INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

Minister Takamaro Fukuoka
Ministry of Health, Labour and Welfare
1-2-2 Kasumigaseki
Chiyoda-ku
Tokyo, 100-8916

21 February 2025

Dear Minister Fukuoka,

On behalf of the International Society for Stem Cell Research (ISSCR), I write to share our comments regarding Japan's recent amendments to the Act on the Safety of Regenerative Medicine (ASRM). The ISSCR is the leading professional organization of stem cell scientists, representing nearly 5,000 members around the world, including Japan. Our members are scientists, clinicians, ethicists, and educators dedicated to the responsible advancement of stem cell research and its translation to the clinic. The ISSCR commends Japan for taking steps to strengthen the ASRM to protect patient safety. To realize this objective, we urge the Ministry to use its authority to implement regulations that adhere as closely as possible to accepted international guidelines for the administration of regenerative medicine (RM) interventions.

Japan's leadership in stem cell research has driven remarkable advances that have transformed the field of regenerative medicine globally and paved the way for new therapies to address major public health problems. As the field progresses, ensuring a regulatory framework that both encourages responsible innovation and safeguards patient well-being remains essential. The recent ASRM amendments offer an opportunity to strengthen Japan's approach to regenerative medicine oversight. We respectfully offer the following recommendations in support of this goal.

Designate in vivo genetic medicine as a Class I regenerative medicine therapy.

Administering in vivo genetic medicines presents significant risks due to the complex and highly specialized nature of these therapies. Similar to other Class I products like ex vivo genetic medicines and induced pluripotent stem cell therapies, provision plans for these procedures should be subject to pre-approval by the Ministry to mitigate safety risks and ensure efficacy. In vivo genetic medicines can trigger immune responses that lead to adverse events, have off-target effects that cause genetic mutations, and carry long-term uncertainty due to their novelty. In some cases, the treatment and its effects may be irreversible. These procedures should be subject to the strictest level of review by the

Ministry and its proxies to protect patient safety and ensure ethical standards are upheld.

Increase oversight of committees reviewing Class II RM provision plans.

Certified committees have faced challenges in directly regulating the administration of unproven RM intervention and in ensuring appropriate scientific and ethical evaluation. A recent study identified gaps in expertise among committee members, and the Ministry's own commissioned report highlighted concerns such as physicians submitting plans outside their areas of specialization, a reliance on questionable scientific evidence to support safety assessments, and members with conflicts of interest on some committees. The Ministry's report also identified issues with duplication of documents and application language that implies supporting information for Class II plans is sometimes recycled.

To guarantee to the public that Class II RM procedures have been appropriately evaluated for safety, scientific validity, and ethical acceptability, we encourage the Ministry to enhance oversight of certified committees by ensuring that members possess the necessary expertise to evaluate submitted plans effectively and to maintain independence from those submitting proposals. Additionally, clear disqualification standards should be established to address potential conflicts of interest and to ensure accountability in the review process. In cases of noncompliance, the Ministry should also retain the authority to disband committees to protect patients. Such measures would help reinforce the integrity of the approval process for Class II RM interventions.

Address the high volume of Class II RM approvals.

The ASRM framework currently permits the administration of Class II RM interventions outside of formal clinical trials, provided the provision plans are reviewed and approved by a certified committee. However, this structure differs from international best practices, including the ISSCR Guidelines for Stem Cell Research and Clinical Translation. The widespread availability of unproven RM interventions, particularly outside the scope of research settings, raises concerns about patient safety and scientific rigor.

Since the ASRM's implementation in 2014, more than a thousand Class II RM provision plans have been approved, resulting in over ten thousand patients receiving interventions each year. This volume suggests that some plans may be approved without adequate assessment of risks and potential benefits. There have also been documented adverse events, including a case in Tokyo reported last year where patients experienced vision impairment following an intravenous infusion of adipose-derived mesenchymal stem cells. Similar instances of adverse events have been reported in Japan and worldwide, demonstrating that unproven RM interventions pose a significant risk. While we understand that the Ministry does not have discretionary authority to deny Class II RM provision plans, we encourage the Ministry to explore ways to ensure that approvals for these plans are granted cautiously and align more closely with internationally recognized scientific and ethical standards.

The ASRM amendments represent a critical step in advancing regenerative medicine

isscr.org | isscr@isscr.org | +1 (224) 592-5700
630 Davis St, Suite 200, Evanston, IL 60201 USA

in Japan. By applying a rigorous review process to high-risk interventions such as in vivo genetic medicine, enhancing oversight of the review process for Class II RM provision plans, and ensuring that approvals are granted judiciously, Japan can continue to be a global leader in regenerative medicine. We appreciate the Ministry's consideration of these recommendations and would welcome the opportunity for further dialogue.

Respectfully,

Valentina Greco, Ph.D.
President
ISSCR