HYPE, HEALING & HOAXES

A BALANCED LOOK AT STEM CELL THERAPY IN THE CARIBBEAN

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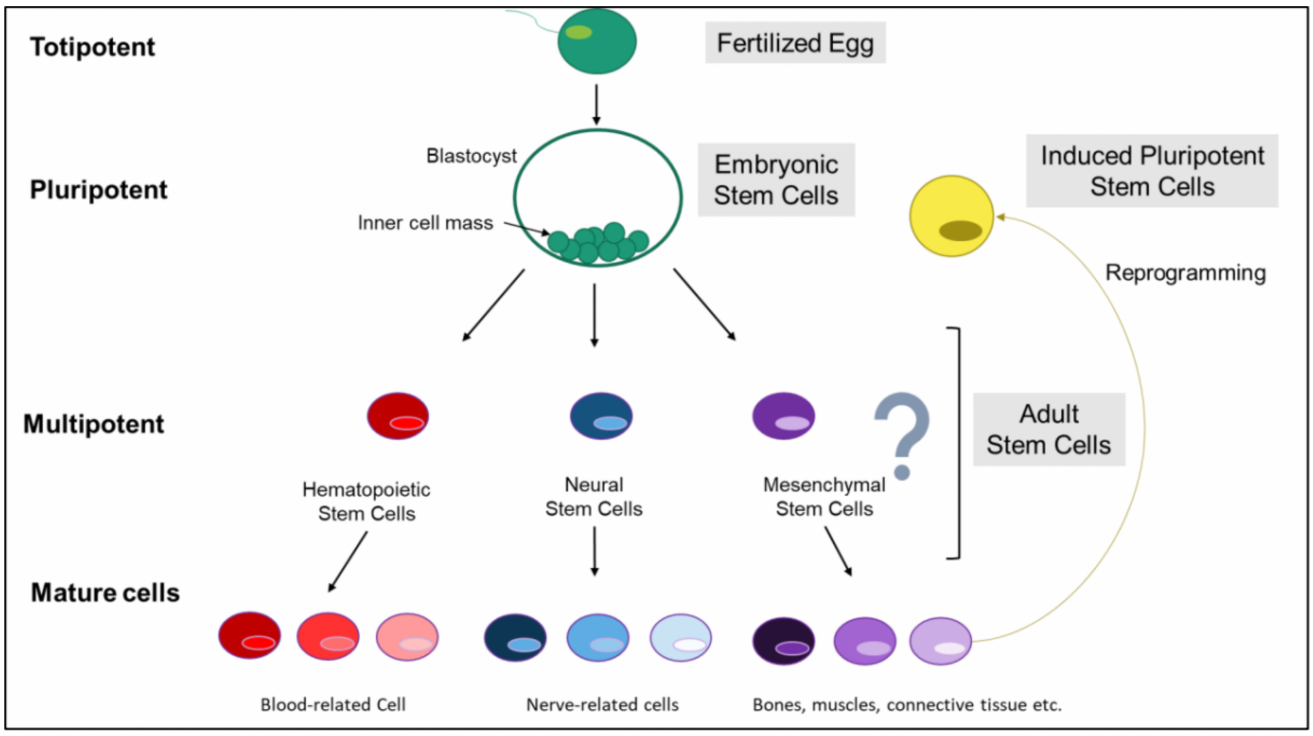

Figure 1: Potency of Stem Cells as defined by the International Society for Stem Cell Research [1]

WHAT ARE STEM CELLS?

Stem cells are characterized by two features. They can: 1) Differentiate into different cell types and 2) Self-replicate many times.

Within the first few days of fertilization, the resulting cells are totipotent and capable of developing into a viable embryo; after this, the cells become pluripotent - able to form almost any cell in the body, save notably those of the placenta. The next level of potency is multi-potent; these cells are progenitors of multiple, but specific, cell lines. Some multipotent cells are found in the body throughout life and are therefore adult stem cells. These include hematopoietic stem cells and neural stem cells, and supposedly mesenchymal stem cells. There are also tissue-specific stem cells for organs that are continuously replenished, such as the skin. These are not multi-potent, but simply dedicated precursor cells for the specific tissue.

Various stem cell types have been investigated for their use in

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research and as a therapeutic, among other things. Using **embryonic stem cells** (ESC) has created a tremendous amount of controversy as it involves the destruction of a blastocyst, which will eventually become an embryo. Ethical issues aside, their extreme self-replication ability poses a problem, as ESC therapy is associated with tumor formation [2]. **Induced pluripotent cells** (iPSCs) are mature cells that were programmed back into the pluripotent state by the insertion of specific genes; the discovery of this technique led Yamanaka to win the Nobel prize in 2012 [3]. While iPSCs eliminate the ethical issue involved with ESCs, iPSCs can also be tumorigenic. Further, they are expensive as a therapeutic and can be unstable; nonetheless they present opportunity for a variety of uses [4]. **Hematopoietic stem cell** therapy is essentially a blood stem cell transplant (this is the case for bone marrow transplants). These stem cell transplant procedures are widely accepted by regulatory agencies as a treatment option, particularly for blood cancers. The rest of this report will not focus on these types of stem cells, but on the most common, unregulated stem cell on sale: mesenchymal stem cells.

Mesenchymal stem cells (MSCs) are key players in the regenerative medicine field. The name originated in 1991 when Caplan et al. showed that cells isolated from bone marrow could differentiate *in vitro* into adipocytes, osteocytes, and chondrocytes [5]. The International Society for Cellular Therapy was not comfortable with the name 'stem' and proposed that MSCs be called mesenchymal stromal cells, defining them according to the respective presence/absence of several protein markers, their adherence to a flask when cultured, and their ability to differentiate into fat, bone, and cartilage tissue in vitro [6]. The name was ignored by many, though the identification criteria has remained in usage. Interestingly, Caplan argues that 'stromal' is a misnomer anyway because the cells did not originate in the connective tissue layer [5]. Cells meeting these criteria can be obtained from many sources, including bone, fat, placenta, and

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umbilical cords, relatively easily [7]; this immediately removes the ethical hurdle associated with embryonic stem cells.

The idea of a multipotent cell, that could be obtained so easily sparked considerable interest in the therapeutic potential of MSCs. As such, amid the controversy and lack of information about the identity, efficacy, and method of action of MSCs, publications, pilot tests, and private clinics have abounded, spurred on by the idea that MSCs could provide astounding regenerative effects [8]. Now, therapeutic effect was shown for a variety of indications but there was little-to-no *in vivo* differentiation observed once the MSCs were injected; and this has been known for over a decade [9] [7]. In fact, mounting evidence supports the fact that MSCs do **not** function as stem cells either *in vivo* or *in vitro* (though they do play other roles). This led Caplan himself in 2017 to suggest that 'stem cell' was a misnomer and request that MSCs be rebranded as 'medicinal signaling cells' [5]. Instead, it is widely accepted that their therapeutic effect is due to their ability to home to sites of injured tissue and their paracrine effect (signaling to other cells) [10] .

> ***"While MSCs can be caused to form various cell lineages in vitro, it is apparent that they do not differentiate in vivo, whether supplied as a therapy or under ordinary circumstances."***

A final interesting property of MSCs is that they appear to be immune evasive, triggering little immune response even when sourced from unmatched donors [11][12]. However, it is an ongoing question what the degree of safety difference is between autologous and allogeneic cells (i.e., using your own cells for therapy vs. that of a donor), and indeed if there is any at all [13].

In summary, MSCs are:

- Not stem cells;
- Not associated with ethical issues;
- Derived with little difficulty from adult humans;
- Capable of exerting a healing effect through homing and cell signaling;
- Are immune evasive.

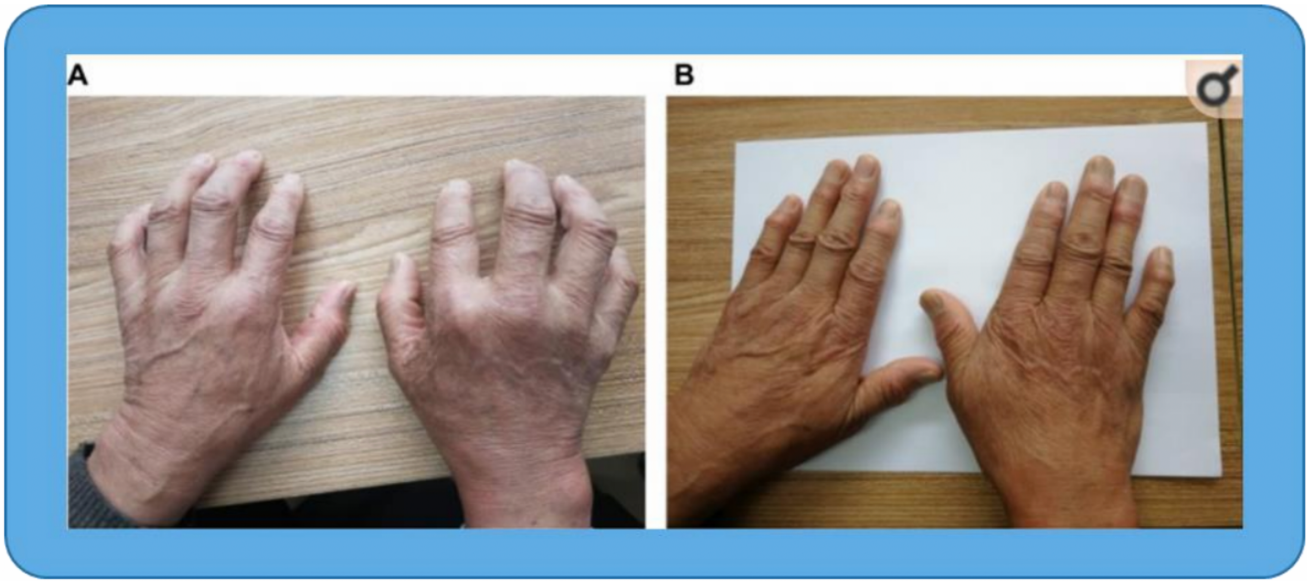

Figure 2: A picture from a 2019 clinical trial in China [14] . (A) The patient is unable to unclench his hand because of rheumatoid arthritis; (B) 3 years post-treatment from MSCs he can stretch his hands freely.

HYPE & HOAX

Today, mesenchymal stem cell therapy is being offered for any number of indications, including cardiovascular, autoimmune (e.g., rheumatoid arthritis), degenerative diseases (e.g., osteoarthritis), and even neurological disorders (e.g., Alzheimer's). In the scientific community interest has abounded – one measure of this is a steady increase in the registration of clinical trials using MSCs as the investigational product; in 2020 around 125 trials were registered [7] . Despite this, there remains very limited large-scale data that shows that the MSC treatments work, and consequently very limited regulatory approval.

Now, there are MSC treatments approved by major regulatory boards. Cumulatively,

- South Korea and Japan have approved 6 autologous treatments;
- The EU, India, Japan, Canada/New Zealand, South Korea have approved 5 allogeneic treatments.

However, the majority of clinics worldwide offer unregulated therapy. This does not only apply to the developing world; for

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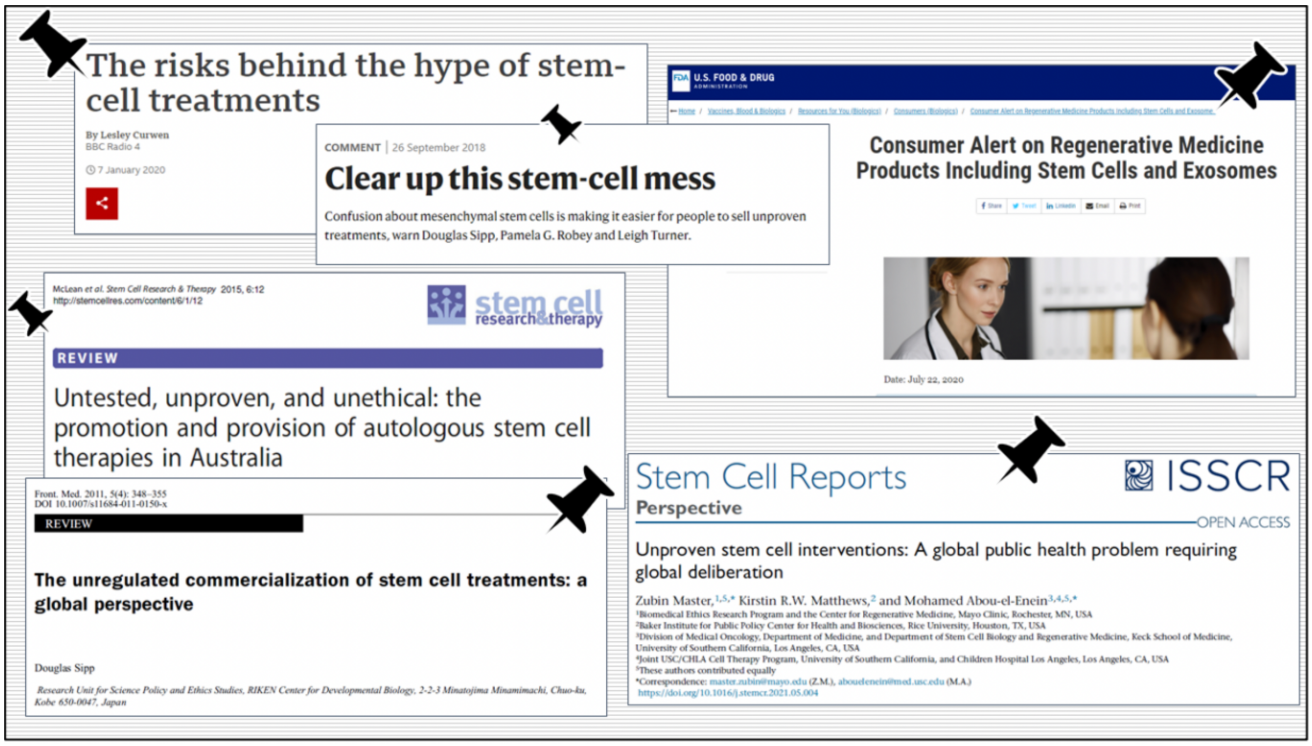

Figure 3: Snapshots of news articles, scientific reviews, and government body briefings on the dangers of unproven stem cell therapy

example, in Europe many MSC therapies are being offered as mainstream despite a severe lack of clinical data to support efficacy, according to a survey conducted in 2017 [15] .

The purported regenerative potential of MSCs, combined with the uncertainty surrounding their identity and functionality, has allowed large-scale profiteering, employing potentially dangerous direct-to-consumer marketing.

This has sparked backlash from regulatory agencies and the scientific community. Notably, the Food & Drug Administration (FDA) of the United States, regarded as the regulatory gold-standard, has not only not approved mesenchymal stem cell therapy, but has issued stern warnings against it.

Does this mean all is lost? No – one should not throw out the proverbial baby with the bathwater. The presence of fraudulent clinics does not imply the absence of respectable ones. Making this distinction is a pertinent issue, as

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both the 'good' and 'bad' present the same features (e.g., sophisticated website, journal publications)! [16] .

Some proponents of stem cell therapy have argued that "big pharma doesn't like it" [17] . And there may be validity to this. Autologous stem cell therapy uses your own cells – removing requirement for centralized manufacturing and prevents monopolizing of the market. Further, big pharma objectively benefits from chronic conditions that require prolonged treatment [18] . Drugs that can cure one-off are 'not a sustainable business model' [19] – a case in point is a recently approved gene therapy which costs $2.1 million USD, its cost being justified because only one dose is required [20] .

Others argue that the regulatory procedures are too bogged down in bureaucracy to flex with the rapidly changing field of regenerative medicine. DVC Stem, a clinic in the Cayman Islands, may have a point with this [21] ; a 2016 review quoted over 10 years and $1,000,000,000 for the cost to bring new drugs to market [22] .

It seems likely that there are bureaucratic complications and capitalist agendas at play. Nonetheless, "Regulations don't exist to hold people back; they exist for a reason," according to Dr. Qasim Rafiq, associate professor of cell and gene therapy at University College London – a view held by many in the scientific community. So, what do these regulatory agencies need to give stem cell therapy a stamp of approval? On paper at least, it is a demonstration of safety and efficacy.

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To assess safety and efficacy, clinical trials are employed, testing the therapy on a sample of people. However, not all clinical trials are created equal; design, analysis of results, and number of participants all determine whether the results are in fact valid and generalizable. For example, having a control group is important to consider, with participants randomly assigned to account for placebo effects – a Randomized Controlled Trial (RCT) is considered the current gold standard; better yet if both the researchers and

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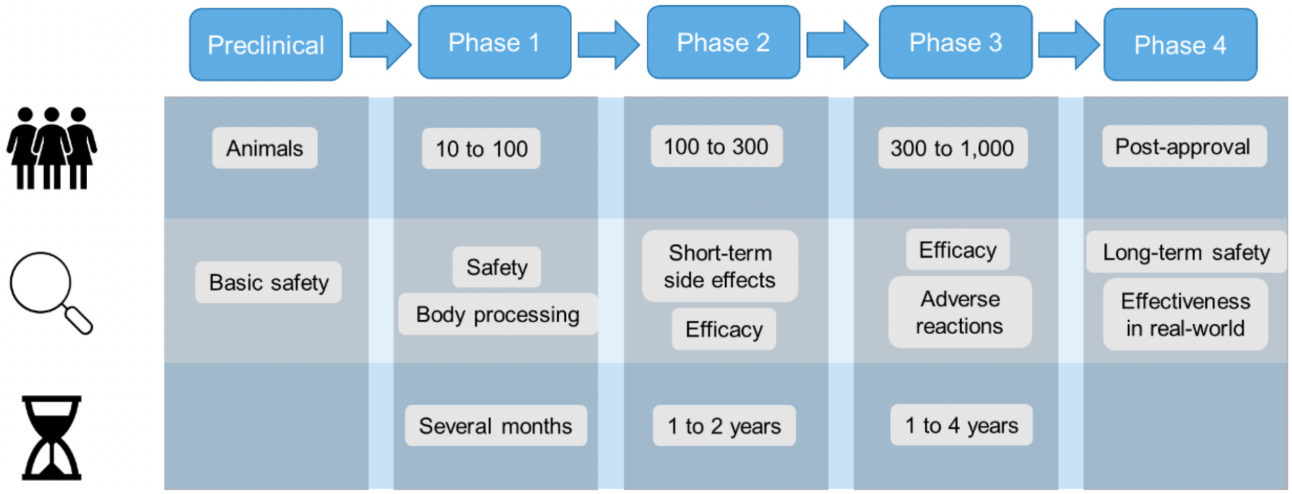

Figure 4: The drug approval process of the Food and Drug Administration (FDA)

participants are unaware of assignment, in which case the trial is double blind.

The current trial structure, used by the FDA, among others, requires preclinical testing on animals for basic safety, three phases of pre-market tests, and then continual monitoring post-approval. As mentioned, this is a rigorous process, taking many years, and much expense. Additionally, the FDA requires an inspection of the manufacturing facility [23][24] .

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Regarding safety, a comprehensive review in 2018 looked at reported adverse effects in the scientific literature and mass media [25].

They found 35 in total (a relatively low number) and these resulted from:

- Hazardous injection sites e.g., directly into brain, vitreous body (fills space in eyeball between lens and retina);
- Improper processing of cells: e.g., grossly filtered bone marrow aspirate, contaminated cells;
- Unideal selection of cells e.g., animal-based;
- Patients coming into procedure with compromised health;
- The only case of tumors was associated with usage of embryonic stem cells.

There were no adverse effects for a 'standard' MSC procedure (i.e., proper processing, injection into a

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safe target site etc.) Of course, this article covered reported adverse effects. One can imagine that naturally not all adverse events would be reported, but perhaps the serious ones would, for the most part, be reported in some fashion, so this is promising. Continuing, a systematic review of MSCT in 2012 reviewed 36 clinical trials, of which 8 were randomized, and concluded that the therapy was safe for a number of indications, with no adverse effects (including cancer formation), save transient fever [26].

A 2020 BBC article reports of blindness in one eye after a 'botched injection' at a UK clinic – the clinic argues that this was 1 out of 1,700 [27]; this suggests a case of isolated clinical failure as opposed to a dangerous procedure. Likewise, the New York Times published a cautionary article after a 66-year-old stroke victim received stem cell therapy in Mexico, Argentina, and China, and proceeded to develop extremely aggressive tumors, which proved fatal. Given the presence and rapid growth of the tumors, it is highly likely that these were ESCs or iPSCs [28][29]. However, the warning the article leaves with us is worth noting as a general principle, "If something is too good to be true, it probably is."

In summary, the data lead to the conclusion that MSCs are a safe treatment, once prepared and administered correctly – unfortunately, given the lack of clinical regulation, and therefore standardization, this cannot be guaranteed. Even so, if there were more serious adverse effects, the media would likely be quick to pounce on these opportunities, so safety-wise, the therapy seems satisfactory even given the unregulated landscape. The one notable caveat being that in some cases of cancer, MSCs can help the cancer metastasize [5][10].

EFFICACY

But what about efficacy? After all, if a vaccine were 100% safe but only worked in 1 in 10 people, it's unlikely that it would receive regulatory approval. Many have conducted scientific reviews of existing clinical trials for various conditions. Recent reviews of clinical trials are examined below.

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Disease	Safe	Efficacious	# of CT (s)	Reference	Year Published
Spinal Cord Injury	Yes	Variable	38	[30]	2020
Multiple Sclerosis	Yes	No	5*	[31]	2019
Osteoarthritis	Yes	Variable	18	[32]	2021
Rheumatoid Arthritis	Yes	Variable	9	[12]	2020
COPD	Yes	No	14	[13]	2021

Table 1: Safety and Efficacy of Stem Cell Therapy based on recent reviews of clinical trials for various conditions. *Not a review – conglomerate of clinical trials

Spinal cord injury (SCI) – Can cause paralysis and other severe medical complications with limited treatment options available. Both reviews noted promising results in preclinical studies, but most trials lacked a control group, so more RCTs are necessary. There was a wide range of results – from remarkable motor improvement to none, and many times improvement was transient. Scaffolds may be an option to promote stem cell longevity.

> ***"Moreover, patients should be aware of the poor clinical results obtained thus far in clinical trials to prevent exaggerated expectations and dramatic psychological consequences in the case of failure to obtain significant results."***
>
> 2019 MSCs for Spinal Cord Injury Review [33]

Overall, there was statistically significant improvement, but results were extremely variable, and largely underwhelming.

Multiple sclerosis (MS) – Inflammatory disease of nervous system which often leads to irreversible disability. Results were not statistically significant [34].

Osteoarthritis (OA) – the degeneration of joint cartilage in isolated joints. Of the 11 MSC trials analysed some showed significant and sometimes remarkable improvement for up to 18 months post trial, but the results across trials were highly variable.

Rheumatoid arthritis (RA) – an autoimmune disease in which the immune system attacks the synovial membrane protecting joint. The 9 published trials had highly variable results; there were some cases of significant, long-term improvement.

Chronic obstructive pulmonary disease (COPD) – chronic lung disease that causes restricted airflow in lungs. For the most part the therapy results in no significant improvement.

It should be noted that one of the main issues plaguing stem cell therapy is heterogeneity of cell population (especially for autologous procedures), as well as in processing. This is likely a limiting factor in showing efficacy at large scale. Heterogeneity also occurs for trial parameters such as dosage size and method of delivery.

Practicable strategies for robust clinical trials

RCTs, aside from being more difficult to coordinate, present two major challenges because it is unethical to leave whether a critical patient gets a placebo or (potential) cure up to chance, and because one cannot charge patients for a placebo treatment, leading to funding issues. Additionally, getting enough patients for a trial to be acceptably powerful (able to generate significant results) can be challenging for some indications e.g., severe SCI. The MS trial-conglomerate combined 5 semi-independent trials across 4 countries, and harmonized procedures, essentially creating one large, better-powered trial. Additionally, they did a cross-over, so half the patients got a placebo in the first half and half received the therapy, and then vice versa.

There is still a significant gap between preclinical and clinical success. For example, in the rheumatoid arthritis case, nearly 100 preclinical studies showed that MSC therapy significantly reduced arthritis induction and progression, yet clinical results were certainly underwhelming. There were cases of remarkable recovery, but these were often transient, and the results highly variable within and across trials. Without fail, each review called for further Phase III testing, with a control group, to reliably determine efficacy.

CARIBBEAN LANDSCAPE

The Caribbean and Latin America are ideal targets for endeavoring stem cell clinics because of their proximity to the U.S. and lack of regulation.

CARIBBEAN LANDSCAPE

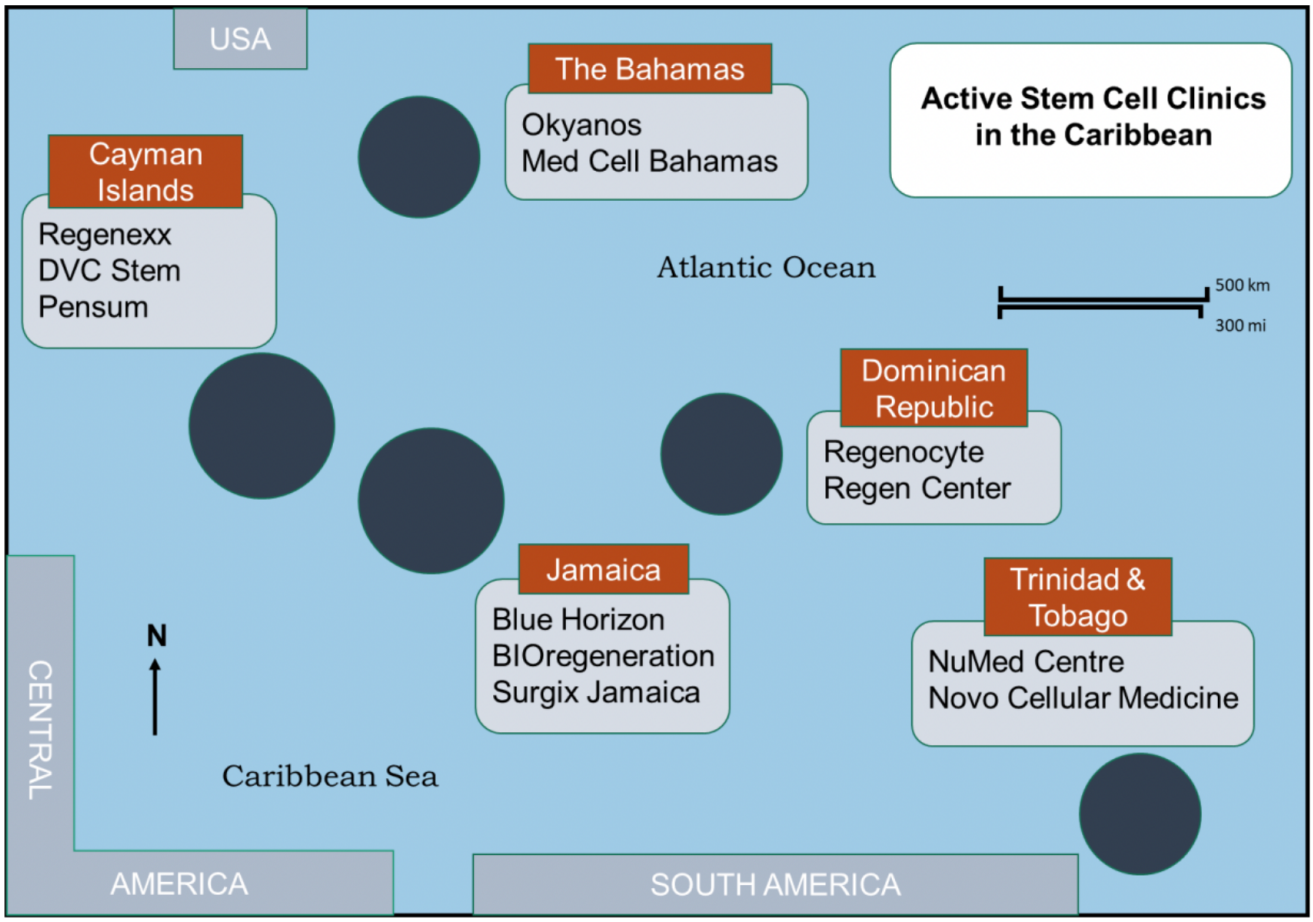

Figure 5: Active Stem Cell Clinics in the Caribbean as of July 2021, with an online presence.

Regulatory Status

According to the Food and Drugs Act of T&T, a 'drug' includes any substance sold or represented for use in the treatment of a disease or disorder; further, any drug on the market in T&T must be approved by the Food & Drug Advisory [35]. From 1999 to 2021 there is no record of a stem cell therapy (or any cell therapy) being approved for use in T&T. This may also be the case in the Dominican Republic and Jamaica. Antigua & Barbuda passed a Stem Cell Research and Therapy Act in 2019, but that seems to be the extent of the government's involvement. However, in the Cayman Islands and the Bahamas there seem to be regulations in place. The Bahamas has a Stem Cell Ethics Committee which oversees

all SCT in the country, and the facilities in Cayman Islands are reportedly 'fully licensed and inspected by the government', which, as a British Overseas Territory, may carry a reasonable amount of weight (granted, Britain has its own unregulated stem cell therapy issues).

Doctors

Three doctors in prominent positions within the T&T public health system were interviewed [personal correspondence]. None of them was aware of stem cell clinics in Trinidad, and they had only heard of stem cell therapy vaguely. They confirmed that while the practice was likely to be illegal officially, in practice the lack of regulatory approval was unlikely to make a difference.

Insurance

Another factor that carries great weight in the advance of SCT is the stance of insurance companies – if they were to cover the therapy, it would lend massive credibility to its efficacy, as well as increase its accessibility. In this regard also Cayman Islands seems to be paving the way, with insurance companies covering stem cell treatments for locals.

A senior official at Guardian Life Trinidad confirmed that, according to policy, experimental therapies are not covered [personal correspondence]. What makes a therapy experimental? Guardian Life has agents, locally and overseas, that curate networks of trusted hospitals and healthcare providers, and to join this network the facility must be extremely reputable and there should be widespread agreement in the scientific and medical communities about the treatment being offered. Further, they will generally only cover a treatment overseas if a local (regulated) treatment provider does not exist. They were aware of a stem cell clinic operating in Trinidad, and point-blank rejected any related claims.

However, in rare cases, a business decision can be made at the company's discretion to fund an experimental procedure, but this is often at its expense, without the aid of reinsurance. Considering reinsurance companies, a report from Reinsurance Group of America (RGA) said they would

likely only consider covering therapies that had been commissioned as 'acceptable clinical practice' by the WHO and/or local government entities [36].

EVERYTHING IS NOT WHAT IT SEEMS

A notable point when considering SCT is that surface appearances can be misleading. A good case in point is Regenocyte, a clinic in the Dominican Republic [37]. On the surface, the website looks professional, advertises their cutting-edge practices, and features numerous testimonials; but the website does not show that their head doctor, Zannos Grekos had his license revoked by the State of Florida after two of his SCT patients died [38]. This is not to say necessarily that the testimonials are not true, or that Grekos is not now legitimate, but certainly, there is more than what meets the eye.

Another case study is Novo Cellular Medicine Institute in Trinidad [39]. They advertise all their procedures as being part of 'clinical trials', but upon checking the ClinicalTrials.gov registry one would find only two trials were ever registered by this facility, one being an apparent duplicate, and the other being terminated. Similarly, they claim to be approved by 'the' Institutional Review Board (IRB) or Ethics Review Committee (ERC). Which IRB or ERC they are associated with remains unknown. This is not to say that this particular clinic is misleading per sé, but rather to highlight the lack of reliability of superficial claims.

As an aside, clinical trials should always be assessed judiciously; a 2021 review of MSC clinical trials found 1,138 registered (which sounds wonderful at first) but noted that of those, only 18 had published results [7]. One should further bear in mind that "the safety and scientific validity of a study is the responsibility of the study sponsor," which is listed prominently at the top of the ClinicalTrials.gov webpages.

A 2017 perspective report from a global group of researchers featured a robust list of 'co-opted tokens of scientific legitimacy' which stem cell clinics use to give the impression that the clinic is

CONCLUSION

Co-opted Tokens of Scientific Legitimacy	
Accreditations and awards	Claiming accreditation of products or international training
Boards and advisors	Featuring boards with highly accoladed academics/medics
Clinical study registration	Registering trials without any real scientific backing
Ethics review	Simply using this term without evidence
Location	Renting of space withing legitimate institutions
Membership	Joining established academic or professional societies
Outcome registries	Relying on voluntary, self-reporting registries instead of controlled clinical trials
Patenting	Advertising patent applications (that have not even been approved)
Publication	Publishing results in [often sub-standard] journals
Rationales	Citing preclinical data and 'promising' results
Self-regulation	Forming organisations to self-regulate
Technical language	Using scientific-sounding words
Testimonials and endorsements	Judiciously selecting favorable testimonials, or using celebrity comments

Figure 6: Co-opted Tokens of Scientific Legitimacy – used by disreputable clinics to give the impression of a respectable and reliable treatment, adapted from Sipp et al., 2017 [40]

scientifically sound [40]; an adapted version is presented below. Many of these tokens were present in Caribbean clinics, such as membership with an international organization

> ***"It can be difficult even for professionals, let alone patients, to determine whether these tokens demonstrate true compliance with the evidentiary standards for developing and testing stem cell therapies."***
>
> Sipp et al., 2017 [40]

requiring only a subscription fee without any accountability [personal correspondence]. The utilization of these tokens makes the issue of unregulated stem cell therapy particularly pressing, since patients, and even doctors, will find it challenging to distinguish between the sincere and the shady.

CONCLUSION

Efficacy – Proof of large-scale efficacy seems to be lacking for every application of SCT, so one may be paying for a life-changing therapy, but instead only receive transient pain-relief.

CONCLUSION

Uniformity – The lack of regulation means that one clinic's standards are not another's, leaving it to patients to make decisions without enough information.

Insurance – Costs are still quite high, and many insurance companies will not cover experimental treatments, thus limiting accessibility.

Greed – The human factor of greed cannot be ignored and is likely the driving force behind harmful profiteering.

'Inertia' – For any new treatment, there is a degree of resistance, and this is amplified by capitalism and/or bureaucracy. There is also a great degree of inefficiency in small island governments, which can hinder innovation. This lends some weight to the idea of using a treatment before full traditional regulation has approved it.

Easy – The MSCT procedure is relatively non-invasive, usually involving a bone marrow aspirate or liposuction, and there is little-to-no recovery time.

Safety – The safety of MSC therapy has consistently been shown through clinical trials and other reports.

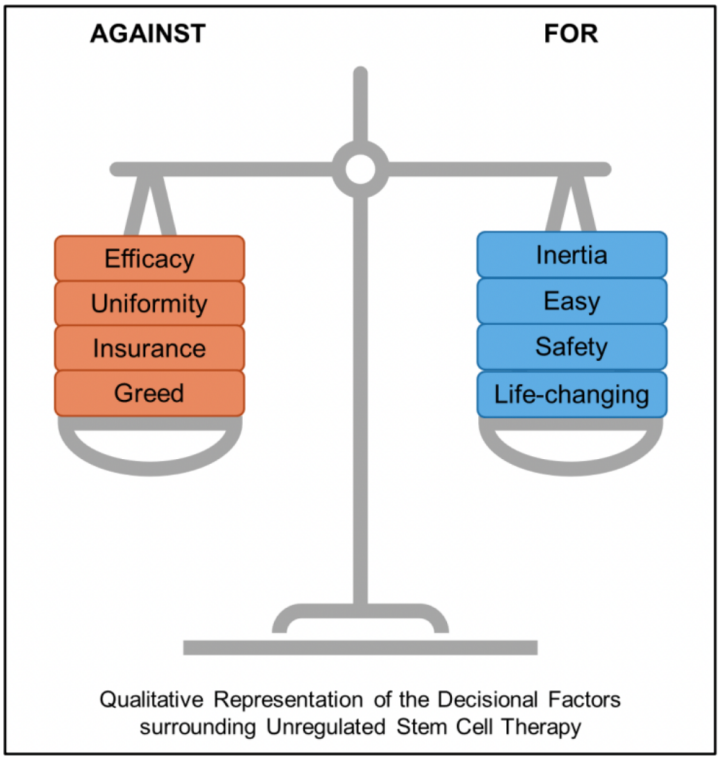

Figure 4: A Balanced look at unregulated stem cell therapy.

Life-changing – There seems to be evidence that for some people the treatment has made a significant life impact. Given the right-to-try principle, and safety of the procedure, this is precedent for allowing the therapy, once patients are well informed.

NEXT STEPS

Based on previous publications on strategies to address unregulated stem cell

NEXT STEPS

therapy [8][40][42], as well as knowledge of the local landscape, I would recommend the following steps as the most practicable.

The first step is information. Taking example from the Cayman Islands and the Bahamas, Stem Cell Ethics Committees can be commissioned to monitor novel therapies worldwide & regionally and conduct research to track any local instances of the therapy. Information from this committee will feed into recommendations for regulatory agencies and medical societies – keeping doctors on the ground well-informed is critical.

Next, regulatory agencies should be given more power. It is well accepted that the regulatory agencies in many Caribbean countries have little bark and even less bite. However, this need not be the case; in 2006 it was discovered that a stem cell therapy clinic in Barbados was involved with a highly scandalous and unethical scheme in Ukraine using aborted fetuses; the government creditably took swift and severe action, and completely wiped their hands of stem cell therapy (to this day there is none in Barbados). This shows that small island governments can take effective stands once there is sufficient motivation.

Once there is a viable threat to operability, clinics will be far more likely to comply with measures mandated by the government. To enforce the measures, the wheel need not be re-invented. International organizations, such as the International Society for Stem Cell Research [1] and the International Society for Cell & Gene Research [43] have developed protocols for clinical trials and research which can be implemented locally. These will include regulated procedures, standards for informed consent, facility inspections, and independent review of patient outcome.

This regulation will feed into a clinic accreditation program, which is essential if patients and healthcare providers are to make an informed choice. The International Cellular Medicine Society – (now defunct) [44], proposed over 10 years ago the a 'Stem Cell Clinic Accreditation Program.' Unfortunately, this did not get off the ground for a variety

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of reasons – for example, Regenocyte in the DR argued that reporting results might make the clinic look bad (in other words it would allow patients to make decisions with hard data, instead of selective testimonials) [45]. However, given the correct incentive (as discussed above) these hesitancies can be overcome, and this program would be able to generate real-world data (once clinics had shown basic safety), while overcoming funding issues, as business would continue.

A step further, apart from just reporting, would be conglomerate clinical trials, much like the MS group [31]. Clinics across the Caribbean would use a standardized protocol for a specific disease, and a cross-over style to ensure everyone is treated. This may be challenging as clinics will likely argue standardization would stall progress in this nascent field, much as Apple argued that uniform charger design would hinder innovation [46], but perhaps government funding can aid here. Certainly, if stem cell therapy can aid in diseases like osteoarthritis, Caribbean governments would certainly have incentive to investigate.

Finally, it seems expedient to change the name of 'stem cell therapy'. Clinics to date are busily advertising these cells that can 'essentially become any type of new cell or tissue' which is untrue on several levels. Stem cell clinics should perhaps be called Cell Therapy Clinics and should thoroughly explain the limitations of the therapy thus far, so patients can make an informed decision. It should be noted that some clinics, such as Regenexx in the Cayman Islands, have these procedures already.

Cell therapy may hold substantial healing potential – appropriate regulation will ensure that any benefits are maximised and scamming is minimised.

DISCLAIMERS

This report is not intended to provide medical advice of any kind.

I declare no conflicting interests.

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BIBLIOGRAPHY

[1] International Society for Stem Cell Research n.d. https://www.isscr.org/ (accessed July 22, 2021).

[2] Blum B, Benvenisty N. The Tumorigenicity of Human Embryonic Stem Cells. Adv Cancer Res 2008;100:133–58. https://doi.org/10.1016/S0065-230X(08)00005-5.

[3] The 2012 Nobel Prize in Physiology or Medicine - Press release - NobelPrize.org n.d. https://www.nobelprize.org/prizes/medicine/2012/press-release/ (accessed July 18, 2021).

[4] Karanika S, Karantanos T, Li L, Corn PG, Timothy C. Current Challenges of iPSC-Based Disease Modelling and Therapeutic Implications. Cells 2019;8:403.

[5] Caplan AI. Mesenchymal stem cells: Time to change the name! Stem Cells Transl Med 2017;6:1445–51. https://doi.org/10.1002/sctm.17-0051.

[6] Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini FC, Krause DS, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy 2006;8:315–7. https://doi.org/10.1080/14653240600855905.

[7] Rodríguez-Fuentes DE, Fernández-Garza LE, Samia-Meza JA, Barrera-Barrera SA, Caplan AI, Barrera-Saldaña HA. Mesenchymal Stem Cells Current Clinical Applications: A Systematic Review. Arch Med Res 2021;52:93–101. https://doi.org/10.1016/j.arcmed.2020.08.006.

[8] Sipp D, Robey PG, Turner L. Clear up this stem-cell mess. Nature 2018;561:455–7. https://doi.org/10.1038/d41586-018-06756-9.

[9] Caplan AI. Why are MSCs therapeutic? New data: new insight. J Pathol 2009;217:318–24. https://doi.org/10.1002/path.

[10] Musiał-Wysocka A, Kot M, Majka M. The Pros and Cons of Mesenchymal Stem Cell-Based Therapies. Cell Transplant 2019;28:801–12. https://doi.org/10.1177/0963689719837897.

[11] Ankrum JA, Faii Ong J, Karp JM. Mesenchymal stem cells: immune evasive, not immune privileged. Nat Biotechnol 2014;32:252–60. https://doi.org/10.1038/nbt.2816.Mesenchymal.

BIBLIOGRAPHY

[12] Lopez-Santalla M, Fernandez-Perez R, Garin MI. Mesenchymal Stem/Stromal Cells for Rheumatoid Arthritis Treatment: An Update on Clinical Applications. Cells 2020;9. https://doi.org/10.3390/cells9081852.

[13] Glassberg MK, Csete I, Simonet E, Elliot SJ. Stem Cell Therapy for COPD. Chest 2021. https://doi.org/10.1016/j.chest.2021.04.020.

[14] Wang L, Huang S, Li S, Li M, Shi J, Bai W, et al. Efficacy and safety of umbilical cord mesenchymal stem cell therapy for rheumatoid arthritis patients: A prospective phase I/II study. Drug Des Devel Ther 2019;13:4331–40. https://doi.org/10.2147/DDDT.S225613.

[15] Gay MHP, Baldomero H, Farge-Bancel D, Robey PG, Rodeo S, Passweg J, et al. The survey on cellular and tissue-engineered therapies in Europe in 2016 and 2017. Tissue Eng 2021;27:336–50. https://doi.org/10.1089/ten.tea.2020.0092.

[16] Sipp D. The unregulated commercialization of stem cell treatments: A global perspective. Front Med China 2011;5:348–55. https://doi.org/10.1007/s11684-011-0150-x.

[17] NuMed's modern, controversial approach to curing diseasesStem cell healing n.d. https://newsday.co.tt/2018/02/03/numeds-modern-controversial-approach-to-curing-diseasesstem-cell-healing/ (accessed July 22, 2021).

[18] Vaccine Capitalism: five ways big pharma makes so much money – Corporate Watch n.d. https://corporatewatch.org/five-ways-big-pharma-makes-so-much-money/ (accessed July 19, 2021).

[19] It's Official! Curing Patients Is Bad for Business | MedPage Today n.d. https://www.medpagetoday.com/opinion/revolutionandrevelation/72407 (accessed July 19, 2021).

[20] Zolgensma From Novartis Is The Most Expensive Drug Ever Approved: Shots - Health News: NPR n.d. https://www.npr.org/sections/health-shots/2019/05/24/725404168/at-2-125-million-new-gene-therapy-is-the-most-expensive-drug-ever (accessed July 19, 2021).

BIBLIOGRAPHY

[21] DVC Stem: Advanced Stem Cell Therapy Clinic n.d. https://www.dvcstem.com/ (accessed July 22, 2021).

[22] DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: New estimates of R&D costs. J Health Econ 2016;47:20–33. https://doi.org/10.1016/j.jhealeco.2016.01.012.

[23] How Drugs are Developed and Approved | FDA n.d. https://www.fda.gov/drugs/development-approval-process-drugs/how-drugs-are-developed-and-approved (accessed July 22, 2021).

[24] Minneci PC, Deans KJ. Clinical trials. Semin Pediatr Surg 2018;27:332–7. https://doi.org/10.1053/j.sempedsurg.2018.10.003.

[25] Bauer G, Elsallab M, Abou-El-Enein M. Concise Review: A Comprehensive Analysis of Reported Adverse Events in Patients Receiving Unproven Stem Cell-Based Interventions. Stem Cells Transl Med 2018;7:676–85. https://doi.org/10.1002/sctm.17-0282.

[26] Lalu MM, McIntyre L, Pugliese C, Fergusson D, Winston BW, Marshall JC, et al. Safety of Cell Therapy with Mesenchymal Stromal Cells (SafeCell): A Systematic Review and Meta-Analysis of Clinical Trials. PLoS One 2012;7. https://doi.org/10.1371/journal.pone.0047559.

[27] The risks behind the hype of stem-cell treatments - BBC News n.d. https://www.bbc.com/news/health-51006333 (accessed July 19, 2021).

[28] A Cautionary Tale of 'Stem Cell Tourism' - The New York Times n.d. https://www.nytimes.com/2016/06/23/health/a-cautionary-tale-of-stem-cell-tourism.html (accessed July 19, 2021).

[29] Berkowitz AL, Miller MB. Glioproliferative Lesion of the Spinal Cord as a Complication of "Stem-Cell Tourism." N Engl J Med 2016;375:195–6. https://doi.org/10.1056/nejmc1605534.

[30] Yamazaki K, Kawabori M, Seki T, Houkin K. Clinical trials of stem cell treatment for spinal cord injury. Int J Mol Sci 2020;21. https://doi.org/10.3390/ijms21113994.

BIBLIOGRAPHY

[31] Uccelli A, Laroni A, Brundin L, Clanet M, Fernandez O, Nabavi SM, et al. MEsenchymal StEm cells for Multiple Sclerosis (MESEMS): A randomized, double blind, cross-over phase I/II clinical trial with autologous mesenchymal stem cells for the therapy of multiple sclerosis. Trials 2019;20:1–13. https://doi.org/10.1186/s13063-019-3346-z.

[32] Agarwal N, Mak C, Bojanic C, To K, Khan W. Meta-Analysis of Adipose Tissue Derived Cell-Based Therapy for the Treatment of Knee Osteoarthritis. Cells 2021;10:1365. https://doi.org/10.3390/cells10061365.

[33] Cofano F, Boido M, Monticelli M, Zenga F, Ducati A, Vercelli A, et al. Mesenchymal Stem Cells for Spinal Cord Injury: Current Options, Limitations, and Future of Cell Therapy. Int J Mol Sci 2019;20.

[34] Preliminary Results Show Mesenchymal Stem Cell Therapy in Multiple Sclerosis is Safe — MS Society of Canada n.d. https://mssociety.ca/resources/news/article/preliminary-results-show-mesenchymal-stem-cell-therapy-in-multiple-sclerosis-is-safe (accessed July 22, 2021).

[35] Chemistry, Food And Drugs Division | Ministry of Health n.d. https://health.gov.tt/services/chemistry-food-and-drugs-division (accessed July 22, 2021).

[36] Woh Yoke Meng S. Stem Cell Therapy. RGA Glob Heal Br 2018. https://www.rgare.com/docs/default-source/newsletters-articles/global-health-brief---stem-cell-therapies---sept-2018.pdf?sfvrsn=ce8b9288_2 (accessed July 22, 2021).

[37] Regenocyte Adult Stem Cell Therapy | Stem Cell Treatment for COPD, Dementia, Cardiomyopathy, Pulmonary Hypertension n.d. https://www.regenocyte.com/ (accessed July 22, 2021).

[38] Florida suspends doctor accused of illegal stem cell therapy - CNN n.d. https://edition.cnn.com/2012/03/08/health/stem-cell-doctor-suspension/index.html (accessed July 21, 2021).

BIBLIOGRAPHY

[39] Clinical Research and Stem Cell Biology in India and Trinidad n.d. http://www.novomedinstitute.org/ (accessed July 22, 2021).

[40] Sipp D, Caulfield T, Kaye J, Barfoot J, Blackburn C, Chan S, et al. Marketing of unproven stem cell-based interventions: A call to action. Sci Transl Med 2017;9:1–6. https://doi.org/10.1126/scitranslmed.aag0426.

[41] Rosenbaum L. Tragedy, Perseverance, and Chance — The Story of CAR-T Therapy. N Engl J Med 2017;377:1313–5. https://doi.org/10.1056/nejmp1711886.

[42] Master Z, Matthews KRW, Abou-El-Enein M. Unproven stem cell interventions: A global public health problem requiring global deliberation. Stem Cell Reports 2021;16:1435–45. https://doi.org/10.1016/j.stemcr.2021.05.004.

[43] Home - International Society for Cell & Gene Therapy n.d. https://www.isctglobal.org/home (accessed July 22, 2021).

[44] Stem Cells | ICMS -- Advancing Stem Cell Treatments, Stem Cell Medicine, Stem Cell Clinics n.d. http://www.cellmedicinesociety.org/home (accessed July 21, 2021).

[45] Sick and desperate fueling 'stem-cell tourism' n.d. https://www.nbcnews.com/health/health-news/sick-desperate-fueling-stem-cell-tourism-flna1c9447889 (accessed July 22, 2021).

[46] The EU Wants All Phones to Work With Interoperable Chargers, Here's What That Means for Apple's Lightning Port - MacRumors n.d. https://www.macrumors.com/guide/eu-charging-standard-proposals-and-apple/ (accessed July 21, 2021).