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Inclusivity and diversity: Integrating international perspectives on stem cell challenges and potential

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SUMMARY

Regenerative medicine has great potential. The pace of scientific advance is exciting and the medical opportunities for regeneration and repair may be transformative. However, concerns continue to grow, relating to problems caused both by unscrupulous private clinics offering unregulated therapies based on little or no evidence and by premature regulatory approval on the basis of insufficient scientific rationale and clinical evidence. An initiative by the InterAcademy Partnership convened experts worldwide to identify opportunities and challenges, with a focus on stem cells. This was designed to be inclusive and consensus outputs reflected the diversity of the global research population. Among issues addressed for supporting research and innovation while protecting patients were ethical assessment; pre-clinical and clinical research; regulatory authorization and medicines access; and engagement with patients, policy makers, and the public. The InterAcademy Partnership (IAP) identified options for action for sharing good practice and building collaboration within the scientific community and with other stakeholders worldwide.

Introduction

Scientific advances in regenerative medicine continue to offer great promise in our attempts to tackle intractable diseases, including those presented by aging populations and, potentially, to reduce health care costs. These advances will be applicable worldwide. However, as noted in a recent editorial (Pera, 2020), there is still much to be done to involve hitherto underrepresented groups in their contribution to research and in ensuring that research studies collectively address therapeutic priorities and have the potential to benefit all patients.

In 2020, the InterAcademy Partnership (IAP), the global network of more than 140 academies of science, engineering, and medicine, constituted a working group on regenerative medicine to integrate perspectives from researchers worldwide on the opportunities and challenges in this field with the following objectives:

1. To use advances in research and development as rapidly as possible, safely and equitably, to provide new routes to patient benefit worldwide.
2. To support medical claims by robust and replicable evidence so that patients and the public are not misled.

This IAP work focused on stem cells for unmet medical needs but it is expected that many of the conclusions

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would be relevant more broadly for regenerative medicine. In this context, regenerative medicine is described as comprising various novel interdisciplinary approaches to health care, including the use of cell and gene therapies, aimed at tissue regeneration, repair, restoration, and reorganization. Regenerative medicine strategies depend upon harnessing, stimulating, guiding, or replacing endogenous development and repair processes. In this commentary we take the opportunity to draw attention to some key points from the statement (IAP, 2021) and discuss emerging messages in the context of recent developments.

Scientists, nominated by IAP member academies, provided inputs from Bangladesh, Brazil, Cuba, Czech Republic, Ecuador, Egypt, France, Germany, India, Ireland, Italy, Japan, Lithuania, New Zealand, Philippines, Serbia, South Africa, Taiwan, and the UK, with expertise in medical disciplines, biosciences, and ethics. At the time of writing this commentary, the consensus statement has been endorsed by the majority of IAP academies. One of the starting points for preparation of the IAP statement was a comprehensive joint report by the academies of science and medicine across the European Union (EU) (Cossu et al., 2020; EASAC and FEAM, 2020) that incorporated discussion from an academies-organized session at the World Science Forum in 2019.

IAP global statement main messages

Although stem cell therapy has proved itself, so far, in the treatment of only a limited number of approved clinical indications, there is very active research and development underway for many others, including neurological, hepatic, cardiovascular, retinal, and musculoskeletal disorders, as well as cancers. There is potential for transformative change in addressing disease causes rather than symptoms. The pace of science has continued to advance rapidly, and one of the key messages from the academies is that it is vital to grow investment worldwide in basic science to understand cell and tissue biology and to provide the resource for future innovation. However, enthusiasm about the broad potential of regenerative medicine applications has led to a disconnect between expectations and the realities of translating technologies into clinical practice. The academies endorsed a call for substantial rethinking of the social contract (Cossu et al., 2018) that enables public support for research and clinical practice. It is vital to tackle multiple issues for poor-quality science, inconsistent ethical and regulatory policies, unclear funding models, unrealistic hopes, and unscrupulous commercial clinics. In the social contract, citizens pay tax and/or insurance to get the best available treatment for diseases that may affect them. They expect that therapy will constantly improve, but this requires research, especially on basic mechanisms of diseases, which funding agencies are less inclined to fund than translational research. Moreover, incurable diseases lead patients to uncritically accept any proposed therapy, exposing themselves to possible clinical risks and certain economic damage. The consequences of not tackling the challenges and finding the right balance for research and innovation would be to waste investment and researchers' time, as well as to undermine patient trust and protection.

There are two main problems. First, in many countries, commercial clinics offer unregulated products and services promising a wide range of benefits using poorly characterized treatments with little or no evidence of efficacy, with safety concerns, misleading scientific rationale, and with the primary intention of profit. The IAP statement offers guidance on the principles that must be embedded in information for patients contemplating such offerings. One crucial criterion is emphasized for patients deciding on whether to consent. Patient consent must be fully informed in terms of the information on risk and effectiveness. In addition, patients should not be expected to pay to participate in clinical research on regenerative medicine until it becomes an approved treatment that may be reimbursed according to the specific procedures of each country's health system, whether public or private. However, this payment is now happening in some countries. A requirement to pay to participate is not unique for the field of regenerative medicine, despite restraints offered by current safeguards by regulatory authorities and institutional review committees and the standards of medical professionalism. The ethical issues may be complex (Shaw et al., 2017) and it is crucially important that the research oversight system is sufficiently robust to ensure that all trials satisfy the standards of ethical research (Lynch and Joffe, 2019).

Second, there is an evidence crisis as a result of premature marketing approval and commercialization of expensive approaches based on some, but insufficient, scientific rationale and clinical evidence, facilitated by regulatory authority initiatives for accelerated access. Conditional approval or other accelerated access mechanisms have been introduced in the EU and in other countries, including Japan, the United States, and Canada. Efforts to provide accelerated access to innovation are welcome in principle, and it is acknowledged that, when the number of available patients is low, there may be a need, for example, to combine work on proof of concept with dose finding. It must also be generally recognized that there is an accelerating pace in moving from research discovery to human applications: this has been

noteworthy recently during the coronavirus disease 2019 (COVID-19) pandemic and will be discussed later. However, granting early access transfers financial costs and the burden of medical uncertainty from drug developers to health care systems and from trial participants (who should be required to undergo rigorous informed consent procedures) to health care consumers (who are not). Further discussion on early access, for example on problems related to surrogate endpoints and weak post-marketing obligations, is provided in the European academies' work (EASAC and FEAM, 2020).

In this era of increasing pressure for international competitiveness, where some medicines regulatory frameworks become increasingly permissive, it is important that countries do not lower their regulatory thresholds without fully considering the consequences for patient safety, health care budgets, and public trust in science, and without ensuring that commitments on post-marketing studies are respected. Undesirable practices inherent in stem cell tourism in some countries (e.g., Skeen et al., 2019; Julian et al., 2020) are one consequence of the relative laxity in some national regulatory frameworks.

HOSPITAL EXEMPTION PROCEDURES

In some countries, unlicensed medical products in development can be used under certain regulated procedures to allow named patients early access to innovation in situations of unmet clinical need. For example, in the EU, there is the hospital exemption provision (regulation 1394/2007/EC). While it is important not to preclude any accelerated procedures such as hospital exemptions and compassionate use, they must be carefully scrutinized and authorized when sufficient evidence suggests a possible therapeutic effect; the reason cannot be that there is no other therapeutic option. In 2017, a child affected by epidermolysis bullosa, already considered a terminal patient, was returned to a normal life thanks to the autotransplantation of autologous, genetically corrected epidermis (Hirsch et al., 2017). Although this treatment was outside of a regular clinical trial, it was supported by a previous proof-of-concept study (Mavilio et al., 2006) and by 40 years of successful clinical practice of epidermis autotransplantation in large burns.

Within the EU there is substantial variation in national hospital exemption provisions relating to the criteria for unmet medical needs and benefit/risk balance (Hills et al., 2020). Thus, there are considerable challenges for using hospital exemption consistently as a mechanism in support of innovation, while also safeguarding public health and ensuring that evidence-based clinical trials are not circumvented (EASAC and FEAM, 2020). In EU member states and elsewhere, it is important to counter the perception that hospital exemption should be used as a cheaper and quicker approach for therapies that would typically be approved under a market authorization.

Supporting responsible science and innovation

The IAP statement assessed a range of issues for supporting responsible science and innovation (Table 1). One cross-cutting issue is the need to do more to facilitate internationally agreed frameworks for robust, interdisciplinary assessment of research protocols and evidence collection. This has implications for research infrastructure and for sharing (and possibly certifying) skills worldwide, particularly for low- and middle-income countries (LMICs). There is also interest worldwide in ethical guidelines for research on regenerative medicine (Table 1), including recently, for example, in Iran (Afshar et al., 2020). IAP has previously published general guidance (IAC and IAP, 2012) for promoting responsible science, with recommendations for researchers, research institutions, research funders, and journals. These broad recommendations are relevant to the conduct of regenerative medicine when integrated with community standards of medical practice. Academies, with their power to convene experts from many scientific disciplines, can also help by building inclusivity to tackle the interdisciplinary weakness that may hinder the pace of progress in this field (Cheuy et al., 2020).

A second pervasive theme is for setting the balance between promotion of innovation and the obligation to put patients first. For example, the objective to increase investment in basic and clinical research must be accompanied by solutions to the problem of how expensive therapies can be reimbursed, otherwise medicine pipelines will be filled with innovation that cannot be afforded. Expensive therapies appear inequitable but it is necessary to take a long-term health economic perspective. Advanced technologies in regenerative medicine, if treating the cause of disease, may bring sustained and substantial cost savings and may eliminate the long-term costs of poorly efficacious current therapies.

The issues for responsible science and its applications are illustrated by the experience of the COVID-19 pandemic. Although there is a need for urgent intervention with novel therapies, proposed use of stem cells during a pandemic must also be based on rigorous evidence of safety and efficacy following strict research protocols that address the ethical issues and characterize the cells used, focusing on a defined stage of the disease and in the hands of a team with capacity to undertake the intervention. Unfortunately, as the US Food and Drug Administration (FDA)

Table 1. Supporting research and innovation in regenerative medicine while protecting patients

Priorities	Summary of points covered in IAP statement
Ethical assessment	Ethical issues relate to uncertainty, patient consent, professional responsibilities, equity, and fairness. Concerns are evaluated further by Hermeren (2021) amid increasing momentum worldwide to discuss ethical issues. There are implications for professional training and constitution of ethics committees
Research *in vitro* and in animal models	Need for robust scientific foundation for clinical research and for ensuring consistency in composition and viability of a novel agent as it moves through successive stages of research and development
Clinical trials	Should be conducted according to approved design and monitoring procedures with transparency in data collection. The orphan nature of some rarer applications must be recognized in trial design to ascertain the acceptable level of evidence for safety and efficacy
Regulatory authorization and access to new medicines	Proportionate and consistent regulation must be based on replicable science and international development of standards as a step toward necessary regional and global regulatory coordination in addressing discrepancies (Qiu et al., 2020). LMICs must be included in global convergence on quality, efficacy, safety, and post-marketing surveillance (WHO, 2020)
Engaging with patients, policy makers, and the public	Notwithstanding the excellent work of the International Society for Stem Cell Research, there is more to be done to describe the difference between evidence-based practice and unproven, erroneous, and illegitimate practices. This requires an informed public and well-advised health professionals and regulators worldwide

For the IAP statement, see IAP (2021).

observed early during the pandemic (Marks and Hahn, 2020), some of the same clinics that have been offering unproven stem cell therapies for diverse conditions are now offering unproven treatments for the complications of COVID-19. There is the additional concern during the pandemic that if such approaches are used outside of the conventional hospital setting, then the unproven claims for efficacy may encourage purchasers to refrain from taking other steps, such as wearing face masks and social distancing, to protect themselves and others from COVID-19. While the early claims were premature and risked undermining confidence in regenerative medicine approaches, recent assessment is helping to clarify the scientific rationale and limitations of stem cells to halt the inflammatory cascade in COVID-19 (Durand et al., 2020; Monguio-Tortajado et al., 2021). It remains the case that stem cells might prove to be of value, and well-designed experimental medicine studies (Lanzoni et al., 2021) can form a starting point for larger, collaborative trials designed to evaluate efficacy. A publication by IAP (https://www.interacademies.org/sites/default/files/2021-05/IAP_strenghtening_research_0.pdf), on the challenges for strengthening research on COVID-19 more broadly, discusses the general issues associated with improving research questions, study design, trial conduct, and reporting (all areas where some COVID-19 research has been of insufficient quality to inform practice; Glasziou et al., 2020).

Engaging within the scientific community and with stakeholders worldwide

Scientific and medical communities worldwide have a responsibility to provide reliable sources of information and ensure that discussions and decisions are evidence based and that voices, previously muted, are now heard. In conclusion, we emphasize two overarching points: building research capacity to address unmet medical needs, and tackling misinformation so as to discourage unproven practices.

First, although there is a long history of valuable comment from researchers in developed economies (e.g., McMahon and Thorsteinsdottir, 2011) about the priorities for LMICs in building their research capacity and addressing their research priorities, less has been heard from the researchers themselves in LMICs in contributing to engagement worldwide. The IAP statement aims to help redress this lack of inclusivity and diversity. This requires further discussion—and action—on research and innovation priorities and capabilities worldwide, and on their connection with policy and practice. In seeking to catalyze the raising of community awareness of the value of greater inclusivity (Pera, 2020), IAP also builds on earlier work in LMICs with other academy networks and national academies, for example in training and mentoring African scientists in stem cell and regenerative medicine, and there is scope to

do more in collaboration with professional societies.

Second, previous guidelines by scientific societies and others, while of great importance, have provided insufficient guidance to curtail the rise of the use of stem cells of unproven benefit. It is time here also for renewed and inclusive efforts worldwide involving multiple stakeholders and researchers, regardless of their locations. The risks created by misinformation go deeper than possible harm to individual patients—crucially important though that is—because there is wider potential to harm the credibility of research and scientific integrity. Academies have strengths in public outreach and education and can help to support the scientific community in countering misinformation. However, this is not enough (Matthews and Iltis, 2017); scientists must also engage with policy makers.

The commitment by scientific experts to this IAP project has identified several opportunities where the relationship between academies and scientific societies can be augmented, at national and regional levels, and where, collectively, the scientific community can support national regulatory agencies and their international connectivity The significant potential for academies worldwide can be exemplified by the follow-up in Europe, where academy advice was delivered earlier (EASAC and FEAM, 2020). European academies and their experts continue to engage with the European Medicines Agency and with other stakeholders and policy makers, e.g., in the new Alliance for Transformative Therapies, with particular interests in the education of patients and health care professionals (https://rpp-group.com/files/eaftt/index-lp.html) as well as in other established networks of researchers, patients, educators, and regulators (e.g., www.eurostemcell.org). There will be equivalent opportunities in other regions. For example, the new initiative in Asia to harmonize pharmaceutical and medical device regulations, including those appertaining to regenerative medicine (Executive Committee on Global Health and Human Security, 2020), includes objectives for capacity building in regulatory science as well as in clinical development infrastructure and other opportunities for developing academia-industry-government collaboration. The specific requirements for skills and training in regenerative medicine should also be considered in the wider context of responsible science (IAC and IAP, 2012) and alongside other efforts to improve research governance, reporting, and dissemination. For example, IAP has a current project on combatting predatory academic journals (https://www.interacademies.org/project/predatorypublishing).

IAP encourages its academy members and their regional networks to continue to engage worldwide, in advising on formulation of guidelines for research and its reduction to practice; in appraisal of the evidence base for claims about quality, efficacy, and safety; in engaging in public debate about the value of innovation; and in helping policy makers to decide on priorities for pursuing health and equity.

AUTHOR CONTRIBUTIONS

Initial drafting of the manuscript was by R.F. All authors contributed to the discussion and revision of the manuscript draft and to the response to reviewers. All authors also contributed to the working group discussion that led to the preparation of the IAP Statement on Regenerative Medicine (IAP, 2021).

CONFLICT OF INTERESTS

A.C. is CEO of Dragon BioMed-USFQ and M.S.P. is founder of the biotech company Antion biosciences (https://antion.ch/#1). Other authors declare no competing interests.

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