Stem cell innovation in the United States:

the benefits of the minimal state

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Introduction

The United State is the leading global player in the biotechnology industry yet it has no national strategy on stem cell science – a field that many regard as the platform for regenerative medicine and one of the most promising of emerging health technologies. Does this matter? For the most part, national policies on stem cell science are driven by the twin political emotions of ambition and fear. Ambition that a state should benefit from the global economic potential of the field. Fear that rivals will get there first. Given the long term economic and health advantages that stem cell science may deliver for their citizens, governments are reminded that should they choose to ignore the promise of stem cell science they may find themselves portrayed as irresponsible if they neglect their citizens' future welfare. Furthermore, it is argued, if other countries profit from an early mover commitment to the stem cell field, less prescient states will find it too late to catch up. Finally, ethical issues relating to embryonic stem cells and their application to research and therapeutic applications have attracted limited government and industry investment in the United States, providing other countries such as the United Kingdom with 'early mover' advantages. This has not been the case however in the research and therapeutic application possibilities for adult (somatic) stem cells, where the United States is a world leader.

From this perspective, strategic state leadership such as that provided by the United Kingdom in its 2005 Pattison Report is seen as a necessary launchpad for the achievement of national advantage.[1] Here the UK set out a ten year strategy for the development of stem cell research, therapy and technology making clear its ambition 'for the UK to consolidate its current position of strength in stem cell research and mature…..into one of the global leaders in stem cell therapy and technology'.[2] More recently, a German government study, whilst noting Germany's leading international position in regenerative medicine, argued trenchantly for urgent policy changes to facilitate the translation from the science to the therapeutic product.[3]

However, the federal government of the US remains unimpressed by the calls for state intervention and has come under much criticism for this stance. In an editorial on 10th November 2007 echoing its comments on prior occasions, *The New York Times* lamented the inactivity in stem cell science of the US federal government observing that 'stem cell research is of such importance and promise for the entire world that it deserves to be carried forward by a national program underwritten by federal funding'. Individual US states alone, it maintained, could not shoulder the burden of development.[4] Similar sentiments were expressed in the US Department of Health and Human Services' 2006 report *2020: A new vision. A future for regenerative medicine* whence came the dire prediction that as a result of inadequate national leadership 'the U.S. pre-eminence in the field of regenerative medicine is in jeopardy'.[5]

In this article we question whether the absence of a federal strategy is important to the success or failure of stem cell science in America and its ability to compete in the global stem cell market. Given its inherent strengths in biotechnology, does the US

need substantial federal government intervention to enable one particular sub-sector to succeed in the global competition for advantage? To what extent are the network driven activities of science, industry and private funding agencies able to construct infrastructures of innovation that substitute the possible interventions of government through an organic response to the market advantages to be gained from the stem cell field? How far would state intervention merely serve to stifle the competitive instincts release by the alleged current limitations on federal involvement in the stem cell field?

The viability of the stem cell future

Given that neither public/private resources nor political will are infinite commodities, there is a prior question regarding the potential of the stem cell field and the basis of any government or non-state interest. Is it worth the candle? When assessed in terms of future patient population demand, interest in stem cell science, from whatever quarter, would seem to be justified. The United States National Academies of Science report *Stem Cells and the Future of Regenerative Medicine* estimates that in the US the market for stem cell–based therapies includes more than a hundred million patients with conditions such as cardiovascular disease, autoimmune diseases, diabetes, cancer, neurodegenerative diseases, and burns [6]. In terms of financial value, one source 'conservatively estimates' the worldwide market for regenerative medicine to be $US500 billion by 2010 [7], while another announces that the European market is expected to reach $15 billion by the same year [8] – though precisely how these figures are calculated is not revealed. Forecasts by consultancy firms on the stem cell market include a US market of $3.6 billion and a world market of $8 billion by the same year. Others are less optimistic, predicting a world market of $100 million by 2010 rising to $2 billion by 2015.[9]

Although the market forecasting of the stem cell field produces highly variable results depending on what stem cell types, diseases, technologies, and types of firm are included, it is nonetheless sufficiently prevalent to help establish the impression of an achievable future reality even though the precise nature of this reality may be elusive. Once a critical mass of political interests have accepted this future, regardless of its objective probability, global competition is engendered and, as the manoeuvring for position intensifies, becomes self-sustaining.

Whilst the developed countries of the West may be anxious that their dominance or access to new health technologies are not eroded, developing countries are equally concerned that their ability to compete is not undermined by their own failure to anticipate and invest in basic research and development so as to be able to participate in these new opportunities. Responding to the future promise of stem cell science, states such as China, India, South Korea, and Singapore have all made starts in stem cell research in recent years. China's annual investment in stem cell research was recently said to be between US$4 and 10 million with 300 researchers working in 30 separate institutions.[10] However, these figures are set to increase significantly. Estimates quoted in the UK's Pattison Report suggest that over the next five years China's Ministry of Science and Technology (MOST – the main source of public research funds) is expected to spend between RMB 500 million (US $63 million) and RMB 2 billion (US $0.25 billion), depending on how productive the science turns out to be.[11] In January 2005 India's Department of Biotechnology (DBT) and the Indian

Council of Medical Research (ICMR) announced plans for a national stem cell initiative that would prioritise research funding, focus on clinical applications and promote 'stem cell city clusters'.[12] Despite (or because of) the fallout from the Hwang affair,[13] South Korea remains firmly committed to the aggressive expansion of stem cell research and in May 2006 allocated $454 million to the field over the next decade.[14] Meanwhile, Singapore's vast investment in its Biopolis complex ($8 billion committed through to 2010) continues to act as a magnet for Western stem cell scientists.[15]

Supporting stem cell innovation

When analysed in terms of their support for stem cell innovation from bench to bedside, state and private interests have a range of choices regarding the point and mode of intervention in this process when measured against the requirements of the science itself, society and the future market. Some of these choices may take the form of the introduction of public policies or private governance arrangements, whilst others may simply require the commitment of resources, public or private.

Choices about the *science* have much to do with the creation and husbanding of the resources necessary for the enterprise to have an explicit domestic platform. This may require investment, direction and the capacity to ensure the appropriate supply of scientific labour and research materials such as oocytes and stem cell lines. Secondly, regardless of political system, the response of *society* to stem cell science may require choices to be made about how that response is negotiated both domestically and internationally if public trust in the field is to be maintained. Even if, as in China, the public voice is muted, both elite and international opinion nonetheless act to request, if not require, policies that regulate the science in the public interest – not only in terms of risk and safety but also the sensitivities of cultural values. Without such policies, future consumer demand may be fatally undermined.

Finally, the risk of *market* failure during the long gestation from basic science to eventual therapy means that early government funding intervention is necessary to motivate patenting, venture capital investment and pharmaceutical engagement in this emerging industry. For countries such as the UK, it is primarily the state which is seen as the appropriate agent for interventions in the innovation process with private interests playing a minor role. In the case of the US, we explore the extent to which this equation is reversed

Science

In the discussions on the federal funding of stem cell science, much play is made of President Bush's decision that federal grants should only be available for work on human embryonic stem cell (hESC) lines created before 9 August 2001, thus preventing any further destruction of embryos using federal money. Although this obviously restricts the resources for one sector of stem cell science, its impact has been limited. Currently investigators from ten laboratories in the United States, Australia, India, Israel, and Sweden have derived stem cells from 71 individual, genetically diverse blastocysts that meet the President's criteria for use in federally funded human ESC research and can be accessed via the National Institute of Health (NIH) Human Embryonic Stem Cell Registry.[16] In the last 6 years 2003-08, the NIH has committed just over US$200 million to human ESC research (Table 1). Rather

more significantly, over the same period adult stem cell research has attracted US$1.2 billion of NIH funding and the stem cell field as a whole US$3.78 billion. As we can see from the figures quoted earlier, no other country in the world remotely approaches this level of government investment in stem cell science. If the responsive mode of research funding can generate such comparatively large amounts of money for the field, it is difficult to see why a federal-led programme of research should be considered necessary.

Table 1[17]

Federal Government funding for stem cell research (millions of USD)

	2003	**2004**	**2005**	**2006**	**2007**	**2008** ***estimate***	**Total**
Stem cell research	517	643	657	656	655	656	3784
Human embryonic	20	24	40	38	42	41	205
Non-human, embryonic	113	89	97	110	106	105	620
Human non-embryonic	191	203	199	206	203	203	1205
Non-human, non-embryonic	230	236	273	289	306	305	1639
Cord Blood/Placenta	19	18	18	19	22	22	93
Human cord blood/placenta	1	16	15	16	19	19	83
Non-human cord blood/placenta	2	3	3	4	2	2	16

In any case, other money from the public purse is flowing into stem cell science as the result of a growing competition between individual US states for position in the future stem cell market. At present, seven states head up this competition: California, Connecticut, Illinois, Maryland, Massachusetts, New Jersey, New York and Wisconsin. In the 2005-06 two year period they collectively awarded some US $230 million in grants.[18] New Jersey was the first mover appropriating $10 million in January 2004. Then, in November later that year, California voters seriously raised the stakes by agreeing to a US$3 billion investment over a 10 year period. In 2005, Connecticut allotted US$100 million, also over 10 years. In 2006, Illinois committed US$15 million to stem cell research. Maryland approved US$15 million in 2006 followed by US$23 in 2007 and in the same year New York established the Empire State Stem Cell Trust with US$650 million to fund a 10 year research programme. Meanwhile, Wisconsin has created a US$750 million building fund to construct a stem-cell research laboratory at the University of Wisconsin, Madison.[19]

With over US$4.5 billion currently committed to stem cell science by the competing US states in addition to NIH grants, the dynamic of the internal US public research funding market in this field is well-established at both national and state levels. Further energy is supplied by funding contributions from the private sector. Medical charities with a stake in the potential therapeutic products have already committed funds to support the science. In the 2002-07 period, the Juvenile Diabetes Research Foundation (JDRF) invested between US$8 and 10 million a year.[20] Private philanthropists have also been attracted to the field with increasingly large donations for both embryonic and non-embryonic stem cell research (Table 2). Smaller contributions to single research institutes have also gathered speed: as of June 2007, the Harvard Stem Cell Institute had raised some $60 million from private sources.[21] As a rough guide, when this figure is added to the donations in Table 2 it brings the total in the period up to 2007 to over US$260 million.

Table 2[22]

Private donations to stem cell science

Donor	Amount	Recipient
William Bowes, founding partner of U. S. Venture Partners	$3 million (announced Oct 2007)	University of California, Santa Barbara Center for Stem Cell, Biology and Engineering
Eli Broad, real estate entrepreneur	$55 million (announced September 2007 and February 2006)	University of Southern California ($25 million) University of California, Los Angeles ($20 million)
Tom Ellison, the chairman of Savers Inc. of Bellevue	$5 million (announced June 2007)	University of Washington
Lorry I. Lokey, founder of Business Wire	$33 million (announced February 2007)	Stanford University
Bill Gross, founder of investment company PIMCO	$10 million (announced July 2006)	University of California, Irvine
Ray Dolby, sound system businessman	$16 million (announced May 2006)	University of California, San Francisco
Starr Foundation	$50 million (announced May 2005)	Weill Medical College of Cornell, Memorial Sloan-Kettering and Rockefeller University
Stephen Weiner, founder of real estate firm	$6 million (announced in March 2005)	Beth Israel Deaconess Medical Center
Anonymous donor	$25 million (announced in March 2004)	University of Texas, Health Science Center at Houston

Finally, basic stem cell research and development of therapeutic applications are being undertaken by biotechnology companies such as Geron, and Advanced Cell Technology in the embryonic stem cell segment, and by companies such as Osiris and Stem Cells Inc with adult stem cells.

The United States' powerful mix of federal, state and private funding for stem cell science resonates easily with its dominant model of how innovation in the biotechnology industry moves from basic science to commercial product. In place of a federal led programme there is instead a market emphasis on a close engagement between academy and industry.[23] University technology transfer offices help their scientists to patent their findings and identify private investment opportunities. Individual states regularly intervene to support commercialisation by ensuring three critical elements of the research infrastructure: 'robust university research is in place, investment dollars from venture capitalists and angels readily available to spin off university-developed technology, and an existing base of companies to provide and attract a workforce'.[24] In some cases these elements are formalised into public-private partnerships through biotechnology business incubators such as Connect and BioSTAR in the University of California system and the Austin Technology Incubator at the University of Texas. Also important is the role of networks that play an important role in facilitating the linkages between scientists, small companies and venture capitalists (VCs) necessary for commercialisation to succeed. Examples in the stem cell field include BayBio, the Coalition for the Advancement of Medical Research (CAMR), the Bay Area Start-up Network (BASN), the Alliance for Stem Cell Research (AFSCR), and the Stem Cell Action Network (SCAN). In this context, the federal role is to provide business development support in the form of facilities, managerial expertise, legal advice and networking opportunities through programmes such as the Small Business Initiative Research and the Small Business Technology Transfer Initiatives.[25]

It is out of this approach that leading biotech companies such as Biogen in Boston, Genentech in San Francisco and Hybritech in San Diego have emerged.[26] The lesson is that the US states that can build on their existing life sciences clusters to enable the emergence of this supportive model in stem cell science are likely to be the ones to profit from its future.[27]

The significance of United States' vast preponderance in the global stakes of stem cell science investment lies not only in its impact on its internal and global knowledge markets but also in its positive implications for the viability of the US workforce and labour market in stem cell science. Although there has been some media speculation concerning the 'brain drain' of US stem cell scientists to the UK (usually presented as a response to Bush's restrictions on NIH hESC research),[28] there is little evidence that this is happening in practice. Research shows that stem cell scientists in the US are potentially more mobile than their colleagues in other disciplines and receive more domestic and international job offers, as one might expect given the demand for scientific labour generated by the resources invested in the field.[29] The level of committed funding in California through the Proposition 71 referendum (US$3 billion over ten years), coupled to the establishment of a permanent specialised funding body (CIRM) to invest in academic research and stem cell companies progression of technology to clinical trials, has caused disquiet in other states fearing the loss of leading researchers. However, whilst the regulatory climate in the US will be one factor in their decision (see below), equally important will be the long term sustainability of the resources to fund their work. On the basis of the latter criterion, only a few elite figures are likely to move to other countries whilst the bulk of US stem cell researchers will either stay where they are or simply re-locate to the more attractive research pastures created by the leading state investors within the US.

Rather more complex is the related issue regarding the ability of the US to attract and retain stem cell scientists. Traditionally the US has been heavily reliant on overseas science and engineering (S & E) labour: foreign born scientists are more than a quarter, and possibly a third, of the S & E doctoral labour force.[30] In 2003, 37% of US doctorates in the biological sciences were awarded to foreign born scientists.[31] Given that the biological sciences are expanding rapidly this is an important statistic for stem cell science. In April 2006, around half (49%) of US-educated S & E doctorate recipients in post doc positions had doctorates in the biological sciences, well above the 23% of all S & E doctorates awarded in 2005 and an indication of the growing importance of the biological sciences.[32] In the past, the US reliance on overseas scientific labour in an important discipline like the biological sciences would have been mitigated by the tendency for the majority of graduates from, for example, China and India to remain in the US once qualified.[33] [34] However, of late the global competition for scientific labour has intensified to the point where the US National Science Board has warned that the US may not be able to rely on this market to fill its unmet skill needs.[35] Governments in developed and developing countries are reducing entry barriers by adjusting their visa programmes to encourage the inflow of temporary high-skilled workers at precisely the same point as the US is making such migration more difficult. Meanwhile, countries such as China that have hitherto accepted the loss of their S & E labour to the US are introducing substantial incentives, particularly in stem cell science, to ensure that they return once qualified.[36]

Society

Without broad societal support for a particular medical innovation, the viability of public and private investment and future market becomes vulnerable and the innovation process may stall. In the case of stem cell science, the primary political struggle in the US has centred on the status of the human embryo when used, and necessarily destroyed, in the course of basic human ESC research. This struggle is of course not a new phenomenon but a continuing feature of the experience of medical science in such arenas as assisted reproductive technologies (ART), pre-implantation genetic diagnosis (PGD) and, most notably, abortion with its focus on the second development stage of the foetus. In the US, cultural divisions over the status of the human embryo have produced acrimonious and long standing conflicts on abortion policy to the extent that they have assumed the mantle of 'culture wars'.[37]

In the UK, this debate produced a policy characterised by a legally defined licensing system for embryo research under the 1990 Human Fertilisation and Embryology Act within which hESC science operates. In the US, the policy response has taken the form of conditions attached to federal, but not state or private, research funding. President Bush's ban on NIH funded research using hESC lines created after 9th August 2001 was a policy compromise largely in line with the results of previous debates on the issue. In 1996 during the Clinton administration, Congress banned the use of federal funds for any experiment in which a human embryo is either created or destroyed. Known as the Dickey-Wicker Amendment for its Congressional authors, the ban passed as a rider attached to the appropriations bill for the Department of Health and Human Services. Congress has actively renewed that ban each year since, thus relegating all human embryo research to the private sector. Even if Bush's policy

was revoked, the Dickey-Wicker would remain in place and an obstacle to federal funding of early stage hESC research.

Unless, that is, it is supplanted by other legislation as a result of the continuing conflict over hESC science at the federal level. In the years following the Bush ban, both the 109th Congress (2005-06) and the 110th Congress (2007-08) passed bills supportive of hESC research using cell lines created from surplus IVF embryos. Both were vetoed by President Bush. In vetoing the latter (the 2007 Federal Stem Cell Research Enhancement Act) the President at the same time issued an executive order encouraging government agencies to support promising research that might craft useful stem cells without destroying human embryos.[38] Further attempts to introduce pro-hESC research legislation, as well as legislation encouraging non-hESC alternatives, are in train.[39]

Whilst the struggle over the federal control of the hESC policy agenda remains unresolved, with regard to somatic cell nuclear transfer (SCNT – 'therapeutic cloning'), federal funding of research involving cloning for the purpose of reproduction or research is prohibited. However, there is no federal law banning human cloning altogether. Although the Food and Drug Administration (FDA) has claimed authority over the regulation of human cloning technology as an investigational new drug (IND) and stated that they would not approve any projects involving human cloning for safety reasons, Congress has yet to pass legislation confirming the FDA's authority to prohibit cloning.[40]

Although the national statutory response in the US to societal concerns surrounding stem cell science remains inconclusive, other, more indirect, mechanisms of national governance have nonetheless responded to these concerns. The President's Council on Bioethics has produced a series of reports on hESC science though, given that its members are appointed by the President, the Council, and hence its arguments, lacks the authority of an independent bioethics body.[41] [42] [43] Rather more persuasively, and recognising the absence of national guidance, the US National Academy of Sciences produced its own *Guidelines for human embryonic research* which recommended that all institutions engaged in stem cell research should establish specialist Stem Cell Oversight Committees.[44] However, these guidelines are of course only advisory and subject to whatever statutory regulation exist at state level.

In the absence of a federal ruling on non-federal hESC research, states and private bodies have, as we have seen, made their own funding choices. States have also made their own choices about whether and how to regulate the availability and use of the materials required for basic stem cell science: oocytes, embryos, foetuses and other human tissues. Influenced by an array of local cultural values, existing biotech commitments and political imperatives, states have produced a patchwork of diverse legal arrangements to overlay their funding decisions. Table 3 provides an initial profile of the complexity of these arrangements, though it should be born in mind that the legal variations between states occur both across and within categories.

Table 3[45]

State embryonic and fetal research laws

State	Specifically permits research on fetus/embryo	Restricts research on aborted fetus/ embryo	Consent provisions to conduct research on fetus/embryo	Restricts research on fetus or embryo resulting from sources other than abortion	Restrictions of purchase/sale human tissue for research
Arizona	No	Yes	No	Yes	No
California	Yes	Yes	Yes	Yes	Yes
Connecticut	Yes	No	Yes	No	Yes
Florida	No	Yes	No	No	No
Illinois	Yes	Yes	Yes	Yes	Yes
Indiana	Yes	Yes	Yes	Yes	Yes
Iowa	Yes	No	No	No	No
Kentucky	No	No	No	No	Yes
Lousiana	No	No	No	Yes	No
Maine	No	No	No	Yes	Yes
Maryland	Yes	No	Yes	Yes	Yes
Massachusetts	Yes	Yes	Yes	Yes	Yes
Michigan	No	Yes	Yes	Yes	No
Minnesota	No	No	No	Yes	Yes
Missouri	No	Yes	No	No	Yes
Montana	No	Yes	No	No	No
Nebraska	No	Yes	No	Yes	Yes
New Hampshire	No	No	No	Yes	Yes
New Jersey	Yes	No	Yes	No	No
New Mexico	No	No	No	Yes	Yes
New York	Yes	No	No		
North Dakota	No	Yes	Yes	Yes	Yes
Ohio	No	Yes	No	No	Yes
Oklahoma	No	Yes	No	No	Yes
Pennsylvania	No	Yes	Yes	No	Yes
Rhode Island	No	No	Yes	Yes	Yes
South Dakota	No	Yes	No	Yes	Yes
Tennessee	No	No	Yes	No	Yes
Texas	No	No	No	No	Yes
Utah	No	No	No	No	Yes
Virginia	No	No	No	Yes?	Yes
Wyoming	No	No	No	No	Yes

For successful innovation to occur, the governance of science and that of society are necessarily interconnected and, in the case of the US states, this linkage has become a site for political competition. States are competing in terms of both the funding they commit to stem cell science and the moral values and regulatory frameworks they consider should guide its development. Thus we find that the states that have an established biotech base and have invested heavily in stem cell science also tend to be the ones with the most progressive stem cell research legislation. On the pro-stem cell science side, we find that California, Connecticut, Illinois, Maryland, New Jersey, New York and Wisconsin have all introduced supporting legislation. Against are

states that have reinforced their existing bans on human reproductive cloning to outlaw embryonic stem-cell research within their borders: Arkansas (2003), Indiana (2003), North Dakota (2003) and South Dakota (2004). Meanwhile, in 2000 Louisiana banned all research using human embryos created in fertilisation clinics. It is an intense and swiftly evolving political market. The recent experience of New Jersey in November 2007, where a proposed loan of US$450 million for stem cell research to build on its existing commitments was rejected by voters, demonstrates the volatility of this particular political economy.[46]

In such a political market, scientists, companies and investors will make their own choices about where to locate based on the best available information. In this situation, networks that facilitate such information flows become an important feature of the innovation process. In addition to those networks mentioned above, the Interstate Alliance on Stem Cell Research (IASCR) was launched in 2007 'to facilitate coordination among states that wish to advance stem cell research'.[47] At its inaugural meeting the IASCR was clear that it should not advocate specific policies but 'should serve as a clearing-house for information about how participants have gone about developing stem cell research programmes in their state or jurisdiction'.[48] Interestingly, the Alliance extends this 'clearing house' networking function to include relevant regulatory information in the international domain of governance through its links with organisations such as the International Society for Stem Cell Research (ISSCR) and the International Stem Cell Forum (ISCF), both of which are concerned with the development of the technical and ethical standards governing the field.

Market

It is indicative of the American approach to knowledge production in health biotechnology that the more direct is the relationship between the research and the clinical product, the greater is the federal presence to ensure the technical regulation of safety, risk and efficacy. Protection of the potential consumer has a much greater resonance with the US federal state than does the regulation of the ethics that should guide the basic science. For the most part, that aspect is left to individual states. The federal government is principally concerned with maintaining consumer confidence and the viability of the potential stem cell market.

As a class of therapeutic agents, stem cell-based products meet the definitions of several kinds of US regulated products; biologic products, drugs, devices, xenotransplantation products, and human cells, tissues and cellular and tissue-based products.[49] The governing statutes for the regulation of these products are the 2002 Public Health Safety Act and the 2002 Food, Drugs and Cosmetics Act and the enforcement agency is the US Food and Drug Administration (FDA). In 2006 the FDA published its regulations for human cells, tissues and cellular and tissue based products in order 'to create a unified registration and listing system for establishments that manufacture human cells, tissues, and cellular and tissue-based products (HCT/P's) and to establish donor-eligibility, current good tissue practice, and other procedures to prevent the introduction, transmission, and spread of communicable diseases by HCT/P's'.[50] Embedded within these regulations are requirements for principles of good manufacturing practice (GMP) to be applied to the sourcing, process and pre-clinical evaluation, thus ensuring the ability to trace a given sample of

a product back to its source in order to deal with any adverse clinical outcomes. The regulations are administered by the Office of Cellular, Tissue and Gene Therapies (OCTGT) within the FDA's Centre for Biologics Evaluation and Research (CBER) which encourages those considering an investigative new drug application (IND) to engage in early contact and discussion with the agency.[51]

The comprehensiveness of these regulations in addressing issues of risk and safety indicates the degree to which the federal state is concerned to assure consumer confidence in the eventual stem cell product. But if stem cell science is successfully to make the long transition from laboratory bench to consumer bedside (usually estimated at 10-15 years), it requires more than simply the promise of consumer demand. It also needs venture capital investment to help develop the product during the difficult translational period where its potential is anticipated but cannot be guaranteed. If VCs are to be interested then they have to be assured that the future value of the stem cell product is legally embodied in the ownership of the current stage of its development – in other words, that it is both patentable and patented. If this is not the case, then the potential of market failure in this risky field is increased.[52]

Countries vary considerably in their approach to the patenting of stem cell science in terms of both the technical definition or scope of the patent and its moral acceptability.[53] Depending on how these issues are resolved, a country will be more or less attractive to inward VC investment in the stem cell field. For example, the European Patent Office (EPO) is currently involved in a long-running dispute over the morality of the patenting of human ESCs that inevitably impacts on VC investor interest in Europe.[54] In contrast to this, the federal US approach to patenting forms part of its established view that basic science is the first stage on the route to commercialisation: the ethical dimension does not form part of a patenting equation that is driven by the needs of the market. Beginning in 1980 with the Bayh-Dole Act and the Stevenson-Wydler Act, the US government encouraged commercial enterprises to invest venture capital directly in university-based biotechnology research via sympathetic university-based intellectual property regimes and public-private partnership research funding.[55] In the same year, in its decision on *Diamond v Chakrabarty*, the US Supreme Court ruled that a living organism (in this case a bacterium of the genus *pseudomonas* modified using molecular techniques) could be patented. In general, it commented, patents could be granted for 'anything under the sun that is made by man' and in this respect living organisms are not exceptional. Through these two actions, the US state created a patenting regime apparently ideally placed through its permissive criteria to support the early commercialisation of a field such as stem cell science.[56]

Subsequent events have shown that the politics of stem cell patenting in the US are not quite so straightforward, particularly with regard to human ESCs. Here, access to lines and processes for many academic and small biotech researchers have been rendered difficult by the 'high wall' IP approaches of some key players where tight and expensive access conditions have been placed on licensees. In particular the patent filed by James Thomson, the University of Wisconsin scientist whose laboratory first cultured human embryonic stem cells in 1998, exemplifies the innovation bottlenecks this can create for the field as a whole. [57] The patent, held by the Wisconsin Alumni Research Foundation (WARF) is very broad, covering both the

method for isolating primate and hESCs and three cell lines developed from them—neural cells, cardiomyocytes and pancreatic islet cells. A further patent claims all mesodermal, endodermal and ectodermal hES cell lines, regardless of the way they were derived. This effectively gives WARF rights over virtually all available hESC lines, if it chose to enforce them.[58] Given this level of IP control, it is perhaps unsurprising that the cost of access is high: in 2005 a commercial research license from WARF included a US$100,000 up-front fee and a US$25,000 annual maintenance fee, a significant barrier to academic and start-up commercial research. In 2002, WARF entered into an exclusive agreement with the regenerative medicine company Geron for certain therapeutic fields.

The WARF patent has generated considerable internal opposition from scientists, patient groups and analysts claiming that it is both slowing down research through its 'anti-commons' and 'patent thicket' effect and creating an anti-competitive environment for the industry.[59] [60] In 2006, a coalition of scientist and activist groups mounted a challenge to the patents on the grounds that they did not fulfil the requirement for novelty and non-obviousness. Although an initial judgement in 2007 favoured the opposition, in February 2008 a non-final decision from the US Patent and Trademark Office (USPTO) went in WARF's favour. Nonetheless, the scientists and consumer groups are determined to press the case and the conflict will undoubtedly continue.[61] [62]

As with all patenting policy, there is tension in the US approach to patenting between, on the one hand, the need of science for open (or low cost) access to information and materials, on the other, the need of industry and the investment community for ownership of the early stage science. However, when measured in global terms, this has not prevented the US from taking a substantial lead in the stem cell patenting arena. A 2005 report showed that of the over 3,000 patent applications have been published in the field since 2000, the United States had four times as many first filings as the next three countries (Japan, Australia, and the UK) combined. Furthermore, by far the majority of patents had been granted in the United States (more than 1,300, compared with sixty-four in Europe), and US companies or multinationals constituted the majority of applicants.[63] A subsequent 2006 report confirmed this view showing that the US had easily the largest number of the rapidly growing number of priority filings in stem cell research: 51 per cent of all applications filed between 2000 and 2005.[64]

Despite this, US venture capitalists remain visibly unimpressed by the alleged promise of stem cell science. Between 1994 and 2003, only about US$300 million in private venture money flowed into the small number of US biotechnology companies carrying out research in the stem cell field (Table 4). Not only was this venture capital investment highly volatile, varying between US$12.5 and $95.9 million per year, but it also constituted a mere 0.01 percent of the total US$30 billion venture capital flowing into biotechnology over that time. As might be expected, most of the investment went into companies doing the politically less risky research with adult, not embryonic, stem cells.

Table 4[65]

Investments in US companies conducting embryonic and adult stem cell science: selected venture capital rounds, 1994-2003

Year	*Company*	*Amount of VC invested ($m)*	*Total invested per year ($m)*
1994	Geron Corporation	12.6	**12.6**
1995	Aastrom Biosciences Inc	10.0	**10.0**
1996	Geron Corporation	11.7	
	Osiris	10.0	
	Biotransplant Inc	7.0	**28.7**
1999	Bresagen	7.6	
	ViaCell	6.0	**13.6**
2000	Geron	25.0	
	ViaCell	59.0	
	NeuraStem Biopharmaceuticals	5.5	
	NeuroNova AB	3.4	
	VistaGen Inc	1.0	
	Cythera Inc	2.0	**95.9**
2001	ViaCell	15.0	
	Layton Biosciences	11.0	
	MorphoGen Pharmaceuticals	8.5	
	StemCells Inc	7.0	
	StemSource	2.5	
	Nephros Therapeutics Inc	8.7	**52.7**
2002	ViaCell	1.5	
	StemCells Inc	1.1	
	Nephros Therapeutics Inc	17.0	**19.6**
2003	ViaCell	41.5	
	Geron	18.4	
	StemCells Inc	8.1	
	Cythera Inc	2.0	**70.0**

Data from subsequent years indicates a similar trend. In 2005 venture capital invested about US$5.9 billion in the Life Sciences sector (biotechnology and medical devices) of which only US$120 million went into stem cell research (0.02 per cent of the total).[66] Most recently, with Life Sciences now the most attractive venue for VC money having replaced Software as the top industry, the third quarter of 2007 shows a mere US$77 million committed to 8 stem cell or regenerative medicine companies out of a US$2.2 billion in the Life Sciences sector as a whole (0.03 per cent of that sector).[67] The lukewarm attitude of VCs to stem cells is summed up by Fred Schwartzer, managing director of the venture capital firm Charter Life Sciences in Palo Alto: 'I think most VC have looked at this research and said, "Yeah, it'll

probably happen someday, but I can't count on it. So when it does happen, call me and I'll adapt"'.[68]

For the most part, the large pharmaceutical companies are taking a similar view of the stem cell field and keeping their powder dry. There is evidence that companies such as Becton, Dickinson and Company, GE Healthcare and Johnson and Johnson have, or plan to have, some in-house stem cell research though the focus and scale of this is unknown.[69] As for corporate venture capital investment from pharmaceuticals, so far Novocell Inc, a privately held biotech specialising in hESCs, is one of the biggest recipients having attracted US$25million from Johnson and Johnson. Similarly, Roche and Novartis made contributions to the US$38 million raised by Celerex Corporation in September 2007.[70] However, the major pharmaceutical companies have kept their distance from stem cell science. Indeed, in the UK it has taken a government subsidy to attract GlaxoSmithKline, AstraZeneca and Roche into the public/private partnership 'Stem Cells for Safer Medicine' (SC4SM) with the aim of developing stem cell tools for toxicology testing.[71]

Conclusion

The idea that a national government should intervene to support the commercialisation of a particular area of science presupposes that, left to their own devices, science, society and the market will not achieve the same, or a better, effect. Where the national scientific resource base is limited, the expertise scarce, and the international competitive position weak, such an approach is rational. Where none of these things are true, it is highly questionable. Despite alarmist reports to the contrary, the analysis presented here strongly suggests that, compared to its global competitors, the US engine of biotechnology is well able to deal with the complex and volatile dimensions of stem cell development. The question is not whether the infrastructure is present (it clearly is) but whether its efficiency in the exploitation of the speculative future of stem cell science might be improved.

The aggregate commitment to stem cell science of NIH, state and private funding dwarfs the resources of any other country. With stem cells an established feature of federal allocations over the past five years, combined with an intensifying competition between US states for stem cell advantage and increasing interest from the private sector, the science is well provided for. When placed in this context, the resource implications of the Bush decision on the federal funding of hESC research diminish to the point of insignificance. What is significant is what that decision tells us about the societal concerns regarding this sub-field of stem cell science and the need for a regulatory response. Given the diversity, strength of feeling and range of statutory positions on human embryo research at the state level, the achievement of a sustainable legal compromise at federal level is unlikely. Bush's compromise and the *de facto* delegation of regulatory responsibility to a combination of state and self-regulatory mechanisms then becomes a not unreasonable political route to take, particularly when supported by networked flows of regulatory information. The conflict will continue, but it will be managed through a political market.

Although hESC research is but one sub-field among several in stem cell science, it has also proved a problem child for the market. The difficulties surrounding the WARF patent show how the structure of a state's patenting policy can impact unequally on

the interests of science (by constraining or facilitating information flows) and those of the market (by providing expanded or restricted ownership rights). Given the absence of a morality clause in its patenting legislation, what the US has so far avoided, unlike Europe, is the expression of societal concerns in patenting challenges.[72] Potential conflicts over social values are also avoided in the American approach to the regulation of stem cell-based products by the FDA where the focus is exclusively on safety, risk and efficacy.

As stem cell science moves to clinical testing the ability of the FDA to reassure both potential consumers and VC investors that process and products are safe assumes centre stage. At least three leading embryonic stem cell companies are planning to begin human testing in 2008: Geron (spinal cord injury), Advanced Cell Technology (vision loss diseases) and Neuralstem (spinal cord injury).[73] Meanwhile, several adult stem cell companies are already conducting clinical trials in the US: Osiris (Phase III trial of Prochymal, a mesenchymal stem cell based therapy that has orphan drug status with the FDA, for Graft versus Host Disease (GVHD) and Crohn's disease),[74] Stem Cells Inc. (Phase I trial in infants for Batten's Disease using their patented neural stem cells),[75] Aastrom Biosciences Inc. (Phase I/II trial using bone marrow derived stem and progenitor cells for accelerating healing of long bone fractures),[76] and Mesoblast (Phase II trial of NeoFuseTM, an allogeneic adult stem cell product for the treatment of degenerative intervertebral disc disease).[77] With the VCs and Pharma still unconvinced of the stem cell future, much depends on how well early clinical trials or new 'breakthroughs' at the research level will play out, and how well regulations developed for their passage to clinically approved products and GMP approved cell production processes perform. The recent announcement in November 2007 of a new scientific method for achieving pluripotent stem cells, the 'reprogramming' of adult stem cells through induced pluripotent cells, has injected further instability into the market with Geron's stock falling 40 per cent in the following 3 months.[78]

It is this very uncertainty that in the US case renders directive state intervention an unnecessary and counterproductive panacea. Other states may be obliged to second guess the stem cell future because their innovation infrastructure lacks the resources to adapt and exploit the commercial opportunities of the field as they arise. The US does not have that problem and it would be politically unwise for it to act as though it does.

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