

Chapter 2

Characterizing International Stem Cell Research Niches

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2.1 Introduction

This chapter assesses global research climates for stem cell-related research, analyzing infrastructure, governance, and funding patterns within regions and their interactions with social, historical, and political influences. Our findings derive primarily from site visits, interviews, and experience working with stem cell researchers in multiple research institutions in North America, Europe, and Asia. Authors Palecek, Schaffer, and Zandstra participated in a global assessment of stem cell engineering to identify emerging innovations, identify opportunities and barriers in the field, and provide information for funding agencies for the future (Nerem et al. 2013). Hogle has interviewed stem cell scientists and engineers in North America and Europe for more than a decade. We add to these firsthand observations some contextual understanding of why and how stem cell research more broadly has emerged in the way it has in different regions. In this chapter, we compare the contexts of global research environments. The chapter is not meant to be a comprehensive global

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analysis, which would take several volumes. Also, available published data and analyses are uneven; information on current governance, capital and financing, or stem cell training is more readily accessible for some regions than others. Instead, we have selected countries with which we are more familiar and which have salient features to discuss to illustrate our points. We begin with an overview of general trends we have observed, followed by activities in regional niches. We do not pretend to have sufficient empirical data to provide precise prescriptions; rather, we offer the benefit of our individual and collective observations through study of and collaboration with labs across these regions.

While many existing analyses of stem cell activities focus on cell therapy applications, we include stem cell-related diagnostics, disease modeling, drug discovery, and more, all of which require expertise from various engineering and computational sciences as well as biological sciences. More than simply identifying locales and describing existing research activity, our observations help to illuminate why and how research has been shaped as it has in various regions. This insight will provide a window to understanding where opportunities exist for improvements in science policy and, more specifically, research program planning for regenerative biosciences.

Existing descriptions of the state of the field often assume that regenerative medicine has developed where and how it has because of ethical or regulatory environments, which either constrain or support the research. Certainly policy that restricts the use of particular procedures or cell types limits access to materials and blunts knowledge, and there is a possibility of a brain drain as researchers move to locales more favorable to stem cell research. There is some evidence suggesting that researchers may shift their research as a result of the sheer uncertainty. Other feasible assumptions are that particular locales dominate because of powerful key scientists or political advocates who drive the research or because funding is more easily available. While there is no doubt that these elements affect the direction and tempo of any research, we argue that these explanations alone are too simple: there are far more complex interweavings of political, historical, economic, moral, and technical specificities that shape regenerative medicine research differently within locales. This is not to say that stem cell research microenvironments exist in isolation: regional and local-level conditions interact with international trends in much the same way as stem cell niches in the body affect and are affected by their interactions with other bodily systems.

In some of the countries we include in our discussion, research flourishes in spite of a lack of policy or regulatory clarity or with funding flows that are less than optimal for the particular needs of stem cell research. In other areas, it has failed to get traction in ways one might have predicted. Taking a fresh look, without taken-for-granted assumptions, we can ask different questions. Rather than simply asking where the favorable or unfavorable policies are, we can ask broadly what are the most important situational components that appear to help or hinder research? When we understand the contexts in which regenerative medicine science and policies are shaped, it is possible to identify needs and promote policies to enable researchers to capitalize on opportunities: where are natural avenues for collaborations, and how

have collaborations been supported (or not) in various environments? What are identifiable skills and resources needs for the longer term as well as immediate needs? As we learned, there is insufficient data on some regions to make comparisons evenly. What information is needed to provide insight into what governance forms do or do not work well? We hope that our observations about the experiences in various countries will stimulate fresh strategic thinking about how to develop policies to transcend differences in ways that will meet real global health needs while supporting both translational and discovery research.

2.2 Global Patterns of Activity

Our review shows that where regenerative sciences are emerging, there are diverse rationales for pursuing regenerative medicine, various ways of organizing and funding research, and differing degrees to which collaborations are being formed (within or across national borders). Countries may consider investing in innovative science (and regenerative medicine in particular) for economic growth, a way to grow innovation processes or science infrastructures or a way to serve the country's health needs. Politics and science thus are co-produced. Development of a new area requires the political will to do so, which in turn affects regulatory policies, legislation, and funding.¹

2.2.1 *Investments in Global Knowledge Economies*

Funding is central to the development of new scientific endeavors. However, it is not only the level but the type of financial arrangements that matter. Funding in Singapore, China, Japan, and the state of California, among other locales, has been a part of strategic government-sponsored initiatives. In other countries, there may not be an explicit national strategy or coordinated effort, but a mix of public and private funding is available.

The countries which have made stem cell research a central part of a national science strategy are not necessarily those with the kind of existing industries capable of taking up product development once innovations leave the lab (Salter 2009a). Countries still in development and those which had devastated economies after World War II focused on building specific industries in the second half of the twentieth century that would aid in rebuilding and enable their participation in global markets. These were largely manufacturing and mass production technologies.

¹It is also important to remember that bounded entities such as “the state” may be friction with supranational entities such as the European Union, the World Trade Organization, and other transnational entities attempting to enforce global harmonization of policies, definitions, and practices (Jasanoff 2004).

By the end of the century, there was a recognition that expertise was equally important as a national resources as production capacity. The transition to “knowledge economies” required specialized labor competencies, and the global focus shifted to communications and life sciences (Etzkowitz and Leydesdorff 2000). However, the life sciences are less developed in many of these countries, and regenerative medicine is uncertain with high initial investment costs. Also, developing nations, particularly those with central economies, have little experience or institutional structure with which to proceed with scientific or clinical innovation, especially when it is market based. In economies that are restructuring, the capacity to refocus national commitment comes with a concomitant need to restructure laws and social policies, in order to be globally competitive. As we have seen with several countries, this has been a struggle when approaching multifaceted life sciences sectors, especially those such as stem cell research which have faced public controversy.

We note that translational approaches dominate in almost every locale pursuing regenerative medicine research. While “translational medicine” is most simply defined as getting ideas from “bench to bedside,” indicating the application of research for clinical purposes, the term is often taken to mean “commercialization,” since product development, production, marketing and pricing are involved in getting products into circulation. This has implications both for academic-industry relations and for research funding. Conventional funding mechanisms are designed to support individual labs in discovery-level, disciplinary-based research. The kind of interdisciplinary, often pragmatic work that is necessary for bench-to-bedside work has not historically been rewarded by grant mechanisms or through merit systems in the university. However, some new funding initiatives are beginning to support translational work, such as EU Framework initiatives built around a particular problem, encouraging multi-investigator projects and potentially aimed at clinical translation. The National Center for the Advancement of Translational Science (NCATS) within the NIH was established in 2011 to support activities to “reduce, remove or bypass bottlenecks in the development of new treatments and tests that will ultimately improve human health” (<http://www.ncats.nih.gov/>). Translation-related initiatives and centers include the Berlin-Brandenburg Center for Regenerative Therapies, Canadian Center for the Commercialization of Regenerative Medicine, Fraunhofer IZI, McGowan Institute for Regenerative Medicine, and the California Institute for Regenerative Medicine (CIRM), among others.

The participation of strong private funds and venture capital in novel areas of science depends largely on whether decentralized, private investment is encouraged or discouraged by financial and scientific regulatory institutions (Bruton et al. 2005; Salter and Salter 2010). As Salter points out, the effect of investments in innovation relies on a country’s environment for intellectual property rights, tax laws or incentives, and managerial freedom to exploit the value of an innovation as much as on the nature of the innovation itself (Salter 2009a). These factors help potential investors weigh risk against potential gains. In this sense, the environment has been most favorable in the USA, which had 76 % of the global total of venture capital funds in 2011 (Burrill 2012). Nevertheless, there is still a significant problem of the “valley of death” for start-up businesses; that is, the trough between obtaining angel or venture capital before the product is able to bring in revenue. For regenerative medicine

(RM) firms, there is also often a gap between initial funding for early phase clinical trials and the enormous investment needed for scaling up for phase II trials. Especially since the financial crisis in 2008, potential investors have been more risk averse, and pharmaceutical and biotech companies have been less inclined to invest in the highly risky market for clinical stem cell products, particularly in locales with more formidable or unsettled regulatory climates (Brindley et al. 2011; Pagnol et al. 2009; Rao 2009). This situation may be changing as the industry picture improves, but it is too early to tell (Mason et al. 2012; see also Martin et al. 2006).

For highly specific, high-tech enterprises such as regenerative medicine, intellectual property (IP) is a valuable resource. For some high-tech fields, patents may be worth less because the technology goes out of date quickly, but patent protection is seen to be paramount because of the high costs and long development times. Patents have become central to the uptake and growth of innovative science, but firms (especially new start-ups) must also have the kind of knowledge and expertise needed to attract talent, collaborators, and investors in the global market: “For capitalization of a new knowledge market to occur, investors need to be reassured that the *value of the knowledge*, as opposed to the value of the eventual product, is in the hands of the company concerned” (Salter 2009b, p.411, emphasis added). Knowledge includes not only scientific expertise but also expertise in all the processes needed to scale up, distribute, and get products into the hands of users. A country with a history of a strong centralized economy transitioning to a market-based economy is unlikely to have a strong private capital base or institutional structures to support it, much less the kind of expertise that entrepreneurial academic researchers would need to launch new products. In our observations, there may be a concentration of wealth in some countries, but investors may be reluctant to invest in a country if it has insufficient capital and talent infrastructure to support new technology development.

Funding mechanisms that comprehend the necessity of interdisciplinary and applied work will be crucial if translational approaches continue to dominate. The National Academy of Sciences recently acknowledged the need for more integrative science, stating that the new biology is an integration of many subdisciplines as well as the integration of physicists, chemists, computer scientists, engineers, and mathematicians in order to solve complex scientific and social problems (National Research Council 2009). For translational regenerative medicine to succeed, a more systems-based approach will be needed, that is, the ability to identify components of complex systems and understand how they work together. This requires knowledge from diverse fields not normally associated with stem cell research including materials science and biophysics, improvements on scaling up laboratory culture systems for biomanufacturing, better quality control mechanisms that may not be based on conventional biology, computational techniques for modeling cell behavior and tissue construction, and other integrative ways of approaching problems. Engineering, chemistry, and physics have become a critical part of tissue engineering and stem cell research, not only due to their contributions to “enabling technologies,” such as culture systems, high-throughput techniques for screening molecules, biomaterial scaffolds and matrices, and process automation, but also in identifying physiologic and mechano-physical properties crucial to

in vitro cell processes. Consequently, these fields are making major contributions to discovery science.

Companies producing research tools, culture systems, and reagents have been successful in the market. Ironically, they are not as successful in raising investment due to a lower ROI than therapeutic products (Rao 2009).

2.2.2 Policy Variability

The considerable variability in policies around the world has affected the procurement of biological materials (including cells, tissues, and genes), derivation of cell lines, data and materials sharing, and ultimate use of cell lines for both basic and clinical research (Isasi 2009; see also Appendix B). This was particularly true in the early years, when the variance in informed consent standards, derivation practices, or ultimate use restrictions for cell lines derived from embryos hindered sharing of materials and collaborations across national or even institutional lines (Caulfield et al. 2009; Elster et al. 2008; McCoy 2009).

The reason often named for the variance in policy stances on stem cell research is religion—more specifically, Catholic and evangelical protestant sects—which tend to object to embryo use in research and almost any science that “tampers with nature.” It is important to note that the political influence of religion is diverse and the existence of increasingly politically assertive religion(s) in some parts of the world is a much broader phenomenon than what has been experienced with stem cell research alone (Toft et al. 2011). The role of religion in influencing public policy and law in various countries has not always been consistent over time. The relative role of religion in governance is in constant interaction with other economic, social, and political forces and activities are often connected to other social movements. Also, while some generalizations can be made, it is a mistake to presume that “religion” means opposition to science, as many commenters have. No group is so homogenous that there are not differing stances within each religion.

While the field has evolved, and the focus is shifting to nonembryonic sources, policy (and analyses of policy impacts) has continued to focus on constraints related to embryo-derived cell lines.² A number of emerging issues facing the field as a whole have yet to be addressed or are addressed unevenly in different regions, including data sharing, intellectual property issues, and potential ethical concerns about synthetic biology and gene-editing techniques, the use of epigenomic data, and more.³

²de Vries et al. (2008) track the proportion of articles devoted to HESC, cloning, and other topics, showing the dominance of embryo-oriented concerns of bioethics articles.

³Chapters 4 and 5 address the tensions between enforced data sharing (especially for genomic data) and capturing intellectual property. Given the debates on synthetic biology in Europe and, to a more limited extent, the USA, and the history of debates and policy implementation on gene therapy, it is remarkable that such issues have not been raised in stem cell research.

Efforts have been made to harmonize standards and regulations across political, ethical, and national borders. International organizations such as the International Society for Stem Cell Research (ISSCR) and the International Stem Cell Forum actively promulgate standards for protocols, guidelines for research ethics, and norms for human trials (ISSCR 2008). Still, with such differing historical and cultural backgrounds in various locales, this is nearly impossible to accomplish.

For all the discussion in science policy literature about harmonizing policy to facilitate development of a field, governments can make their own decisions about science and technology matters, weighting morality, religious traditions, economics (or perhaps more specifically, markets), public opinion (or perhaps projected constituency votes), or other pragmatic decision-making factors. It is not enough simply to acknowledge that there is significant variance in policies or attitudes toward regenerative medicine; rather, in order to navigate the differences, it is helpful to understand why particular social values become embedded in decision-making processes (cf Gottweis, Salter and Waldby 2009).

For some countries, there are competing incentives on the road to global competitiveness. Conforming to higher regulatory and research ethics standards promulgated by a few countries may provide greater credibility in the global scene, but following less restrictive guidelines may enable faster entry into clinical trials, faster results, and draw more capital than others. For-profit firms with investor expectations of a fast and high return on investment may be tempted to find less challenging regulatory and ethical environments to explore stem cell products. This is not new: pharmaceuticals have regularly been tested in resource-poor countries with fewer regulatory limitations. The potential danger to the product sponsor is acceptability of the data to more stringent review authorities in the USA or EU. For the research subjects in those locales (frequently the vulnerable members of society who otherwise have little health care), the risks of participating in experimental trials are multiplied, especially if there is no ability to care for them post-trial (Petryna 2009).

2.2.3 *Stem Cell Tourism*

More controversial are clinics advertising treatments which have not been proven through more rigorous standards of conventional oversight and accessed through established clinical researchers but, instead, are offered directly to the public (Regenberg et al. 2009). This growing phenomenon has been a concern due to potential risk to patients but also risk to the field as a whole, should patients be harmed. It also raises an important question about the pressure to do translational stem cell research and the rush to get into the clinic without first gaining important knowledge from discovery science.

The “hype” around stem cell treatments is at least partly to blame for the increasing number of clinics around the world offering treatments for a wide variety of disorders. The clinics are not always transparent about their processes, expertise, or even the type of cells being used. Many of these clinics (but not all) are in resource-poor

countries which may not have stringent oversight or regulation over research or therapeutic practices. Patients—usually from wealthy countries—spend tens of thousands of dollars for procedures to travel to these sites, hence the term “stem cell tourism.”

Medical tourism is not new; patients desperate to find treatments for rare or terminal diseases have long sought treatments outside of the bounds of conventional allopathic, scientifically proven medicine (Turner 2007). At the same time, there is a rapidly growing industry of clinics offering routine high-tech medical care in countries where the costs are more affordable than others, which may confuse health consumers in terms of which clinics offer proven treatments (*ibid*). This may make it more difficult for patients to discern legitimate trials from offers of treatments advertised by clinics which have not undergone rigorous review.

Not all sites recruiting patients are outside of North America and Europe.⁴ One US-based web site positions itself explicitly as a patient advocacy organization, helping people to find a stem cell treatment and physician for members but goes further by to claiming entitlements to treatments as a self-determination and patient rights issue. From their web site: “We believe in the human voice and the human spirit. We believe that if people take care of their bodies and become their own advocates for determining what treatments are right for them that we can start an uprising for the general public” (Med Rebels, found at <http://medrebels.org/about-us/>). This is confusing for patients who seek treatments, particularly for disorders with few treatment options, particularly in the neoliberal public policy climate of the past two decades in many countries promoting patient self-care and “empowerment”.

The current atmosphere pits cautious, risk-minimizing approaches to stem cell treatments against aggressive approaches framed as progressive and patient-consumer oriented. Countries restricting clinical use until extensive tests for safety are sufficient to proceed may appear to be blocking access to needed treatments (much like any other novel, first-in-human therapy), while others, promoting their services directly to patients, promise easy access to treatments that home countries refuse to provide for political reasons (Petersen and Seear 2011).

Furthermore, legitimacy is established when governmental authorities explicitly allow experimental treatments to proceed before evidence exists that they are safe and efficacious. The Italian Parliament, for example, is considering a new law making it legal to conduct such treatments in Italian public hospitals, outside of EU and Italian regulatory laws (Bianco et al. 2013). In Texas, new guidelines allow stem cell procedures as long as they are done for research, receive approval from an institutional review board (which could be private and profit-making entities, not attached to medical institutions), and patients must sign an informed consent form (Cyranoski 2012b; Park 2012).

While patients are warned against participating in treatments that have not been validated, clinics often use a narrative framework of offering hope and often post

⁴See, for example, the 2013 report on practices at US-based Precision Stem Cell at <http://www.alsworldwide.org/documents/PrecisionStemCellReviewMarch192013.pdf> and a subsequent blog-post discussing the report at <http://www.healthintheglobalvillage.com/2013/05/06/precision-stemcell-selling-stem-cells-treating-individuals-with-als-as-human-guinea-pigs/>.

positive testimonials on the Internet (ISSCR 2008; Lau et al. 2008; Lindvall and Hyun 2009). In the Italian case, public campaigns in favor of allowing treatments claimed that compassionate therapy was being denied to dying children if they were denied. In the Texas case, the debate was shaped by the governor, Rick Perry, who had himself undertaken autologous stem cell treatments and strongly supported allowing the procedure to continue. Such narratives frame the participation in experimental treatments as a patient right and autonomy issue and add credence to the effectiveness of treatments. At the same time, they may take advantage of the hopes and fears of patients in a vulnerable state.

The operation of questionable clinics with treatments that have not been validated (or worse, are based on pseudoscience) is disturbing, as patients may indeed be harmed. Yet focusing on the spectacle of stem cell tourism obscures an equally disturbing situation; that is, the phenomenon makes the environment far more difficult for legitimate researchers to navigate. The already-difficult decision about what sort of trials to execute and where, and how much preclinical data is sufficient before testing experimental treatments in humans, becomes far more sensitive in light of the spotlight on such controversial treatments.

2.2.4 Collaborations and Expertise

A number of organizations have arisen to galvanize research, help researchers to coordinate efforts, and garner public support. These have all taken different forms, in some cases being public-private partnerships and in others formed as not-for-profit advocacy groups. Such groups can sometimes bridge the gap when there is weak national leadership or there are no clear national strategies or where there is a need to bring patient groups together with researchers. A few examples include the Alliance for Regenerative Medicine (ARM) in the USA (a nongovernmental consortium of industry, university, and patient organizations which lobbies for favorable policy and regulatory environments and sponsors scientific exchanges), the Genetics Policy Institute, and the Tissue Engineering and Regenerative Medicine International Society-North America, among others. Internationally, groups include the International Society for Stem Cell Research (ISSCR), the Stem Cell Network (SCN) in Canada (which provides funding for scientific and policy research as well as conducting public education activities), the UK SCN (a publicly funded organization for scientific exchange and to promote commercialization), Stem Cells Australia (a recently reformulated effort focused on interdisciplinary collaborative interactions), and the Scottish National SCN (publicly funded for a fixed term and functioned as an advocacy and scientific community organization). The Japan Society for Regenerative Medicine was created in 2001 to promote research but has not been seen to be a strong coordinator of efforts across universities or link universities with industry; individual researchers have instead created the collaborations that exist. Chinese scientists also do not appear to have as much of a social infrastructure for collaboration and exchange as other countries.

We also observed a need to establish an adequate knowledge base or a way to acquire expertise through collaborations (cf Johnson et al. 2010). Collaborations for translational work are more effective where there are existing ties to industry and strong links between researchers and clinicians. For example, there are natural relations of industry and academia in places like Switzerland, which has a strong industrial base in pharmaceuticals. Also important is the capacity to conduct clinical trials. Locales where hospitals have appropriate equipment and expertise and where there is a critical mass of research expertise near clinical sites have an advantage. Research centers with close ties to clinics can not only obtain materials more easily (donated embryos for cell line derivation, cells for reprogramming, or bone marrow-derived stem cells) but have facilities in which patients can be treated and monitored.

As for expertise, we observed strong engineering components in stem cell research in Switzerland (EPFL), Germany, and the Netherlands. Japan has a strong engineering base, but integration of engineering and manufacturing with stem cell science is still in early stages. By comparison, engineering research in the USA and Canada is far more integrative with biology and addressing more fundamental discovery questions. This may be due in part to more experience with interdisciplinary research and training. Some countries adhere to strictly disciplinary training and ways of thinking about the role of specific types of expertise such as engineering, computational fields, or biology. They may utilize expertise from various fields but have not as readily taken up the kind of integrative, interdisciplinary research needed in regenerative medicine. In countries that have more at stake for economic development, there may be a tendency to use engineering as a practical way of building industry, rather than as a discovery science. For example, Portugal is capitalizing on historical experience in bioprocessing to move into regenerative medicine. It may also be that work on technical tools and aspects of research (e.g., the development of cell sorting and tracking systems or computational modeling) may be easier for policy-makers and funders to justify in an emerging, controversial field than research dealing directly with the use of embryos or genetic manipulations.

With this overview, we have introduced general patterns, which can be used to identify needs in this increasingly global field. In the next sections, we provide more situational analysis that helps to explain how regenerative medicine has developed the way it has within specific locales.

2.3 North America

This section provides an overview of funding and governance in the USA and Canada, adjacent countries with very distinct health-care and regulatory systems. Although there are many similarities, the two countries have approached the coordination of funding and support in very different ways. There is a considerable degree of cross-border collaboration, facilitated by the lack of language barriers and relative ease of access to researchers.

2.3.1 *Canada*

Canada occupies a unique position in the rise in regenerative medicine. Canada is home to James Till and Ernest McCullough, who helped define the fundamental properties of stem cells and thus catalyzed the development of stem cell therapies. A physicist and a physician, they studied the effects of radiation on bone marrow and demonstrated in 1963 the cardinal properties of stem cells, the ability to divide and give rise to other cells with similar developmental potential, and the ability to differentiate into the many cell (in this case) of the hematopoietic system.⁵ Because their work had direct impact on cancer biology and therapeutics, it is not surprising that cancer research and regenerative science research emerged as a unified strength in Canada; that is, existing attention to cancer draws young investigators to the field, and funders would support this new, related area of research, focusing, initially, on bone marrow-derived cells and the hematopoietic system and expanding to other stem cell types with time and increased activity.

Stem cell research now occurs in several sites, dominated by large medical-academic centers in Toronto, Vancouver, and Montreal. However, there are few researchers relative to other countries, and they are spread across a large geographic territory. A stem cell network (SCN) was created and funded by the Canadian government to aid collaborations, support education and research in the field, and coordinate efforts, especially toward commercialization. The network covers costs that are not generally eligible for funding under federal research programs. The SCN has funded more than \$42 million in interdisciplinary projects across Canada, resulting in 962 publications, 399 patent applications, 60 issued patents, and 43 licenses as of 2012 (Nerem et al. 2013).

Major sources of science funding in Canada are the Canadian Institutes for Health Research (CIHR) and the Natural Sciences and Engineering Research Council (NSERC), which funded the SCN. Through its funding and governance policies, the Canadian government places emphasis on how science can contribute to the Canadian economy, particularly in the past few years. For example, grant applicants are typically encouraged to discuss translational aspects of the impact of their projects as a part of their scientific proposals. Funds for basic science have not maintained the same growth rate as earlier years, although new funding mechanisms have been created to support academic-industry collaborations, including the Centres of Excellence for Commercialization and Research (CECR), created in 2007.

In an early effort to align research and commercialization efforts in Canada, the SCN set up a company, Aggregate Therapeutics, aimed at collecting stem cell IP and expertise from labs across Canada under one umbrella. Aggregate Therapeutics was eventually folded into MaRS, a Toronto-based organization created to promote and commercialize Canadian science.

A recent effort to commercialize regenerative medicine related technologies is Canada's Centre for Commercialization of Regenerative Medicine.⁶ The CCRM

⁵Their work was published in 1963 in *Nature* (Becker et al. 1963).

⁶Coauthor Peter Zandstra is currently Chief Scientific Officer of the CCRM.

(funded by the CECR) was created as a not-for-profit organization to commercialize stem cell technology platforms based on Canadian researchers' strengths. Developed in close partnership with MaRS Innovation and the Canadian SCN, key platforms include reprogramming and engineering, biomanufacturing, and materials research. The CCRM is essentially a consortium of hospitals, universities, and industry members. Innovators can have their ideas and IP evaluated in terms of potential for commercialization and business model, and receive feedback, while members and potential investors have a right of early access to emerging IP. This arrangement is designed to be a more collaborative and transparent way of working on precompetitive research and a way to support research that is beyond the stage eligible for traditional basic research grants, but not yet at a stage for licensing or company creation. The CCRM may provide seed funding or co-funding with other organizations.

Key legislation affecting stem cell research includes the [Assisted Human Reproduction Act](#), which governs embryo research in Canada. The Act prohibits buying or selling of gametes and embryos as well as human cells or genes for use in creating a human being. The [Tri-Council Policy Statement \(TCPS2\)](#), Canada's federal research ethics guidelines, contains a similar prohibition. The Canadian Institutes of Health Research updated guidelines specific to pluripotent stem cell research in 2010, which were adopted by the major funding agencies.⁷ The guidelines address research ethics issues specific to the use of stem cells but also issues around commercialization, including a provision that donors must be informed if products from their biospecimens may ultimately be used commercially.

Possibly unique to Canada, a significant amount of funding has been designated for stem cell policy analysis, ethics training for researchers, and outreach to the public. A series of white papers and clear explanations of ethical and social issues is posted on the SCN web site, and several meetings have been convened on various aspects of stem cell research governance and ethics (see <http://www.stemcellnetwork.ca/index.php?page=ethics&hl=eng>).

In terms of regenerative medicine education in Canada, most graduate activity is centered around medical school or biomedical/bioengineering-related research programs in the larger academic centers (such as the Institute for Biomaterials and Biomedical Engineering at the University of Toronto). The CIRH supports a national Training Program in Regenerative Medicine, with online national and international courses and laboratory exchange programs. At the undergraduate and high school level, one strategy has been to educate high school teachers and key classroom leaders through the StemCellTalks program, a national stem cell biology outreach initiative in partnership with Let's Talk Science and the SCN. From a more translational perspective, the NSERC of Canada recently funded a Collaborative Research and Training Experience (CREATE) Program in RM Manufacturing, Materials and Mimetics (M3). Despite these initiatives, a coordinated national strategy for fundamental and translational (both clinical and manufacturing) regenerative medicine training remains to be developed.

⁷ A summary of the guidelines can be found at <http://www.cihr-irsc.gc.ca/e/42071.html>.

2.3.2 *United States*

Ever since James Thomson became the first to successfully cultured nonhuman primate and then human embryonic stem cells, the USA has been considered as the leader in the field. The USA has strong labs and sufficient private capital and institutional support to sustain research.⁸ Productivity (as measured by publications) is high in the USA, with an estimate of 38 % of world publications in stem cell research. One quarter of these had author collaborations with researchers in other countries (Luo et al. 2011). Yet the USA has no dedicated national strategy for stem cell research, and research and funding policy has been in flux since the early years of stem cell research.

In the absence of centralized federal leadership, some individual states have made stem cell research an explicit priority and have allocated budgets for this purpose.⁹ Of particular note, California voters passed a state initiative creating a \$3 billion fund for stem cell research at California institutions for a 10-year period. The organization created to fund and oversee the research is the California Institute for Regenerative Medicine (CIRM). Because the primary justification for its existence was to translate research into products beneficial to the taxpayers of California who voted in the initiative, the current focus of projects is on translational research and commercialization (Longaker et al. 2007). CIRM has agreements with the UK, Canada, and Japan to collaborate on research and recently contracted with a private company, Cellular Dynamics, to produce a bank of iPS cell lines for disease research, drug discovery, and other research.

The USA is characterized by more active public interest groups advocating for or against stem cell research than many countries. Advocacy and lobbying groups on both sides have actively worked to change public policy, influence public opinion, and attract funding. Most, but not all, opposition groups are conservative religious groups (American Right to Life Committee, Focus on the Family, etc). Many of these are more broadly engaged in American politics, particularly opposing abortion, and were key constituents in the mid-1990s political shift to the right, setting the stage for the President Bush era rulings on stem cell research. Stem cell research entered this climate in 1998 with James Thomson's successful creation of an embryonic stem cell line. Their activities do not end with HESC research, however; ongoing attempts to influence legislation will likely affect many forms of regenerative medicine-related research (see Chap. 1). Groups promoting stem cell research include the Alliance for Regenerative Medicine (ARM), which works to promote legislation as well as regulatory and reimbursement plans to create favorable environments for stem cell research and product development. ARM also focuses on attracting VC and other private and public funds to the field. The Coalition for the

⁸The USA has been extensively discussed elsewhere; therefore, only key points for comparison will be covered here. See, for example, Johnson et al. (2011), Lysaght et al. (2008), Rao (2009), and Salter and Salter (2010).

⁹States enacting stem cell funding mechanisms are listed at <http://stemcells.nih.gov/research/pages/stateResearch.aspx>.

Advancement of Medical Research (CAMR), a consortium of patient advocacy groups, scientific societies, and university research centers, also lobbied for increased federal funding.¹⁰ The Genetics Policy Institute is a pro-cures organization that hosts a unique forum which brings together patients and disease advocacy groups with scientists and industry representatives to discuss issues facing the field.

After considerable public debate and activities from these groups, the federal government made a decision not to outlaw HESC research but to disallow funding with federal (taxpayer) money. The 2001 Presidential Statement by President Bush disallowed federal funding for the derivation and use of embryonic stem cell lines except a small number which were already in use.¹¹ The lines approved by the NIH were included in a registry, and a national stem cell bank was created to house and distribute the approved lines.¹² With little federal funding, the overwhelming majority of embryonic stem cell research was done with private funds. This is significant, because there was little oversight or transparency about derivation or research practices in privately funded research. Another direct result was that individual states began instituting their own rules. Some states made bans of HESC or cloning research more explicit, while others, as mentioned above, created mechanisms to support it. CIRM also developed its own governing body to review guidelines as well as protocols, creating an analog to NIH review processes.

Executive Order 13505 (“Removing Barriers to Responsible Scientific Research,” 2009) replaced the 2001 policy, allowing federal funding for HESC research and creating a new set of ethical guidelines for research and derivation of new lines.¹³ However, for both existing and new lines, proof of provenance was required before lines could be included in the new registry. Provenance information included demonstration that informed consent forms for donated embryos had appropriate language informing donors in greater detail about the disposition of their embryos. Because a number of lines had been derived from embryos donated years before embryonic stem cells were successfully cultured and came from a variety of public and private clinics in several countries and because there has never been consistency in informed consent language across these sites, provenance was extremely difficult to track. As a result, many of the gold standard lines could not be used in federally funded research projects for more than a year after the new rules went into effect. Researchers had to stop work or obtain approval to switch to another line if the line

¹⁰ CAMR recently merged into the ARM.

¹¹ The statement on August 9, 2001 attempted to make a compromise, by allowing limited federal funding for certain lines approved by the NIH as meeting the following criteria: They must have been derived with donor consent and without financial incentives; they must have come from embryos created for reproductive purposes but not used. Lines from 14 countries were initially included; ultimately only 21 were available to researchers for use, as many were of poor quality or had restrictions on use.

¹² The National Stem Cell Bank was housed within WiCell at the University of Wisconsin. Federal funding for the bank ended in 2010, but banking services continued as the WISCBank, which now distributes both embryonic and induced pluripotent stem cell lines.

¹³ Also rescinded was Executive Order 13435 which opened funding for nonembryonic, alternative sources of stem cells. <http://www.gpo.gov/fdsys/pkg/FR-2007-06-22/pdf/07-3112.pdf>.

they were using was not already approved under the new registry, even if it had been accepted in the previous registry and approved by the NIH. Ultimately, new lines were approved, and there are more than 200 HESCs are on the current NIH registry (http://grants.nih.gov/stem_cells/registry/current.htm). In the meantime, a number of competing private and public banks proliferated around the world.

The change in policy, while permitting federal funding, meant a lengthy time for approval of long-used lines and uncertainty over which would be approved for use. Then, just as the bottleneck was easing, additional law suits attempted to block funding once the new guidelines took effect.¹⁴ All of this made for considerable uncertainty for researchers and investors regarding the stability of funding and research policy. The impact on ongoing and future research was palpable, affecting international collaborations as well as work within the USA.¹⁵ A survey of US stem cell scientists found that almost half of those using embryonic stem cells indicated that the ongoing uncertainty of national policy had a substantial impact on their research plans, but a number of those using human nonembryonic pluripotent stem cells also reported significant impact (Levine 2011).

In the USA, funding for most basic biomedical scientific research comes primarily from the National Institutes of Health, with additional funding for development phases coming from private industry. The National Science Foundation funds non-clinical science and engineering.

About \$1.45 billion of NIH funds was spent on stem cell-related research in 2012, with most of this going to nonhuman, nonembryonic research, which includes all materials and techniques research. Only about 10 % (\$146 million) of the total was devoted to HESC research, a relatively small increase since the pre-Executive Order amount of \$88 million in 2008 (about 8 %).¹⁶ By comparison, CIRM has a \$3 billion fund over 10 years, New Jersey invested \$380 million investment in a state

¹⁴ *Sherley v Sibelius* U.S. Court of Appeals 11-5241. The case challenged whether embryonic stem cell research would violate the Dickey-Wicker Amendment which prohibits federal funding for any research which harms or destroys embryos. The final ruling favored allowing funding to continue (see Chap. 1).

¹⁵ Levine, for example, surveyed 370 US researchers about the effect of the uncertain policy environment regarding embryonic stem cells (2011). The survey was taken after the 2009 US policy change allowing federal funding for HESC research and after *Sherley v Sibelius*. Of those surveyed, 18 % said that the resulting uncertainty meant they would either delay plans to begin HESC research, and 16 % said it would impede ongoing research (this group included those who had not previously used HESCs but were considering using them). Others reported shifting their research focus from HESCs to induced pluripotent stem cells. The disruption in recruiting new employees, consideration of a relocation, and disruption of collaborations were also mentioned as specific impacts, but these responses constituted fewer than 10 % of respondents. However, only 4 % said they would avoid using HESCs, and 3 % said they would consider relocating.

¹⁶ A chart showing the pattern of NIH funding for stem cell research can be found at <http://stem-cells.nih.gov/research/funding/pages/Funding.aspx>. The most recent NIH funding figures, including estimates for 2013, are found at http://report.nih.gov/categorical_spending.aspx. Umbilical cord blood is not counted in these figures, and the categories consist of research using keywords as defined by data mining algorithms, so may not pristinely reflect actual research projects related to stem cell research.

stem cell institute, and Connecticut committed to \$100 million over 10 years. An NIH Center for Regenerative Medicine was recently established to coordinate intramural research across centers. As mentioned above, the NCATS was also created to help facilitate the commercialization of research products.

In general the USA has a strong entrepreneurial base. There are incentives for academic researchers to commercialize their work, and many academic scientists have close ties to industry (see Chap. 1). Still, there is a gap between discovery and commercialization which has not been adequately addressed. Venture capital supported research to a limited degree initially, but after the financial downturn in 2008, investors became more risk averse (Rao 2009). The instability of private capital and difficulty in obtaining capital to get past scale-up and clinical trial hurdles, coupled with the stagnation or even decrease in federal research, is a major concern for technological innovation in the USA (*ibid*).

While entrepreneurial science is strong in the USA, so is discovery research. Engineering, for example, is more discovery-oriented than many other countries, where engineering is seen more as an applied science. Another strength of the USA is its educational infrastructure. Outstanding graduate and postgraduate education programs dedicated to regenerative medicine have been developed, and other countries encourage students to obtain training in the USA. Beyond laboratory training, however, students are provided with skills to be prepared to work in academia, government, or industry positions. As such, training programs are consistent with the National Science Foundation's goal of investing public funds to develop a strong scientific workforce capable of both basic discovery and commercialization.

2.4 Europe

The Lisbon Agenda, adopted by the European Council in 2000, was intended to make the European Union “the most competitive and dynamic knowledge-based economy in the world capable of sustainable economic growth with more and better jobs and greater social cohesion” by 2010.¹⁷ The strategy was based on concepts of innovation and the knowledge economy, in which medical science technology plays a central role.¹⁸ By most accounts, it was a failure, due in part to a lack of coordination among member states and the lack of political will to prioritize such an initiative among other pressing EU issues. The EU has since struggled to coordinate innovation policies, and there are key features that have kept it from being competitive with

¹⁷ The rationale and goals can be found at http://www.consilium.europa.eu/uedocs/cms_data/docs/pressdata/en/ec/00100-r1.en0.htm.

¹⁸ The term “knowledge economy” has been applied to the restructuring of economies through specialized expertise. In contrast to mass production or labor which characterized earlier agricultural and industrial manufacturing economies, it is knowledge—particularly in terms of engineering, science, mathematics, and information sciences—that drives the economy, and it is more global and interconnected in scope.

the USA, including comparatively weak ties between academia and industry; historically little venture capital investment, especially in high-risk innovations; and fragmented intellectual property laws (Hogarth and Salter 2010). The Innovation Union Strategy of 2010 was an attempt to rescue the aims of the Lisbon Agenda by coordinating innovation efforts across member states. Still, for regenerative medicine, major impediments remain, including limited availability of funding and intellectual property issues, especially in light of the exclusions from patentability which have constrained the research using embryos (see Noonan, Chap. 4, this volume).

Institutional structures within and across member states have also hampered development of stem cell-based regenerative medicine. Health technology assessments for new technologies, including regenerative medicine, are performed at the state level, with varying outcomes and recommendations. For example, the National Health Service structure in the UK is not a friendly environment for expensive, unproven innovations, which poses a problem for implementing stem cell products and therapies. As a result, the EU suffers from what has been called “the European paradox”: excellent science without the capability of capitalizing on innovations and turning them into social and economic benefits (Hogarth and Salter 2010).

Research initiatives across the EU have been coordinated through the Framework Programmes (FP), and this mechanism is generally considered to be a more important source of funding than internal country funds. Each FP has supported the creation of networks of excellence as well as targeted programmatic themes. The current Seventh Framework Programme (FP7) runs from 2007 to 2013. There are specific programs within each, all meant to foster European scientific excellence.¹⁹ Frameworks 6 and 7 have both provided funding for regenerative medicine projects (European Commission 2009). By mid-2010, about €187 million was spent on RM-related research (Kessler 2010). FP7 additionally encourages greater interaction between academia and industry. To address limits to research funding at the EU level, which had historically emphasized applied or industrial research, the European Research Council was created within FP7 in 2007 to fund peer-reviewed, “frontier” research broadly across the life sciences, engineering, and physical sciences. It is supported by the European Commission, with contributions from both member states, and associated states and is chartered through 2013.

The FPs have been an important way to draw additional disciplines such as advanced mathematical modeling into stem cell research. Cross-EU initiatives include European Consortium for Stem Cell Research (<http://www.eurostemcell.org>)

¹⁹There are additional programs, such as the [Competitiveness and Innovation Framework Programme \(CIP\)](#), Education and Training programs, and regional programs for competitiveness. The Innovative Medicines Initiative (IMI), somewhat similar to the National Institutes of Health “critical path initiative” in the USA, is one of the joint programs within FP 7. It was intended to identify new tools and new areas for drug discovery and related health technologies (Goldman 2012). It has a considerable budget; however, in controversial areas such as embryonic stem cell research, there are issues related to coordinating efforts across countries. It has also been criticized because of the large investment required by universities relative to other funding mechanisms (Sinha 2011).

and several coalitions around particular research problem spaces. Still, collaborations appear to be more common among researchers within a country, or perhaps with one other country, than Europe-wide collaborations. Nevertheless, A Europe-wide online database of HESC lines generated within Europe contains information on the origin and provenance of lines, plus genetic information, pluripotency, and other marker expressions (Elster et al. 2008).

There has also been a strategic emphasis on developing science clusters. However, these have not always worked well. As one commission report put it: “Europe does not lack clusters, but persistent market fragmentation, weak industry-research linkages and insufficient cooperation within the EU mean that clusters in the EU do not always have the necessary critical mass and innovation capacity to sustainably face global competition and to be world-class” (Cooke 2001; see also European Commission 2011). Although one aim of cluster research initiatives has been to aid poorer member countries, there is not enough concentration of scientific expertise in some regions to support sustained efforts; instead, efforts to support science infrastructures are focused mostly in well-established sites with expertise in biotechnology or drug development. These are supported at both the EU and state levels.

Disputes about policy and ethics regarding stem cell research in the EU have taken place within historical and political contexts about protections of individuals which differ somewhat from other regions. The aftermath of medical experimentation under National Socialism, as well as challenges in many areas of postwar science and technology (in particular, genetic engineering of organisms and crops), affirmed the need to adhere to a precautionary principle as the basis for policy decision-making. The precautionary principle, simply put, is the concept that when deciding whether to go forward with a new technology, and where there is no scientific consensus on whether it is harmful, the burden of proof that it is not harmful lies with those wanting to pursue that area of science or technology. Intended primarily for use for the prevention of environmental harms, it has been applied to a broad range of research, including medical research on humans. The precautionary principle has driven policy in the EU perhaps more than anywhere else: authorities consistently resort to this argument when attempting to write policy in response to controversies over emerging technologies such as genetically modified foods and gene transfer technologies (Dratwa 2011; Marchant and Mossman 2004).

Regenerative medicine policy has been entangled in this history. In 1989, amidst genetic engineering debates, proposed legislation in the European Parliament called for prohibiting gene transfer in the human germ line. The discussions set the stage for battles over intervening at the beginning of life as well as definitions and legal status of the human embryo. The term “human embryo” had been included in Article 6(2)(c) of Directive 98/44/EC of the European Parliament (see Chap. 4, this volume). However, while Article 6 prohibits “uses of human embryos for industrial and commercial purposes,” which could be interpreted to be contrary to morality, no clear definition of an embryo was made either here or in the EU Council of 6 July 1998 statement on the legal protection of biotechnological inventions.

The ambiguity of definitions of the embryo became crucial when attempts were made to patent products of embryonic stem cell lines. Ultimately the European

Court of Justice determined that such products cannot be patented due to the so-called morality clause of the European Patent Convention which states that European patents will not be granted for innovations, the exploitation of which are contrary to *ordre public* (public morality) (EPC Article 53 (a)).²⁰

FP6 negotiations resulted in Article 3 of European Parliament's amendments to allow use of supernumerary embryos but not embryos created from gametes for purpose of research. Nevertheless, member countries have authority to have their own guidelines. There is a broad range of country-specific policies, from the UK's Human Fertilization and Embryology Authority (HFEA) regulations of 2001, which permit use of embryo regardless of source, to Ireland's constitution which limits research, specifying the right to life of the unborn. In Belgium, France, and Denmark, research on embryos is allowed only if embryos left over from IVF procedures are used, and if the research relates to fertility or the prevention or treatment of disease.²¹ In the UK, the HFEA is the agency which oversees all fertility procedures and has licensing authority for all research on donated embryos and gametes, including stem cell research. The 1990 Act which created the HFEA was amended in 2008 and again in 2011 to allow for research uses of embryos and the admixture of embryos containing human and nonhuman materials. Several countries, including India, have used the HFEA guidelines as a model for their own regulations (Bharadwaj and Glasner 2009).

A few features of individual countries help to illustrate the point about differing political, social, and historical contexts. The UK has been viewed as one of the more permissive countries, allowing not only HESC research but also the use of cybrids. There are a number of prominent research centers, including Cambridge University, Sheffield, and Imperial College London. The UK initially invested £29 million in SC research from 2003 to 2007 (Hogarth and Salter 2010). Most of the funding comes from the Medical Research Council (MRC), which funds basic and translational work, and stated regenerative medicine as a national priority for the UK economy and health care (Office of Life Sciences, UK Department of Health 2011). In 2009–2010, funding was at the level of £39 million per year, with plans to increase spending to £130 million in 2011–2014, including £100 million for a new technology innovation center.

The UK Stem Cell Initiative summarized the state of the field in the UK and made recommendations for action in a 2005 document called the "Pattison Report" (found at <http://www.york.ac.uk/res/sci/events/FinalConfPres/Connolly.pdf> see also MRC

²⁰ Greenpeace v Brüstle (see Chap. 4 and Gibney 2013)

²¹ Belgium and France further specify that there must be no alternative therapy available (Loi relative à la recherche sur les embryons in vitro (Belgium); Loi no 2011-814 relative à la bioéthique (France)). Unlike most countries which allow embryo research up to 14 days of development, France requires that embryos be destroyed at 7 days. France updated its bioethics laws in 2011 to state that embryo research (including HESC) is only permitted in exceptional cases and is subject to approval by the Biomedicine Agency (see http://www.loc.gov/lawweb/servlet/lloc_news?disp3_1205402748_text). Articles 40–44 of the new law reiterate that research should only be done if there is likely to be a major medical breakthrough and there is no better alternative. Danish law derives from law on artificial fertilization, Lov nr 535 om kunstigbefrugtningsomaendretved.

2012). The lack of venture capital and other sources of funding for translational SC research was noted as a weakness, as well as the lack of clarity regarding IP and regulatory issues, and a consistent pattern of losing innovations to the USA in commercialization phases. Recommendations included the institutionalization of public-private partnerships and an increase in national funding for clinical and translational research.

Private capital in Britain has been slow to materialize (BIS 2011).²² The Cell Therapy Catapult, launched in 2013, is one part of a national strategic initiative to grow new industries in Britain, aimed at bringing together academic and industrial partners.²³ It initially receives funding from the UK, with some support from the EU, but is intended to be sustained through public-private R&D collaborations.

Scotland is home to the Roslin Institute, an animal science and quantitative genetics research institute where Professor Ian Wilmut was first to succeed in using somatic cell nuclear transfer to create a sheep clone (Dolly). Stem cell research continues primarily in Edinburgh and Glasgow. A new Scottish Centre for Regenerative Medicine was created and funded by University of Edinburgh, Scottish Enterprise, the MRC, and the British Heart Foundation.

The organization of research in France is interesting because of its powerful patient advocacy groups and their direct involvement in influencing the direction of research. The Institute for Stem cell Therapy and Exploration of Monogenic diseases (I-Stem) was created in 2005 as a public-private collaboration between the French muscular dystrophy patient organization (AFM, which provided significant private, philanthropic funding), INSERM (French National Institute for Health and Medical Research), and the University of Evry-Val-d'Essonne (<http://www.istem.eu/en/>).²⁴ I-Stem, perhaps more than other collaborations, is tied to research on specific diseases, with a focus on rare genetic diseases, in particular, neuromuscular disorders. I-Stem has biobank stocks of patient cells, from which to make iPS lines, and works with Genethon, a clinical trial network for gene therapy also tied to the AFM.

Germany presents an interesting context in that there is a strong history of having leading basic and applied research institutes in Europe (resulting in a strong science and economic base). Germany took an early lead in clinical trials of stem cell therapies, aggressively pursuing cardiovascular therapies. Yet the history of human experimentation (resulting in strong protections of human dignity in the postwar constitution) created a difficult environment in which to pursue the use of embryos in regenerative medicine. As a result, Germany has the most restrictive policies in Europe (Stafford 2009). Interestingly, Germany allowed the import of HESCs while

²² A report produced by the Department of Business Innovation & Skills of the Office of Life Sciences, Dept Public Health can be found at <http://www.bis.gov.uk/assets/biscore/innovation/docs/t/11-1056-taking-stock-ofregenerative-medicine> For a picture of patenting in the UK, see https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/32456/11-1087-regenerative-medicine-patent-landscape.pdf.

²³ The catapult has produced a UK cell therapy clinical trial database, which can be found at <https://catapult.innovateuk.org/documents/10726/1553967/CTC+UK+Clinical+Trials+Database/0451f336-4e2a-4907-a909-355e940b67b4>.

²⁴ See Callon and Rabeharisoa for a detailed study of the way the AFM became a powerful stakeholder in national funding initiatives (2008).

banning the destruction of embryos on German soil.²⁵ Nevertheless, Germany's cross-departmental innovation strategy, the High-Tech Strategy (2006–2009) and High-Tech Strategy 2020 (2010–2013), include provisions for the support of non-embryonic stem cell research (German Federal Ministry 2007).

Core centers of translational regenerative medicine in Germany include the Berlin-Brandenburg Center for Regenerative Medicine, which has perhaps one of the most sophisticated structures in terms of integrating research projects with business organization. In addition to a matrix of research groups supporting diverse basic and translational projects, the center includes formal functions in business development and regulatory affairs, to help launch and sustain products successfully. Other research centers with strengths include the Fraunhofer Institute for Biomedical Engineering, which has historically focused on devices and technology, but increasingly works on regenerative medicine technologies, such as cell assays, tissue engineering (especially skin, liver, vasculature), biomaterials, and “lab on a chip” technologies.²⁶ Since its inception in 1987, it has focused on translational work and enhancing relations with industry.

Funding is jointly provided by the Federal and Länder (state) governments. The Deutsches Forschungsgemeinschaft (German Research Foundation (DFG)) is the major science funder and provides both project funding, capacity-building funds (for institutions or for centers of excellence), and Europe-wide collaboration funds. The DFG provided an estimated €17.9 million in 1999–2007 for stem cell research (individual grants) and €13.2 million for embryonic and tissue-specific stem cells under Priority Research Programmes plus €1.9m in 2001–2007 for clinical research.²⁷

There is a strong engineering component to regenerative medicine efforts in the École Polytechnique Fédérale de Lausanne (EPFL) and Eidgenössisches Technische Hochschule (ETH) Basel, in Switzerland. Switzerland is also in the enviable position of having a strong pharmaceutical industry and close ties between academic and industrial researchers with better possibilities for VC than other countries.

Denmark and Sweden have long-established histories of using human fetal tissue in research, particularly for Parkinson's disease (Kingman et al. 1992). This likely makes conditions easier in terms of regulatory and public support to conduct embryonic stem cell research. The fact that these countries are predominantly Protestant rather than Catholic may also play a role in how fetal and embryonic tissues are viewed for governance purposes. Sweden also has existing infrastructural and institutional capacities for translational research, which contributes to capacity building.

²⁵ Germany is a good illustration of the way that institutional histories shape governance of new areas of science. For a brief but fascinating analysis of the history of ethics decision-making bodies, see Jasanoff (2005, p.196).

²⁶ The Fraunhofer Institute for Immunology and Cell Therapy is also engaged in SC research. Information can be found at <http://www.fraunhofer.de/en/research-topics/health-environment-nutrition/regenerative-medicine.html>.

²⁷ *Regenerationstechnologien für Medizin und Biologie—Beiträge für ein strategisches Förderkonzept* (2007) found at <http://www.biotechnologie.de/BIO/Redaktion/PDF/de/Studien/capgemini-regmed-2007.property=pdf,bereich=bio,sprache=de,rwb=true.pdf>.

The Netherlands has been active in tissue engineering for many years and is the home to Eurotransplant, the central registry for transplant medicine. As such, there is considerable expertise in policy and logistics of tissue donation and exchange. The Institute for Regenerative Medicine supplies funding and support for tissue engineering and stem cell research. Ironically, there appears to be less integration with medical communities than might be expected and more in vitro work than translational cell therapy.

In terms of centers of education in Europe, a doctoral training program at Loughborough University stands out. In collaboration with the Universities of Keele and Nottingham, the program emphasizes skills in biomanufacturing but also provides training in several novel research platforms. In some countries, such as Germany, education has traditionally been strongly disciplinary-based, with little support or reward for interdisciplinary training or research. Strategies to deal with the inherently interdisciplinary work of regenerative science could be used to couple expertise from various labs or provide internships and training for junior researchers in relevant areas different from their home discipline.

2.5 Asia

While each country has its own political and cultural history, national health priorities, and ways of governing science, there are some regional commonalities in Asia when it comes to investments in biotechnology. Asian countries are attempting to assert themselves on the global scene as a part of nationalist projects to regenerate political identities in the wake of the turbulent twentieth century. The manufacturing industries of postwar developing Asia have given way to knowledge economies, in which biomedical research plays a significant role. Major national investments in science and technology are being made in China, Singapore, Taiwan, Korea, and other countries, and there has been renewed interest in alliances with non-Asian countries. The increased focus on science has turned scientists into highly visible national symbolic heroes, for example, Shinya Yamanaka in Japan and Hwang Woo-Suk in Korea. Before his fall from grace due to misconduct, Hwang Woo-Suk inspired a national postage stamp and a national campaign of volunteers to donate biological materials for his research.²⁸

2.5.1 China

The rise of China on the global economic and scientific scene has been impressive. While NIH budgets have been relatively flat for several years, it has been estimated

²⁸ Hwang Woo-suk was a national celebrity and symbol of Korean resurgence in modern science after the announcement that he had successfully cloned human embryos. Later, it was discovered that he had engaged in scientific fraud and he was removed from his position (cf Gottweis and Kim 2010).

that Chinese investment in science and technology has increased 20 % per year. Venture capital (VC) investment grew rapidly after regulatory reforms in the 1990s began to open possibilities for private capital, and the “Patent law of the People’s Republic of China” was passed in 2001. Foreign-based VC increased to 60 % of total VC by 2008 (Salter 2009b). Still, researchers have told coauthors of this chapter that they have little faith in the enforcement of Chinese intellectual property law, and this is seen as a significant barrier to commercialization.

Researchers funded by the Chinese Academy of Science (CAS) published 3.5 times as many papers in journals listed by the Science Citation Index (SCI) in 2009 as in 1998, and the number of papers published in the top 1 % of SCI journals (as judged by impact factor) was 12 times that in 1998 (Qiu 2011). The CAS has nonetheless urged researchers to shift their efforts away from quantity to quality; that is, rather than simply attempting to produce as many papers as possible, they should work toward genuine originality and innovation (<http://www.cas.cn>). Educating future scientists and retaining Chinese expertise is also a priority. Lab experience and education in the USA, Europe, and Japan are still strongly encouraged, which may be a problem for retaining well-qualified scientists in China. Programs such as the Thousand Young Talents Program have been created to recruit Chinese scientists to return to China and to recruit foreign postdoctoral students (<http://www.cas.cn>). Nevertheless, preventing brain drain is a significant problem and barrier to developing a top-notch research environment.

To understand how regenerative medicine research is unfolding in China, one must first understand the transformation of health care and scientific research within the post-Maoist economy. There has been a shift from preventive, collectivist health-care characteristic of the Mao era to more high-tech, innovative science that can compete on the global stage. However, China lacks the infrastructure needed for commercializing research or directing it toward national needs. Still in transition from a centralized economy, Chinese researchers and governmental authorities have less history of working with industry than other countries. There were simply no incentives to create new industries until program 863 (State High-Tech Development Plan), which began a transition to more capitalist forms of enterprise and incentivized scientists to get training in advanced research centers and then return to China to establish firms there. The 863 Program applies funding to critical areas of research in order to limit China’s reliance on foreign powers (Huang et al. 2004; Thornley et al. 2011).

Perhaps because of a new desire to “catch up” on the global scene, China has invested more in translational research than basic. Yet “catching up” does not mean adopting Western or Northern globalizing ways of commercializing technologies. President Hu Jintao made this clear in a speech in 2006, when he called for China to create “a new path of innovation *with Chinese characteristics* and strive to build an innovation-oriented country” (quoted in Salter 2009a, p.402, emphasis added). Whatever is intended by “Chinese characteristics,” China’s Eleventh Five-Year Plan (2006–2010) emphasized the need to develop its own science and technology platform and capacity and exploit its own intellectual capital rather than relying on cheap labor to develop inventions of others (Ibid).

Salter points out that in the USA and other countries, venture capital is usually a source of management advice, recruitment, and fostering of talent. There is no such

history in China; rather, individuals in companies relate to each other through *quanxi*, a system of mutual obligations and benefits between individuals and firms (Ibid). Trust or obligation established through such social relations affects investment patterns and responses to risk (high-risk products or firms). There are virtually no private foundations or sources of funds.

Also, there are tensions between China's desire to maintain tight government control, including financial protections, and the need to globalize. For example, venture capital normally looks for a 5-year exit plan by offering shares, preferably via an IPO. Markets are less fluid in the Shenzhen and Shanghai stock exchanges markets than this strategy allows, however, and government controls on the export of capital makes it hard to exit through other foreign exchanges (Ibid 2009).

Regenerative medicine is one of seven research priorities named by the CAS in its Innovation 2020 plan. Most funding for stem cell research comes from grants from the Ministry of Science and Technology in two programs, one for basic discovery science and the other for applied research. Approximately 100 million yuan (roughly US\$12 million) was allocated between 2000 and 2005. The National Science Foundation of China (NSFC) is another major source of funds. Matching funds have typically come from local governments, in particular, Beijing and Shanghai (Murray and Spar 2006). Although estimates vary widely, and data reported by the CAS are incomplete or outdated, funding for stem cell research from 2000 to 2005 was approximately 300 million yuan (about US\$38 million) and estimated to increase to about 400 million yuan in 2011 (Yuan et al. 2012; Murray and Spar 2006; Salter 2008). A national stem cell bank (primarily for HESCs) was also planned by the MOST (Xu 2008).

Research institutes at Beijing, Shanghai, Guangzhou, and Kunming are the pillars of the 2020 plan, and three science parks will be built in Beijing, Shanghai, and Guangdong to do translational research in informatics, biomedicine, and renewable energy (Qiu 2011). Stem cell research sites include Peking University's Stem-Cell Research Center and the Institute of Zoology at the CAS (Beijing) Xinhua Hospital (Shanghai) and Xiangya Medical College (Changsha), the National Institute of Biological Sciences (Beijing), the Shanghai Institutes for Biological Sciences of the CAS, and the Guangzhou Institute of Biomedicine and Health of the CAS (Guangdong). Large pharmaceutical companies such as Pfizer and Johnson & Johnson, as well as smaller biotech companies, have actively engaged with researchers in these sites and have initiated clinical trials under the "Developmental and Reproductive Research Initiation," organized and sponsored by the Ministry of Science and Technology of China.

An example of the new arrangements is the Bieke Biotechnology Company, a company using cord blood and bone marrow-derived stem cells to treat a variety of disorders. Beike Biotech was the first Chinese company to receive accreditation for cord blood and bone marrow-derived stem cells. Bieke has a network of clinics and researchers throughout China but is based in Shenzhen, a special economic zone (SEZ). SEZs were created under the reform policies of Deng Xiaoping to attract foreign investors (especially ex-patriot Chinese) and as such are exempt from many of the usual province regulations. Cells can be shipped to clinics within the network,

and if one province does not allow a type of procedure, it can be easily moved to another site.²⁹ A web site, China Stem Cell News (found at <http://www.stem-cellschina.com>), billed as a news and information service for patients wanting to know about stem cell research, steered potential patients to Bieke for treatments. The online tool became a primary recruitment mechanism for patients around the world with a variety of disorders to receive treatments in China.

The practice of direct-to-consumer advertising for patients, using treatments with little documentation, makes China a key target for international criticism about clinics which offer stem cell treatments which have not been proven to be safe or efficacious. In fact, China is sometimes derogatorily referred to as the “wild east” of regenerative medicine, as though there are no rules or oversight. Chen argues that it is not that there are no rules and a passive populace; oversight does exist, but in a way that researchers are somewhat easily able to navigate or bypass regulations (Chen 2009; see also Rosemann et al. 2013).

The Beijing Ministry of Health (MOH) Medical Ethics Committee and Southern Chinese Human Genome Research Centre Ethical, Legal, and Social Issues Committee (ELSI) proposed ethical guidelines for HESC research in 2001, including the establishment of a new organization to centralize ethical management of stem cell research in China. In 2003, the Ministry of Science and Technology and MOH issued ethical guidelines for HESC research. However, while there are local ethics committees, there is no centralized management to date (McMahon et al. 2010; Zhang 2012b). As a result, there is little infrastructure for oversight or penalties for noncompliance with guidelines. The MOH did make a provision regarding cloning, allowing somatic cell nuclear transfer (cloning for therapeutic purposes) but not cloning for reproductive purposes. The guide is referred to as the “Four No’s”: Under no circumstances will human reproductive cloning experiments be endorsed, permitted, supported, or accepted.³⁰ The only source of materials for research officially permitted includes supernumerary blastocysts after in vitro fertilization (IVF) procedures, fetal cells from accidental spontaneous or voluntarily selected abortions, parthenogenetic split blastocyst obtained by somatic cell nuclear transfer technology, or voluntarily donated germ cells. Still, some have argued that the history of state-forced abortions and birth control makes it easier for the State to intervene in reproductive issues, including potentially making human oocytes available for research. In fact, one Chinese researcher interviewed claimed that oocyte donation was little different from blood donation and that oocytes were easily acquired from cooperating IVF clinics without special consent (Sleeboom-Faulkner

²⁹ The first patient, an American with amyotrophic lateral sclerosis, was offered free treatment in 2005. The procedure was performed at Nanshan Hospital in Shenzhen. Cells from a lab in Zhenzhou were used. Another patient wanted to have cells injected directly into the lamina for multiple sclerosis, but physicians at Nanshan refused; the patient was sent to another province where a clinic was willing to perform the procedure (Song 2011, p 147).

³⁰ People’s Republic of China Ministry of Health (PRC MOH) guidelines for clinical use of biomedical technologies is available at <http://www.mmoh.gov.cn/publicfiles/business/htmlfiles/mohyszs/s3585/200903/39511.htm>.

2013). There is also a large pool of potential research subjects for all forms of medical research, with relatively easy access compared to other countries.

Responding to the international concern about unproven therapies being offered, in May 2009, the Chinese MOH classified stem cell treatments as high-risk medical technologies, requiring the approval of an audit board. Sponsors using stem cells were asked to register their research and clinical activities, the source of the stem cells, and ethical procedures. The Ministry also asked local health authorities to stop any unapproved clinical uses and called for a nationwide moratorium on new clinical trials for stem cell therapies on 10 January 2012 (Durfee and Huang 2012). In July 2012, 50 clinics were selected to conduct approved stem cell trials or treatments. At the time of this writing, other clinics continue to operate, leading many to believe the practice is not being well regulated.

On 1 May 2009, the MOH promulgated the “Management Measures for the Clinical Use of Medical Technologies,” a regulation that classified a range of new medical technologies and procedures into three categories. Stem cell transplant technology was grouped under category III, which included technologies considered as risky, ethically controversial, and in need of clinical verification (Qiu 2011). To implement the regulation, the MOH assigned five institutions, among them the Chinese Medical Association, the Chinese Hospital Association, and the Chinese Doctors Association to take the lead. Clinics using stem cells were supposed to register with these institutions, and licenses would be granted on the basis of assessment criteria and approval by review and inspection committees (Chen 2009, p. 271). In practice, this regulation has not yet been implemented, particularly in district and military-owned hospitals, partly due to disagreements about how the policy should be implemented (Chen 2009). On 6 January 2012, the MOH issued a regulatory document called “Notification on Self-Evaluation and Self-Correction Work regarding the Development of Clinical Stem Cell Clinical Research and Applications.” The four stages of this approach are self-evaluation (*zicha*), self-correction (*ziju*), re-certification (*chongxin renzheng*), and standardized management (*guifan guanli*) (Rosemann 2013). Still, it is not evident that regulations are being followed (Cyranoski 2012a).

Priscilla Song situates medical tourism for stem cell research in China within the context of changes in political economy of health care and market reforms in China (Song 2011). Under Ding Xiaoping, funding for state-owned hospitals was significantly cut. In the transition toward what has been referred to as “socialism with Chinese characteristics,” there was a mix of decentralization and central control of many economic sectors: Hospitals were allowed to raise fees on some services but were mandated to have price controls on services defined as “essential.” Hospitals responded by moving toward high-tech, lucrative services and creating elite wards, which they reserved for wealthier clients (including foreign) or leased to companies for clinical trials. While there are national regulatory limits to companies (especially foreign firms) accessing patients this way, Song observed that companies circumvent legal constraints on such arrangements by working through universities and local governments which do not go by national rules. Companies can thus gain legitimacy and access to clinical facilities and patients (Song 2011, p.143).

It is important to note that legitimate trials are being conducted at the same time as questionable ones. This creates even more of a dilemma for China as it strives to achieve world status in regenerative medicine.

2.5.2 *Japan*

In 2003, The Japanese Ministry of Education, Culture, Sports, Science, and Technology (MEXT) wrote a white paper in which regenerative medicine was named as a priority strategy for science and technology.³¹ As an economic stimulus program, the RIKEN Institute (under MEXT) led an initiative to support regenerative medicine in 2003–2008. After the Yamanaka discovery of iPS cells in 2007, MEXT added about ¥ 1 billion to the budget for RM for 2008–2012. The Japan Science and Technology agency (also under MEXT) has been a major funder of IPSC research. Additionally, the Ministry of Trade, Economy and Industry (METI) also provided funding for industrial applications of stem cells including cell culture systems and automation systems, cell sheet manufacturing, and measuring devices with a budget of about ¥5.5 from 2008 to 2014 (Japan Science and Technology).

Japan was the earliest Asian nation to industrialize, developing a strong base of manufacturing industries and expertise, including electronic and mechanical engineering. Significantly, Japan has strengths in robotics and optics, which will be important to developing tools for automated bioprocessing and scale-up as well as cell tracking and other imaging uses. This is not surprising, from the history of auto industry, photographic equipment and supplies, and electronics devices manufacturing. Some of the firms in these industries are retooling into biosciences as markets for conventional products shrink. For example, the Fujifilm Corporation, a company which previously made photographic film, is utilizing its expertise in chemistry to enter the tissue engineering field by partnering with Japan Tissue Engineering. They aim to build on knowledge of collagen and polymers, as well as mass production techniques, to make scaffolds and microspheres. Olympus (a maker of cameras and microscopes) is expanding to live cell imaging, and Nikon is now selling specialized stem cell equipment, including automated cell culture and monitoring stations. In addition to engineering expertise, there is considerable expertise in developmental biology and transgenics. There is a solid pharmaceutical industry presence, and a number of these firms are starting to work with stem cells. The pharmaceutical industry in Japan appears to be somewhat more risk averse, in entering new areas, in contrast to other Asian countries like China, which has engaged in high-risk strategies.

Japan has almost exclusively pursued IPSCs rather than HESCs. Some might argue that the successful research by Shinya Yamanaka on induced pluripotent cells has been a primary influence on direction for the nation. Others might argue that cultural preferences not to use embryos is the reason, although there are somewhat conflicting accounts of the extent to which this is true. The dominant religion,

³¹<http://www.mext.go.jp/english/whitepaper/1302732.htm>.

Buddhism, would likely be less concerned with the beginnings of life than the end. The use of stem cells from aborted fetuses has been allowed since 2004, and research on cell lines from embryos has been allowed since 2001.³² Sleeboom-Faulkner's research in Japan revealed that there has been little public discussion about embryonic stem cell research but suggests that contrary to assumptions that the status of the embryo is unimportant in Japan, embryos do have significant moral status (2008). Indeed, the Bioethics Committee of the Council for Science and Technology Policy (CSTP) defined an embryo as *seimei no myooga* (the "germ" of life). Japan also has a morality clause regarding patenting of products deriving from the destruction of embryos and was the first country to utilize this concept.³³ Sleeboom-Faulkner argues that permission to use embryos and fetuses has less to do with religious views than with political priorities of building a large-scale infrastructure for science in the beginning of the twenty-first century, such as the Millennium Project (Sleeboom-Faulkner 2008).³⁴

While therapeutic applications are being pursued, Shinya Yamanaka, the Nobel Prize-winning scientist and inventor of iPS cells, has called for a national priority to be in areas other than cell therapies: "My goal is for 20 % or so of iPS cell applications to be in regenerative medicine and the remaining 80 % to be in finding the causes of diseases and developing drugs. Japan is making advances in researching regenerative medicine, but we are lagging behind the West in other applications" (Yamanaka, quoted in Oiwa 2013; see also Cyranoski 2012c).

To build an infrastructure around iPS cell technologies, Japan is creating a national biobank for iPS cells. The Health Ministry in 2012 approved the addition of umbilical cord blood samples from the eight national cord blood banks to other cell stocks that might be used to derive cell lines. Notably, fewer subjects would be needed to make a biobank in Japan, because a smaller number would still represent a majority of the population due to the relative genetic homogeneity and similarity of HLA profiles.³⁵ Dr. Yamanaka plans to create 75 iPS cell lines that could be

³² The derivation of new HESC lines requires a two-stage approval process (Institutional Review Board and Ministry level review). There is also considerable structure regarding research ethics, including a requirement that each institution have bioethics and technical training courses approved by the Ministry.

³³ Chapter 2, Sect. 32, concerning "unpatentable inventions" contains the clause: "the inventions liable to contravene public order, morality or public health shall not be patented." See http://www.wipo.int/clea/docs_new/pdf/en/jp/jp006en.pdf. The language of the law allows some room for interpretation about respecting an embryo while permitting it to be used to create life-saving therapies.

³⁴ The Millennium Project, a national initiative created in 1999 as an economic stimulus project, was intended to develop an infrastructure for science and technology. A public-private collaboration, it was jointly sponsored by the Ministry of Education, Sports, Science and Technology (MEXT); the Science and Technology Agency (STA); the Ministry of Health Labor and Welfare (MHLW); and the Ministry of Economy Trade and Industry (METI), linking education, commerce, and R&D into a networked initiative.

³⁵ Three key genes that code for cell surface proteins involved in the immune response (human leukocyte antigens, or HLA) must be matched to prevent possible rejection of the cells in the recipient. Banked cord blood in Japan will have already been characterized for HLA.

matched by 80 % of the population. One possibility for the Japanese citizenry is the stockpiling of cell lines, particularly blood cells, suitable for the majority of Japanese for emergencies (interview with Yuri Oiwa 2013; see also Cyranoski 2012b). With the history of radiation poisoning and subsequent bone marrow depletion in affected citizens in World War II, and again with the Fukushima nuclear disaster, coupled with a rise in blood-related cancer rates, this is not a surprising strategy. Recently acquired government-sanctioned access to the cord blood cells will facilitate the work but raises questions about donor consent, since the cells would be used for purposes other than what was specified to them at the time of donation (see also Chaps. 6 and 7 regarding problems of informed consent in cell-based research).

The MEXT is responsible for the enforcement of guidelines regarding stem cell research. Guidelines in Japan are guided by an Expert Panel on Bioethics, reporting to the CSTP, which has a reputation for being cautious and taking time to make decisions. Recently, the Panel did recommend to relax guidelines on admixture of human cells into animals (Normile 2013). Previously, this was allowed in vitro but not in vivo. The change was announced just prior to an announcement of the successful growth of human liver tissue from iPS cells, which began in vitro but needed to be completed in vivo to more properly form three-dimensional structures. Guidelines for Derivation and Utilization of Human Embryonic Stem Cells were created in 2001 and amended to relax requirements in 2009. Clinical trials must go through the Ministry of Health, Labor and Welfare (MHLW) for approval. Guidelines on clinical research using human stem cells were created in 2006 and amended in 2010.³⁶ Paragraph 5 of the guidelines specifies medical conditions in which stem cells (iPS or ES) may be used, which are restricted to life-threatening illnesses, treatments for which stem cells are expected to produce significant improvements over existing therapies, and the benefits are expected to outweigh the risks. Interestingly, the guidelines also specify the kinds of expertise that should constitute an ethics review committee, including expert(s) in molecular biology, cell biology, genetics, clinical pharmacology or pathology, law, ethics, and clinicians in the area for which a therapeutic protocol is being developed, but not stem cell researchers (paragraph 8).

In terms of education and training, only four Asian universities are ranked among the top 100 in the world, and all of them are in Japan.³⁷ Fewer Japanese students are studying abroad, in contrast to China and India.³⁸ Key sites for regenerative medicine research include the University of Tokyo and the Institute of Advanced Biomedical Engineering of the Tokyo Women's Medical University. The institute also has links with other Japanese universities.

³⁶ These can be found at <http://www.mhlw.go.jp/english/policy/health-medical/medical-care/dl/guidelines.pdf>.

³⁷ These are the University of Tokyo, Kyoto University, Osaka University, and Nagoya University.

³⁸ The number of Japanese college students studying overseas dropped by 28 %, from 82,900 in 2004 to 59,900 in 2009, according to figures from the Ministry of Education, Culture, Sports, Science and Technology. In the USA, the number of Japanese scholars has fallen to half of what it was during the peak year of 1997 (Asahi Shimbun; see http://ajw.asahi.com/article/behind_news/people/AJ201210100003).

2.6 Discussion

As we have shown, regenerative medicine has developed differently in global regions, but not only because of funding or differences in policies. Rather, regenerative medicine has emerged within historical and political moments particular to regions and countries.

Research is flourishing or being constrained in part due to policies, but this entails policy regarding intellectual property and investments in science more broadly, not just policy regarding stem cell research. Research ethics policy regarding clinical trials or the use of embryos significantly affects what research may or may not be done, but so does policy about foreign investments or data and materials sharing across labs or national borders. Stem cell-specific guidelines in some areas are made to be similar to other countries for interoperability, or to assert international credibility, whereas in other areas, guidelines adhere to country-specific, long-held cultural ideas.

There are other influences: in some countries, advocacy groups and patient organizations searching for cures for particular diseases have pushed governments for experimental stem cell treatments, while in others, patients take matter into their own hands and depart for countries offering treatments, even without substantiated evidence of effectiveness and safety. The health-care systems into which stem cell therapies and other products will go also makes a fundamental difference in whether or not technologies, once translated, are taken up by payers and incorporated into clinical care under budgetary strain or in transition from a central economy.

Funding amounts do matter, but the source and type of funds, and the conditions under which they are provided shape what sort of research goes forth (or not). Where funds are tied to specific economic goals, they are likely to support commercialization efforts or the development of enabling technologies more than discovery research. There also may be short-term thinking, due to political exigencies or the conviction that choosing to invest in the development of a particular technology over another may provide short-term economic benefits or might be more politically digestible. Where one approach to research is controversial, public money will be shunted to approaches less likely to cause debate. When funding comes from venture capital or existing industry sources, products with a better return on investment will develop, but those for smaller markets or rare diseases will have to find other sources of support. Also, funds from industry or venture capital will likely be less likely to flow to projects requiring longer development times.

One thing is clear: research follows the money, and the money appears to be in all locales toward translational research and more commercially viable products and therapies than basic discovery science. However, as one coauthor (David Schaffer) put it, translational research cannot exist without something to translate. That is, commercialization only makes sense when we have high-quality science to commercialize, as Peter Zandstra adds. Funding cuts in basic discovery research

may thus result in an empty translational pipeline in the future. The question then becomes, can recommendations be made for future funding and research policy to “lift all boats” of regenerative medicine research? If so, how can the field as a whole be served while preserving national or regional priorities for science, science education, the economics of science, and ultimately, health care? Which funding mechanisms would be most effective to draw together interdisciplinary perspectives needed for translational RM, and which would encourage collaborations across laboratory and national borders in order to leverage and capitalize on existing cores of expertise?

There are several possible ways of reorienting research policy, including a clinical strategy, a research organization strategy, a translational strategy, or a hybrid of these and other strategies:

- Are there clinically strategic ways of prioritizing types of research based on a disease-oriented basis (e.g., matching disease incidence with expertise in that area)? Currently, health needs in countries are not necessarily well matched with types of research being pursued. Alternatively, might it be more productive to support translational research where natural relations with clinics already exist, or should policies be directed toward bridging the gap between basic researchers and clinical practitioners? Should countries prioritize certain health needs in their federal funding initiatives or should this be left to private sources in locales where a strong patient advocacy base exists around a particular health need?
- Are there natural venues to collaborate around specific research problems or around a technique or approach? (Examples of emerging areas could be computational methods, or bioprocessing/biomanufacturing, reprogramming, or gene-editing techniques). If so, how can communities of interdisciplinary expertise be supported? How can funding agencies be made to understand and support such efforts (even internationally) in addition to conventional funding mechanisms?
- Where are opportunities to develop better working relations between academic researchers and companies that could develop nascent innovations, and what form of public-private partnerships might be most effective?

The WTEC report, aimed at American competitiveness, concluded that funding agencies should establish interagency programs for interdisciplinary stem cell research, joining engineering, biology, and computational scientists, among others. It also recommended mechanisms to support academic-industry partnerships, particularly those with innovative translational models. Additionally, grant programs which allow for collaborations across countries would leverage strengths across labs and national research programs in much the same way as intranational networks have done (see also US DHHS 2006).

Whatever approach is employed, there is a need to address the current disconnect between expertise, resources, and political will in many locales. A good deal of expertise exists in pockets around the world, and niches have developed in which

experts interact within and across disciplines that may regulate the fate of stem cell research. Yet there is a need to identify and then build up expertise needed for the long term. That includes not only knowledge needed for translation and scale-up but also regulatory and business infrastructures. Microenvironments may work well to advance particular areas of research, but better matching of resources, expertise, cGMP facilities, and access to clinics will be needed for translation.

We have described a few experimental models created to accomplish translational stem cell research, including the CCRM in Canada, the Berlin-Brandenburg Centre in Germany, and the recently introduced Cell Catapult in the UK. Such novel models involve unique public-private partnerships and will bring together academic and industrial researchers. Such models are still experiments in process, and it remains to be seen what may be the best form. What is also needed is incorporation of more clinical practitioners to provide a better understanding of disease mechanisms and clinical picture of patients' actual needs, in addition to providing strategic access to patients for potential trials (Johnson et al. 2007). The mundane, less-studied, less-funded, yet crucial piece of clinical translation involves design of cell preservation and delivery methods, biomanufacture and scale-up, and other processes needed to make a therapeutic procedure workable.

In the future, translational centers will also need to incorporate the burgeoning information coming from genomics and data analytics to develop in vitro models of disease and conduct population level analyses in addition to personalized approaches. Countries with established information technology industries and the infrastructural ability to connect health, population, and bioscience databases may be able to capitalize on these strengths.

At the same time, a number of groups are reformulating training and education to focus on the interdisciplinary field of regenerative medicine rather than maintaining silos of disciplinary expertise. Loughborough University, for example, in collaboration with the Universities of Keele and Nottingham, created a program emphasizing skills in biomanufacturing in addition to training in several novel research platforms. Interdepartmental doctoral programs are arising to join disciplines, or in some cases, link basic and clinical sciences.

Individual institutions are beginning to innovate new ways to deliver education, including programs targeting international audiences. Stanford University's biomedical engineering design courses in India, formed as a collaboration between Stanford, the Indian Institute of Technology, and the All India Institute of Medical Sciences (<http://biodesign.stanford.edu/bdn/india/>), is one example among many others where universities partner bilaterally with institutions in China, India, Africa, and other resource-poor countries. Other universities are creating focused, international short-course training programs (such as Georgia Tech's new course in biomanufacturing). On a broader scale, new forms of open online courses are being implemented by universities as a part of a movement to make higher education more accessible to larger numbers of people rather than traditional campus-based, direct-interaction models. An extension of distance education, the concept allows learners in any locale (including resource-poor countries) to enroll in top-level courses and

obtain college credit.³⁹ Although these forms are somewhat controversial, and there are many problems to work out, some version of such versions in stem cells and regenerative medicine may accelerate transmission of knowledge in these rapidly expanding fields from a small number of centers of excellence to the broader international community.

Future empirical research will provide more fine-grained analysis than we have been able to present here. In particular, it would be helpful to analyze disease incidence and to what extent existing stem cell research programs match patterns of health needs within locales. Longitudinal analysis could provide insight into the extent to which funding, or the creation of research communities around a technique or research problem, or hubs of interdisciplinary collaborations attract investigators to the regenerative medicine space, and whether they disperse when venues for collaboration decline. For our purposes in this chapter, we provided an overview with which to consider future policy directions and raised questions for further exploration.

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³⁹Examples include massive open online courses (MOOCs) such as Coursera, a for-profit company that initially partnered with Stanford University, the University of Michigan, University of Pennsylvania, and Princeton University. Others include Kahn University (a not-for-profit model supported by Google Project 10 and the Gates Foundation) and edX (a not-for-profit partnership of Harvard, MIT, and the École Polytechnique Fédérale de Lausanne in Switzerland). See also Leber (2013). The jury is out on the value and effectiveness of such unconventional offerings. Many universities are rushing to develop similar offerings, hoping to capture revenues during a time of declining public and private support of higher education, but there are numerous hurdles to launching and maintaining courses, including standardization and quality control of course content, licensing, and the time-intensiveness for high-quality, busy professors with little expertise in teaching international audiences to prepare online materials and monitor and evaluate students coming from radically different backgrounds and cultural settings. Language translation is also an issue; currently, most courses are in English only.

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