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CLINICAL TRANSLATION OF STEM CELL THERAPIES - INTELLECTUAL PROPERTY AND ANTICIPATORY GOVERNANCE

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Abstract

Though promoted as the next pillar of medical care, stem cell research has yet to make a major clinical impact. After an extremely difficult period in the late 90's and the early 2000's, the potential for clinical translation of stem cell therapies has been portrayed in a more positive light for the past three years. However, evidence demonstrates that the recovery of the stem cell industry is still incomplete and that recent success has been modest. There is still considerable reluctance to invest in stem cell research. One of the factors causing this reluctance is the uncertainty surrounding stem cell patents. In this paper we discuss the impact of patents on stem cell research and propose an anticipatory governance/real-time monitoring platform to promote the technology transfer of stem cell research. This approach would provide an ideal framework to anticipate hurdles raised by patents, select reflexive strategies and develop a shared vision of the role intellectual property should play in the clinical translation of stem cell research.

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1. Introduction

Although scientists have promoted stem cell research as the next pillar of medical care, the field has yet to make any major clinical impact on medical practice.¹ After an extremely difficult period in the late 90's and the early 2000's, the potential for clinical translation of stem cell therapies has been portrayed in a more positive light for the past three years. In the US, the convergence of public policy support after years of federal opposition, significant funding opportunities at the state and federal level, the first ever clinical trials using human embryonic stem cells, advances in basic science and the emergence of a few burgeoning public-private partnerships have prompted optimistic talk about regenerative medicine 2.0.² According to these discussions, this dynamic new paradigm of clinical development is generating significant interest in the private sector market.³ However, this overly optimistic picture must be tempered by harsh market realities; evidence demonstrates that the recovery of the stem cell industry is still incomplete and that the recent modest commercial successes still do little to offset the initial collapse of the field.⁴ Venture capital interest in stem cell science is still limited and start-up biotech companies are struggling to find long term financing that would enable them to navigate past the current global financial crisis.⁵ Moreover, pharmaceutical and biopharmaceutical companies have so far shown only a limited interest in the field.⁶

Putting aside the problem of clinical utility, the difficulty in convincing private investors and “big pharma” to finance clinical development of stem cell products and therapies has been identified as a major hurdle to successful translation.⁷ A variety of socio-economic, legal and ethical factors explain the prevailing reluctance to invest in stem cells. Among them, the current uncertainty surrounding stem cells patents is a major issue. The current patent thicket, along with the necessity for defensible intellectual property rights and freedom to operate, are vexing issues both for venture capitalists

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¹ T McAllister et al, “Cell-based therapeutics from an economic perspective: primed for a commercial success or a research sinkhole?” (2008) 3 *Regenerative Medicine* 925-936, at 925.

² C Mason, “Regenerative Medicine 2.0” (2007) 2 *Regenerative Medicine* 11-18, at 11.

³ A Konski and D Spielthener, “Stem Cell Patents: A Landscape Analysis” (2009) 27 *Nature Biotechnology* 722-726, at 722; M Lysaght et al, “Great Expectations: Private Sector Activity in Tissue Engineering, Regenerative Medicine, and Stem Cell Therapeutics” (2008) 14 *Tissue Engineering* 305-314, at 309-314.

⁴ See note 1 above.

⁵ M Herder, “Two Models of Commercializing Stem Cell Science: Creating Conditions for Collaboration” (2009) available at http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1437690 (accessed 15 March 10); A Parson “Stem Cell Biotech: Seeking a Piece of the Action” (2008) 132 *Cell* 511-513, at 511-513.

⁶ See Parson in note 5 above.

⁷ J Lebkowski, “Discussions on the Development of Human Embryonic Stem Cell Based Therapies” (2009) 4 *Regenerative Medicine* 569-661, at 660.

potentially keen to invest and for big pharma.⁸ Because it is time-consuming and expensive to develop stem cell therapies, and because of the uncertainty surrounding the commercial and therapeutic potential of the field, private investors need some reassurance that they will be able to recoup their substantial investments.⁹ In another field of health innovation, that of pharmaceutical research and development, this “insurance” role is played by patent rights that will grant pharmaceutical companies a period of commercial exclusivity for novel drugs.¹⁰ Could the patent system play a similar role for private investors and pharmaceutical companies involved in the clinical translation of stem cell research?

In this paper, we will discuss the impact of patents and patenting practices on the field of stem cell research and development and propose an anticipatory governance/real-time monitoring platform to promote the technology transfer of stem cell research. Because patents affect the willingness of the private sector to participate in the clinical translation of stem cell research, creative models and guidance are needed to ensure that the system is used in an optimal way to promote technology transfer and commercialisation. Looking at the various solutions proposed by experts to resolve patenting issues, we suggest that, although these approaches are well informed from a short term economic perspective, they lack a broader socio-political understanding of the issues and stakeholders that would make them truly useful. We propose a participatory approach based on anticipatory governance and real-time monitoring. This approach would provide an ideal framework to anticipate hurdles raised by patents, select reflexive strategies and develop a shared vision of the role that intellectual property should play in the clinical translation of stem cell research.

2. Patents: Facilitating or Hindering the Translation of Stem Cell Research?

Patents are exclusive rights granted by national governments to foster research, development and technology transfer. The importance of patents for the survival of the private biopharmaceutical sector has been the subject of academic debates.¹¹ For example, in some circumstances, patents have been reported to have the adverse effect of slowing down research and promoting an academic culture of secrecy.¹² However, patents, because they are a means of capturing and commodifying the otherwise intangible capital of new knowledge, have a core role in both the economic strategies of states and in the business models of biotechnology entrepreneurs. In the latter case, IPRs are perceived as a crucial means of giving small or medium-sized biotechnology

⁸ C Mason, “ISSCR Industry Panel Session: Promoting Translation and Commercialization” (2009) 5 *Cell Stem Cell* 379-384, at 382.

⁹ See note 1 above.

¹⁰ F Scherer, “The Economics of Human Gene Patents” (2002) 77 *Academic Medicine December* 1348-1367, at 1351-1352.

¹¹ M Herder and E Gold, “Intellectual Property Issues in Biotechnology: Health and Industry” (2008) available at <http://www.oecd.org/dataoecd/16/9/40181372.pdf> (accessed 15 Mar 10).

¹² Y Joly, F Wahnou and B Knoppers, “Impact of the Commercialization of Biotechnology Research on the Communication of Research Results: North American Perspective” (2007) 8 *Harvard Health Policy Review* 46 – 60, at 47; T Caulfield et al, “Evidence and Anecdotes: An Analysis of Human Gene Patenting Controversies” (2006) 25 *Nature Biotechnology* 1091-1094, at 1092-1093.

companies some proprietary assets that they can use to attract speculative investment or to help forge alliances during the long lead-time to eventual product development.¹³ Large pharmaceutical companies have also often stressed the importance of the patent system for their business model.¹⁴

The application of the patent system to the field of stem cell research and development has raised its share of controversy.¹⁵ According to recent studies, a large number of stem cell patent applications were filed between 2000 and 2003. Following this peak period, patent activity in the field seems to have slowed down.¹⁶ Nevertheless, the patenting of stem cell lines, stem cell preparations and growth factors has remained intense, with ownership fragmented across multiple organisations.¹⁷ Already, a substantial number of stem cell patents (over 2000) have been granted.¹⁸ These patent applications and granted patents constitute a significant mass of intellectual property claims through which commercial products will have to navigate to reach the market.¹⁹ Contrasting with other fields of therapeutic development, a considerable proportion of stem cell patents (around 50%) are held by the public sector.²⁰ Moreover, a relatively small number of dominant stem cell patents cover the most fundamental technologies on which most stem cell research and development depends. These are the technologies that inform and support the wider field. Thus, these dominant patents have a proportionately greater potential for blocking commercialisation of a range of stem cell applications.²¹

Several factors contribute to making stem cell patents a source of anxiety for all stakeholders:

- The ownership of stem cell patents is fragmented between many public and private institutions, thereby impeding the negotiation process.²²
- Broad, dominant patents (e.g. the WARF patent), because of their large scope, have had a disproportionate influence on research and development.²³

¹³ G Bahadur and M Morrison, "Patenting Human Pluripotent Cells: Balancing Commercial, Ethical and Academic Interests" (2010) 25 *Human Reproduction* 14-21, at 15.

¹⁴ M Stott and J Valentine, "Gene patenting and medical research: a view from a pharmaceutical company" (2004) 3 *Nature Reviews Drug Discovery* 364-368, at 364-368.

¹⁵ K Vrtovec and C Scott, "Patenting pluripotency: the next battle for stem cell intellectual property" (2008) 26 *Nature Biotechnology* 393-395, at 393.

¹⁶ K Bergman and G Graff, "The Global Stem Cell Patent Landscape: Implications for Efficient Technology Transfer and Commercial Development" (2007) 24 *Nature Biotechnology* 419-424, at 420.

¹⁷ See notes 5 and 16 above.

¹⁸ See note 17 above.

¹⁹ See note 16 above.

²⁰ See notes 3 and 16 above.

²¹ See note 16 above.

²² M. Herder, "Proliferating Patent Problems with Human Embryonic Stem Cell Research?" (2006) 3 *Bioethical Inquiry* 69-79.

²³ F Murray, "The Stem-Cell Market — Patents and the Pursuit of Scientific Progress" (2007) 356 *New England Journal of Medicine* 2341-2343, at 2342.

- The patentability of certain stem cell technologies, especially those involving hESCs, varies across jurisdictions, thereby creating legal uncertainty.²⁴
- Recent US Court decisions on the use of patented materials for academic research have been inconsistent.²⁵
- Different sources of funding and institutional policies in the public sector create confusion as to the applicable ownership and intellectual property policies.²⁶
- Stem cells patents have a negative impact on academic collaboration.²⁷
- It is possible that, because of the length of the clinical process, patents filed by bio-pharmaceutical companies in phase I or II could have expired by the time the innovation reaches the market.²⁸
- National policies applicable to stem cell research and those applicable to stem cell patenting are often misaligned (stem cell policies intra-operability problems).

In the academic research setting, patent issues were seen as creating obstacles to the development of collaborative architecture between researchers and hindering technology transfer.²⁹ A number of legal models (protected commons, patent pool, patent clearinghouse, etc), data and material-sharing guidelines, stem cell banks, and data registries have been developed to address the constraints imposed by these issues.³⁰ Some models were meant to facilitate collaborative research, others to improve technology transfer. A final category of models targeted both of these objectives. Herder discusses two of these open models³¹ (Stem Cells for Smarter Medicine, Cancer Stem Cell Consortium)³² in a recent paper. George analyses a third one in this issue of *Script-*

²⁴ T Caulfield et al, “The Stem Cell Research Environment: A Patchwork of Patchworks” (2009) 5 *Stem Cell Reviews and Reports* 82-88, at 84-85.

²⁵ See note 5 above; Y Joly, “Wind of Change: in Re Fisher and the Evolution of American Biotechnology Patent Law” (2006) 24 *Law in Context* 67-84, at 67-70.

²⁶ See note 5 above.

²⁷ J Walsh et al, “Working Through the Patent Problem” (2003) 299 *Science* 1021, at 1021; J Walsh et al, “View from the Bench: Patents and Material Transfers” (2005) 309 *Science* 2002-2003, at 2002 (2005) T Bubela and A Strotmann, *Designing Metrics to Assess the Impacts and Social Benefits of Publicly Funded Research in Health and Agricultural Biotechnology* 6 The Innovation Partnership, Working Document, (2008), available at http://theinnovationpartnership.org/data/ieg/documents/cases/TIP_Innovation_Metrics_Case_Study.pdf (accessed 18 Mar 10); E Campbell and D Blumenthal, “Academic Industry Relationships in Biotechnology: A Primer on Policy and Practice” (2004) 2 *Cloning* 129-136.

²⁸ See note 1 above at 934.

²⁹ D Winickoff, K Saha and G Graff, “Opening Stem Cell Research and Development: A Policy Proposal for the Management of Data, Intellectual Property and Ethics” (2009) 9 *Yale Journal of Health Policy & Ethics* 51-127, at 54; M Herder and J Dyck Brian, “Canada’s Stem Cell Corporation: Aggregate Concerns and the Question of Public Trust” (2008) 77 *Journal of Business Ethics* 73-84, at 78.

³⁰ See note 5 above.

³¹ For more on open biotechnology model see Y Joly “Open Biotechnology: Licenses Needed!” (forthcoming *Nature Biotechnology*).

³² See note 5 above.

Ed (UK Stem Cell Bank),³³ while authors Winickoff, Saha and Graff recently proposed their own ambitious multi-stage collaborative alternative to promote stem cell research and development.³⁴ The recognition by scientists and other stakeholders of the limitations of the patent system and of the importance of collaboration in the field of stem cell research is a positive sign. However, as stem cell research moves closer to the clinic, the proliferation of novel approaches and business models to address patent and commercialisation issues could create more uncertainty than good and become a concern for industry. Moreover, it would seem that these models are often artificially conceived as “business experiments” without sufficient thought being given to social acceptability, commercial uptake and long term viability. This could explain why several of these models are already out of business, while many others have yet to reach their stated objectives.

Open models of collaboration in the field of biotechnology are still recent creations.³⁵ From a legal standpoint, several substantial ownership and licensing issues remain unresolved,³⁶ while, from a business perspective, the private sector’s interest in participating has yet to be demonstrated. The long term viability of those models has not been studied in depth, even in the field of information technology where open source development is now largely perceived as a successful business model.³⁷ A shared long term vision of intellectual property, open biotechnology and impediments to technology transfer in the field of stem cell research is needed. The remainder of this paper will propose a participatory framework to develop such a vision based on anticipatory governance and real-time monitoring.

3. The Need for Foresight: Anticipatory Governance

Anticipatory governance (AG) is a new concept that has considerable relevance for policy-making and health technology translation in rapidly evolving fields, such as stem cell research. AG, which has its origins in part in public administration literature, means to govern with vision and foresight.³⁸ Foresight is the process of identifying and interpreting information and data by looking ahead. It is often long-term, and can be both strategic and financial in nature.³⁹ In parallel, the notion of “governance”

³³ C George, “Open Biotechnology and the Regulation of Commercialisation of Human Stem Cell Lines” (forthcoming *Nature Biotechnology*).

³⁴ See note 30 above.

³⁵ See note 33 above.

³⁶ *Ibid.*

³⁷ Digital Connections Council of the Committee for Economic Development, *Open Standards, Open Source, and Open Innovation: Harnessing the Benefits of Openness*, (Washington (D.C.): Committee for Economic Development, 2006) at 18; G Von Krogh and S Spaeth, “The Open Source Software Phenomenon: Characteristics that Promote Research” (2007) 16 *Journal of Strategic Information Systems* 236-253, at 242.

³⁸ K Chi, “Four Strategies to Transform State Governance” (Washington DC: IBM Center for the Business of Government, 2008) 6; V Ozdemir et al, “Personalized Medicine Beyond Genomics: New Technologies, Global Health Diplomacy and Anticipatory Governance” (2009) 7 *Current Pharmacogenomics and Personalized Medicine* 225-230, at 228.

³⁹ See Ozdemir in note 41 above.

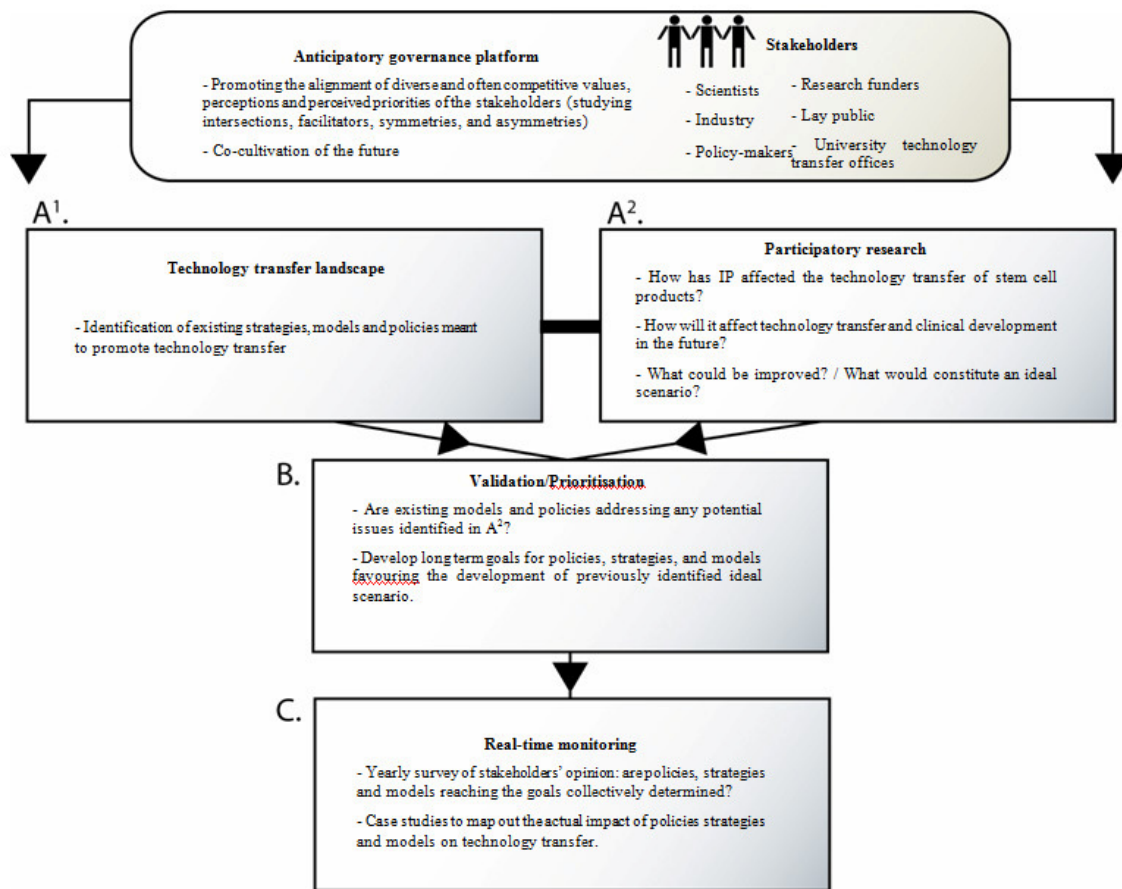
commonly refers to a move away from a top-down government approach to an approach where management by people, private actors and institutions becomes possible without detailed and compartmentalised regulation from the top. According to this governance strategy, effective action must be based on more than good analytical capacities and relevant empirical knowledge; it also emerges out of a distributed collection of social and epistemological capacities, including collective self-criticism, imagination, and the disposition to learn from trial and error.⁴⁰

A variety of lay and expert stakeholders both individually and through an array of feedback mechanisms and forward-looking activities collectively imagine, critique and thereby shape the issues presented by emerging technologies before they become reified in particular ways.⁴¹ Such activities could include: workshops, conferences, Delphi exercises, consultations, the creation of associations, etc. A framework based on anticipatory governance would allow strategies promoting the clinical development of stem cell products to be based on informed trends and facts. It would also promote the adoption of evidence-based decisions and strategies leading to preferred futures designed together by state officials, entrepreneurs, pharmaceutical industry and scientists. Finally, it would favour a proper alignment of all scientific, legal, ethical and socio-economical activities toward efficient technology transfer.⁴²

⁴⁰D Barben et al, “Anticipatory Governance of Nano-Technology: Foresight, Engagement and Integration” in E Hackett et al (eds), *The Handbook of Science and Technology Studies* (Cambridge, Mass: MIT Press, 2007) at 979 –1000.

⁴¹ See note 43 above.

⁴² See Ozdemir in note 41 above.



The key to the success of our suggested approach will be to build a forward-looking technology transfer platform that is continually reflexive, so as to favour the collective adaptive management of emerging obstacles that could negatively influence technology transfer in the field of stem cell research.⁴³ Because multiple factors (some of which are unforeseeable beforehand) shape the evolution and commercial uptake of a new technology, there will be limits to the extent to which we can anticipate the impact of intellectual property, open models and technology transfer policies. We propose calibrating and fine-tuning the predictions made by AG through real-time monitoring of the *actual* technology transfer process using empirical methods. Real-time monitoring (RTM) is a concept left over from the cold war era when there were two competing super powers in global politics.⁴⁴ RTM would ground and fine tune our anticipatory governance framework through real-time analysis, providing a longitudinal temporal framework of the impact of open models and technology transfer policies on the actual uptake of stem cell research by the private sector. It would permit our anticipatory governance approach to be more responsive to unanticipated events by providing regular feedback on the impact of our commonly developed framework on our chosen objective. The suggested RTM should extend for a suitably long time frame, in order to

⁴³ D Guston and D Sarewitz, "Real-Time Technology Assessment" (2002) 24 *Technology and Society* 93-109.

⁴⁴ See Ozdemir in note 41 above.

identify and respond to unexpected and unintended impacts.⁴⁵ Indeed anticipatory governance would promote the implication of all stakeholders to prospectively identify potential hurdles and positively influence the evolution of the field.

Although both anticipatory governance and real-time monitoring have been used to improve public governance of emerging technologies, the capacity of these two strategies to improve private actions affecting science and technology remains untested. The greatest challenge to our approach could be to ensure participation of all stakeholders and to achieve efficient democratic co-cultivation of collectively desirable futures on emerging issues and strategies.

4. Conclusion

The enormous potential of stem cell research for modern medicine is now recognised by the scientific community. The glorious destiny of stem cell science has however yet to materialise and sceptics about the commercial potential of this research abound in the private sector. Thus, stem research has yet to make a significant commercial or clinical breakthrough. Surely, there remain major scientific issues to resolve in order to promote broad integration of stem cell science into clinical practice.⁴⁶ However, in the end, it may be the socio-economic, legal and ethical issues that will block the technology transfer in this field.

Patents (or patenting practices) have been identified as a substantial hurdle to stem cell technology transfer. Real or perceived patent issues have negatively impacted the clinical uptake of stem cell research by private actors. Policy changes and open models proposed by scientists, academics and entrepreneurs to improve the current outlook are often conceived in a social void that could make them ill-adapted to the complex, fast-paced environment of stem cell commercialisation. Moreover, by promoting the adoption of a large number of different models, some of questionable legal validity, actors are likely contributing to the high degree of uncertainty already existing in the field.

In this paper, we proposed the adoption by members of the stem cell community of a commercialisation platform based on anticipatory governance and real-time monitoring to collectively identify prospective issues and positively influence future outcomes concerning stem cell technology transfer. This platform would favour the development of harmonised strategies, both prospective and responsive, and promote the elaboration of a more positive vision of stem cell commercialisation. It would also encourage reflexivity among scientists. Working closely with policy-makers, bioethicists and legal experts, they would develop a greater awareness of the broader social, ethical and policy consequences of their own research. It will be interesting to see how anticipatory governance can influence the actions of private actors, as our strategy, if successful, could be expanded to other spheres of biotechnology research.

⁴⁵ See Ozdemir in note 41 and 46 above.

⁴⁶ A Patel et al, "Personalizing Stem Cell Research and Therapy: The Arduous Road Ahead or Missed Opportunity?" (2010) 8 *Current Pharmacogenomics and Personalized Medicine* 25.