Stem cell research: Trends in and perspectives on the evolving international landscape

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Stem cell research is an exciting yet complex and controversial science. The field holds the potential to revolutionize the way human diseases are treated, and many nations have therefore invested heavily in stem cell research and its applications. However, human stem cell research is also controversial with many ethical and regulatory questions that impact a nation’s policies.

Elsevier recently partnered with EuroStemCell and Kyoto University’s Institute for Integrated Cell-Material Sciences (iCeMS) to study publication trends in stem cell research. The resulting paper was published online to coincide with the World Stem Cell Summit in San Diego on December 6th, 2013. The study provides an overview of the stem cell research field as a whole, with particular focus on pluripotent stem cells.

Pluripotent stem cells are of particular interest because they are undifferentiated cells, which have the potential to differentiate into virtually any cell type in the body (1; see Figure 1). This property opens the door to clinical applications such as cell and organ replacement (2) and may accelerate drug discovery, drug screening and toxicological assessment. There are different kinds of pluripotent stem cells: embryonic stem cells (ES) are sourced from a blastocyst (an early embryo), and when sourced from human blastocysts are called human embryonic stem cells (hES), while induced pluripotent stem cells (iPS) - which were only recently discovered in 2006 by Shinya Yamanaka and colleagues at Kyoto University - are sourced from body cells, and then genetically reprogrammed to become pluripotent. For more detailed information on stem cells, please refer to our study (3).

The document sets underlying our analyses were created using keyword searches which are provided in the methodology section of our study, and were limited to articles, reviews and conference proceedings. They include primary research articles as well as other publication types, such as reviews, papers on policy and regulation, ethical considerations, etcetera. In this article we briefly review some key findings of our study, and expand by having a closer look at the clinical theme ‘drug development’ using Scival. We will also examine the publication trends of China and the United States specifically, to see whether we can observe the impact of country level policy decisions in the publication data.

### Three Key Facts About Stem Cells

1. **The defining characteristic of a stem cell is that it can self-renew or differentiate.**
2. **Stem cells enable the body to grow, repair and renew.**
3. **There are three types of stem cells:**

#### Tissue Stem Cells

- In the fetus, baby and throughout life.
- Found throughout the body, each type gives rise to at least one type of more specialized cell.
- For example, blood stem cells are found in the bone marrow.

#### Embryonic Stem Cells

- A blastocyst
- The cells inside are the inner cell mass.
- These cells, then grown in the lab, are called embryonic stem cells.
- Varying factors are added to differentiate the ES cells into any cell type.

#### Induced Pluripotent Stem Cells (iPS)

- Cell from the body
- Genetically reprogrammed
- Pluripotent cell (‘embryonic-like’)
- iPS cells are grown in the lab
- Varying factors are added to differentiate the iPS cells into any cell type.

Embryonic stem cells and iPS cells are pluripotent; they can generate all the specialized cells of the body.

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Figure 1: Stem Cell types and characteristics.
Publication output, growth and field-weighted citation impact

Our study found that the overall corpus of stem cell related papers shows a relatively fast growth rate and citation impact.

Stem cell publications show a Compound Annual Growth Rate (CAGR) of 7.0% from 2008 to 2012, which is more than twice as great as the 2.9% CAGR for global publication output on all topics in the same period. Stem cell publications have a Field-Weighted Citation Impact (FWCI) of approximately 1.5 throughout the 2008-2012 period, which indicates that stem cell papers, on average, received 50% more citations than all other papers published in related disciplines in that period. Stem cells and its subtypes are custom subject areas that were created using keyword searches. Each document set therefore includes publications belonging to various disciplines of the All Science Journal Classification.

Looking at specific types of stem cell research, the emergence of the iPS cell field (first publication in 2006) stands out. iPS cell papers show explosive growth and the highest impact of all types of stem cell research papers. The FWCI of the iPS field was extremely high just after its discovery, as might be expected of an emerging field. The FWCI calculated at the beginning of the period was based on relatively low publication counts, which are more subject to outlier effects than later data-points, which are based on larger publication volumes. The decline in FWCI (see Figure 3) should not be interpreted as a decrease in quality of research, rather it should be seen as a natural and expected decline as publication volume increases. Nonetheless, the 3,080 iPS cell papers published between 2008-2012 have a FWCI of 2.93, which is almost 3 times world level for all papers published in related disciplines. That is strong evidence to support the sustained recognition and importance of the emerging field of iPS cell research.

We observed that hES cell publication output peaked in 2010, and while ES cell research overall shows a high publication volume, it is predominantly represented by non-human ES cell research (see Figure 2). The FWCI for ES cell and hES cell publications also remained relatively stable during the same period, at around 1.8 times the world average for ES cell publications, and over two times world average for hES cell publications.

Clinical themes: Regenerative Medicine and Drug Development

Our study also examined the extent to which stem cell publications are aligned with the societal goals of developing new treatments for diseases, by analyzing the publications for use of keywords related to two themes: regenerative medicine and drug development. The results show that more than half of all stem cell publications do not use keywords related to either theme (see Figure 4). Such publications may be related to basic research which addresses the fundamental biology of stem cells. These specific themes may also not be relevant to many clinical or translational publications, e.g., those related to hematopoietic stem cell transplantation and cancer (translational research is scientific research that helps to make findings from basic science useful for practical applications that enhance human health and well-being). It should also be noted that the search used 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.
It is not surprising to see that regenerative medicine is significantly represented within each type of stem cell research. Alongside positive developments in stem cell biology, regenerative medicine has enabled the development of new biotechnologies that promote self-repair and regeneration, such as the construction of new tissues to improve or restore the function of injured or destroyed tissues and organs (4).

Drug development is represented by a much smaller share of each type of stem cell research. The fact that many more iPS cell papers were related to drug development (11%) compared to ES cells (4%) and stem cells overall (2%) stands out. This may reflect the particular potential that iPS cells hold for the development of disease models, personalized medicine, and drug toxicity testing. iPS cells can be derived from selected living individuals, including those with inherited diseases and their unaffected relatives, which could allow the screening process to account for genetic differences in response to potential new drugs.

Exploring Drug Development using SciVal
To expand on the analysis done in the study, we used the new generation of SciVal to examine stem cell papers related to drug development by setting up the relevant research fields using the same keywords applied in our initial study. The results are presented in Figure 5. The number of iPS cell papers related to drug development has clearly grown fast since the first iPS cell paper was published in 2006, as it has since surpassed the numbers of ES and hES cell papers related to drug development.
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. 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. This has not been the case, as the stem cell field continues to rely both on ES and iPS cell research to progress the understanding of pluripotency and potential applications (5). Furthermore, iPS cell research is not free of ethical considerations in terms of how they may be used as well as the question of tissue ownership. Looking at the data, we see continued publications in ES and hES, but do observe that the global volume of iPS publications has surpassed the volume of hES cell publications in 2010 (see Figure 6). There also seems to be an overall slowing in growth, and even a recent decrease in world ES and hES cell publication output. These findings should be interpreted with caution, keeping in mind that our datasets represent publications which use keywords related to stem cell research, and not solely “stem cell research papers”. 

Stem Cells in China
We also examined the publication trends of China and the United States specifically, to see whether we can observe the impact of country level policy decisions in the publication data.

China is a country which shows steady growth in stem cell research supported by its major funding initiatives. In 2001, the Chinese Ministry of Science and Technology (MOST) launched two independent stem cell programs followed by a number of funding initiatives intended to further promote stem cell research, applications and public awareness. At the same time, China has been working to strengthen ethical guidelines and regulations. In total, the national government’s stem cell funding commitment is estimated at more than 3 billion RMB (close to 500 million USD) for the 5 year period from 2012 to 2016. Confronted with the healthcare needs of a rapidly aging population of nearly 1.4 billion, the impetus behind much stem cell research, so far, has understandably been clinical translation and development (6).
Looking at the publication data from our study, we see that stem cell publications have grown from representing 0.2% of China’s total publication output in 2001 to a peak of 0.82% in 2008, followed by a marginal decline to 0.76% by 2012 (see Figure 7). As also observed globally, China’s iPS cell publication output surpassed hES cell publication output in 2010, after which hES cell output shows fluctuation.

Science policy and Human Embryonic Stem Cell (hES) research in the USA

The United States is an interesting case study because, as reported in our study, they are the world leader in stem cell research considering that they produce the highest absolute publication volume, as well as high relative activity levels, indicating a high focus on stem cell research, and show high field-weighted citation impact. Yet, they have had to grapple with the practical and ethical dilemmas that are inherent in this field, and changing views of different administrations, as governments changed.

The result is a series of policy changes, some of which limited federal funding for hES cell research, while others loosened the limitations. In Figure 8 we map such policies along with the corresponding publication output (relative to total country output). Despite the restrictive policies between 2001 and 2009, the United States show steady output growth, which has been supported through individual, state and industry funding as well as donations. We do observe changes in hES cell publication output that coincide with changes in regulation. While such changes in publication output are probably not best explained using a one factor model, these findings are hardly surprising, as we expect science policy to greatly impact scientific activity. Such an analysis can provide insight into the degree to which science policy has indeed affected publication output.

Conclusion

In recent years, stem cell research has grown remarkably, showing a growth rate 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 showed that both ES and hES fields have grown more slowly than the stem cell field overall. In contrast, iPS cell publications have shown explosive growth, as would be expected of a new and promising field of research, and iPS cell publication volumes surpassed that of hES cell publications in 2010. However, both cell types continue to be highly active areas.

Stem cell research has attracted considerable attention within the scientific community: stem cell publications overall are cited 50% more than all other publications in related disciplines, while ES cell publications are cited twice the world rate, and iPS cell publications nearly three times the world rate. 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 clinical promise, approximately half of all stem cell publications are associated with regenerative medicine or drug development, a trend that is particularly pronounced in iPS cell research.

Stem cell research is developing fast, with some experimental pluripotent stem cell treatments already in clinical trials. Active debates are underway to adapt regulatory frameworks to address the specific challenges of developing, standardizing, and distributing cell-based therapies, while advances in basic research continue to provide a fuller understanding of how stem cells can be safely and effectively used. Cell replacement or transplantation therapies are not the only application of stem cell research: already the first steps are being taken towards use of cells derived from pluripotent stem cells, in drug discovery and testing. It is with great interest and anticipation that we watch the further development of this exciting field of science.

References: