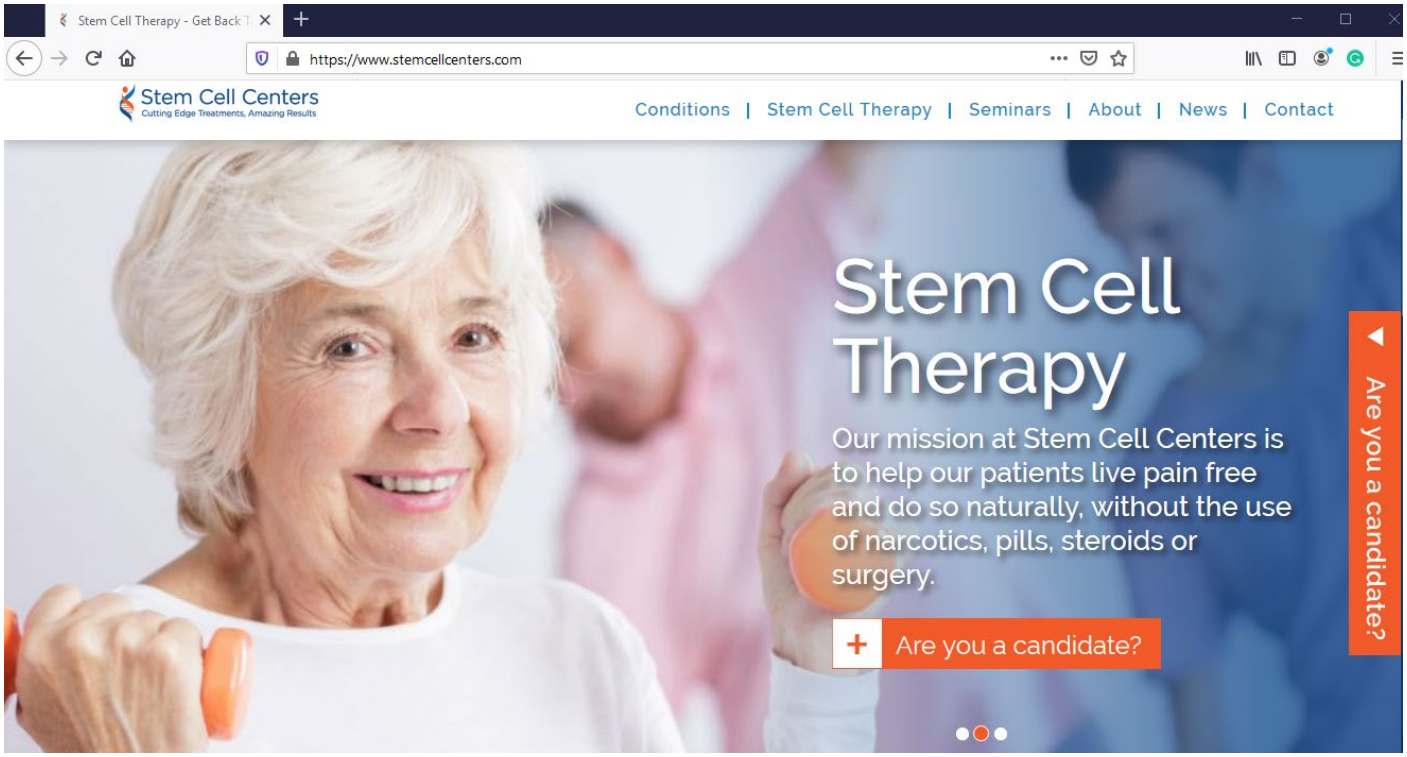
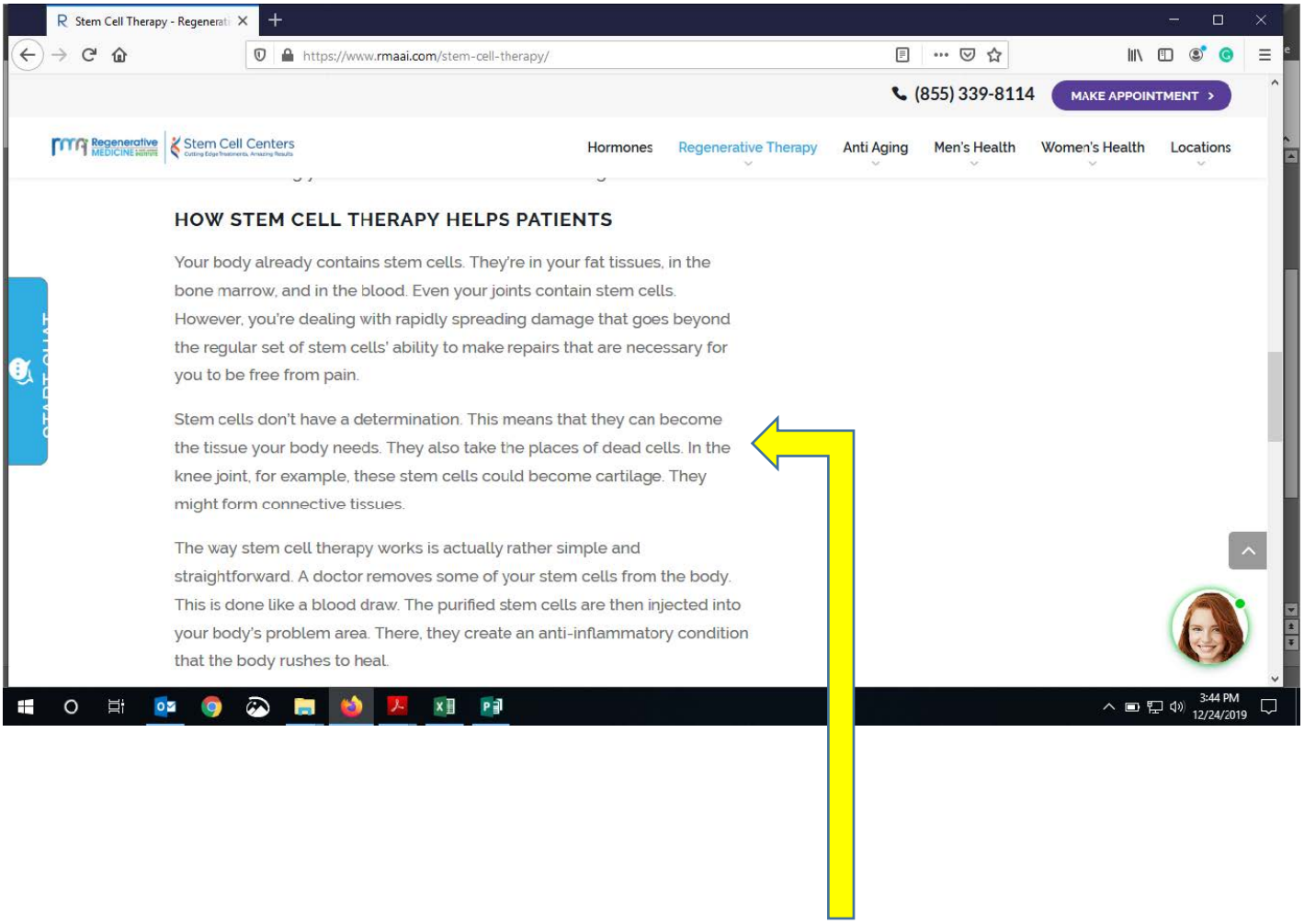

Stem Cell Therapy - Get Back
https://www.stemcellcenters.com
Stem Cell Centers
Cutting Edge Treatments, Amazing Results
Conditions | Stem Cell Therapy | Seminars | About | News | Contact
Stem Cell Therapy
Our mission at Stem Cell Centers is to help our patients live pain free and do so naturally, without the use of narcotics, pills, steroids or surgery.
Are you a candidate?
Are you a candidate?

FIGURE 5:



Stem cells don't have a determination. This means that they can become the tissue your body needs. They also take the places of dead cells. In the

34. Defendants have claimed and continue to claim, either expressly or by implication, that their stem cell therapy can heal, cure, treat, or mitigate a variety of injuries, diseases and health conditions, including but not limited to joint pain, back pain, osteoarthritis, neuropathy, erectile dysfunction, and cardiac/pulmonary disease (COPD).

35. The advertisements, educational seminars, and promotional materials referenced in Paragraphs 32 and 33 contain misleading and deceptive statements and depictions of material fact, including but not limited to:

a. "As an innovative leader in regenerative medicine and stem cell therapy, we have successfully treated thousands of patients suffering from chronic joint pain and other conditions." (Exhibit F)

b. "Today' regenerative medicine offers a revolutionary treatment that helps to heal your injured tissue." (Exhibit G)

c. "If you suffer from injured or degenerative conditions in your back, knees, hips, shoulders or have arthritic joints or suffer from neuropathy or respiratory diseases like COPD, Stem Cell Therapy can help you get out of pain and discomfort!" (Exhibit G)

d. "Prevent your own cells from dying prematurely." (Exhibit G)

e. "[Stem cells] become the tissue your body needs." (Exhibit G)

f. "Regenerative treatments can repair tissues in your body that are damaged due to age, disease and defects." (Exhibit H)

g. "Our doctors are trained to utilize all the available types of stem cells currently allowed for clinical use in this country." (Exhibit G)

36. Defendants' representations to consumers suggest that Defendants' stem cell therapy recommendations are given under the direction of a doctor. However, neither Defendants' recommendations for treatment, nor the treatments themselves, were provided by or administered in the presence of a doctor.

37. At all times relevant to this Complaint, Defendants' stem cell therapy was provided by nurse practitioners or an employee of Defendants under the supervision of a nurse practitioner.

38. To further induce consumers to undergo stem cell therapy, Defendants' advertisements typically included an invitation for consumers to attend in-person "educational seminars," where Defendants' representatives made presentations regarding Defendants' stem cell therapies.

39. These "educational" seminars were, in fact, highly-choreographed sales presentations.

40. At each seminar, a representative trained by Defendants led consumers through a PowerPoint presentation crafted by Defendants.

41. Defendants' presentations often contained testimonials and/or references to individuals that have had successful stem cell therapy.

42. One of those testimonials is a video testimonial by Mike Pavey, in which Mr. Pavey describes recovery from back pain after undergoing stem cell injections into his spinal discs and other areas. Mr. Pavey concludes his testimonial by advising viewers to "give stem cell therapy a long, solid look."

43. Defendants utilized the aforementioned testimonial while failing to disclose that Mr. Pavey has been the Chief Operating Officer of Defendant SCC and Defendant RMAAI since 2015.

44. Defendants' failure to disclose Mr. Pavey's role as one of Defendants' paid employees is deceptive and misleading.

45. Defendant held at least 84 seminars in Nebraska between April 2018 and September 2019.

46. On August 22, 2019, Defendants' held one of these educational seminars at Home2Suites, located at 17889 Chicago Street, Omaha, Nebraska (hereinafter "the August seminar").

47. The August seminar, much like Defendants' other seminars, provided an overview of Defendants' organization and discussed the stem cell therapies offered at Defendants' local clinic in Omaha, including but not limited to, the types of stem cell products and exosomes used.

a. During the August seminar, Defendants' representative reiterated and elaborated on Defendants' unfounded claims that stem cell therapy could treat, mitigate, heal, cure, or even reverse certain medical conditions, including arthritis, COPD, neuropathy, chronic back pain, ligament and tendon injuries, meniscus and muscle tears, erectile dysfunction, and female sexual dysfunction.

b. During the August seminar, Defendants make misleading statements regarding the experimental nature of the therapy they were selling by stating, "The FDA, however, we believe is on our side, but what experimental means is they just leave it up to the physicians to do their own research and determine what conditions they want to treat."

c. Throughout the August seminar, and without adequate substantiation, Defendants also claimed that stem cell therapy will not be rejected by the body and that any joint in the body can be regenerated.

48. The August seminar concluded with a discussion on the cost of therapy and available financing and discounts.

49. The price of Defendants' stem cell therapy varies depending on the type and frequency of treatments selected by the consumer. Certain therapies offered by Defendants may cost as little as $900 or as much as $16,997.

50. From April 2018 to September 2019, Defendants generated at least $2.2 million in sales for all their stem cell therapy treatments sold in Nebraska. During this time period, Defendants also encouraged many consumers to undergo multiple treatments.

51. Certain consumers also financed some or all of their purchase from Defendants through a third party, resulting in additional expense to the consumer in the form of finance charges and interest payments.

52. Defendants padded their profits by pushing consumers to buy larger and more expensive doses of Defendants' stem cell therapies.

53. In their seminars and in other representations to consumers, Defendants made unfounded claims that more and larger doses of stem cells and exosomes were most effective at treating certain medical conditions.

54. Defendants' PowerPoint presentations included, for example, the following statements:

a. "Our Stem Cell Therapy: Two Birds, One Stone. Both an injection and an IV. Our results show this is the most successful and effective treatment and can treat the whole body versus one area."

b. "More Exosomes = Better Results."

55. Defendants' stem cell therapy treatments have not been approved by the U.S. Food and Drug Administration (FDA) for any purpose.

56. Defendants have not completed any clinical or scientific studies and/or reports that have evaluated the reliability, safety, or efficacy of their stem cell therapy treatments, products or services.

57. Instead, Defendants cite to studies and reports of third-parties.

58. However, the studies and reports cited to by Defendants do not support the claims made by Defendants regarding their stem cell therapy treatments.

59. In reality, there is no competent and reliable scientific evidence establishing that stem cell or exosomes therapies are able to cure, treat, or mitigate the diseases or health conditions identified in paragraph 34.

CAUSE OF ACTION I
VIOLATIONS OF THE CONSUMER PROTECTION ACT
(Neb. Rev. Stat. § 59-1601 et seq.)

60. The State of Nebraska re-alleges and incorporates by reference all of the allegations contained in paragraphs 1-59 as though fully set forth herein.

61. Defendants are "persons" within the meaning of the Consumer Protection Act, Neb. Rev. Stat. § 59-1601(1).

62. Defendants conduct "trade" or "commerce" within the meaning of the Consumer Protection Act, Neb. Rev. Stat. § 59-1601(2).

63. The Consumer Protection Act, Neb. Rev. Stat. § 59-1602, prohibits "[u]nfair methods of competition and unfair or deceptive acts or practices in the conduct of any trade or commerce."

64. Defendants violated the Consumer Protection Act and engaged in unfair and deceptive acts or practices in violation of Neb. Rev. Stat. § 59-1602 by, without limitation:

a. Representing, expressly or by implication, that their stem cell therapy cures, treats, or mitigates specific diseases or health conditions, including but not limited to, joint pain, back pain, osteoarthritis, neuropathy, erectile dysfunction, and COPD, without possessing competent and reliable scientific evidence to substantiate the aforementioned representations;

b. Representing, expressly or by implication, that their stem cell therapy is comparable to or superior to conventional medical treatments in curing, mitigating, or treating specific diseases or health conditions, including but not limited to, joint pain, back pain, osteoarthritis, neuropathy, erectile dysfunction, and COPD, without possessing competent and reliable scientific evidence to substantiate the aforementioned representations;

c. Representing, expressly or by implication, that stem cell therapy is safe and will not be rejected by the body, without possessing competent and reliable scientific evidence to substantiate the aforementioned representations;

d. Representing, expressly or by implication, that their stem cell/exosome therapy is supported by the Food and Drug Administration (FDA) to cure, treat, or mitigate specific diseases or health conditions, including but not limited to joint pain, back pain, osteoarthritis, neuropathy, erectile dysfunction, and COPD;

e. Representing, expressly or by implication, that more stem cell therapy, or larger doses of stem cells and exosomes, were most effective at treating certain medical conditions, without possessing competent and reliable scientific evidence to substantiate the aforementioned representations; and

f. Disseminating misleading testimonials to consumers regarding Defendants' stem cell therapy without adequately disclosing the connection between the person providing the endorsement or testimonial and Defendants, when such connection may materially affect the weight or credibility of the endorsement.

65. Defendants' representations are deceptive because they had the capacity to mislead a substantial number of consumers.

66. Defendants' representations are unfair because they are unethical, oppressive or unscrupulous.

67. Each and every advertisement, failure to disclose information, misrepresentation, and representation without adequate substantiation constitutes a separate and independent violation of the Consumer Protection Act, Neb. Rev. Stat. § 59-1602.

CAUSE OF ACTION II
VIOLATIONS OF THE UNIFORM DECEPTIVE TRADE PRACTICES ACT
(Neb. Rev. Stat. § 87-301 et seq.)

68. The State of Nebraska re-alleges and incorporates by reference all of the allegations contained in paragraphs 1-59 as though fully set forth herein.

69. Section 87-302(a) of the Uniform Deceptive Trade Practice Act specifies multiple practices, which, when conducted in the course of business may constitute a deceptive trade practice.

70. Defendants are "persons" within the meaning of the Uniform Deceptive Trade Practices Act, Neb. Rev. Stat. § 87-301.

71. Defendants violated the Uniform Deceptive Trade Practices Act and engaged in deceptive trade practices in violation of Neb. Rev. Stat. § 87-302 by, without limitation:

a. Representing, expressly or by implication, that their stem cell therapy cures, treats, or mitigates specific diseases or health conditions, including but not limited to, joint pain, back pain, osteoarthritis, neuropathy, erectile dysfunction, and COPD, without possessing competent and reliable scientific evidence to substantiate the aforementioned representations, in violation of Neb. Rev. Stat. § 87-302(a)(5), 87-302(a)(8), and 87-302(a)(22)(i)-(ii);

b. Representing, expressly or by implication, that their stem cell therapy is comparable to or superior to conventional medical treatments in curing, mitigating, or treating specific diseases or health conditions, including but not, limited to joint pain, back pain, osteoarthritis, neuropathy, erectile dysfunction, and COPD, without possessing competent and reliable scientific evidence to substantiate the aforementioned representations, in violation of Neb. Rev. Stat. § 87-302(a)(5), 87-302(a)(8), and 87-

302(a)(22)(i)-(ii);

c. Representing, expressly or by implication, that stem cell therapy is safe and will not be rejected by the body, without possessing competent and reliable scientific evidence to substantiate the aforementioned representations, in violation of Neb. Rev. Stat. § 87-302(a)(5), 87-302(a)(8), and 87-302(a)(22)(i)-(ii);

d. Representing, expressly or by implication, that their stem cell/exosome therapy is supported by the Food and Drug Administration (FDA) to cure, treat, or mitigate specific diseases or health conditions, including but not limited to, joint pain, back pain, osteoarthritis, neuropathy, erectile dysfunction, and COPD, in violation of Neb. Rev. Stat. § 87-302(a)(2) and 87-302(a)(22)(i)-(ii); and

e. Representing, expressly or by implication, that more stem cell therapy, or larger doses of stem cells and exosomes, were most effective at treating certain medical conditions, without possessing competent and reliable scientific evidence to substantiate the aforementioned representations, in violation of Neb. Rev. Stat. § 87-302(a)(5), 87-302(a)(8), and 87-302(a)(22)(i)-(ii).

f. Disseminating misleading testimonials to consumers regarding Defendants' stem cell therapy without adequately disclosing the connection between the person providing the endorsement or testimonial and Defendants, when such connection may materially affect the weight or credibility of the endorsement, in violation of Neb. Rev. Stat. § 87-302(a)(2) and 87-302(a)(3);

72. Defendants' actions constitute deceptive trade practices in violation of Neb. Rev. Stat. § 87-302. Each and every advertisement, failure to disclose information, misrepresentation, and representation without adequate substantiation constitutes a separate and independent violation of

the Uniform Deceptive Trade Practices Act.

PRAYER FOR RELIEF

WHEREFORE, the State of Nebraska, respectfully requests that this Court:

A. Permanently enjoin and restrain Defendants, their agents, employees, and all other persons and entities, corporate or otherwise, in active concert or participation with any of them, from engaging in unfair or deceptive acts or practices, in violation of the Consumer Protection Act and the Uniform Deceptive Trade Practices Act, in connection with the advertising, marketing, distribution, and sale of stem cell therapy, pursuant to Neb. Rev. Stat. § 59-1608 and Neb. Rev. Stat. § 87-303.05;

B. Permanently enjoin and restrain Defendants, their agents, employees, and all other persons and entities, corporate or otherwise, in active concert or participation with any of them, from violating the Consumer Protection Act and Uniform Deceptive Trade Practices Act, pursuant to Neb. Rev. Stat. § 59-1608 and Neb. Rev. Stat. § 87-303.05;

C. Order Defendants to pay civil penalties for each violation of the Consumer Protection Act and Uniform Deceptive Trade Practices Act pursuant to Neb. Rev. Stat. § 59-1614 and Neb. Rev. Stat. § 87-303.11, respectively;

D. Order Defendants to restore to every person any money acquired by Defendants as a result of their violations of the Consumer Protection Act and Uniform Deceptive Trade Practices Act, pursuant to Neb. Rev. Stat. § 59-1608(2) and Neb. Rev. Stat. § 87-303.05(1);

E. Order Defendants to pay the State's costs and attorney fees in this matter, pursuant to Neb. Rev. Stat. §§ 59-1608 and 87-303(b); and

F. Order any other relief that the Court deems just and equitable.

DATED this 16th day of July, 2020.

THE STATE OF NEBRASKA, ex rel.
Douglas J. Peterson, Attorney General

By: Douglas J. Peterson, Attorney General, #18146

By: /s/ Shereece Dendy-Sanders
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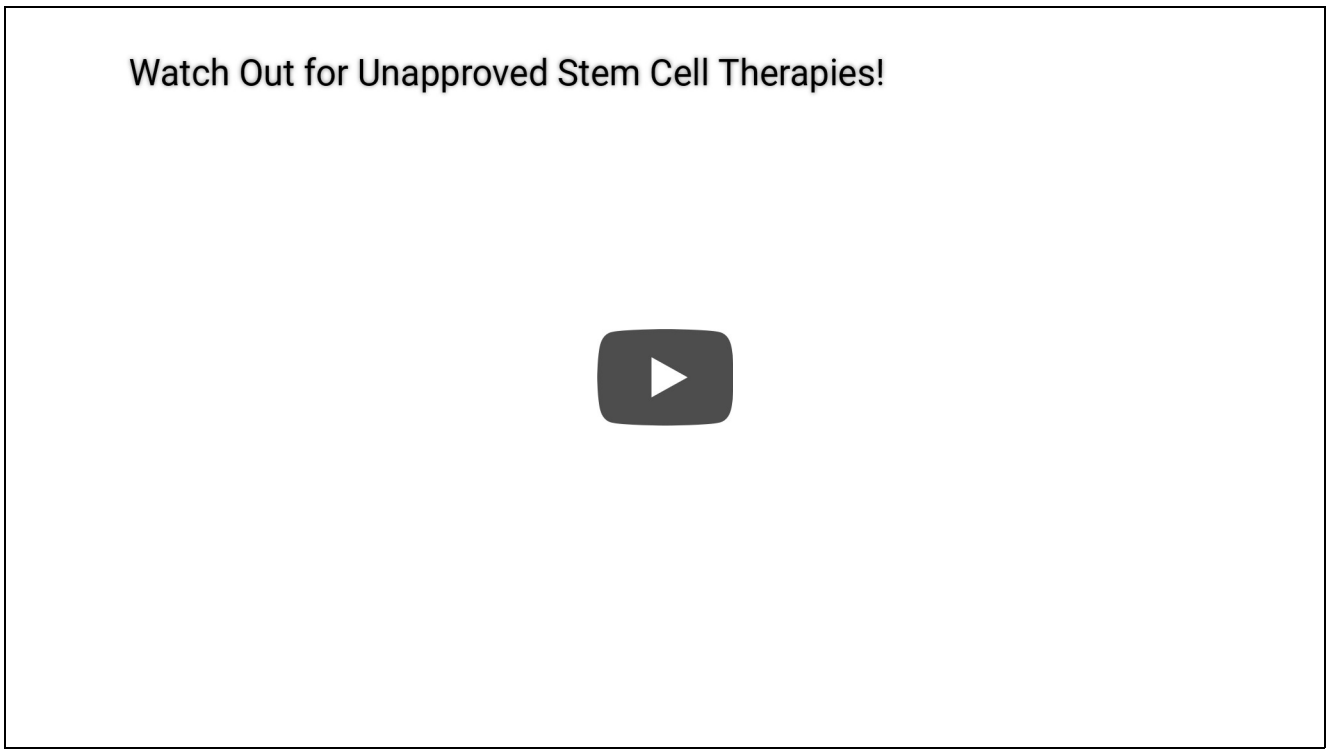
FDA Warns About Stem Cell Therapies

Some patients may be vulnerable to stem cell treatments that are illegal and potentially harmful.



Español (/consumers/articulos-en-espanol/la-fda-advierte-sobre-las-terapias-con-celulas-madre)

Researchers hope stem cells will one day be effective in the treatment of many medical conditions and diseases. But unproven stem cell treatments can be unsafe—so get all of the facts if you're considering any treatment.

Stem cells have been called everything from cure-alls to miracle treatments. But don't believe the hype. Some unscrupulous providers offer stem cell products that are both unapproved and unproven. So beware of potentially dangerous procedures—and confirm what's really being offered before you consider *any* treatment.

The facts: Stem cell therapies may offer the potential to treat diseases or conditions for which few treatments exist. Sometimes called the body's "master cells," stem cells are the cells that develop into blood, brain, bones, and all of the body's organs. They have the potential to repair, restore, replace, and regenerate cells, and could *possibly* be used to treat many

medical conditions and diseases.

But the U.S. Food and Drug Administration is concerned that some patients seeking cures and remedies are vulnerable to stem cell treatments that are illegal and potentially harmful. And the FDA is increasing its oversight and enforcement to protect people from dishonest and unscrupulous stem cell clinics, while continuing to encourage innovation so that the medical industry can properly harness the potential of stem cell products.

To do your part to stay safe, make sure that any stem cell treatment you are considering is either:

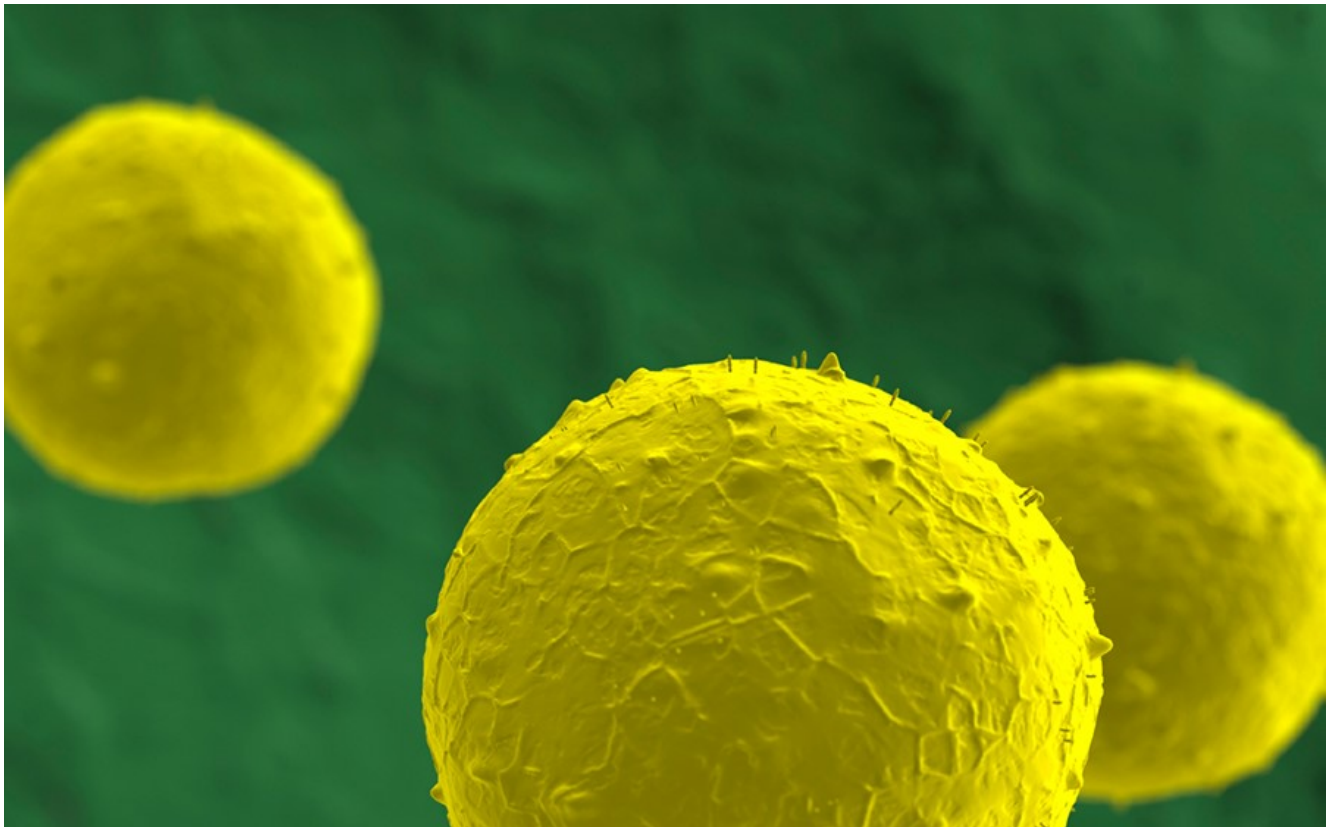
- FDA-approved, or;
- Being studied under an Investigational New Drug Application (IND), which is a clinical investigation plan submitted and allowed to proceed by the FDA.

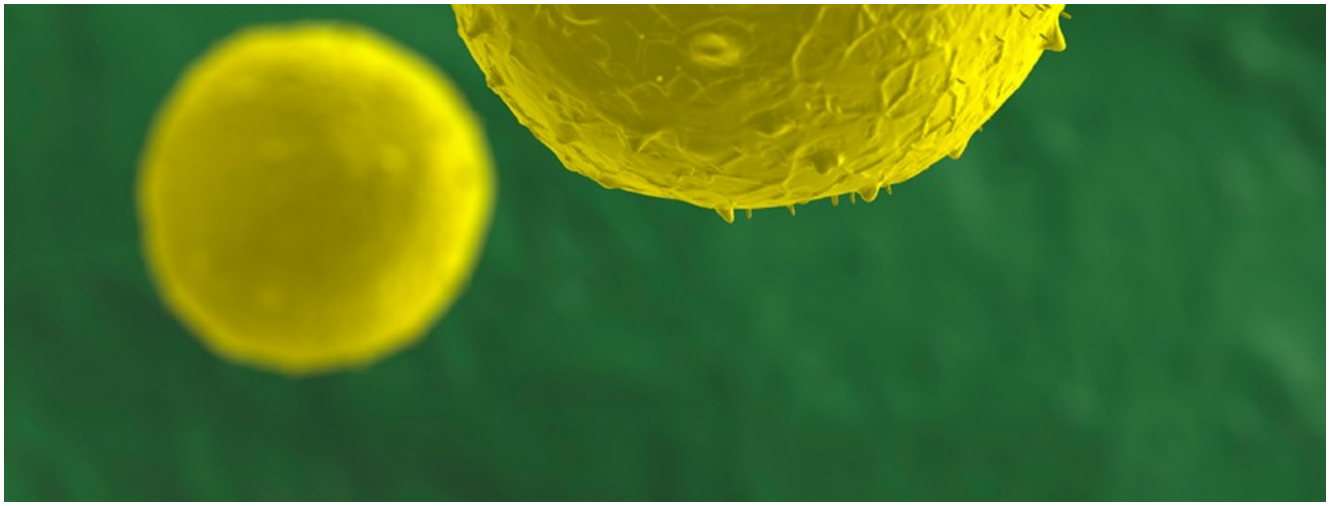
And see the boxed section below for more advice.

Stem Cell Uses and FDA Regulation

The FDA has the authority to regulate stem cell products in the United States.

Today, doctors routinely use stem cells that come from bone marrow or blood in transplant procedures to treat patients with cancer and disorders of the blood and immune system.





Electron micrograph of stem cells, color-enhanced for visual clarity.

With limited exceptions, investigational products must also go through a thorough FDA review process as investigators prepare to determine the safety and effectiveness of products in well-controlled human studies, called clinical trials. The FDA has reviewed many stem cell products for use in these studies.

As part of the FDA's review, investigators must show how each product will be manufactured so the FDA can make sure appropriate steps are being taken to help assure the product's safety, purity, and strength (potency). The FDA also requires sufficient data from animal studies to help evaluate any potential risks associated with product use. (You can learn more about clinical trials on the FDA's website (https://www.fda.gov/forpatients/clinicaltrials/default.htm).)

That said, some clinics may inappropriately advertise stem cell clinical trials without submitting an IND. Some clinics also may falsely advertise that FDA review and approval of the stem cell therapy is unnecessary. But when clinical trials are not conducted under an IND, it means that the FDA has not reviewed the experimental therapy to help make sure it is reasonably safe. So be cautious about these treatments.

About FDA-approved Products Derived from Stem Cells

The only stem cell-based products that are FDA-approved for use in the United States consist of blood-forming stem cells (hematopoietic progenitor cells) derived from cord blood.

These products are approved for limited use in patients with disorders that affect the body system that is involved in the production of blood (called the "hematopoietic" system). These FDA-approved stem cell products are listed on the FDA website (/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products). Bone marrow also is used for these treatments but is generally not regulated by the FDA for this

use.

Safety Concerns for Unproven Stem Cell Treatments

All medical treatments have benefits and risks. But unproven stem cell therapies can be particularly unsafe.

For instance, attendees at a 2016 FDA public workshop (/vaccines-blood-biologics /workshops-meetings-conferences-biologics/public-workshop-scientific-evidence-development-human-cells-tissues-and-cellular-and-tissue-based) discussed several cases of severe adverse events. One patient became blind due to an injection of stem cells into the eye. Another patient received a spinal cord injection that caused the growth of a spinal tumor.

Other potential safety concerns for unproven treatments include:

- Administration site reactions,
- The ability of cells to move from placement sites and change into inappropriate cell types or multiply,
- Failure of cells to work as expected, and
- The growth of tumors.

Note: Even if stem cells are your own cells, there are still safety risks such as those noted above. In addition, if cells are manipulated after removal, there is a risk of contamination of the cells.

FDA Actions on Unapproved Stem Cell Products

When stem cell products are used in unapproved ways—or when they are processed in ways that are more than minimally manipulated, which relates to the nature and degree of processing—the FDA may take (and has already taken) a variety of administrative and judicial actions, including criminal enforcement, depending on the violations involved.

In August 2017, the FDA announced increased enforcement of regulations and oversight of stem cell clinics. To learn more, see the statement from FDA Commissioner Scott Gottlieb, M.D., on the FDA website (/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-fdas-new-policy-steps-and-enforcement-efforts-ensure).

And in March 2017, to further clarify the benefits and risks of stem cell therapy, the FDA published a perspective article in the *New England Journal of Medicine* (http://www.nejm.org/doi/full/10.1056/NEJMp1613723?query=featured_home&) (http://www.fda.gov/about-fda/website-policies/website-disclaimer).

The FDA will continue to help with the development and licensing of new stem cell therapies where the scientific evidence supports the product's safety and effectiveness.

Advice for People Considering Stem Cell Therapies

Know that the FDA plays a role in stem cell treatment oversight. You may be told that because these are your cells, the FDA does not need to review or approve the treatment. That is not true.

Stem cell products have the potential to treat many medical conditions and diseases. But for almost all of these products, it is not yet known whether the product has any benefit—or if the product is safe to use.

If you're considering treatment in the United States:

- **Ask if the FDA has reviewed the treatment.** Ask your health care provider to confirm this information. You also can ask the clinical investigator to give you the FDA-issued Investigational New Drug Application number and the chance to review the FDA communication acknowledging the IND. Ask for this information *before* getting treatment—even if the stem cells are your own.
- **Request the facts and ask questions if you don't understand.** To participate in a clinical trial that requires an IND application, you must sign a consent form that explains the experimental procedure. The consent form also identifies the Institutional Review Board (IRB) that assures the protection of the rights and welfare of human subjects. Make sure you understand the entire process and known risks before you sign. You also can ask the study sponsor for the clinical investigator's brochure, which includes a short description of the product and information about its safety and effectiveness.

If you're considering treatment in another country:

- **Learn about regulations that cover products in that country.**
- **Know that the FDA does not have oversight of treatments done in other countries.** The FDA typically has little information about foreign establishments or their stem cell products.
- **Be cautious.** If you're considering a stem cell-based product in a country that may not require regulatory review of clinical studies, it may be hard to know if the experimental treatment is reasonably safe.

FDA STATEMENT

Statement from FDA Commissioner Scott Gottlieb, M.D. on FDA's comprehensive new policy approach to facilitating the development of innovative regenerative medicine products to improve human health

For Immediate Release:

November 15, 2017

Statement From:

One of the most promising fields of science is the area of cell-based therapies and their use in regenerative medicine. These new technologies, most of which are in early stages of development, hold transformative promise for patients.

Given this area's rapid growth, dynamism and complexity, this field has also presented unique challenges to researchers, health care providers and the FDA. We need to provide a clear, efficient pathway for product developers, while making sure that we meet our obligation to help ensure the safety and efficacy of these medical products so that patients can benefit from these novel therapies.

To achieve these goals, today we're taking steps to advance an innovative framework for how we intend to apply the existing laws and regulations that govern these products. Our aim is to make sure we're being nimble and creative when it comes to fostering innovation, while taking steps to protect the safety of patients.

The FDA originally established a regulatory framework for these products that went into effect in 2005. But in the last decade, we've seen improbable advances that hold out great hope for patients. I believe that with the ability to facilitate the regeneration of parts of the human body, we're bearing witness to the beginning of a paradigm shift in the practice of medicine.

These concepts are no longer the stuff of science fiction, but rather real-life science where cells and tissues can be engineered to grow healthy, functional organs to replace diseased ones; where new genes can be introduced into the body to combat disease; and where adult stem cells can generate replacements for cells that are lost to injury or illness. The promise of this technology is why the FDA is so committed to encouraging and supporting innovation in this field.

But the rapid growth and promise of this field has increasingly sowed the ground for the entry of some unscrupulous actors, who have opportunistically seized on the clinical potential of regenerative medicine to make deceptive claims to patients about unproven and, in some cases, dangerous products. By exploiting the lack of consumer understanding of this area, as well as the fear and uncertainties posed by the diseases these bad actors claim to treat, they're jeopardizing the legitimacy and advancement of the entire field. This underscores the importance of having a clear regulatory framework for developers, and ensuring that those who skirt these regulations are held accountable.

To realize the full potential of regenerative medicine, we need to support the innovation pursued by responsible product developers – who represent the vast majority of the field – to help ensure that they clearly understand where the regulatory lines are drawn. We must advance a modern, efficient and least burdensome framework that recognizes the breakneck speed of advancement in the products we're being asked to evaluate, while ensuring patient safety. That is the goal of the policy we're announcing today.

To achieve this balance, embedded in our comprehensive framework are many proposed novel and modern approaches to regulation, where we intend to adapt our regulatory model to meet the revolutionary nature of the products we're being asked to evaluate.

One example is how we're considering innovative trial designs whereby individual academic investigators would follow the same manufacturing protocols and share combined clinical trial data in support of approval from the FDA. This is an innovative way of making sure that small investigators who are working with cells that are being manufactured in ways that render them subject to our current laws and regulations -- because the cells are, for example, more than "minimally manipulated" -- can nonetheless seek the FDA's approval through a less burdensome process.

There are other similarly proposed novel approaches embedded in our broad policy framework. Our goal is to achieve a risk-based and science-based approach to support innovative product development, while clarifying the FDA's authorities and enforcement priorities and making sure we are protecting patients.

The suite of four guidance documents we are making public today also delivers on important provisions of the 21st Century Cures Act (/21st-century-cures-act), including our continued promise to fully implement the Regenerative Medicine Advanced Therapy (RMAT) designation program (/vaccines-blood-biologics/cellular-gene-therapy-products /regenerative-medicine-advanced-therapy-designation), which is designed to expedite the development and review of regenerative medicine advanced therapies.

We understand that there will be questions and it will take time for product developers to determine whether their products require FDA approval. Our policy will allow product

manufacturers that time to engage with the FDA to determine if they need to submit a marketing authorization application and, if so, seek guidance on how to submit their application to the FDA for approval.

To be clear, we remain committed to ensuring that patients have access to safe and effective regenerative medicine products as efficiently as possible. We are also committed to making sure we take action against products being unlawfully marketed that pose a potential significant risk to their safety. The framework we're announcing today gives us the solid platform we need to continue to take enforcement action against a small number of clearly unscrupulous actors.

With this balanced approach, we're well positioned to support and help advance breakthrough science, like regenerative medicine, and promote responsible and flexible regulation that leverages science to advance public health.

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

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301-796-0393

Consumer:

888-INFO-FDA

Related Information

FDA announces comprehensive regenerative medicine policy framework (/news-events/press-announcements/fda-announces-comprehensive-regenerative-medicine-policy-framework)

More Press Announcements (/news-events/newsroom/press-announcements)

Public Safety Notification on Exosome Products

December 6, 2019

The Food and Drug Administration (FDA) is informing the public, especially patients, health care practitioners, and clinics, of multiple recent reports of serious adverse events experienced by patients in Nebraska who were treated with unapproved products marketed as containing exosomes. These reports were brought to the agency's attention by the Centers for Disease Control and Prevention, among others, and the agencies worked with the Nebraska Department of Health and Human Services. FDA is carefully assessing this situation along with our federal and state partners.

There are currently no FDA-approved exosome products. Certain clinics across the country, including some that manufacture or market violative "stem cell" products, are now also offering exosome products to patients. They deceive patients with unsubstantiated claims about the potential for these products to prevent, treat or cure various diseases or conditions. They may claim that they these products do not fall under the regulatory provisions for drugs and biological products – that is simply untrue. As a general matter, exosomes used to treat diseases and conditions in humans are regulated as drugs and biological products under the Public Health Service Act and the Federal Food Drug and Cosmetic Act and are subject to premarket review and approval requirements.

The clinics currently offering these products outside of FDA's review process are taking advantage of patients and flouting federal statutes and FDA regulations. This ultimately puts at risk the very patients that these clinics claim to want to help, by either delaying treatment with legitimate and scientifically sound treatment options, or worse, posing harm to patients, as evidenced by these recent reports of adverse events.

Health care professionals and consumers should report any adverse events related to exosome products or any other unapproved product to the FDA's MedWatch (/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program) Adverse Event Reporting program. To file a report, use the MedWatch Online Voluntary Reporting Form (https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home). The completed form (/safety/medical-product-safety-information/medwatch-forms-fda-safety-reporting) can be submitted online or via fax to 1-800-FDA-0178. FDA monitors these reports and takes appropriate action necessary to ensure the safety of medical products in the marketplace.

Patients considering treatment with exosome products in the United States should:

- Ask if the FDA has reviewed the treatment. You also can ask the clinical investigator to give you the FDA-issued Investigational New Drug Application (IND) number and the chance to review the FDA communication acknowledging the IND. Ask for this information before getting treatment and follow up with your personal health care provider to confirm this information.
- Request the facts and ask questions if you don't understand. To participate in a clinical trial that requires an IND application, you must sign a consent form that explains the experimental procedure. The consent form also identifies the Institutional Review Board (IRB) that assures the protection of the rights and welfare of human subjects. Make sure you understand the entire process and known risks before you sign. You also can ask the study sponsor for the clinical investigator's brochure, which includes a short description of the product and information about its safety and effectiveness.

Patients considering treatment using an exosome product in another country should:

- Learn about regulations that cover products in that country.
- Know that FDA does not have oversight of treatments done in other countries. FDA typically has little information about foreign establishments or their products.
- Be cautious. If you're considering an exosome product in a country that may not require regulatory review of clinical studies, it may be hard to know if the experimental treatment is reasonably safe.

FDA remains committed to protecting patients. Our work to ensure compliance with the law does not take away from our firm commitment to advance an efficient path for the safe and effective development of novel regenerative medicine therapies and to help foster beneficial new innovations. We'll continue to work closely with investigators and firms legitimately working in this field and will do so in the most effective manner possible, while meeting the FDA's standards for safety and efficacy. We look forward to working with those who share our goal of bringing safe and effective products to market to benefit individuals in need.

Edgar *BMC Biology* (2016) 14:46
DOI 10.1186/s12915-016-0268-z

BMC Biology

QUESTION AND ANSWER Open Access

Q&A: What are exosomes, exactly?

James R. Edgar

Abstract

Exosomes are extracellular vesicles first described as such 30 years ago and since implicated in cell–cell communication and the transmission of disease states, and explored as a means of drug discovery. Yet fundamental questions about their biology remain unanswered. Here I explore what exosomes are, highlight the difficulties in studying them and explain the current definition and some of the outstanding issues in exosome biology.

What is the current definition of an exosome?

That is a very good question. Since the original description of exosomes over 30 years ago, the term has been loosely used for various forms of extracellular vesicle, muddying the field and contributing to the scepticism with which the research has sometimes been met. Exosomes are best defined as extracellular vesicles that are released from cells upon fusion of an intermediate endocytic compartment, the multivesicular body (MVB), with the plasma membrane. This liberates intraluminal vesicles (ILVs) into the extracellular milieu and the vesicles thereby released are what we know as exosomes (Fig. 1).

There are other types of microvesicle, including apoptotic bodies and ectosomes, which are derived from cells undergoing apoptosis and plasma membrane shedding, respectively. Although apoptotic bodies, ectosomes and exosomes are all roughly the same size (typically 40–100 nm) and all also contain 'gulps' of cytosol, they are different species of vesicles and understanding differences between them is of paramount importance but has too often been overlooked.

How were exosomes first recognized as distinct entities?

The presence of membranous vesicles outside cells was first recognized 50 years ago, although these were originally assumed to be waste products released via shedding of the plasma membrane. The recognition of what we now call exosomes didn't come until 1983, from studies on the loss of transferrin during the maturation of reticulocytes into erythrocytes [1]. These studies showed, by following transferrin-gold conjugates through the endocytic system, that ILVs generated in MVBs can be released to the extracellular space through fusion with the plasma membrane [2], although it was not until 1987 that the term 'exosome' was coined for them [3].

Even then, however, these extracellular vesicles were largely ignored, forgotten or, again, dismissed as a means of cellular waste disposal. It is only in the past decade that interest in exosomes has exploded, with a nearly tenfold increase in publications in as many years (115 in 2006, 1010 in 2015).

Why this explosion of interest?

For at least three reasons. First, they are thought to provide a means of intercellular communication and of transmission of macromolecules between cells. Second, in the past decade, exosomes have been attributed roles in the spread of proteins, lipids, mRNA, miRNA and DNA and as contributing factors in the development of several diseases. And third, they have been proposed to be useful vectors for drugs because they are composed of cell membranes, rather than synthetic polymers, and as such are better tolerated by the host. In fact, some of the earliest exosome research indicated that they can carry the MHC–peptide complexes that are recognized by T lymphocytes [4] and that secretion of such exosomes could promote antitumour immune responses in mice in vivo [5]. Exosome therapies are now being explored in anti-cancer clinical trials and recent reports claim taxol-filled exosomes can be used to treat cancers in mice at 50-fold lower doses than conventional treatments, with the additional benefit that exosomes do not invoke an immune response [6].

Yet despite 20 years of research, the very basics of exosome biology are in their infancy and we know little of the part they play in normal cellular physiology.

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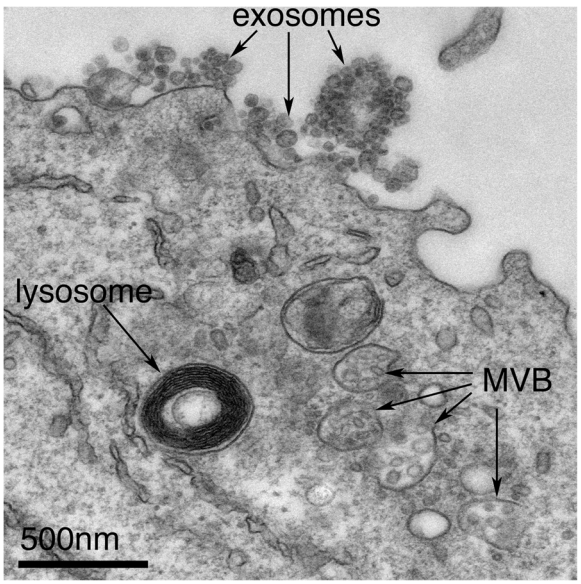

Fig. 1. Exosomes correspond to intraluminal vesicles of multivesicular bodies. A transmission electron micrograph of an Epstein–Barr virus-transformed B cell displaying newly expelled exosomes at the plasma membrane. Multivesicular bodies (*MVB*) can be seen which can deliver content to lysosomes for degradation or can fuse with the cell surface to release intraluminal vesicles as exosomes, indicated by the *arrows* at the top of the picture

So do we know how they are generated?

Yes and no. We do know that they are made as ILVs; but first of all, not all ILVs finish up as exosomes, and second, the mechanism of their generation in endosomes is not fully understood. Most conventional membrane budding processes deform membrane from an organelle into the cytoplasm but in ILV formation the membrane buds away from the cytoplasm and into the endosome. This unconventional budding process is not limited to ILV generation but also takes place during enveloped virus budding from the cytosol and during cytokinesis [7], and it requires specialised machinery.

ILVs (and thus exosomes) can be generated at the endosomal limiting membrane by at least two mechanisms, one of which depends on the ESCRT machinery (ESCRT stands for endosomal sorting complexes required for transport) whereas the other is ESCRT-independent (Fig. 2).

The ESCRT machinery consists of a set of cytosolic protein complexes that are recruited to endosomes by membrane proteins that have been tagged, usually with ubiquitin on their cytosolic domains. The ubiquitin tag is recognized by the first of the ESCRT complexes, ESCRT-0, which is thus recruited to the endosomal membrane and passes ubiquitinated cargos to ESCRT-I, one of whose components, Tsg101, also recognizes ubiquitin. The recruitment of the ESCRT machinery acts to both cluster the ubiquitinated cargo proteins on the endosome and induce curvature of the endosomal membrane to form ILVs.

But ILVs are still able to form in the absence of ESCRTs [8], so other means of generating ILVs must exist, although the mechanisms for their generation are less clear. Generation of these ESCRT-independent ILVs requires the tetraspanin CD63—a protein abundant on ILVs but with unclear function [9]—and may be facilitated by cone-shaped bending properties of lipids such as ceramide [10].

If not all ILVs become exosomes, what determines the fate of an ILV?

The destiny of ILVs is directed by the fate of the MVB they reside in. Confusingly, in addition to different types of ILVs, there are also different types of MVBs [11] and what regulates the fate of these endosomes is another interesting question. MVBs have several potential fates (Fig. 2) and can either fuse with lysosomes (where contents are degraded and recycled), fuse with the plasma membrane (where ILVs are released as exosomes), as I have already mentioned, or contribute to the generation of specialised organelles, such as melanosomes (in melanocytes), Weibel-Palade bodies (endothelial cells), azurophilic granules (in neutrophils) and secretory granules (in mast cells). The levels of cholesterol on MVBs appear to play a part in regulating their fate, cholesterol-rich MVBs being directed to the plasma membrane for exosome release, while cholesterol-poor MVBs are targeted to the lysosome [12].

But what regulates the balance between exosome release and alternative fates of ILVs remains engimatic.

What about differences between cells: do all cells release exosomes?

Well, not all cells have an endomembrane system, so no. But most mammalian cells contain endomembranes and generate ILVs within MVBs, though remarkably little is known about exosome release in most cell types.

Some cells—for example, the B cells, dendritic cells and mast cells of the immune system—appear to release exosomes constitutively; in fact, most of the data we have on exosomes comes from immune cells. As well as releasing exosomes constitutively, these cells may also be stimulated to secrete exosomes by cellular interactions. For example, murine dendritic cells, which are specialized to activate T lymphocytes, secrete higher levels of exosomes upon interaction with antigen-specific CD4+ T lymphocytes [13]. In fact, lymphocyte interactions generally can be accompanied by exosome release; human T cells (including primary T cells from blood, T cell clones and Jurkat cell lines) release exosomes upon activation of their antigen receptors [14]

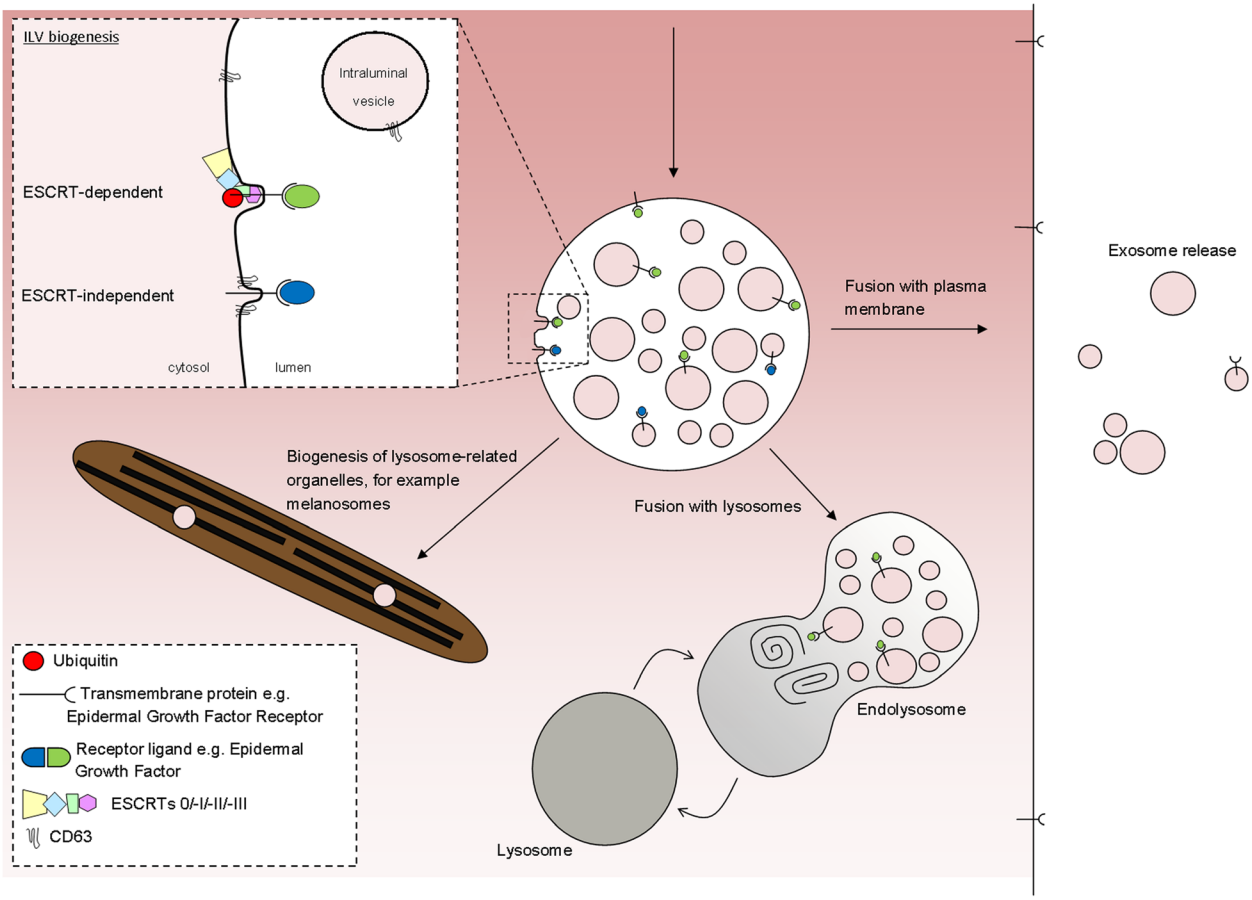

Fig. 2. ILVs are generated by invagination of the endosomal membrane and have three possible fates. *Inset*: intraluminal vesicles (*ILV*) are formed by invagination of the endosomal membrane by either ESCRT-dependent or ESCRT-independent mechanisms. Matured endosomes accumulate ILVs within their lumen and have three distinct fates. They may deliver content that contributes to the biogenesis of specialized lysosome-related organelles (for example, melanosomes, Weibel-Palade bodies, azurophilic granules), they may fuse with lysosomes or they may fuse with the plasma membrane where released ILVs are now termed 'exosomes'

and B cells release more exosomes upon engagement with antigen-specific CD4+ T cells [15].

Other cell types can be pushed to secrete exosomes by means of calcium ionophores or other stimuli [16, 17], but the extent of physiological exosome secretion in non-immune cells is largely unknown.

What happens when exosomes reach an acceptor cell?

We don't know exactly. Exosomes that transfer membrane proteins or luminal content to the acceptor cell may be engulfed whole or the exosome membrane may fuse directly with the host plasma membrane (Fig. 3). Alternatively, exosomes may not need to be taken up by cells to elicit a physiological response: follicular dendritic cells, for example, carry on their cell surface exosomes that bear MHC–peptide complexes and other proteins that they do not express and are thereby enabled to activate immune cells with which they interact [18].

For intercellular transmission, various mechanisms of phagocytosis and endocytosis of extracellular vesicles have been described and which mechanism operates may depend upon vesicle size, which may in turn depend upon the cargo carried by the vesicle. In order for material to be released to an acceptor cell, exosomes must fuse with the host cell and this takes place via either direct fusion with the plasma membrane or a 'back-fusion' step from within a host endocytic organelle after the exosome has been engulfed. The process of back-fusion is not entirely clear, although it appears to require the unconventional lipid LBPA and protein Alix [19] (and is exploited by anthrax toxin lethal factor to escape from endosomes to the cytosol [20]).

Whether exosomes fuse with target cells or act via interactions with cell-surface proteins, or both, is another fundamental cell biology question that will need to be addressed if we are to understand the functions of exosomes.

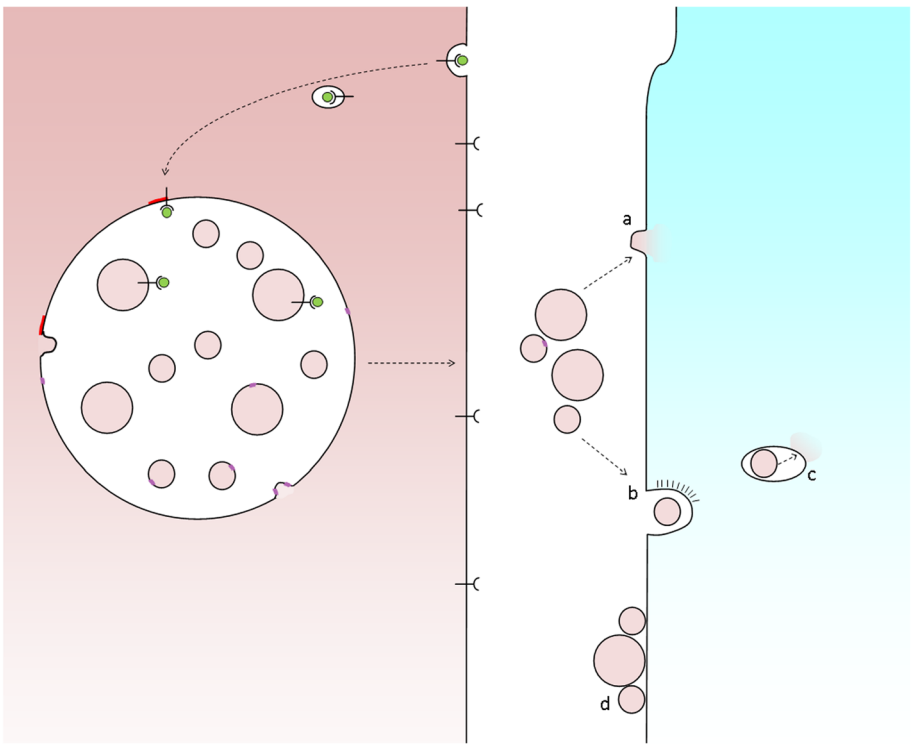

Fig. 3. Exosome uptake by recipient cells. Fusion of MVBs with the cell surface releases ILVs as exosomes. In order for exosomes to elicit a response from recipient cells they might either fuse with plasma membrane (**a**) or be taken up whole via endocytosis (**b**), following which the exosome must be delivered to the cytosol, for example, via a back-fusion event (**c**). Alternatively, exosomes may attach to the surface of recipient cells to elicit a signalling response (**d**)

So what are the consequences of all this information transfer? What biological functions have been established for exosomes?

There are many proposed functions for exosomes, the best-established being in immune responses. Exosomes isolated from B lymphocytes and bearing MHC class II molecules were shown in early experiments [4] to activate T lymphocytes in vitro, suggesting that they were communicating with the T lymphocytes in just the way that the parent B cells did. I have already mentioned later work by the same group, who showed that exosomes derived from dendritic cells, which are specialized to activate T cells in the initiation of immune responses, could promote antitumour immune responses in mice [5], exciting interest in the possibility of practical applications.

Or, as with follicular dendritic cells, exosome-associated MHC II can be found on the surface of cell types that neither express MHC II nor secrete exosomes, indicating that exosomes are delivered from one cell type to another [18].

However, exosomes may have roles other than in immune responses as several non-immune cells secrete exosomes. The only physiological role so far reported for non-immune cells is in keratinocyte-derived exosomes, which have been shown to modulate melanin synthesis by increasing the expression and activity of proteins within the melanosomes that modulate skin pigmentation [21].

How exactly would exosomes from one cell influence the expression and activity of proteins in an acceptor cell?

Exosomes transfer not only protein and lipids but mRNA and microRNA into acceptor cells and these RNAs have been shown in experiments in vitro to have functional effects in recipient cells. For example, exosomes from mice can be transferred to human cells and mRNA can be translated into mouse protein [22]. Similarly, microRNAs—double-stranded RNA fragments that can regulate specific sets of mRNA (and so protein levels)—can act functionally in acceptor cells. The mode of action of exosomes has been a focus of special interest in cancer biology. Exosomes from breast cancer cell lines, for example, have been shown to be enriched for miRNAs relative to nontumorigenic breast cell lines and exposure of normal cells to exosomes derived from breast cancer cell lines increased both cell survival and proliferation, accompanied by loss of expression of some tumour-suppressor proteins [23]. Exosome levels are elevated in the serum of some cancer patients versus controls. However, whether these vesicles are exosomes or

other forms of extracellular vesicle, or a mix, is unclear—I have already mentioned this persistent problem in exosome research.

So exosomes can also contribute to disease?

Yes indeed. As exosomes provide a means of intercellular communication, they may also act as vehicles for 'bad' communication or spread. As well as miRNAs in the case of cancer, exosomes have been shown to contain numerous disease-associated cargos—for example, neurodegenerative-associated peptides, such as Aβ [24] (in Alzheimer's disease), tau [25] (in numerous neurodegenerative diseases), prions [26] (in transmissible spongiform encephalopathies), alpha-synuclein [27] (in synucleinopathies, including Parkinson's disease) and superoxide dismutase 1 [28] (in amyotrophic lateral sclerosis). Exosomes have thus been suggested to be propagators of neurodegenerative protein spread, although some cargos are easier to envisage than others.

Of the neurodegenerative-associated proteins, only some are integral membrane proteins, that is, proteins inserted into lipid bilayers, rather than cytosolic. Sorting of proteins into ILVs (and thus exosomes) is easier to envisage for membrane proteins, where tags such as ubiquitin regulate where they end up. So far, the presence of both Aβ [29] and PrPc [26] has in fact been shown in ILVs, though this has not been demonstrated for other membrane proteins, such as alpha-synuclein and tau.

The mechanism whereby cytosolic proteins may be sorted to ILVs/exosomes, however, is not clear. In order for cytosolic proteins to become concentrated in ILVs, they would require positive incorporation and sorting, possibly by membrane-associated components on endosomes. All we can say is that there is evidence that this does in fact happen; cytosolic factors such as miRNAs are enriched in exosomes relative to cytosol, indicating that sorting must occur whereby certain miRNAs are concentrated and others are not [30].

The means by which disease-associated factors spread between cells remains poorly understood and exosomes would provide a means for such transmission. The presence of exosomal proteins, such as Alix, in association with Alzheimer's senile plaques strengthens the circumstantial case for exosomes as a mediator in such spread. The hope is that having a means to regulate exosome release and spread may be useful in combatting some of these diseases but much more basic biology needs to be established before then.

Now I'm confused—what determines what exosomes contain?

Exosomes will contain whatever is sorted into them during their formation (as ILVs). For membrane proteins, this usually occurs through ubiquitination, which acts as a substrate for recruitment of the ESCRT machinery and subsequent generation of ESCRT-dependent ILVs.

The mechanisms that concentrate cytosolic factors are currently unknown. Although it seems clear that miRNAs, for example, are enriched relative to the amount in their parent cells, and are not randomly incorporated into exosomes, it is not clear how some are enriched more than others. There are currently a few hypotheses for miRNA sorting, including sorting via sumoylated heterogeneous nuclear ribonucleoproteins [31] or by a miRNA-induced silencing complex (miRISC) [32].

Because of the difficulties in separating exosomes from other extracellular vesicles, it is likely that some cargos reported to be enriched in 'exosomes' may in fact be contained in contaminant vesicles that are not exosomes. While many researchers are very stringent about applying the labels 'exosomes' and 'extracellular vesicles' correctly, others unfortunately are not. In addition, as I have said before, cytosolic proteins are likely to be found in exosome preparations because the exosome lumen is made of cytosol.

So how exactly can you be sure that a given extracellular vesicle is an exosome and not something else?

This is an interesting question that has a complex answer. Ideally, an intracellular compartment is identified by a specific biological marker, as, for example, in the case of the Golgi, nucleus or mitochondria, all of which carry proteins not found, or found at much lower levels, elsewhere.

One problem is that ILVs, and thus exosomes, represent an intermediate compartment of an intermediate. MVBs are not static organelles but rather undergo continuous maturation, in the course of which they gain and lose proteins. There will never be an exclusive marker for exosomes because any cargo on the ILV/exosome membrane must first be on the limiting membrane of the endosome and anything found inside must first come from the cytosol. A cargo may be concentrated on ILVs/exosomes but it will also be elsewhere. CD63 could be thought of as a pseudo-marker for exosomes. ILVs and exosomes are enriched in several such tetraspanins and my colleagues and I have show that CD63 is required for ESCRT-independent ILV formation [9]. Alix also appears to be concentrated in ILVs/exosomes [33], as does Tsg101, a component of ESCRT-I, which has been used as a marker of exosomes in numerous studies [33, 34], although the presence of Tsg101 in ILVs or exosomes does not fit with conventional models of ILV formation. Although Tsg101 is involved in ESCRT-dependent ILV formation, as mentioned earlier, it, along with other ESCRT components, should disassociate from the endosomal membrane prior to an ILV pinching off the endosomal membrane to allow

it to participate in further events [35]. Exactly when ESCRT-I components 'fall off' the membrane is unknown but it is conventionally thought to be prior to ILV formation, so Tsg101 should remain cytosolic and available for subsequent rounds of ILV formation. It is possible that some Tsg101 may be 'swallowed' into the forming ILV lumen, but levels should be negligible.

So are you saying there is no reliable marker for endosomes?

There may not be—not a single reliable one. Ultimately, perhaps the best method of defining exosomes biochemically may be through a combination of markers, including tetraspanins, Alix and others, with a concomitant exclusion of resident plasma membrane proteins. Although ILVs/exosomes will by their nature contain some plasma membrane proteins and the plasma membrane will contain some ILV/exosomal proteins, it should be possible to define relative levels and/or enrichment of proteins of exosomes that distinguish them from other microvesicles. Cargos such as MHC II from B cells and other cell type-specific antigens may also help to distinguish exosomes from other forms of extracellular vesicle. Common exosomal cargos include tetraspanins (CD63, CD81, CD9), antigen presentation molecules (MHC I and MHC II) and others (Alix, flotillin-1). An online database exists [36] where proteins, lipids and RNA are catalogued from published and unpublished exosomal studies.

If they are so hard to characterize reliably, how are exosomes isolated and studied?

Exosomes are rarely imaged by conventional methods as they are too small to be resolved by fluorescence microscopy and their release may be a rare event. A few studies have imaged exosome release occurring in cell cultures by various electron microscopic techniques but, more commonly, exosomes are pooled from cellular supernatant or animal fluids. Traditionally, they have been isolated by differential centrifugation from culture medium whereby larger contaminants are first excluded by pelleting out through increasing speeds of centrifugation before exosomes, small extracellular vesicles and even protein aggregates are pelleted at very high speeds ($\sim 100{,}000 \times g$) [37]. These preparations therefore represent an enrichment rather than a purification. Enriched preparations are commonly analysed by biochemistry, mass spectrometry or electron microscopy. Electron microscopy of isolated fractions as 'whole mounts' make it possible to immuno-label vesicles, with the limitation that isolated preparations do not provide the same internal controls as labelling sections of cells. Remarkably little attention has been paid to the characterization of exosomes, although efforts are being made to repair this omission with guidelines and criteria for defining groups of extracellular vesicles [38].

What would you say are the most important issues in exosome research?

Without doubt the single most important issue is actually understanding the biological significance of these structures. With so little known about their basic physiological functions, it may seem hard to understand how exosomes have been implicated in the pathogenesis of so many disparate disease states. Fundamental questions remain about exosome generation, fate and normal function but, ultimately, in order to understand exosomes, one must first understand ILVs, a fact that is too often overlooked. Meanwhile, it is important that publications on exosomes give a careful and explicit account of the criteria used for distinguishing them from other extracellular vesicles to avoid confusing the field and encouraging scepticism.

Acknowledgements
The author wishes to thank Scottie Robinson, Paul Luzio and Paul Manna for critical reading of this article.

Competing interests
The author declares that he has no competing interests.

Published online: 13 June 2016

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WARNING LETTER

EUCYT Laboratories LLC

MARCS-CMS 607182 — JUNE 04, 2020

Delivery Method:

VIA UNITED PARCEL SERVICE

Product:

Biologics

Recipient:

Travis H. Bird

Chief Executive Officer

EUCYT Laboratories LLC

5670 Wynn Road, Suite D
Las Vegas, NV 89118
United States

Issuing Office:

Office of Biological Products Operations - Division II

United States

WARNING LETTER

Warning Letter #OBPO 20-603498

June 04, 2020

Dear Mr. Bird:

During an inspection of your firm, EUCYT Laboratories, LLC (EUCYT), located at 5670 Wynn Road, Suite D, Las Vegas, NV 89118, conducted between November 12, 2019, and November 21, 2019, the United States Food and Drug Administration (FDA) documented EUCYT's manufacture of products derived from human umbilical cord blood and umbilical cord, VidaCord™, VidaGel™ and VidaStem™; an exosome product, XOsomes™; and an amniotic fluid derived product, VidaFlo™, all for allogeneic use. You distribute your products to multiple health care providers and facilities throughout the United States.

Information and records gathered prior to, at the time of, and following the inspection, including product labeling and information on the EUCYT website, https://eucyt.com, reflect that the above-referenced products are intended for clinical use in humans to treat a variety of diseases or conditions. Therefore, these products are drugs as defined in section 201(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) [21 U.S.C. 321(g)] and biological products as defined in section 351(i) of the Public Health Service Act (PHS Act) [42 U.S.C. 262(i)].

Some of the products are also human cells, tissues, or cellular or tissue-based products (HCT/Ps) as defined in 21 CFR 1271.3(d)[1] and are subject to regulation under 21 CFR Part 1271, issued under the authority of section 361 of the PHS Act [42 U.S.C. 264]. HCT/Ps that do not meet all the criteria in 21 CFR 1271.10(a), and when no exception in 21 CFR 1271.15 applies, are not regulated solely under section 361 of the PHS Act [42 U.S.C. 264] and the regulations in 21 CFR Part 1271. Such products are regulated as drugs, devices, and/or biological products under the FD&C Act and/or the PHS Act, and are subject to additional regulation, including appropriate premarket review.

EUCYT does not qualify for any exception in 21 CFR 1271.15, and your HCT/Ps derived from umbilical cord blood or umbilical cord fail to

meet all the criteria in 21 CFR 1271.10(a). Therefore, these HCT/Ps are not regulated solely under section 361 of the PHS Act [42 U.S.C. 264] and the regulations in 21 CFR Part 1271.

Specifically, your HCT/Ps derived from umbilical cord blood or umbilical cord fail to meet the criterion in 21 CFR 1271.10(a)(2) that the HCT/Ps be "intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent."[2] Because these products are not intended to perform the same basic function or functions of umbilical cord blood or umbilical cord in the recipient as in the donor, such as forming and replenishing the lymphohematopoietic system (for cord blood) and serving as a conduit (for umbilical cord), using the products to treat arthritis or for cushioning joints, for example, is not homologous use as defined in 21 CFR 1271.3(c).

In addition, your HCT/Ps derived from umbilical cord blood or umbilical cord fail to meet other criteria set forth in 21 CFR 1271.10(a). For example, your umbilical cord blood product, VidaStem™, fails to meet 21 CFR 1271.10(a)(4). This product, manufactured from donated umbilical cord blood, is dependent on the metabolic activity of living cells for its primary function and is not for autologous use, allogeneic use in a first-degree or second-degree blood relative, or reproductive use. Additionally, the umbilical cord derived products, VidaGel™ and VidaCord™, fail to meet the minimal manipulation criterion set forth in 21 CFR 1271.10(a)(1) and defined for structural tissue in 21 CFR 1271.3(f)(1). These products do not meet this criterion because your processing alters the original relevant characteristics of the umbilical cord related to its utility for reconstruction, repair, or replacement.

With regard to your unapproved exosome product XOsomes™, we direct your attention to FDA's Public Safety Notification on Exosome Products, available at https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/public-safety-notification-exosome-products (https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/public-safety-notification-exosome-products). FDA issued that public safety notification following multiple reports of serious adverse events experienced by patients who were treated with XOsomes™.

Most recently, you began marketing an exosome product, COVIXO, for the treatment or prevention of patients' Coronavirus Disease 2019 (COVID-19).[3] Your https://eucyt.com/products/covixo/ website states "COVIXO drives cellular functionality including augmenting the type 1 interferon pathway . . . that is important for anti-SARS-CoV-2 activity" and "[t]he unique mechanism of action for COVIXO enables each patient to generate their own adaptive immune response against SARS-CoV-2, including memory T cells and antibodies, which will further protect each patient from subsequent exposures and infections."

These exosome products, XOsomes™ and COVIXO (formerly known as XOCYT™) are regulated as drugs and biological products under section 351 of the PHS Act and the FD&C Act and are subject to premarket review and approval requirements.

Please be advised that to lawfully market a drug that is a biological product, a valid biologics license must be in effect [42 U.S.C. 262(a)]. Such licenses are issued only after showing that the product is safe, pure, and potent. While in the development stage, such products may be distributed for clinical use in humans only if the sponsor has an investigational new drug application (IND) in effect as specified by FDA regulations [21 U.S.C. 355(i); 42 U.S.C. 262(a)(3); 21 CFR Part 312]. None of your products are the subject of an approved biologics license application (BLA), nor is there an IND in effect for any of them. Based on this information, we have determined that your actions have violated the FD&C Act and the PHS Act.

Additionally, during the inspection, FDA investigators documented evidence of significant deviations from current good manufacturing practice (CGMP) and current good tissue practice (CGTP),[4] including deviations from section 501(a)(2)(B) of the FD&C Act and 21 CFR Parts 210, 211, and 1271. The deviations in manufacturing processes observed as well as those noted in documents collected during the inspection indicate that the use of your products raises potential significant safety concerns. For example, EUCYT's deficient donor eligibility practices, unvalidated manufacturing processes, deficient environmental monitoring, and inadequate aseptic practices, as described below, pose a significant risk that your products may be contaminated with viruses or microorganisms or have other serious product quality defects. Additionally, there have been reported safety concerns with one of your products.

At the close of the inspection, the FDA investigators issued a Form FDA 483 to you listing inspectional observations, which described a number of significant CGMP deviations applicable to all your products that were the subject of the inspection as well as significant CGTP deviations applicable to your HCT/Ps. FDA has found additional significant deviations upon further review of the information collected during the November 2019 inspection, as discussed below. The deficiencies include, but are not limited to, the following:

1. Failure of a responsible person to determine and document the eligibility of a cell or tissue donor based upon the results of donor screening and donor testing [21 CFR 1271.50(a)]. EUCYT is the establishment responsible for making donor eligibility determinations for donors of umbilical cord blood and/or umbilical cord sourced from your supplier, **(b)(4)**. Although your firm receives relevant medical records, including a donor medical history interview and a physical examination from your supplier, you have not determined donor eligibility for the donors of umbilical cord blood and/or umbilical cord used to manufacture your products. Since operations began in April 2018, your firm has failed to document whether donors of umbilical cord blood and/or umbilical cord

sourced from **(b)(4)** are eligible.

2. Failure to screen a donor of human cells or tissue by reviewing the donor's relevant medical records for risk factors for, and clinical evidence of, relevant communicable disease agents and diseases [21 CFR 1271.75(a)]. FDA has identified Zika virus (ZIKV) as a relevant communicable disease agent or disease (RCDAD) under 21 CFR 1271.3(r)(2); therefore, review of relevant medical records, as defined in 21 CFR 1271.3(s), must indicate that a potential donor is free from risk factors for, or clinical evidence of, ZIKV infection for the purpose of determining donor eligibility. The DT-001 Form 4 "Donor Risk Assessment Interview" your firm receives from its primary cord and cord blood supplier, **(b)(4)**, does not adequately assess a donor's risk for ZIKV. We note that **(b)(4)** is located in **(b)(4)**, which has been identified by the Centers for Disease Control and Prevention as an area with current or past transmission of ZIKV.

3. Failure to establish and maintain procedures for all steps performed in testing, screening, and determining donor eligibility, and complying with all other requirements of Subpart C "Donor Eligibility" in 21 CFR 1271.45-1271.90. "Establish and maintain" means define, document (in writing or electronically), and implement; then follow, review, and as needed, revise on an ongoing basis [21 CFR 1271.47(a)]. Specifically, your firm failed to establish and maintain procedures for determining donor eligibility to adequately and appropriately reduce the risk of transmission of relevant communicable diseases.

4. Failure to establish and follow appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile, including procedures for validation of all aseptic and sterilization processes [21 CFR 211.113(b)]. For example:

A. The aseptic processes used to manufacturer your products, VidaCord™, VidaGel™, VidaStem™, XOsomes™, and VidaFlo™ have not been validated since manufacturing operations began in April 2018. Based on your product labeling, these products purport to be sterile and are expected to be sterile.

B. Written procedures have not been established and followed for gowning.

C. During the inspection, FDA investigators observed personnel practices that do not adequately protect against microbiological contamination of your products, including operators with exposed skin and hair, as well as non-sterile gowns, gloves, bouffant caps and shoe covers.

5. Failure to have an adequate system for monitoring environmental conditions in an aseptic processing area [21 CFR 211.42(c)(10)(iv)]. Specifically, your firm has not established an adequate system for environmental and personnel monitoring in the aseptic processing area where the products are manufactured. Only **(b)(4)** step of processing is monitored **(b)(4)** with settle plates.

6. Failure to establish written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess [21 CFR 211.100(a)]. Specifically, the manufacturing processes for your products have not been validated.

7. Failure to establish and follow written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures [21 CFR 211.80(a)]. For example, there are no written procedures describing in sufficient detail the criteria for approval or rejection of incoming umbilical cord blood and umbilical cord.

8. Failure to establish and follow written procedures for cleaning and maintenance of equipment used in the manufacture, processing, packing, or holding of a drug product [21 CFR 211.67(b)]. For example:

A. Your firm has not adequately established and followed written procedures for cleaning and maintenance of the **(b)(4)** Biological Safety Cabinets (BSCs) used to manufacture your products:

i. Your firm failed to validate the cleaning process for your BSCs.

ii. Cleaning with **(b)(4)** is conducted **(b)(4)** of a BSCs; however, your SOP entitled "Use and Maintenance of **(b)(4)** Biological Safety Cabinet" does not require cleaning in between the manufacture of batches.

iii. Your firm does not maintain cleaning records.

iv. There is no data or rationale for the cleaning agents used or their rotation.

v. Expired **(b)(4)** were observed being used to clean BSC #**(b)(4)** after production of VidaCordTM (Donor ID #**(b)(6)**) on **(b)(4) (b)(6)**.

B. Your firm has not adequately established and followed written procedures for cleaning and maintenance of the cutting boards used in the aseptic processing of umbilical cord. On November 13, 2019, cleaning of a plastic cutting board in the eye wash station was observed.

9. Failure to thoroughly investigate any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed. [21 CFR 211.192]. For example, from April 2018 to November 2019, your firm failed to thoroughly investigate 152 sterility failures. The overall failure rate per product ranged from approximately **(b)(4)**%.

i. The contaminating organism(s) were identified, but your firm destroyed these batches without conducting thorough investigations. Organisms included: *Acidovorax temperans, Clostridium perfingens, Enterococcus faecalis, Escherichia coli*, Gram positive cocci, Gram negative rods, *Klebsiella pneumonaie, Kocuria varians*, and *Streptococcus*.

ii. Corrective or preventive actions were not implemented.

iii. In one instance, your firm failed to thoroughly investigate the failure of a lot (Lot # **(b)(4)**, Donor ID #**(b)(6)**) to meet specifications after a sterility failure for *E. coli*. The firm discarded the lot without conducting a thorough investigation that extended to other lots manufactured the same day (**(b)(4)(b)(6)**). Another lot manufactured that day (Lot #**(b)(4)**, Donor ID #**(b)(6)**) was later associated with a report of a patient testing positive for *E. coli*.

10. Failure to establish and follow a written testing program designed to assess the stability characteristics of drug products and to use the results of such stability testing to determine appropriate storage conditions and expiration dates [21 CFR 211.166(a)]. For example, your firm assigns a two-year expiration date without supporting data for your VidaCord™, VidaGel™, VidaStem™ and XOsomes™ products.

11. Failure to establish and follow written procedures describing the handling of all written and oral complaints regarding a drug product [21 CFR 211.198(a)]. For example, your firm has not established and followed written procedures that describe a process for documenting and investigating complaints.

12. Failure to test your non-penicillin drug products for the presence of penicillin although a reasonable possibility exists that the non-penicillin drug products have been exposed to cross contamination with penicillin [21 CFR 211.176]. For example, penicillin was used in an **(b)(4)** during the manufacture of VidaCord™ and XOsomes™, from **(b)(4)** to **(b)(4)** and there is no documentation that testing for penicillin has been performed.

13. Failure to prepare batch production and control records that include documentation of the accomplishment of each significant step in manufacturing, processing, packing, or holding [21 CFR 211.188(b)]. For example, the aseptic processing steps described in your SOP entitled "Processing and Storage of Umbilical Cord Tissue - **(b)(4)**", were not documented to assure that all steps were performed as directed, including the total time of the **(b)(4)**.

We have reviewed your written response, dated December 10, 2019, to the inspectional observations on the Form FDA 483 issued at the conclusion of the inspection. We acknowledge your commitment at that time to quarantine all products processed from HCT/Ps recovered in Zika risk areas, and to accept only HCT/Ps recovered within the continental United States. We also acknowledge your commitment to implement corrective actions for the CGMP and CGTP deficiencies documented on the FDA 483; however, the adequacy of all corrective actions will need to be verified during reinspection of your firm.

During a subsequent FDA investigation at your firm, conducted from February 19 through February 20, 2020, our investigator confirmed that your finished product inventory was under quarantine and remained the same as the finished product inventory documented at the conclusion of the November 12 through November 21, 2019, FDA inspection of your firm. At the time of the February 2020 investigation, you stated that you had not shipped or destroyed any finished product since the conclusion of the November 2019 inspection. Further, you represented to FDA that, as of February 20, 2020, no product had been distributed from EUCYT since November 21, 2019.

During the February 2020 investigation, you also stated that in January 2020, you had processed umbilical cord into both Wharton's jelly and exosome products that had resulted in **(b)(4)** vials of XOsomes™ and VidaGel™; you further stated that these finished products were in quarantine. As of February 4, 2020, you represented to FDA that your firm is not conducting any manufacturing operations including processing, labeling, storing or shipping.

We note that FDA has also observed other products marketed on EUCYT's website that were not the focus of the agency's inspection or investigation. These products, which appear to be HCT/Ps, include EUFILL™, an allogeneic product derived from donated birth tissue, and OsteoFlow™ and OsteoGel™, products consisting of, in part, cortical and cancellous and demineralized cortical allograft bone **(b)(4)**, respectively. Based on our review, it appears that EUCYT does not qualify for any exception in 21 CFR Part 1271.15 and that these products fail to meet all the criteria in 21 CFR 1271.10(a) for regulation solely under section 361 of the PHS Act and regulations in 21 CFR

Part 1271. As such, it appears that these products would be regulated as drugs, devices, and/or biological products under the FD&C Act and/or section 351 of the PHS Act and subject to additional regulation, including appropriate premarket review

Neither this letter nor the observations noted on the Form FDA 483, which were discussed with you at the conclusion of the inspection, are intended to be an all-inclusive list of deficiencies that may exist at your facility. It is your responsibility to ensure full compliance with the FD&C Act, PHS Act, and all applicable regulations.

You should take prompt action to correct these violations. Failure to promptly do so may result in regulatory action without further notice. Such actions include seizure and/or injunction.

For further information about IND requirements, please contact the Center for Biologics Evaluation and Research (CBER), Division of Regulatory Project Management, Office of Tissues and Advanced Therapies, at (240) 402-8190, or OTATRPMS@fda.hhs.gov. Please include a copy of this letter with your initial submission to CBER.

We request that you respond in writing within fifteen (15) working days from your receipt of this letter, outlining the specific steps you have taken or plan to take to correct the noted violations and prevent their recurrence. Include any documentation necessary to show that correction has been achieved. If you do not believe your products are in violation of the FD&C Act, PHS Act, or applicable regulations, include your reasoning and any supporting information for our consideration. If you cannot complete all corrections within fifteen (15) working days, please explain the reason for your delay and the time frame within which the remaining corrections will be completed.

Your response should be sent to the following address: Daniel W. Cline, Compliance Officer, U.S. Food and Drug Administration, 19701 Fairchild, Irvine, CA 92612 or emailed to Daniel.Cline@fda.hhs.gov. If you have any questions, please contact Mr. Cline at (949) 608-4433 or via e-mail.

Sincerely,
/S/

Karlton T. Watson
Program Division Director
Office of Biological Products Operations – Division II

Cc: Mindy Sauter
Partner
Elliot Sauter PLLC
7557 Rambler Road, Suite 525
Dallas, TX 75231

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1 HCT/Ps are defined as “articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.” 21 CFR 1271.3(d). The definition of HCT/P excludes secreted or extracted human products; accordingly, secreted body fluids, such as amniotic fluid, are generally not considered HCT/Ps subject to regulation under 21 CFR Part 1271. Although not an HCT/P, your product derived from amniotic fluid, VidaFlo™, is also regulated as a drug and biological product under section 351 of the PHS Act and the FD&C Act.

2 Under 21 CFR 1271.3(e), manufacture “means, but is not limited to, any or all steps in the recovery, processing, storage, labeling, packaging, or distribution of any human cell or tissue, and the screening or testing of the cell or tissue donor.”

3 There is currently a global outbreak of respiratory disease caused by a novel coronavirus that has been named “severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2). The disease caused by the virus has been named “Coronavirus Disease 2019” (COVID-19). On January 31, 2020, the Department of Health and Human Services (HHS) issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS. Secretary of Health and Human Services Alex M Azar, Determination that a Public Health Emergency Exists. Jan. 31, 2020. (Accessible at: https://www.phe.gov/emergency/news/healthactions/phe/Pages/2019-nCoV.aspx (https://www.phe.gov/emergency/news/healthactions/phe/Pages/2019-nCoV.aspx)). The declaration was renewed for another 90 days on April 21, 2020. Secretary of Health and Human Services Alex M. Azar II, Renewal of Determination that a Public Health Emergency Exists. April 21, 2020. (Accessible at: https://www.phe.gov/emergency/news/healthactions/phe/Pages /covid19-21apr2020.aspx (https://www.phe.gov/emergency/news/healthactions/phe/Pages/covid19-21apr2020.aspx)). In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19. President Donald J. Trump, Proclamation on

Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19). Mar. 13, 2020. (Accessible at: https://www.whitehouse.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/ (https://www.whitehouse.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/)).

4 During the November 2019 inspection, FDA investigators also gathered evidence of your manufacture of another HCT/P, EuFixx™, an amniotic membrane patch product for allogeneic use. Although EuFixx™ is not the focus of this letter, we note that certain of your CGTP deviations described below also pertain to your manufacture of EuFixx™.

More Warning Letters (/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters)

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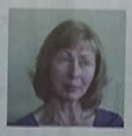

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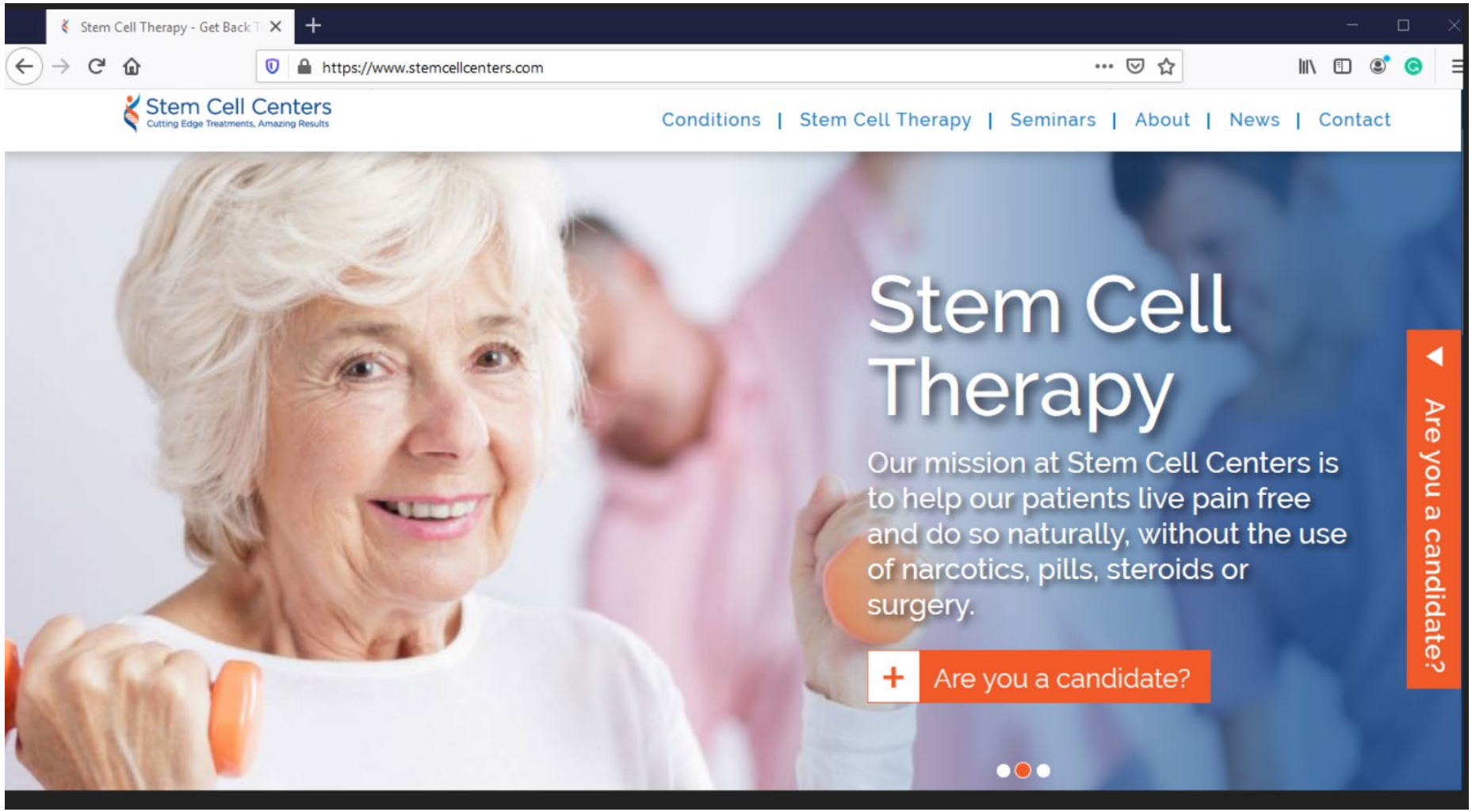
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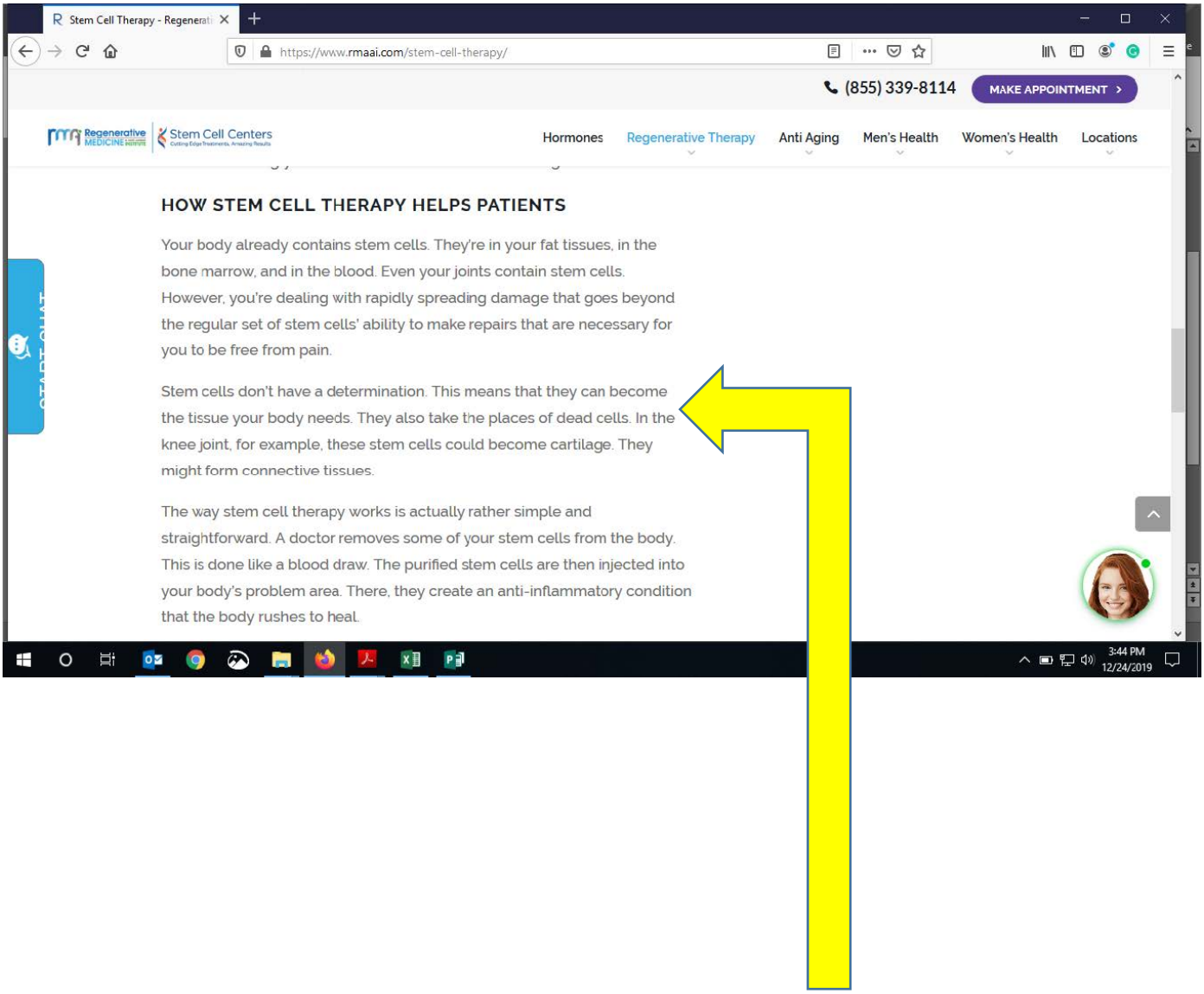
Are you a candidate?



Stem cells don't have a determination. This means that they can become the tissue your body needs.