STEM CELL RESEARCH

Trends and Perspectives
on the Evolving International Landscape

Contents

Preface

Human pluripotent stem cells (hPSCs), represented by embryonic stem (ES) and induced pluripotent stem (iPS) cells, possess a great potential for application in cell therapy and drug discovery. With their ability to produce an unlimited number of many kinds of human cells, hPSCs help overcome the challenge of producing large numbers of useful cells to conduct research, perform drug screening or enable cell transplantation therapy.

In the US and the UK, human ES cell-based clinical trials for retina regeneration have already begun, and the world's first iPS cell-based pilot clinical study is now approved by the Japanese government. Successful outcomes of these clinical studies are essential, and the next step is to implement innovative technological solutions to deliver safe and affordable hPSCs-based therapies to many patients.

More specifically, the challenge for the coming decade is to expand on multi-disciplinary and multi-sector collaboration aimed at large-scale production of high-quality hPSCs, and also, robust and reliable production of high-quality differentiated cells.

In order to provide adequate support to accelerate such research, a nation should take an evidence-based approach with an understanding of the global trend from a multitude of perspectives. This report aims to provide a comprehensive view of the stem cell research landscape with a focus on each nation's activity for hPSCs. I hope this will serve as a catalyst to invoke constructive discussion to further accelerate the translation of stem cell research to clinic.

Norio Nakatsuji
Professor and Founding Director, Institute for Integrated Cell-Material Sciences (iCeMS), Kyoto University

The stem cell field has grown very rapidly over the past decade, and continues to be one of the most exciting aspects of biomedical research. The volume of research output, and thus publication, has increased significantly in all areas, and has expanded particularly rapidly in topics related to embryonic stem (ES) cells and induced pluripotent stem (iPS) cells. At Cell Press, we have been proud to support this development through coverage of stem cell topics in many of our journals, including our flagship publication *Cell* and our field-dedicated journal *Cell Stem Cell*, launched in 2007. Cell Press is committed to advancing the progress of science through the publication of exciting research and reviews, and to disseminating important scientific progress to a broad audience.

The analysis presented in this report gives an overview of stem cell research activity that complements more specific coverage in journal articles and reviews. It also illustrates how application of Elsevier's SciVal solution can provide insight into the overall dynamics of a research area and the way that the landscape develops over time. We hope that the information presented in this report will be valuable for the stem cell community and beyond as a backdrop to continued development of national and international policies that support future progress in regenerative medicine.

Emilie Marcus
CEO, Cell Press; Editor-in-Chief, Cell

Deborah Sweet
Publishing Director, Cell Press; Editor of Cell Stem Cell

Stem cell research holds a strong potential to deliver new treatments for serious diseases and injuries for which today few effective treatments exist. In order to further advance this research, governments and industries worldwide are increasing R&D funding in this area with the hope and expectation that the basic research findings will translate into clinical practice, and thus come to the assistance of patients in need.

As a global provider of information solutions, Elsevier is committed to making genuine contributions to help advance science and innovation. We strive to deliver world class information through our role as traditional publisher while providing innovative tools and services that noticeably improve the productivity and outcomes of those we serve.

We are proud to partner with EuroStemCell and the Institute for Integrated Cell-Material Sciences (WPI-iCeMS), Kyoto University, along with twelve other stem cell experts who have provided valuable insights and perspectives to further deepen the understanding of the current and future trends in this field.

Along with its launch, the report will be discussed at the World Stem Cell Summit 2013, the community of thought leaders, innovators, and visionaries in the fields of stem cell and regenerative medicine who are committed to accelerating the discovery and development of lifesaving cures and therapies. We are honored with this opportunity and it is our genuine hope that the findings from the report will provide insights to further advance the progression of stem cell science.

Ron Mobed
Chief Executive Officer, Elsevier

Executive Summary

This report was jointly prepared by EuroStemCell, Kyoto University's Institute for Integrated Cell-Material Sciences (WPI-iCeMS), and Elsevier. It presents the results of a study that uses publication output metrics to gain a bird's-eye view of the stem cell field, both overall and specifically with regard to embryonic stem (ES) cells and induced pluripotent stem (iPS) cells. While it is beyond the scope of this study to provide in-depth policy analysis or recommendations, we have drawn on expert input across the field to illustrate areas to which the data may relate, including national policies, regulations, funding strategies, and research practices.

High-Level Key Findings

The rapidly growing field of stem cell research

Research in the field has grown from 4,402 publications in 1996, which represented 0.4% of global publication output, to 21,193 publications in 2012, or 1% of global output. Between 2008 and 2012, stem cell publications showed a compound annual growth rate of 7.0% compared to the world average growth rate of 2.9% across all disciplines. The field of ES cell research has grown more slowly than the stem cell field as a whole, with a growth rate of 4.9% from 2008 to 2012. This trend was also reflected in the subset of ES cell research focused on human embryonic stem (hES) cells, which showed a growth rate of 5.1%. In contrast, the emerging field of iPS cell research has grown rapidly, from 108 papers in 2008 to 1,061 in 2012, representing a compound annual growth rate of 77%. This is as would be expected from an emerging research area.

Stem cell publications are highly cited

Stem cell research showed an overall field-weighted citation impact (FWCI) of approximately 1.5 (2008-2012), indicating that stem cell publications, on average, were cited 50% more than the world average for all related subject areas. ES cell publications maintained a citation impact of above 1.80 (2008-2012), while the hES cell citation impact declined marginally from 2.35 in 2008 to 2.08 in 2012. The emerging field of iPS cell research showed the highest impact within the stem cell field, with a FWCI of 2.93 (2008-2012).

Approximately half of all stem cell papers use keywords related to "drug development" or "regenerative medicine"

Using a keyword analysis, we found that approximately half of all stem cell publications were aligned with two categories: "regenerative medicine" and "drug development". Overall, 47% of stem cell publications used keywords related to regenerative medicine, while 2% used keywords related to drug development. However, iPS cell publications featured drug development more prominently (11% of iPS cell publications). The use of keywords related to "drug development" was also associated with higher citation impact.

Singapore, Italy, the USA, Japan, and Israel show the highest activity levels in stem cell research

When exploring the international landscape of stem cell publications we found that, while the USA and China produced the highest volume of research (as they do in many subject areas), a number of countries showed higher levels of relative activity. Relative activity is a measure that relates country output levels to global activity level, therefore, enabling clearer assessment of each country's performance on the international stage; a value of 1.00 indicates that the country's research effort in stem cells corresponds precisely with the world average. Countries with the highest relative activity levels in stem cell research were: Singapore (1.8 times the global level), Italy (1.65 times the global level), the USA (1.61 times the global level), Japan (1.53 times the global level), and Israel (1.52 times the global level).

Korea and Singapore show the largest increase in relative activity between 2008 and 2012

The greatest increase in relative activity in stem cell research between 2008 and 2012 was observed in Singapore and Korea. In Singapore, this likely reflects significant investment in the field. Korea's government has also made stem cell research a strategic life science research focus. In contrast, the relative activity levels of Switzerland, Germany, Israel, and Sweden have all decreased, though they remain high.

Notable decreases of activity in human embryonic stem cell and increased activity in induced pluripotent stem cells

A number of countries showed notable decreases in relative activity in hES cell research publications from 2008 to 2012—most strikingly Sweden, but also Denmark, Switzerland, the Netherlands, and the UK. As most countries also showed an increase in relative iPS cell research publications, it is likely that this reflects a focal shift toward iPS cell research among new researchers entering the stem cell field.

Increasing levels of international collaboration

Previous studies have shown that international scientific research collaborations are becoming more prevalent; this is equally true for stem cell research. International collaboration in stem cell research generally increased from 2008 to 2012. Researchers from European countries, Singapore, Australia, and Canada were engaged in higher levels of international collaboration, while researchers from Russia, Iran and many Asian nations included in this study appeared to engage in international collaboration less frequently. As with previous findings in other subject areas, a higher level of stem cell research collaboration was associated with a higher FWCI.

Academic-corporate collaboration

Academic-corporate collaboration on studies published during the analysis period accounted for approximately 2% of all stem cell publications worldwide. Singapore, Denmark and Switzerland stand out, with higher than average academic-corporate co-publication for this field. However, the outputs resulting from such collaboration are much less commonly reported in publications than developments in other aspects of the field.

Scope and Methodological Overview

Stem cell research has the potential to revolutionize the way we treat many conditions, including degenerative diseases for which few effective treatments currently exist. Great hope is invested in this field by researchers, governments, and the general public alike, based on the expectation that we will learn how to replace damaged cells in patients with new, healthy cells grown or produced in the lab, or by inducing organ regeneration from stem cells in the body. The field has attracted priority status in many countries and has advanced rapidly. Indeed, some basic research findings are now being translated into new treatments. Furthermore, with the discovery of iPS cells the field has recently provided a step-change in biological understanding that will affect the way new drugs are identified and tested, and potentially, the way that cells can be generated in the lab.

Amid this unprecedented growth, stem cell research has also raised new ethical issues, not only regarding initial concerns about the use of embryos for research and the possibilities of reproductive cloning, but, more recently, regarding the broader challenges of regulation and ensuring fair access to treatments. In addition, some regions now offer unlicensed interventions that are unsupported by scientific and clinical evidence of benefit but claim to cure a wide range of conditions while, at the same time, new evidence-based treatment strategies are beginning to make the challenging transition from lab to clinic.

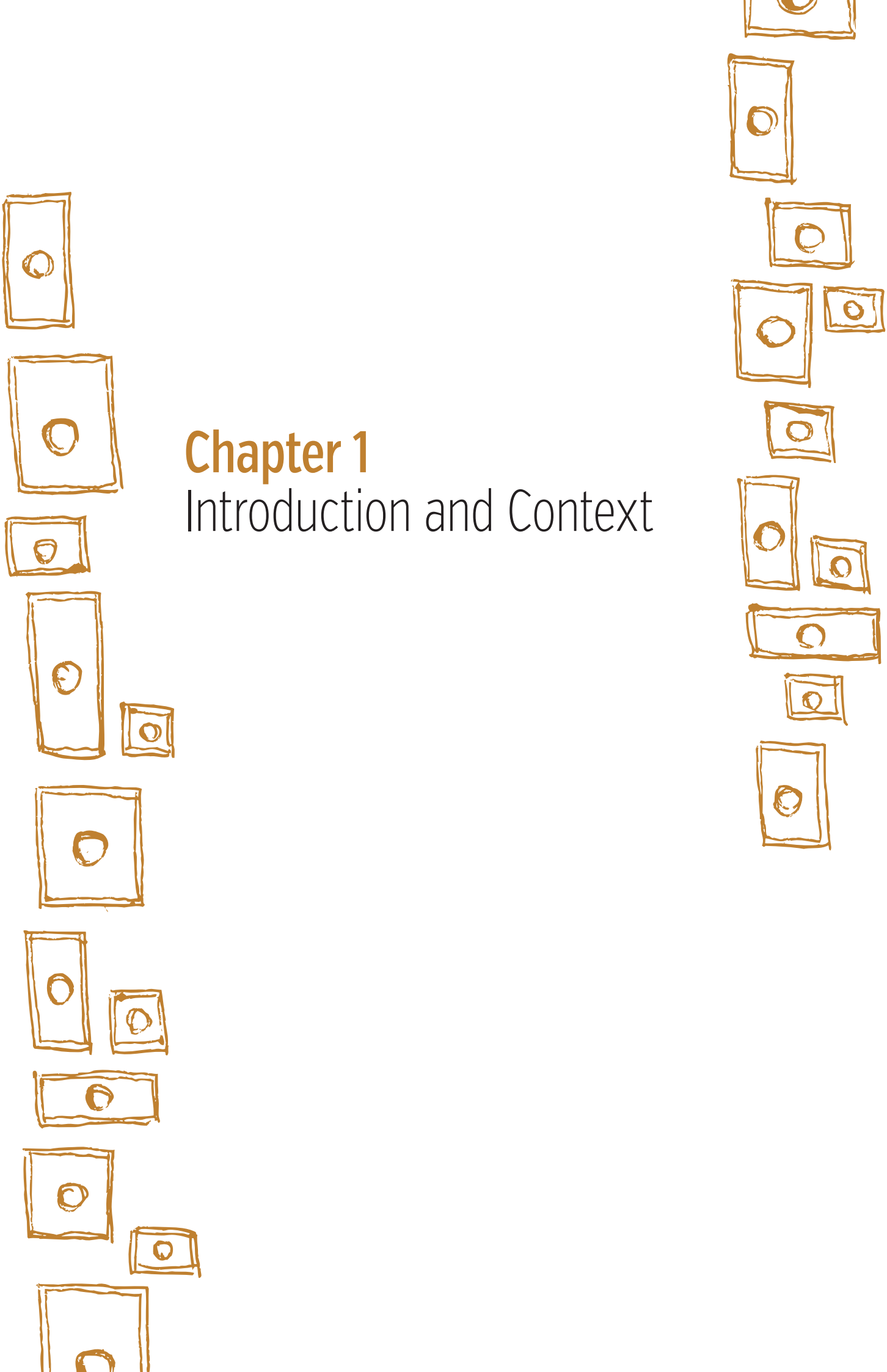
In this report, we present a publication output based analysis of the growth and development of the stem cell field from 1996-2012. Our analysis looks at the field as a whole, then more closely examines embryonic stem (ES) cell and induced pluripotent stem (iPS) cell research outputs. When we selected this focus, we considered a variety of factors, including scientists' and other stakeholders' views on current progress and future expectations for the field. The decision to examine ES and iPS cells, in particular, reflects both the clinical promise of these stem cell types, and the emphasis many policy-related discussions place on them.

To explore stem, ES, and iPS cell publication data, we extracted the relevant bodies of research from Scopus[1], the largest publication and citation database of peer-reviewed scientific literature. To find relevant publications, we searched for keywords nominated by subject matter experts in the title, abstract, and keyword fields of the publication records in a May 2013 snapshot of Scopus. The datasets were refined to include only articles, reviews, and conference proceedings, and were subsequently used to calculate the metrics for this study.

We examined global stem cell publication activity and citation impact, as well as the relative activity, citation impact, and co-publication rates of selected countries and institutions active in the field. The data presented herein have been reviewed by industry and academic experts for construct validity and any other major concerns; where possible, searches were subsequently refined in response to this input. Selected industry and academic experts were also interviewed to gauge responses to specific findings and contextualize the data.

This report details the key findings from this analysis, alongside discussion of relevant policies and funding strategies. In-depth analysis of national and international policies, regulations, funding strategies, and research practices is beyond the scope of this study; rather, we hope it serves as a catalyst for informed discussions of future strategies. Chapter 1 introduces the field of stem cells and its applications. Chapter 2 discusses publication output, growth, and the citation impact of stem cell research as a whole. Chapter 3 looks at the international landscape of stem cell publications, examining the activity levels and citation impact of various selected countries, as well as international and corporate collaboration trends; additional information on institutional collaboration is shown in Appendix H, however we have chosen not to present data at the individual researcher level, as we seek to understand trends on a macro level. Finally, in Chapter 4, we present conclusions based on our analyses. Our research methodology, including data sources, search terms, quality indicators used, and discussion of the limitations of this approach, is detailed in the appendices, along with further publication output metrics that may be of interest to our readers.

1 www.scopus.com



Chapter 1
Introduction and Context

1.1 What Are Stem Cells?

Stem cells, whether they occur in the body or in the lab, are defined by two cardinal properties: they can self-renew (generate perfect copies of themselves upon division) and differentiate (produce specialized cell types that perform specific functions in the body). The promise of stem cells as new tools for benefiting human health resides in these twin properties that, in principle, allow production of unlimited quantities of defined cell types (e.g., for use in drug screening or transplantation).

Beyond this primary definition, stem cells are classified into two major sub-types, based on the range of specialized cells they can generate.

Tissue (or adult) stem cells are found throughout the body, where they function to maintain the organ or tissue in which they reside, throughout the lifespan. Most rapidly renewing tissues are maintained by stem cells, with the notable exception of the liver, which is maintained by specialized liver cells called hepatocytes. Under normal physiological conditions, each type of tissue stem cell only generates cells of the organ or tissue system to which it belongs: the blood (hematopoietic) stem cell generates blood, the skin stem cell generates skin, and so on. An exception is the mesenchymal stem cell, which can generate bone, cartilage, and muscle (Bianco et al., 2013); however, while the mesenchymal stem cell field has generated much valuable research, it has also attracted controversy.[2]

Pluripotent stem cells, in contrast, have the potential to generate any type of cell found in the body. Pluripotent stem cells are generated in the laboratory by capturing or recreating cell types that exist only transiently during embryonic development, and have not been identified in the adult body.

There are currently three types of pluripotent stem cell, each generated by a different route:

Embryonic stem (ES) cells are derived from early-stage, pre-implantation embryos, and were the first type of pluripotent stem cells to be discovered: first in mice (Evans and Kaufman, 1981, Martin, 1981) and then in humans (Thomson et al., 1998) and several additional species.

Epiblast stem cells are a type of pluripotent mouse stem cells derived from a slightly later stage of embryonic development than mouse ES cells; they more closely resemble the hES cells (Tesar et al., 2007, Brons et al., 2007).

Induced pluripotent stem (iPS) cells were discovered in 2006 using mouse cells (Takahashi and Yamanaka, 2006); just a year later, this finding was replicated in human cells (Takahashi et al., 2007, Yu et al., 2007). iPS cells are generated from specialized cells by using a technique called "reprogramming". This groundbreaking work was awarded the Nobel Prize in Physiology or Medicine in 2012. Researchers have rapidly adopted iPS cells for study, although there is ongoing discussion in the field about whether they are completely interchangeable with ES cells (Yamanaka, 2012).

1.2 Health And Societal Benefits Presented By Stem Cell Research

Tissue stem cells have been used therapeutically for many years in the contexts of hematopoietic stem cell transplantation (HSCT), a vital component in the successful therapy of many types of blood cancer; stem cell-based skin grafting (Green et al., 1979, Green, 1989), which can save the lives of patients with extensive third-degree burns; and limbal stem cell grafting, which can restore sight to patients with impaired vision caused by corneal damage (Rama et al., 2010). In HSCT, stem cells are harvested from the patient or donor and, following leukemia treatment, are transplanted back into the patient to restore their blood and immune systems. In the case of stem cell-based skin or corneal grafting, skin or limbal stem cells are obtained from the patient, and then grown in the lab to produce sheets of cells sufficient to cover the burn or wound area. These applications exemplify two different approaches to transplanting tissue stem cells: one requires expanding cell numbers through lab culture, while the other does not.

Subsequent advances, including the derivation of hES cell lines and the advent of human iPS cell

2 The term "mesenchymal stem cell" is also often used incorrectly to describe as-yet poorly characterized cell cultures from tissues other than bone marrow (where true mesenchymal stem cells reside). Patient-applied infusions of cells from this type of culture (either from bone marrow or other tissues), improperly referred to as stem cells, have been widely used in unregulated practices and some official clinical trials. These practices do not harness stem cell properties; rather, the cells themselves are generally cleared rapidly from the body, and any claimed benefits would result from a "bystander" effect, such as the release of growth factors. See BIANCO, P., CAO, X., FRENETTE, P. S., MAO, J. J., ROBEY, P. G., SIMMONS, P. J. & WANG, C. Y. 2013. The meaning, the sense and the significance: translating the science of mesenchymal stem cells into medicine. *Nat Med,* 19, 35-42, BIANCO, P. 2013. Don't market stem-cell products ahead of proof. *Nature*, 499, 255.

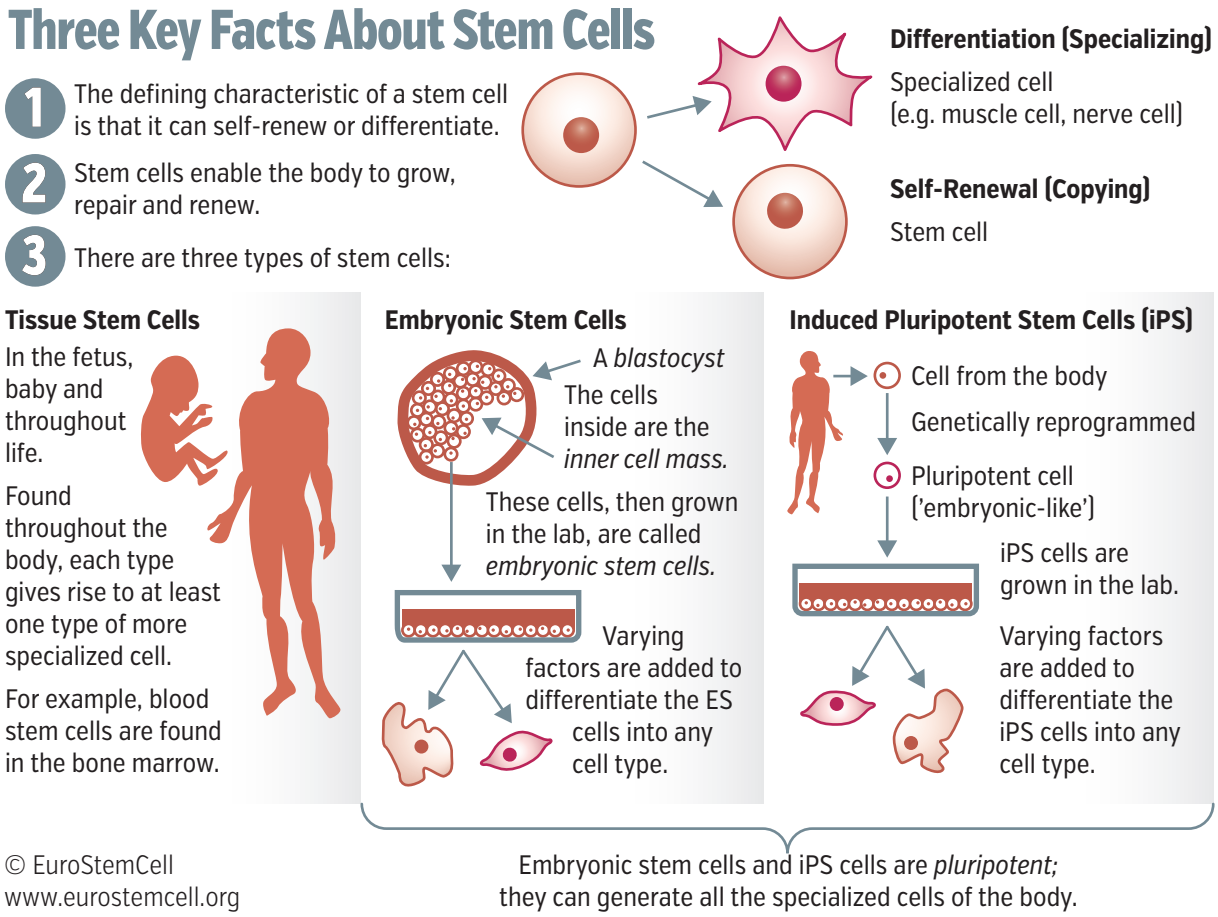


Figure 1.0: *Stem cells and their types.*

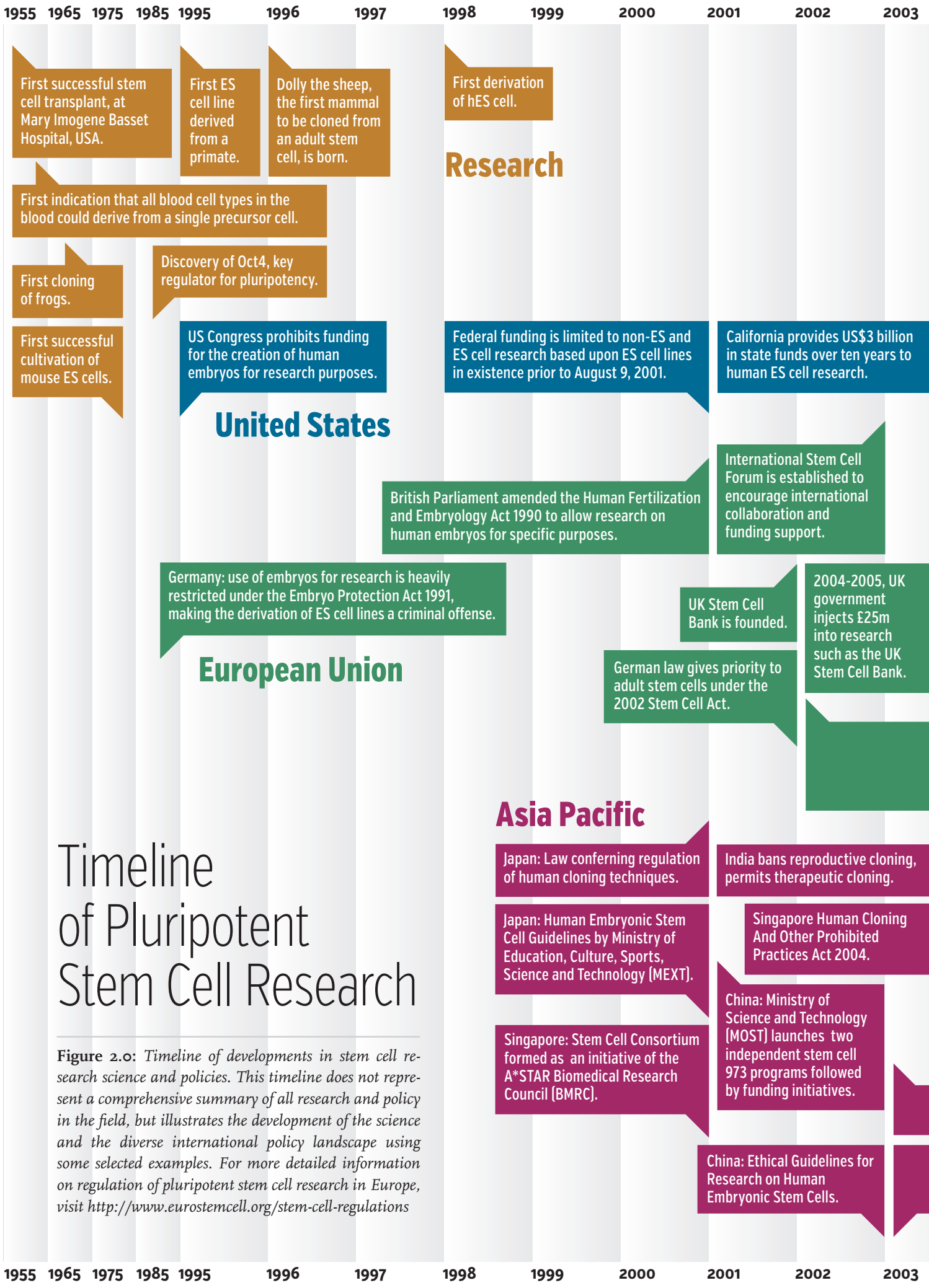
technology, as well as progress in making specific specialized cells from stem cells in the laboratory, have suggested that stem cell therapies may be more broadly applied to aid a wide range of disorders.

Stem cells in drug discovery, toxicity testing, and disease modeling

Stem cell research has the potential to improve and accelerate drug screening, drug discovery, and pre-clinical toxicological assessment of new drugs. Controlled differentiation of human pluripotent cells and/or *ex vivo* expansion of human tissue stem cells could produce unlimited supplies of defined human cell types. Once developed, this technology should permit screening of more compounds in shorter time and at less expense than is currently possible. Additionally, as it will allow primary screens to be conducted on human cells, it may reduce the number of promising drugs that fail in late Phase II/III clinical trials because of unexpected differences between animals and humans, as well as the number of animal tests needed.

iPS cell technology has also made it possible to conduct parallel high-throughput compound screens on defined cell types derived from a large number of different individuals. This technology will allow the screening process to account for genetic differences in the response to potential new drugs. As iPS cells can now be easily generated from patients, including those with inherited diseases and their unaffected relatives, they also provide a new way to investigate the molecular basis of disease by comparing healthy and disease-prone cells side-by-side in the lab, enabling the development of improved pharmaceutical interventions (Robinton and Daley, 2012). As these examples illustrate, stem cell biology therefore links directly to the emerging field of personalized medicine (Takahashi and Yamanaka, 2013).

Some progress has been made towards these goals. For instance, in recent tests, hES cell-derived hepatocytes performed as well as the current FDA gold standard primary adult cells at predicting human hepatotoxicity (Szkolnicka D et al., 2014). However, the ability to control the differentiation of both tissue and pluripotent stem cells remains a challenge for the field (see below).



Timeline of Pluripotent Stem Cell Research

Figure 2.0: *Timeline of developments in stem cell research science and policies. This timeline does not represent a comprehensive summary of all research and policy in the field, but illustrates the development of the science and the diverse international policy landscape using some selected examples. For more detailed information on regulation of pluripotent stem cell research in Europe, visit http://www.eurostemcell.org/stem-cell-regulations*


2004
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2013
Discovery of iPS cells which demonstrate that adult skin cells from the mouse can be reprogrammed into any cell type.
Human iPS cells made.
Epiblast stem cells discovered in mice and rats in UK.
US FDA approves world's first human ES cell clinical trial.
Nobel Prize in Physiology and Medicine is awarded jointly to Shinya Yamanaka and John Gordon for discovering that mature cells can be reprogrammed to become pluripotent.
Nobel Prize in Physiology or Medicine is awarded jointly to Mario Capecchi, Martin Evans and Oliver Smithies for introducing specific gene modifications in mice by the use of ES cells.
A federal judge orders to block all federally funded stem cell research, following a law suit (Sherley v. Sebelius). The ban is lifted in 2011 despite the plaintiffs' further appeals in 2012 and 2013.
House of Representatives votes 238-194 to loosen the limitations on federally funded ES cell research.
President George W. Bush vetoes the 2004 bill and passes two bills which make it illegal to create, grow, and abort fetuses for research purposes.
President Barack Obama removes certain restrictions on federal funding for research involving new lines of human ES cells.
UK Stem Cell Initiative (UKSCI) is announced, encouraging both public and private funding.
European human ES cell registry set up.
European Commission Regulation 1394/2007 classifies stem cell therapies as Advanced Therapy Medicinal Products.
European Court of Justice rules that technologies' inventions based on human ES cells cannot be patented in the EU (Bruestle vs. Greenpeace)
UK Government publishes a bill allowing creation of human admixed embryos.
Italy: Stem cell research is regulated by the Law 40 (2004). It prohibits the use of embryos for any research unless specifically aimed toward improving the therapeutic and medical condition of the embryo concerned.
2007-2013: EU Framework 7 programme supports stem cell research consortia; 27 projects in the Health program include research on human ES cells.
2002-2006: EU Framework 6 program supports first EU-funded large-scale stem cell research consortia.
Japan revises hES cells guideline, and establishes a system of international distribution of human ES cell lines.
Japan: Ministry of Health, Labour and Welfare (MHLW) approves world's first iPS cell clinical study for retinal regeneration.
India: Ethical Guidelines for Biomedical Research on Human subjects released by Indian Council of Medical Research (ICMR).
India: ICMR and the Department of Biotechnology (DBT) together lays down Guidelines for Stem Cell Research and Therapy.
China: Ministry of Health and the State Food and Drug Administration (SFDA) proposes draft regulations governing stem cell clinical trial management.
India: ICMR amends its 2006 guideline.
Japan spends 110 billion yen (approx. US$1.1 billion) over the next decade to support iPS cells research.
South Korea: Bioethics and Safety Act.
Australia: Revision of 2002 act, also allowing under license the creation of embryos other than by a process of fertilization of a human egg by a human sperm.
China: regulatory will halt new applications for clinical trials of stem-cell products.
India: Dept. of Biotechnology opens new national stem cell institute, inStem.
Singapore: Biopolis (A*STAR) established.
South Korea (2011 and 2012): Food and Drug Administration (FDA) approves the world's first three stem-cell treatments.
Australia: Research Involving Human Embryos Act 2002, and a law to prohibit reproductive human cloning, enacted.
South Korea: Ministry of Health and Welfare (MOHW) announces funding boost of 33 billion won (approx. US$29 million) in 2012.
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Cell replacement therapies

Stem cell research is also anticipated to contribute to new cell-based therapies through the use of cells generated from ES and/or iPS cells, or of *ex vivo* tissue stem cells, to replace missing or damaged cells, and (in the future) to generate artificial organs for transplantation. Although it is not yet possible to generate many cell types in the lab, or to expand many tissue stem cell types *ex vivo*, clinical trials using human fetal and adult cells, as well as hES and iPS cell-derived cells, are already in progress or on the horizon. For example, retinal pigment epithelial cells have been produced from both hES and human iPS cells (Carr et al., 2013, Jin et al., 2009), and both cases are conducting clinical trials to test the capacity of these pluripotent cell-derived cells to treat macular degeneration.

Regenerative therapies

In addition to cell replacement strategies, increased understanding of the intrinsic regenerative potential of individual organs, coupled with knowledge of how to control the scarring response in damaged tissues, may allow the development of drugs aimed at stimulating the body's own (endogenous) stem cells to initiate or enhance repair. This approach is expected to prove more suitable than cell replacement for some diseases.

1.3 Challenges

Biological

While cell replacement offers hope for the treatment of many diseases in the long term, it may still be some time before large-scale clinical use is available for most applications. Understanding how to produce many of the specialized cell types *in vitro* remains a major hurdle. Furthermore, the field faces challenges around quality control. It is essential that only defined cell populations are introduced into patients; this requires careful characterization of the cell populations intended for transplantation, in terms of gene expression and epigenetic profiles and functional attributes, and also to ensure that the populations do not contain other potentially harmful cell types. For cells generated from human pluripotent cells, for example, contamination of the transplant population with even a small number of residual ES or iPS cells could promote tumor formation. Additionally, as cells can acquire mutations during the culture process, stringent quality control is essential to ensure that cultured cells intended for transplantation have not acquired undesirable properties.

The ability to functionally integrate transplanted cells into damaged organs is also a major challenge. For some cell types, such as pancreatic beta cells and retinal pigment epithelial cells, it appears that transplantation of the cells alone will be sufficient to ameliorate symptoms or cure the disease (in these examples, diabetes and macular degeneration, respectively). For others, it is likely that complex organ structure creation through *in vitro* tissue engineering will be required. Here, the challenge is not only to derive the correct organ structure at scale, but also to maintain long-term function following transplantation. To achieve this will require new collaborations between tissue engineers and stem cell and vascular biologists, as well as improved understanding of how stem cells are controlled by their specific environment (niche) within the body.

Finally, where use of a patient's own cells is not possible, either because a sufficient number of cells cannot be obtained or because protocols for generating the required cell type in the lab (e.g., from iPS cells) have not yet been developed, the consequences of immunosuppression must also be considered. Banking hES and iPS cell lines is one way to ensure that patients can receive cells with a good immunological match, thus minimizing any required immunosuppression (Turner et al., 2013).

Ethics, policy, and regulation

Like many areas of biomedical science, stem cell research has provoked debate regarding the ethics and regulation of the research and resulting therapies. Initially these discussions focused largely on the moral status of the embryo (EuroStemCell, 2011). Governments responded with different regulations and legislation, leading to international complexities (Kawakami et al., 2010, Nakatsuji, 2007, STEMGEN, 2013). Countries including Australia, Singapore, Spain, South Korea, Belgium, the UK, and Sweden take a tightly regulated but permissive approach to research involving the use of human embryos to generate ES cell lines. Others have placed some restrictions on research in this area, either through direct legislation or by limiting the uses of research funding. For instance, in Germany, no new hES cell lines can be generated, but research using imported lines generated prior to May 1, 2007 is permitted,[3] while in the USA, a series of restrictions implemented between 1995 and 2009 limited federal funding for

3 Before 2008, the country used the earlier cutoff of January 1, 2002. StZG - Stem Cell Act, August 14, 2008. Available at http://bundesrecht.juris.de/stzg/index.html [accessed November 5, 2013].

hES cell research (see Figure 2.0). The patentability of hES cells and lines is similarly complex (The Hinxton Group, 2013). Some countries, including the US, place little or no restriction on this practice, while in 2011 the European Court of Justice ruled that patents cannot be granted in Europe for any technologies based on research using hES cells.[4]

The discovery of iPS cells raised the possibility that ES cell research would no longer be necessary, thereby circumventing the ethical issues present in embryonic research. To date, this has not been the case: the stem cell field continues to rely on both ES and iPS cell research to progress the understanding of pluripotency and its potential applications (Smith and Blackburn, 2012). Further, it has become clear that iPS cell research is not free of ethical considerations (Hug and Hermeren, 2011). For instance, the potential of these cells to generate sperm and egg cells, or even a whole new individual, raises new ethical questions about the status of the cells themselves and how they may be used.

> ***"Changes in the scientific landscape may bring about changes in the ethical landscape. Neither science nor values are static. Ongoing dialogues between different stakeholder groups on how to address the ethical issues raised by different therapies is a long term investment which will pay off, particularly if the decisions taken are regarded as preliminary and updated if and when there is new evidence or changes in the landscape of values."***
> *— Göran Hermerén, Prof. em. Medical ethics, Lund University; Chair, permanent working group on science and ethics of ALLEA (All European Academies)*

Broader ethical questions include tissue ownership, informed consent when donating cells for stem cell banking, patient safety and data protection, and access to treatments (Hug and Hermeren, 2011, Hermeren, 2012).

Finally, it is clear that all types of stem cell research, including ES and iPS cell research, must take place within a carefully considered ethical and regulatory framework, and that therapies based on living cells pose new challenges for regulators.

> ***"There is obviously a moral obligation to provide new and better treatments for patients. But there are also obstacles on the road, regulatory as well as technical. If the problem of standardization, in particular of iPS cell lines, is not addressed, this will create regulatory hurdles as long as the FDA regards every cell line as a new treatment. Moreover, if cell therapies are to be commercially successful and affordable, solutions to the problem of scaling up have to be found."***
> *— Göran Hermerén*

4 Case C-34/10: *Oliver Brüstle v Greenpeace eV* [2011], ECR I-09821.

Interview with Shinya Yamanaka

Shinya Yamanaka, together with Sir John Gurdon, received the 2012 Nobel Prize in Physiology or Medicine.

What do you consider the most important factors affecting how the stem cell research field has developed in Japan?

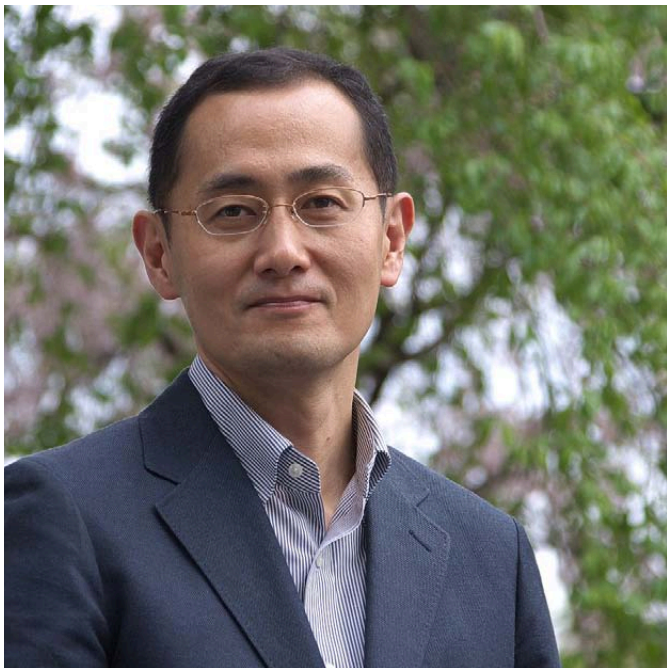
Yamanaka: After the discovery of mouse and human iPS cells, the Japanese government made a significant effort to support the advancement of research focusing on regenerative medicine. Thanks to that, I believe Japan is taking a global lead in addressing macular degeneration, spinal cord injuries, Parkinson's disease and more.

Do you think the discovery of iPS cells has had any impact on the direction of the field as a whole and if so, in what way?

Yamanaka: I believe the biggest impact to date of iPS cell technology is not in regenerative medicine, but in making disease models, drug discovery and toxicology testing. With iPS cells we can generate huge amounts of human cells such as hepatocytes, cardiomyocytes, and neurons from both healthy people and patients. Those somatic cells are very useful to recapitulate disease models based on the patient's phenotype and to perform drug screening. Because of this, I believe iPS cells as a tool have a very strong impact on medical biology and medicine.

How do you view the value of continued hES cell research today?

Yamanaka: My hope is that one day we can use iPS cells instead of hES cells, but at the moment, we still don't know whether all applications using hES cells can be replaced by human iPS cells. For example, clinical research for macular degeneration is in place using both hES and human iPS cells. Until we know the result of those studies, we cannot be 100% sure whether iPS can fully replace hES cells. For the sake of patients who really need a new treatment, we have to pursue both applications side-by-side.



Professor Yamanaka is Director, Center for iPS Cell Research and Application (CiRA), Kyoto University; Past President, The International Society for Stem Cell Research (ISSCR).

There has been much discussion about how similar or different iPS cells are from hES cells. What are your comments on this?

Yamanaka: This is a very important topic and we have been spending lots of our time on that question. In principle, iPS cells are very different from hES cells because they are artificial cells generated through reprogramming, but their properties including morphology, proliferation, gene expression, DNA methylation and differentiations are remarkably similar. At the same time, there are a small number of differences between hES and iPS cells; at the moment we don't know how significant those small differences are in terms of function and safety. We hope they don't matter, but it takes some time to be sure about that question.

Are there any societal or ethical issues in this field or a related area of science that you think may influence how policy about stem cell research develops in the future?

Yamanaka: We have two new major challenges using iPS cells; germ cell differentiation making sperm and oocytes, and animal chimeras, which is about making human organs in animals. This research is banned in many countries and requires a lot of ethical debate, as it's also true that it could be very helpful for many patients. These are very important but still controversial issues.

How do you expect international collaboration to expand in the future?

Yamanaka: International collaboration is essential, and there are two challenges to overcome. One is to have a unified approach to obtaining informed consent from donors and patients. Today, the FDA[a], EMA[b] and PMDA[c] each have different regulations. We hope there will soon be a global standard in place. The other is the challenge in exchanging cells between countries, which is regulated under Good Manufacturing Practice (GMP). If we want to use iPS cells for regenerative medicine, they have to be generated following the GMP guidelines of each country, and because these guidelines differ by country, researchers are faced with challenges in importing and exporting GMP grade cells.

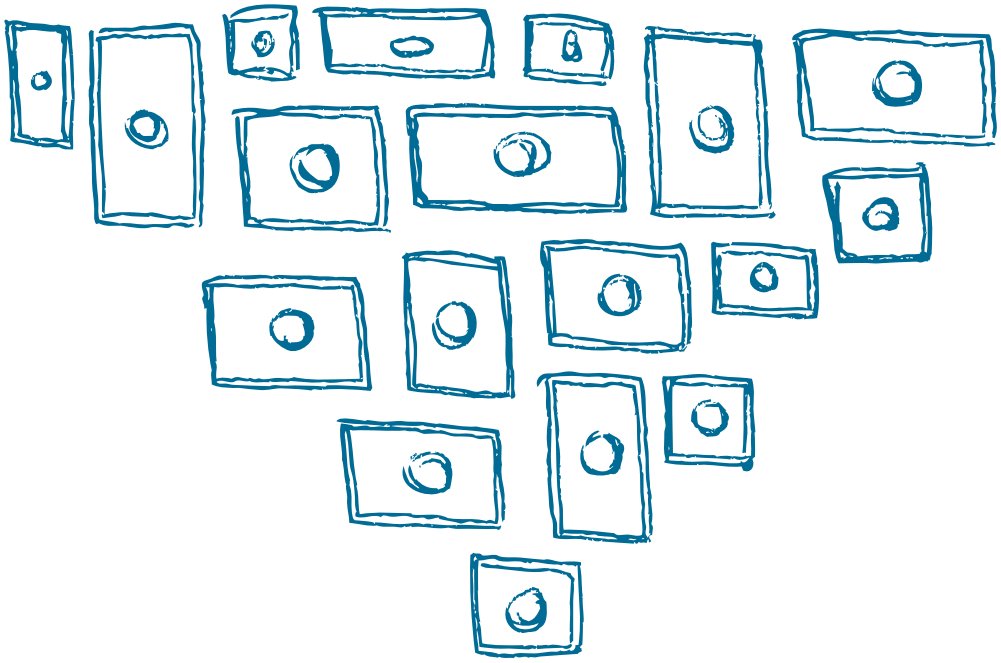
What do you think will be the earliest applications of iPS cell research? And how do you think it will continue?

Yamanaka: For toxicology testing, it's just around the corner. Many pharmaceutical companies have already started using heart cells derived from iPS cells, in predicting cardiac side effects such as arrhythmia. iPS cells are also being used for drug screening by many researchers and companies, and some very promising drug candidates have been identified. In regenerative medicine, in Japan, the very first clinical study using iPS cells for macular degeneration has been approved by the government. I expect several other projects to follow including Parkinson's disease, spinal cord injuries, heart failure, and platelet deficiency, with the hope that clinical research will be starting within the next three to five years. In the next 20 to 30 years, I hope organs can be generated maybe by animal-human chimeras or by new technologies such as 3D printing, in collaboration with a wide field of researchers.

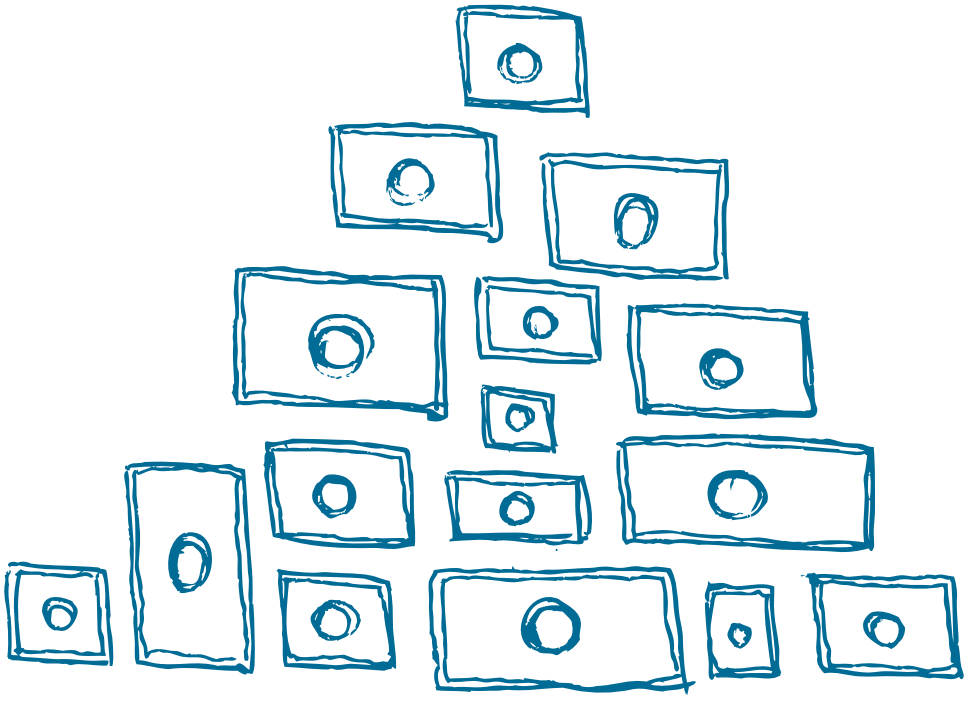
a U.S. Food and Drug Administration

b European Medicines Agency

c Pharmaceutical and Medical Devices Agency, Japan



Chapter 2
The Dynamic Field of Stem Cell Research



The Dynamic Field of Stem Cell Research: World Trends in Stem Cell Publications from 1996 to 2012

The analysis presented here examines the stem cell publication landscape from 1996-2012. For details of the methodology used, including its limitations, see **Appendix A**. As discussed, we have focused on pluripotent stem cells because of their clinical relevance and the attention they have received from policymakers and regulators. Within the pluripotent stem cell field, we examined publication data for both ES cells and iPS cells, and further refined our search to identify publications specifically related to hES cells (but not human iPS cells). Pluripotent cells have been the focus of public, political, and ethical debate, and are subject to distinctly different regulations in different nations around the world. Our analysis answers the following salient questions: How is the field changing? Where are the research activity hotspots? Do changes in publication output correlate to national regulatory changes and funding initiatives?

2.1 Overview of Publication Output and Growth

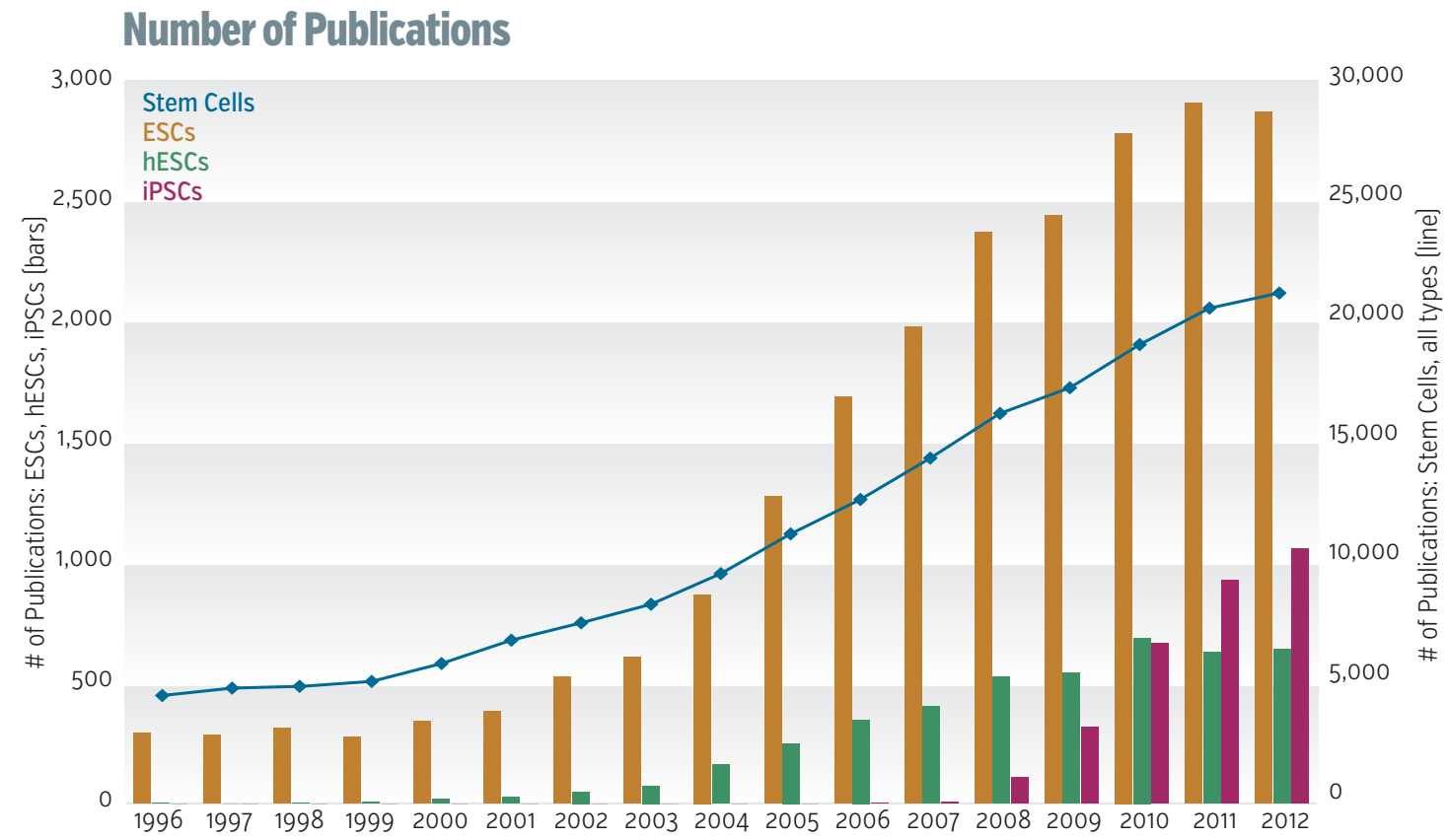
Global patterns show rapid growth in research output (Figure 3.1) and the number of active researchers (Figure 4.0) across all categories of stem cell research analyzed. Stem cell research represented 0.4% of world publication output in 1996; by 2012, this increased to 1%. This growth reflects activity in a broad range of subjects, including existing stem cell-based clinical applications, basic research on fundamental cell biology and development, and bioethics and social science related to stem cell research. However, analysis suggests that the latter class has made a relatively small contribution to the field overall (see **Appendix B** for a detailed breakdown of the most common topics present in the publications in the stem cell dataset).

Analysis of the compound annual growth rate (CAGR), defined as the year-over-year constant growth rate over a specified period of time and calculated as described in **Appendix A**, shows exceptionally strong growth in all aspects of stem cell research (Table 1.0). Between 2008 and 2012, stem cell research publications grew by 7.0% per year, compared to a much lower CAGR of 2.9% for publications across all academic disciplines covered in the Scopus database in the same period.

Both total ES cell and hES cell research publications grew at a rate consistent with that of overall stem cell research from 2008 to 2012 (Table 1.0). In contrast, following seminal papers in 2006 and 2007, iPS cell research output grew explosively during the same period, showing a CAGR of 77%. This partially reflects the relative infancy of the field: high growth rates are easier to achieve when the first measurement period exhibits low volume (i.e., an increase from 1 to 2 papers exhibits 100% growth), but the sustained growth also indicates the rapid recognition this new technology's importance. In line with this increased publication output, the number of active iPS cell researchers also increased dramatically from 2006 to 2012 (Figure 4.0), again reflecting the field's rapid recognition, both by established stem cell scientists and researchers from other fields. We discuss some particular influences on pluripotent cell research in more detail later in this report (see **Section 3.2**).

	World Publications		Growth CAGR
	2008	2012	2008-2012
Stem Cells	16172	21193	7.0%
ES cells (all)	2375	2875	4.9%
hES cells	527	642	5.1%
iPS cells (all)	108	1061	77.0%
Total World output all subjects	1,894,727	2,121,740	2.9%

Table 1.0: *CAGR for stem cells overall, ES cells (all organisms), hES cells, and iPS cells (all organisms) from 2008 to 2012.* Source: *Scopus*



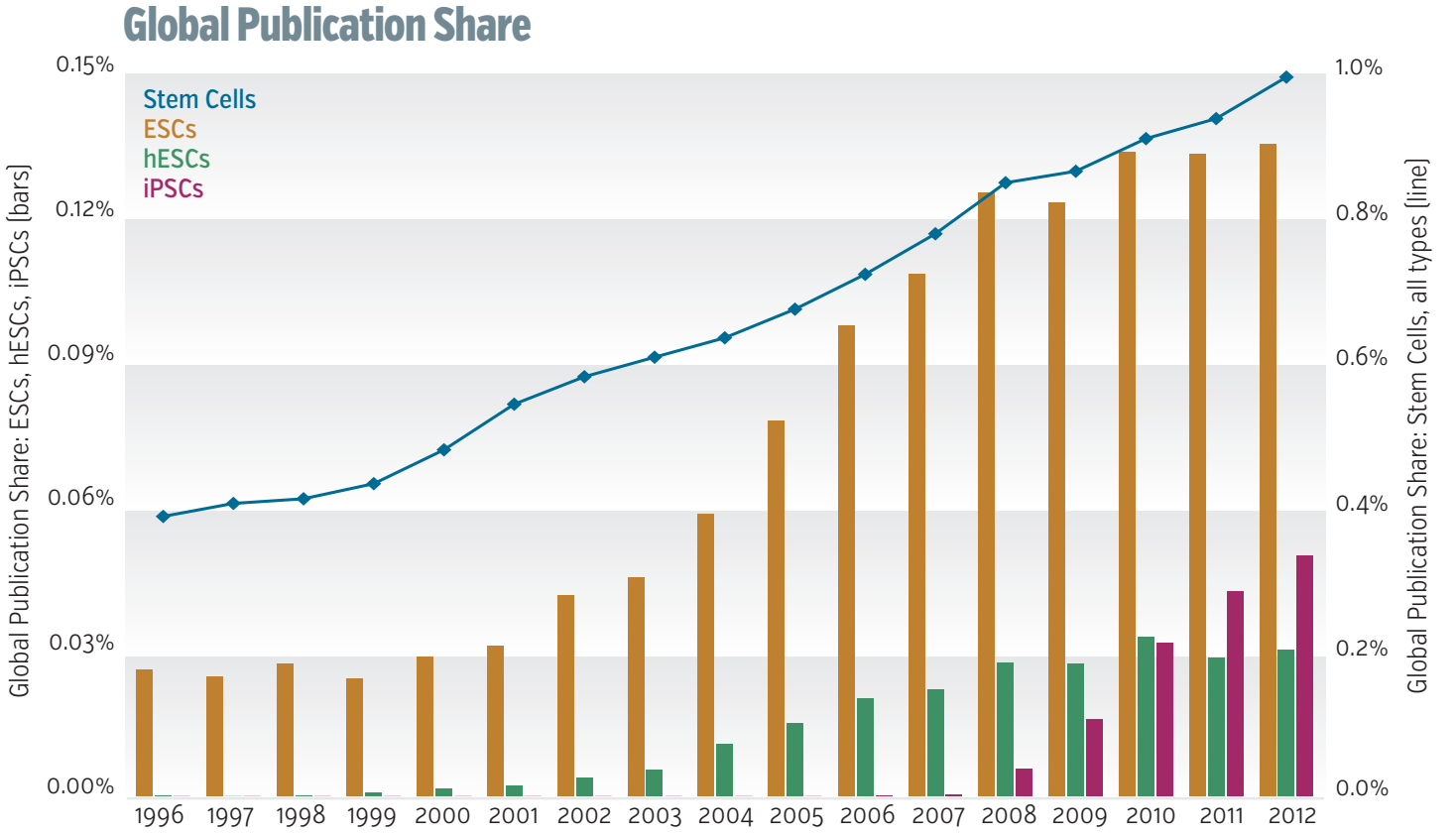


Figure 3.1 (Top): *Global publication count.* **Figure 3.2** (Bottom): *Global publication share. Graphs show data for all stem cells, (StemCells), ES cells (all organisms; ESCs), hES cells, (hESCs), and iPS cells (iPSCs) from 1996-2012. See Appendix B for a breakdown of the key concepts contained within each data set.* Source: *Scopus*

"I would say the single most important development [in the last eight years] has been the development of iPS cells. I think if that had not occurred you would not see the explosive growth in stem cell biology, as it made human stem cells accessible to everyone."

— Sandra Engle, Senior Principal Scientist, Pluripotent Stem Cell and Molecular Biology Lab, PDM-NCE Primary Pharmacology Group, Pfizer, Inc.

Research on all pluripotent stem cell types accounted for 14% of total stem cell publications between 2008 and 2012 (Figure 5.1). The majority of papers on pluripotent stem cell types reported work on non-human (principally mouse) ES cells. Almost a quarter (21%) discussed iPS cells either alone or in combination with ES cells, and the equivalent proportion analyzed hES cells (21%, Figure 5.2). Unsurprisingly, the ES and iPS fields overlapped to some extent, given their shared properties and the need for comparative studies to determine similarities and potential differences between the two (Yamanaka, 2012).

In this respect, this analysis presents a picture at odds with the perception of stem cell research in society, where ES cell research usually is taken to mean hES cell research. It does, however, point to the importance of work on ES cells from mice and other model organisms for helping to understand how to control the differentiation of these cells *in vitro*, as well as the technical difficulties and high costs associated with hES cell research. It is likely that this balance between mouse and human pluripotent cell work will shift toward human cell studies in the near future as technology advances and becomes more tractable, and as funding initiatives increasingly require researchers to work with human cells.[5]

"Coming from the area of bioethics I suppose I was a little surprised to realize what proportion of the field as a whole is actually taken up with ES cell research as opposed to other forms of stem cell research...if you think about the ethical debate overall, ES cells are at the heart of that, whereas looking at the scientific literature more broadly, the publications on hES cells are a much smaller proportion of the field than I'd have intuitively thought."

— Sarah Chan, Research Fellow in Bioethics and Law, Deputy Director, Institute for Science, Ethics and Innovation, University of Manchester

2.2 Field-weighted citation impact

While publication volume is a useful indicator of the size and shape of the field, additional measures add depth to the picture. Citation numbers are often used as a measure of research quality (Davis, 2009). To assess how often a given body of publications is cited relative to the world average for the subject area, a normalized measure of citation impact is recommended, rather than an absolute number. Accordingly, this study uses field-weighted citation impact (FWCI), a measure of citation impact that normalizes differences in citation activity by subject field, article type, and publication year. The world citation impact is indexed to a value of 1.00 for publications across all subject areas assigned to journals in which stem cell research publications appear.

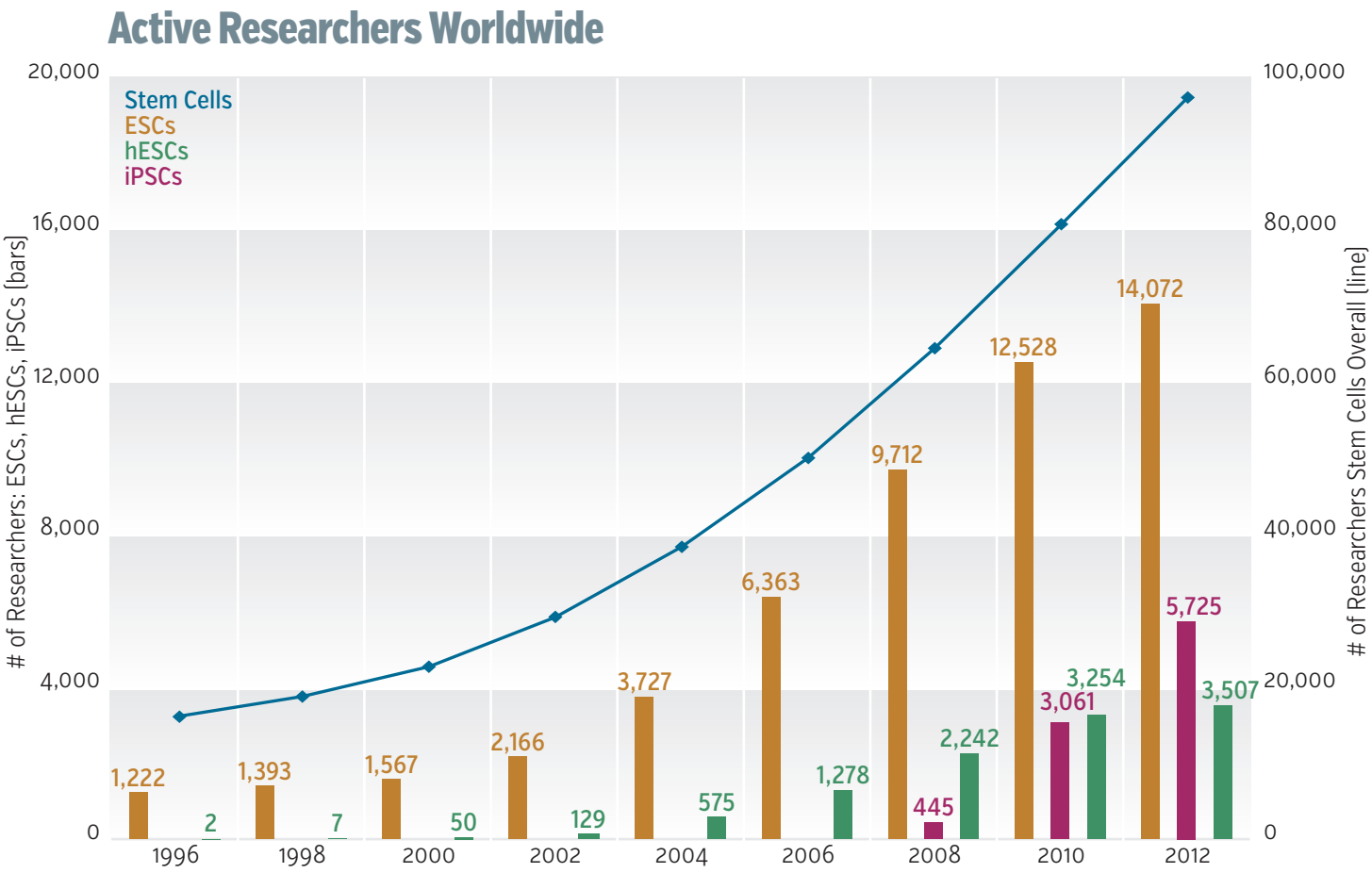
Overall, stem cell publications have a FWCI of 1.5 (Figure 6.0), meaning they are, on average, cited 50% more than publications in relevant subject areas. This citation impact level has remained relatively stable from 2008 to 2012, reflecting the strength of the field as a whole. The citation impact levels for ES cell and hES cell publications have also remained relatively stable over the same period, at around 1.8 times the world average for ES cell publications, and more than double the world average for hES cell publications. The high citation impact of hES cell publications underscores the perceived importance of hES cell research, both in its own right and as a comparative tool for assessing and understanding iPS cell research (Puri and Nagy, 2012).

"The high field-weighted citation impact across the stem cell field may also reflect the strength of research networks within the field, where matched and cross/co-citation among members is especially likely as the field establishes and consolidates a shared intellectual position as it matures. "

— Andrew Webster, Director, Science and Technology Studies Unit, Department of Sociology, University of York

Published iPS cell studies showed a very high FWCI in 2008, although caution is required when interpreting this metric, as citation impact in a field with low publication volume may be inflated by a small number of highly cited papers. The simultaneous

5 In the last call for its funding program Framework 7, the European Commission requested and exclusively funded only stem cell projects that principally focus on human stem cells, per "Work Programme 2013: Cooperation. Theme I: Health." July 9, 2012. Available at ftp://ftp.cordis.europa.eu/pub/fp7/health/docs/fp7-health-wp-2013_en.pdf [accessed November 5, 2013].



increase in iPS publication volume (Figure 3.1) and decrease in citation impact (Figure 6.0) is pattern typical to new fields, and does not necessarily imply a decrease in research quality. Our method for calculating FWCI takes multiple years into account (see **Appendix A**), such that the 2012 impact is based on published studies from 2008 to 2012. The 3,080 iPS cell papers published between 2008 and 2012 achieved a citation impact of 2.93, still well above the citation impact for stem cell papers overall, and almost three times the overall citation impact of publications in related subject areas, further attesting to the immediate and sustained recognition of the importance of this emerging field.

"You know it's a new field and you should see a decline from a high citation impact for iPS cells as more people enter the field. Then the citation impact should stabilize closer to the average being higher or lower depending on whether the field is more or less exciting."

— Mahendra Rao, Director, NIH Intramural Center for Regenerative Medicine (NIH-CRM), US Department of Health and Human Services

Figure 4.0: *The number of world researchers active in stem cell research as estimated using the number of Scopus author profiles with at least one stem cell publication in the relevant year as a proxy. The bars represent ES cell (ESCs), human ES cell (hESCs), and iPS cell (iPSCs) research, and refer to the left-hand Y-axis; the line represents stem cell research overall (Stem Cells), and uses the right-hand Y-axis.* Source: *Scopus*

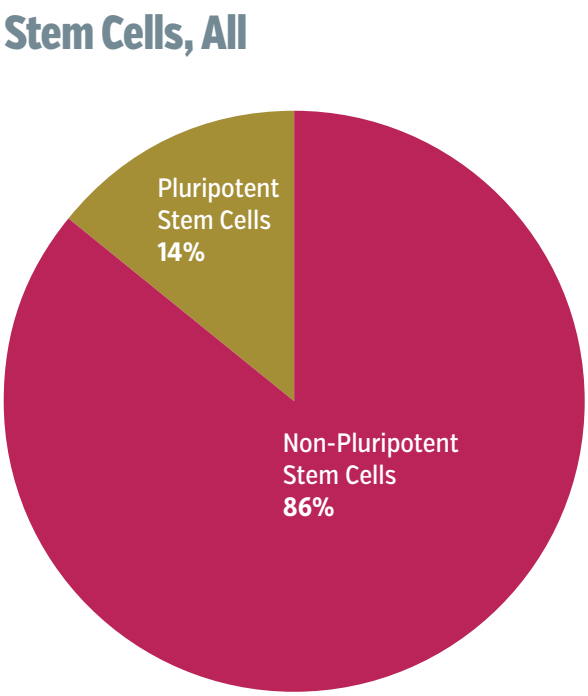


Figure 5.1: *Global stem cell research output from 2008 to 2012, broken down by pluripotent stem cells (ES, hES and iPS cells) and non-pluripotent stem cells (others).* Source: *Scopus*

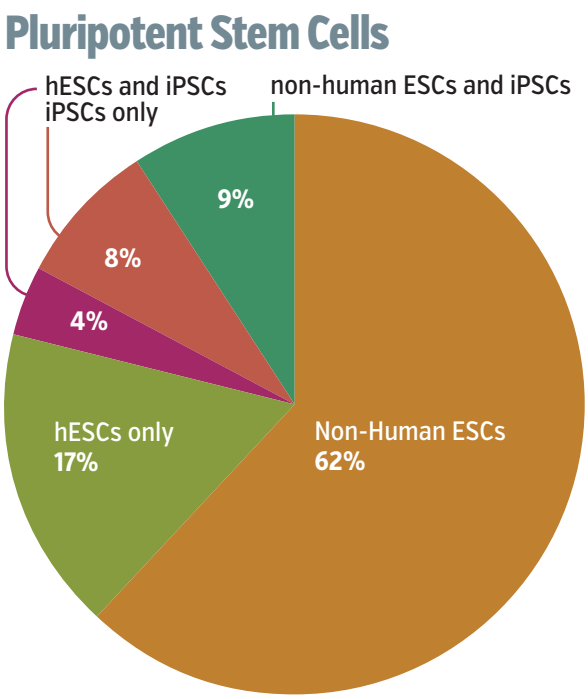


Figure 5.2: *Global pluripotent stem cell research output from 2008 to 2012, broken down by cell type ES cells (all organisms), hES cells, non-human ES cells and iPS cells (all organisms), iPS cells (all organisms) only, and iPS cells (all organisms) with hES cells. Publications on pluripotent cell types represent 17% of stem cell publications overall.* Source: *Scopus*

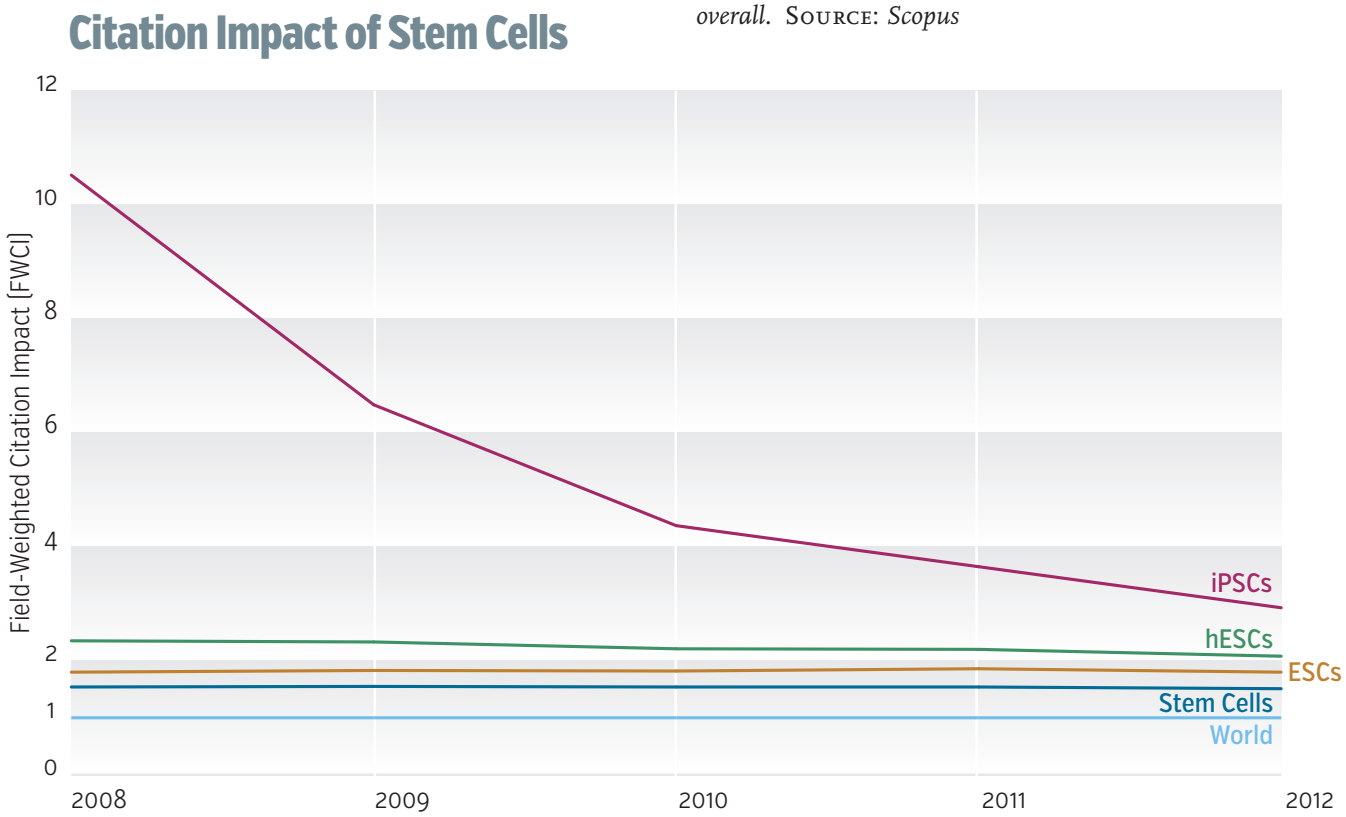


Figure 6.0: *The FWCI of publications on stem cells overall and by cell type from 2008-2012. The pale blue line represents the global average citation impact for all publications in the various subject areas assigned to the journals in which stem cell papers are published.* Source: *Scopus*

2.3 Promise and Practice: Stem Cells in Regenerative Medicine and Drug Development

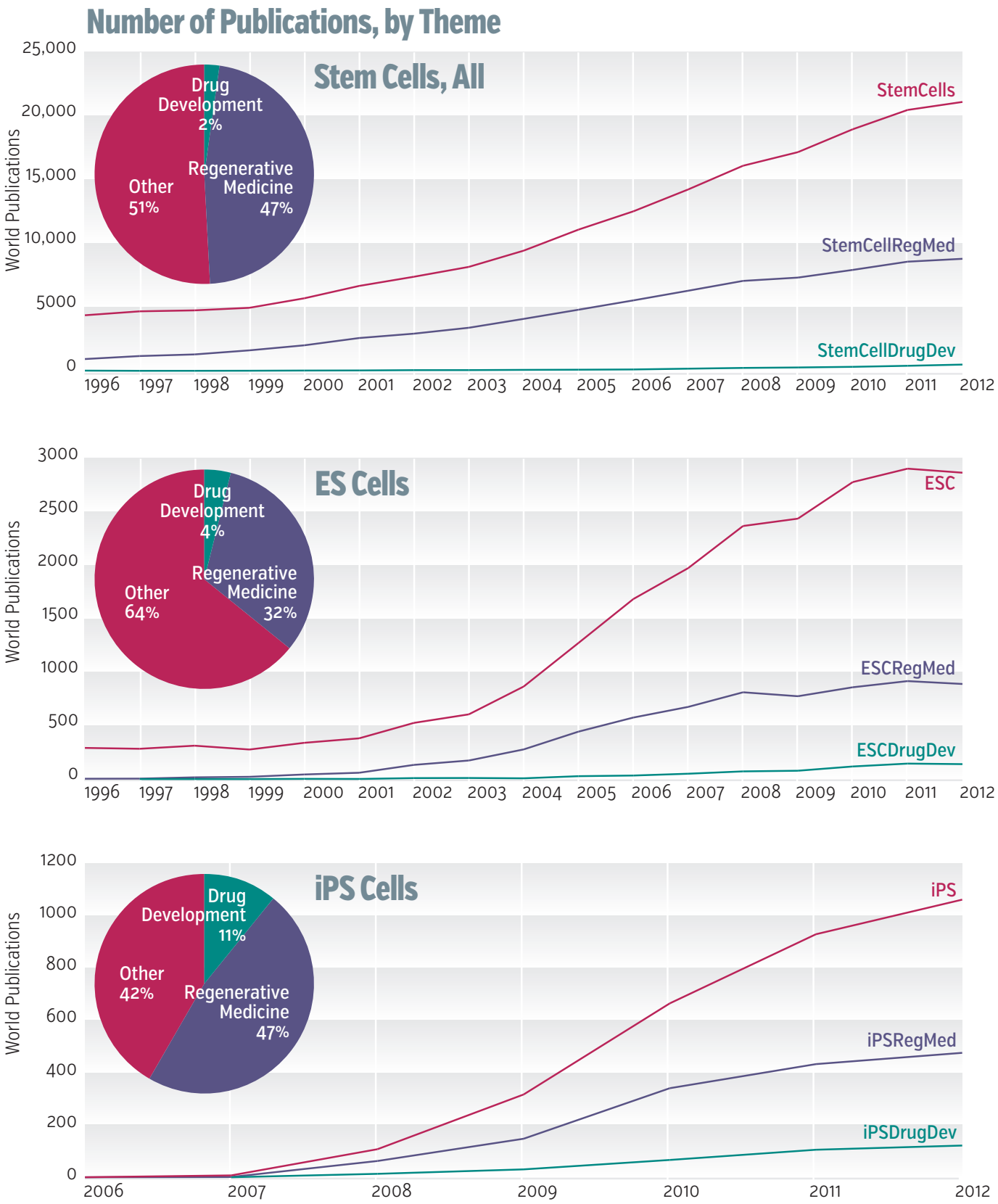
To review the extent to which the stem cell field aligns with society's goals of developing new treatments for diseases, we analyzed the publication data using a collection of search terms related to the themes "regenerative medicine" and "drug development" (see **Appendix A** for a detailed discussion of this process). Almost half of all stem cell publications were aligned with one of these two topics, with most of the focus devoted to regenerative medicine (Figure 7.1). One reason for this may be that these terms reflect authors' aspirations for the future of their work, rather than study's current applicability. That 51% of stem cell publications did not align with either drug development or regenerative medicine is unsurprising, despite the societal and strategic drivers toward clinical application. Considerable research effort addresses the fundamental biology of stem cells in normal and diseased states, and is required to both advance the field and improve understanding of wider biological principles. Furthermore, these terms may not be relevant to many clinical or translational publications (e.g., those related to hematopoietic stem cell transplantation and cancer). In fact, both terms have only recently emerged into common usage.

> ***"Today, stem cell research is more about understanding than about treating illnesses. I do think it's most important to understand how our tissues are formed, and how they get ill. I'd go further and say that understanding stem cells means understanding where we come from. If we think of the embryonic stem cells, they tell us a lot about how our bodies develop from an embryo. They provide a window on events which we couldn't otherwise observe."***
>
> *— Elena Cattaneo, Full Professor, Director, UniStem, Center for Stem Cell Research, University of Milan*

Within the ES cell field, publications associated with drug development or regenerative medicine were under-represented compared to the stem cell field as a whole. This likely reflects the broad reach of the ES cell field: for instance, ES cells are widely used as tools for generating genetically modified mouse strains and mouse or human cell lines, many of which are used in research areas unrelated to regenerative medicine or drug discovery. Among iPS cell publications, however, the representation of both terms was noticeably higher; in particular, the percentage of iPS cell publications related to drug development was more than 5 times that of the stem cell field as a whole. Since iPS cells can be directly generated from individuals affected by a disease, they hold particular promise for the development of disease models and personalized medicine. While researchers interested in particular diseases or conditions have rapidly adopted iPS cell technology, the data may still under-represent work in clinically focused areas because of the time lag between research activity and publication, and due to intellectual property issues.

> ***"I was surprised to see that practically half of the iPS cell papers were focusing on regenerative medicine. I thought there was probably more of a balance [shift] toward drug development from the iPS stem cell field…the echoes that we have here is that they show greatest promise perhaps in the drug development field, but time will tell."***
>
> *— Charles Kessler, Principal Scientific Officer, European Commission*

Publication outputs indicate the field of iPS cell research is growing rapidly. Within this field, the area of drug development appears to be growing faster and with higher citation impact than that of regenerative medicine (Figure 8.0). Similarly, the CAGRs of stem cell and ES cell publications related to drug development are higher than the growth rates for each of those fields overall. These findings support expectations that the first widely adopted benefits from stem cell research will relate to new drug development. This in part reflects the lower perceived risks for both patients and investors compared to cell therapy routes and the greater complexities involved in developing effective delivery systems and in determining when to move to clinical trials for cellular therapy. It also reflects that regulatory frameworks for drug development may be more readily adapted to accommodate drug discovery and testing using stem cell-derived cells.



Figures 7.1, 7.2 & 7.3: *The number of publications incorporating the terms "regenerative medicine" [RegMed] and "drug development" [DrugDev] by cell type.* Pie Charts: *The percentage stem cell studies published from 2008 to 2012 incorporating "drug development," "regenerative medicine," or "other" by cell type.* Source: *Scopus*

Stem Cells and Themes, 2008-2012

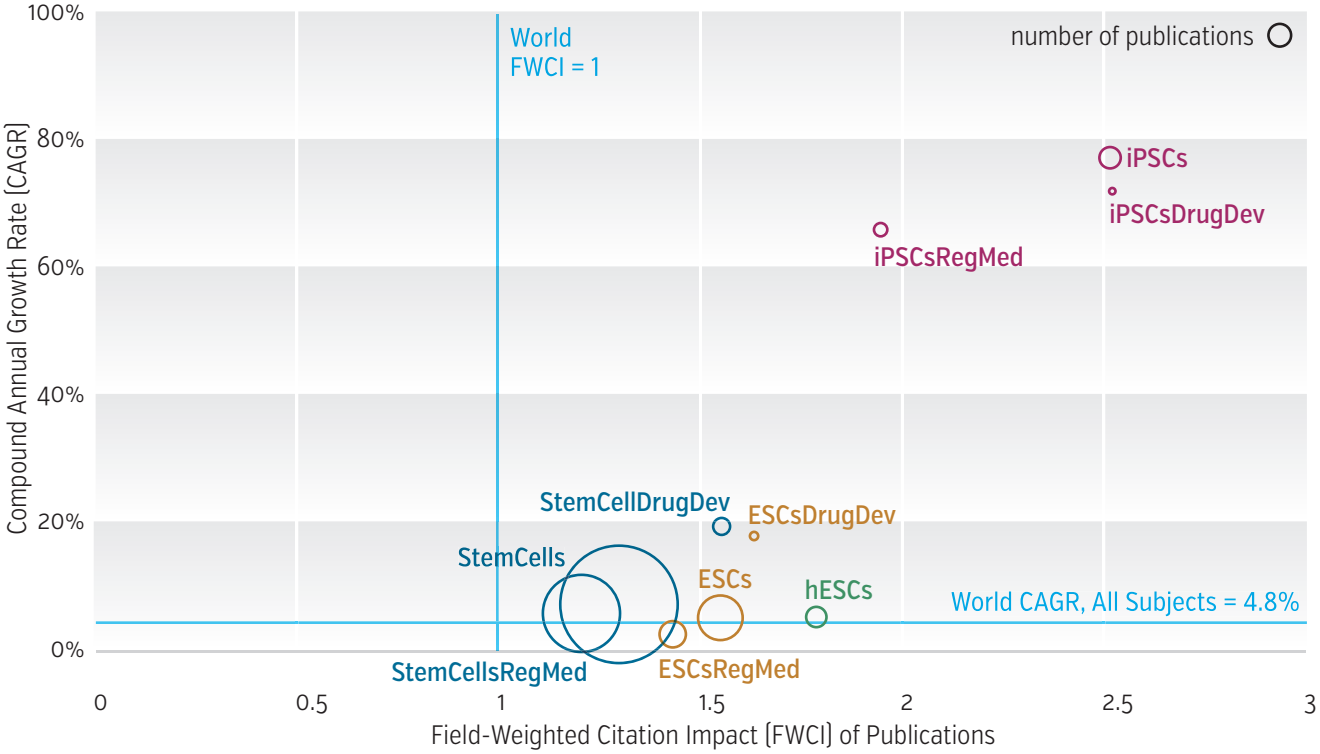
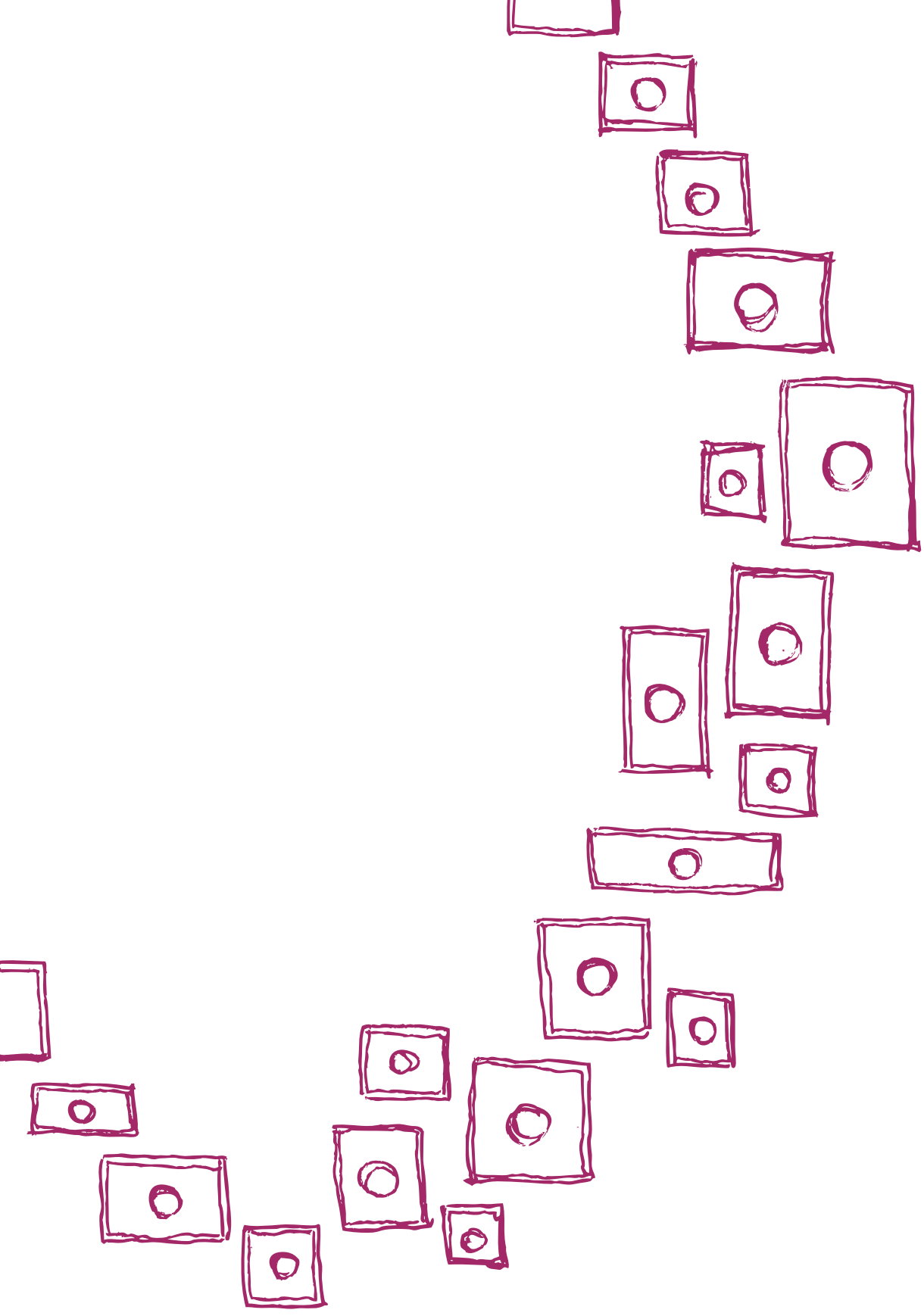


Figure 8.0: *World publication output, FWCI, and CAGR from 2008 to 2012 for stem cell research overall, by cell type, and by thematic alignment (regenerative medicine [RegMed] and drug development [DrugDev], excluding hES). Bubble size represents number of publications, the x-axis represents the FWCI of those publications, and the y-axis represents the CAGR. The same publication may be represented in more than one bubble. See* **Appendix A** *for methodological details.* SOURCE: *Scopus*

"The most immediate benefit of stem cells is not necessarily in regenerative medicine at this time but in providing patient-specific cells for drug discovery, and I think that paradigm shift is actually starting to make the promise to stem cells more of a reality…I think the trajectory of both ES cells and mostly iPS cells and drug development is going to be significantly higher in the future. I think this comes with the realization that stem cells for regenerative medicine purposes, using them either as replacement tissue or a target for small molecules or some sort of drugs, it's just much harder to achieve, so I actually thought this chart was a nice fitting of my world view and I think the trend will be much more in the direction of using stem cells for drug discovery. It will take a while for stem cells for regenerative medicine really to go somewhere because it's just very difficult at this point to get them into the clinic."

— Sandra Engle, Senior Principal Scientist, Pluripotent Stem Cell and Molecular Biology Lab, PDM-NCE Primary Pharmacology Group, Pfizer, Inc.



Chapter 3
The International Landscape

The International Landscape

The stem cell field as a whole is expanding and developing, with increasing levels of active researchers, global research publications, and citation impact. How is this growth distributed globally, and which countries are key players or rising stars in the field? Here, we present our findings on the international stem cell research landscape, examining various selected countries' activity levels and citation impact

3.1 Global Output, Growth, and Impact

Our analysis examined 21 countries from 2008 to 2012; these countries were selected through discussion with experts in the field. The United States stands out in terms of absolute publication numbers (Figure 9.0, see next page), consistent with its high publication rates across all science and engineering fields:[8] previous research has shown the United States has globally above-average activity levels in clinical sciences, health and medical sciences, biological sciences, social sciences, business, and humanities (Elsevier, 2011). From 2006 onwards, China's growth curve is strikingly similar to that of the USA, making China the second most productive country by volume of publications (for trends by stem cell type, see **Appendix D**).

Beyond absolute publication numbers, it is interesting to examine the share of each country's stem

8 In 2012, the United States' science and engineering publication output was more than three times that of the next-ranked country, China. See National Science Foundation 2010. "Chapter 5: Academic Research and Development." Science and Indicators 2010. Available at http://www.nsf.gov/statistics/seind10/c5/c5s4.htm [accessed 8th November 2013].

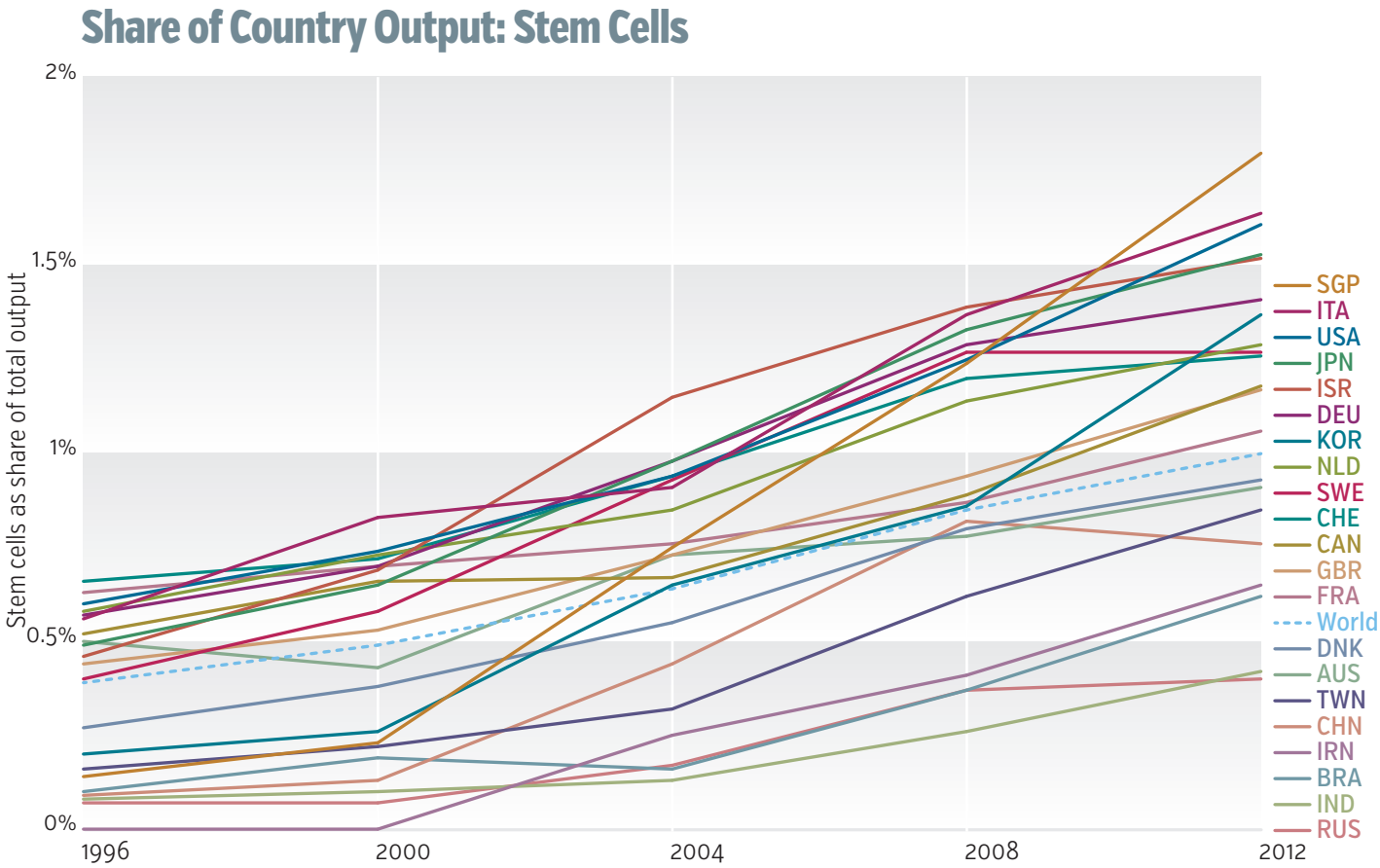


Figure 10.0: *Stem cell publications as share of each country output 1996, 2000, 2004, 2008, and 2012. The dotted pale blue line represents global stem cell research output.* SOURCE: *Scopus*

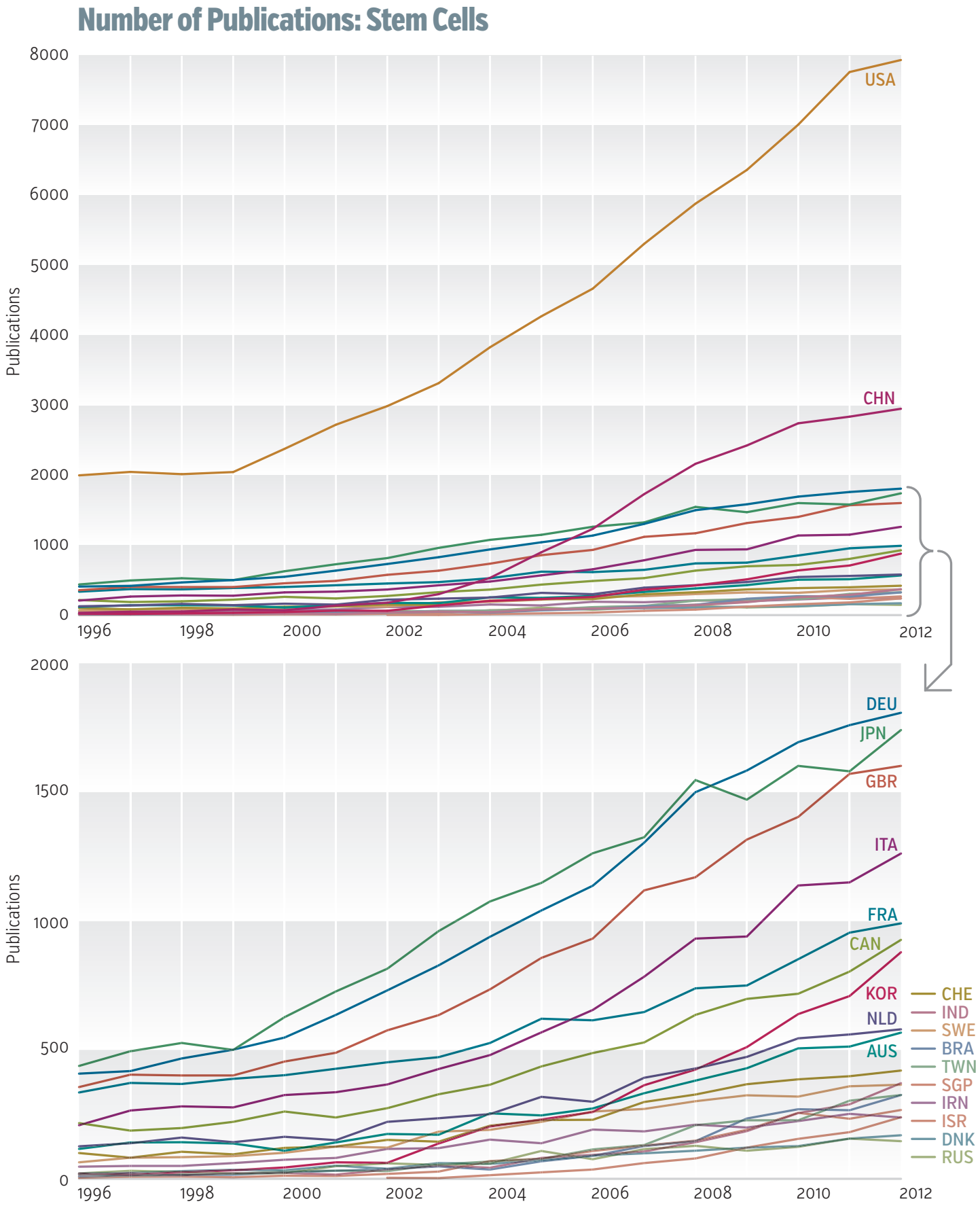


Figure 9.0: *The number of stem cell publications per country from 1996-2012. For a key to country codes used here, refer to* **Appendix C.** *Country order in legend listing indicates ranked order.* SOURCE: *Scopus*

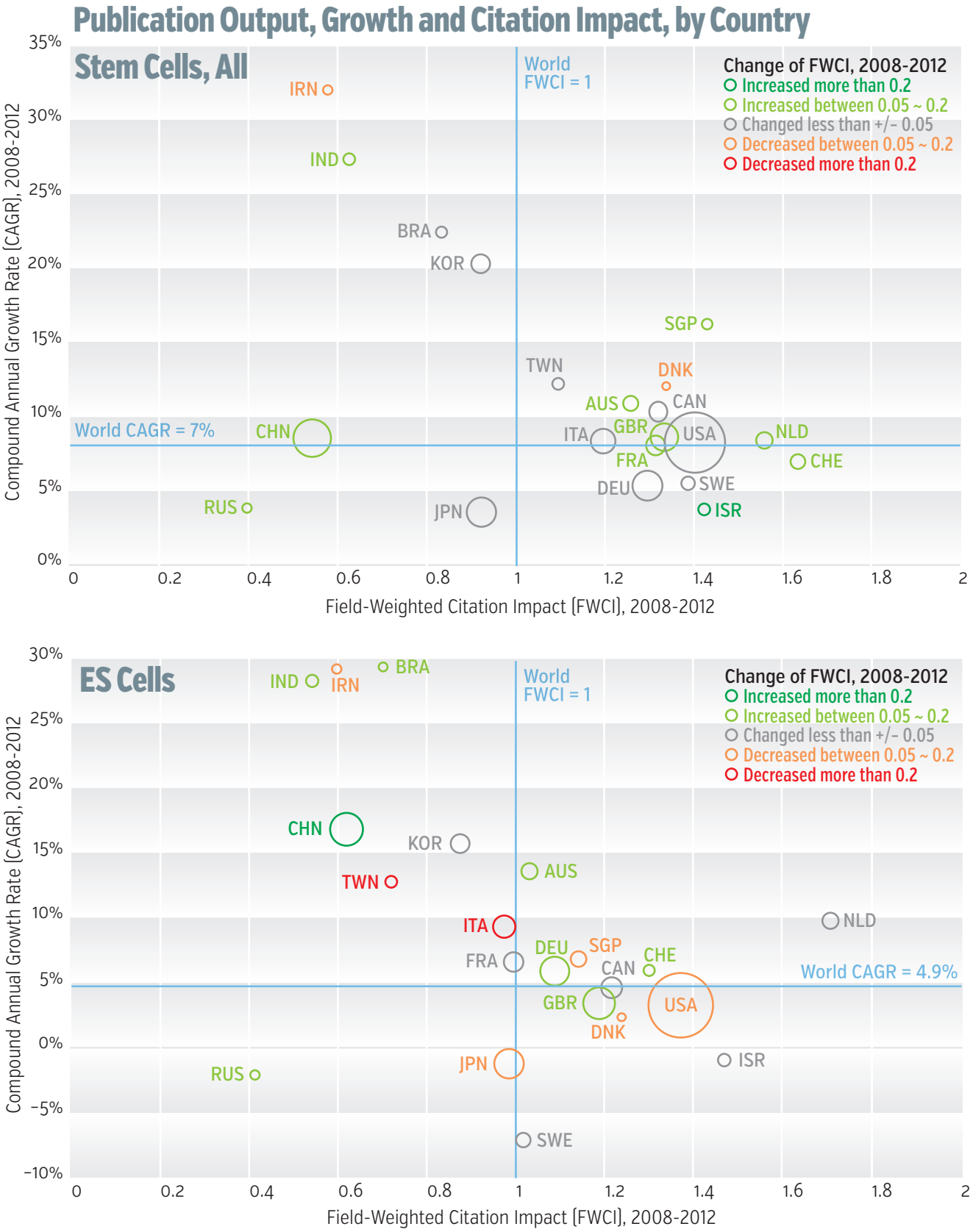
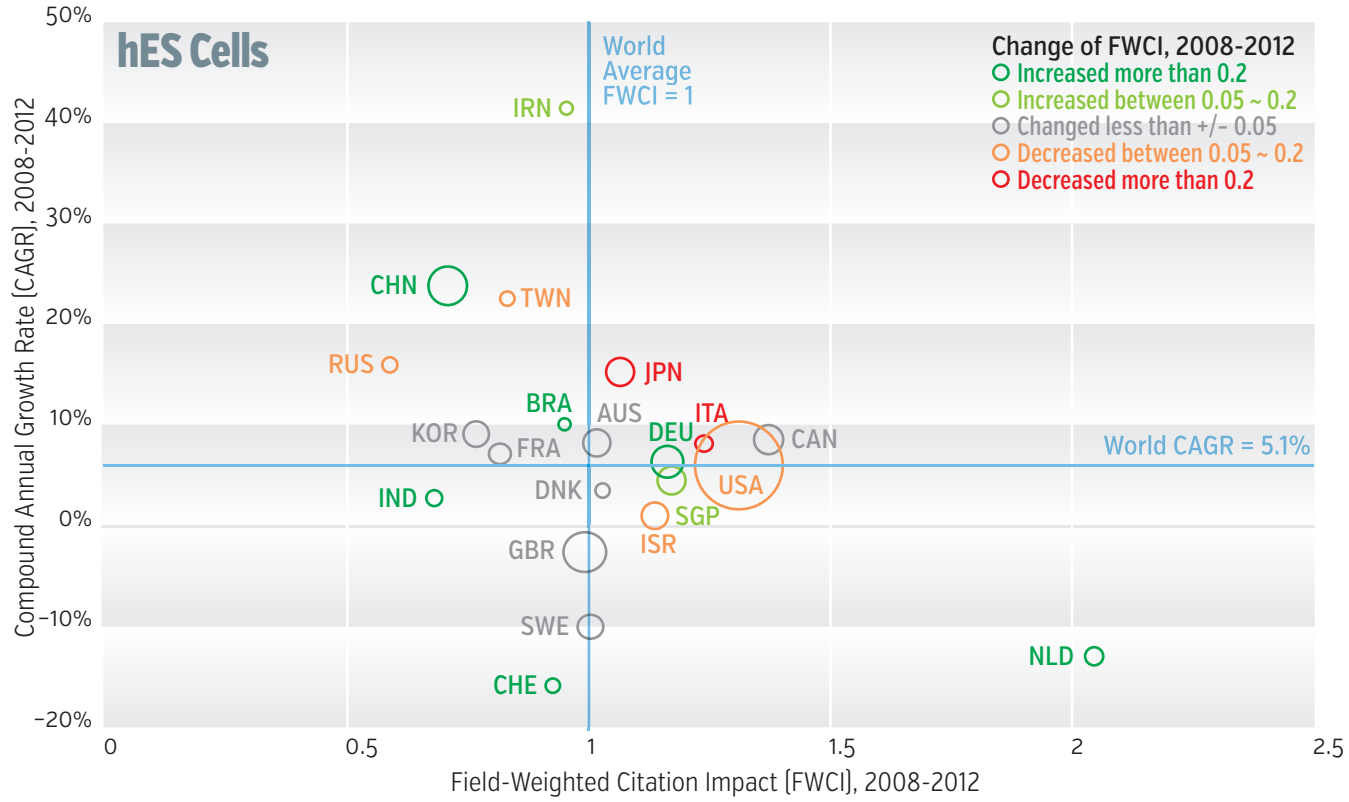


Figure 11.1 – 11.3, Two above, and opposite top: *The publication volume is represented by bubble size, FWCI on the x-axis, and CAGR on the y-axis. The color of the bubbles represents changes in FWCI between 2008 and 2012. For this country-level analysis, we have manually indexed the stem cell, ES cell and hES cell global average FWCI to a value of 1.00. Source: Scopus*



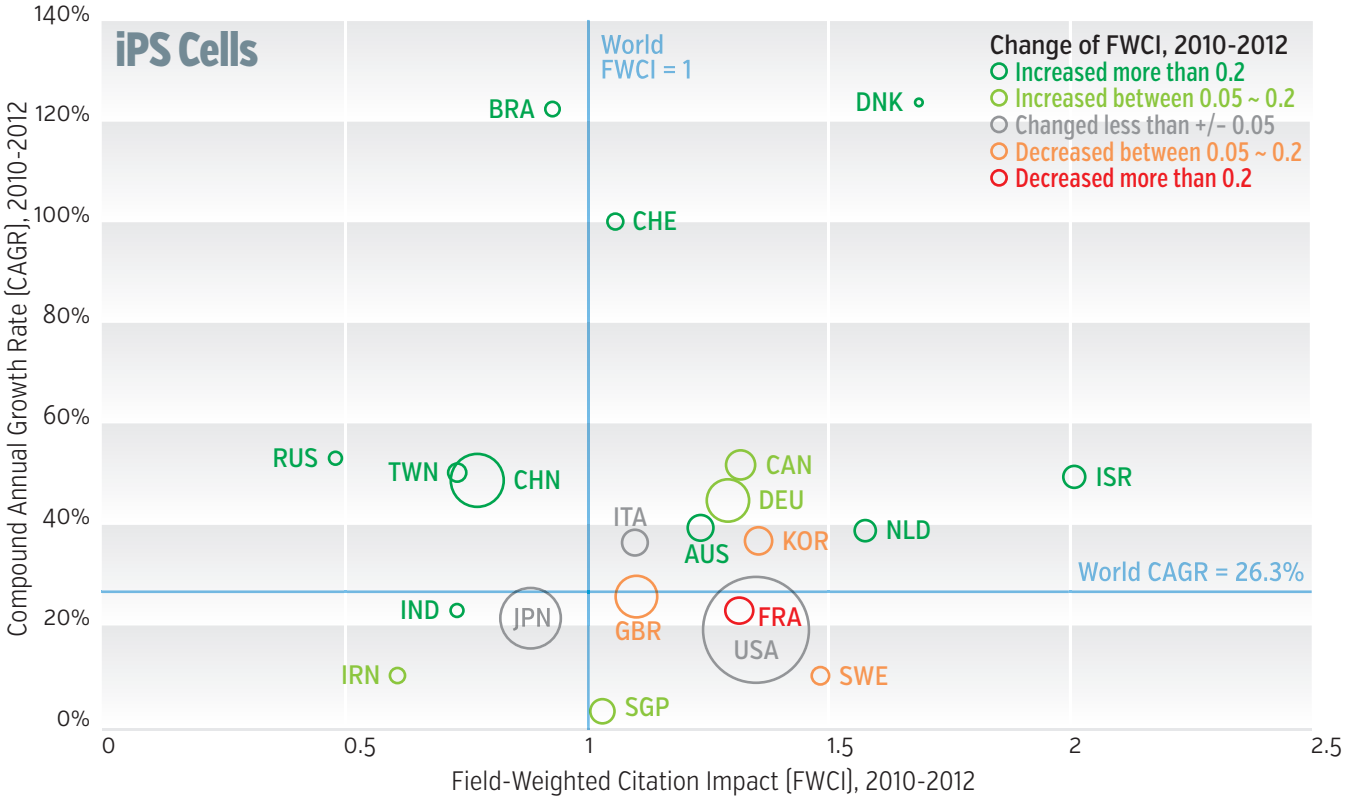


Figure 11.4, Above, Bottom: *iPS cell publication output, growth, and citation impact by country from 2010 to 2012. Note the shorter period analyzed compared to Figures 11.1-11.3; iPS cell publications were too low in number to identify trends before 2010. The publication volume is represented by bubble size, FWCI is represented on the x-axis, and CAGR for the period (2010-2012) on the y-axis. The color of the bubbles represents the extent and direction of the change in FWCI between 2010 and 2012. For this country-level analysis, we have manually indexed the iPS cell global average FWCI to a value of 1.00. Source: Scopus*

cell research output. As noted above, the field as a whole more than doubled its share of global research output from 1996 to 2012 (from 0.4% to 1.0%; see Figures 3.1 and 10.0). Analyzing the data by country reveals that, while many countries roughly follow global patterns, some show accelerated growth in this sector. Singapore in particular stands out with a more than tenfold increase in stem cell research as a proportion of national research publications (from 0.14% in 1996 to 1.8% in 2012). This finding correlates with Singapore's investment in biomedical sciences, including the establishment in 2000 of the Biomedical Sciences Initiative, as a key pillar of its economy (see **Section 3.3** for further discussion of Singapore's policies and practices).

Other countries with a higher proportion of 2012 stem cell publications than the world average include Italy (1.64%), the USA (1.61%), Japan (1.53%), Israel (1.52%), Germany (1.41%), and Korea (1.37%). Indeed, only one country shows an overall decline in its share of stem cell research publications from 1996 to 2012: China. This surprising finding must reflect strong growth in other research areas, rather than a decline in the stem cell field since, as we have seen, China's stem cell publications continued to increase over this period (Figure 9.0). The UK's share of stem cell publications, at 1.17%, is also lower than one might expect in the light of the government's significant strategic investment in the field (Pattison, 2005). Several factors may have contributed to this decline, including changes in activity in other fields, economic trends in the country as a whole, and research funding practices.

A deeper insight into variations in international stem cell research activity can be gained by comparing three measures for each country: publication output, growth, and citation impact. As illustrated in Figures 11.1 to 11.4, combining these measures gives a clear visual indicator of the different countries' comparative performance (see **Appendix E** for the underlying data), showing:

- which countries have published most (by bubble size);
- which countries' publication rates have increased or decreased (by y-axis location);
- the citation impact achieved by each country's publications (by x-axis location); and
- changes in each country's impact (by bubble color).

Countries that appear in the top-right quadrant of Figures 11.0–11.4 show a higher-than-average CAGR and FWCI for research on all stem cell types during the period analyzed (2008-2012 in Figures 11.1–11.3 2010-2012 in Figure 11.4). This high-growth, high-impact category includes North American and many European countries, as well as Singapore, Australia, and Israel.

A number of countries stand out from the data. Iran showed a very high CAGR in stem cell research as a whole, and in both ES and hES cell, but not in iPS cell publications. Further, Iran's hES cell research growth rate and citation impact nearly match the global average. As Iran has a relatively low overall output, it has a greater capacity for high growth than countries that have already established high output levels. The observed trend is also consistent with an overarching increase in scientific publication in Iran (Coghlan, 2011), as well as strategic government support for science in general and stem cell research in particular (Gheisari et al., 2012). The data also show development in China: China's citation impact, though below average, increased during the analyzed period, and its growth rate was high across all types of pluripotent stem cell research.

In Europe, Sweden achieved average or above-average FWCI across all the research sectors examined, though its publication growth rate was below average. Italy, Germany and the Netherlands all achieved relatively high citation impact and growth rates in all pluripotent cell research, with the exception of hES cell research in the Netherlands. Between 2008 and 2012, hES cell publications from the Netherlands decreased in volume, with a CAGR of –13.1%. This decline contrasts with the country's high positive CAGR (38.4%) in iPS cell research, suggesting a shifting emphasis from hES to iPS cell research.

Denmark also stands out as having high citation impact across all three stem cell categories, with a particularly high growth rate and citation impact in the iPS cell field. However, as Denmark's publication volume is small, these data may reflect the activities of a few high profile research groups; our analysis did not examine individual publication-level data. Other possible contributing factors include a major stem cell funding initiative recently launched in Denmark, and the presence of a number of companies active in the field.

Meanwhile, the UK's citation impact was stable at or above average across all stem cell types; ES cell research citation impact slightly increased, while no

significant change in hES cell citation impact was observed. As the iPS cell field is growing in the UK, the slight decline in citation impact for these publications is likely due to the increasing volume of papers in this research area.

Japan showed below-average growth and citation impact in iPS cell publications between 2010 and 2012, a surprising finding considering its status as originator of the iPS field and its government's investment in this area (however, see **Appendix G** for institutional level data). Previous bibliometric studies have explained Japan's lower citation impact as the result of a lower level of interdisciplinary research compared to other countries, such as the UK and USA (Watatani et al., 2013). These results may also be a product of the country's high initial publication volume and citation impact in this area, as well as a possible funding plateau following strong early governmental support.

Publication output, growth, and citation impact are inevitably linked with many economic and strategic factors across the international landscape. Some of these influencing factors are discussed further in Section 3.3.

3.2 Policy and Pluripotency

Our above analyses suggest a complex relationship between policy and research practice and the many other factors that can influence the development of a research field. Since hES cells have been a particular focus of policy decisions in many nations, we examined the hES cell data in order to compare trends in countries with contrasting policy positions.

Human ES cell research in both Germany and Italy showed at or above average growth and citation impact despite restrictive legislation. Both countries forbid the derivation of hES cell lines for research, though they allow the use of imported hES cell lines (if, in Germany's case, they were derived before a cutoff date of May 1, 2007). Germany is also one of the few countries to show a strong increase in FWCI for hES cell publications over the survey period (Figure 11.3). In contrast, while the UK and Sweden take a much more permissive approach to hES cell derivation, both countries showed below-average growth and citation impact. Part of the explanation for these findings may lie in how legislative positions are transposed into regulation and practice. For example, although UK legislation is permissive, the country has comparatively restrictive regulations controlling how and where the research may be practiced. Meanwhile, other factors, such as the differing maturity of the field in different countries, the general research funding level or specific strategic funding initiatives, also strongly affect these outcomes.

> ***"I think the way that we approach regulating stem cell therapies from a global perspective is going to be very important to the way that these eventually come out: when we have new things like uniform standards for safety and efficacy of treatments, whether we are able to collect all the data that maybe out there about new therapies in order to bring them to the clinic earlier, in order to prove them safe and socially acceptable. If we regulate in a way that is facilitative and promotes transnational cooperation, and is aimed at bringing these therapies online faster, we will probably end up with some better treatments sooner and hopefully more affordable."***
>
> *— Sarah Chan, Research Fellow in Bioethics and Law, Deputy Director, Institute for Science, Ethics and Innovation, University of Manchester*

Comparing the relative activity levels of each country in the different pluripotent stem cell research areas further underlines this complex relationship.[11] Figure 12.1–12.4 provides snapshots of the proportion of each country's stem cell research activity relative to global activity in 2008 and 2012. In this period, Germany achieved approximately 1.5 times the global activity level in ES cell research, but aligned more closely to the global level in terms of hES cell publications. Meanwhile, the UK's relative hES cell research activity dropped to approximately 1.45 times the global level in 2012.

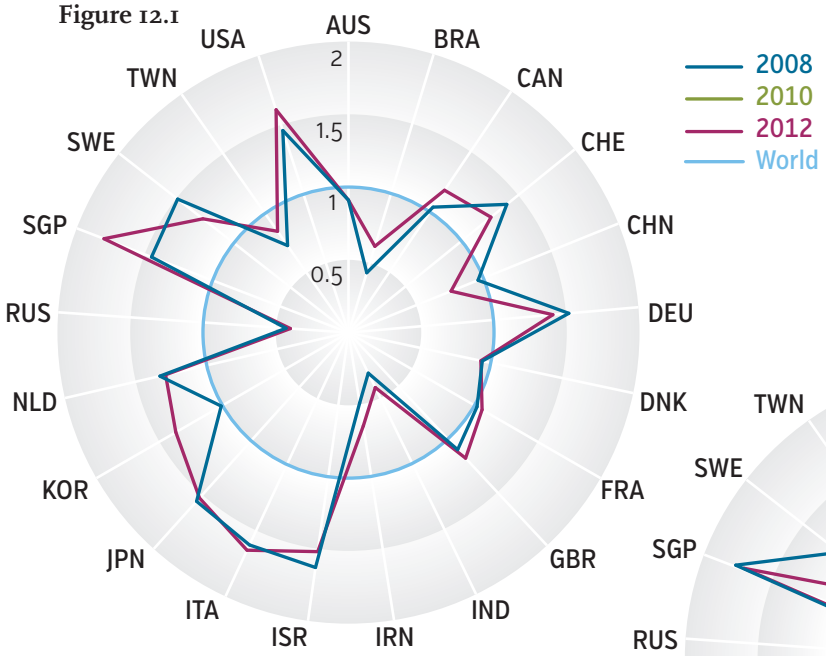
A number of countries show notable decreases in relative hES cell research activity during the analyzed period—most strikingly Sweden, but also Denmark, Switzerland, the Netherlands, and the UK. It is likely that this reflects a focal shift toward iPS cell research among new researchers entering the stem cell field, with most countries showing an increase in relative iPS cell research activity (Figure 12.4).

Across all cell types, the United States' relative activity is consistently 1.5 to 2 times above the global level. Japan, the country with the second-highest iPS cell research output, displays a correspondingly high level of relative iPS cell research activity, as one would expect given this country's pioneering efforts

11 *Relative activity* for a specific year is calculated as: the proportion of country X's publications that are stem cell research in that year divided by the proportion of total world publications that are stem cell research in the same year. A value of 1.00 indicates that the country's stem cell research effort corresponds to the world average.

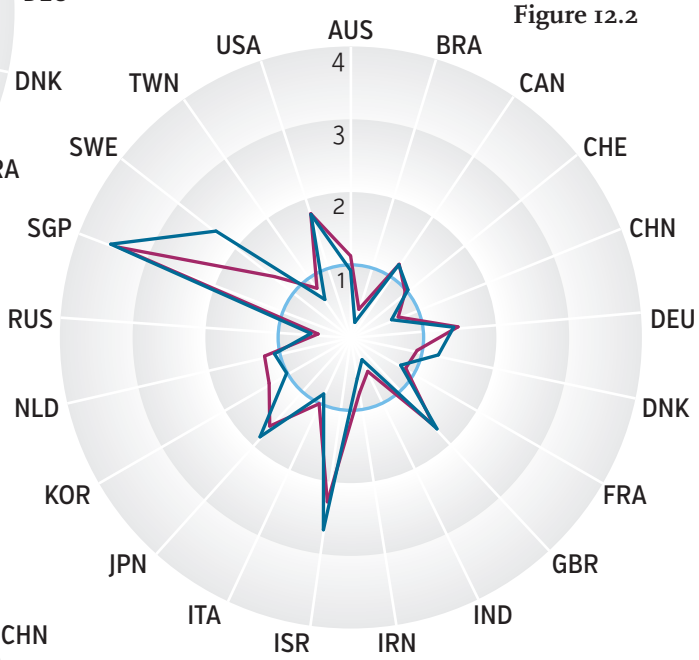
Relative Activity Stem Cells, All

Figure 12.1



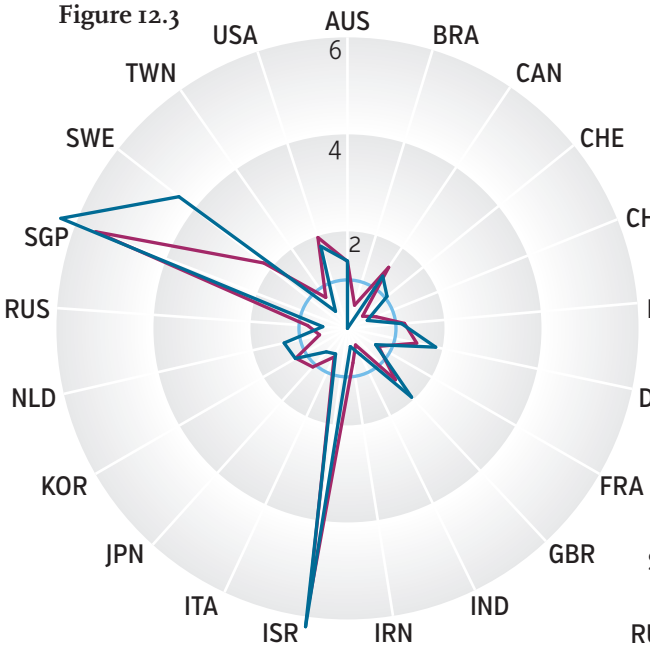
ES Cells

Figure 12.2



hES Cells

Figure 12.3



iPS Cells

Figure 12.4

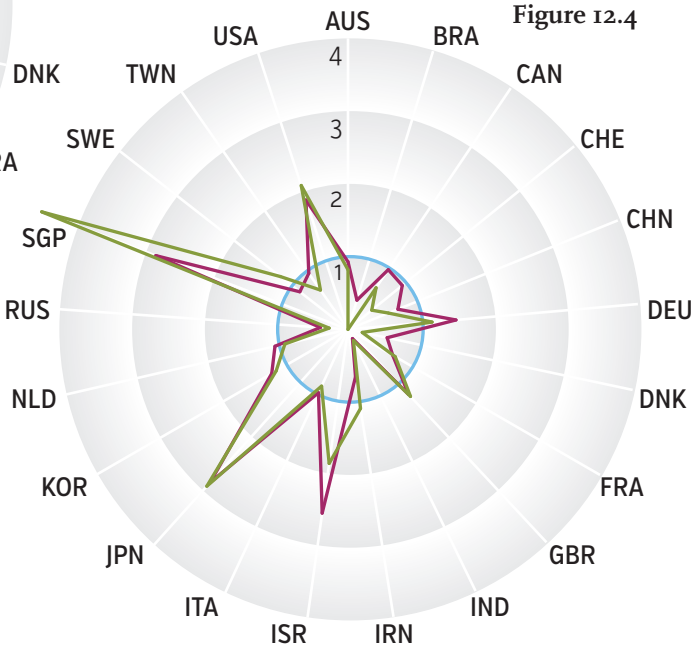


Figure 12.1–12.4: *Stem cell research activity by country and cell type from 2008 to 2012, relative to the global average. Global activity level has been indexed to a value of 1.00.* **Appendix F** *gives a comprehensive breakdown of relative activity per country in each of the areas shown here for the analyzed period.*
SOURCE: *Scopus*

and continued strong focus on this area and irrespective of its recent below-average growth at the country level (Figure 11.4). Israel shows high activity in both hES (over 5 times the world activity level) and iPS (2.55 times the world level) cell research. Indeed, an Israeli research group was involved in the first hES cell study (Thomson et al., 1998), and the country's stem cell research community is known to be highly active, as well as engaged in strong collaborations with the USA (Luo and Matthews, 2013).

3.3 Collaboration, Partnerships, and Funding Strategies

International and corporate collaboration

With stem cell research significantly contributing to research activity in many countries, it is important to consider the role of international collaboration in this field. This study infers collaboration from *co-authorship, and assumes international collaboration when at least one author is affiliated with an institution in another country (co-authorship is not the only indicator of collaboration, as discussed below in the context of academic-corporate collaborations)*. Previous studies have shown that international scientific research collaborations are becoming more prevalent and cover increasing geographical distances (Tijssen et al., 2011, He, 2009). Additionally, international collaboration has been shown to positively affect citation impact (Glänzel, 2001, ScienceEurope and Elsevier, 2013, Stockholm International Water Institute and Elsevier, 2012).

Almost all countries included in this study show higher levels of international collaboration in 2012 than in 2008 (Figure 13.0). In addition, high citation impact tends to correlate with a high level of international collaboration in the stem cell field (Figure 13.1). This analysis also reveals clear differences between nations, with European countries, Singapore, Australia, and Canada showing high levels of international collaboration, with relatively less international collaboration observed in the other Asian nations and developing countries included in this study. National and regional cultures, languages, funding, policies, and infrastructures are likely to be strong influences here, as in other trends seen in the field. Here, we discuss selective illustrative examples.

International Collaboration, Stem Cells

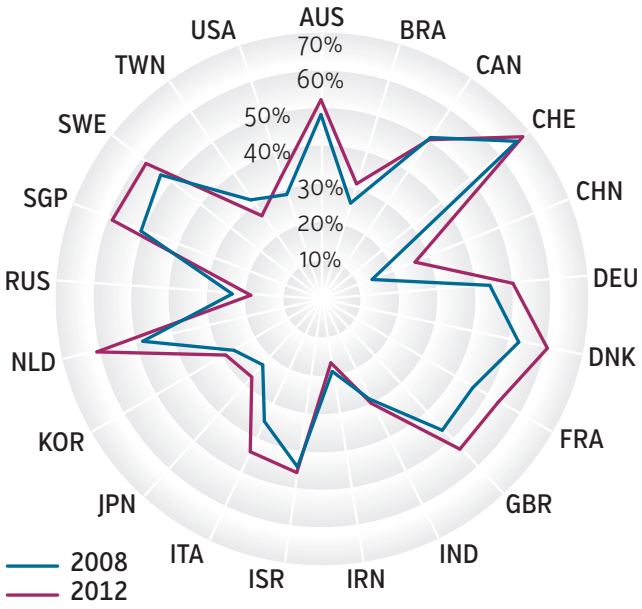


Figure 13.0: *Internationally co-authored papers as a share of total stem cell publication output by country from 2008 to 2012.* SOURCE: *Scopus*

> ***"International collaboration is essential if we are to realize the great potential of stem cell research and regenerative medicine in improving human health globally. This is particularly true in Australia, where our stem cell research community is of high quality, but small, relatively underfunded and geographically isolated. Therefore international collaboration is essential to our competitiveness and to bringing the benefits of this research to the Australian people. We have maintained a high level of international collaboration during the period 2008-2012, and it is essential that we expand these efforts."***
>
> *— Martin Pera, Prof. Stem Cell Science, The University of Melbourne; Program Leader, Stem Cells Australia - Australian Government funded Special Research Initiative*

The European Commission's funding programs have, since 1984, explicitly required European researchers to form collaborative networks (Defazio et al., 2009). These programs have underpinned efforts to establish an integrated European Research Area and have fostered the organic development of collaborative partnerships and co-authored papers. Indeed, in an impact assessment survey, 60% of the participants in health-related research projects (including stem cell projects) funded by the commission's Framework 6 and 7 programs declared

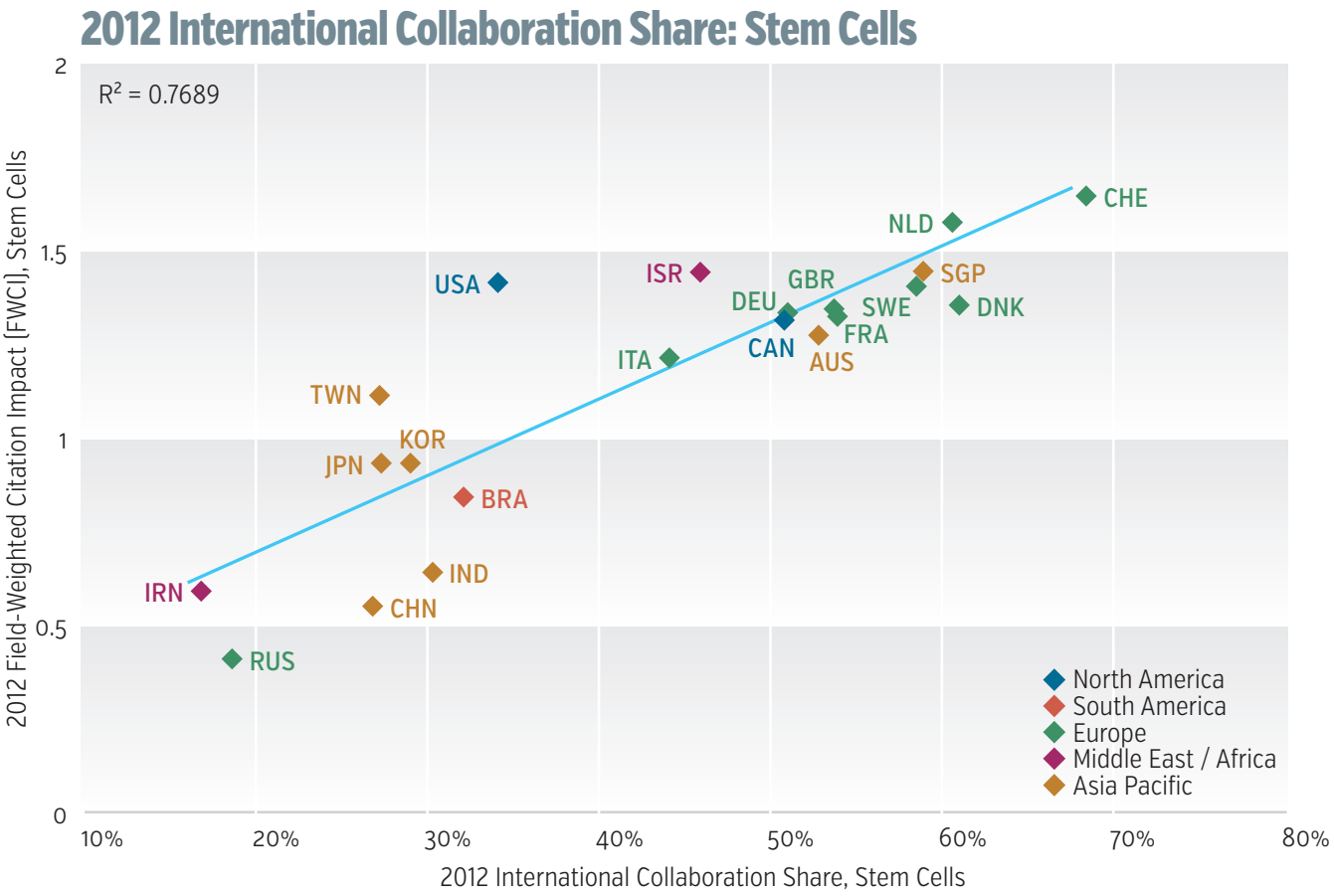


Figure 13.1: *International collaboration as share of total stem cell output vs. overall FWCI of stem cell research by country in 2012.* SOURCE: *Scopus*

that their research networks continued to formally collaborate after the completion of the funded research project. Moreover, collaboration and network building was cited as the second most important outcome of the projects, after academic publication.[12] European initiatives to support researcher mobility[13] also aim to foster collaboration. The academic collaborations supported by EU framework funding are widely believed to accelerate research progress beyond the impacts reflected in collaborative outputs. Switzerland, albeit not a member of EU, is part of the European Research Area, and generally across all fields of science show a very high degree of international collaboration.

12 European Commission 2011. Impact assessment of health research projects supported by DG Research and Innovation 2002-2010. Available at http://ec.europa.eu/research/health/pdf/impact-assessment-of-health-research-projects-on-research-2002-2010_en.pdf [accessed November 5, 2013]

13 For example, the EURAXESS Researchers in Motion program [http://ec.europa.eu/euraxess/] and the Marie Curie Actions Research Fellowship Program [http://ec.europa.eu/research/mariecurieactions/].

"The funding model [in the EU] has encouraged collaboration which leads to better science... there's no doubt that working together, your work is more likely to be repeatable and your work is more reliable if there are multiple authors on papers. Repeatability in stem cells we know is a major issue and we often hear about scientists who get results, then other people can't repeat their experiments or they can't isolate the cells or can't grow them or don't believe that they exist. If you get a multi-authored paper, particularly a multinational one, I think you're much less likely to get that problem."

— Charles Kessler, Principal Scientific Officer, European Commission

Singapore, which has invested heavily in its biotechnology and biological research sectors, also shows a high rate of international collaboration. The country has attracted a number of well-established international researchers with its supportive research environment and state-of-the-art new facilities. Singapore particularly offered an attractive alternative to some researchers in this field when the USA was restricting federal funding of hES cell research under the Bush administration. The resulting researcher diaspora—where researchers based in Singapore

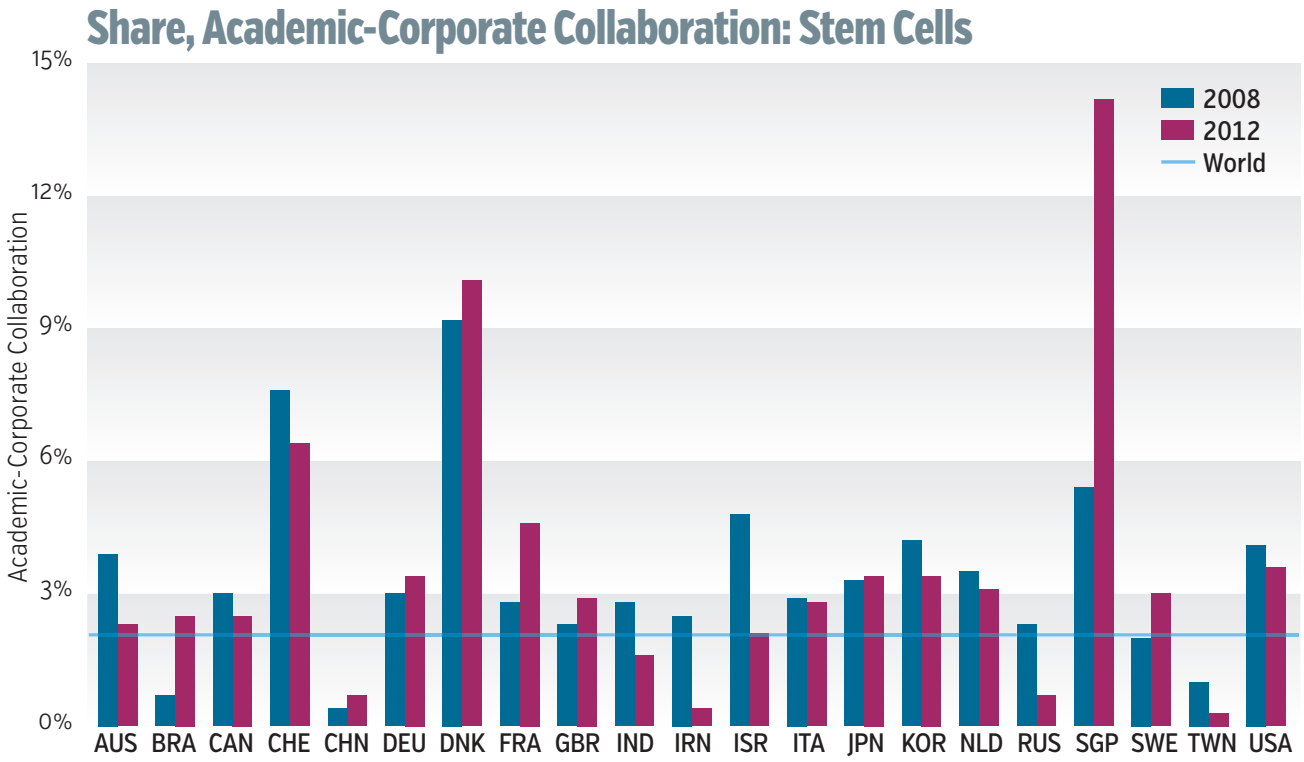


Figure 14.0: *Academic-corporate collaboration in overall stem cell research by country in 2008 and 2012.* SOURCE: *Scopus*

retain strong ties to the USA and other countries—is likely one contributing factor to the country's high rate of publications listing affiliations in more than one country.

> ***"Apart from the Singapore Stem Cell Consortium Funding framework, most of the other stem cell funding is based on a competitive funding mechanism. So stem cell researchers have to compete with the other fields to get government funding. There is no special mechanism to preferentially fund stem cells at the moment, which is an indication that the field is more matured than before, because if you really want to push the initiation of a field you may think of dedicated funding, but once the field is more mature, the researcher should be competing with the other fields to get the share of government funding."***
>
> *— Huck Hui Ng, Executive Director, Genome Institute of Singapore, A*STAR*

In contrast, the USA is somewhat off-trend, with a comparatively low level of international collaboration relative to its high citation impact (Figure 13.1). This does not imply that USA researchers do not collaborate: on the contrary, network analysis shows USA stem cell science is highly collaborative (See **Appendices G** and **H** for a list of the 30 institutions with the highest stem cell research output worldwide, and their co-publication networks). However, the country's size and number of research institutes, together with funding mechanisms that support internal partnerships, result in largely domestic collaborations that therefore would not feature in this analysis (ScienceEurope and Elsevier, 2013).

In addition to affecting international collaborations, funding strategies and markets in different regions of the world can affect the nature and extent of academic-corporate collaborations. For example, the EU's Framework programs have increasingly encouraged, and most recently required, partnerships between commercial and academic organizations. This correlates with an increase in academic-corporate collaboration (Figure 14.0) for almost all European countries analyzed in 2008 and 2012; however, our analysis does not clarify whether or not this relationship is causal.

Overall, academic-corporate collaboration during the analysis period accounts for approximately 2% of all world stem cell publications (Figure 14.0). This level appears consistent with other subject areas. However, co-publication is only one measure of collaboration; due to intellectual property considerations, publication in academic journals may not always be the most immediate or important outcome of academic-corporate partnerships. Additionally, some com-

panies currently involved in the stem cell field focus on devices, tools, and techniques rather than therapies or basic science, and collaborative work in these area is much less commonly reported in publications than are developments in other aspects of the field.

> ***"When you are talking about stem cells and companies, we identified two groups of companies: one is the companies which are involved in therapies, and the other is all the companies doing the ancillaries and equipment–like reagents, tracking devices, microscopes, markers, media, bioreactors and things–and a lot of the developments in those fields don't get into the [research] papers at all."***
> *— Charles Kessler*

Nevertheless, three countries show noticeably higher-than-average academic-corporate collaboration: Switzerland, Denmark, and Singapore. In Denmark, the existence of a number of companies strongly engaged with academia, including Novo Nordisk, may explain this result. In Switzerland, this collaboration may be influenced by its high concentration of pharmaceutical companies, while Singapore's strong increase is again consistent with recent funding strategies.

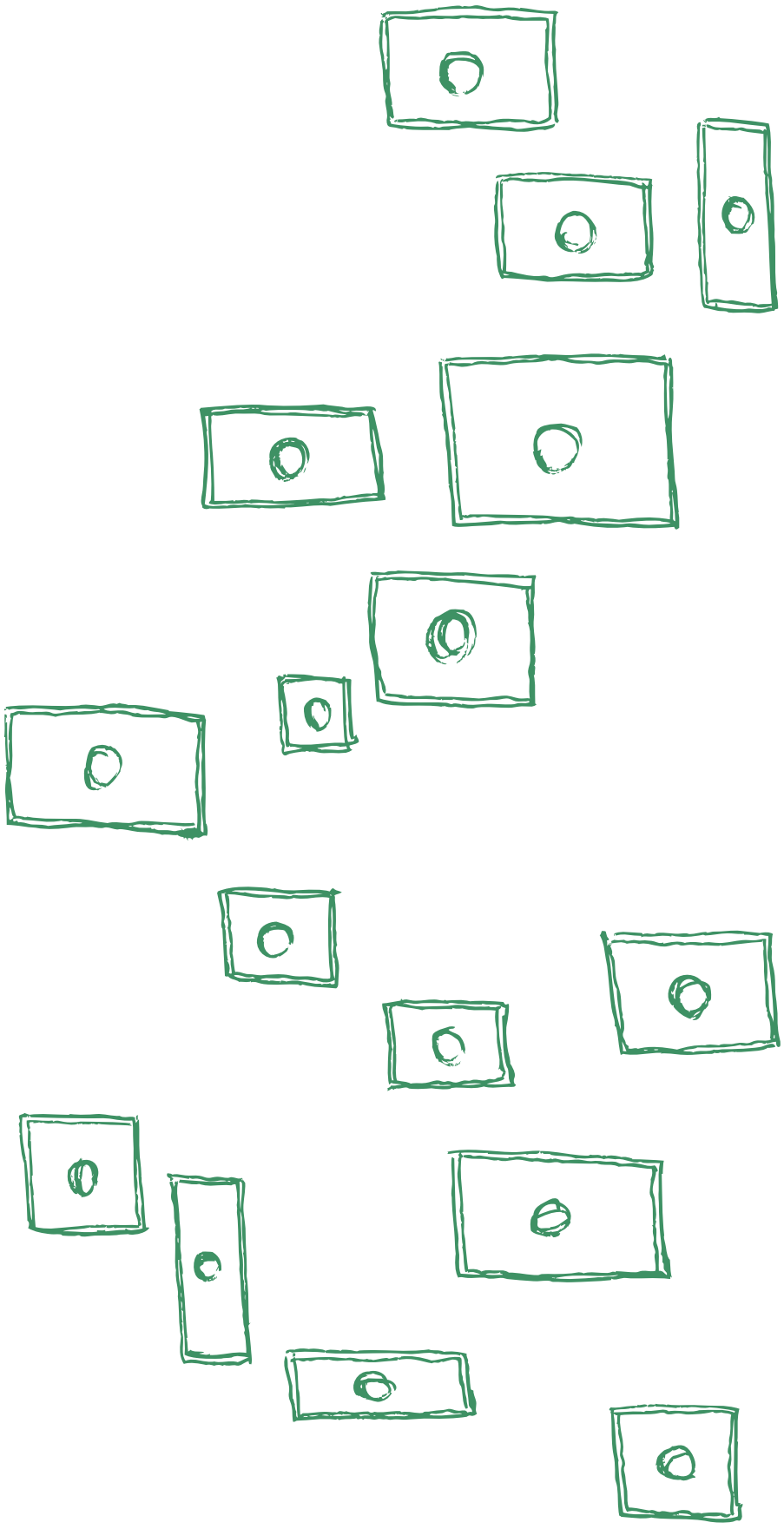
> ***"There was a significant change in [Singapore's] funding policy at one of their major biotechnology research projects, Biopolis, a few years ago. This seems to have affected the way the research is done in Singapore, as the new program required basic scientists, many of whom haven't necessarily actively collaborated with industry, to make the effort to have such a collaboration in order to maintain their full funding level."***
> *— Doug Sipp, Leader, Science Policy and Ethics Studies Unit, Center for Developmental Biology, RIKEN*

As the field moves forward, it seems clear that academic-corporate collaborations, especially those of a multidisciplinary nature, will be instrumental to globally realizing the full potential of the stem cell field as a whole.

> ***"I would expect that you're going to see that it's [the iPS cell field] going to have a huge amount of industry academic collaboration."***
> *— Sandra Engle, Senior Principal Scientist, Pluripotent Stem Cell and Molecular Biology Lab, PDM-NCE Primary Pharmacology Group, Pfizer, Inc.*

> ***"The data on international collaborations in stem cell and regenerative medicine illustrate the truly international scope of this growing area of research, and it also shows us that there are still more opportunities to bring different communities together to enhance the progress of the field."***
> *— Janet Rossant, PhD, FRS, FRSC, President, ISSCR; Chief of Research and Senior Scientist, Northbridge Chair in Paediatric Research, Research Institute, The Hospital for Sick Children; Professor, Departments of Molecular Genetics, and Obstetrics and Gynecology, University of Toronto*

Chapter 4
Conclusion



A dynamic and expanding field

In recent years, stem cell research has grown and changed remarkably. Despite the global economic recession, the field has continued to grow rapidly, with stem cell publications increasing at more than double the rate of world research publications from 2008 to 2012. However, this increase is not uniform across all stem cell research areas. Our analysis, which focused specifically on ES and iPS cell research, revealed that both ES cell and hES cell fields have grown more slowly than the stem cell field overall. In contrast, the emerging field of induced pluripotent stem cell (iPS) research has grown rapidly from 2008 to 2012. The field as a whole has also attracted considerable attention within the scientific community: stem cell publications are cited 50% more than all articles in related subject areas. This high-growth, high-impact field encompasses research across many cell types, with a focus ranging from the most fundamental to the clinical. Reflecting the field's ongoing development and clinic promise, approximately half of all stem cell publications are associated with drug development or regenerative medicine, a trend that is particularly pronounced in iPS cell research.

Public and policy discussions have placed an emphasis upon pluripotent cells, as a result of their potential to provide an unlimited source of specialized human cells for medical applications, and the ethical questions they raise. Within the pluripotent stem cell field, ES cell studies dominate publications by volume and are cited at around twice the rate of world research publications across related disciplines. However, the emerging iPS cell field is growing explosively, and papers in this area are even more highly cited than ES cell research, at almost three times the world rate. It is clear that both fields remain highly active areas of research and continue to contribute significantly to the stem cell field. Although we did not conduct a detailed investigation of the individual aspects of tissue stem cell research, its continued impact and importance is also evident from the volume of stem cell publications that do not pertain to pluripotent cells.

The international landscape

Many nations around the world are contributing to stem cell research; the dynamic nature of the field suggests the landscape is likely to shift as new players develop research programs and refine their expertise. In our analysis of international stem cell research output, we found that, while the USA and China produce the highest number of publications (as they do in many subject areas), several countries show higher levels of relative activity in stem cell research. In the wake of significant strategic investment in the field, Singapore stands out in our analysis as having both high growth and citation impact, as well as dedicating the highest share of its overall research activity to stem cells. Other countries with a high ratio of stem cell research to overall research output include Italy, the USA, Japan, Israel, Switzerland, Germany, and Korea, though both Japan and Korea show below-average citation impact. Within hES cell research, we found that countries with restrictive policies, such as Germany and Italy, nevertheless achieved high citation impact, illustrating the complex relationship between policy and practice.

Stronger together

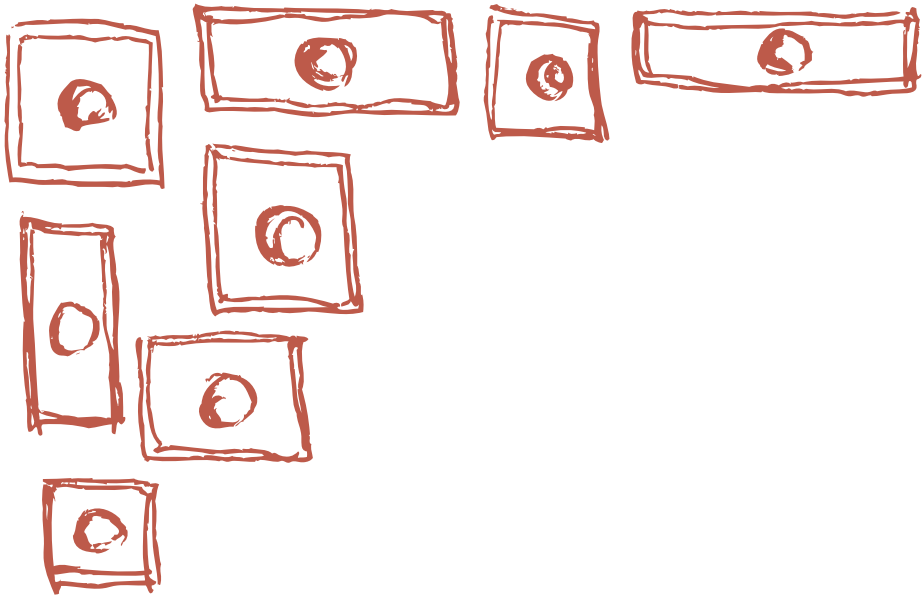
As is seen in other fields, international stem cell research collaboration positively affects citation impact. European countries, Singapore, Australia, and Canada exhibit higher levels of international collaboration, underpinned by strategic funding initiatives in both Europe and Singapore. Many Asian nations and developing countries included in this study, however, appear to engage less frequently in international collaboration. In contrast, academic-corporate collaboration in the stem cell field appeared low across all countries, with the notable exceptions of Singapore, Denmark, and Switzerland. Although such cooperative efforts may be underrepresented in this analysis since their outputs are much less commonly reported in publications than developments in other aspects of the field, our findings do suggest that further work to develop connections between academic researchers and industry partners will be needed to facilitate translation of research discoveries.

Looking to the future

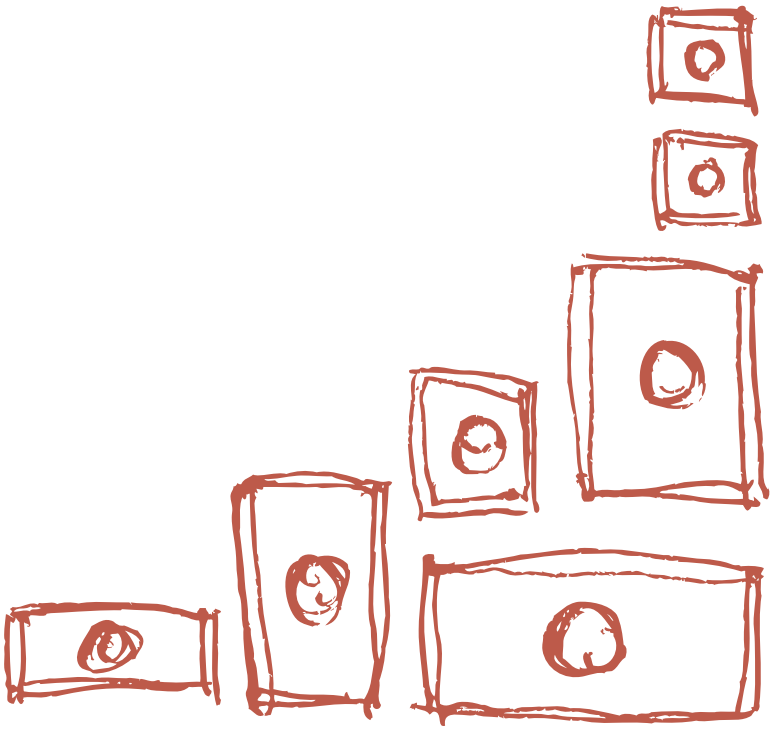
Some clinical applications of tissue stem cells are already well established and importantly, some experimental pluripotent cell treatments are in clinical trials. However, if tissue and pluripotent stem cells are to fulfil their promise of meeting unmet medical needs, the challenge to further foster a regulatory, funding and corporate environment that facilitates the process of taking laboratory developments towards the clinic will be of major importance. Active debates are underway to adapt existing regulatory frameworks to address the specific challenges of developing, standardising and distributing cell-based therapies, and meanwhile advances in basic research continue to provide a fuller understanding of how stem cells can be safely and effectively used. For progress in both areas, collaboration across national borders is likely to be essential.

As our analysis has shown, cell replacement or transplantation therapies are not the only possible application of pluripotent stem cell research under active investigation. Already, the first steps are being taken towards use of cells derived from pluripotent stem cells in drug discovery and testing. Just over a decade after the first hES cells were obtained in the laboratory, and less than a decade after the discovery of iPS cells, the field overall can look back on great progress, and indeed look forward with continued excitement towards a new horizon in global healthcare.

> ***"Society has high expectations toward stem cell research. I hope society will be tolerant enough to support and nurture an atmosphere where challenge is welcomed. Not all research always sees its light and there are countless errors behind the scenes. Science builds upon the footprints of other researchers, and encouraging challenge is what strengthens the research power of a nation as a whole...In translational research, scientists are there to provide evidence to inform risks. It's then for society to judge whether that should be brought to the clinic."***
>
> *— Akihiro Umezawa, Deputy Director, Research Institute, National Center for Child Health and Development*



Appendix



Appendix A – Methodology

Identifying the relevant documents

We used a keyword-based approach to identify document sets relevant to both stem cell research in general, and ES, hES, and iPS cell research specifically. The keywords, which were nominated by subject matter experts, were subsequently used to construct the search queries.

These queries were used to search the title, abstract, and keyword fields of the publication records derived from a May 2013 Scopus data-cut. The resulting publication sets were then assessed by industry and academic subject matter experts for construct validity. This crosschecking identified some limitations of the approach, described below, which should be considered when evaluating the data. The datasets were subsequently refined to include only articles, reviews, and conference proceedings, which were then used to calculate the metrics employed in this study.

The Searches

#	Name	Scopus Search
1	**Stem Cells (ALL)**	(TITLE-ABS-KEY("stem cell*"))
2	**ES**	(TITLE-ABS-KEY("embryonic stem*"))
3	**hES**	TITLE-ABS-KEY ("human embryonic stem*")
3	**iPS**	(TITLE-ABS-KEY("induced pluripotent"))
4	**Stem Cells (ALL) & Drug development**	(TITLE-ABS-KEY("stem cell*")) and (TITLE-ABS-KEY("drug discovery") OR TITLE-ABS-KEY("drug development") or TITLE-ABS-KEY("Pharmaceutical development") or TITLE-ABS-KEY("Pharmaceutical research") or TITLE-ABS-KEY("drug screening") or TITLE-ABS-KEY("clinical pharmacology") or TITLE-ABS-KEY("toxicity assessment") or TITLE-ABS-KEY("predictive toxicology"))
5	**ES & Drug Development**	(TITLE-ABS-KEY("embryonic stem*")) and (TITLE-ABS-KEY("drug discovery") OR TITLE-ABS-KEY("drug development") or TITLE-ABS-KEY("Pharmaceutical development") or TITLE-ABS-KEY("Pharmaceutical research") or TITLE-ABS-KEY("drug screening") or TITLE-ABS-KEY("clinical pharmacology") or TITLE-ABS-KEY("toxicity assessment") or TITLE-ABS-KEY("predictive toxicology"))
6	**iPS & Drug Development**	(TITLE-ABS-KEY("induced pluripotent")) and (TITLE-ABS-KEY("drug discovery") OR TITLE-ABS-KEY("drug development") or TITLE-ABS-KEY("Pharmaceutical development") or TITLE-ABS-KEY("Pharmaceutical research") or TITLE-ABS-KEY("drug screening") or TITLE-ABS-KEY("clinical pharmacology") or TITLE-ABS-KEY("toxicity assessment") or TITLE-ABS-KEY("predictive toxicology"))
7	**Stem Cells (ALL) & Regenerative Medicine**	(TITLE-ABS-KEY("stem cell*")) and (TITLE-ABS-KEY(("regenerative medicine") OR ("regenerative therapy") or ("cell therapy") or ("tissue engineering") or ("cell transplantation") or ("cell transplant")))
8	**ES & Regenerative Medicine**	(TITLE-ABS-KEY("embryonic stem*")) and(TITLE-ABS-KEY(("regenerative medicine") OR ("regenerative therapy") or ("cell therapy") or ("tissue engineering") or ("cell transplantation") or ("cell transplant")))
9	**iPS & Regenerative Medicine**	(TITLE-ABS-KEY("induced pluripotent")) and (TITLE-ABS-KEY(("regenerative medicine") OR ("regenerative therapy") or ("cell therapy") or ("tissue engineering") or ("cell transplantation") or ("cell transplant")))

Table A: *Scopus searches that correspond to the Solr searches used in this study.*

1. Searches were created to identify the following datasets:
   a. **Stem cells** – the overall field of stem cell research
   b. **ES cells** – publications related to embryonic stem cells
   c. **iPS cells –** publications related to induced pluripotent stem cells
2. Searches were created to identify publications related to the following topics *within* the datasets specified above:
   a. **Drug development**
   b. **Regenerative medicine**
3. Later during analysis, we added one search to isolate hES cells, but did not combine this with the themes of drug development and regenerative medicine. We did not carry out a search to isolate human iPS cells from the overall dataset of iPS cells.

The searches

Solr™ [14] queries were performed on the title, abstract, and keyword fields of a Scopus dataset that was customized for analytics. These queries are based on keyword searches where Solr takes into account language, grammar, and stemming[15] within texts.

Table A provides the Scopus advanced search queries similar *but not identical* to the keyword searches used for this study. We provide these searches so that readers with Scopus access may explore the search results. Please do note that the Scopus search results will not be identical to those used in this study because we used a Solr search of a customized Scopus snapshot dated May 2013, which is different than doing an advanced search in Scopus.com. The analyses were also further limited to article, review and conference proceedings document types.

Limitations

It should be noted that the while the datasets were assessed for overall construct validity, we did not examine each and every article returned by the searches to confirm whether it specifically concerned the cell type in question. In some cases, document sets of one cell type may contain irrelevant articles or articles that belong to another cell type due to references made to another cell type in the title, abstract, and/or keyword sections of the publication. For example, 4% of pluripotent cell publications discuss both iPS and hES cells, and 10% referred to both iPS and non-human ES cells. (The fingerprint analysis in **Appendix B** sheds further light on this issue.) This sort of keyword use may reflect authors' aspirations for future applications of their work, and may therefore incorporate these terms to connect work to broader fields. Additionally, use of queries such as "regenerative medicine" and "drug discovery" may exclude some papers related to these areas where authors have used different but related keywords. It should also be noted that the search to compile the document set for overall stem cell research was purposely broad, and can be expected to include stem cell research of all kinds, as well as research which refers to stem cells in the title, abstract, and keywords, but may not necessarily be considered "stem cell research" per se. Future studies may wish to address these methodological limitations.

Methodology and rationale

Our methodology employs the theoretical principles and best practices developed in the field of quantitative science and technology studies, particularly in research on science and technology indicators. The *Handbook of Quantitative Science and Technology Research: The Use of Publication and Patent Statistics in Studies of S&T Systems* (Moed, Glänzel, and Schmoch, 2004)[16] gives a good overview of this area. The field draws on the pioneering work of several notable scholars: Derek de Solla Price (1978),[17] Eugene Garfield (1979),[18] and Francis Narin (1976)[19] in the USA, Christopher Freeman, Ben Martin, and John Irvine in the UK (1981, 1987).[20] Several European institutes have also contributed to this area of study, including the Centre for Science and Technology Studies at Leiden University, the Netherlands, and the Library of the Academy of Sciences in Budapest, Hungary.

14 http://lucene.apache.org/solr

15 http://en.wikipedia.org/wiki/Stemming

16 Moed H., Glänzel W., & Schmoch U. (2004). Handbook of Quantitative Science and Technology Research, Kluwer: Dordrecht.

17 de Solla Price, D.J. (1977–1978). "Foreword," Essays of an Information Scientist, Vol. 3, v–ix.

18 Garfield, E. (1979). Is citation analysis a legitimate evaluation tool? Scientometrics, 1 (4), 359-375.

19 Pinski, G., & Narin, F. (1976). Citation influence for journal aggregates of scientific publications: Theory with application to literature of physics. Information Processing & Management 12 (5): 297–312.

20 Irvine, J., Martin, B. R., Abraham, J. & Peacock, T. (1987). Assessing basic research: Reappraisal and update of an evaluation of four radio astronomy observatories. Research Policy, 16(2-4), 213-227.

The analyses of bibliometric data in this report are based upon recognized advanced indicators (e.g., the concept of relative citation impact). Our base assumption is that such indicators are useful and valid, though imperfect and partial measures, in the sense that their numerical values are determined by research performance and related concepts, but also by other, influencing factors that may cause systematic biases. In the past decade, the field of indicators research has developed best practices that dictate how indicator results should be interpreted and which influencing factors should be taken into account. Our methodology builds on these practices.

Article types

For all analyses, only the following document types are considered:

- Article (ar)
- Review (re)
- Conference Proceeding (cp)

Compound annual growth rate

The CAGR is defined as the year-over-year constant growth rate over a specified period. Starting with the first value in any series and applying this rate for each of the time intervals yields the amount in the final value of the series.

$$\mathrm{CAGR}(t_0, t_n) = \left(V(t_n)/V(t_0)\right)^{\frac{1}{t_n - t_0}} - 1$$

$V(t_0)$: start value, $V(t_n)$: finish value,
$t_n - t_0$: number of years.

It should be noted that, while we have used a Scopus data-cut from May 2013, the Scopus database will have continued to index publications after that date, more so for 2012 than previous years. CAGR calculated using 2012 as the final year is therefore somewhat low, but still suitable for the purpose of comparison.

Counting

All analyses make use of whole, rather than fractional, counting. For example, if a paper was co-authored by one author from the UK and one author from the Netherlands, that paper counts toward both the publication counts for both the UK and the Netherlands. Total counts for each country reflect the unique publication count.

Data sources

Scopus is a proprietary academic database developed and owned by Elsevier. It is the largest abstract and citation database of research literature in the world, featuring abstracts and citation information from more than 50 million scientific research articles in 21,000 peer-reviewed journals published by over 5,000 publishers spanning all science sectors, including the arts and humanities (in which field Scopus covers more than 3,000 publications). Scopus covers approximately 5,900 titles from North America, 8,400 from Europe, 2,800 from the Asia-Pacific region, and 800 from Latin America and Africa.

Bibliometric indicators

Publication output: The number of publications per country that have at least one author affiliated to an institution in that country. A publication that is co-authored by authors from different countries thus counts toward the publication outputs of both countries.

Global publication share: The global share of publications for a specific country expressed as a percentage of the total output within the field of stem cells, ES cells, or iPS cells. Using a global share in addition to absolute publication numbers provides insight by normalizing for increases in world publication growth and expansion of the field in question (or of the entire Scopus database).

Relative activity: Relative activity compares each country's activity in each subject area to the global activity level in the same subject area. Relative activity is calculated as: share of country X's stem cell research publications divided by share of total stem cell research publications worldwide in the same year. A value of 1.00 indicates that the country's stem cell research effort in corresponds precisely with the global average.

International collaboration: Collaboration is inferred from publication co-authorship. A paper is considered an international collaboration if at least one of the authors is affiliated to an institution in a different country.

Academic-corporate collaboration: Collaboration is inferred from publication co-authorship. A paper is considered an academic-corporate collaboration if at least one author is affiliated to an academic institution and at least one author is affiliated to a corporate organization.

Field-weighted citation impact: A measure of citation impact based on the average number of citations received by a group of publications compared to the global number of citations received by the same type of publications. This metric is field-weighted in that

it adjusts for differing citation practices across different subject fields, and therefore for the different subject emphases of comparator countries. FWCI for each year looks at the citations that publications in that particular year have received in that same year and up to 4 years after publication, and compares this value of actual citations to the number of expected citations based on the subject in question, the year in question, and the article types in question.

In this study, we created 5-year overlapping windows where, for example, the FWCI reported for the year 2010 is based on publications from 2006 to 2010, the FWCI report for 2011 is based on 2007-2011, etc. For iPS cells, we created 2-year windows to accommodate the fact that many countries only recently began publishing in this area.

Interviews

Elsevier, EuroStemCell and iCeMS invited a number of interviewees to review and comment on this report. The interviewee selection and engagement process was as follows:

Twelve interviewees (see Interviewees section) were selected to represent areas of expertise rather than their organizations. To give as broad a range of perspectives as possible, candidates were also selected based on geographical region, and organizational category (academia, government (policy), and industry.)

The networks of Elsevier SciVal analytics, Global Academic Relations and Publishing, EuroStemCell, and iCeMS were used to select candidates. The final selection was determined in collaboration with Elsevier, EuroStemCell and iCeMS. Beyond those who accepted the invitation to be interviewed, three potential interviewees declined or did not respond.

Confirmed interviewees received a draft of the analysis material. EuroStemCell, Elsevier, and iCeMS then conducted parallel interviews, which were transcribed in full and shared with the project team (except for 2 interviews where recording was not available for technical reasons). EuroStemCell then selected the comments to be included in the text, which subsequently informed the analytical interpretation as represented in the report. All interviewees agreed to proceed after having the opportunity to review the use of their input and quotes from their interviews within the report.

The interviewees were offered a symbolic reimbursement (50 euros) for their participation. Alternatively, the same amount could be donated to the charity "Book Aid International".

The views expressed do not represent the views of the interviewees' organizational affiliations, but rather their opinions as individual experts in the field.

Appendix B – Fingerprints (key concepts)

To provide further insight into the nature of the publications identified in this analysis, we provide below the fingerprints (key concepts) represented most often in the stem cell, ES cell and iPS cell document sets. These key concepts were extracted by the Elsevier Fingerprint Engine, which scans abstracts from Scopus and extracts meaningful concepts termed 'fingerprints'.[21] The result is a set of high-quality key concepts that most often lack duplicates and synonyms. Figures B1-B3 present the 25 most frequently occurring key concepts in each dataset; bar length and number refers to the number of documents in the set that match the key concept.

21 The engine uses a variety of thesauri spanning all major subject areas, along with Natural Language Processing (NLP) techniques, to scan and analyze publication abstracts, and to map terms and combinations of terms to key concepts.

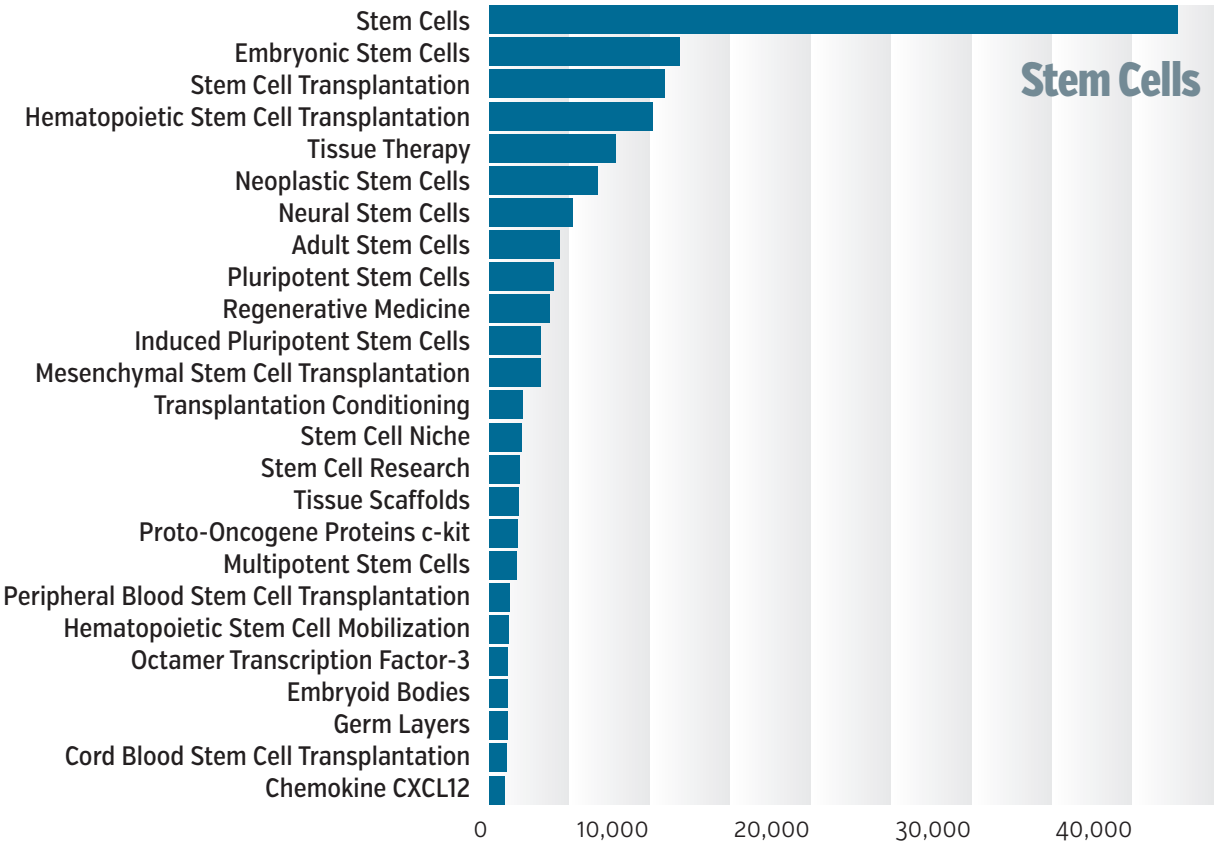


Figure B1: *The 25 most frequent key concepts in the stem cell document set (2008-2012).* SOURCE: *Scopus*

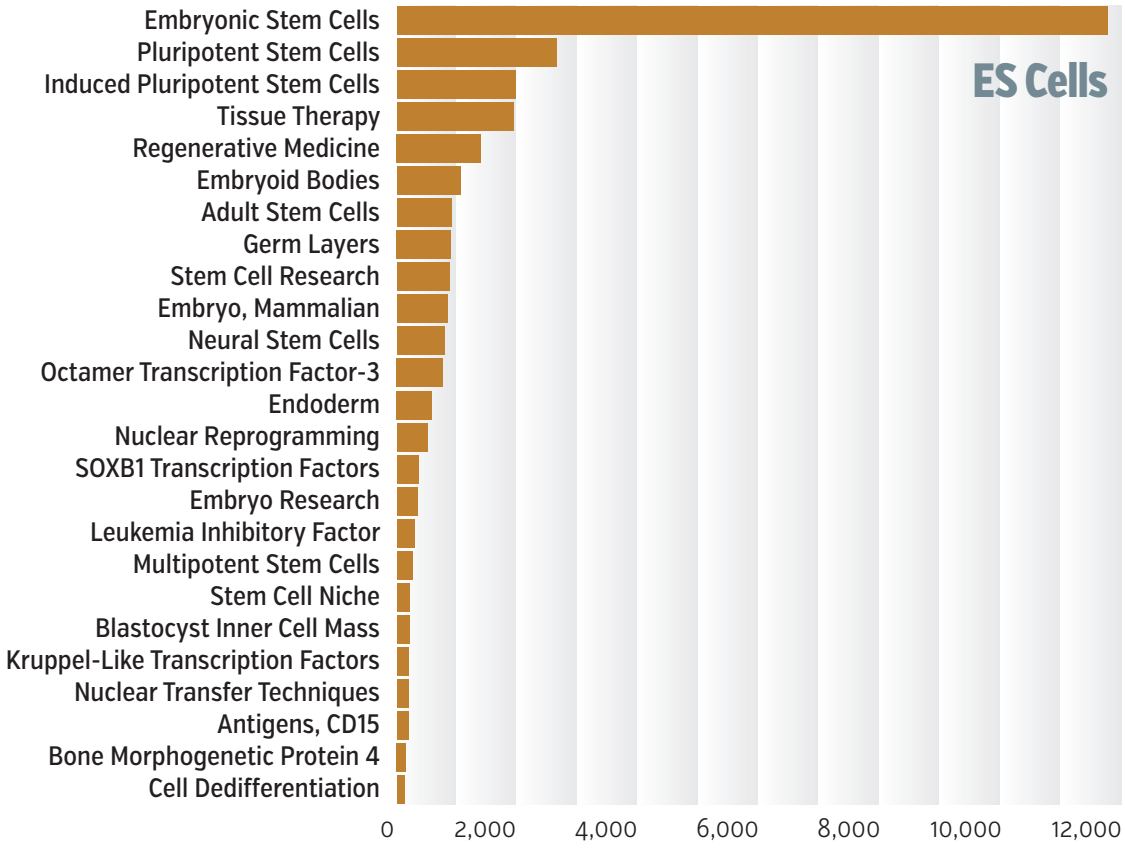


Figure B2: *The 25 most frequent key concepts in the ES cell document set (2008-2012).* Source: *Scopus*

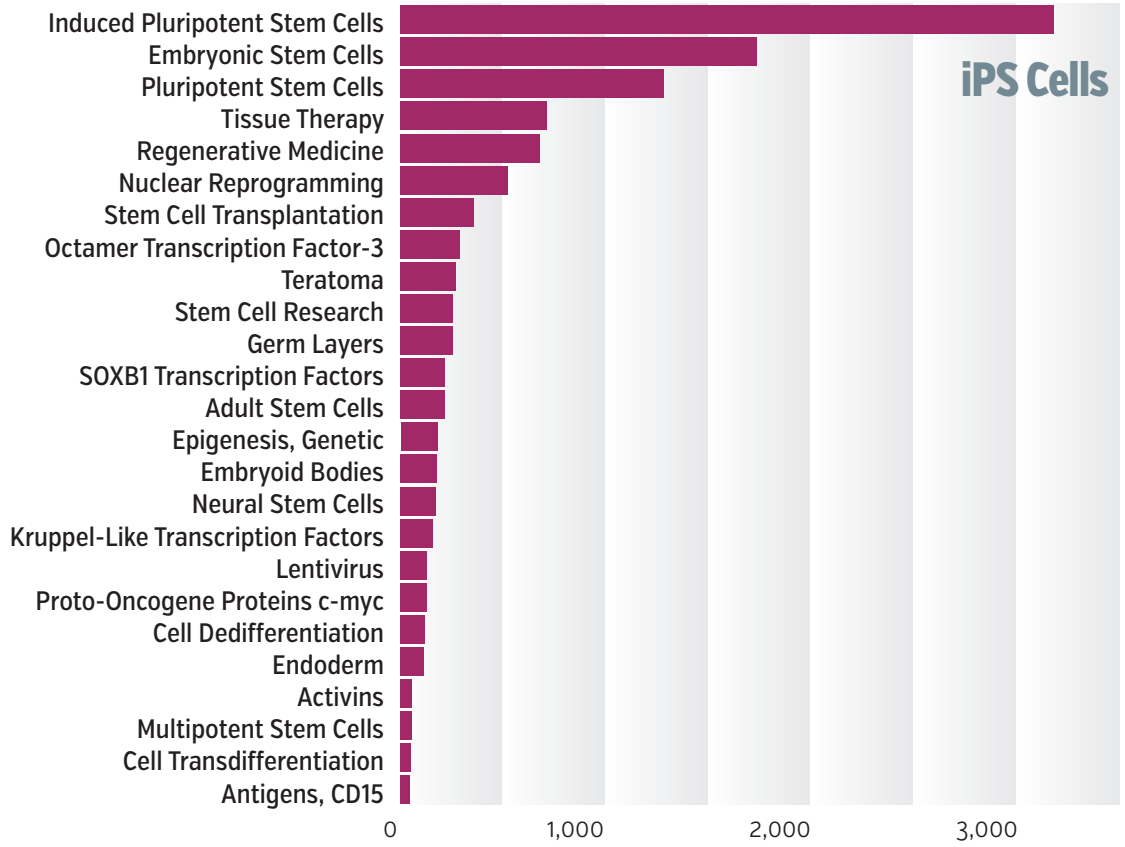


Figure B3: *The 25 most frequent key concepts in the iPS cell document set (2008-2012).* Source: *Scopus*

Appendix C – Country Codes

The below table explains the country codes used in this report.

Country Abbreviations

ISO 3-character country code	country
AUS	Australia
BRA	Brazil
CAN	Canada
CHE	Switzerland
CHN	China
DEU	Germany
DNK	Denmark
FRA	France
GBR	United Kingdom
IND	India
IRN	Iran
ISR	Israel
ITA	Italy
JPN	Japan
KOR	Korea, republic of
NLD	Netherlands
RUS	Russian Federation
SGP	Singapore
SWE	Sweden
TWN	Taiwan (Chinese Taipei)
USA	United States

Table C: *These are the current officially assigned ISO 3166-1 alpha-3 codes using the English short country names employed by the ISO 3166 Maintenance Agency.*

Appendix D – Trends in Publication Output by Country

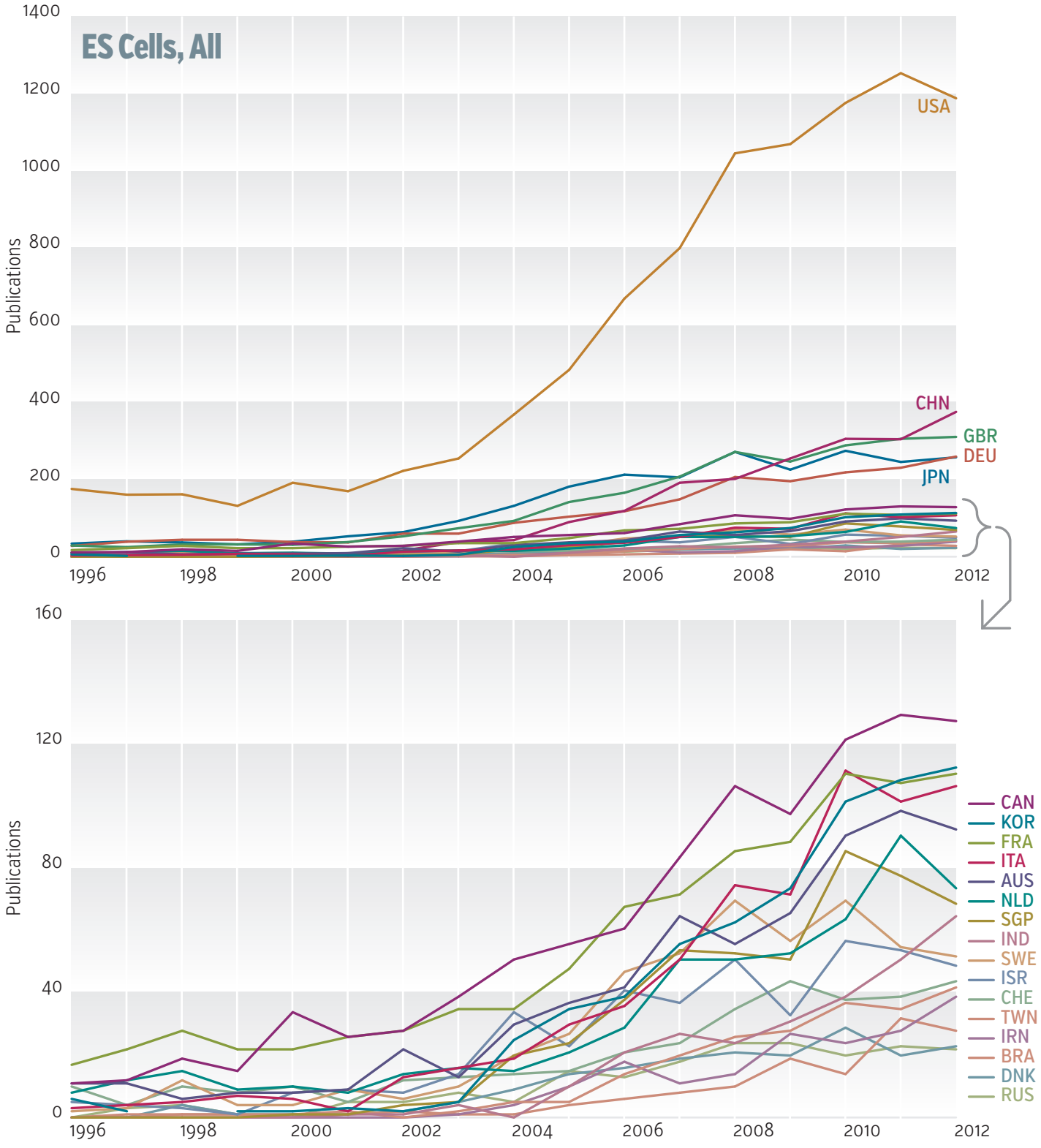


Figure D1: *The number of ES cell publications per country from 1996-2012.* SOURCE: *Scopus*

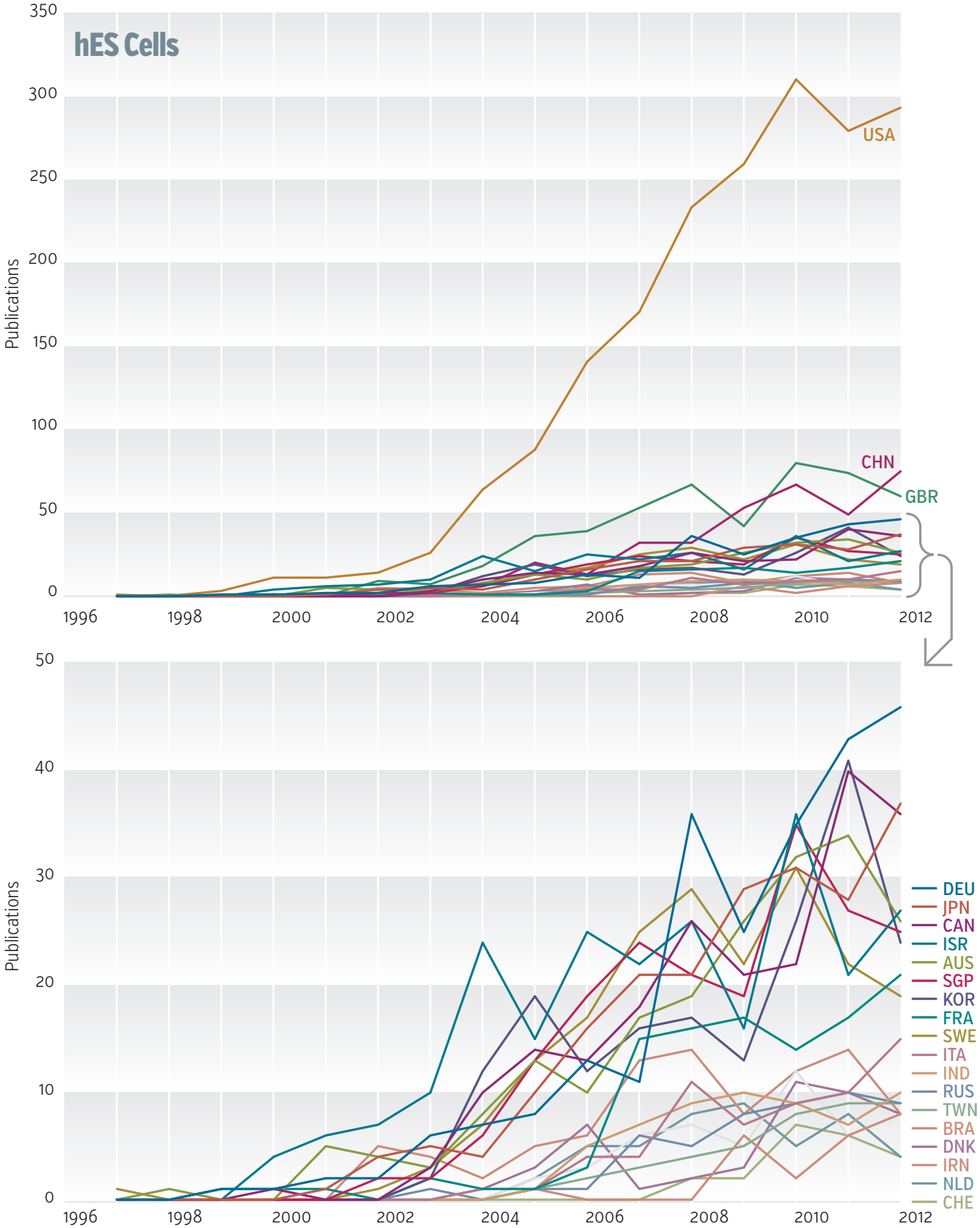


Figure D2: *The number of hES cell publications per country from 1996-2012.* SOURCE: *Scopus*

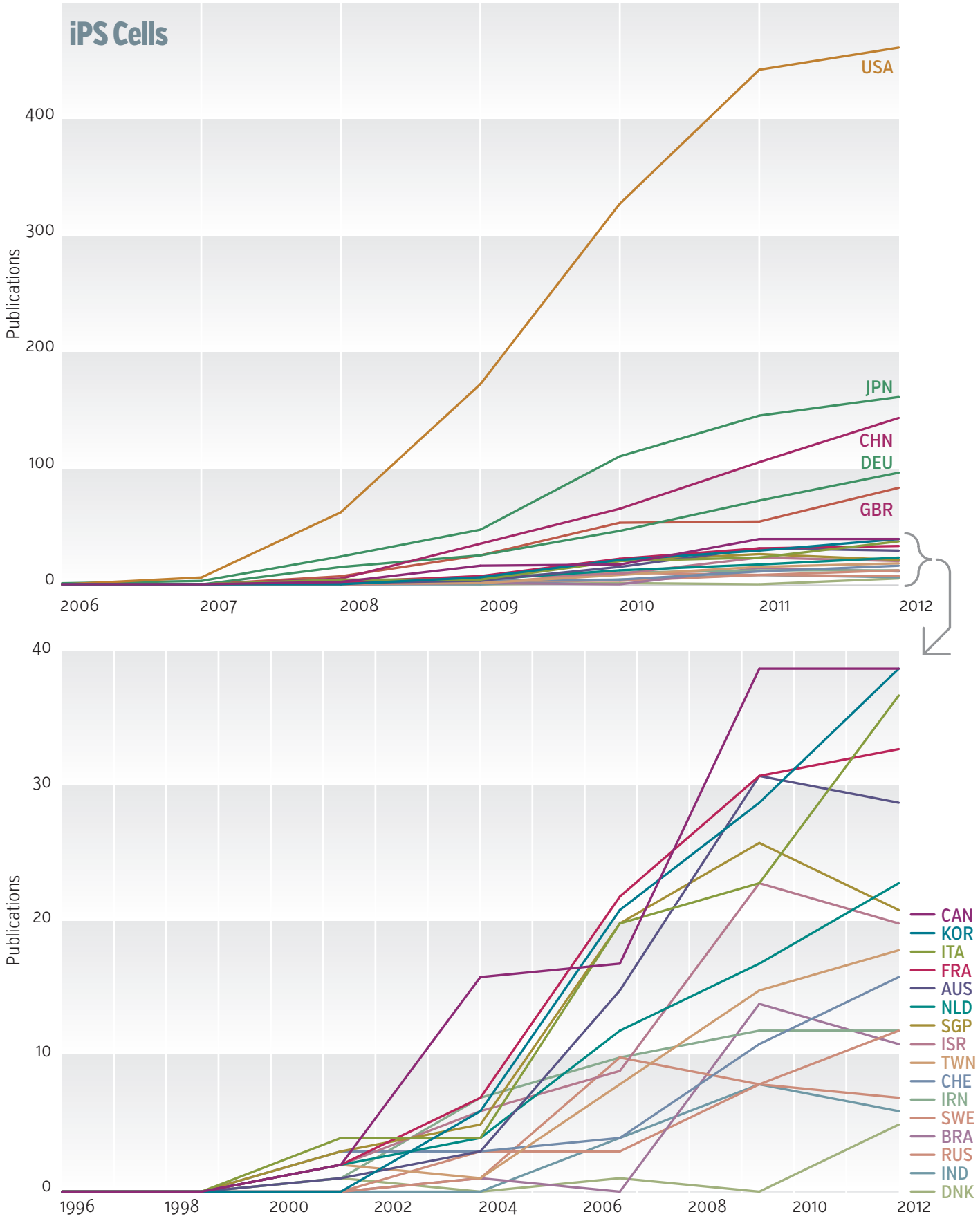


Figure D3: *The number of iPS cell publications per country from 1996-2012.* SOURCE: *Scopus*

Appendix E – Publication Output, Growth and Citation Impact per Country

StemCells	FWCI	CAGR	Publications	FWCI Change
USA	1.40	7.8%	34957	0.01
CHN	0.54	8.1%	13117	0.14
DEU	1.30	4.8%	8346	0.04
JPN	0.92	3.0%	7942	0.00
GBR	1.33	8.2%	7063	0.11
ITA	1.20	7.9%	5422	0.00
FRA	1.31	7.6%	4287	0.15
CAN	1.32	9.9%	3783	-0.02
KOR	0.92	20.0%	3162	-0.04
NLD	1.56	7.9%	2586	0.19
AUS	1.26	10.4%	2396	0.07
CHE	1.63	6.5%	1898	0.21
SWE	1.39	4.9%	1668	0.01
TWN	1.10	11.8%	1290	-0.04
IND	0.63	27.1%	1242	0.15
BRA	0.83	22.1%	1241	0.00
ISR	1.42	3.2%	1123	0.20
SGP	1.43	15.9%	1094	0.16
IRN	0.58	31.9%	775	-0.08
DNK	1.34	11.6%	682	-0.10
RUS	0.40	3.3%	663	0.05

ESCs	FWCI	CAGR	Publications	FWCI Change
USA	1.37	3.3%	5741	-0.05
CHN	0.62	16.8%	1444	0.23
GBR	1.19	3.4%	1425	0.09
JPN	0.98	-1.3%	1277	-0.15
DEU	1.09	5.9%	1113	0.11
CAN	1.21	4.6%	585	0.01
FRA	0.99	6.6%	505	-0.02
ITA	0.97	9.3%	468	-0.36
KOR	0.87	15.7%	461	-0.02
AUS	1.03	13.5%	405	0.05
SGP	1.14	6.8%	337	-0.15
NLD	1.71	9.8%	333	0.03
SWE	1.02	-7.2%	304	-0.04
ISR	1.47	-1.0%	244	-0.01
IND	0.54	28.3%	210	0.08
CHE	1.30	5.9%	200	0.18
TWN	0.72	12.7%	168	-0.42
IRN	0.60	29.2%	132	-0.09
DNK	1.24	2.3%	113	-0.08
RUS	0.41	-2.2%	113	0.07
BRA	0.70	29.4%	103	0.17

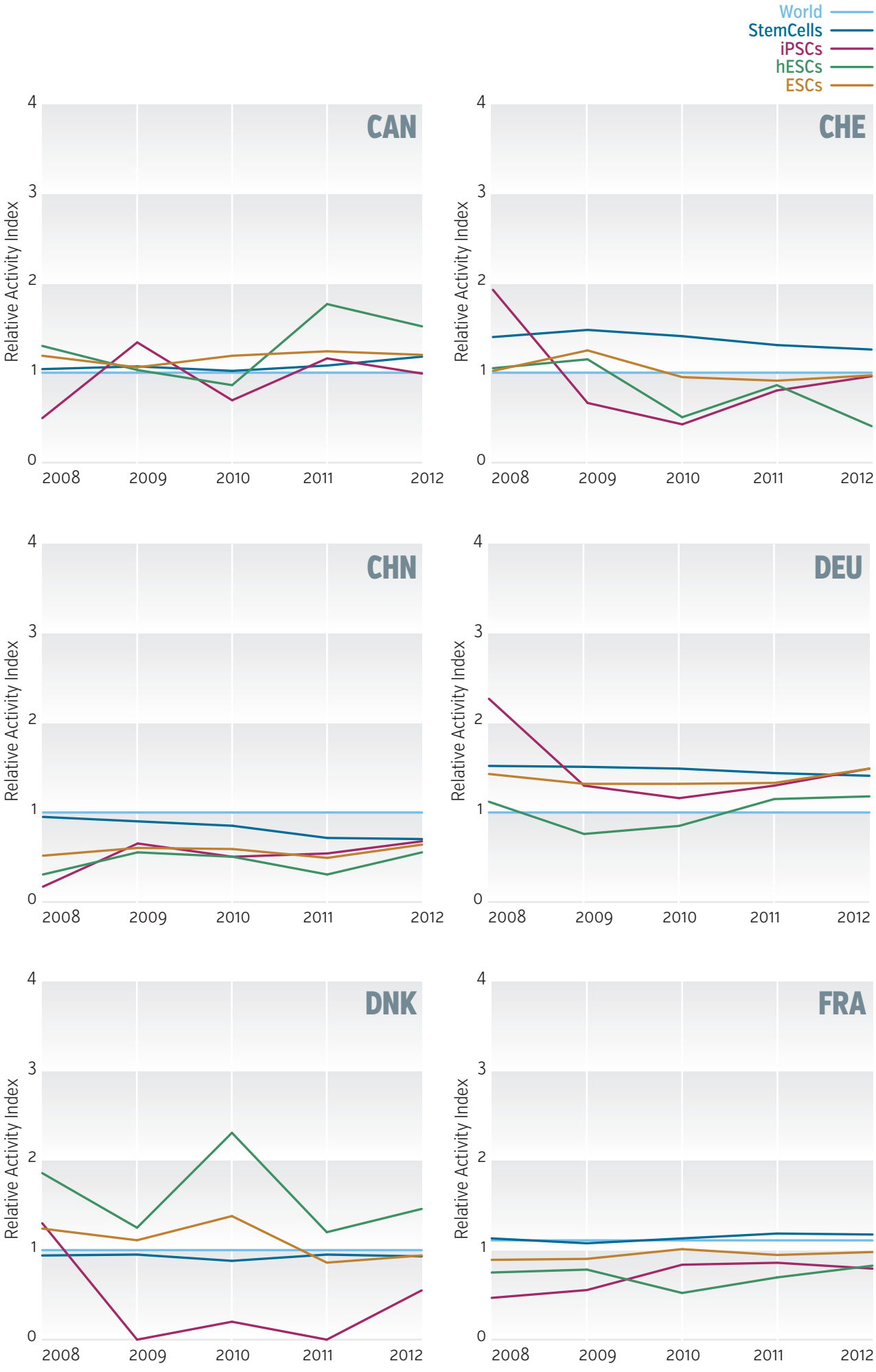
hESCs	FWCI	CAGR	Publications	FWCI Change
USA	1.31	5.9%	1379	-0.11
GBR	0.99	-2.7%	323	-0.01
CHN	0.71	23.7%	276	0.28
DEU	1.16	6.3%	185	0.32
JPN	1.07	15.2%	146	-1.08
CAN	1.37	8.5%	145	-0.03
AUS	1.02	8.2%	137	0.03
SGP	1.17	4.5%	127	0.18
ISR	1.14	0.9%	126	-0.12
SWE	1.01	-10.0%	123	-0.04
KOR	0.77	9.0%	121	0.00
FRA	0.82	7.0%	85	0.02
NLD	2.04	-13.1%	56	0.27
ITA	1.24	8.1%	52	-0.62
IND	0.69	2.7%	45	0.32
RUS	0.59	15.8%	41	-0.16
DNK	1.03	3.4%	38	-0.01
TWN	0.84	22.5%	35	-0.13
CHE	0.93	-15.9%	34	0.44
IRN	0.96	41.4%	34	0.18
BRA	0.95	10.1%	22	0.79

iPSCs	FWCI	CAGR	Publications	FWCI Change
USA	1.35	18.7%	1230	-0.03
JPN	0.89	21.0%	416	0.04
CHN	0.78	48.3%	313	0.24
DEU	1.29	44.5%	214	0.08
GBR	1.10	25.1%	190	-0.09
CAN	1.32	51.5%	95	0.18
KOR	1.36	36.3%	89	-0.11
FRA	1.32	22.5%	86	-0.70
ITA	1.10	36.0%	80	-0.01
AUS	1.24	39.0%	75	0.26
SGP	1.03	2.5%	67	0.15
ISR	2.01	49.1%	52	0.45
NLD	1.58	38.4%	52	0.84
TWN	0.73	50.0%	41	0.36
SWE	1.48	9.5%	34	-0.13
CHE	1.06	100.0%	31	0.78
IRN	0.61	9.5%	30	0.12
BRA	0.93	122.4%	25	0.93
IND	0.73	22.5%	18	0.30
RUS	0.49	52.8%	18	0.34
DNK	1.69	123.6%	6	0.62

Table E: *The publication output, compound annual growth rate, and field weighted citation impact (FWCI), and change in FWCI for Stem, ES, hES, and iPS cells publications, per country, 2008-2012.*

Appendix F – Relative Activity Index by Country

Figures F below display the relative activity per country in the field of stem cell research overall, ES, hES, and iPS, years 2008–2012. The same scale has been applied to all countries with the exception of Israel and Singapore, which use a larger scale because they both show especially high levels of relative activity. Israel and Singapore are displayed first followed by the remainder of the countries, which are displayed in alphabetical order.


World
StemCells
iPSCs
hESCs
ESCs
CAN
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DEU
DNK
FRA
Relative Activity Index
0
1
2
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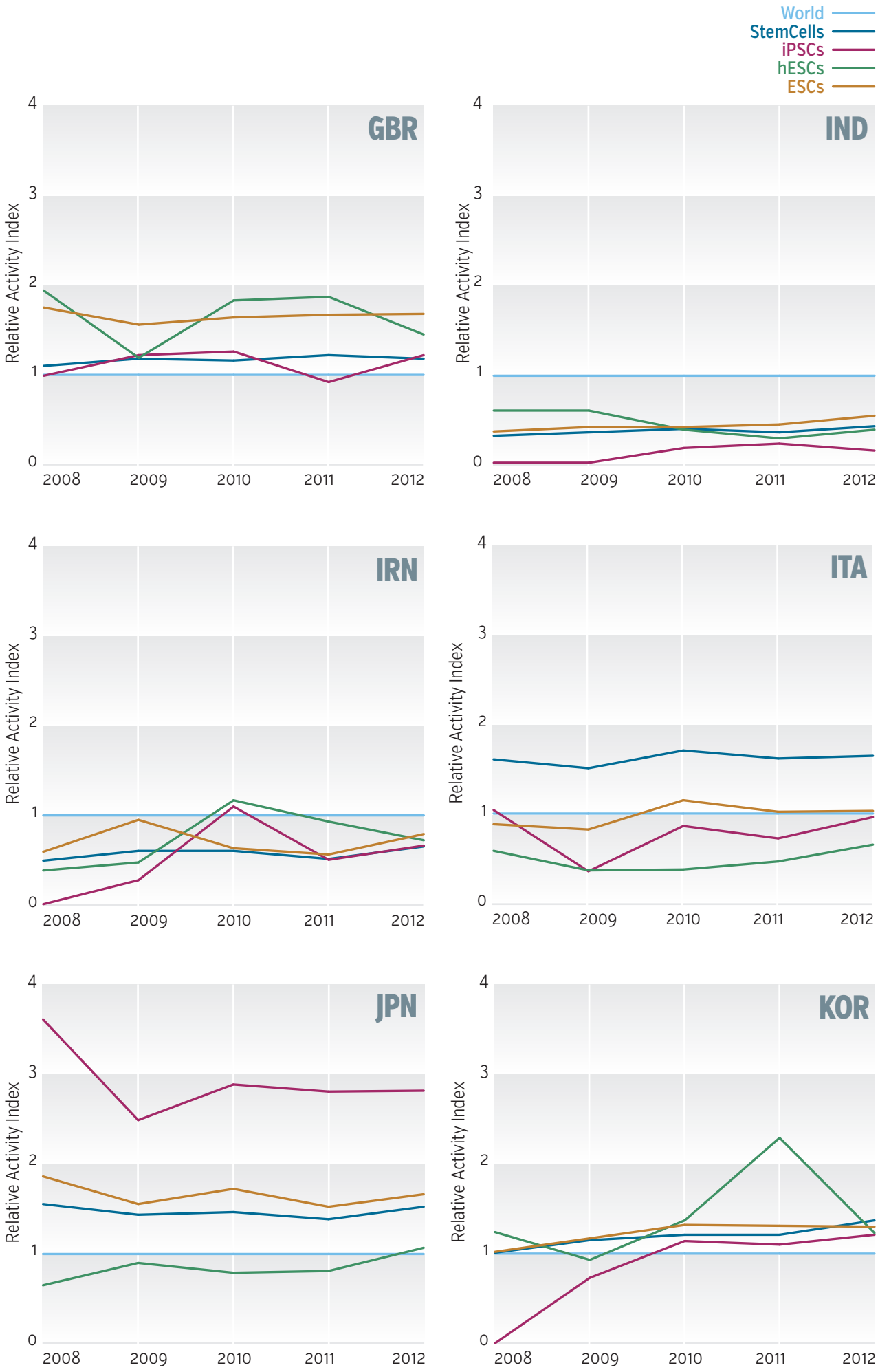
4
2008
2009
2010
2011
2012


World
StemCells
iPSCs
hESCs
ESCs
GBR
IND
IRN
ITA
JPN
KOR
Relative Activity Index
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1
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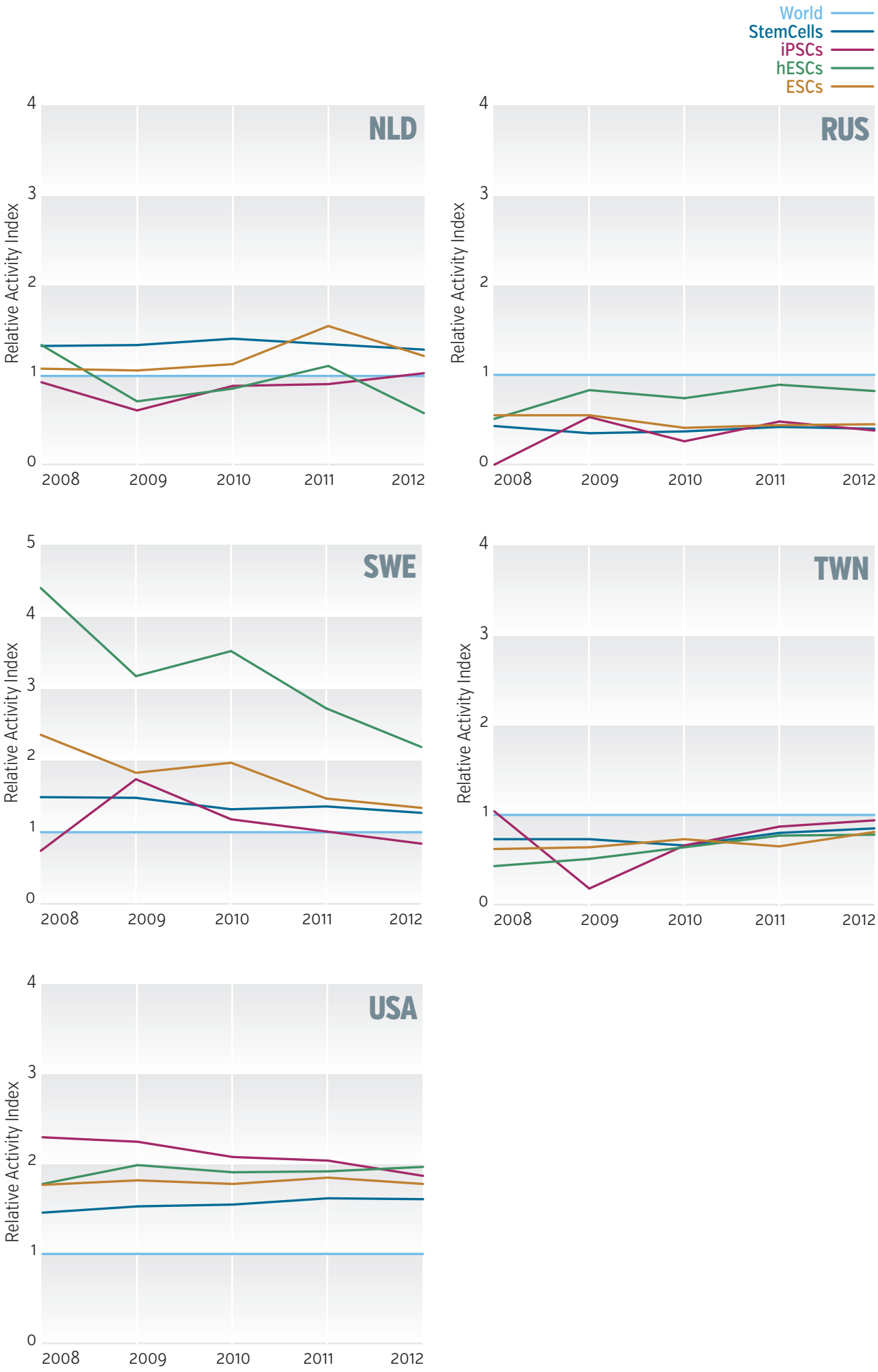
4
2008
2009
2010
2011
2012


World
StemCells
iPSCs
hESCs
ESCs
NLD
RUS
SWE
TWN
USA
Relative Activity Index
0
1
2
3
4
5
2008
2009
2010
2011
2012

Appendix G – Top Institutions

The charts below identify the 30 institutions which produced the highest volume of stem cell, ES and iPS cell publications in the 2008-2012 period. The x-axis represents the publication volume and the y-axis represents the FWCI of those publications. These are the same institutions represented in the collaboration network charts in Appendix H. Source: Scopus

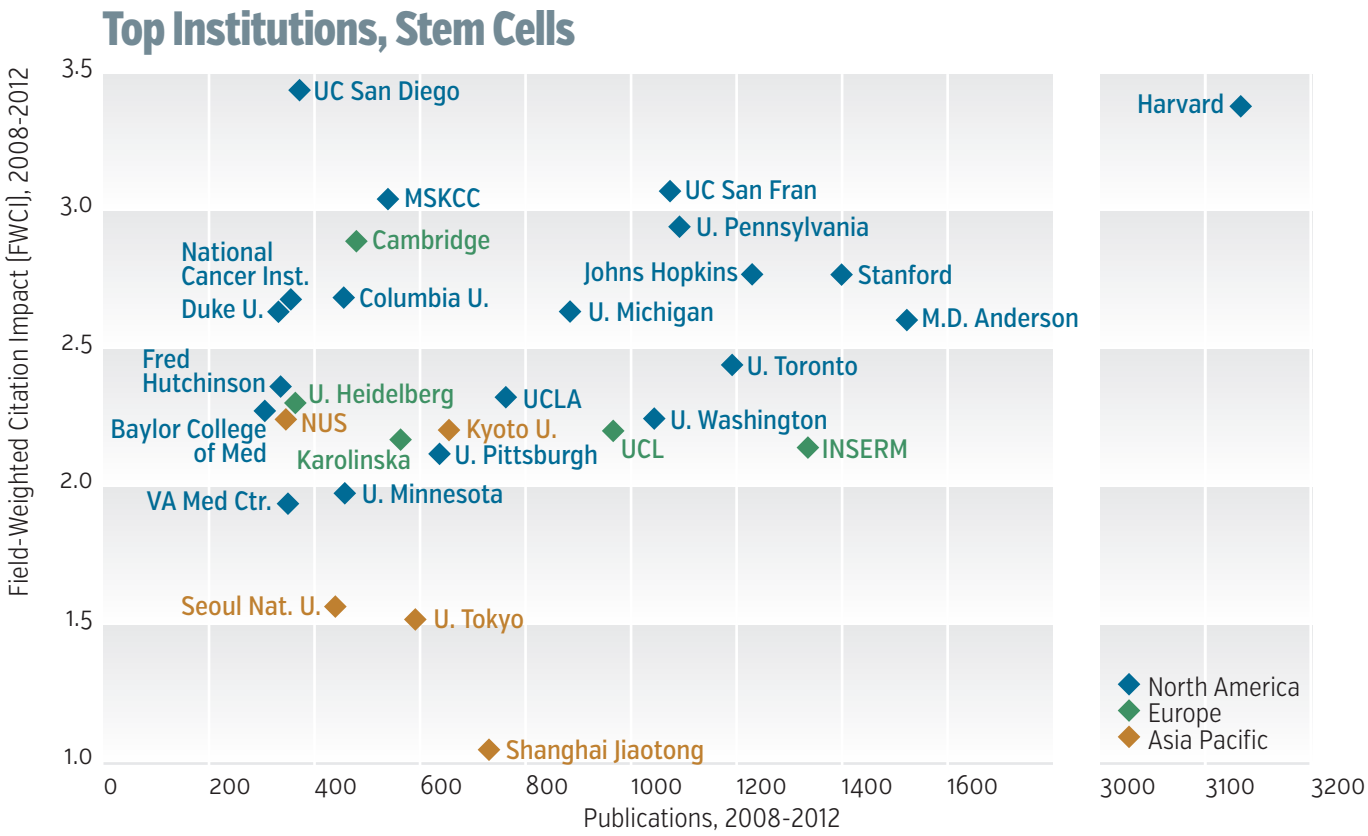


Figure G1: *The top 30 institutions based on number of stem cells publications 2008-2012. The x-axis represents the number of stem cells publications 2008-2012 and the y-axis represents the citation impact of those publications.*

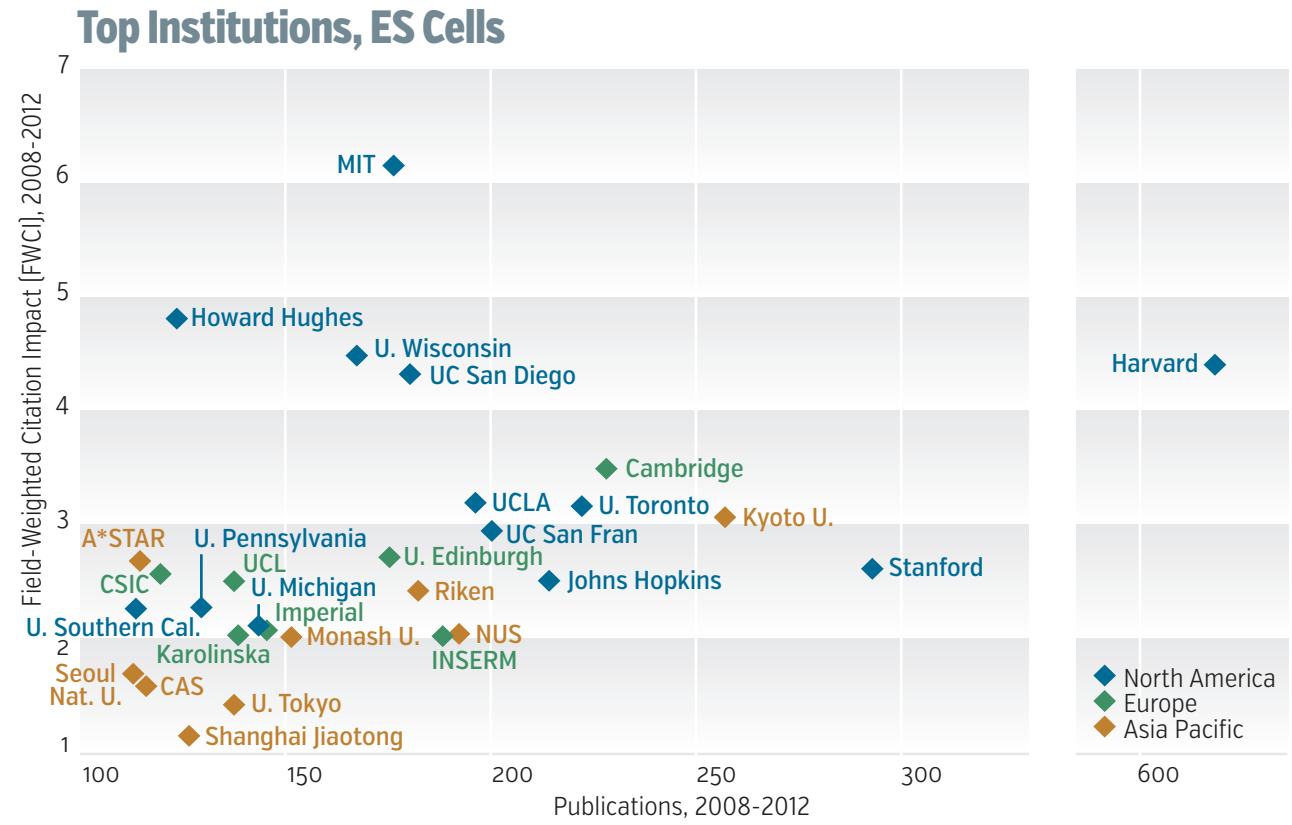


Figure G2: *The top 30 institutions based on number of ES cells publications 2008-2012. The x-axis represents the number of ES cells publications 2008-2012 and the y-axis represents the citation impact of those publications.*

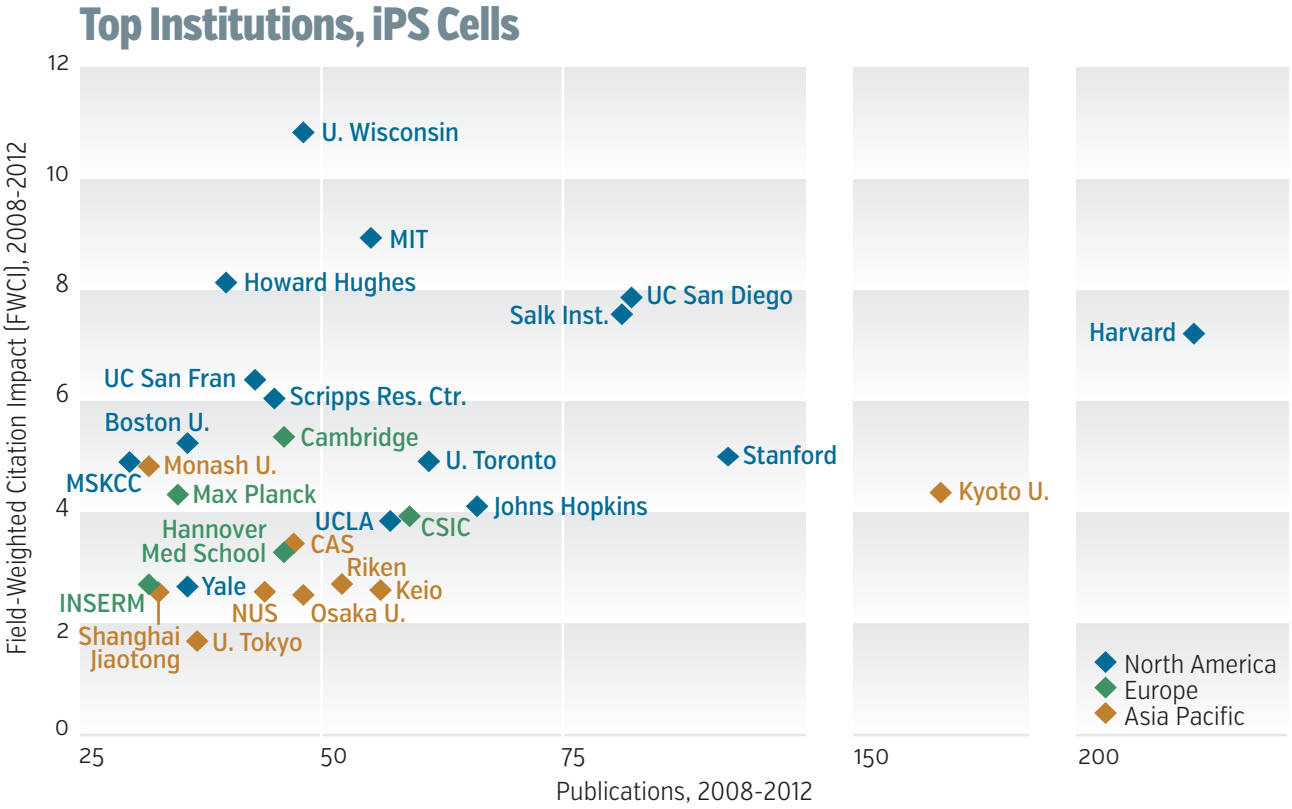
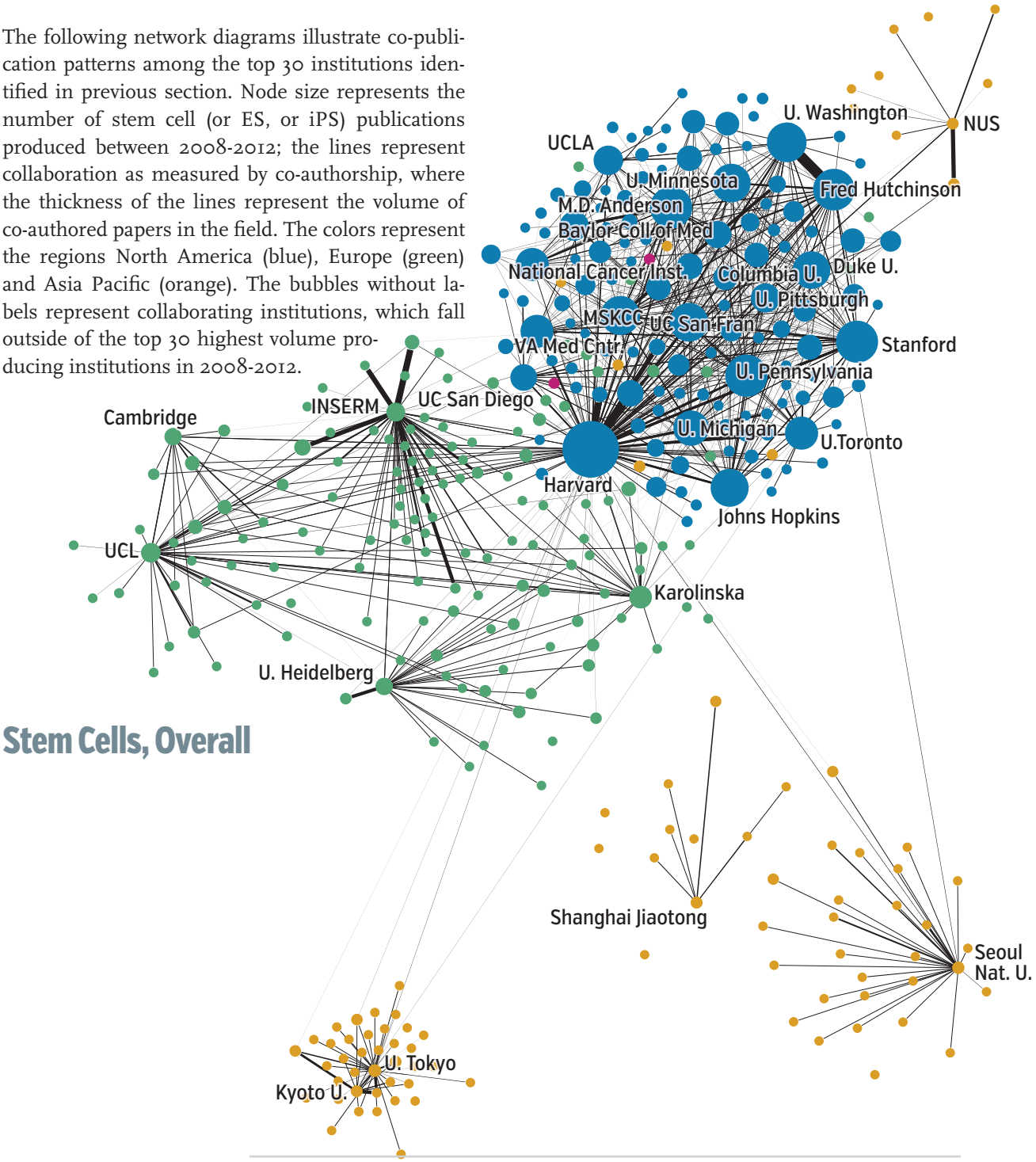


Figure G3: *The top 30 institutions based on number of iPS cells publications 2008-2012. The x-axis represents the number of iPS cells publications 2008-2012 and the y-axis represents the citation impact of those publications.*

Appendix H – Institutional Collaboration Networks

The following network diagrams illustrate co-publication patterns among the top 30 institutions identified in previous section. Node size represents the number of stem cell (or ES, or iPS) publications produced between 2008-2012; the lines represent collaboration as measured by co-authorship, where the thickness of the lines represent the volume of co-authored papers in the field. The colors represent the regions North America (blue), Europe (green) and Asia Pacific (orange). The bubbles without labels represent collaborating institutions, which fall outside of the top 30 highest volume producing institutions in 2008-2012.



Stem Cells, Overall

Figure H1: *The collaboration networks of the 30 most active institutions with more than 10 co-authored publications in stem cell research during the 2008-2012 period. Node size represents volume of stem cell publications (2008-2012), the thickness of the lines represents the volume of co-publications between institutions (2008-2012) and the color represents the region.* SOURCE: *Scopus*

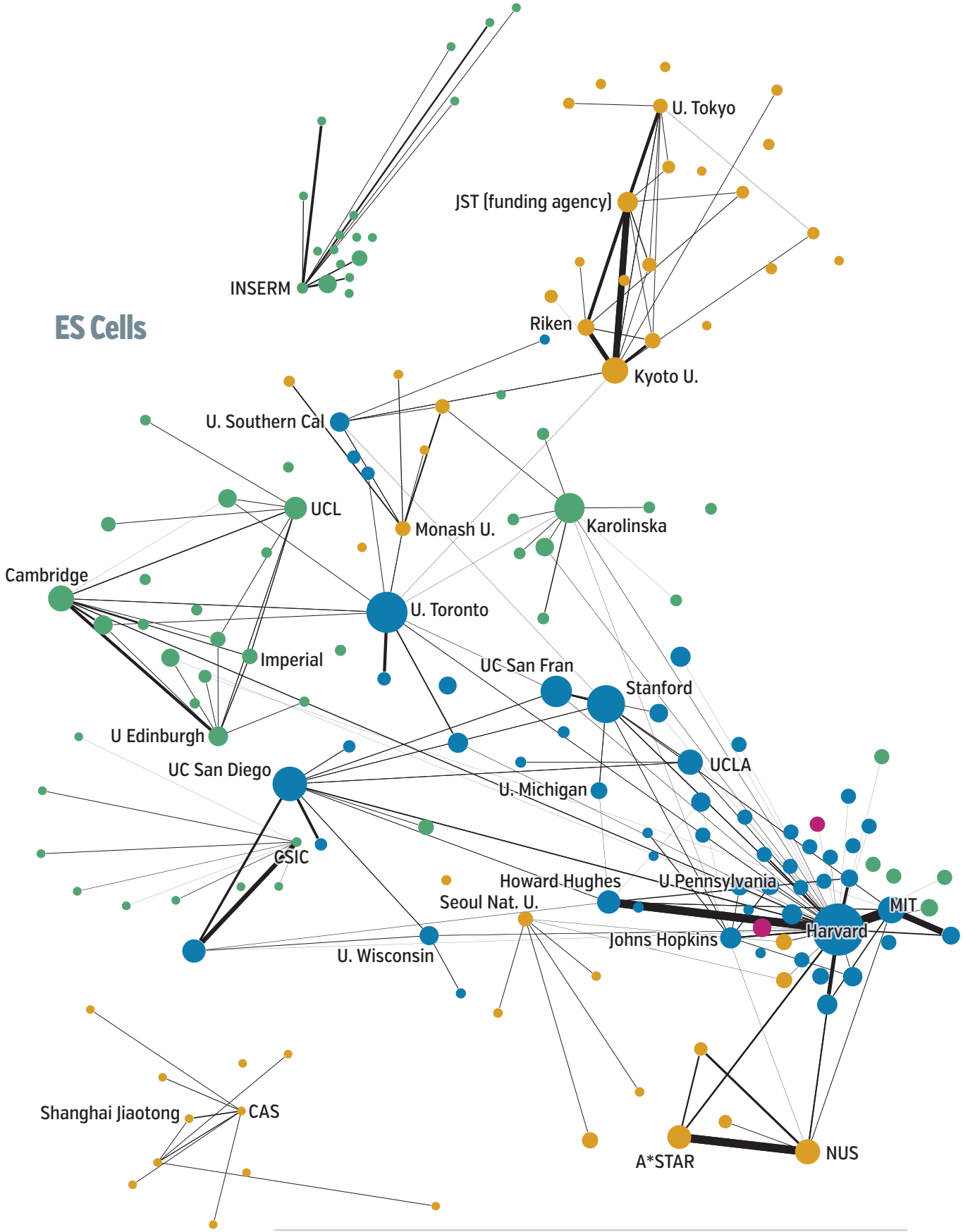


Figure H2: *The collaboration networks of the 30 most active institutions with more than 10 co-authored publications in embryonic stem cell research during the 2008-2012 period. Node size represents volume of embryonic stem cell publications (2008-2012), the thickness of the lines represents the volume of co-publications between institutions (2008-2012) and the color represents the region.* SOURCE: *Scopus*

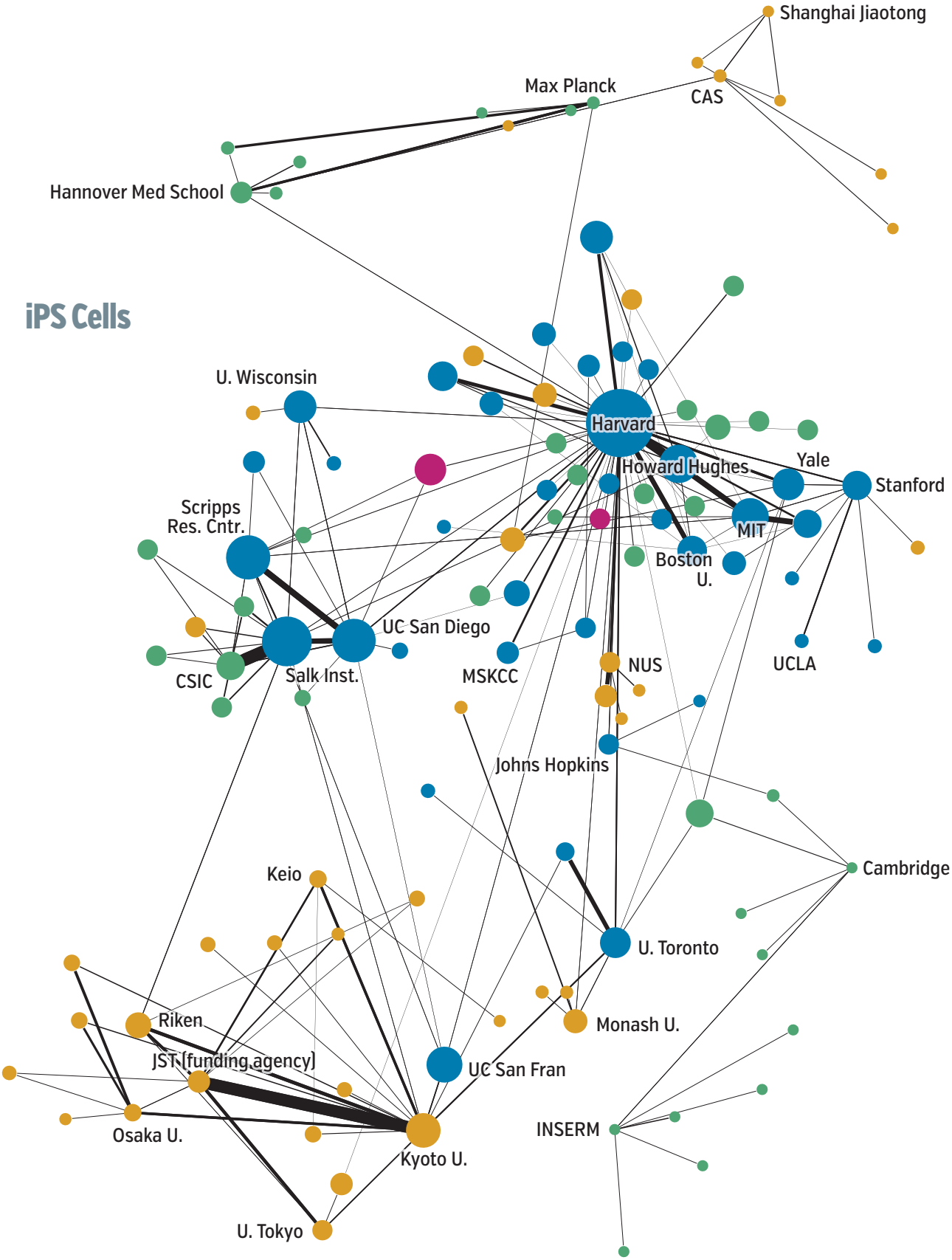


Figure H3: *The collaboration networks of the 30 most active institutions with more than 2 co-authored publications in embryonic stem cell research during the 2008-2012 period. Node size represents volume of embryonic stem cell publications (2008-2012), the thickness of the lines represents the volume of co-publications between institutions (2008-2012) and the color represents the region.* SOURCE: *Scopus*

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Following a PhD in cancer cell biology, Jan joined the Scottish Initiative for Biotechnology Education (SIBE), managing collaborative educational and dialogic projects, becoming deputy director in 2004. During this time, she edited and co-authored a publication for teachers "Stem Cells: Science and Ethics". Jan is currently working with the EC-funded stem cell research consortia OptiStem and EuroStemCell. Her engagement work focuses on stem cell clinical trials, fostering debate about policy and open access to stem cell research.

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Emma Kemp has developed public engagement and information programmes for three European stem cell research consortia over the past five years. She writes and edits extensively for the website eurostemcell.org and is author of several teaching tools and classroom activities on stem cell research. Her previous experience includes development and delivery of educational programmes on specialist topics from climate change to citizenship, for the corporate and public sectors. She began her career editing for the journals *Angewandte Chemie* and *ChemBioChem*.

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Kate manages online communications, including a busy multilingual website, for EuroStemCell –– a pan-European EC-funded project that aims to help European citizens make sense of stem cells. Her 9 years' experience communicating stem cell science includes developing and implementing other public engagement programmes and producing the award winning short film *A Stem Cell Story*. She has also worked in the non-profit sector, managing high-profile engagement campaigns such as Scottish Adult Learners' Week, and in the film industry.

Professor Clare Blackburn

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Clare Blackburn's research aims to develop improved stem-cell-based interventions for boosting function of a key organ of the immune system, the thymus. Prof. Blackburn also has a strong interest in public engagement, and leads the pan-European EC-funded project EuroStemCell, which brings together more than 90 European stem cell and regenerative medicine research labs into a coordinated effort to engage with European publics.

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Glossary

autologous cell therapy: A therapy using cells derived from a patient's own body. This often involves the extraction of cells and an 'ex vivo' (outside the body) step of growing and multiplying them before transplanting them back into the patient.

cancer cell of origin: Precancerous cell that gives rise to a cancer stem cell. May be a mutated stem cell, or a progenitor cell that has acquired self-renewal capacity through mutation.

cancer-initiating cell: Cell that can produce a new cancer upon transplantation. A key property of a cancer stem cell.

cell culture: The growth of cells in a laboratory dish for experimental research. The cells are grown in a solution, or medium, that contains nutrients and growth factors. Different factors can be added to the culture medium to initiate changes in cell behavior.

cell line: A population of cells all carrying the same genes, grown in the laboratory through many cycles of growth and division over many generations of cells.

clinical translation: The process of turning scientific knowledge into approved medical treatments, through a series of carefully controlled research and approval steps.

clinical trial: A research study in human subjects to answer specific questions about vaccines or new therapies or new ways of using known treatments. Clinical trials are used to determine whether new drugs or treatments are both safe and effective. Trials take place in four phases: Phase I tests a new drug or treatment in a small group; Phase II expands the study to a larger group of people; Phase III expands the study to an even larger group of people; and Phase IV takes place after the drug or treatment has been licensed and marketed.

differentiation: The process by which cells become specialized to perform particular tasks.

embryonic stem cell: Pluripotent stem-cell lines derived from early embryos before formation of the tissue germ layers.

epiblast stem cell: A mouse pluripotent stem cell derived from a slightly later stage of embryonic development than the mouse embryonic stem cell; the epiblast stem cell more closely resembles the human ES cell.

genotype: The genetic make-up of a cell or organism.

hematopoietic stem cells: Stem cells that give rise to all the blood cell types.

hepatocyte: The functional cell type of the liver. Hepatocytes make enzymes for detoxifying metabolic waste, synthesise proteins for the blood plasma, produce bile and help control blood sugar levels within narrow limits.

induced pluripotent stem (iPS) cells: A type of pluripotent stem cell derived from a non-pluripotent cell, typically an adult somatic cell, by manipulating expression of certain genes.

pluripotent: Able to form all the body's cell lineages, including germ cells, and some or even all extraembryonic cell types. *Example: embryonic stem cells.*

regenerative medicine: Reconstruction of diseased or injured tissue by activation of resident cells or by cell transplantation.

reproductive cloning: The process of producing a genetically identical copy of a whole organism.

reprogramming: Increase in potency. Occurs naturally in regenerative organisms (dedifferentiation). Induced experimentally in mammalian cells by nuclear transfer, cell fusion, genetic manipulation or in vitro culture.

stem cell: A cell that can continuously produce unaltered daughters and also has the ability to produce daughter cells that have different, more restricted properties.

tissue stem cell: Stem cell derived from, or resident in, a fetal or adult tissue, with potency limited to cells of that tissue. These cells sustain turnover and repair throughout life in some tissues. *Synonyms: adult stem cell.*

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