European Academies

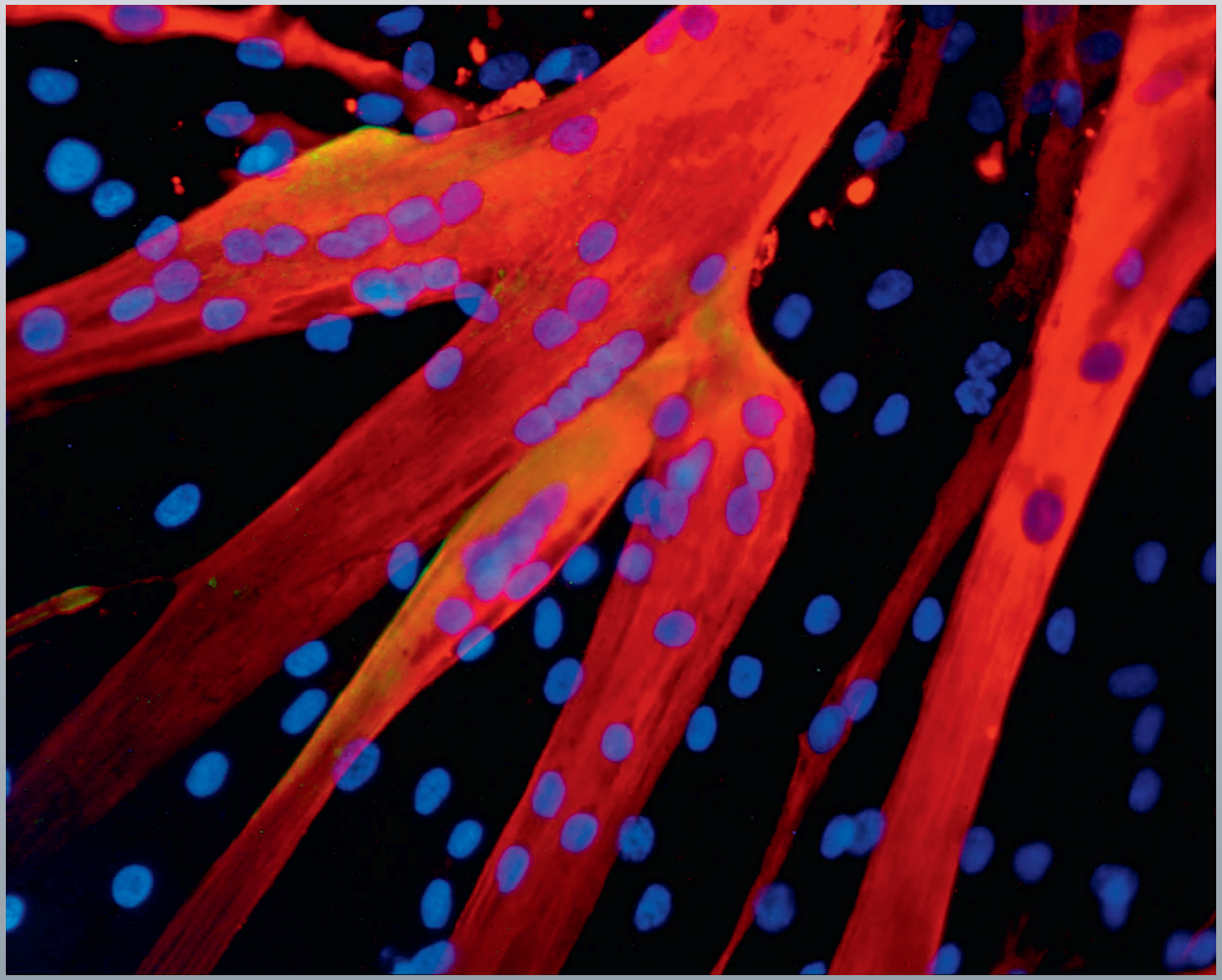
easac

Science Advisory Council

FEAM

Federation of European Academies of Medicine

# Challenges and potential in regenerative medicine



EASAC policy report 40

June 2020

ISBN: 978-3-8047-4144-7

This report can be found at
www.easac.eu and www.feam.eu

Science Advice for the Benefit of Europe

# EASAC

EASAC – the European Academies' Science Advisory Council – is formed by the national science academies of the EU Member States to enable them to collaborate with each other in giving advice to European policy-makers. It thus provides a means for the collective voice of European science to be heard. EASAC was founded in 2001 at the Royal Swedish Academy of Sciences.

Its mission reflects the view of academies that science is central to many aspects of modern life and that an appreciation of the scientific dimension is a pre-requisite to wise policy-making. This view already underpins the work of many academies at national level. With the growing importance of the European Union as an arena for policy, academies recognise that the scope of their advisory functions needs to extend beyond the national to cover also the European level. Here it is often the case that a trans-European grouping can be more effective than a body from a single country. The academies of Europe have therefore formed EASAC so that they can speak with a common voice with the goal of building science into policy at EU level.

Through EASAC, the academies work together to provide independent, expert, evidence-based advice about the scientific aspects of public policy to those who make or influence policy within the European institutions. Drawing on the memberships and networks of the academies, EASAC accesses the best of European science in carrying out its work. Its views are vigorously independent of commercial or political bias, and it is open and transparent in its processes. EASAC aims to deliver advice that is comprehensible, relevant and timely.

EASAC covers all scientific and technical disciplines, and its experts are drawn from all the countries of the European Union. It is funded by the member academies and by contracts with interested bodies. The expert members of EASAC's working groups give their time free of charge. EASAC has no commercial or business sponsors.

EASAC's activities include substantive studies of the scientific aspects of policy issues, reviews and advice about specific policy documents, workshops aimed at identifying current scientific thinking about major policy issues or at briefing policy-makers, and short, timely statements on topical subjects.

The EASAC Council has 29 individual members – highly experienced scientists nominated one each by the national science academies of EU Member States, by the Academia Europaea and by ALLEA. The national science academies of Norway, Switzerland and the United Kingdom are also represented. The Council is supported by a professional Secretariat based at the Leopoldina, the German National Academy of Sciences, in Halle (Saale) and by a Brussels Office at the Royal Academies for Science and the Arts of Belgium. The Council agrees the initiation of projects, appoints members of working groups, reviews drafts and approves reports for publication.

To find out more about EASAC, visit the website – www.easac.eu – or contact the EASAC Secretariat at secretariat@easac.eu

# FEAM

FEAM is the umbrella group of Academies of Medicine, Medical Sections of Academies of Sciences, Academies of Veterinarian Sciences and Academies of Pharmaceutical Sciences. FEAM promotes cooperation between national Academies and provides a platform to formulate their collective voice on matters concerning medicine, health and biomedical research with a European dimension. Its mission is to extend to the European authorities the advisory role that national Academies exercise in their own countries on those matters.

To find out more about FEAM, visit the website – www.feam.eu – or contact the FEAM secretariat at info@feam.com.

European Academies

Science Advisory Council

FEAM

Federation of European Academies of Medicine

# Challenges and potential in regenerative medicine

## A joint report from EASAC and FEAM

ISBN 978-3-8047-4144-7

© German National Academy of Sciences Leopoldina 2020

Apart from any fair dealing for the purposes of research or private study, or criticism or review, no part of this publication may be reproduced, stored or transmitted in any form or by any means, without the prior permission in writing of the publisher, or in accordance with the terms of licenses issued by the appropriate reproduction rights organisation. Enquiries concerning reproduction outside the terms stated here should be sent to:

EASAC Secretariat
Deutsche Akademie der Naturforscher Leopoldina
German National Academy of Sciences
Jägerberg 1
D-06108 Halle (Saale)
Germany

Telephone: +49 345 4723 9833
Fax: +49 345 4723 9839
Email: secretariat@easac.eu
Web: www.easac.eu
Twitter: @EASACnews
Facebook: www.facebook.com/EASACnews/

FEAM
Rue d'Egmont 13
1000 Brussels
Belgium

Telephone: +32 (0)2 793 02 50
Email: info@feam.com
Web: https://www.feam.eu/
Twitter: @FedEuroAcadMed

Cover image: Muscle cells differentiated from human stem cells in culture, from ongoing research by Working Group member Professor Giulio Cossu, University of Manchester, UK, on stem-cell therapy for muscular dystrophy. Muscle fibres are characterized by the expression of proteins such as myosin, which are responsible for muscle contraction, stained using antibodies that appear red in the image. The nuclei of the muscle cells are stained with Hoechst stain, which reflects blue light when binding to DNA. Duchenne muscular dystrophy is a genetic disease causing weakness and progressive deterioration of heart and skeletal muscles due to the muscle cells' impaired ability to produce the protein dystrophin. Ongoing research is exploring ways to preserve, and possibly restore, muscle function by transplanting dystrophin-producing cells into patients.

Copy-edited and typeset in Frutiger by The Clyvedon Press Ltd, Cardiff, United Kingdom

Printed by Schaefer Druck und Verlag GmbH, Teutschenthal, Germany. Printed on FSC-certified paper.

# Contents


| | | page |
|---|---|---|
| **Foreword** | | **v** |
| **Summary** | | **1** |
| **1** | **Introduction** | **3** |
| **2** | **Clinical and regulatory context: where are we?** | **7** |
| 2.1 | Issues for quality of the evidence base | 7 |
| 2.2 | Regulatory background | 9 |
| 2.3 | Accelerated access | 9 |
| 2.4 | Evolving financial models | 11 |
| 2.5 | Unregulated provision and undocumented claims | 11 |
| 2.6 | Global context | 13 |
| 2.7 | Ethics of stem cell research | 13 |
| **3** | **Future challenges: expectations, demands and practicalities** | **16** |
| 3.1 | Improving the evidence base: what can we do? | 16 |
| 3.2 | Research infrastructure and new approaches to translation | 17 |
| 3.3 | Academia–industry partnerships | 17 |
| 3.4 | Medical education | 18 |
| 3.5 | Publication practices | 18 |
| 3.6 | Health services institutional readiness | 18 |
| 3.7 | Engaging with the public and patients, and countering misinformation | 19 |
| **4** | **Recommendations and key messages** | **20** |
| **Appendix 1** | **Working Group composition and procedures** | **23** |
| **Appendix 2** | **Use of stem cells *in vitro* for disease modelling and drug testing** | **24** |
| **Appendix 3** | **'The ethics of regenerative medicine', a session organised by EASAC at the World Science Forum, Budapest, 22 November 2019** | **25** |
| **Appendix 4** | **FEAM Forum on 'Regenerative medicine: scientific advances and regulatory framework in Europe', Brussels, 28 November 2019** | **26** |
| **Abbreviations** | | **27** |
| **Glossary** | | **27** |
| **References** | | **28** |

# Foreword

Regenerative medicine comprises various novel approaches to health care, representing a complex and heterogenous group of products, including those based on cell and gene therapy, aimed at tissue regeneration and repair. In this report, the European Academies' Science Advisory Council (EASAC) and the Federation of European Academies of Medicine (FEAM) explore opportunities and challenges for regenerative medicine in the EU, focusing particularly on stem cells but also drawing more general conclusions for the field, with the objective of raising awareness and catalysing action by the scientific community, regulators, health services and public policy-makers.

Where are we now? This report was finalised during the COVID-19 crisis and it is understandable that the rampant spread of the novel coronavirus disease has dominated the attention of health services, policy-makers and all citizens, necessarily limiting activity on other societal priorities. The COVID-19 pandemic has reminded us all of the urgent and continuing need to improve preparedness and responsiveness to tackle communicable diseases, a message that EASAC and FEAM have repeatedly emphasised during the past two decades. A second message, applicable both to communicable and to non-communicable diseases, is that the countries of Europe must do much more to work together to foster solidarity in the face of a collective crisis[1], using robust scientific evidence to inform policy. Clearly, this essential coordination applies increasingly to health strategy and the European Union (EU) must now recognise the paramount needs for EU-level policy in health care as well as public health, rather than derogating such policies to the national level.

The recent disruption to the progress of clinical trials of regenerative medicine as a result of the coronavirus pandemic[2] is also entirely understandable. However, as we look forward to the EU entering the COVID-19 recovery phase and reaffirming its broader health and economic goals, the opportunities and challenges of regenerative medicine, set out in our report, merit early consideration. A business perspective contributed to the World Economic Forum earlier this year[3] postulated that stem cells could be the medical innovation of this century, noting the rapid increase in start-up companies worldwide (with particularly strong growth in the cancer stem-cell market) and the opportunities arising from new funding models for research and development that may facilitate tackling other non-communicable diseases. Whatever the eventual contribution to be made by regenerative medicine in an uncertain and changing world, there is transformative potential, to treat causes not symptoms.

What do the academies advise? Our report aims to take a realistic view of the opportunities and we caution about distortions induced by hyperbole and competitive pressures. In building a robust evidence base, there is continuing need to ensure that the EU commits resources across the spectrum of research – from basic to clinical – so that patients can benefit from the rapidly advancing pace of science in regenerative medicine. At the same time, there is continuing need to ensure that patients and their families are not misled by unproven claims, whether inadvertently or deliberately. The European Commission has already expressed strong support for the category of Advanced Therapy Medicinal Products (including gene therapy and somatic-cell therapy medicinal products, and tissue-engineered products) — to facilitate their access to the EU market and to foster European competitiveness while guaranteeing health protection for patients. Our report identifies and prioritises several areas where preclinical and clinical research and regulatory approaches need further attention to ensure balancing of the support for innovation with protection of patient safety. We also examine where action is required from the scientific and policy communities to sustain new forms of research partnership, reform publishing practices and medical education, build health service institutional readiness, and engage with the public and patients to counter misinformation and deter the provision of unregulated offerings.

Where next? Our report provides recommendations on the principles and options for change rather than being overly prescriptive. We address our key messages to the European institutions and Member States and we urge our academy members to take forward discussion at the country level —including dissemination of information about the opportunities and challenges to their citizens. The project outputs reflect a very effective collaboration between FEAM and EASAC to enable and encourage inclusion of all relevant disciplines and expertise across the EU, to provide timely and transparent evidence-based advice.

[1]See, for example, discussion by Ursula Von Der Leyen and the European Parliament, 'Commission chief, MEPs slam lack of EU solidarity in COVID19 crisis', https://www.euractiv.com/section/coronavirus/news/commission-chief-meps-slam-lack-of-eu-solidarity-in-covid19-crisis/, 26 March 2020.
[2]Alliance for Regenerative Medicine, www.alliancerm.org, 2 April 2020.
[3]Mike Moradi, https://www.weforum.org/agenda/2020/01/how-will-stem-cells-impact-the-future-of-medicine/, 16 January 2020.

Our focus has been on the EU but we recognise, of course, that the issues are relevant worldwide. EASAC and FEAM will now be working together with other academies, through the auspices of the InterAcademy Partnership, the global network of more than 140 academies of science, engineering and medicine, to share perspectives. This expansion of our European assessment aims to identify good practice, and to seek solutions to advise on policy options worldwide, motivating and integrating national, regional and global action.

This report has been prepared by consultation with a group of experts nominated by the national science academies. We thank the Working Group members for their considerable commitment and expertise. We also thank the independent peer reviewers, the EASAC Biosciences Steering Panel, the FEAM Forum and our respective councils for their help and thoughtful guidance.

We welcome discussion on any of the points raised in our report.

Professor Christina Moberg
EASAC President

Professor George Griffin
FEAM President

# Summary

Regenerative medicine comprises novel interdisciplinary approaches, including several based on cell and gene therapies, aimed at tissue regeneration and repair. All regenerative medicine strategies depend upon harnessing, stimulating, guiding or replacing endogenous developmental or repair processes. Regenerative medicine offers significant promise for treating intractable diseases but, so far, has proved itself in only a few specific clinical indications, for example for haematopoietic and skin disorders. Stem-cell-based medicine is now established and will undoubtedly advance towards treating a progressively larger spectrum of diseases, so it is essential to address some critical scientific issues for evidence-based implementation and regulation. The consequences of not doing this would be to waste investment, researcher activity and aspirations to cure, as well as to undermine patient protection.

This report, from a project conducted by EASAC (European Academies' Science Advisory Council) and FEAM (Federation of European Academies of Medicine), explores opportunities and challenges in this rapidly advancing field, discusses what principles should be offered for guidance in policy development and what the strategic priorities are in the European Union (EU) for products in the category of advanced therapy medicinal products, which includes those used for regenerative medicine. One principal focal point for the project is on stem cells – specifically biological, ethical and social issues – but many of the conclusions are generalisable to other fields of regenerative medicine. While we recognise that there are many previous publications that have reviewed the field, we see that the science and the commercial environment are changing rapidly and we anticipate further progress in the technology and its applications. We acknowledge that some health care issues are reserved for national action at the Member State level, but we urge greater coordination across the EU, accompanied by EU leadership in addressing issues at the global level.

Although there are considerable scientific and clinical opportunities, there are also major concerns. First, there is an increasing problem in some countries of commercial clinics offering unregulated products and services, promising a wide range of benefits using poorly characterised medicinal products with little evidence of effectiveness, vague rationale and with the primary intention of financial profit. Secondly, there is premature marketing approval and commercialisation of approaches based on some, but insufficient, evidence as a result of evolving business models facilitated by regulatory authority initiatives for accelerated access. Enthusiasm about the broad potential of regenerative medicine applications has led to a gap between expectations and the realities of translating regenerative medicine technologies into clinical practice. In an era of pressure on international competitiveness, whereby some regulatory systems have become increasingly permissive, it is important that the EU does not lower its regulatory threshold without fully considering the consequences for patient safety, health care budgets and public trust in science.

Our assessment covers a wide range of issues, including the following:

- Quality of the preclinical and clinical evidence base.
- Regulatory frameworks, in particular the new concerns emerging from the pressures for conditional, early market approval, and access based on only limited evidence of efficacy and safety.
- Responding to the challenges of provision of unregulated products.
- Balancing the promotion of innovation with patient protection.
- Understanding and addressing the ethical dimensions, particularly those associated with uncertainty about safety and efficacy, patient consent on the basis of complex information, fairness and equity of access.

Our key messages can be summarised as follows:

- Regenerative medicine is designed to treat serious medical conditions with unmet needs. We consider cosmetic applications as currently out of scope.
- We are now at the threshold of being able to offer treatments for major genetic and other diseases — but for many, more evidence is needed on their likely benefit or efficacy, especially for the more complex polygenic and acquired degenerative diseases.
- It is vital to promote good biomedical science — from fundamental research to its translation to clinical trials. This has implications for EU commitment to funding of well-planned first-in-human trials with reliable, shared and objective endpoints determined with input from supporting expert networks (which should also consider engagement with the public and media).
- Proportionate and consistent regulatory authorisation for marketing must be based on

robust and replicable science. Unregulated provision of unproven regenerative medicine procedures must be deterred. The ethical issues and regulatory challenges discussed in this report need to be addressed in a rigorous, consistent and constructive way.

- Researchers must follow professional guidelines on responsible research and its translation, and standard-setting, in pursuit of good practice.
- Teaching on regenerative medicine should be part of the medical curriculum.
- Patient interests must be put first. Appropriate education of first line medical care in this context is essential. It is necessary to ensure a robust scientific basis for the clinical intervention and for the endpoints selected for measurement of efficacy and safety. A crucial criterion for patients in deciding whether to consent to novel therapies is that, at least in Europe, they should not be expected to pay clinical research costs.

Derived from these key messages, our recommendations for improving the knowledge base, better governance and building trust include the following:

- Engaging with the public and patients and countering misinformation. Providing reliable sources of information, such as the International Society for Stem Cell Research document 'A closer look at stem cells', is integral to this process.
- Ensuring that regulatory procedures are robust, transparent, evidence based and harmonised.
- Re-invigorating EU research infrastructure, particularly for clinical research and its translation, and ensuring support for basic science.
- Supporting new partnerships between academia and industry.
- Informing medical education and professional training.
- Reforming journal publication practices and opposing predatory journals.
- Building health services' institutional readiness.

In aggregate, we support previous calls for responsible research and innovation in regenerative medicine to deliver better science, better funding models for science and for health care provision, better governance and better communication to the public and patients. Our messages on research, innovation, regulation and information provision are directed to the European Commission and its European Medicines Agency, the European Parliament, to Member States, to academies worldwide and to international policy-makers and stakeholders. For the new European Commission, there are opportunities to ensure that Europe has accessible, innovative medicines, for reaffirming commitment to health technology assessment, and for taking a lead in the international harmonisation of regulatory frameworks.

# 1 Introduction

Regenerative medicine can be defined (Cossu *et al.*, 2018) as an emerging medical endeavour aimed at restoration of tissue function via small-molecule drugs, biological therapies, medical or tissue-engineered devices, or cells and genes. It is an interdisciplinary approach, in which the objectives are to replace or repair human tissues and organs, and thus restore their normal function. All regenerative medicine strategies depend upon harnessing, stimulating, guiding or replacing endogenous developmental or repair processes. For example, stem cell transplantation has the aim of replacing lost cells (such as neurons in the brain or beta cells in the pancreas), requiring that the transplanted cells are committed to a specific fate and, once differentiated, functionally integrate in the tissue. Alternatively, stem cells may provide trophic support (short- or long-term influence on cellular growth, differentiation or survival via secreted products) or mediate immunomodulation or promote plasticity, functions that are indirect and often not easy to measure especially in patients. Claims for immunomodulatory or other difficult-to-define functions have contributed to lack of clarity in the field. A succinct definition of stem cell function recently proposed (Post and Clevers, 2019) focuses on the core property: '*the ability to replace lost tissue through cell division*'. In agreement with the remit taken by the Lancet Commission on regenerative medicine (Cossu *et al.*, 2018), our report does not cover cell and gene therapy in cancer research. While these approaches are of great importance, their main goal is to eliminate cancer rather than to regenerate diseased tissues.

Regenerative medicine offers significant promise to tackle intractable diseases, including those presented by ageing populations, and to reduce medical costs (Rosenthal and Badylak, 2016; European Commission, 2017). For decades, stem cell therapy was predominantly linked to bone marrow transplantation and epidermis transplantation of large burns, but the past 10 years have seen an exponential growth in experimental therapies in regenerative medicine entering the clinic (Cossu *et al.*, 2018). So far, however, regenerative medicine has only proved itself in the treatment of a few specific indications, usually for rare or very rare diseases (Marks and Gottlieb, 2018) but some for more common conditions such as age-related blindness or burns of the cornea, although few patients have been treated and those mostly in the context of clinical trials.

In this report, EASAC (European Academies' Science Advisory Council) and FEAM (Federation of European Academies of Medicine) review the opportunities and challenges in the rapidly evolving field of regenerative medicine, exploring what principles might be offered as guidance to researchers, patients, medical practitioners and regulatory authorities, and what the priorities are for determining EU strategic options. We recognise that there have been previous publications reviewing this field and we will refer to these when appropriate. We consider that it is timely to publish our new assessment because both the science and the commercial environment are changing rapidly: our objective is to continue our academies' tradition of bringing authoritative statements on relevant and challenging issues to the attention of policy-makers.

FEAM and EASAC have previously worked jointly on various European health issues, for example relating to vaccines (EASAC and FEAM, 2018), antimicrobial resistance (EASAC and FEAM, 2016) and genetic testing (EASAC and FEAM, 2012). The academy networks have also addressed a wide range of other EU issues in health: for example FEAM has focused on personalised medicine (FEAM, 2019) and human genome editing (FEAM, 2017); EASAC has reviewed the health problems associated with climate change (EASAC, 2019) and food and nutrition insecurity (EASAC, 2017) and infectious diseases more broadly (EASAC, 2011).

### Scope of the EASAC–FEAM project

There is a wide range of approaches to regenerative medicine, including the following:

- Cell transplantation, where the cells originate from human embryonic stem cells, induced pluripotent stem cells or tissue specific (adult) stem cells or other forms of (stem) cell therapy, for example mobilisation of endogenous stem cells (see Box 1).
- Gene therapy, both *in vivo* and *ex vivo*, the latter being a form of cell therapy.
- Genome editing, by different nucleases.
- *In vivo* reprogramming, by forcing cells *in situ* (back) into a proliferative or undifferentiated state, although usually maintaining commitment.
- Tissue engineering, using either natural scaffolds or artificial, biocompatible materials, and including 3D printing.
- Organoids, from adult and pluripotent stem cells.
- New generation drugs, for example oligonucleotides designed to skip a mutated exon or repair a gene mutation via homologous recombination (CRISPR–Cas-mediated gene correction).

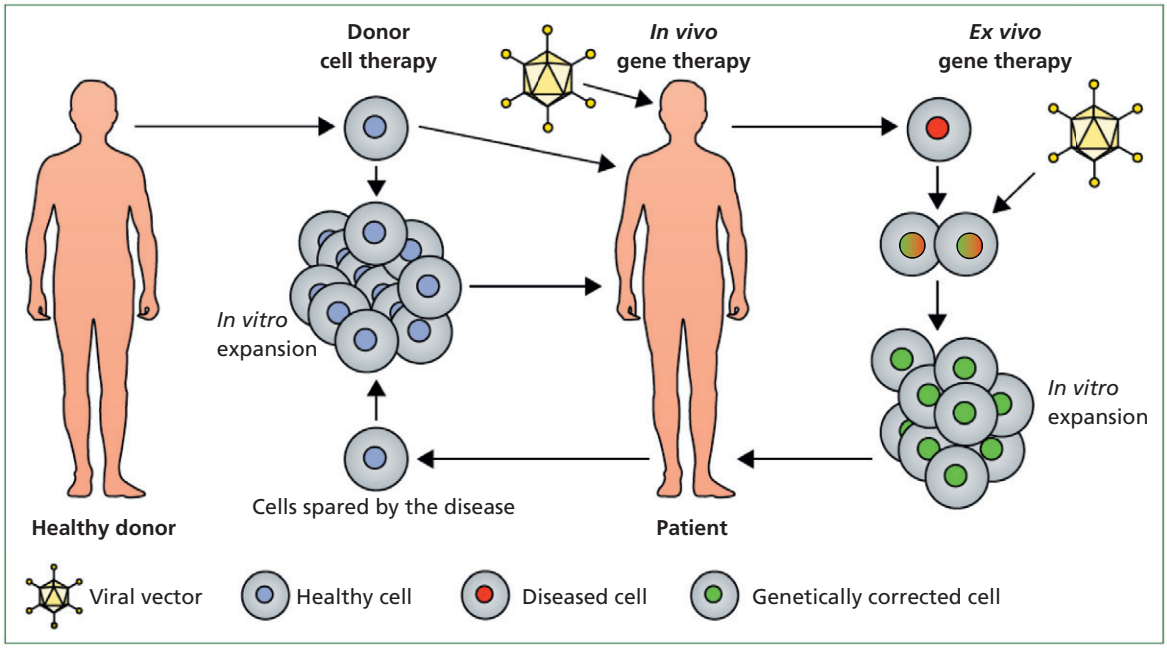



*Figure 1 Cell and gene therapy. Reprinted from Cossu et al. (2018) with permission from Elsevier.*

**Box 1 Stem cell types**

Pluripotent cells are either embryonic stem cells or induced pluripotent stem cells. Embryonic stem cells are derived from the inner cell mass of the blastocyst before implantation in the maternal uterus. They can be proliferated indefinitely and, upon appropriate treatments, induced to differentiate into the desired cell type. Undifferentiated cells may give rise to tumours *in vivo*, mainly teratomas.

Induced pluripotent stem cells are adult cells, reprogrammed to a stage equivalent to embryonic stem cells, through the expression of four factors, Oct4, Sox2, cMyc and Kif4. Once reprogrammed, induced pluripotent stem cells behave very similarly to embryonic stem cells.

Multipotent stem cells originate from post-embryonic tissues and have been, so far, the large majority of stem cells used in the clinic. They have variable, although finite, proliferation potency (high in epidermal stem cells, lower in alleged stem cells of the mesoderm such as mesenchymal stromal cells) and are able to differentiate only into the cell types of the tissue in which they reside. In some cases, such as the inter-follicular epidermal stem cells, they are unipotent since they only give rise to epidermal cells.

Gene therapy is the use of genetic material to treat genetic diseases by replacing or correcting the gene defect either *in vivo* or by modifying cells outside the body (*ex vivo*) for subsequent return (Figure 1). Cell therapy is based upon the use of cells taken from the patient or donor. These can be stem cells which subsequently specialise (differentiate) into different types of specific tissue and may or may not be genetically altered before transplantation to the patient to be treated (in the first case this corresponds to *ex vivo* gene therapy) (Figure 1).

Cell and gene therapy as well as tissue engineering have reached the clinical stage of testing and some are available as therapies. In our report we cover those scientific approaches that are closest to the clinical use, with a particular focus on stem cells, either heterologous or autologous (often genetically corrected) plus a brief mention of in vivo gene therapy and other methodologies when they illustrate recent advances in the science[4]. Progress in intrauterine therapy is advancing broadly and it may become possible in the future to administer gene (or cell) therapy by this route. We do not now cover embryo genome editing because that is currently being addressed in other international academy work[5]. Our particular focus on stem cells as a case study is because there are urgent, complex challenges for research, innovation, implementation and patient information, and ethical issues have been raised relating to stem cell transplantation, and because research on stem cells represents an area of European strength. We will discuss when and how conclusions and recommendations from our assessment of stem cell therapeutics can be generalised to other approaches in regenerative medicine. Although cancer therapies

[4] A recent report from the US National Academies of Science, Engineering and Medicine (NASEM, 2019a) describes other examples of regenerative engineering approaches, including some that may be further in the future. Among the possibilities described are smart scaffolds for bladder regeneration (in spina bifida); autologous endothelial cells for tissue revascularisation (in peripheral artery disease); 3D printed bioresorbable scaffolds; and islet transplantation to the omentum (in diabetes, with engineering to be intrinsically antioxidant).
[5] Human Germline Genome Editing Commission, https://royalsociety.org/topics-policy/genetic-technologies/international-commission, 2019.

were excluded during the scoping of our project, it is important to mention here CAR T-cell (chimeric antigen receptor T-cell) therapies as an example of a clinically effective combined cell and gene therapy that is helping to frame viable business plans for cell-based approaches[6].

Stem cell research and development (R&D) typifies some of the problems for an emerging technology. Well-characterised stem cells represent a significant advance for some, hitherto, unmet medical needs, for example haematopoietic disorders and skin disorders (Hirsch *et al.*, 2017) while monogenic disorders of other tissues begin to be treated (Biffi *et al.*, 2013), although often through genetic correction of haematopoietic stem cells. Results vary from unequivocal efficacy for previously intractable diseases to only modest effects that may encourage premature licensing, as will be discussed in chapter 2. Where a poorly efficacious therapy currently exists, strong evidence must be presented that a novel regenerative medicine treatment is clearly superior. Most importantly, there is an increasing problem of unregulated clinics promising a wide range of medical benefits using poorly characterised stem cells on the basis of very little evidence and vague rationale, and with the apparent intention of significant commercial gain. Enthusiasm about the broad potential of applications has led to a gap between expectations, often inflated by media reports, and the realities of translating regenerative medicine technologies into clinical practice.

Although the longer-term solution to poor practice resides in robust and evidence-based regulatory frameworks, properly supported by specific legislation, in the shorter-term there is need to inform prospective patients, health services and others about the availability of robust evidence and the known risks involved. In this respect, commendable initiatives have been undertaken by the International Society for Stem Cell Research (ISSCR) and by EuroStemCell (see section 3.2) but these initiatives have to face many compelling internet advertisements for patients and families desperately seeking cures. There are ethical and resource implications arising from the weak evidence base. The combination of poor-quality science not providing adequate evidence, unrealistic hopes and unscrupulous private clinics claiming to use stem cells will ultimately undermine the confidence of the public, research funders and health services in regenerative medicine. Furthermore, as will be discussed later, the scenario continues to change as several clinics have elaborated more sophisticated strategies, based on preliminary scientific evidence and publications that make distinction between academic and private clinical centres more difficult to define.

Our starting point is the biological and clinical potential but we also explore some of the ethical and social issues. Our purpose is to evaluate how to use the knowledge currently available to inform options for the management of research and innovation, how to engage with the end users of that knowledge (patients, health services, industry, regulators, and the publishing and medical education sectors) and how to identify knowledge gaps so as to improve the science-policy interfaces. We are also aware of the importance of health economics and pricing (see, for example, discussion in Cossu *et al.*, 2018). We do not discuss health economics issues in detail in this report, but it is critically important for health systems and insurers to plan how to respond to the very high costs of potentially curative therapies at a time of resource constraints[7]. Financial costs are an intrinsic part of the ethical debate since not all patients can be treated, and will be considered in that context in section 2.7.

In commenting on recent developments, we seek to add value to previous analyses and we believe that the distinctiveness of our collective academies' project resides in the following:

- Bringing together extensive biomedical and clinical expertise from across Europe, drawing on other disciplines in the natural and social sciences as appropriate, to focus on scientific perspectives.
- Emphasising core principles for future directions in the conduct of research, innovation and the translation to clinical practice.
- Supporting the engagement of the scientific and medical communities with key stakeholders, including patient groups, regulators, scientific journal editors, industry and public policy-makers.
- Providing a basis for sustained follow-up at national as well as EU level through our academies.
- Providing a basis to catalyse further evidence-gathering and analysis worldwide through the work of the InterAcademy Partnership, the global network of academies of science and medicine.

[6] T-cells are redirected against the tumour after engineered expression of chimeric antigen receptors. Proof-of-principle has been demonstrated in haematological malignancies and the approach may be able to treat solid tumours (June *et al.*, 2018).
[7] Among options that have been recently proposed (Anon., 2019b) are (1) 'lump sum' contracts, whereby national payers contribute a set total amount in return for unlimited access to the therapy for all relevant patients; and (2) 'pay-for-performance' utilising risk-sharing contracts with a money-back guarantee if efficacy targets are not met.

Our messages on research, innovation, regulation and information provision are directed to the European Commission and its European Medicines Agency (EMA), the European Parliament, Member States and our academies as well as the wider scientific community. The issues that we cover are of global interest but our focus here is on providing recommendations for the EU. We acknowledge that some health care issues are reserved for national action at the Member State level but the issues we cover in the next chapters are relevant to action at the EU level or are of such importance as to merit coordinated action in every country. We also observe that, according to the most recent Eurobarometer responses[8], 70% of European citizens would like to see more EU health collaboration.

Project procedures are described in Appendix 1.

[8] 2017, https://www.europarl.europa.eu/infographic/eurobarometer/2017/index_en.html#health.

# 2 Clinical and regulatory context: where are we?

It is not the intention of this report to duplicate published reviews of scientific progress in cell and gene therapy trials (e.g. De Luca *et al.*, 2019; Blau and Daley, 2019; Abou-El-Enein and Hey, 2019)[9], nor to discuss in detail individual examples of progress. Variable clinical progress has been made (see the analysis by Hanna *et al.*, 2017 for gene therapy) although the momentum is increasing. It is also worth noting that a rapid pace of advance in understanding interactions between cells and biomaterial scaffolds is helping the development of biological functional constructs in tissue engineering (Pajorova *et al.*, 2018). For stem cells, the EASAC–FEAM Working Group restricted the discussion to several clinical indications, including neurology (Lindvall, 2016), hepatic and muscle disorders (such as muscular dystrophy), retinal disorders (such as macular degeneration) and cystic fibrosis. Although it was beyond the scope of the Working Group to consider all clinical indications, we note also the progress made, for example, in bone-regeneration tissue engineering (Shanbhag *et al.*, 2019) and congenital immune deficiencies (Booth *et al.*, 2016)[10].

As noted previously, there is significant strength across the EU in stem cell R&D (Box 2).

There is much more to be done to understand critical success factors for developing regenerative medicine. Approaches are ideally tissue specific, and stem cell therapy seems more likely to succeed if they are based on a strategy to replace the destroyed or dysfunctional tissue, a problem compounded if the host cells do not usually regenerate (e.g. cardiac muscle or brain) at a significant rate. There may be problems with stem cell differentiation to the correct cell type in tissue reconstruction, such as the generation of appropriate subtypes of neuron, glial cell, liver, kidney or heart, and failure of stem cells or their progeny to integrate with host tissue. Moreover, priming behaviour of the new cells will be significantly influenced by the nature of the tissue environment as altered by disease, for example a highly inflammatory cytokine milieu (Najar *et al.*, 2018). Advances in regenerative medicine will be supported by advances in a deeper understanding of immunology, inflammation and fibrosis.

The recent report from the US National Academies of Sciences, Engineering and Medicine (NASEM, 2019a) reviews the multiple factors that contribute to the clinical variability of effects of stem cells. These include variability in cell origin (according to health status, age and sex of donor) and in the recipient (if different, disease process and its stage, genetics). The genetic stability of stem cells during the passaging process in the laboratory before clinical use may also be a concern. Other procedural steps that affect cell viability include transport logistics, freezing and thawing: hence the importance of standardising and managing protocols. For example, these issues were recently discussed in a systematic review on standardising the manufacturing protocol for mesenchymal stromal cells for reconstitution of alveolar bone (Rojewski *et al.*, 2019).

In addition to new clinical approaches, the methodologies of regenerative medicine (including convergence between the gene therapy and stem-cell research fields) have application *in vitro* for the modelling of disease processes and for the screening and assessment of new small-molecule drugs. Some examples are presented in Appendix 2.

**Box 2 Mapping activity in Europe**

The European Society of Gene and Cell Therapy[8] has recently mapped activities of academia, biotechnology and pharmaceutical companies, charities, patient organisations and others across Europe in this area. A survey of cellular therapy and regenerative medicine in Europe has been published by the International Society of Cell Therapy and the Tissue Engineering and Regenerative Medicine Society, European Chapter. The most recent survey (2014–2015 data) was published in 2017 (Ireland *et al.*, 2017).

Tissue engineering trends have been monitored across major scientific disciplines and research themes (Santisban-Espejo *et al.*, 2018) and in most productive countries (Santisban-Espejo *et al.*, 2019).

See also ten Ham *et al.* (2018) for a survey of advanced therapy medicinal product (ATMP) development among companies in the EU.

## 2.1 Issues for quality of the evidence base

Issues for improving the quality of preclinical data were raised in earlier work by the UK Academy of Medical Sciences[12] and will also be discussed later in this chapter in the context of regulatory requirements. Safety assessment must start in preclinical work. For

[9] See also A. Boyd, 'Where are we with gene therapy', Faculty of Pharmaceutical Medicine, Royal College of Physicians, www.rcplondon.ac.uk/file/8918/download?token=qJdHAf7s. There is currently evidence of a boom in pharmaceutical company R&D on gene therapy (Mullard, 2019).
[10] See also the Alliance for Regenerative Medicine, https://alliancerm.org for further details on approved products worldwide.
[11] www.esgct.eu.
[12] Academy of Medical Sciences Regenerative Medicine Regulatory Workshop, October 2012, published 2013. http://www.acmedsci.ac.uk/viewFile/51d179911937d.pdf

example, new standards are emerging for evaluating the developmental and malignant potential of human pluripotent stem cells (Allison *et al*., 2018). Furthermore, cell viability should be assessed using specific, sensitive methods able to detect the presence of apoptotic or necrotic cells in the cell pool (Garzon *et al*., 2012). Guidelines for stem cell research and clinical translation have been produced by the ISSCR (2016) and these will be referred to subsequently together with perspectives from elsewhere in the literature and from the EASAC–FEAM Working Group.

There is a major problem in the stem cell field in that stem-cell-based approaches are often moved to patient application with very weak experimental basis and mechanistic understanding of the pathophysiology. Even if the clinical trial is well-planned and performed, it becomes meaningless without a solid experimental basis. The problems have been exemplified by the controversy that surrounds research on mesenchymal stem cells, which is often based on poor scientific definition of what the cells are and rationale for the proposed use; this has led to inflated expectations for multiple therapeutic applications (Sipp *et al*., 2018). A position statement from the International Society for Cell & Gene Therapy (Viswanathan *et al*., 2019) recommended that the fibroblast-like cells commonly called mesenchymal stem cells should now be called mesenchymal stromal cells to reflect the lack of evidence that, when used as a medical treatment, these cells can renew themselves and form different tissues.

There are other fundamental issues that require consideration. When compared with chemical compounds, cells will necessarily lack a precisely definable chemical and molecular composition (MacPherson and Kimmelman, 2019). This means that, even with efforts to standardise as much as is feasible the methods, protocols and starting materials, each medicinal product will vary when prepared in different research centres and at different times within the same centre. The crucial question here is to what extent this affects cell functionality since this will set limits to variability. When moving stem cell research from the laboratory to the clinic, it is essential that the cells intended for clinical use are tested for efficacy in preclinical models. Detailed protocols and standard operating procedures are available for controlled laboratory environments. Although good laboratory practice and extensive and rigorous preclinical work will increase the reproducibility of data, imposing good manufacturing practice conditions for preclinical work would not solve the basic problems, but would raise the costs such that they would be prohibitive for academics. Furthermore, stringent rules for controlled and reproducible preclinical work may become a substantial burden for start-up companies that need to initiate clinical trials in the shortest time in order not to lose momentum and to be able to report to investors. Moreover, there is need to consider better approaches to empower preclinical research models of complex disease environments. There is no easy solution to these problems.

Defining new safety criteria for cell-based therapies is a significant regulatory challenge. Although regulatory requirements for cell-based therapies have been largely derived from drug-based safety considerations, the requirements are not necessarily interchangeable. Therefore, more work is needed to define safety criteria for cell-based therapeutic products and it is also important to emphasise the proportionality principle in approaches to assessing risk (see section 2.7).

For clinical data, the Cochrane resource has a wide range of relevant material on clinical research particularly for the review of stem cell applications[13]. The quality of the evidence base is often described as being low (e.g. for cardiovascular indications; Fisher *et al*., 2016). There have also been particular problems with the reproducibility of data on which major clinical studies have been based, and the retraction of a series of prominent research papers using adult cells from bone marrow and adipose tissue to treat heart disease has been a serious cause of concern to the field and beyond (Chien *et al*., 2019).

Other systematic reviews and meta-analyses have also found many studies with relatively low-quality evidence, characterised by poor study design, high risks of bias and large heterogeneity (e.g. for studies on stem cells treating patients with knee osteoarthritis; Iijima *et al*., 2018). Moreover, for some clinical trials, reliable and unbiased outcome measures have been difficult to establish. For example, in 2009 a group of neurologists created Treat-NMD, initially as a network funded by the European Commission and later as a multi-task organisation to improve diagnosis, care and treatment for patients affected by neuromuscular disorders[14]. One of the first tasks was to standardise outcome measures so that results of a particular trial could be quantified and compared with other trials for that indication. This was not simple because these measures are based on performance by patients (e.g. the 6-minute walk test), which may be influenced by compliance, especially in children and possibly also confounded by a placebo effect.

[13] www.cochranelibrary.com.
[14] http://www.treat-nmd.eu/about/network.

More generally, problems of availability and distribution of funds, protocol design, and at the peer-review and editorial stages of publication may all contribute to poor-quality reports that describe a non-existing (biologically insignificant effects above controls) or minimal beneficial effect. Such reports can raise unjustified expectations with consequences that are detrimental to all stakeholders, but especially for patients.

## 2.2 Regulatory background

At present, patients in the EU can access regenerative medicine in four ways:

- When the therapy has been tested and received regulatory authority approval.
- In the context of a clinical trial.
- Through permitted access to a treatment that does not have centralised marketing approval, for example hospital exemption within EU compassionate use (1394/2007/EC) provisions[15].
- Through direct recruitment, for example via the internet by commercial entities whose activity is not scrutinised or approved by any regulatory body.

Only ten regenerative medicines have been granted an EU marketing licence (the first bullet point above) (ten Ham *et al*., 2018) and the procedures for doing so will be discussed later in this report. Increased openness and harmonisation in hospital exemption procedures (third bullet) is desirable[16]. Procedures may vary between Member States and there is often no transparency with regard to adverse events and efficacy data, which is essential to accumulate knowledge. However, the greatest risk lies in those offerings that escape any supervision (fourth bullet) and these risks will also be discussed in further detail subsequently.

In the EU, regulation of health claims is the responsibility of the European Commission, DG Sante, as implemented by the EMA. Issues for support of laboratory and clinical research and its translation are covered by DG Research and Innovation. General guidelines from the European Commission are available on good clinical practice, good manufacturing practice, viral vectors for gene therapy, human cell-based medicinal products, and pharmacovigilance. These guidelines, together with other sources of advice, for example from the World Health Organization and the International Organization for Standardization, can be accessed via the professional societies[11].

Regenerative medicine (genes, cells, tissues) is covered by the European Commission's Advanced Therapy Medicinal Products (ATMPs) Regulation 1394/2007, which came into force in 2008 (Box 3)[17]. The Committee for Advanced Therapies is responsible for assessing quality, safety and efficacy, and for following scientific developments. A survey of European company ATMP development (ten Ham *et al*., 2018), albeit with a limited response rate, showed that, of the products in development, 72% were in early clinical development. Most developers were small or medium-sized enterprises (65%) and the most frequently mentioned challenges were country-specific requirements (16%), manufacturing (15%) and clinical trial design (8%). A survey of clinical implementation of academic ATMPs in the Netherlands (de Wilde *et al*., 2016) identified some different major hurdles in addition to clinical-study-related problems: inadequate financial support, rapid pace of change, lack of regulatory knowledge, lack of collaborations and issues of responsibility. de Wilde *et al*. (2016) conclude that '*creating an academic environment stimulating and planning ATMP development and licensing as well as investing in expanding relevant regulatory knowledge in academic institutions seems a prerequisite to develop ATMPs from bench to bedside*.'

## 2.3 Accelerated access

An EMA pilot programme in 2014–2016, 'Adaptive pathways', explored additional ways to grant faster patient access to innovative biomedicines, exemplified

[15] A separate procedure exemplified by the French ATU (autorisation temporaire d'utilisation; temporary use authorisation) can be considered distinct from hospital exemption in allowing treatment of a named patient or cohort with a drug whose efficacy and safety is presumed. For further discussion of hospital exemption and compassionate-use procedures, see Elsanhoury *et al*. (2017). Such procedures must not be used as a mandate in product development to circumvent evidence-based clinical trials. Criteria for hospital exemption and differences in implementation at the national level (UK, Lithuania and Poland) are also discussed by Ivaskiene *et al*. (2017) and it is important to explore how greater coherence between countries in hospital exemption procedures can be achieved to control their unjustified exploitation.

[16] European Biopharmaceutical Enterprises, www.ebe-biopharma.eu/advanced-therapy-medicinal-products. See also guidance in the ATMP regulations (footnote 14).

[17] ATMPs are defined by the European Commission as medicines for human use that are based on genes, tissues or cells, and includes applications in cancer (which are not within the scope of our report). See also the EMA 2015 reflection on the classification of products, https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-classification-advanced-therapy-medicinal-products_en-0.pdf. Further characterisations of ATMPs and the roles of the EMA and the Committee for Advanced Therapies are described on https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview. A recent (October 2019) publication of Good Clinical Practice guidelines on ATMPs (https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/atmp_guidelines_en.pdf) covers issues for the protection of clinical trial subjects, clinical trial design, non-clinical studies, quality, traceability and safety of ATMPs. Although not specific to ATMPs, the European Commission's recent (October 2019) evaluation of the Union legislation on blood, tissues and cells notes that the current legal framework does not keep up with the high level of innovation (https://ec.europa.eu/health/blood_tissues_organs/policy/evaluation_en).

**Box 3 Relevant activities and regulatory challenges for the EU relating to ATMPs: points from the literature and the EASAC–FEAM Working Group**

Issues for updating the regulation of ATMPs are being considered by DG Sante together with the EMA. A stakeholder consultation on regulatory science, including ATMPs ended in June 2019[18].

The current progression of EMA's goals for regulatory sciences includes a proposal on ATMPs to increase early interaction between developers and regulators as well as with health technology assessment (HTA) bodies and payers (Hines *et al*., 2019). The EMA's PRIME initiative is also relevant in aiming to enhance support for the development of medicines that target an unmet medical need, by interacting with developers to optimise the generation of robust data and enable accelerated assessment of medicines' applications.

Other discussions between the European Commission and stakeholders[19] have also explored authorisation issues for quality, safety and innovation for cell therapy, including traceability of source and options for introducing more stringent rules if there are multiple recipients of stem cells from a single source. Establishment of the ATMP Interest Group of the European Compliance Academy (mainly comprising pharmaceutical/biotechnology companies and regulators) additionally provides a networking platform to exchange lessons of good practice between those involved in development, manufacturing, quality management and marketing authorisation[20].

An initial evaluation of the first cohort of ATMP marketing authorisation applications (Barkholt *et al*., 2018) disclosed several common obstacles which, if not resolved, would prohibit licensing. These included product quality and clinical data demonstrating efficacy and safety. For cell therapy, the early characterisation of product identity, purity, stability and strength is vital to understand the critical parameters that will be used for in-process release and stability.

Research on legal and ethical aspects of regulation needs to continue to address the challenges at all stages in the development of ATMPs: early and late manufacturing, marketing and authorisation procedures, and post-marketing. Future reform is likely to encompass the issues for: enhanced scientific support; guidelines on investigational ATMPs; setting common standards for assessment; and options for development of a central resource of information for all stakeholders. It is also particularly important for the EMA Committee of the Advanced Therapies to assess the current disparities in hospital exemption procedures between EU countries.

by market authorisation of a stem cell product (Lee and Lysaght, 2017). Efforts to accelerate patient access to innovation are welcome in principle and it is acknowledged that, when the number of available patients is low, there may be need to combine work on proof-of-concept with dose finding (Barkholt *et al*., 2018). But there is concern that schemes for conditional marketing approval lead to medicinal products with limited evidence of clinical benefit. Granting conditional (accelerated) access transfers financial costs and the burdens of medical uncertainty from drug developers to health care systems; and, consequently, from trial participants (who should be required to undergo a rigorous informed consent process) to health care consumers (who are not) (MacPherson and Kimmelman, 2019). Particular potential problems are that conditional approval may be based on surrogate endpoints and that the medicine sponsor's capacity for long-term monitoring and compliance with post-marketing obligations may be weak (see, for example, Kesselheim and Avorn, 2017). A case can be made for conditional approval information to be publicly accessible (Lee and Lysaght, 2017). Independent assessment of the initial cases of EMA conditional licensing (Banzi *et al*., 2017) concluded that better evidence of safety and efficacy was needed at the time of conditional approval and even more convincing data before full approval. Furthermore, as the cost of treatment will be a key factor in whether approved ATMPs reach patients, parallel Health Technology Assessment (HTA) should be encouraged, to collect relevant cost–benefit data (Barkholt *et al*., 2018)[21].

The EASAC–FEAM Working Group expressed concern that some companies are advancing poorly efficacious therapies (and perhaps inducing patient organisations to lobby for marketing authorisation) that result in high costs for health systems (see also section 2.4). Companies may defend this behaviour by saying that the profits from such products will be reinvested in future generation treatments, more efficacious and cheaper, but there is little evidence that this re-investment in innovation is happening. The concern about financial interactions between companies and patient groups is a more general one (Ozieranski *et al*., 2019) and might partly be resolved by an openly accessible standardised disclosure database of payments.

Accelerated access and conditional approval mechanisms have been introduced in other countries (Zarzeczny *et al*., 2018), including Japan (Sipp, 2015), USA (Avorn and Kesselheim 2015; Shapiro *et al*., 2019) and Canada (Reicin *et al*., 2012). In the USA, the potential therapeutic value of stem cells has been used

[18] EMA Regulatory Science to 2025 strategic reflection, press release 19 December 2018, https://www.ema.europa.eu/en/news/regulatory-science-2025-launch-six-month-public-consultation.
[19] Minutes of the meeting between the International Society for Cell Therapy and DG Sante B4, 14 June 2018. https://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/ev_20180614_mi_en.pdf
[20] www.atmp-group.org.
[21] A recent publication from the Alliance for Regenerative Medicine (an alliance comprising companies and other stakeholders), 'Getting ready: recommendations for timely access to advanced therapy medicinal products (ATMPs) in Europe', July 2019, www.alliancerm.org/wp-content/uploads/2019/07/ARM-Market-Access-Report-FINAL.pdf, provides the commercial perspective on issues for conditional reimbursement schemes, HTA frameworks for ATMPs, the needs for pan-European initiatives to support real-world evidence use, early dialogue and cross-border access issues and options for new funding arrangements.

politically in calls for deregulation, and more generally for 'right-to-chose' medicines (Bianco and Sipp, 2014). Proponents of deregulation suggest that regenerative medicines should be allowed onto the market after proof-of-concept and safety testing. However, it is important to understand that phase 1 trials only reveal whether a product is safe enough for continued testing, not whether it is appropriate for widespread use. Recent fast-track market approval for a Japanese university for stem cell treatment of spinal cord injury is controversial, the nature of the cells involved unclear and the clinical evidence deemed weak (Anon., 2019a). The problem in Japan is compounded by an apparent instruction from Japan's Ministry of Health to researchers not to engage in scientific publication of the data (because of concerns that data could then be used in promoting the treatment). A response to these concerns from the Ministry of Health (Miyamoto, 2019) rejects the criticisms, noting that other ethical issues might be raised by insistence on double-blind clinical studies (if involving sham operation on a control group) or by delaying/withholding access to the treatment. Related issues for demonstrating and approving safety and efficacy and for obtaining informed consent are raised by the recent news on a proposal that select elite hospitals in China will be able to sell experimental therapies without approval (Cyranoski, 2019a).

In summary, in sections 2.1–2.3, throughout the field of regenerative medicine, there may be lack of data of the type usually expected for marketing authorisation of pharmaceutical products, and evolving financial models seem to be compounding the problem. Regenerative medicine trials are usually small, lack controls and are often 'first in human', so the risk to the patient is difficult to assess and quantify (Abou-El-Enein and Hey, 2019).

### 2.4 Evolving financial models

As noted previously, the scenario is changing in some respects. For some novel approaches, limited experimental evidence may be available, based on a reasonable starting hypothesis, published in reputable journals and involving expert scientists. But the data are then promoted in an unbalanced way by company sources, with the consequence that the distinction between validated and replicated or premature and unsubstantiated therapeutic claims may become harder. That is, instead of the initial simple scenario where 'good' and 'bad' clinical centres could easily be contrasted, there is now a continuum from one extreme to the other, without clear boundaries. Lack of published information may indicate a more general lack of evidence, for example on cell characteristics and clinical effects, and an intention to claim beneficial properties in multiple indications. While there are many deficiencies in the examples of information available (Figure 2), an acceptable evidence package must encompass preclinical research, insight into mechanisms, and published clinical design and outcomes. Absence of some or all of this information raises concern.

For example, autologous stem cell therapy for amyotrophic lateral sclerosis is being tested because of the ability of cells to secrete neurotrophic factors and modulate the immune response (Oskarsson *et al.*, 2018). However, none of the early-phase clinical trials have been powered for efficacy, although subjective benefits have been reported (Petrou *et al.*, 2016). Autologous stem cell therapy has received fast track designation from the US Food and Drug Administration (FDA) for amyotrophic lateral sclerosis and been granted orphan status by both the FDA and EMA. In 2018, a company suggested that it would offer its experimental stem cell therapy to patients with amyotrophic lateral sclerosis under US newly enacted 'right-to-try' legislation (offering terminally ill patients access to unapproved treatments) but subsequently decided not to proceed in this way[22]. While the need for small and medium-sized enterprises (SMEs) to attract investor financing should be generally acknowledged, this case illustrates some of the problems arising from the excessive optimism found in smaller companies disposed to view their situation as a 'glass half-full' rather than 'half-empty'. These cases also emphasise the need for regulatory authorities to build good scientific links with the companies and their regulatory advisory committees to ensure existence of an appropriately robust evidence base, even when encouraging early access to innovation by patients who may have few or no other options. There are also related issues for what should be allowed in terms of promotional medical claims on company websites when no marketing authorisation has yet been granted and the use by companies of selected patient results when other information is not supportive[23].

### 2.5 Unregulated provision and undocumented claims

In addition to the challenges faced by researchers, companies and regulators in providing and assessing evidence for authorisation through regulatory

[22] https://www.statnews.com/2018/06/26/als-drug-maker-walks-back-plan-to-profit-from-right-to-try-law-following-heavy-criticism/, 26 June 2018.
[23] For example, there is a recent case of a company promoting its product ('multipotent adult progenitor cells', an allogenic product to modulate the immune system) in development for the treatment of ischaemic stroke (www.statnews.com, 26 June 2019), when the published phase 2 trial showed no difference in the treatment from a placebo group at the primary endpoint of 90 days stroke recovery (Hess *et al.*, 2017).
[24] This is a major problem worldwide although the magnitude is not always clear. Assessment in the USA (Turner and Knoepfler, 2016) has ranked 24 broad conditions for which direct-to-consumer stem cells are promoted. The most common conditions are orthopaedic (more than 300 businesses involved), pain (more than 150), sports medicine (about 100), neurological (fewer than 100) and immune (fewer than 100).

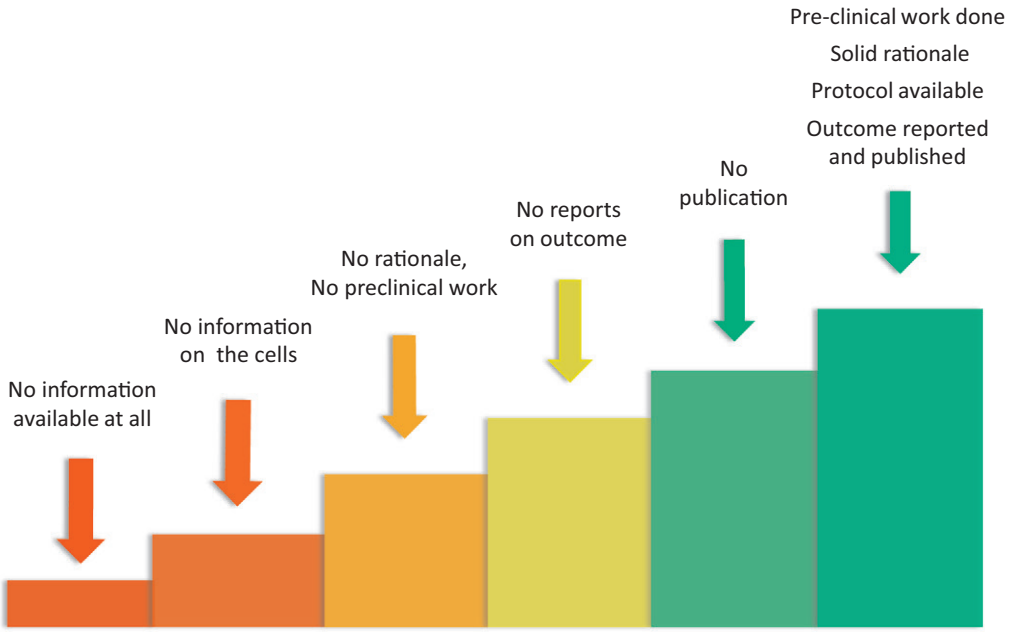



*Figure 2 Ascending steps for evidence. Figure by Giulio Cossu.*

frameworks, as described above, there is another problem: clinics selling promises of benefit with poorly characterised stem cells, on the basis of very little evidence[24]. Part of this problem can be traced back to the regulatory authority in allowing stem cells, if minimally manipulated and homologous, not to be subject to the same regulatory mechanism as drugs (MacPherson and Kimmelman, 2019). However, in recent years, regulators around the world have clarified that stem-cell-based products should be regulated as ATMPs. But the consequences of the initially ambiguous policy have been dramatically exaggerated by the behaviour of unscrupulous clinics. Unregulated, unproven 'pay to participate' therapies share several characteristics: limited or missing information on the stem cells to be used (frequently derived from fat or bone marrow and referred to as 'mesenchymal stem cells'), unclear or unsubstantiated rationale for efficacy, insufficient data from *in vitro* and animal studies and from safety studies in humans, inadequate information for patient consent, and lack of supportive scientific publications in good quality, peer-reviewed journals. There are problems of inconsistency and ambiguity (Sipp *et al*., 2018) and there is continuing risk of invalid and dishonest claims, and potential harm (see, for example, FDA, 2017; Kuriyan *et al*., 2017). Many of the clinics that advertise stem cell treatments do not have relevant training; so not only are they operating outside the bounds of scientific evidence, but also outside their own professional qualifications (Fu *et al*., 2019).

In 2010, the EMA expressed concern (EMA, 2010) about unregulated medicinal products claiming to contain stem cells and provided for a wide range of serious or life-threatening diseases, which may result not only in little or no benefit to patients but could also be detrimental as safety may not have been properly assessed. These concerns persist. In 2017, the US FDA also warned (FDA, 2017) about the unscrupulous provision of stem cell products that are unapproved and unproven, and finalised a new regulatory framework in 2017. Recently, in a landmark judgement, the FDA won a lawsuit against a stem cell company whose activities had caused patient harm[25]. The FDA framework emphasises the distinction between therapies that require pre-market authorisation and those that do not in the USA, usually because of minimal manipulation and homologous use (Marks and Gottlieb, 2018). The new guidance might be unlikely to deter unscrupulous clinics. Civil litigation efforts may help to drive or augment regulatory enforcement (Horner *et al*., 2018).

Direct-to-consumer marketing of unapproved stem cell treatments for medical conditions has become prevalent in the past few years (Lee *et al*., 2017), for example in the USA, Australia, Japan, Canada and India (Sipp *et al*., 2017, 2018; Tiwari and Desai, 2018; Turner, 2018; Cyranoski, 2019b). In Australia, where autologous stem cell treatments (again often claimed as being based on mesenchymal stem cells) had been allowed on the basis of little evidence, regulatory changes were made recently to address the sale of

[25] 'FDA wins groundbreaking case against for-profit stem cell company' 4 June 2019, https://www.pharmacist.com/article/fda-wins-groundbreaking-case-against-profit-stem-cell-company.

unproven stem cell treatments, increasing safeguards to protect patients[26].

Crowd-funding campaigns to raise money for stem cell interventions may exaggerate potential benefits, bias public opinion and place new pressures on health services (Snyder *et al*., 2018). There is evidence of harm being caused (Marks and Gottlieb, 2018) and there are also longer-term safety concerns, related to the consequences of (uncontrolled) proliferation, differentiation and migration, the very characteristics that also make stem cells valuable under controlled conditions.

The ISSCR has produced guidelines (ISSCR, 2016) for stem cell research and clinical translation, including recommendations on publication of negative as well as positive results in peer-reviewed journals and on maximising information available from early-phase trials. However, in an analysis of clinical trial outputs (Fung *et al*., 2017), of the total number of trials identified (1,052), only 179 out of 393 completed trials had published results; and of the 48 trials that had been registered by known stem cell tourism clinics, none had published results. The trend towards unregulated, premature use of unverified results (often originating from a subset of participants before completion of the trial) heightens expectations: stem cell tourism is driven in part by anecdotal information and celebrity testimonials.

## 2.6 Global context

Stem cell tourism (Gunter *et al*., 2010) and the global reach of the expanding industry, exploiting differences in regulatory infrastructure, reveals the need for an international approach to report and monitor harms and benefits. Stem cell tourism should be distinguished from evidence-based compassionate use, where patient protection is foremost; further guidance is available from ISSCR.

There is evidence that some national regulatory systems have become too permissive and there are examples (such as in Asia) where regulatory review pathways have been amended specifically to encourage approval of regenerative medicine (Sipp and Sleeboom-Faulkner, 2019; Cyranoski, 2019b). In this era of international competitiveness there is a risk that other governments will be tempted to lower regulatory thresholds without sufficiently considering implications for patients or health care budgets or recognising that premature commercialisation can undermine trust in scientific R&D standards. More attention must be paid to these unwarranted competitive pressures using current methods for international regulatory harmonisation (see chapter 4). It has also been suggested (Lee *et al*., 2017) that the World Health Organization should develop guidelines or otherwise coordinate international activity, for example by convening expert advisory panels on issues relating to manufacturing, licensing and proper use and by providing platforms for cross-jurisdiction information-sharing and monitoring of countries' positions. If new international guidance on regenerative medicine were to be developed, it is important not to undermine previous international agreements whereby countries '*undertake to respect the freedom indispensable for scientific research and creative activity*'[27] while, at the same time, they '*recognize the right of everyone … to enjoy the benefits of scientific progress and its applications.*'

## 2.7 Ethics of stem cell research

There are strict frameworks for clinical experimentation. However, it has been observed (Asplund and Hermerén, 2017), in the context of the recent controversy about synthetic trachea transplantation, that part of the World Medical Association's Helsinki Declaration might be misinterpreted, and merits revision to provide better safeguards against experimentation at the physician's own discretion. In this respect, the ISSCR guidelines help to provide a robust alternative framework for applying innovative methods outside a clinical research project. Linkage to additional ISSCR guidance on clinical indications and on informed consent is made in the next chapter.

Ethical issues for patient access to experimental treatments, including gene and cell therapies, have also been considered further in the European context by the UK Nuffield Council of Bioethics (2018; see also Zarzeczny *et al*. (2018); MacPherson and Kimmelman (2019) and NASEM (2019b)[28] for other international

[26] 'Stem cell treatments and regulation – a quick guide for consumers', Department of Health Therapeutic Goods Administration, Australia, 25 June 2019, https://www.tga.gov.au/community-qa/stem-cell-treatments-and-regulation-quick-guide-consumers.
[27] UN Human Rights 'International Covenant on Economic, Social and Cultural Rights' implemented 1976, https://www.ohchr.org/en/professionalinterest/pages/cescr.aspx.
[28] In their synthesis work on emerging biomedical technologies, the US National Academies of Science, Engineering and Medicine propose a general framework for approaching ethical issues that encompasses the following:

- Promote societal value.
- Minimise negative societal impact.
- Protect the interests of research participants.
- Advance the interests of patients.
- Maximise scientific rigour and data quality.
- Engage relevant communities.
- Ensure oversight and accountability.
- Recognise appropriate governmental and policy roles.

reviews). Ethics concerns relate to information, consent and risk–benefit assessment, and include the following:

- Safety and efficacy: when limited research evidence is available, including uncertainty about appropriate dosage and long-term effects and where uncertainty about effects may be outweighed for the patient by their lack of other options.

- Patient consent: patients are not always informed that the intervention is experimental, and their medical state may affect their ability to assess risks and benefits. These challenges can be particularly acute if a parent or guardian is seeking experimental treatment for a child or person who lacks capacity to consent. The open dialogue between patient and health professional can also usefully encompass potential ethical issues for regenerative medicine insofar as the discussion contributes to the well-being of the patient as a person holding certain values.

- Information: a large amount of information about emerging treatments is now available online. This availability can empower patients but the information might often be misleading, complex, confusing and fail to specify risks.

- Professional responsibilities: there have been examples of conflicts of interest where medical professionals are incentivised to provide innovative approaches in ways that may conflict with their responsibilities including those to avoid hyperbole and to report adverse effects.

- Equity and fairness: patient access to experimental treatments is unequal and often limited by substantial costs. Early access to expensive treatments may also raise issues of distributive justice when resources are diverted from elsewhere in health services. There might be long-term financial cost savings from implementation of efficacious (possibly even curative) regenerative medicine therapies, avoiding subsequent care costs. But even if this is the case, the shorter-term increased costs of therapy are a major consideration. Very high financial costs for some treatments after regulatory authority approval is also an increasing problem for patients and their families. The calculation both of costs and patient benefits is complex: further work on the cost–benefit of regenerative medicine is essential for fairness for patients and for health insurers and health services[29].

- Donated biological material: one other ethical issue was raised in the recent discussion between the European Commission and ISCT[19]. Tissue and cell legislation is based on principles of altruistic donation, and the commercialisation of the donated biological material, once it becomes classified as a medicinal product, needs to be addressed — with transparent information and rules.

It should be emphasised that many other fields of medical research also share ethical and societal challenges, for example in terms of a propensity to publish only positive results, insufficient patient communication and high cost of novel therapies. The specific discussion here on regenerative medicine is considered in those broader contexts.

Different forms of regenerative medicine share a common feature in that many of the concerns are related to, and dependent on, uncertainty and knowledge gaps. Some general recommendations for researcher responsibility have been produced in the revised Code of Conduct for Research Integrity (ALLEA, 2017) and in the 'Guide to Responsible Conduct in the Global Research Enterprise' report by the InterAcademy Partnership[30]). There is more to be done to train researchers in regenerative medicine on the ethical, legal and social issues (Illes *et al.*, 2017). There is also need to do more to understand the responsibilities of other stakeholders such as the research-funding organisations, physicians and health services, regulators, medical journals, those in the product supply chain, and patients and their families. It is likely that there are conflicts between values of different stakeholders: the value landscape is changing, in consequence, for example, of demographic change that will affect health care priorities. To try to resolve such conflicts, research is needed so that values can be specified, ranked and debated.

As noted above, early access to expensive treatments may require that resources are diverted from elsewhere in health services to novel treatments without good evidence of their benefit. What is more important: uncertain investment in a treatment of, so far, unmet medical needs that may be cost-effective in the future or using the resources for treatment of less dramatic conditions where the benefits are known? There is no simple answer but the question requires analysis and debate.

[29] Although the final decision on cost–benefit assessments rests with the Member States, should the EU do more to take a position? Individual Member State decisions may have implications for their neighbours and for the efficient implementation of Directive 2011/24/EU on the application of patients' rights in cross-border health care.
[30] InterAcademy Partnership (2016). Doing global science: a guide to responsible conduct in the global research enterprise. https://www.interacademies.org/33345/Doing-Global-Science-A-Guide-to-Responsible-Conduct-in-the-Global-Research-Enterprise.

Ethical problems are raised by conflicting values, and by interests that pull in different directions. If and when interests or values clash (when certain values or interests can only be achieved at the expense of others), principles are available that can guide the decision-making. Two such principles with implications for the particular issue of patient access to experimental treatments are the precautionary principle and the principle of proportionality.

If the precautionary principle implies 'do nothing if there are unknown risks', this will halt progress; doing nothing also entails risks. But if the principle means only 'act with caution', it has to be made clear what this means in practice. Safety is obviously important, but so is efficacy. One possibility, but not the only one, is to say that it suggests, 'act according to the principle of proportionality'.

The precautionary principle, if strictly interpreted, requires us to stop if there are uncertainties about the risks involved, and it places the burden of proof of safety on those who want to promote a change. But the principle of proportionality is more open: its essence comprises four conditions (Hermerén, 2012), which at all times can be discussed, assessed, argued for and applied in the light of the present evidence. Decisions can then be taken which are not permanent but can be changed as the scientific evidence and value landscape changes:

(1) Importance of objective: the intended goal, theoretical or practical, should be important.

(2) Relevance of means: the means should bring about or at least help to achieve the goal.

(3) Most favourable option: there is no other less controversial or risky means to achieve the goal(s).

(4) Non-excessiveness: the means used should not be excessive in relation to the intended goal — which requires analysis, argument and interpretation.

This suggests an approach, termed stewardship, that implies or encourages an ongoing overview of processes in the light of changing evidence and values within restrictions imposed, for example, by respect for human rights, by concern for animal welfare and informed by the ISSCR guidelines. Moreover, the principle of proportionality can be applied in very different contexts, and it is important to make explicit what is taken for granted in each context. What can we learn from the history of medicine? Patient safety is obviously of paramount importance. But we can learn that willingness to take some calculated risks, with informed consent, has sometimes been necessary for the advancement of new knowledge and improved diagnostic and therapeutic methods. To insist on zero risk would halt progress — and limit possibilities to help patients in the future.

# 3 Future challenges: expectations, demands and practicalities

## 3.1 Improving the evidence base: what can we do?

The risks of regenerative medicine can be controlled in two main complementary ways (Cossu *et al.*, 2018): by governance and by individual consent, allowing the individual to control their own risk if properly informed. In both eventualities there is need for more precision, characterisation, validation and objective evidence, for regularity authority clarity and specificity, scientific and clinical specificity and transparency, and clarity of explanations for patients (see Zarzeczny *et al.*, 2018). As discussed above, there is now an irregular continuum of evidence, a hierarchy in quality, to substantiate claims made by proponents of regenerative medicine: from the well-documented, robust evidence base reviewed by regulatory authorities for conventional marketing authorisation ranging to limited but possibly good-quality research eliciting potentially premature requests for accelerated access, to the extreme cases of unregulated, vague and unsubstantiated assertions of benefit.

Among the priority actions to construct the knowledge base for better governance and better-informed patients are the following:

- Coordinated effort to improve understanding of the biology involved in the therapeutic approach, to ensure advances in fundamental science at a time when 'market-oriented' funding strategies often dominate. This better understanding is required at all levels — secondary and tertiary education, for medical professionals, journalists and the lay public.

- Commitment from researchers, journal editors and research funders to use more precise labels. The option to establish a registry of cell therapies, using standardised data, might be considered (NASEM, 2019a), and might enable long-term patient follow-up (MacPherson and Kimmelman, 2019), but would probably need a significant budget.

- Recruitment of trained, impartial and informed expert reviewers and regulators, with a particular need to ensure appropriate expertise in biology in all the regulatory agencies.

- Recognition that clinical studies on regenerative medicine must all adhere to the same standards of research design and monitoring that apply to any responsible clinical trials[9] while keeping in mind unavoidable differences in the logistics and in the nature of the medicinal product. These standards include satisfying ethical obligations. There must be reaffirmed commitment to collection of robust data post-marketing, particularly if conditional access has been granted.

- Differentiating carefully designed and conducted clinical trials (which should not require a patient to bear any financial costs) from those in which private clinics are essentially taking advantage of patients' vulnerability (Cossu *et al.*, 2018).

- Enforcement of rigorous methodological standards by regulatory authorities within a context that carefully balances feasibility and costs to continue supporting early-phase research.

- Conforming to most recent recommendations on regenerative medicine quality and product characterisation from scientific societies such as ISSCR.

These priority actions should be coordinated, both in countries established in regenerative medicine research and in those regions, for example in parts of Africa (Gaobotse, 2019), where such research has started only recently.

With regard to collecting and assessing clinical data for regenerative medicine, large randomised controlled trials may not be possible in most cases and there is scope for using systematic review and meta-analysis to pool studies of sufficient quality and transparency. To do this, the conduct and description of clinical trials must be clear in terms of population tested, patient sampling, primary endpoints, nature of interventions, randomisation and other statistical procedures, and characteristics of the trial setting (Abou-El-Enein and Hey, 2019). Use of emerging methods of evidence synthesis, for example evidence mapping, might be possible if the data sets are too heterogeneous for traditional meta-analysis

One other issue in clinical trial design is how to incorporate what is important for patients – including subjective improvement in symptoms/quality of life – into an evidence-based assessment of changes in function. An involvement of patients in setting clinical endpoints requires identifying the main problems perceived by patients, what is a meaningful change and what is cost-effective — the complication of a placebo effect might be particularly high with stem cells. It is important to distinguish variability from uncertainty (NASEM, 2019a): if disparate data are collected, do they represent biological variability or is it an issue of imprecise measurement? There is also much more to be done to appraise the health economics of regenerative medicine (see, for example, McCabe and Bubela, 2017; Hettle *et al.*, 2017).

What more needs to be done to improve the evidence base? High-quality science is important and must be promoted in close interaction with clinicians, ethical advisory committees, journals and rigorous but constructive regulatory oversight. The basic and clinical science communities are already active in promoting quality[31]. Guidelines have been very useful but the situation is now more complex than trying to distinguish between what is 'good' and 'bad' in research and in the quantity and quality of the evidence available. This is because, as observed previously (section 2.4), there is a significant volume of research activity characterised by protocols and reputable journal publications yet still without adequate evidence for benefit and risk, and applied prematurely in clinical practice. To do better in distinguishing between 'good' and 'bad' science outcomes across the spectrum of activities, and thereby promote good practice, various tasks have to be addressed in the scientific enterprise, as described in the following sections.

### 3.2 Research infrastructure and new approaches to translation

Promoting the translation of science to clinical application requires robust ethical review and the commitment of research sponsors. Clinical research is expensive and EU-level funding mechanisms are warranted, in particular to progress from limited phase 1 studies to academic investigator-initiated, clinically based research, including clinical trials (and active comparator designs). EU funding can help to coordinate and build initial critical mass in clinical research, for example as demonstrated in an allograft trial with foetal dopamine cells for Parkinson's disease (Barker *et al.*, 2019). However, studies by the European Investment Bank find that the lack of funding for SMEs in the EU is limiting the growth of European life sciences R&D, and the European Investment Bank itself is one source of funds for investment in health and life sciences innovation[32].

New models for regenerative medicine translation (Toure *et al.*, 2018) may benefit from involvement of patients in research design and follow-up. There is also scope for EU-level public investment in developing platform technologies that can be used in multiple applications, for example gene therapy vectors. And there is scope for a closer relationship between the clinical and social sciences and humanities — so that researchers can better understand ethical and social implications and public perceptions of regenerative medicine (Edwards *et al.*, 2017) and so that social scientists can understand more about the practicalities of a clinical trial.

The emphasis in sections 3.1 and 3.2 has been on clinical and translational research, but sustained EU investment in basic science is also essential to provide the fundamental basis for all subsequent work.

### 3.3 Academia–industry partnerships

Partnership is vital and there are opportunities to build new links between academia and industry in regenerative medicine (Corbett *et al.*, 2017). The EU public–private research collaboration, the Innovative Medicines Initiative (IMI), consulted on ATMPs in 2016 with the goal of identifying IMI as a platform for enhancing ATMP R&D. A summary of feedback to this consultation was published on the IMI website[33], highlighting current gaps in research, clinical development, manufacturing facilities, quality standards and education. An IMI stakeholder forum, also in 2016, further discussed the issues for advanced therapies[34]. While this consultation may lead to new partnerships in regenerative medicine, previous IMI work in this area is exemplified by the completed STEMBANCC project[35]. This explored the use of human induced pluripotent stem cells as a research tool for *in vitro* disease modelling, toxicology testing and screening drug candidates, particularly in diabetes, metabolic disorders and psychiatric diseases. A proposal by the European Commission for Horizon Europe (from 2020 onwards) describes the 'European Partnership on Innovative Health' roadmap[36], to expand on the scope and partners of IMI. The topic of regenerative medicine could become an important part of this partnership. SMEs are a vital part of technology innovation with many potential roles, for generating tools, promoting applications and clinical translation. However, compared with the USA, private funding of SMEs in the EU is less secure and, moreover, IMI publicly funded initiatives have included only a limited number of SME partners. EU competitiveness would be aided by initiatives to bridge the financial gaps in early product development.

[31] For example through ISSCR, www.isscr.org, and the International Society for Cell & Gene Therapy, www.celltherapysociety.org, and through the work of EuroStemCell, a consortium of researchers, social scientists and patients, with a strong focus on providing independent expert review, education and public engagement, www.eurostemcell.org. The International Alliance for Biological Standardization (www.iabs.org) is also active in promoting methods for standardising the quality of biological products.
[32] European Investment Bank 'Financing the next wave of medical breakthroughs – what works and what needs fixing?' March 2018, www.eib.org/en/publications/access-to-finance-for-life-sciences-rd.
[33] https://www.imi.europa.eu/sites/default/files/archive/uploads/documents/ATMPconsultation2016/ATMP_consultation_feedbacksummary.pdf.
[34] https://www.imi.europa.eu/news-events/events/imi-stakeholder-forum-2016.
[35] https://stembancc.org/.
[36] 'European Partnership on Innovative Health', DG Research and Innovation Inception Impact Assessment, July 2019. https://ec.europa.eu/info/law/better-regulation/

The European Commission is encouraging regenerative medicine from early testing *in vitro* to clinical trials as part of the Horizon 2020 programme 2018–2020 under the Societal Challenges Pillar (health, demographic change and well-being). However, the longer-term proposal to implement a project, RESTORE[37], as one of the flagship initiatives for the future Horizon Europe, seems to have been a casualty of the European Commission's strategic decision to abandon the flagship concept. A good case can be made for EU commitment to regenerative medicine research to be extended to include all EU Member States, even if the flagship concept has been discontinued, together with better recognition that moving research beyond phase I trials is very expensive.

Sustained EU and national funding are also important to promote networks bringing together multiple disciplines in regenerative medicine (e.g. EuroStemCell) to explore clinical potential, but also to build the fundamental research base that provides the initial resource for any future pipeline in regenerative medicine (de Haan *et al*., 2017).

Horizon Europe tools for training, including various Marie Curie training networks, also represent a good opportunity to increase the number of scientists needed for translational research in regenerative medicine. Industry–academia partnerships, including clinical partners, in focused training projects, would be particularly helpful.

### 3.4 Medical education

Little mention is made of regenerative medicine in most Member States' medical schools at either undergraduate or postgraduate level although there are some examples of good practice represented by courses on haematological stem cell approaches. Gaps in health care education on regenerative medicine have also recently been discussed in the USA (Wyles *et al*., 2019). Efforts to improve medical education need to take into account two other points discussed in previous sections. First, tackling gaps in training on ethical, legal and societal issues in regenerative medicine, including how to involve other stakeholders, especially patients, in research design and review (Illes *et al*., 2017). Secondly, training for primary care professionals to advise patients on how to access and assess good evidence[38]. In this regard, a recent study points out the need to improve information for these professionals about regenerative medicine (Sola *et al*., 2019).

In addition to these specific points for regenerative medicine, the Working Group also expressed a more general concern that the science content in medical education is being downgraded by many universities. Undergraduate medical students should be taught more biology to enable better understanding of the processes underlying regenerative-medicine approaches.

### 3.5 Publication practices

Collective activity to ensure integrity in publishing research has included the development of policies for data and reproducibility, reporting guidelines, registration of clinical trials and other study designs[39]. Some of the challenges evoked by selective reporting of the outcomes of regenerative medicine trials have been noted in previous sections (and see MacPherson and Kimmelman, 2019). There is need to ensure that the outcomes of failed trials are documented, since journals give priority to successful trials or trials claimed as such. Instead, there should be mechanisms supporting the open availability of negative data to facilitate independent analysis as part of robust and comprehensive procedures to track and coordinate evidence development.

But the challenges for regenerative medicine are compounded by sector-wide problems in the scientific journal industry, for example the advent of predatory, non-peer-reviewed journals, and the paucity of expert reviewers for the increasing number of manuscripts. The scientific community may understand the need to take care in appraising the quality of journal publications — but how can a patient know? There is a role for patient groups and medical research charities to provide resources whereby patients can seek advice.

### 3.6 Health services institutional readiness

There is variability among EU countries but all have in common a commitment to social systems supporting health care and an interest in EU collaborative research. Opening up the potential of health services to enable clinical trials, access to patients, product development and to support the development of health economic models in cost–benefit assessment, to inform approaches to reimbursement of regenerative medicine,

[37] The RESTORE Roadmap is on https://www.restore-horizon.eu/wp-content/uploads/2019/11/RESTORE_RoadMap_07.11.19.pdf; www.restore-horizon.eu.
[38] Disease factsheets prepared by ISSCR as a resource for physicians (and others interested in clinical applications of stem cell research) currently cover age-related macular degeneration; amyotrophic lateral sclerosis; diabetes; Huntington's disease; liver disease; multiple sclerosis; myocardial infarction/heart failure; osteoarthritis; Parkinson's disease; and paediatric leukodystrophies.
[39] COPE, https://publicationethics.org.

would help the field to progress. Research in the social sciences has shown the importance of institutional readiness to complement technological readiness: this will depend on several factors including the comparative benefit of regenerative medicines, cost consequences, impact on patient pathways and wider health services workflows.

### 3.7 Engaging with the public and patients, and countering misinformation

As discussed in previous sections, the scientific and medical communities have responsibilities in public engagement. For example, to explain to potential recipients of stem cells that an informed patient should only consent to receiving stem cells (even if autologous) if the cell population is well-characterised, if clinical evidence on efficacy and side-effects is well documented, and if the number of patients treated previously with the same procedure is clearly disclosed[40]. Expressing support for generating and monitoring high-quality research and its translation to well-regulated innovation is important while raising concerns where there is a lack of sufficient evidence or there are dubious practices by commercial clinics. Informed patient advocacy groups can help to counter premature provision of regenerative medicine (Horner *et al*., 2018). The risk goes deeper than the possible harm to individuals. There is concern about the long-term credibility of regenerative medicine research and scientific integrity.

It is often a challenge to interpret regenerative medicine data, given the present state of knowledge and limited clinical assessment. To deliver sustainable, clinically significant and equitable benefits, a coordinated strategy is required to cover the points discussed throughout this chapter and to encompass better science, better funding, better governance, and better public and patient engagement (Cossu *et al*., 2018). The EU push for flexibility to prepare for innovation and competitiveness has to be accomplished without causing harm. And, whatever the reform of regulatory frameworks, there must be concomitant collective action to deter unscrupulous clinics[41]. Key messages from the EASAC–FEAM Working Group are summarised in the next chapter.

[40] Recent advice from the ISSCR 'Informed consent standard for stem-cell-based interventions offered outside of formal trials', August 2019, provides detail on the categories of information that should be provided regardless of jurisdiction. http://www.isscr.org/docs/default-source/policy-documents/isscr-informed-consent-standards-for-stem-cell-based-interventions.pdf

[41] For example, recent action by Google to ban advertising for speculative medical treatments, including unproven stem cell therapies, is welcome, see ISSCR comment on Google policy, https://support.google.com/google-ads/answer/9475042?hl=en, September 2019.

# 4 Recommendations and key messages

The prerequisites for research in regenerative medicine are (1) a potentially tractable disorder, (2) an identifiable target tissue and (3) information on a mechanism as a basis for collecting and validating evidence for engineering an approach that is therapeutically relevant and has the desired performance characteristic. As discussed in the previous chapters, opportunities and challenges in regenerative medicine test the limits of some standard assumptions in health care innovation, for example leading to a requirement for new clinical trial paradigms. Assuming the prerequisites can be satisfied, what are the challenges for the EU in promoting regenerative medicine innovation?

The conclusions of the EASAC–FEAM Working Group were broadly supportive of the key messages and recommendations made by the Lancet Commission (Cossu *et al.*, 2018), which provides more detail on some of the issues covered in this report. In addition, the Lancet Commission addressed various other issues associated with health economics, product value and reimbursement, and the use of limited resources for competing priorities, matters that we have not investigated in detail. As a general point, the Working Group noted that the rapid evolution of the field of regenerative medicine requires continuing scrutiny with updating of criteria to ensure responsible research and innovation, and standardisation of protocols to enable data comparisons.

The points discussed in the previous chapters have implications for the European Commission, EU and Member State regulatory agencies and for the scientific community. EASAC and FEAM recognise their responsibility for continuing to catalyse examination of the issues and for bringing those issues to the attention of EU policy-makers. The responsibilities of the European Commission for regenerative medicine, as for other innovative medicine, must combine sustained support for research and its translation with the continuing development of a flexible, proportionate and rigorous framework to protect patients from harm.

In Table 1, we summarise the main points discussed in the previous chapters where improvement must be sought in developing the field of regenerative medicine for the benefit of patients and EU innovation.

How best should these recommendations be brought together into a coherent framework? There is need to strengthen capabilities for researchers, policy-makers and regulators, and for the wider community, to understand the opportunities and challenges. Even if some attempts to commercialise regenerative medicine are proceeding disproportionately quickly, running the risk of outpacing both scientific understanding and regulatory safeguards, the elements embedded in the four pillars presented in the work of the Lancet Commission (Cossu *et al.*, 2018), and exemplified in Table 1, remain of core relevance in protecting patients while supporting innovation. We now emphasise the following additional considerations for these four pillars.

### Pillar 1: Better science

In addition to the points summarised in Table 1 and discussed in more detail in previous chapters, including the need to support basic science to improve stem cell protocols, we draw attention to the work of the UK Academy of Medical Sciences (2017), which provides a broad overview of the strengths and limitations of different sources of clinical evidence and how to enhance accuracy and reliability of clinical study results, and their reporting.

### Pillar 2: Better funding models

The challenges relate not only to models of research funding, although these are very important, but also to health care reimbursement models. There are challenges both for producers and for users (Anon, 2019b) but value-based agreements seem a good compromise to stimulate thinking about new models for sharing responsibilities to incentivise innovation. There may be opportunities to reduce R&D costs by increasing efficiency, for example by sharing platform technologies and applying lessons learnt from research in different clinical conditions.

### Pillar 3: Better governance

Governance issues in promoting translational research in regenerative medicine are complex (McKelvey *et al.*, 2018). Decisions on regenerative medicine must balance the need for sufficient high-quality evidence – on efficacy and risk – to make an informed decision on the use of a medicine with a societal desire for faster access to innovative medicines. As the UK Academy of Medical Sciences report (2017) concluded, '… *the concept of perfect evidence is illusory* …'. Transparency, both around the decision-making process and about the information on which decisions are made, is needed at all levels, be it in research, regulation or clinical practice.

Existing regulatory initiatives must be consolidated and clarified to reduce fragmentation and provide a consistent framework to reduce the scope for uncertainty and disputes. Governance mechanisms must be kept updated to ensure that patients' rights keep pace with technology advances. In addition to implications for regulatory frameworks there are also major implications for health care systems. Health care providers need to address challenges associated with decisions on regenerative medicine provided as a single or small number of treatments at high cost, when cost–benefit requires whole lifetime assessment and when the evidence base is still being developed. As discussed previously, high costs affect accessibility and raise the issue of accountability: who decides about access?

### Pillar 4: Better public and patient communication

Communication must ensure that patients' interests are put first, that independent and evidence-based sources of information are promoted (and distinguished from advertising), that patients and their families (with the help of professional experts) are enabled to compare different treatment options and that inequalities in access to health information are addressed[42]. Coordinated EU action is needed to advise and guide patients in their choices within the changing situation in regenerative medicine, which brings increasing complexity in decision-making with implications for increasing public and patient involvement in research.

### Seeking EU strategic coordination

There is a new era in medicine, characterised by new biological targets, tools and therapeutics. Our report is an invitation to the new European Commission to think about the emerging practice of regenerative medicine and its targeting of cells and tissues.

**Table 1 Summary of recommendations from previous chapters**

| Area for investigation or reform | Examples of action proposed for improving responsible research and innovation | Section in text |
|---|---|---|
| Preclinical research | Understanding pathophysiology, for example nature of tissue environment and alteration by disease.<br>Elucidating factors contributing to stem cell variability and issues for product standardisation.<br>Updating approaches to safety assessment on the basis of scientific advances.<br>Studies to elucidate mechanism of action (see ISSCR Guidelines for detail on procedures and objectives). | 2, 2.1 |
| Clinical research | Addressing ethical issues.<br>Better understanding of valid outcome measures.<br>Elucidating factors contributing to clinical response variability.<br>Ensuring design and monitoring standards for regenerative medicine adhere to similar principles as for other clinical trials.<br>Recognising that patients should not bear costs of clinical trials.<br>Both preclinical and clinical researchers should follow most recent recommendations from scientific societies, for example ISSCR. | 2.7<br>2.1, 3.1<br><br>3.1<br><br>3.1, 3.2 |
| Regulatory frameworks | Reforming EU ATMPs strategy to increase interaction between science and regulation to promote quality, safety and efficacy, and to generate sufficient robust evidence while taking care not to jeopardise capacity in early-phase research.<br>Exploring options for creating expert networks and centralised resources of information for all stakeholders.<br>Addressing various concerns e.g. for accelerated/conditional access approval. Assess potential of reforms, including initiatives to enable open access to data used for approval, and information on financial arrangements between companies and patient groups, and commitment to HTA.<br>Addressing hospital exemption procedures. | 2.2, 2.4, 3.1<br><br>3.1<br><br>2.3<br><br><br><br>2.2 |
| Unregulated provision | Urging EU and Member State regulatory authorities to exert tighter control on unscrupulous providers up to the closure of clearly fraudulent websites.<br>Providing appropriate and impartial advice to public and patients on what evidence is needed for informed consent.<br>Reviewing how EU can support international initiatives, including option to establish registry of cell therapies. | 2.5<br><br>2.7, 3.7<br><br>2.6, 3.1 |
| Research infrastructure and partnerships | Exploring how to attract new EU sustained support for research and its translation, including new models of academia–industry collaboration and pan-EU involvement.<br>Making the case for EU support for interdisciplinary networks (clinical and fundamental research) with a potential role to discuss and review results.<br>Involving health services institutions in clinical research and its translation to clinical practice. | 3.2, 3.3<br><br>3.3<br><br>3.6 |
| Professional education and training | Introducing regenerative medicine into undergraduate and postgraduate curriculum and increasing use of Marie Curie training networks in Horizon Europe.<br>Promoting code of conduct to include responsibility to follow professional guidelines.<br>Including teaching on ethical, legal and social issues.<br>Recognising the responsibility of health professionals to educate and inform the public. | 3.4<br><br>3.8<br>2.7<br>3.7 |
| Reporting, dissemination and engagement (including publication practices) | Improving reporting of outcomes of failed trials.<br>Supporting mechanisms for sharing availability of data within the scientific community to underpin objectives to track and coordinate evidence development.<br>Collective commitment to improving use of information in providing advice to patients. | 3.5 |

There is a danger that insufficiently regulated and unproven approaches undermine public trust in science. Reliable governance and patient engagement must both be built on robust science. European countries often have well-established processes at the national level for consultation to regulate emerging technologies but there may not always be similar processes at the EU level. There is room for the EU Institutions to do more in capitalising on the lessons learnt at the country level to bring together the various science (including social science) inputs to policy development. We emphasise that, in this case, the objective is to incentivise the tackling of unmet medical needs rather than incentivising one particular technology more than another. In this context, we welcome the focus by DG Sante on HTA, with common standards across the EU, as central for both patient safety and innovation, and we look forward to seeing action by the new European Commission to take forward the commitment to HTA made in the DG Sante Strategic Plan[43].

There are other opportunities for the new European Commission and European Parliament. In the mission letter[44] from the new European Commission President, Ursula von der Leyen, to the new DG Sante Commissioner, Stella Kyriakides, the first priority was described as '*… to help ensure Europe has the supply of affordable medicines to meet its needs … support the European pharmaceutical industry to ensure that it remains an innovator and world leader.*' Finding the balance between access to medicine and innovation is a challenge but DG Sante has additional powers in the new Commission in overseeing the regulation of medical devices and pharmaceuticals, previously under the competence of the Internal Market and Industry Commissioner. This new coordination for health care innovation policy is an opportunity for regenerative medicine. It is also an opportunity for the European Commission to strengthen its voice in international fora on regulatory frameworks, in particular the International Conference on Harmonisation, to support progress on global regulatory harmonisation (Lindstrom-Gommers and Mullin, 2018).

We summarise the **key messages from this EASAC–FEAM project** as follows:

## Regenerative medicine key messages: protecting patients and promoting research

- Regenerative medicine is designed to tackle devastating conditions with unmet needs. Cosmetic applications, for example, are inappropriate, at least for the time being.
- We are now at the threshold of being able to correct major genetic and other diseases — but for many, more evidence is needed, especially for the more complex polygenic and acquired degenerative disorders.
- It is vital to promote good biomedical science — from fundamental research to its translation to clinical trials. This has implications for EU commitment to well-planned first-in-human trials with reliable, shared and objective endpoints determined with input from supporting expert networks (which should also consider engagement with the public and media).
- Proportionate and consistent regulatory authorisation for marketing must be based on robust and replicable science. Unregulated provision of regenerative medicine must be deterred. The ethical issues and regulatory challenges discussed in this report need to be addressed in a rigorous, consistent and constructive way.
- Researchers must follow professional guidelines on responsible research and its translation, and standard-setting, in pursuit of good practice.
- Teaching on regenerative medicine should be part of the medical curriculum.
- Patients' interests must be put first. It is necessary to ensure a robust scientific basis for the clinical intervention and for the endpoints selected for measurement. A crucial criterion for patients, in deciding whether to consent to novel therapies, is that they, at least in Europe, should not be expected to pay clinical research costs.

[42] Points adapted from BEUC (Bureau Européen des Unions de Consommateurs) work on 'Direct to consumer information' X/21/2008-07/04/08, https://ec.europa.eu/health/sites/health/files/files/patients/respons_publ_consult_200805/consumer/beuc_en.pdf.
[43] DG Health and Food Safety Strategic Plan 2016–2020, Ares (2016) 2075174-02/05/2016; http://ec.europa.eu/info/sites/info/files/strategic-plan-2016-2020-dg-sante_may2016_en.pdf
[44] 10 September 2019, https://ec.europa.eu/commission/sites/beta-political/files/mission-letter-stella-kyriakides_en.pdf.

# Appendix 1 Working Group composition and procedures

The project proposal was discussed and approved by the officers and councils of EASAC (Halle and Bucharest) and FEAM (Brussels) during the period September to November 2018.

The report was prepared by consultation with a Working Group of experts acting in an individual capacity and nominated by member academies of EASAC and FEAM:

Volker ter Meulen (Chair, Germany)
Lucie Bačáková (Czech Republic)
Dominique Bron (Belgium)
Antonio Campos (Spain)
Giulio Cossu (Italy, UK)
Hermann Einsele (Germany)
Göran Hermerén (Sweden)
Jérôme Larghero (France)
Olle Lindvall (Sweden)
Tamás Masszi (Hungary)
Christine Mummery (The Netherlands)
Balázs Sarkadi (Hungary)
Riitta Seppänen-Kaijansinkko (Finland)
Rosa Castro and Elisa Corritore (FEAM)
Robin Fears (EASAC) (secretariat)

The Working Group met in April and November 2019 in Brussels, together with George Griffin (President of FEAM) and Helene Rønning (EASAC).

An announcement of the project was made on www.feam.eu and www.easac.eu on 6 August 2019.

In addition to the Working Group meetings, evidence was gathered in a workshop organised by the FEAM Forum (Brussels, November 2019) and in a session at the World Science Forum (Budapest, November 2019) (Appendices 3 and 4). The draft report was peer reviewed by academy-nominated experts in January and February 2020.

EASAC and FEAM thank all who contributed to preparing and reviewing the text.

# Appendix 2 Use of stem cells *in vitro* for disease modelling and drug testing

Convergence in the fields of stem cells and gene therapy are bringing new opportunities and challenges for therapy (Azvalinsky, 2019; Cavazzana *et al.*, 2019). In addition to the therapeutic applications, the methodologies of regenerative medicine are being used increasingly for *in vitro* assessment of biological function, evaluation of disease mechanisms and discovery and screening of novel pharmacological entities (Rowe and Daley, 2019). Recent publications illustrate the range of scientific advances:

- Differentiated pluripotent stem cells may provide suitable toxicology screening systems for hard-to-obtain human tissue. Combined with targeted genome editing, stem cells may be used to generate both normal and disease-specific models, exemplified by work on cardiomyocytes, hepatocytes and neural cultures (Apáti *et al.*, 2018) for both safety and efficacy assessment.

- An organoid is a 3D construct composed of multiple cell types that originate from stem cells through self-organisation, and can simulate the architecture and functionality of native organs (Li and Izpisua Belmonte, 2019). Organoids are being used, for example, in disease modelling and drug discovery for neural, gastrointestinal, liver, kidney, lung and cardiac applications and for modelling infections (Rowe and Daley, 2019). In recent work, an organoid platform for ovarian cancer replicates both intra- and interpatient heterogeneity (Kopper *et al.*, 2019) for screening purposes, and a model of hypoxic brain injury of prematurity facilitates study of mechanisms of injury (Pasca *et al.*, 2019). Organoids have further potential in modelling diseases of the central nervous system, both neurological and psychiatric disorders (Amin and Pasca, 2018). Human airway organoids may represent versatile models for the study of hereditary, malignant and infectious pulmonary disease (Sachs *et al.*, 2019). Organoids represent an important interface between biology and engineering (Takabe and Wells, 2019) and provide a potential resource for transplantation-based therapies.

# Appendix 3 'The ethics of regenerative medicine', a session organised by EASAC at the World Science Forum, Budapest, 22 November 2019

The event was organised at the World Science Forum (https://worldscienceforum.org) to stimulate discussion of the scientific, medical and ethical issues in regenerative medicine with the broader scientific and policy community worldwide.

Moderator: Volker ter Meulen (InterAcademy Partnership)

Speakers: Robin Fears (EASAC, Working Group secretariat); Goran Hermerén (Sweden, Working Group member); Anne Cambon-Thomsen (France, European Group on Ethics); Balazs Sarkadi (Hungary, Working Group member); Beata Sperlagh (Hungary, EASAC Biosciences Steering Panel member); Elisa Corritore (FEAM, Working Group secretariat).

Among topics addressed by presenters were the following:

- Consequences of the rapid pace of advance in the regenerative medicine landscape of basic, translational and clinical research.
- Differences between regenerative medicine and other (medicinal chemistry-based) approaches: for example, specificity and selectivity may not be testable and interpretable in a traditional way and depend on recipient tissue environment. Clinical variability can also depend on cell origin and stability during processing. The consistency of cell preparations cannot be characterised in the same detail as expected for chemical compounds.
- Importance of understanding and clarifying e thical issues in terms of stakeholder values and to specify whether, and where, there are conflicts of interest, and what modes of consent may be appropriate.
- Ways of addressing the substantial knowledge gaps. Risk–benefit analysis is of prime importance to provide the information basis for seeking consent and for assuring equity and fairness.
- There are, therefore, overarching goals for independent provision of evidence-based information and for a robust value-base. Poor-quality science can harm patients and undermine trust in research.
- The commercial environment is changing rapidly. In circumstances where research contexts are evolving and are intrinsically bound to novelty, medical applications often suffer from an evidentiary time lag. Ethicists and regulators are often regarded as 'too negative' or 'too late'. Many also judge that the EU historical emphasis on the precautionary principle may impede progress. The challenges are compounded by recent developments in accessing medical innovation – actual or claimed – for example, via crowd-funding campaigns.
- In balancing the interests for patient protection and support for innovation, scientists, regulators and health services must do more to combat unregulated provision of regenerative medicine that is based on little or no evidence, and to distinguish clinical goals from biological enhancement applications. The EU Advanced Therapy Medicinal Products Regulation provides a set of rules within the general pharmaceutical framework — this focus has been variously criticised as insufficiently flexible or insufficiently rigorous but there is general agreement about the need to deter unauthorised treatments.

In general discussion, self-regulation was highlighted as an important part of scientific responsibility and the issues raised for regenerative medicine exemplified well the expected interlinkages made in designing the World Science Forum programme vision 'Science, Ethics and Responsibility'. Because of the uncertainties in regenerative medicine, it is vitally important to secure the input of views from different stakeholders and to manage the public spread of unreliable information as part of attempts to inform patients. Academies of science and medicine have an important continuing role in catalysing discussion and action throughout the EU and in elevating engagement to the global level.

# Appendix 4 FEAM Forum on 'Regenerative medicine: scientific advances and regulatory framework in Europe', Brussels, 28 November 2019

The FEAM Forum (a platform for discussing key policy issues for the biomedical community) organised an event on regenerative medicine, bringing together speakers from the European Commission, EMA, public health services, science communication, academia and industry (https://www.feam.eu/events/regenerative-medicine-scientific-advances-and-regulatory-framework-in-europe/).

Moderator: Jackie Davis

Speakers: George Griffin (FEAM); Isidoros Karatzas (European Commission); Patrick Celis (EMA); Sile Lane (Sense about Science); Giulio Cossu (Working Group member); Johan Hyllner (Astra Zeneca); James Griffin (NHS Blood and Transplant); Lorenzo Piemonti (Hospital San Raffaele); Graziella Pellegrini (University of Modena and Reggio Emilia).

A report of the workshop was published by FEAM (https://www.feam.eu/wp-content/uploads/RM-Summary-report-FINAL-V3-14-Jan-2020.pdf); in this appendix a brief summary is provided of some of the themes addressed. Discussion of policy and ethical issues was informed by a series of stem-cell clinical case studies on haematology and malignancy, diabetes and epithelium disorders. Among the areas reviewed were the following:

- How to take account of ethical principles in progressing regenerative medicine, particularly when advising the European Commission and European researchers?
- Clarifying the role of the EU Advanced Therapy Medicinal Products Regulation in providing the framework for regenerative medicine, and the implications for conduct of clinical trials and the level of evidence required at time of regulatory approval. While less evidence may be available for authorisation, there must be commitment to collect data subsequently.
- Opportunities and challenges in helping patients and their families make sense of claims about therapeutic benefits at a time when the gap between expectations and reality makes the public vulnerable to unscrupulous providers. One option to inform communication would be to develop a new register, listing trials characterised by appropriate standards of robustness and trustworthiness.
- Member State Heath Technology Assessment and reimbursement challenges associated with the high cost of novel therapies and the implications for methods to assess risk–benefit and cost–benefit over the long-term.
- How should the EU regard increasing competitive pressure to accelerate innovation arising from other regions who may take a different view of regenerative medicine regulation? There are implications for ensuring sufficient regulatory expertise (in biology), for emphasising the determinants of research quality and for monitoring international developments.
- Are there other potential disconnects between regulatory frameworks? For example, are there differences in the national regulatory procedures for stem cell transplantation and for novel medicines?

General discussion highlighted the opportunities for the EU in recognising the importance of investing in basic science, in generating quality data, and in promoting multidisciplinary and multisectoral collaboration to enable innovation and its translation to clinical practice.

# Abbreviations

| | |
|---|---|
| ATMP | Advanced Therapy Medicinal Product |
| EASAC | European Academies' Science Advisory Council |
| EMA | European Medicines Agency |
| EU | European Union |
| FDA | Food and Drug Administration (USA) |
| FEAM | Federation of European Academies of Medicine |
| HTA | Health Technology Assessment |
| IMI | Innovative Medicines Initiative |
| ISSCR | International Society for Stem Cell Research |
| R&D | Research and Development |
| SMEs | Small and Medium-sized Enterprises |

# Glossary

| | |
|---|---|
| Allograft | A tissue graft from a donor that is of the same species as the recipient but genetically different. |
| Alveolar bone | Thickened ridge of bone that contains the tooth sockets on the jaw bones. |
| Apoptotic cells | Cells undergoing programmed cell death (apoptosis). |
| Autologous stem cells | Stem cells obtained from the same individual. |
| Blastocyst | A structure formed in early mammalian embryo development consisting of cells surrounding a cavity (blastocoel), called trophoblasts and fated to form the extra-embryonic membranes, and of an inner cell mass composed of cells fated to form all the tissues of the embryo. |
| Cardiomyocytes | Cardiac muscle cells. |
| Chimeric antigen receptor T-cells | T-cells (lymphocytes bearing T-cell receptors on the cell surface) that have been genetically engineered to produce artificial receptor proteins that give them the ability to target a specific protein. The term 'chimeric' refers to the receptors' dual function of antigen-binding and T-cell activation. CAR T-cells are used in immunotherapy. |
| Endogenous stem cells | Tissue-specific adult stem cells with the capacity to self-renew and differentiate into one or several specific cell types. |
| 'First in human' trial | A key step in medicine development, where a medicine already tested *in vitro*, in animals or in other preclinical studies, is administered to people for the first time. |
| Genetic disease | Disease that is caused by a change, or mutation, in an individual's DNA sequence. |
| Glial cell | Non-neuronal cells in the central nervous system (brain and spinal cord) and the peripheral nervous system that maintain homeostasis, form myelin, and provide support and protection for neurons. |
| Haematopoietic stem cells | Stem cells in the bone marrow that produce blood cells. |
| Heterologous stem cells | Stem cells from a different donor of the same species. |
| Homologous recombination | A type of genetic recombination in which nucleotide sequences are exchanged between two similar but not identical molecules of DNA. |
| Mesenchymal stem cells | Multipotent stem cells found in bone marrow that are important for making and repairing skeletal tissues, such as cartilage, bone and the fat found in bone marrow. They are not able to differentiate into other cell types except smooth muscle. As their bona fide nature of stem cells has not been unequivocally demonstrated, they are more properly named 'mesenchymal stromal cells'. |
| Mesenchymal stromal cells | Spindle shaped cells isolated from bone marrow, adipose, and other tissue sources, with different differentiation capacity *in vitro*. |
| Neurotrophic factor | A family of biomolecules that support the growth, survival, and differentiation of both developing and mature neurons. |
| Pluripotent stem cells | Cells that have the capacity to self-renew by dividing and to develop into the three primary germ cell layers of the early embryo and therefore into all cells of the adult body. |
| Teratoma | A tumour consisting of several different types of tissue, such as hair, muscle, teeth or bone. |
| Tissue engineering | The practice of combining scaffolds, cells, and biologically active molecules into functional tissues. The goal of tissue engineering is to assemble functional constructs that replace, restore or improve damaged tissues or whole organs. |

# References


Abou-El-Enein M and Hey SP (2019). Cell and gene therapy trials: are we facing an 'evidence crisis'? *EClinicalMedicine* **7**, 13–14.

Academy of Medical Sciences (2017). Sources of evidence for assessing the safety, efficacy and effectiveness of medicines. London: Academy of Medical Sciences.

Allison TF, Andrews PW, Avior Y *et al.* (2018). Assessment of established techniques to determine developmental and malignant potential of human pluripotent stem cells. *Nature Communications* **9**, 1925.

ALLEA (2017). The European code of conduct for research integrity. Revised edition. Berlin: ALLEA.

Amin ND and Pasca SP (2018). Building models of brain disorders with three-dimensional organoids. *Neuron* **100**, 389–405.

Anon. (2019a). Japan should put the brakes on stem-cell sales. *Nature* **565**, 535–536.

Anon. (2019b). Gene therapy's next instalment. *Nature Biotechnology* **37**, 697.

Apáti A, Varga N, Berecz T *et al.* (2018). Application of human pluripotent stem cells and pluripotent stem cell-derived cellular models for assessing drug toxicity. *Expert Opinion on Drug Metabolism & Toxicology* **15**, 61–75.

Asplund K and Hermerén G (2017). The need to revise the Helsinki Declaration. *Lancet* **389**, 1190–1191.

Avorn J and Kesselheim AS (2015). The 21st Century Cures Act — will it take us back in time? *New England Journal of Medicine* **372**, 2473–2475.

Azvalinsky A (2019). Molecular scissors cut in on stem cells. *Nature Medicine* **25**, 864–866.

Banzi R, Gerardi C, Bertele V and Garattini S (2017). Conditional approval of medicine by the EMA. *BMJ* **357**, j2062.

Barker RA, Farrell K, Guzman, NV *et al.* (2019). Designing stem-cell-based dopamine cell replacement trials for Parkinson's disease. *Nature Medicine* **25**, 1045–1053.

Barkholt L, Voltz-Girolt C, Raine J, Salmonson T and Schissler-Lenz M (2018). European regulatory experience with advanced therapy medicinal products. *Nature Reviews Drug Discovery* **18**, 8–9.

Bianco P and Sipp D (2014). Sell help not hope. *Nature* **510**, 336–337.

Biffi A, Montini E, Lorioli L *et al.* (2013). Lentiviral hematopoietic stem cell gene therapy benefits metachromatic leukodystrophy. *Science* **341**, 1233158.

Blau HM and Daley GQ (2019). Stem cells in the treatment of disease. *New England Journal of Medicine* **380**, 1748–1760.

Booth C, Gaspar HB and Thrasher AJ (2016). Treating immunodeficiency through HSC gene therapy. *Trends in Molecular Medicine* **22**, 317–327.

Cavazzana M, Bushman FD, Miccio A, Andre-Schmutz I and Six E (2019). Gene therapy targeting haematopoietic stem cells for inherited diseases: progress and challenges. *Nature Reviews Drug Discovery* **18**, 447–462.

Chien KR, Frisen J, Fritsche-Danielson R *et al.* (2019). Regenerating the field of cardiovascular cell therapy. *Nature Biotechnology* **37**, 232–237.

Corbett MS, Webster A, Hawkins R and Woolacott N (2017). Innovative regenerative medicines in the EU: a better future in evidence? *BMC Medicine* **15**, 49.

Cossu G, Birchall M, Brown T *et al.* (2018). *Lancet* Commission: stem cells and regenerative medicine. *Lancet* **391**, 883–910.

Cyranoski D (2019a). Chinese hospitals set to sell experimental cell therapies. *Nature* **569**, 170–171.

Cyranoski D (2019b). The potent effects of Japan's stem-cell policies. *Nature* **573**, 482–485.

de Haan G, de Crom R, Dzierzak E and Mummery C (2017). Regenerative medicine funding policies in Europe and The Netherlands. *npj Regenerative Medicine* **2**, 1.

De Luca M, Aiuti A, Cossu G, Palmer M, Pellegrini G and Robey P (2019). Advances in stem cell research and therapeutic development. *Nature Cell Biology* **21**, 801–811.

de Wilde S, Veltrop-Duits L, Hoozemans-Strik M *et al.* (2016). Hurdles in clinical implementation of academic advanced therapy medicinal products: a national evaluation. *Cytotherapy* **18**, 797–805.

EASAC (2011). European public health and innovation policy for infectious disease: the view from EASAC. Halle (Saale): EASAC.

EASAC (2017). Opportunities and challenges for research on food and nutrition security and agriculture in Europe. Halle (Saale): EASAC.

EASAC (2019). The imperative of climate action to protect human health in Europe. Halle (Saale): EASAC.

EASAC and FEAM (2012). Direct-to-consumer genetic testing for health-related purposes in the European Union. Halle (Saale): EASAC.

EASAC and FEAM (2016). Joint statement of the presidents on antimicrobial resistance. Halle (Saale): EASAC.

EASAC and FEAM (2018). Vaccination in Europe. Commentary on the EC roadmap "Strengthened cooperation against vaccine preventable diseases". Halle (Saale): EASAC.

Edwards J, Thomas R and Guilliatt R (2017). Regenerative medicine: from the laboratory looking out. *Palgrave Communications* **3**, 27.

Elsanhoury A, Sanzenberher R, Reinke P and Abou-El-Enein M (2017). Accelerating patients' access to advanced therapies in the EU. *Molecular Therapy Methods & Clinical Development* **7**, 15–19.

EMA (2010). Public statement on concerns over unregulated medicinal products containing stem cells. EMA/763463/2009.

European Commission (2017). Regenerative medicine: from new insights to new applications. Horizon 2020 Pillar: Societal Challenges call.

FDA (2017). FDA warns about stem cell therapies. Consumer updates on https://www.fda.gov/consumers/consumer-updates/fda-warns-about-stem-cell-therapies.

FEAM (2017). Human genome editing in the EU. Brussels: FEAM.

FEAM (2019). Precision medicine and personalised health. Summary of a FEAM conference organised by the Swiss Academy of Medical Sciences. Brussels: FEAM.

Fisher SA, Doree C, Mathur A, Taggart DP and Martin-Rendon E (2016). Stem cell therapy for chronic ischaemic heart disease and congestive heart failure. *Cochrane Database of Systematic Reviews* **4**, CD007888.

Fu W, Smith C, Turner L *et al.* (2019). Characteristics and scope of training of clinicians participating in the US direct-to-consumer marketplace for unproven stem cell interventions. *Journal of the American Medical Association* **321**, 2463–2464.

Fung M, Yuan Y, Atkins H, Shi Q and Bubela T (2017). Responsible translation of stem cell research: an assessment of clinical trial registration and publications. *Stem Cell Reports* **8**, 1190–1201.

Gaobotse G (2019). Stem cell research in Africa - legislation and challenges. *Journal of Regenerative Medicine* **7**, **1**: doi:10.4172/2325-9620.1000142.

Garzon I, Perez-Kohler B, Garrido-Gomez J *et al.* (2012). Evaluation of the cell viability of human Wharton's jelly stem cells for use in cell therapy. *Tissue Engineering Part C Methods* **18**, 408–419.

Gunter KC, Caplan AL, Mason C *et al.* (2010). Cell therapy medical tourism: time for action. *Cytotherapy* **12**, 965–968.

Hanna E, Remuzat C, Auquier P and Tourni M (2017). Gene therapies development: slow progress and promising prospect. *Journal of Market Access & Health Policy* **5**, 1265293.

Hermerén G (2012). The principle of proportionality revisited: interpretations and applications. *Medicine, Health Care and Philosophy* **15**, 373–382.

Hess DC, Wechsler LR, Clark WM *et al.* (2017). Safety and efficacy of multipotent adult progenitor cells in acute ischaemic stroke (MASTERS): a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Neurology* **16**, 360–368.

Hettle R, Corbett M, Hinde S *et al.* (2017). The assessment and appraisal of regenerative medicines and cell therapy products: an exploration of methods for review, economic evaluation and appraisal. *Health Technology Assessment* **21** (**7**), i–xxix and 1–204.

Hines PA, Guy RH, Humphreys AJ and Papaluca-Amati M (2019). The European Medicines Agency's goals for regulatory science to 2025. *Nature Reviews Drug Discovery* **18**, 403–404.

Hirsch T, Rothoeft T, Teig N *et al.* (2017). Regeneration of the entire human epidermis using transgenic stem cells. *Nature* **551**, 327–332.

Horner C, Tenenbaum E, Sipp D and Master Z (2018). Can civil lawsuits stem the tide of direct-to-consumer marketing of unproven stem cell interventions? *npj Regenerative Medicine* **3**, 5.

Iijima H, Isho T, Kuroki H, Takahashi M and Aoyama T (2018). Effectiveness of mesenchymal stem cells for treating patients with knee osteoarthritis: a meta-analysis toward the establishment of effective regenerative rehabilitation. *npj Regenerative Medicine* **3**, 15.

Illes J, Sipp D, and Kleiderman E (2017). A blueprint for the next generation of ELSI research, training and outreach in regenerative medicine. *npj Regenerative Medicine* **2**, 21.

Ireland H, Gay MHP, Baldomero H *et al.* (2017). The survey on cellular and tissue-engineered therapies in Europe and neighbouring Eurasian countries in 2014 and 2015. *Cytotherapy* **20**, https://doi.org/10.1016/j.jcyt.2017.08.009.

ISSCR (2016). Guidelines for stem cell research and clinical translation. Skokie, Illinois: International Society for Stem Cell Research.

Ivaskiene T, Mauricas M and Ivaska J (2017). Hospital exemption for advanced therapy medicinal products: issues in application in the European Union Member States. *Current Stem Cell Research & Therapy* **12**, 45–51.

June CH, O'Connor RS, Kawalekar OU, Ghassemi S and Milone MC (2018). CAR T cell immunotherapy for human cancer. *Science* **359**, 1361–1365.

Kesselheim AS and Avorn J (2017). FDA approval for eteplirsen for muscular dystrophy – reply. *Journal of the American Medical Association* **317**, 1481–1482.

Kopper O, de Witte CJ, Lohmssaar K *et al.* (2019). An organoid platform for ovarian cancer captures intra- and interpatient heterogeneity. *Nature Medicine* **25**, 838–849.

Kuriyan AE, Albini TA, Townsend JH *et al.* (2017). Vision loss after intravitreal injection of autologous "stem cells" for AMD. *New England Journal of Medicine* **376**, 1047–1053.

Lee T-L and Lysaght T (2017). Adaptive pathways regulations for stem cells: accelerating access to medicine or deregulating access to markets? *SCRIPTed* **14**, 1: doi:10.2966/scrip.140117.81.

Lee T-L, Lysaght T, Lipworth W *et al.* (2017). Regulating the stem cell industry: needs and responsibilities. *Bulletin of the World Health Organization* **95**, 663–664.

Li M and Izpisua Belmonte JC (2019). Organoids — preclinical models of human disease. *New England Journal of Medicine* **380**, 569–579.

Lindstrom-Gommers L and Mullin T (2018). International conference on harmonisation: recent reforms as a driver of global regulatory harmonization and innovation in medical products. *Clinical Pharmacology & Therapeutics* **105**, 926–931.

Lindvall O (2016). Clinical translation of stem cell transplantation in Parkinson's disease. *Journal of Internal Medicine* **279**, 30–40.

MacPherson A and Kimmelman J (2019). Ethical development of stem-cell-based interventions. *Nature Medicine* **25**, 1037–1044.

McCabe C and Bubela T (2017). The health economics for regenerative medicine: how payers think and what that means for developers. In: *Mesenchymal Stromal Cells* (eds Peiman H and Viswanathan S), Chapter 11, pp. 289–307. Academic Press.

McKelvey M, Saemundsson RJ and Zaring O (2018). A recent crisis in regenerative medicine: analysing governance in order to identify public policy issues. *Science and Public Policy* **45**, 608–620.

Marks P and Gottlieb S (2018). Balancing safety and innovation for cell-based regenerative medicine. *New England Journal of Medicine* **378**, 954–959.

Miyamoto S (2019). Japan responds: stem-cell therapy justified. *Nature* **569**, 40.

Mullard A (2019). Gene therapy boom continues. *Nature Reviews Drug Discovery* **18**, 737.

Najar M, Krayem M, Merimi M *et al.* (2018). Insights into inflammatory priming of mesenchymal stromal cells: functional biological impacts. *Inflammation Research* **67**, 467–477.

NASEM (2019a). Exploring sources of variability related to the clinical translation of regenerative engineering products. Washington, DC: National Academies Press.

NASEM (2019b). Framework for addressing ethical dimensions of emerging and innovative biomedical technologies: a synthesis of relevant National Academies reports. Washington, DC: National Academies Press.

Nuffield Council on Bioethics (2018). Patient access to experimental treatments. London: Nuffield Council on Bioethics.

Oskarsson B, Gendron TF and Staff NP (2018). Amyotrophic lateral sclerosis: an update for 2018. *Mayo Clinic Proceedings* **93**, 1617–1628.

Ozieranski P, Rickard E and Mullinari S (2019). Exposing drug industry funding of UK patient organisations. *British Medical Journal* **365**, 277–279.

Pajorova J, Bacakova M, Musilkova J *et al.* (2018). Morphology of a fibrin nanocoating influences dermal fibroblast behaviour. *International Journal of Nanomedicine* **13**, 3367–3380.

Pasca AM, Park J-Y, Shin H-W *et al.* (2019). Human 3D cellular model of hypoxic brain injury of prematurity. *Nature Medicine* **25**, 784–791.

Petrou P, Gothelf Y, Argov Z *et al.* (2016). Safety and clinical effects of mesenchymal stem cells secreting neurotropic factor transplantation

in patients with amyotrophic lateral sclerosis. *Journal of the American Medical Association Neurology* **73**, 337–344.

Post Y and Clevers H (2019). Defining adult stem cell function at its simplest: the ability to replace lost cells through mitosis. *Cell Stem Cell* **25**, 174–183.

Reicin C, McMahon E and Chung C (2012). Stem cell therapy regulation in Canada: implications of the prochymal approach. *West Law Journal* **28**, 1–4.

Rojewski MT, Lotfi R, Gjerde C *et al.* (2019). Translation of a standardised manufacturing protocol for mesenchymal stromal cells: a systematic comparison of validation and manufacturing data. *Cytotherapy* **21**, 468–482.

Rosenthal N and Badylak S (2016). Regenerative medicine: today's discoveries informing the future of medical practice. *npj Regenerative Medicine* **1**, 16007.

Rowe BG and Daley GQ (2019). Induced pluripotent stem cells in disease modelling and drug discovery. *Nature Reviews Genetics* **20**, 377–388.

Sachs N, Papaspyropoulos A, Zomer-van Ommen DD *et al.* (2019). Long-term expanding human airway organoids for disease modelling. *The EMBO Journal* **38**, e100300.

Santisban-Espejo A, Campos F, Martin-Piedra L *et al.* (2018). Global tissue engineering trends: a scientometric and evolutive study. *Tissue Engineering Part A* **24**, 19–20.

Santisban-Espejo A, Campos F, Chato-Astrain J *et al.* (2019). Identification of cognitive and social framework of tissue engineering by science mapping analysis. *Tissue Engineering Part C Methods* **25**, 37–48.

Shanbhag S, Suliman S, Pandis N *et al.* (2019). Cell therapy for orofacial bone regeneration: a systematic review and meta-analysis. *Journal of Clinical Periodontology* **46** (**Suppl. 21**), 162–182.

Shapiro SA, Smith CG, Arthurs JR and Master Z (2019). Preparing regenerative therapies for clinical application: proposals for responsible translation. *Regenerative Medicine* **14**, 77–84.

Sipp D (2015). Conditional approval in Japan lowers the bar for regenerative medicine products. *Cell Stem Cell* **16**, 353–356.

Sipp D, Caulfield T, Kaye J *et al.* (2017). Marketing of unproven stem cell-based interventions: a call to action. *Science Translational Medicine* **9**, eaag0426.

Sipp D, Robey PG and Turner L (2018). Clear up this stem cell mess. *Nature* **561**, 455–457.

Sipp D, Sleeboom-Faulkner M (2019). Downgrading of regulation in regenerative medicine. *Science* **365**, 644–646.

Snyder J, Turner L and Crooks VA (2018). Crowdfunding for unproven stem cell-based interventions. *Journal of the American Medical Association* **319**, 1935–1936.

Sola M, Sanchez-Quevedo C, Martin-Piedra MA *et al.* (2019). Evaluation of the awareness of novel advanced therapies among family medicine residents in Spain. *PLoS ONE* **14**, e0214950.

ten Ham RMT, Hoekman J, Hovels AM *et al.* (2018). Challenges in advanced therapy medicinal product development: a survey among companies in Europe. *Molecular Therapy: Methods & Clinical Development* **11**, 121–130.

Takabe T and Wells JM (2019). Organoids by design. *Science* **364**, 956–959.

Tiwari SS and Desai PN (2018). Unproven stem cell therapies in India: regulatory challenges and proposed paths forward. *Cell Stem Cell* **23**, 649–652.

Toure SB, Kleiderman E and Knoppers BM (2018). Bridging stem cell research and medicine: a learning health system. *Regenerative Medicine* **13**, 741–752.

Turner L (2018). Direct-to-consumer marketing of stem cell interventions by Canadian businesses. *Regenerative Medicine* **13**, 643–658.

Turner L and Knoepfler P (2016). Selling stem cells in the USA: assessing the direct-to-consumer industry. *Cell Stem Cell* **19**, 154–157.

Viswanathan S, Shi Y, Galipeau J *et al.* (2019). Mesenchymal stem versus stromal cells: International Society for Cell & Gene Therapy (ISCT) Mesenchymal Stromal Cell Committee position statement on nomenclature. *Cytotherapy* **21**, 1019–1024.

Wyles SP, Hayden RE, Meyer FB and Terzic A (2019). Regenerative medicine curriculum for next-generation physicians. *npj Regenerative Medicine* **4**, 3.

Zarzeczny A, Atkins H, Illes J *et al.* (2018). The stem cell market and policy options: a call for clarity. *Journal of Law and the Biosciences* **5**, 743–758.

EASAC, the European Academies' Science Advisory Council, consists of representatives of the following European national academies and academic bodies who have issued this report:

**The Austrian Academy of Sciences**
**The Royal Academies for Science and the Arts of Belgium**
**The Bulgarian Academy of Sciences**
**The Croatian Academy of Sciences and Arts**
**The Cyprus Academy of Sciences, Letters and Arts**
**The Czech Academy of Sciences**
**The Royal Danish Academy of Sciences and Letters**
**The Estonian Academy of Sciences**
**The Council of Finnish Academies**
**The Académie des sciences (France)**
**The German National Academy of Sciences Leopoldina**
**The Academy of Athens**
**The Hungarian Academy of Sciences**
**The Royal Irish Academy**
**The Accademia Nazionale dei Lincei (Italy)**
**The Latvian Academy of Sciences**
**The Lithuanian Academy of Sciences**
**The Royal Netherlands Academy of Arts and Sciences**
**The Norwegian Academy of Science and Letters**
**The Polish Academy of Sciences**
**The Academy of Sciences of Lisbon**
**The Romanian Academy**
**The Slovak Academy of Sciences**
**The Slovenian Academy of Sciences and Arts**
**The Spanish Royal Academy of Sciences**
**The Swiss Academies of Arts and Sciences**
**The Royal Swedish Academy of Sciences**
**The Royal Society (United Kingdom)**

**Academia Europaea**
**ALLEA**

FEAM, the Federation of European Academies of Medicine, represents the following European national academies who have issued this report:

**Academy of Athens**
**Austrian Academy of Sciences**
**Belgian Royal Academy of Medicine (KAGB)**
**Belgian Royal Academy of Medicine (ARMB)**
**Croatian Academy of Medical Sciences**
**Czech Medical Academy**
**French Academy of Medicine**
**German National Academy of Sciences Leopoldina**
**Hungarian Academy of Sciences**
**Irish Academy of Medical Sciences**
**Italian Academy of Medicine**
**Lithuanian Academy of Sciences**
**Portuguese Academy of Medicine**
**Romanian Academy of Medical Sciences**
**Royal Netherlands Academy of Arts and Sciences**
**Spanish Royal National Academy of Medicine**
**Swiss Academy of Medical Sciences**
**The French Academy of Pharmacy**
**The French Academy of Veterinarians**
**The Royal Academy of Veterinary Sciences of Spain**
**The UK Academy of Medical Sciences**

For further information:

EASAC Secretariat
Deutsche Akademie der Naturforscher Leopoldina
German National Academy of Sciences
Postfach 110543
06019 Halle (Saale)
Germany

tel +49 (0)345 4723 9833
fax +49 (0)345 4723 9839
secretariat@easac.eu

EASAC Brussels Office
Royal Academies for Science and the Arts of Belgium (RASAB)
Hertogsstraat 1 Rue Ducale
1000 Brussels
Belgium

tel +32 (2) 550 23 32
brusselsoffice@easac.eu

FEAM
Rue d'Egmont 13
1000 Brussels
Belgium

tel +32 (2) 793 02 50
info@feam.com

EASAC is the affiliated network for Europe of

iap SCIENCE HEALTH POLICY
the interacademy partnership

EASAC contributes to the implementation of the

SUSTAINABLE DEVELOPMENT GOALS

Printed by Schaefer Druck und Verlag GmbH, Teutschenthal, Germany