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The urgent need for clear and concise regulations on exosome-based interventions

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SUMMARY

Turner and colleagues recently argued that countries with unclear laws and regulations regarding stem cells, exosomes, and other regenerative medicine products should develop and enforce more comprehensive regulatory structures. We fully agree with this opinion and discuss that failure to do so may lead to troubling predicaments, such as the Japanese cases, where patients are at risk of serious complications or even death.

Turner et al. (2023a) recently reported that 60 clinics from 38 businesses in the US advertise stem cell or exosome-based interventions as treatment or preventive measures for COVID-19. We fully agree with their statement that "Countries with gaps and areas of interpretive uncertainty in legislation related to stem cells, exosomes, and other regenerative medicine products should develop and enforce more comprehensive regulatory structures." In particular, exosome-based interventions are being offered worldwide, not only for COVID-19 but for a wide range of diseases and conditions (Asadpour et al., 2023). There is thus an urgent need to disseminate information and clarify regulations in such countries to protect patients. Failure to do so may lead to troubling predicaments, such as the Japanese cases described in the following, in which not only are patients put at risk of serious complications or even death but also no one can even determine whether a patient has died or not.

Exosomes are a type of extracellular vesicles responsible for intercellular communication through the transfer of various bioactive substances. They are currently being evaluated as diagnostic markers and a means of delivering therapies to target cells (Abbott, 2023). According to Asadpour et al. (2023), 288 clinical trials using exosomes and 127 clinical trials using extracellular vesicles were registered on ClinicalTrials.gov as of November 2022. However, there are currently no approved therapies using extracellular vesicles or exosomes (https://www.isev.org/patient-information-and-safety-notice–extracellular-vesicles-exosomes-and-unproven-therapies), and there are serious risks associated with their administration to the human body, including unexpected side effects such as malignant transformation, contamination, unwanted immune responses, and toxicity (Abbott, 2023; https://www.jsrm.jp/cms/uploads/2024/05/news14993-2.pdf). Indeed, patients in Nebraska who received an unapproved exosome intervention became seriously ill and suffered from sepsis in 2019, prompting the Food and Drug Administration (FDA) to issue a warning (FDA, 2019). The following year, the International Society for Extracellular Vesicles (ISEV) also issued an alert to patients (https://www.isev.org/patient-information-and-safety-notice–extracellular-vesicles-exosomes-and-unproven-therapies).

In the US, exosomes for therapeutic use are regulated as drugs and biological products under the Public Health Service Act and the Federal Food Drug and Cosmetic Act, thus requiring review and approval before marketing (FDA, 2019). In the EU, native exosomes are regulated as biological medicinal products (Silva et al., 2021). Nevertheless, Turner et al. (2023b) reported in another survey that 60 businesses in the US are selling exosome products, and Asadpour et al. (2023) identified 34 businesses and clinics in the US and 14 entities in the EU promoting exosome-based interventions for anti-aging, hair loss, autism, rheumatism, Parkinson's disease, and so forth. If this is occurring in countries with existing regulations, even more alarming situations are likely in countries where regulations on the medical use of exosomes remain unclear or nonexistent.

Japan is, unfortunately, such an example. Because extracellular vesicles, including exosomes, are not considered cells, the Act on the Safety of Regenerative Medicine (ASRM), which regulates the act of physicians administering cells to patients, does not apply (Fukui et al., 2022). Even more alarming is that aside from the ASRM, there are virtually no regulations restricting physicians from performing interventions that lack scientific evidence when operating outside the framework of public insurance (i.e., when a patient pays for the entire treatment). Using

the Ministry of Health, Labor and Welfare (MHLW) website and Google search engine, a think tank surveyed medical institutions claiming to offer "exosome therapy" and "stem cell culture supernatants" (often referred to as exosome therapy in private clinics in Japan) and found that 669 medical institutions provide these therapies (Organization for the Promotion of Safety in Regenerative Medicine, 2023). This number is by far the largest compared to the US and EU. According to this study, the most common treatment targets were skin care and anti-aging (532 cases), hair growth (358 cases), and recovery from fatigue (135 cases), while the most commonly used raw material and tissue were cells derived from allogeneic sources (566 cases) and fat (287 cases), respectively. These trends are similar to those identified in previous studies (Turner et al., 2023b; Asadpour et al., 2023), but the second most common source of derived tissue was teeth (specifically, human deciduous dental pulp), which is unique to Japan for unclear reasons. In total, 488 institutions (73%) used "regenerative medicine" as a keyword on their websites, and 501 institutions (75%) also offered regenerative medicine as defined by the ASRM.

Recently, rumors circulated about patients dying after exosome administration (Kubota, 2023). On October 11, 2023, the Society for Regenerative Medicine and Anti-Aging published a document entitled "Regarding the Occurrence of Death Cases Related to Stem Cell Culture Supernatant," urging society members to carefully consider the use of unapproved products because they had obtained information on patient deaths (https://aarm.jp/news/%E5%B9%B9%E7%B4%B0%E8%83%9E%E4%B8%8A%E6%B8%85%E6%B6%B2%E3%81%AB%E9%96%A2%E3%81%99%E3%82%8B%E6%AD%BB%E4%BA%A1%E4%BA%8B%E4%BE%8B%E3%81%AE%E7%99%BA%E7%94%9F%E3%81%AB%E3%81%A4%E3%81%84%E3%81%A6/). However, according to media reports, the society responded that its members were not involved in the cases. Adding to the confusion, the medical institution where patients were rumored to have died claimed that no such reports had been filed, and an official from the MHLW concluded that the information originated from an unknown source (Kubota, 2023). The situation where no one can even confirm whether the serious adverse event of patient death is a rumor or fact is a serious problem.

The current exclusion of exosomes from the government's system for identifying adverse events for unproven interventions is a serious concern for patient safety. According to media reports, a well-known private cosmetic surgery clinic administered exosomes (contained in stem cell supernatant) to at least four patients, including relatives of staff members with stage IV lung cancer, and found that the cancer rapidly worsened after administration (Ito, 2023). In late November 2023, it was reported that treatment had continued despite advice for discontinuation by an outside oncologist. Although the MHLW reportedly did not know the details, if some regulation, the ASRM, for example, applied to exosome-based interventions, the clinic administering the interventions would have been required to report adverse events when they occur to the government and the Certified Committee for Regenerative Medicine, which reviewed the provision plan of the intervention. If this had been the case, the treatment would have likely been discontinued.

The lesson to be learned from these Japanese cases is that there is an urgent need to develop regulations to protect patients from serious risks associated with interventions based on little or no scientific evidence and to ensure that adverse events are reported to regulatory agencies when they occur. Nevertheless, such regulations should not impede the development of clinical research using exosomes. In October 2023, The Japanese Society for Regenerative Medicine published a proposal to revise the scope of the ASRM, calling for the administration of extracellular vesicles containing exosomes to be regulated under the ASRM to ensure their safety and allow for regulatory oversight (https://www.jsrm.jp/cms/uploads/2023/10/%E5%86%8D%E7%94%9F%E5%8C%BB%E7%99%82%E7%AD%89%E3%81%AE%E3%83%AA%E3%82%B9%E3%82%AF%E5%88%86%E9%A1%9E%E3%83%BB%E6%B3%95%E3%81%AE%E9%81%A9%E7%94%A8%E9%99%A4%E5%A4%96%E7%AF%84%E5%9B%B2%E3%81%AE%E8%A6%8B%E7%9B%B4%E3%81%97%E3%81%AB%E9%96%A2%E3%81%99%E3%82%8B%E6%8F%90%E8%A8%80%EF%BC%88%E6%97%A5%E6%9C%AC%E5%86%8D%E7%94%9F%E5%8C%BB%E7%99%82%E5%AD%A6%E4%BC%9A%EF%BC%89.pdf). In April 2024, it issued guidance outlining what providers of exosome-based interventions should review (https://www.jsrm.jp/cms/uploads/2024/05/news14993-2.pdf). The Japanese Society for Extracellular Vesicles published its position in December 2023 that only those products that have passed strict screening as biological products under the Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices should be brought to clinical practice (https://jsev.jp/docs/jsev_ev_treatment_2023122501.pdf). The International Society for Stem Cell Research (ISSCR) should also take a leadership role in this issue (including collaboration with the ISEV, if possible) to raise awareness for patient protection and to promote regulatory clarity in each country. Since extracellular vesicles, including exosomes, are not stem cells, ISSCR may not consider them to be under its scope for regulation. However, many medical institutions handle them alongside stem cells (Turner et al., 2023a; Turner et al., 2023b; Organization for the Promotion of Safety in Regenerative Medicine, 2023), so how can we expect non-specialist patients to know the difference and, more importantly,

distinguish between safe and unsafe interventions on their own? The ISSCR has had a significant global impact on addressing unproven stem cell-based interventions. We hope that the next revision of its guidelines and patient handbook will include exosome-based interventions.

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AUTHOR CONTRIBUTIONS

T.I. conceived the study and discussed its structure with T.H. and M.F., who prepared the first draft. T.O. provided expert advice. All authors discussed, revised, and approved the final draft.

DECLARATION OF INTERESTS

T.O. is a legal consultant to Salaria Clinic Tokyo.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During manuscript preparation, the authors used DeepL for translation and editing. After using this tool/service, the authors reviewed and edited the content as needed and will take full responsibility for the content of the publication.

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