Speculative Stem Cell Futures: Some Prospective Commercial Models for Induced Pluripotent Stem (iPS) Cell Based Therapies

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Abstract

Billed for over a decade now as potentially providing revolutionary new treatment protocols in biomedicine, the development of clinical therapies from human embryonic stem (hES) cells has faced significant barriers. The recent discovery of induced pluripotent stem cells (iPS) in 2006 however is widely seen to go part-way towards overcoming at least some of these barriers. But to what extent does the use of iPS cells instead of hES cells increase the potential for the prospective development of clinical products from pluripotent stem cells? In particular, what would a commercial model for iPS cell based therapies look like?

Keywords: stem cells, commercial models, bioeconomies, biopolitics

Introduction

Since human embryonic stem (hES) cells were first isolated in 1998 (Thomson, Itskovitz-Eldor, Shapiro, Waknitz, Swiergiel, Marshall & Jones), there has been significant global interest in the potential therapeutic options that might result from this development. Yet advancements towards therapeutic products have been incremental over the last decade or more, with some limited successes in novel therapeutic development (Advanced Cell Therapeutics, 2009; cf. Geron, 2008; Humphries, 2009). Nevertheless, despite the slow and painstaking nature of progress in the field, interest in the nascent 'stem cell industries' has still been huge. For example, governments around the world have been strategically focusing on the best ways of supporting development in their national stem cell industries as a way of building an economically competitive edge in the growing

global bioeconomies surrounding the stem cell sciences (cf. Gottweis, Salter & Waldby, 2009). Such jostling on behalf of governments for international standing in the stem cell industries is emblematic of the hopes pinned on hES cell research and reflects the expectation that stem cell based therapies will be economically significant in the not-too-distant future.

The strategies adopted by governments in building successful industries in the stem cell economies are based on a range of factors considered necessary for future growth (cf. Salter, Dickins & Cooper, 2006; Salter, Dickins, Cooper & Cardo, 2007; Salter & Harvey, 2008). These factors include: strategic funding from governments for basic scientific research and translational research, investment in skills and knowledge development of a scientific workforce, help for start-up companies to develop the necessary business know-how and engineering processes, intellectual property protection that enables companies to make money in the lengthy development process of a commercial product, and opportunities for networking between investors and researchers. Other features include: a strong regulatory regime in line with international standards, rigorous product standardisation across national boundaries, and business support for financial investment industries that would encourage them to invest in biotechnology. This last is particularly important as biotech traditionally has long lead times to product development that tends to fall outside the favoured 3-5 year time line for venture capitalists (Martin, Coveney, Kraft, Brown, & Bath, 2006). Creative solutions to this bottleneck (sometimes referred to as 'the valley of death') are therefore important to the development of the stem cell industries (cf. Prescott, 2008; Perrin, 2005).

Many of these issues stem from the technological difficulties involved in the development of stem cell based therapies. Obtaining embryos, isolating the stem cells, determining their therapeutic qualities, inducing them to grow in the desired fashion, shape and multitude, transplanting them into patients without adverse reactions, making them generalisable to multiple patients, storing them for future use, and developing a commercial model to make all this viable is an arduous process. The technical difficulties at each stage are significant.

Yet by far the biggest hurdle for the stem cell sciences is the ethically contentious and politically sensitive nature of using stem cells derived from human embryos. Much media, policy and scholarly debate since 1998 has covered the various arguments for and against such usage of embryos. The main sensitivity is that in isolating hES cells for use in research, the embryos they are harvested from are destroyed in the process. In the early years of the 21st century media interest in hES cell science was so pronounced that most people living in the developed world could be said to have some form of opinion on the topic (cf. Critchely, 2007). While debate might rage about how just or informed such community views are, the overall point remains that the idea of embryonic stem cell research and the purported therapies that might result from it had captured the public imagination (cf. Critchely & Turney, 2004; Cormick, 2007; Ganchoff, 2004; Downey & Geransar, 2008).

Against this background the development of first the principle of iPS in animals in 2006 (Takahashi & Yamanaka), followed up a year later with the discovery of human induced pluripotent stem (iPS) cells in 2007 (Yu, Vodyanik, Smuga-Otto, Antosiewicz-Bourget, Frane, Tian, *et al*.,) was heralded as a breakthrough in the future

of stem cell based therapies. In brief, iPS cells are regular body cells that have been induced to revert back to a pluripotent state that is akin to the state of the embryonic stem cells (Takahashi & Yamanaka, 2006; Yu, Vodyanik, Smug-Otto, Antosiewicz-Bourget, Frane, & Tian, 2007), where pluripotency is the key factor for the regenerative capacities of stem cells and thus their exciting medical possibilities. No longer touching on the political sensitivities of using hES cells, iPS cells have revolutionised the possibilities for development of the field. The neat point about iPS cells is that it is thought that this process can occur with any kind of cell harvested from any body (Blow, 2008). Thus, by using non-sensitive cells that are easy to collect, some of the ethical hurdles of developing stem cell based therapies are neatly skipped.

But what will the future of stem cell consumption look like? How will businesses deliver stem cell therapies to clients? In short, what are the prospective commercial models for iPS cell based stem cell science? This paper will examine some possible options for commercial models that might be developed around iPS cells.

How Do iPS Cells Compare?

The core question for the future of the stem cell sciences addressed in this paper is: how do the commercial prospects for induced pluripotent stem (iPS) cells compare to those of hES cells? Assuming that the current technical hurdles for iPS cells can be resolved, some of the benefits of using iPS cells over hES cells would be: the avoidance of ethical concerns about the use of embryos; an avoidance of the intellectual property issues regarding the ownership of biological materials that plague hES cell research; iPS cells could potentially be low-tech and low cost to apply and easy to implement in the clinical setting; there are different standardisation and scale-up issues facing iPS cells in comparison to hES cells; and finally, the use of iPS cells would shift legal responsibility from government regulation of science and individualise patient choice instead. But do these transformations add up to an increased opportunity for commercialisation?

As mentioned previously, iPS cells can be created from any adult cell in the body, therefore rendering the politically sensitive need for embryos obsolete and thus avoiding the ethically contentious destruction of embryos in the process of harvesting stem cells. This is such a core argument in favour of iPS cells that is one of the reasons that the discovery of the capacity to induce pluripotency in adult cells was heralded as such a major breakthrough. The main justification for focusing attention on iPS cells is that they are therefore more politically and ethically favourable than hES cells.

Another key issue that iPS cells would potentially overcome is the question of intellectual property. This is somewhat dependent on the commercial model adopted in the application of iPS cells. For example, if iPS cells were stored en masse for general application, then the usual intellectual property issues would apply; namely, that the owner of the remodelled cells also owns the intellectual property. This however is unlikely, as one of the technological advantages of iPS cells is that it creates the possibility of having a perfect genetic match to the donor of the adult cell that is used for inducing pluripotency, thereby mitigating the need for large batches of the product for multiple consumers. Unless there is a potential danger of recreating the original dam-

age by using cells that are a perfect match to the donor (such as has been a criticism of the use of umbilical cord blood, cf. Waldby, 2006 for further discussion), the 'owner' of the biological material would therefore be the patient that the material is being created for.

Potentially this means that iPS cells would be low-cost and easy to apply, as well as being potentially easy to implement in the clinical setting. Patients would stipulate what materials they required, make a 'donation' of a cell, return at a later date and have the resulting treatment implanted. On the clinical side of this process, harvesting an adult cell in which to induce pluripotency would be unproblematic, but the real technical difficulty would be in the growth of tissues and the complexity of the procedure required for implantation. Depending on the scale of the surgical procedure required by the patient, this might range from a relatively simple quick procedure versus a serious operation.

iPS cells have quite different standardisation and scale-up procedures to embryonic stem cells. If materials are only moving from one patient, to the laboratory and back again, then there is no inter-clinic standardisation required other than those imposed by best practice in science. It is true that different clinics under such a model might develop different reputations for successfulness or otherwise, but the international standardisation required for using materials that circulate through global networks are not as important using iPS cells as they are for embryonic stem cells. This is essentially because ES cells are essentially tradeable commodities, whereas iPS cells are patient specific. Scale-up is also different, because no mass production of materials required for widespread use will occur. All that will be required is the capacity to produce-on-demand the materials needed by the patient. This of course poses other technical challenges (at this stage mostly to do with the actual construction of the required material), but they are not the same challenges as face the prospect of the mass production of hES cells for widespread application to multiple patients.

Furthermore, in some ways a shift to iPS cells would remove government responsibility for regulating the uses of iPS cells. Although governments would still be responsible for regulating the ways that iPS cells are handled and applied to patients, the requirement that they supervise the conduct of science through rigorous legislation that is a significant component of current approaches to stem cell science would be waived. While some form of a clinical licensing system might be retained, the need for governments to regulate the amount of research that can be conducted would be unnecessary. The move away from using ethically and politically sensitive materials in effect makes far less problematic the issue of stem cell derived therapies for the community, thus removing the requirement for 'gate-keeping' by governments on behalf of the community that is at the heart of regulating hES cell science.

Finally, the use of iPS cells would place responsibility for adopting these technologies onto individual patients, rather than the broader community. If there are few political, ethical or regulatory issues involved in the use of iPS cells then the choice to obtain iPS cell treatment would be an individual one. Such therapies might be part of a broader approach to healthcare funded by governments and private healthcare insurers, but ultimately the question of what to do about stem cell research would become a question of personal choice and treatment options. That is, under the current regulato-

ry approach to embryonic stem cell science, community consensus is demanded (although it might be noted that in pluralistic communities the consensus is always that the scientific good is not to be countered by moral concerns). But where the moral issues involved in embryonic stem cell science require some level of community consultation, the fact that iPS cells do not have these same issues obviates the need for community agreement. In other words, iPS cell based treatments would just become one more option in an arsenal of expanding medical options.

The commercial prospects of iPS cells

The question is though: how is money to be made out of iPS cells? If there is no intellectual property advantage to be gained from the actual material used for iPS cell based treatments, where would the money making capacity come from? What kinds of options exist for commercialisation based on the presumption that patient demand will exist and that easy delivery will become viable? In what follows I outline four possible commercial models that might be adopted in the iPS cell industry.

The first possibility is that perhaps ownership of centralised production facilities for the creation of tissue types will prove lucrative. That is, clinics collect deposits from their patients, send the material away to be processed, and then receive the material back ready for use in the patient. This model would enable specialised development of services and companies could focus on particular forms of service delivery. The main costs involved would be establishing facilities, hiring technicians and delivering the resultant goods, as well as all the usual costs involved in establishing a business.

There are already several precedents for this business model in the biotech and health care services. Pathology services often operate in this way, with blood and other tissue samples collected on-site and then sent elsewhere for processing, with the results being sent back for interpretation. A more recent example is that of DNA testing. Any individual can order a test kit, be given simple instructions about how to conduct a mouth swab and return the results back to the laboratory for processing. One of the more unusual outcomes of such a process is the results being sent back in the form of a mountable wall image of your own DNA: the gimmick being highly personalised artwork for your home (cf. DNA Art, 2010)

The second option for a commercial model for iPS cell based therapies is the outpatient clinic set-up. This could be developed along the lines of a franchise system or other kind of patient service model much in the same way as private clinics currently operate, with patients paying fees according to the services that they receive. This model could either process materials in-house, or send them offsite to another location for processing. The costs involved would depend on the level of clinical difficulty required and the level of service offered.

A third option is that intellectual property be developed on the training programs for implementing the process for practitioners in much the same way as occurs in the education delivery business model. Practitioners could be trained in different aspects of the process of developing an iPS cell based therapy and this training system is where the money is to be made. The proliferation of physical fitness training programs and other education programs indicates the successfulness of this approach.

And finally, the fourth model that could be possible for commercialisation in the iPS cell based industry is the design and sale of devices and reagents used in the clinical setting. That is, adopting a more traditional biotech business model. There will be plenty of opportunities for designing implements for collecting, storage, production, transportation and implantation in the future. This last model will emerge out of the current practices of the stem cell industries, where a range of different products are used in the laboratory. Stem Cell Technologies is one such example of a successful company using this model.

Current and future issues for commercial success of iPS cell based therapies

Although the options listed above may seem like obvious possibilities for the commercialisation of iPS cell based therapies, there are still a number of challenges facing the future development of an industry. These include: the viability of iPS cell based therapies, the cost-effectiveness of clinical delivery, the cost of materials required for clinical application, the market demand, community reaction, and the regulatory framework of clinical therapies. It remains to be seen what will happen on most of these counts.

While iPS cells seem very promising so far, any clinical applications are still a long way off. Some of the main technical challenges still to be overcome are building three-dimensional architecture into the cell structures. This is a significant engineering challenge. Once this hurdle is overcome then steps can be taken to examine the clinical efficacy of the resultant products. Some examples of such attempts were discussed at the 2009 Annual Meeting of the Tissue Engineering and Regenerative Medicine Society (TERMIS). These include: building scaffolding that gives the right shape for the functional cells to grow on to or over; constructing a 'bio-printer' that takes 3D images of the product required and carefully prints each layer accordingly; or using non-human materials to replace the structure required (TERMIS, 2009). Such technologies are highly technically complex, and research is still very much experimental.

Nevertheless, once clinical efficacy has been established, the next step would be to examine the cost-effectiveness of developing and delivering therapies. It might turn out to be the case that the infrastructure required and the technical skill level necessary will make generating iPS cell based therapies prohibitively expensive and not at all cost-effective. Yet even so, should the technology exist there would always be a market at the high end of consumption for these applications. Consumers with the resources to pay for novel treatment will be the primary market in this instance.

The potential market size is another consideration for the future of iPS cell based therapies. Will there be enough demand for them to warrant the labour, cost and time involved in developing iPS based therapies? While there would certainly be a limited amount of high-end demand, this will no doubt be insufficient to assist in the development of a large-scale industry. In this instance it might transpire that a boutique trade should emerge instead. But should iPS cell based therapies prove cost-effective overall, and the costs to consumers are also affordable, there should be considerable demand for such therapies generally.

But what then of the community engagements with the opportunities presented by iPS cell based therapies? To what extent will community reaction be positive or nega-

tive? Will the cost of iPS cell based therapies provoke concern about inequalities in access to health care? Or will community reaction focus more on the ever expanding choices available for 'turning back the clock'? Will the increased push for more end-of-life options than unlimited healthcare challenge the possible use of iPS cell based therapies? Will iPS cell based therapies be used for cosmetic or superficial reasons, posing questions about the value of continually altering our bodies?

These questions may ultimately prove contentious for the regulatory bodies associated with the therapeutic application of iPS cells. While the usual safety systems that are in place in relation to therapeutic goods and products would almost certainly remain in place, some of the more far-fetched concerns that have been raised by the prospect of regenerative therapies like hES cells are sure to apply to iPS cell based therapies too. As iPS cell based therapies provide more possibilities for transcending previously immutable limits of human identity, perhaps they too will raise the same kinds of criticisms about Frankenstein-ian science that have frequently been applied to hES cells and other new advances in biomedicine (cf. Haran, Kitzinger, O'Neill, & O'Riordan, 2008; O'Riordan, 2008). Biotechnologies that promise to radically reconfigure the boundaries of normal human life are often equated with the horrors of Mary Shelley's (1992[orig.1818]) *Frankenstein* and the unnatural creation made from stolen body parts by Dr. Frankenstein (Harvey, 2010). The story goes that Dr. Frankenstein unwittingly created a monster that he couldn't control and it wrecked havoc and destruction on him and his family. The moral to the story being that science has great capacity to produce untold dangers when meddling with the natural order. These same criticisms have been applied to the possibility of hES cell derived therapies, but will they equally apply to iPS cell based therapies too?

Some additional market complications

The list above however is not exhaustive of the potential problems facing the commercial development of iPS cell based therapies. Some of the other questions that might be raised which could have a definite impact on commercialisation include: who will pay for therapeutic delivery; concerns about equity and access to services; the role of patient compliance with treatment routines; what kinds of therapeutic complications might emerge from the application of iPS cell based therapies; and finally, what of the possibilities for the exploitation of patients and the inevitable 'tissue economies' (Waldby & Mitchell, 2006) that could potentially develop out of these new therapeutic possibilities?

Will taxpayers be forced to pay for regenerative livers for alcoholics for example? A recent case in the UK of a young man being refused a liver transplant because he was at too high a risk of reverting to the alcoholism that put him in need of one in the first place highlights some of the dimensions of this argument (Sky News, 2009). In a system of rationalised healthcare, and where resources are limited, the young man was not given any priority over other less risky patients despite the severity of his condition. The scarcity of the resource, in this case a healthy liver, meant that the value of using the organ was too high to risk on someone who might not be in a position to obtain maximum possible benefit from receiving it.

In the case above, the social contract between recipient and the healthcare provider is one that emphasises the 'gift' that they have been given and imposes that they be suitably respectful of the opportunity they have. But if livers could be readily generated from iPS cells, shouldn't all patients receive one if they need it? What costs would this add to the public healthcare system and what other allocations would need to be taken into account? Would the wealthy alcoholic not dependent on public care simply keep paying for a new liver every time one was deemed necessary?

Although such a scenario is bound to mean escalating health inequalities between the wealthy and the poor, there is another complication in that it would also suggest that ideas about patienthood might be challenged too. In the event that organs could be easily made, what imperatives are there for public health messages about lifestyle factors which impact on disease rates in the first place? Why would anyone bother quitting smoking, exercising well, eating properly and drinking less if there is no scarcity or limit to the capacity of replacing body parts? Could such a scenario represent the ultimate form of individualism and consumerism; that is, one in which we could do what we wanted to when we wanted to and be safe in the knowledge that it would be a simple matter of popping into the local clinic for some bodily engineering when we began to feel poorly?

Another question that might be asked is: will a proliferation of different commercial models undermine the overall effectiveness of the industry? Or, put differently, would an extensive iPS cell based industry lead to the proliferation of shonky practices and put consumers at greater risk? There is some evidence that might suggest this is in fact already happening with human embryonic stem cells, but perhaps the technical challenges of iPS cells and the process in which they might be produced would mitigate this risk overall. By what criteria though would such harms to patients be minimised?

Still another concern would be how capping and/or regulating the possibilities for access to services might create an international market for iPS cell based services. As mentioned above, there is already evidence of an emerging market in stem cell therapies advertised directly-to-consumers over the internet (Lau, Ogbugu, Taylor, Stafinski, Menon, & Caulfield, 2009; Ryan, Sanders, Wang, & Levine, 2010). These are in effect extensions of the already lucrative medical tourism markets in organs and fertility services (cf. Scheper-Hughes, 2003; Whittaker, 2009). The expansion of further opportunities for working on the body would potentially add another dimension to the proliferating global 'tissue economies' (Waldby & Mitchell, 2006). Just what effect would the emergence of global iPS cell based markets do for vendors and purchasers in this market? What social and political complications might be documented as a result?

Conclusion

In conclusion, it might appear evident that iPS therapies avoid some of the difficulties of embryonic stem cell research. As discussed above there are several different possible commercial models that might make iPS cells a reality, but none are yet to be established. Another factor that will affect this is that different national contexts are going to produce different possibilities for commercial models.

These issues are mostly limited to the regulatory dimensions that have been demonstrated to affect the global dynamics of stem cell research (Gottweis, Salter & Waldby, 2009). That is, regulations covering research using embryos, patenting of stem cells, and ownership of biological intellectual property are the biggest factors impacting on market stability and access to services. Overall, the most important outcomes of this global dynamic has been its impact on the credibility of scientists, patient demand for services and the growth of stem cell tourism, the availability of services, and cost-evaluation for governments investing in the stem cell sciences. As iPS cell based therapies mature, the question of who pays for healthcare services in any national context is going to determine the best delivery mechanism from a commercial point of view, but this will also be affected by how iPS cells are regulated and the community reaction to the therapeutic potential of iPS cells. In effect, the commercial prospects for iPS cell based therapies will emerge at the intersection between individual desires for perfect health and function, community reaction to the most far-fetched applications of these desires, and the commercial realities of turning such dreams into money-making products.

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