Cell Stem Cell
Forum

The Challenge of Regulating Rapidly Changing Science: Stem Cell Legislation in Canada

Peter J. Rugg-Gunn,[1,5,*] Ubaka Ogbogu,[2,4,5] Janet Rossant,[1,3] and Timothy Caulfield[2,*]
[1]Program in Developmental and Stem Cell Biology, Hospital for Sick Children Research Institute, 555 University Avenue, Toronto, ON M5G 1X8, Canada
[2]Health Law Institute, Faculty of Law, University of Alberta, 89 Avenue and 111 Street, Edmonton, AB T6G 2H5, Canada
[3]Department of Molecular Genetics, University of Toronto, 1 King's College Circle, Toronto, ON M5S 1A8, Canada
[4]Faculty of Law, University of Toronto, 84 Queen's Park, Toronto, ON M5S 2C5, Canada
[5]These authors contributed equally to this work
*Correspondence: pjrg@sickkids.ca (P.J.R.-G.), tcaulfld@law.ualberta.ca (T.C.)
DOI 10.1016/j.stem.2009.03.004

We describe how recent advances in stem cell research may be interpreted by various regulatory regimes and use Canada as a model to demonstrate how broad-based prohibitive legislation can unintentionally restrict research direction. We encourage scientists and policymakers to collaborate to ensure a clear regulatory framework that accommodates future advances.

Introduction

There is a policy cliché stating that the law lags behind science and is limping a little. There is no doubt that the speed of scientific advances can outpace the often sloth-like tempo of the political and legislative process. In Canada, for example, the reproductive technologies legislation that also governs embryonic stem cell (ESC) research came into force a decade after the publication of the Royal Commission that called for its enactment.

But the law is also often a terribly blunt and clumsy policy tool. It not only lags behind the advances of science but can create unintended hurdles in front of it. Legislation can quickly become an anachronism, no longer reflecting the social mood or scientific realities. If scientific legislation is crafted without careful attention to the underlying science, it may run aground when faced with new scientific realities.

Nowhere are the struggles of law more apparent than in stem cell research—an area in which intense social controversy has led to legislative actions throughout the world (Isasi and Knoppers, 2006). At the same time, new approaches to creating stem cell lines have emerged, some to circumvent challenges posed in adopting human ESCs (hESCs). Notable new techniques include interspecies somatic cell nuclear transfer (iSCNT), induced pluripotent stem (iPS) cells, and ESCs derived from parthenogenetic embryos and from embryos generated from isolated blastomeres (Ogbogu and Rugg-Gunn, 2008). Most, if not all, of these techniques were not contemplated during the political debates that led to the current regulatory environment.

This Forum article examines the challenge of drafting legislation in a changing scientific climate by asking how these emerging technologies fit within existing international regulatory regimes. We believe that regulatory uncertainties created by these new techniques demonstrate the limitations placed on stem cell research by prohibitive regulation. Our primary example is Canadian legislation, which occupies a middle ground between generally permissive regimes (such as the United Kingdom [UK], Singapore, and the state of California) and restrictive regimes (such as Germany and Italy). This approach allows us to examine key features of both regulatory extremes by drawing on a compromise position. However, the challenge of drafting legal frameworks in a changing scientific environment is fundamental to all countries with stem cell research policies, irrespective of the overlying level of permissiveness. Raising this discussion now is extremely timely. The Canadian Parliament is scheduled to revisit the relevant legislation, The Assisted Human Reproduction Act (the Act), in 2009. Also, recent changes in the United States (US) political landscape have led to lifting of federal funding restrictions for stem cell research, and the senate is scheduled to debate stem cell legislation imminently.

The Importance of Definition: Embryos versus Hybrids

The legal status of embryo creation through SCNT divides the world. Some jurisdictions, notably the UK, Australia, South Korea, and California, permit the procedure, while others, including Germany and Canada, prohibit it. In Canada, the prohibition comes with a potential 5–10 year prison sentence.

Creating SCNT embryos for stem cell derivation is one route toward patient-specific therapies. However, the process remains extremely inefficient, and the need for oocytes remains a significant barrier. To circumvent the oocyte shortage dilemma, scientists have turned to iSCNT, which involves using nonhuman oocytes as a receptacle for the human nucleus (Beyhan et al., 2007). But is the iSCNT procedure legal? In Canada, iSCNT creations fit within the legal definition of a hybrid: "non-human ovum into which the nucleus of any human cell has been introduced" (Canada, 2004). Despite the ban on human-to-human SCNT, creation of human-animal hybrids for research purposes is explicitly allowed, provided such creations are not used reproductively. Furthermore, although manipulation of the somatic donor cell (defined as human reproductive material in the Act)

would normally require licensing, because the outcome of this procedure is defined as a hybrid and not an embryo, this technique may fall completely outside the established regulatory regime. Therefore, not only does iSCNT creation appear legal, but a researcher may not even need to obtain a license to conduct these studies in Canada.

It is important to note that our view that iSCNT is legal in Canada is far from certain. The Act bans SCNT, cloning, and creating embryos for research. Since an embryo is defined in the Act as "a human organism in the first 56 days of development following fertilization or creation," regulators could advance the claim that iSCNT creations are embryos because they contain human nuclei—and their creation would therefore be criminally prohibited. Although possible, we believe this interpretation leaves room for ambiguity surrounding the level of human content required for iSCNT creations to be termed embryos and is less persuasive than the more explicit definitions in the Act that distinguish between hybrid and embryo (Ogbogu et al., 2008).

If iSCNT creations are allowed, this permissive stance would create the odd policy paradox whereby Canada now has one of the strictest regulations on SCNT and one of the most liberal on iSCNT. This paradox is heightened when one considers that Australia, a nation that shares many of Canada's sociopolitical ideals, allows SCNT but criminally prohibits iSCNT research. Australian legislation allows the licensed creation of hybrid embryos only by mixing animal oocytes and human sperm, and only for the purpose of testing sperm quality in an accredited facility. The creation of hybrid embryos by any other means or for any other purpose comes with a 10 year potential prison sentence (Australia, 2002).

Both practices are, without doubt, controversial. Public opinion research (conducted in the UK) indicates that a greater proportion of the public views creation and use of iSCNT embryos with concern, as compared to conventional SCNT (Human Fertilisation and Embryology Authority, 2007). Given the conservative ethos that permeated Canadian parliamentary debates leading up to enactment of the legislation (Caulfield and Bubela, 2007), it seems hard to believe that the current state of affairs was intended.

Much of the motivation for the restrictions in the Act flowed from a conventional view of how a human embryo is created—that is, by methods involving the use of human reproductive material. By adopting a view that the embryo possessed moral status, Canadian legislators justified a ban on embryo creation for stem cell derivation. Indeed, relevant parliamentary debates focused on the moral status of embryos and the dangers of human cloning (Caulfield and Bubela, 2007). When the Act was drafted, creation of human-animal hybrids was not canvassed as a method of deriving stem cells and therefore not subject to the same oversight. There is no documentary evidence to suggest that legislators considered derivation of stem cells from hybrids, or that they felt this technique was less controversial because it does not require human oocytes. Given the state of science at the time of the political debates, and the lack of reference to hybrids in parliamentary transcripts, it is more likely that the use of hybrids in this current context was not contemplated.

Regulatory uncertainty surrounding SCNT and its derivatives is not unique to Canada. The legal status of SCNT in the UK was challenged in a 2001 case brought on behalf of the ProLife Alliance, a group opposed to all forms of cloning and research on embryos. ProLife claimed that the definition of embryo in the UK Human Fertilisation and Embryology (HFE) Act did not extend to SCNT-created embryos. This claim, if successful, would have excluded SCNT from the licensing and regulatory scheme established by the HFE Act, thus creating a legislative lacuna for SCNT-derived embryos. The lower court's ruling in favor of the claim was overturned in an appeal affirmed by the House of Lords, which concluded that the intent of the HFE Act is to regulate in vitro embryos regardless of mode of creation, including embryos created by technologies that were unforeseen at the time of enactment.

Definitional ambiguities notwithstanding, UK legislation has proved responsive to change. The spirit of the House of Lords decision described above was reflected in recent amendments to the HFE Act, which includes updated definitions seeking to clarify the legal status of novel creations discussed within this article. In contrast to the Canadian legislative model and its emphasis on prohibitions, UK legislation brings new embryonic technologies into a permissive regulatory scheme based on licensing and oversight. While the UK model deserves credit for providing a framework with enduring relevance, regulators have shown some unease in giving practical effect to the legislative and regulatory scheme. For example, UK regulators recently sought public opinion on the implications of licensing research involving interspecies hybrids, a move that was criticized by many as an abdication of the legislative mandate to make decisions in the spirit of the HFE Act (Ogbogu et al., 2008).

The reasons for the different regulatory approaches are, no doubt, complex. Jurisdictions have diverse legal, cultural, and historical contexts that inform policy development. Timing of regulation also seems important. The UK HFE Act was introduced before human stem cell research became a significant field of study. In Canada, however, the law was debated and introduced at the height of human cloning and embryo controversies, lending rhetorical support for a prohibitive approach (Caulfield and Bubela, 2007).

Stem Cells Derived from Nonviable Embryos

To minimize the ethical stigma associated with stem cell derivation from viable human embryos, novel approaches have been described in proof-of-principle studies. We discuss two of the most promising and suggest that although the techniques may not harm viable embryos, they are unlikely to be afforded less-restrictive regulation than their conventionally derived counterparts.

The first technique involves deriving stem cells from parthenogenetic embryos, which are known to be nonviable in mice because a defined paternal genetic contribution is necessary to complete development (Kawahara et al., 2007; McGrath and Solter, 1984; Surani et al., 1984). The results of these studies are supported in humans, in which naturally occurring parthenogenetic activation of an egg results in disorganized development leading to benign ovarian teratomas (Linder and Power, 1970). The second derivation technique involves extracting

a single blastomere from a cleavage-stage embryo and coaxing the isolated cell to develop into a blastocyst, from which stem cells can be derived (Chung et al., 2008). Blastocysts formed from single blastomeres extracted from eight cell mouse or primate embryos cannot complete development even when implanted into a surrogate host (Chan et al., 2000; Rossant, 1976). Since human embryos blastulate at a similar stage to mouse and primate, current scientific evidence indicates that embryos generated from single human blastomeres are also nonviable.

Our interpretation of Canadian legislation is that both techniques would be treated as creating an embryo for research purposes and would therefore be prohibited. However, this conclusion is not certain, because the term "embryo" is loosely defined in the Act as "a human organism in the first 56 days of development following fertilization or creation" with no guidance on whether nonviable embryos are excluded from the definition. In addition, a parthenogenetic embryo is likely to be considered a clone because all genetic material originated from a single individual, the oocyte donor. A ruling of this nature would re-enforce a ban on the creation of parthenogenetic embryos.

Was this outcome intended at the time of enactment and/or consistent with the goals of the Act? It can be argued that since the Act seeks to control reproductive processes and their effect on specific populations (women and children), it cannot legitimately apply to nonviable creations that can never result in reproduction. Reproductive use of such creations could be expressly outlawed, so why was no consideration given to a more permissive stance on creation of nonviable entities for research? It seems likely that constant focus on "moral status" in parliamentary debates leading to the enactment resulted in lack of understanding of the impact this broad ban would have on future stem cell research. It can also be argued that omnibus legislation, such as the Canadian Act, which groups together multiple complex issues including regulation of fertility clinics, gamete donation, surrogacy, and using embryos for research, is more likely to be prone to inconsistencies and contradictions.

How is the derivation of stem cells from nonviable embryos regulated in other jurisdictions? In the UK, Australia, and the commonwealth of Massachusetts, creation of embryos from single blastomeres is expressly allowed for research. Australia and Massachusetts also permit creation of parthenogenetic embryos. In the UK, it is unclear whether the HFE Act regulates parthenogenetic embryos. The current version of the HFE Act defines an embryo as "an egg that is in the process of fertilisation or [that] is undergoing any other process capable of resulting in an embryo." Although this definition seems circular, it appears to be commonly accepted that the intent of the legislation is to cover all in vitro embryos (Lovell-Badge, 2008), no matter how created. It seems, therefore, that parthenogenetic embryos might be covered by the regulatory scheme provided by the HFE Act.

A New Frontier—Somatic Cells and Induced Pluripotency

Even among staunch critics of SCNT and ESCs, recent successful reprogramming of somatic cells into iPS cells has been lauded as an ethically appropriate technique of stem cell derivation. However, advances in iPS cell research could yield equally weighty ethical considerations. It may be possible to differentiate human iPS cells into sperm and oocytes, and thereby in theory, a single individual could be both mother and father to a child. The individual does not even need to be living if there is a stored sample of their cells.

With respect to legality, iPS cell generation is either unregulated or permitted in most jurisdictions, including those with restrictive policies on SCNT and embryo research. However, there are interesting caveats. A number of jurisdictions ban alteration of the genome of a human cell if the alterations are heritable. All human iPS cells that have been generated so far contain altered genomes due to integration of the reprogramming factors. Furthermore, since ESCs can generate cells that resemble germ cells (Tilgner et al., 2008), it is likely that iPS cells also have this capacity, thus providing a theoretical method of transmitting a genome alteration. In Australia, the relevant legal provision states that the person altering the genome must have "intended the alteration to be heritable by descendants of the human whose cell was altered" (Australia, 2002). Therefore, Australian legislation permits iPS cell differentiation into germ cells for research purposes.

In contrast, Canadian legislation appears to ban differentiation of human iPS cells into germ cells altogether. The Canadian position is likely to be an unintended consequence of the ban on germline genetic alteration, as creating germ cells from genetically altered somatic cells was not discussed during drafting of the Act. Moreover, the likely harm raised by germline genetic alteration is transmitting modified hereditary traits to offspring, a possibility that could not arise directly from the alteration of somatic cells. Arguably, legislative provision preventing reproductive use of altered iPS cells differentiated into germ cells would be sufficiently preventative. However, the Canadian provision explicitly bans any alteration—whether for reproductive purposes or not—if the alteration is "capable" of being passed to offspring. Generating iPS cells without genome alteration using direct protein delivery, chemical modifiers, or nonintegrating expression constructs could circumvent this ban.

Conclusion

Drafting wide-ranging legislation to regulate a field as dynamic and socially controversial as stem cell research is an extremely challenging task. The pace of scientific discovery, combined with the need for scientists to probe new research directions, will result in continuous testing of the limits of any legislation.

We believe that the experience in Canada highlights several lessons that have relevance for any jurisdiction struggling to develop science policy. First, there is great need for ongoing scientific input to law and policy making, especially in providing accurate knowledge and information about technical aspects of research. This is not to say that the scientific perspective should dominate, but that, regardless of one's view on the ethical appropriateness of research techniques, the debate should be properly informed. As such, engaging the policymakers should be an ongoing priority for the scientific community. Canadian stem cell scientists have an opportunity to influence future legislative amendments by ensuring that their interests and positions are taken into account in the upcoming parliamentary review. In doing so, it may prove prudent to "strategically avoid

emphasizing the technical details of science'' (Nisbet and Mooney, 2007), sticking instead to broad principles and clarity of language that promotes better understanding of the matters at stake.

Second, researchers should highlight the challenges associated with restrictive and inflexible legislation and emphasize the advantages of regulatory guidelines that allow rapid response to scientific advances. Again, whether one advocates a cautious or more permissive approach to regulation, it is important to craft legislative provisions that retain the ability to capture the nuances and unpredictable turns inevitably associated with scientific progress.

Finally, and perhaps most importantly, it is imperative that science policy be founded on clear, transparent principles that will have enduring relevance—regardless of where the science takes us. The specific principles must be stated explicitly, such that new developments can be openly considered within that context. Through this process, legislation can comprehensively regulate research while ensuring a clear and fair framework for future scientific advances.

ACKNOWLEDGMENTS

Research and preparation of this work was funded by a grant from the Canadian Stem Cell Network. We thank Laura Geddes, Colin Ouellette, and Michael Sharp for research assistance. P.J.R.-G. is a Canadian Institutes of Health Research (CIHR) Bisby Fellow, and U.O. holds a Social Sciences and Humanities Research Council (SSHRC) Joseph Armand-Bombardier Doctoral Scholarship.

WEB RESOURCES

Australia. (2002). Prohibition of Human Cloning for Reproduction Act 2002: Act No. 144 of 2002 as amended (http://www.nhmrc.gov.au/publications/synopses/_files/prohibit.pdf).

Canada (2004). Assisted Human Reproduction Act, c. 2 (http://www.laws.justice.gc.ca/en/A-13.4).

Human Fertilisation and Embryology Authority (2007). Hybrids and Chimeras: Findings of the Consultation, Appendix F – Public Dialogue: Opinion Poll (http://www.hfea.gov.uk/docs/2007-09-05_Authority_Paper_Hybrids_Chimeras__Findings_of_the_Consultation_396_Annex_F.pdf).

United Kingdom. (1990). Human Fertilisation and Embryology Act 1990, c. 37 (http://www.opsi.gov.uk/Acts/acts1990/ukpga_19900037_en_1); amended as Human Fertilisation and Embryology Act 2008, c. 22 (http://www.opsi.gov.uk/acts/acts2008/ukpga_20080022_en_1).

REFERENCES

Beyhan, Z., Iager, A.E., and Cibelli, J.B. (2007). Cell Stem Cell *1*, 502–512.

Caulfield, T., and Bubela, T. (2007). Am. J. Bioeth. *7*, 51–61.

Chan, A.W., Dominko, T., Luetjens, C.M., Neuber, E., Martinovich, C., Hewitson, L., Simerly, C.R., and Schatten, G.P. (2000). Science *287*, 317–319.

Chung, Y., Klimanskaya, I., Becker, S., Li, T., Maserati, M., Lu, S.J., Zdravkovic, T., Ilic, D., Genbacev, O., Fisher, S., et al. (2008). Cell Stem Cell *2*, 113–117.

Isasi, R.M., and Knoppers, B.M. (2006). Eur. J. Health Law *13*, 9–25.

Kawahara, M., Wu, Q., Takahashi, N., Morita, S., Yamada, K., Ito, M., Ferguson-Smith, A.C., and Kono, T. (2007). Nat. Biotechnol. *25*, 1045–1050.

Linder, D., and Power, J. (1970). Ann. Hum. Genet. *34*, 21–30.

Lovell-Badge, R. (2008). Natl. Rev. *9*, 998–1003.

McGrath, J., and Solter, D. (1984). Cell *37*, 179–183.

Nisbet, M.C., and Mooney, C. (2007). Science *316*, 56.

Ogbogu, U., and Rugg-Gunn, P. (2008). J. Int. Biotechnol. Law *5*, 186–199.

Ogbogu, U., Caulfield, T., and Green, S. (2008). Med. Law Int. *9*, 227–244.

Rossant, J. (1976). J. Embryol. Exp. Morphol. *36*, 283–290.

Surani, M.A., Barton, S.C., and Norris, M.L. (1984). Nature *308*, 548–550.

Tilgner, K., Atkinson, S.P., Golebiewska, A., Stojkovic, M., Lako, M., and Armstrong, L. (2008). Stem Cells *26*, 3075–3086.