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Tackling Ethical Challenges of Premature Delivery of Stem Cell-Based Therapies: ISSCR 2018 Annual Meeting Focus Session Report

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Clinical uses of unproven stem cell-based interventions abound, yet many patients may be harmed by receiving them, raising complex ethical, economic, and societal concerns. Regulators, scientists, clinicians, professional societies, and patient advocacy groups need to collaboratively articulate expectations related to the proper development and delivery of stem cell-based therapies.

The delivery of unproven stem cell-based interventions (SCBIs) is widespread, and sometimes involves businesses engaging in direct-to-consumer (DTC) marketing to patients. The industry using DTC marketing comprises individual clinics worldwide as well as highly organized business alliances operating within advanced economies, such as Australia, Japan, and the United States. Approximately a decade ago, this industry consisted mainly of clinics offering a diverse range of purported stem cell therapies derived from multiple sources (e.g., adipose tissue, bone marrow, embryonic tissue, fetal tissue, placental tissue, and umbilical cord blood) (Lau et al., 2008). The majority of firms, especially those in developed economies, now administer unproven uses of autologous biomaterials, primarily harvested from fat or bone marrow, with some delivering SCBIs in the context of "pay-to-participate" clinical research. Both of these approaches may minimize legal liability (Turner and Knoepfler, 2016; Turner, 2017). The use of "adult" stem cells has also been characterized as a means of avoiding ethical concerns particular to embryonic stem cells (Bianco et al., 2013). However, their premature use in the clinical setting raises other challenging issues.

While the desire to access potentially therapeutic interventions is completely understandable, many patients stand to be harmed by receiving unproven SCBIs as evidenced by recent cases of tumor formation and blindness following stem cell injections (Berkowitz et al., 2016; Kuriyan et al., 2017). Such occurrences also threaten to incur substantial health care costs due to adverse events and derail the legitimate field of regenerative medicine. Of note, the delivery of unproven SCBIs has occurred in the context of widespread medical consumerism, dominant neoliberal ideologies of health care, and the privileging of patient autonomy (including the "right to try" movement) over the integrity and social importance of translational research in the development of therapeutic evidence. The introduction of "coverage with evidence" schemes (whereby payment is made for experimental approaches as data about safety and efficacy are obtained) around the globe and streamlined market authorization pathways for stem cell-based products in major health markets such as Japan and the United States may also limit the ability to assess the safety and effectiveness of emerging and existing therapies (Sipp, 2015; Lee and Lysaght, 2018).

Patients seeking information about SCBIs commonly navigate masses of conflicting information and contending claims found in DTC advertising, news articles, media, and blogs and from various "accidental advisors," who are asked for advice about available treatments (Petersen et al., 2015). For those seeking an option to "do something," attempting to establish the credibility of different information sources is a tortuous undertaking (Tanner et al., 2017). The increasing sophistication of online advertising has compounded the difficulties faced, with many businesses incorporating "tokens of scientific legitimacy" into their marketing strategies (Munsie et al., 2017; Sipp et al., 2017). Such strategies may reinforce patients' beliefs in the trustworthiness and reputability of clinic operators.

The ethical issues raised by the delivery of SCBIs include those related to: respecting the autonomous wishes of patients and their families to access potentially beneficial interventions; maximizing the likelihood that current and future patients benefit and are not unnecessarily harmed in the process of receiving SCBIs; ensuring that claims about SCBIs are accurate and understandable; and working toward the fair allocation of resources in the development and delivery of such interventions. Regulators, scientists, clinicians, and professional societies are positioned to articulate ethical expectations and to set clear standards regarding the appropriate uses of SCBIs. Following the

discussion at a Focus Session at the 2018 Annual ISSCR (International Society of Stem Cell Research) Meeting (Melbourne, Australia, June 2018), each of these possibilities is described in turn, followed by some novel approaches that promise to help alleviate some of the current problems related to SCBIs.

Regulators: Developing Coordinated Frameworks

In most major healthcare markets, stem cell research and treatments are regulated under complex frameworks that involve multiple agencies and institutional actors. Changes in the regulation of the potentially valuable market for new regenerative medicine products have also been introduced as a means of increasing national economic competitiveness. As a result, there is insufficient alignment and coordination between regulators with authority over the various domains of research, clinical practice, and product manufacturing and marketing in relation to stem cell research and treatment. Internationally, there are differences in the legal mechanisms, technical language, and entities that regulate the various domains. However, there are also similarities in how these frameworks generally separate regulatory responsibilities according to sharp distinctions that are typically drawn between research and clinical practice.

The separation of regulatory responsibilities reflect "silos" that may have not only enabled the growth of the DTC market for stem cells, but may also be hampering the translation of stem cell research into demonstrably safe and efficacious products. Many countries that have invested in the basic science and translation of stem cell research have adopted a so-called "risk-based approach." This approach generally sets out an evidence-based pathway for the manufacture and marketing of stem cells as medicinal or advanced therapy products while allowing patients to access medical interventions with stem cells in the context of clinical care (Lysaght et al., 2017). Medical interventions do not fall under the jurisdiction of product regulatory authorities, but are instead regulated under separate, and often de-centralized, governance frameworks for professional practice.

Allowing products that lack the evidence necessary for market licensure to be provided in the context of clinical care may discourage investment in product development. If manufacturers can generate revenue without needing to demonstrate this level of evidence, there is little incentive for them to invest in expensive, late-phase clinical trials capable of formally determining safety and efficacy. Moreover, exemptions that permit the production of stem cells for clinical use without the market entry barriers of regulatory approval provide an unfair competitive advantage against manufacturers willing to invest in efficacy trials. Both situations introduce inefficiencies and uncertainties into the clinical translation process that place patients at risk, burden public health systems with potentially ineffective products, delay access to information about the optimal usage of products that may provide benefit (Kimmelman and London, 2015), and run the risk of derailing cellular approaches to regenerative medicine. A lack of enforcement of laws in place to protect consumers from unprofessional marketing practices has also contributed to products being available without sound evidence of safety and efficacy.

With no single authority responsible across these domains, more coherent and coordinated frameworks are needed to better align the ethics and regulation of biomedical innovation. For this purpose, a cooperative regulatory model that spans multiple domains of regulation is needed (Lysaght et al., 2018). Such a model could potentially bridge the current silos that regulate innovation pathways in clinical research and practice through the establishment, implementation, and enforcement of evidence-based standards for cell processing and manufacturing, for marketing SCBIs, and for introducing them into routine clinical care. This cooperative model is consistent with calls for a coordinated approach to reduce the risks associated with DTC marketing of unproven stem cell products and incentivize scientifically grounded, clinically meaningful, and socially valuable innovation (Sipp et al., 2017).

In addition, attention should be directed at developing regulatory standards with respect to the use of social media platforms designed to target DTC marketing of SCBIs to people based on their online activity. This is especially important for those who may be newly diagnosed or injured and thereby uniquely vulnerable to aggressive sales techniques that promise cures at a reduced (yet still substantial) cost within a very short time period lest the opportunity be lost. In addition, some of these therapies are targeting patients with certain neurological disorders that bring with them issues of whether patients truly understand what is being said given that these conditions can cause major cognitive problems.

Scientists: Harmonizing Standards and Comprehensive Reporting of Experiences

Clear professional standards for developing and testing SCBIs have been articulated (see http://www.isscr.org/docs/default-source/all-isscr-guidelines/guidelines-2016/isscr-guidelines-for-stem-cell-research-and-clinical-translation.pdf?sfvrsn=4). Importantly, assessing the ethical acceptability of particular research initiatives requires incorporating scientific expertise. This is necessary in order to evaluate not only the scientific rationale emerging from *in vitro*, and when applicable, *in vivo* results, but also the risk of abnormal cell function, immunological reactions, the modification of the pathological micro-environment, and long-term health effects. Unfortunately, many SCBIs are now discussed with

respect to their safety and manufacturing fidelity without a careful assessment of the rationale as to why that therapy should or would work in the condition being treated.

This having been said, uniform standards for cell processing, manufacture, and control should be harmonized by international groups of scientists, cell banks, and regulators since stem cells react in response to different stimuli, requiring uniformity and definition of references to assure a realistic prediction of risks and benefits in clinical translation. Mechanisms need to be developed to encourage and/or require the publication of medium- and long-term clinical outcomes, which will facilitate better categorization of the risks of SCBIs. Similarly, reports are needed not only in the cases of success, but also when there are negative results and adverse events.

Clinicians: Managing Competing Obligations

Doctors are increasingly exhorted to practice patient-centered or person-centered medicine, to respect patients' autonomy, to support their judgements, and to share decision-making with them. At the same time doctors are expected to practice evidence-based medicine, to use limited health resources wisely, to avoid over-diagnosis and over-treatment, and to adhere to precepts of medical professionalism. The central challenge for clinicians is that none of these ideas are ethically or epistemologically unproblematic and all create different obligations in healthcare settings. This challenge is becoming more common as healthcare "knowledge" becomes more democratized, biomedical technology becomes more complex, and the traditional standards of therapeutic evidence collapse. Requests by patients for unproven SCBIs illustrate the tensions physicians face in seeking to protect both their patients and the public interest.

Physicians have obvious professional obligations to recommend SCBIs of proven safety and efficacy to their patients. In addition, they should compassionately help patients understand the potential hazards of using unproven SCBIs and apprise them of reasonable alternative therapeutic approaches. Furthermore, physicians ought not to deliver unproven SCBIs except under very limited settings that constitute responsible innovation or in the context of approved research protocols (see http://www.isscr.org/docs/default-source/all-isscr-guidelines/guidelines-2016/isscr-guidelines-for-stem-cell-research-and-clinical-translation.pdf?sfvrsn=4 and http://www.isscr.org/docs/default-source/clinical-resources/isscr-stem-cell-based-clnical-trials-practical-advice_final_23jan2018.pdf).

Professional Societies: Enhancing and Implementing Standards for Clinical Translation

Professional societies, such as the ISSCR, have a vested interest in ensuring the integrity of stem cell research and the ethically appropriate use of SCBIs. Toward such ends, the ISSCR has issued and updated guidelines (see http://www.isscr.org/docs/default-source/all-isscr-guidelines/guidelines-2016/isscr-guidelines-for-stem-cell-research-and-clinical-translation.pdf?sfvrsn=4) in this regard and has provided an array of resources for patients considering SCBIs (http://www.closerlookatstemcells.org/patient-resources/). The International Society for Cellular Therapies has issued similar statements and resources (see https://www.celltherapysociety.org/page/UCT). Some medical societies have also issued expected standards in the clinical provision of SCBIs for their respective members (see https://www.aao.org/clinical-statement/intraocular-stem-cell-therapy; www.thoracic.org/members/assemblies/assemblies/rcmb/working-groups/stem-cell/resources/statement-on-unproven-stem-cell-interventions-for-lung-diseases.pdf; https://www.acsep.org.au/content/Document/ACSEP%20Stem%20Cell%20Position%20Statement%20Nov17%20Final(1).pdf).

Despite such efforts, there are at least two key nodes in the clinical translation pipeline that should be better regulated and made more accountable: ethics review boards and the physicians acting as principal investigators in clinical trials. Both need to be able to assess not only what a clinical trial is attempting to show, but also the basis for the therapy and the rigor with which it is being tested. The focus of such evaluations should not be limited to safety concerns but should address the rationale for the proposed trial and the robustness of the preclinical science underpinning its claims. Both ethics review boards and physicians also have a responsibility to facilitate clinical translation while also protecting patients during these efforts. The process by which they should assess these therapies needs to be better articulated and better supported (Barker et al. 2018). How exactly one does the latter is variable, but a number of possibilities exist, such as setting up international teams of experts who can offer impartial advice on any such trials. Professional societies can and should help develop approaches to doing so.

Discussion

Addressing the ethical issues inherent to the delivery of unproven SCBIs will clearly need to involve the coordinated efforts of: regulators to fill gaps in current policies and to enforce them; scientists engaging in responsible research; clinicians delivering SCBIs that are likely to be helpful; and professional societies articulating appropriate standards and guidelines. In addition, there are some other approaches that should be considered, such as well-structured and independently funded registries, engaging in social media discussions, and finding ways for informed patients to have meaningful conversations with other patients about particular SCBIs. Working in partnership with

consumer and patient advocacy groups to ensure that position statements of professional societies are translated into accessible language and resources for particular patient groups may also assist people in distinguishing legitimate research and treatments from exploitative commercial practice (see https://www.acsep.org.au/content/Document/ACSEP%20Stem%20Cell%20Position%20Statement%20Nov17%20Final(1).pdf).

Outcome registries have been enormously helpful in enhancing understanding of hematopoietic stem cell transplants (Horowitz 2008). In addition, registries are often proposed as a way of helping to assess the long-term benefits and harms associated with innovative therapies or those that are approved with little long-term clinical outcome data. Accordingly, consideration should be given to creating a registry for SCBIs. To be most useful, such a registry would need to capture high-quality clinical data and be well curated. However, it is unclear who might be able to undertake such curation and support this work. Public funding for a well-maintained, stringent outcomes registry could provide a beneficial resource. However, mechanisms need to be developed to protect against using any such registry as a token of legitimacy by those who are inappropriately delivering SCBIs, as has happened on occasions with the clinicaltrials.gov website.

Social media is increasingly playing an influential role in sustaining the market for SCBIs. Consequently, scientists, clinicians, and professional societies should consider the possibility of engaging in social media conversations regarding stem cell research and SCBIs so that accurate information can be introduced in an accessible fashion and to potentially counter spurious claims about the high benefits and low risks of many SCBIs that are amplified via social media. Nevertheless, doing so is fraught with challenges related to time and resources, developing effective communication skills, the potential for misattributions or uses of postings and aggressive backlash and trolling by those keen to protect their own interests.

Finally, although there are a range of web-based resources (including those mentioned above) for patients who are contemplating SCBIs as a possible option to alleviate their suffering, such resources alone may not be powerful enough to overcome the seductive messages of hope offered by DTC marketing. One novel approach to consider would be to find ways for patients to "talk" to other patients regarding what is known about particular diseases and conditions and treatments for them. If patient advocacy groups could become even more meaningfully engaged with scientists and clinicians conducting responsible research regarding SCBIs, they would be better positioned to talk with other patients about the current state of evidence regarding particular SCBIs and when and why caution should be exercised in seeking treatment with them. However, care must be taken in identifying organizations that do not have financial or other ties to the industry engaged in the premature delivery of unproven SCBIs. At the same time, it is important to recognize the very real possibility that patient and consumer advocacy groups may, simply by virtue of their illness experiences, increase utilization of unproven but widely hyped clinical interventions.

While it is unclear what processes would best work to support and address the ethical issues in the delivery of SCBIs, there are several promising approaches that should be considered, some of which we have articulated here.

DECLARATION OF INTERESTS

J.S. is a member of Merck KGaA's Bioethics Advisory Panel and Stem Cell Research Oversight Committee; and he is a member of IQVIA's (formerly Quintiles) Ethics Advisory Panel. R.B. sits on the advisory boards of FCDI, Novo Nordisk, LCT, and Oxford Biomedica. I.K. is a Bone Marrow Transplant Physician, vice-President of the Bone Marrow Transplant Society of Australia and New Zealand and a board member of the NSW Stem Cell Network. He actively recruits patients to industry-funded clinical trials but does not receive any honoraria, salary, research, educational, or travel support from industry. G.P. is a member of the board of directors of Holostem Terapie Avanzate, Modena, Italy and consultant of J-TEC, Gamagori, Japan. D.S., T.L., and C.T. have no conflicts to disclose.

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