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Why Regenerative Stem Cell Medicine Progresses Slower Than Expected

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Stem cell research has been acclaimed to revolutionize the future of medicine, and to offer new treatments for previously incurable diseases. Despite years of research, however, the therapeutic potential of stem cell research has not yet been fully realized. By June 2014, the US Food and Drug Administration had approved only five stem cell-based medicinal products, all of which cord blood derived hematopoietic stem cell products for the cure of blood and immunological diseases. Anticipated treatments for cancer, neurodegenerative disorders, gastroenterological, myocardial, and other diseases are still far from routine applications. What are the reasons for the slow progress in the stem cell field, and the mismatch between public expectations and actual achievements? This article provides eight answers to these questions. J. Cell. Biochem. 115: 2073–2076, 2014.

THE CREATION OF UNREALISTIC EXPECTATIONS

The derivation of the first human embryonic stem cell lines in 1998, and more recently the creation of iPS cells, have led to great enthusiasm about the therapeutic potential of stem cells and a high level of publicity. This enthusiasm has repeatedly turned into hype and given rise to unrealistic expectations, in particular with regard to the time at which new therapies will be available [Knowles, 2010]. These exaggerated expectations can be traced back to several causes: The press trying to sell its products. Scientists who make inflated claims in order to raise funding. Companies that are under pressure to generate shareholder value. Politicians, because stem cells hold the promise of scientific progress and economic profit. And finally, the patients and patient groups that correspond to these claims with huge hopes, exerting pressure on scientists to move toward clinical applications more rapidly [Wilson, 2009]. The overselling of the promise and accessibility of stem cell treatments, however, stands in sharp contrast with the regulatory, financial, organizational, and scientific challenges of the development of stem cell-based therapeutic approaches.

REGULATORY STRINGENCY

Regulatory frameworks for the clinical application of stem cell products are in most countries still evolving, often along with the first applications. In the USA, for instance, at the time Geron Corporation filed its investigational new drug application (IND) for the world's first hESC-based medicinal product, the whitepapers for the regulation of stem cell research were just generated. According to Hans Keirstead, who had developed the product in collaboration with Geron, this emergent situation had resulted in significant delays and financial losses for the company. Instead of setting out clear-cut review criteria from the start, the FDA initiated a long-drawn-out negotiation process that included the development of new assessment parameters in the course of the application process. This resulted not only in demands for additional preclinical studies, but at one point also in a request to repeat an already completed preclinical study along re-defined regulatory specifications [Keirstead, 2012]. Regulatory requirements, as pointed out by Michael Rawlins, the former chairman of the UK National Institute for Clinical Health and Safety (NICE), have over the last few years become increasingly stringent [Rawlins, 2010]. This is well reflected in the stem cell field, where the development of regulation was accompanied by public controversies, scientific uncertainties, and fears of severe adverse effects, such as undesired cell migration and tumorigenicity. The high level of caution that underlies the regulation of stem cell-based therapeutic approaches, at least in the context of the USA and Europe, results also from fears of bad press, litigations, and negative public reactions, as happened after the death of 18-year-old

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Jesse Gelsinger in 1999 in the gene therapy field [Wilson, 2009]. But the slow speed of regulatory approval procedures is also caused by organizational problems within drug regulatory agencies. According to Andrew Eschenbach, the former commissioner of the US FDA, the lack of financial resources, and a shortage of adequately trained staff within the FDA has stalled the realization of stem cell-based clinical applications and other breakthrough technologies [Gaffney, 2012].

HIGH COSTS, LIMITED FUNDING

The increase of regulatory requirements comes along with added costs. In average, the duration of the development of a new medicine from initial preclinical research to market approval is now 10 years, and costs 1.2 billion US dollars [Collier, 2009]. In case of the Geron trial, the preclinical development of its hESC program cost about 200 million US dollar, and was carried out over nearly a decade [Keirstead, 2012]. As stated by Edward Wirth, the former chief scientist of the hESC program at Geron, to test biodistribution, dosing, delivery, toxicity, tumorigenicity, and immune rejection the company conducted 24 preclinical studies before an IND application could be filed at the FDA in March 2008. These studies included in total 1,977 rodents. The IND application that the corporation submitted was 21,000 pages long, with more than 90% consisting of data from the preclinical studies. According to Wirth, this was the longest application the FDA had received at that time [Wirth, 2010]. After submission the FDA put the IND on a halt two times, for six and 13 months respectively, with the request to carry out additional preclinical studies. For academic investigators and small-to-mid-size companies these high costs are difficult to bear, and carry the risk of financial unsustainability. Geron Corporation, for instance, had to halt its first hESC trial for financial reasons in 2011, only months after obtaining regulatory clearance by the FDA [Brennan, 2011].

Clinical stem cell research takes place in a highly challenging funding environment. In high-income countries such as the USA, Japan, Hong Kong, Singapore, and many European societies, the obligatory conduct of Phase I to III clinical trials and subsequent product release costs sum up to hundreds of millions of US dollars. A large part of these expenses is usually covered by the pharmaceutical industry, and sometimes through venture capital. In the stem cell area, however, the industry has hesitated to invest for many years, with companies waiting for further demonstrations of success and potential applications [Doudement and Uppal, 2014]. Moreover, in the aftermath of the financial crisis, the venture capital field was turned on its head. The slow pace of stem cell research, and the uncertain prospect of financial returns are too risky for most venture capitalists to invest [Keirstead, 2012]. Public funding is highly limited. While money from public sources is available, it is usually insufficient to cover the long path from preclinical development to the market, without assistance from the private sector or charitable organizations. At present, the clinical research of many start-up biotech companies and academia-initiated clinical infrastructures in the stem cell field is funded primarily through charitable organizations, and the donations of high net worth individuals (ibid). In sum, safety and scientific rigor come at a price. The imposing of greater regulatory demands on investigators and companies poses new challenges to attract funding, and delimits chances for clinical translation and marketization.

THE HIGH FAILURE RATE OF CLINICAL TRIALS

Another reason that accounts for the slow progress rate of stem cell research is the high failure rate of clinical trials. Between 2003 and 2011 only 10.4 percent of all candidate products that the FDA had approved for Phase I clinical trials were admitted to the market [Hay et al., 2014]. Most of the product failures in Phase I to III trials are because the safety and efficacy of a tested product cannot be reliably proven. But there are other reasons too. These range from the inability to mobilize adequate funding, to flaws in the clinical trial design, and failures in clinical trial management [Ledford, 2011]. In addition to the premature ending of the Geron trial, various failures of stem cell trial have been reported in recent years. In 2012, for instance, a phase II trial of the US biotech company Osiris for type I diabetes produced disappointing results [Bersenev, 2012]. In earlier trials, the company's stem cell product Prochymal was also proven to be ineffective in clinical trials for graft-versus-host-disease, Crohn's disease, heart attack, and knee cartilage repair [Feuerstein 2012]. Alexey Bersenev, a stem cell researcher from the University of Pennsylvania, has reported of failed stem cell trials in 2013 in five medical areas: cardiac repair, chronic ischemic cardio-myopathy, diabetes, stroke, and critical limb ischemia [Bersenev, 2013]. These failures are a reminder that much of the therapeutic potential of stem cell therapies that was reported in the press, was based on promissory expectations, and not on hard clinical evidence.

THE CHALLENGE OF PATIENT RECRUITMENT

Another factor that accounts for delays or discontinuation of clinical trials is the inability to recruit sufficient numbers of patients. In the USA, for instance, 80% of clinical trials fail to meet their initial enrolment goal [Earls, 2012]. This challenge is also reflected in the stem cell field. In the Geron hESC trial, for example, it took 18 months to enroll five patients, over multiple study sites in the USA [Keirstead, 2012]. The China Spinal Cord Injury Network, a transcontinental research organization that is active in Hong Kong, mainland China, Taiwan and the USA, encountered similar problems. A Phase I/II study for chronic spinal cord injury with umbilical cord blood mononuclear cells could not be completed in Hong Kong, due to the inability to recruit sufficient patients. The study was then conducted in mainland China, where recruitment was fast and more easy [Rosemann, 2013]. Wise Young, the Network's director mentioned, in this respect, that the lack of volunteers is a severe problem for stem cell research, especially for diseases with a relatively low prevalence rate such as spinal cord injury. According to Young, the only chance to overcome this problem is the creation of multi-sited clinical studies in multiple countries [Young, 2012].[1]

[1]Blog contribution of Wise Young on *CareCure*, January 21, 2012. URL: http://sci.rutgers.edu/forum/showthread.php?p=1480260 (last accessed August 26, 2012).

THE NEED TO BUILD NEW CLINICAL INFRASTRUCTURES

The absence of established clinical trials infrastructures is another factor that has delayed progress in stem cell research. In more established fields of medicine well functioning research platforms have emerged over decades; these allow for effective and rapid forms of clinical testing [Keating and Cambrosio, 2012]. In the stem cell field, however, the development of clinical infrastructures is often still in initial stages. New alliances between researchers, hospitals, universities, corporations and government institutions have to be formed, and unified coordination structures must be established. These processes are complicated by regulatory demands for good manufacturing practice (GMP) labs and the development of specialized surgical and injection procedures, which requires cooperation between experts from highly divergent disciplines and backgrounds. The formation of such standardized multi-center clinical trial infrastructures is time and labor intensive, and involves significant costs. Moreover, it includes tasks and responsibilities for which medical researchers are not trained, and that can only be learned through experience [Keirstead, 2008]. A substantial amount of energy is necessary to build such infrastructures, long before actual clinical research can be conducted.

REGULATORY DIVERSITY ACROSS COUNTRIES

In contrast to established fields of drug research, that involve the clinical testing of compounds and small molecules, no internationally binding standards or harmonized regulatory framework are yet in place for clinical stem cell interventions. Widely divergent regulatory conditions exist across countries. This diverse regulatory situation necessitates far-reaching forms of scientific self-governance and capacity building. The goal is to create compliance with the demands of drug regulatory authorities in multiple countries. These efforts involve changes of clinical research practices, inter-institutional standardization, and the implementation of an effective control and monitoring structure, so as to safeguard standardized execution of research protocols. For academic research networks or small-to-mid size biotech companies these tasks can be an important obstacle. They require long-drawn-out periods of time, and additional costs. In countries where regulations for clinical stem cell research are currently still emerging, such as in China or India, delays may also be caused through unclear regulatory procedures, or even the temporary refusal to accept new IND applications. In the context of a regulatory reform that was initiated by the China Food and Drug Administration [CFDA, 2012] in 2012, for example, the agency refused incoming IND applications for stem cell-based medicinal approaches for a period of several months. In this period, researchers had either to wait, or to conduct their trials in another country.

PUBLIC CONTROVERSIES

The impact of public controversies is another factor that has slowed developments in stem cell medicine. It is now widely acknowledged, that the ban on federal funding for hESC research during George Bush's term as President in the United States, has stifled the stem cell field in the USA. The ban, which was linked to public discontent on the use of human embryos, had not only resulted in restrictions of public funding, but also in reservations to invest in the private sector [Arrow, 2008]. But public concerns have also been expressed with regard to the safety of clinical stem cell interventions. In 2009, for example, PLOS Medicine reported of a 9-year-old boy with ataxia telangiectasia who was treated with human fetal neural stem cells in a hospital in Moscow. Four years after the first treatment, the boy was diagnosed with a multifocal brain tumor. Researchers showed, that the tumor was of non-host origin; derived from the transplanted neural stem cells [Amariglio et al., 2009]. On July 8, 2014 the new scientist disclosed the case of a woman who received an autologous tissue transplant containing olfactory ensheathing cells in the context of a clinical trial in Portugal in 2006. These cells were implanted in the patient's spine, in the hope of repair of nerve damage. In 2013, due to worsening pain, the woman underwent spinal surgery again. 'The surgeons removed a 3-cm-long growth, which was found to be mainly nasal tissue, as well as bits of bone and tiny nerve branches that had not connected with the spinal nerves' [Wilson, 2014]. Even though the removed tumor was not cancerous, such headlines reinforce public concerns with stem cell research, and give rise to more prudent forms of regulations. These reports of severe adverse effects may, furthermore, increase reservations among patients to take part in stem cell-based trials, and have a constraining effect on public funding, private investments and stock prices.

CONCLUSIONS

The field of stem cell research has been characterized by remarkable developments in recent years. Stem cells are now used for the modeling of diseases, and provide an increasing understanding of disease mechanisms. Also, there has been ongoing progress in the development of new treatments, which is epitomized by the launch of the first iPS trial in Japan this year, by market approval of first stem cell products and by a growing number of stem cell trials worldwide. All in all, though, the realization of the therapeutic potential of stem cell research has been slower than expected, and slower than the promissory rhetoric of the media make the public believe. This article has provided eight reasons that account for the mismatch between public expectations and actual achievements. It has become clear that the translation of stem cells into therapeutic applications has been slowed down by several roadblocks. These range from high costs, to stringent regulation, to a shortage of funding, to the impact of public controversies, scientific challenges, the need to build new clinical infrastructures, and the challenge of navigating between different regulatory systems. With the reluctance of the industry to invest into the stem cell field, moreover, the gap between academia and industry has widened. While academic researchers have made outstanding achievements, these experts are usually not in the position to translate these inventions into the clinic independently. The investment risks for small-to-mid size biotech companies moreover are high, and the resources of these corporations are limited. Another issue is that, at a global level, access to the financial and infrastructural resources that are required

for the conduct of rigorous Phase I to III trials is highly stratified, and usually restricted to a small group of elite scientists. For many physicians and scientists that are involved in stem cell research, access to these resources remains out of reach [Sleeboom-Faulkner and Patra, 2011]. This is true for many researchers in high-income countries, but even more so for researchers in low-to-mid income countries. Against this background, it is not surprising that scientists and clinicians that do not have access to these resources seek for alternatives. In countries with flexible regulations, or the existence of regulatory loopholes, researchers have increasingly translated stem cell-based approaches outside of the clinical trial format, and exterior to the review of drug regulatory authorities [Sipp 2009]. Professional organizations, such as the International Cellular Medicine Society (ICMS), which consists largely of researchers involved in experimental for-profit interventions, have developed alternative guidelines and standards, as well as institutional accreditation procedures that operate independently of drug regulatory agencies (Rosemann, under review). A global landscape of unproven experimental for profit applications with stem cells has emerged. Whether the therapeutic promise of stem cell research can be realized in this way is of course highly questionable. Due to the conflict of interest between commercial and medical interests among experimental for profit providers of stem cell applications, the absence of systematic methodological protocols, and the lack of reliable forms of peer-review, claims regarding therapeutic efficacy and safety can hardly be verified, and more rigorous forms of clinical testing will be indispensable.

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