Cell Stem Cell
Forum

Stem Cell Research in Spain: If Only They Were Windmills …

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DOI 10.1016/j.stem.2009.05.016

Regenerative medicine has been endorsed in Spain as a strategic, interdisciplinary topic to boost biomedical research. Special programs have been developed to promote collaborative research efforts among Spanish basic, applied, translational, and clinical researchers. Here, we present what we consider Spain's main current assets in this area.

Many readers may associate Spain with a delightful vacation place and a paradise for the arts and culture, rather than with a source of competitive science, let alone high-class biomedical research. This image is fortunately changing, and Spain is beginning to occupy a place in the worldwide research and development picture more consistent with her economic, social, and cultural position. Spain's reputation is evolving in a variety of scientific areas, of which stem cell research is a good example and, coincidentally, a strategically chosen driving paradigm.

In the early 2000s, Spain, like many other developed countries, engaged in intense social and political debate over the use of human embryos for research. As the first human embryonic stem cell (ESC) lines were derived in James Thomson's laboratory and their great promise was widely publicized, Spanish policymakers faced the dilemma of whether such research should be allowed. At the time, a surplus of well over 50,000 human embryos derived during in vitro fertilization (IVF) treatments had accumulated and were kept frozen, with no clear destiny. Social perception was largely in favor of allowing the use of such embryos for research, including the derivation of hESCs, and in 2003 the then-ruling People's Party passed an Assisted Reproduction Techniques law (45/2003) that permitted embryos that had been frozen prior to that date to be donated for use in research. Although the main aim of this law was to prevent the accumulation of frozen human embryos in IVF clinics, the new legislation opened the door for hESC research and, quite significantly, suggested that the stem cell debate would not create the political divide in Spain that it has in other countries. In any case, the law was short lived, for 4 months later a new government led by the Socialist Party was elected, which had announced among their priorities the large-scale promotion of regenerative medicine research in Spain.

Current Regulatory Framework

The new government has since passed two new laws that are considered less restrictive than the original 2003 rulings and define the existing legislative framework for hESC derivation and research in Spain. The first law (14/2006) updates the original Assisted Reproduction Techniques ruling and requires that couples with surplus frozen embryos following IVF treatment, regardless of the time of cryopreservation, are presented with four options: keeping them frozen for their own subsequent reproductive use, donation to other couples for reproduction, donation for a specific research project, or disposal without further use. The second law is broader (Spanish Law on Biomedical Research, 14/2007) and explicitly prohibits the creation of human embryos for research purposes but allows the derivation of hESCs for research or therapy using any technology (such as nuclear transfer) that does not involve fertilization to generate viable embryos. In summary, Spain currently has one of the most progressive legislations worldwide with respect to hESC research.

In addition to providing a new regulatory framework, the changes in legislation brought about specific instruments to control the derivation and use of hESCs and to promote regenerative medicine research. Thus, the Carlos III Health Institute (the Spanish counterpart of the NIH in the US, then dependent on the Ministry of Health and now under the auspices of the Ministry of Science and Innovation) created the position of Subdirectorate-General for Research in Cell Therapy and Regenerative Medicine with the aim of harmonizing strategic stem cell research interests and their ethical and legal implications. Toward this end, the Subdirectorate-General oversees the Commission on Guarantees concerning the Donation and Use of Human Tissues and Cells, which monitors and controls all research projects that generate or use hESCs in Spain. The Commission is comprised of 12 members with proven expertise in stem cell research, bioethics, or biomedical law, and who are appointed to 3-year terms of service. This all-powerful Commission provides a regulatory solution that is sufficiently flexible to cope with the rapidly changing field of stem cell research (Rugg-Gunn et al., 2009), in that issues not explicitly covered or foreseen by the Law on Biomedical Research (for instance, the injection of hESCs into mouse blastocysts, the generation of cybrids, or the generation of human iPSCs) can be dealt with by the Commission on a project-by-project basis.

The National Stem Cell Bank

The Subdirectorate-General for Research in Cell Therapy and Regenerative Medicine is also tasked with promoting stem cell research in Spain, and perhaps the most significant initiative undertaken to

achieve this goal was the creation of the National Stem Cell Bank (BNLC). The BNLC was established as a multinode network structure designed to ensure that hESC derivation is conducted according to strict legal, ethical, and scientific guidelines, and that the lines generated are made available to researchers nationwide. In concert with financing from and oversight by the governments of Autonomous Communities Catalonia, Andalusia, and Valencia (Spain is made up of 17 regions and nationalities, known as Autonomous Communities, with ample self-government competences, including healthcare and research), three BNLC nodes were created: in Barcelona, under the direction of Anna Veiga; Granada, under the direction of Pablo Menéndez; and Valencia, under the direction of Carlos Simón. Based on their locations and stem cell research-promoting initiatives from the regional governments, the individual nodes of the BNLC will be integrated into (or linked with) newly created research centers such as the Center for Regenerative Medicine in Barcelona (CMRB), the Andalusian Molecular Biology and Regenerative Medicine Centre (CABIMER) in Seville, and the Prince Felipe Research Centre (CIPF) in Valencia.

Needless to say, research projects involving derivation of hESC lines at the BNLC nodes require prior approval by the Commission on Guarantees concerning the Donation and Use of Human Tissues and Cells. In principle, doing things the right way in Spain implies countless layers of paperwork. In the case of hESC derivation, it took more than 5 years of passing laws, creating commissions and more commissions, and setting up banks and nodes. In the end, Spanish researchers entered quite late into the hESC research race, finally getting the green light in mid-2005. However, the extra effort led to a solid, yet flexible legislative framework that will accommodate new scientific developments and a national commitment to an ambitious, long-term research program. The first five fully characterized Spanish hESC lines were deposited in the BNLC in November 2006. Since that time, at least six more lines have been deposited and have been distributed to dozens of researchers in Spain and elsewhere.

The BNLC acts as a repository of hESC lines derived in Spain but does not intend to become a comprehensive banking service or to compete with other initiatives such as the UK Stem Cell Bank. Indeed, this goal would prove very difficult due to the range of national regulatory policies and the fragmented information available as to the origin and characteristics of existing hESC lines. Realizing these problems, the European Commission backed the development of the Human Embryonic Stem Cell Registry (hESCreg), coordinated by Anna Veiga, from the CMRB, and Joeri Borstlap, from the Berlin-Brandenburg Center for Regenerative Therapies (Borstlap et al., 2008). Currently, the hESCreg contains detailed information regarding the derivation, molecular characteristics, use, and quality of 645 hESC lines, 191 of which are freely available to researchers.

Spain's Main Assets

The majority of scientific output in Spain, by volume, comes from Universities and from the Spanish National Research Council (CSIC), which is composed of multiple public research centers. Both institutions are undergoing profound organizational changes aimed to solve their deeply rooted problems in flexibility and competitiveness. Nevertheless, there are at least three research areas related to stem cell biology in which these more traditional settings have managed to excel, including neuroscience, developmental biology, and gene therapy. The heritage of Santiago Ramón y Cajal is evident in the many excellent neuroscience laboratories scattered throughout Universities and CSIC centers. These groups have made many important contributions to stem cell research, such as the identification of multipotent, glia-like stem cells in the adult carotid body (by the laboratory of José López Barneo at the University of Seville) and their potential use for cell therapy of Parkinson's disease (Pardal et al., 2007), or the characterization of pigment epithelium-derived factor (PEDF) as a crucial niche-derived factor that regulates the self-renewal of neural stem cells (Ramirez-Castillejo et al., 2006). The school of developmental biology, created by Antonio García Bellido and expanded by Ginés Morata (both at the CBMSO, Madrid), gave rise to many talented disciples distributed across Spain and has provided valuable insights into the cellular and molecular mechanisms that control cell differentiation. Finally, a sizable critical mass of competitive laboratories working in gene therapy research has been assembled in Spain over the past 15 years. Hematopoietic stem cells have been the preferred experimental model, and the resulting combination of gene and cell therapy tools has contributed strongly to the present state of the art of stem cell research in Spain. In fact, the Spanish Gene Therapy Association changed its name in 2007 to Spanish Association of Cell and Gene Therapy and now includes a full chapter dedicated to stem cell research. These laboratories make up an invaluable culture broth for the formation of new generations of well-trained scientists, most of whom, unfortunately, pursue their careers elsewhere.

During the last 10 years, a new type of research institution has emerged in Spain to forestall the problems of inflexibility, bureaucracy, lethargy, and inbreeding that burden university- and CSIC-driven research. These centers have in common the legal entity of independent, nonprofit private foundations with their own administration and minimal bureaucracy, a scientific direction with ample decision powers, flexibility in hiring conditions, and evaluation systems based on merit. Two such centers were created in Madrid by the Carlos III Health Institute: the National Cancer Research Centre (CNIO), directed by Mariano Barbacid, and the National Center for Cardiovascular Research (CNIC), directed by Valentín Fuster. This new model of research center has been used extensively in Catalonia, where 38 new centers and institutes have been created in all areas of science. Specially relevant for stem cell research are the CMRB, directed by me (J.C.I.B.); the Centre for Genomic Regulation (CRG), directed by Miguel Beato, which has attracted Thomas Graf to coordinate the Differentiation and Cancer Program; the Institute for Research in Biomedicine (IRB Barcelona), directed by Joan Guinovart with Joan Massagué as Adjunt Director; the Catalan Institute of Cardiovascular Sciences (ICCC), directed by Lina Badimón; the Vall d'Hebron Institute of Oncology (VHIO), directed by Josep Baselga; and the Institute for Bioengineering of Catalonia (IBEC), directed by Josep Planell. In other areas of Spain, similar centers have been created to catalyze biomedical research, such as CIC bioGUNE, directed

by José María Mato in the Basque Country; the CIPF in Valencia, directed by Rubén Moreno, which has attracted Miodrag Stojkovic to lead their program in regenerative medicine; and the Institute for Biomedicine in Seville (IBIS), directed by José López Barneo. This explosion of new, dynamic, well-equipped, and highly specialized research centers is one of Spain's main assets that will help make a difference in the field of stem cell research. Proof that the flexibility bestowed upon these new centers is successful is seen in their recent contributions to the field of induced pluripotency, arguably the most active and competitive topic of stem cell research at the moment. These advances include studies at the CMRB generating the first human iPSC lines in Europe (Aasen et al., 2008) and providing proof of concept that disease-free progenitor cells with potential value for cell therapy can be obtained from patient-specific iPSCs (Raya et al., 2009); analyses at the CRG on the retroviral insertion sites of mouse iPSCs that challenged the importance of insertional effects for reprogramming (Varas et al., 2009); and work at the CNIO on the dynamics of telomere elongation during reprogramming, which highlighted the importance of telomerase for iPSC generation (Marion et al., 2009).

While the overall performance of Spanish biomedical research still lags behind that of the major international players, clinical research fares remarkably well in most comparisons. For instance, papers on clinical medicine by Spanish authors indexed by Thomson Reuters between 2003 and 2007 received an average of 2.69 citations per paper, an impact 11% above the world average. A recent example of the accomplishments of translational research in Spain, particularly relevant for regenerative medicine, was the successful transplantation of a tissue-engineered trachea performed at the Hospital Clinic in Barcelona (Macchiarini et al., 2008). Multiple circumstances converge to determine the strength of Spanish clinical research, including a high-quality healthcare system that provides universal coverage, well-developed structures and logistics associated with translational research and clinical trials, the strong support and active role played by private companies, and most important, the professionalism and dedication of physicians and nurses engaged in clinical research. Many Spanish clinical researchers are among the world leaders in their fields, such as Francisco Fernández-Avilés (Hospital Gregorio Marañon, Madrid) in myocardial infarction, Eduard Tolosa (Hospital Clínic, Barcelona) in Parkinson's disease, Teresa Gómez-Isla (Santa Cruz y San Pau Hospital, Barcelona) in Alzheimer's disease, Joan Rodés (Hospital Clínic, Barcelona) in liver cirrhosis, Ramon Gomis (Hospital Clínic, Barcelona) in diabetes, Josep Baselga (Hospital Vall d'Hebron, Barcelona) in oncology, and Damián García-Olmo (Hospital La Paz, Madrid) in general surgery. Where applicable, Spanish clinical researchers are willing to consider strategies of regenerative medicine (Fernandez-Aviles et al., 2004; Garcia-Olmo et al., 2005). A tightly networked healthcare system of excellence, with some 40.5 million potential users and a large number of highly trained professionals (3.4 practicing physicians per 1000 inhabitants, versus 3.0, the Organisation for Economic Co-operation and Development average), is a key asset for Spain's contribution to bringing the advances in stem cell research into clinical practice. The success of the Spanish National Transplantation Organization (ONT) illustrates the immense potential of the Spanish healthcare system when working in unison. Created in 1989 to promote organ transplantation in Spain, the ONT, under the leadership of Rafael Matesanz, managed to coordinate all parties involved to more than double the donation rate to the highest in the world. The working model of the ONT (known as the Spanish model) is now the reference model for organ transplantation coordination and policies worldwide.

Remarkably, the success of the ONT requires a comparatively low investment (a current annual budget of 4.2 million euro for around 40 staff), highlighting the cost-effectiveness of good coordination and networking once the key elements are in place. On a wider scale, in 2006 the Carlos III Health Institute launched an ambitious program to promote collaborative research in biomedicine among basic, applied, and clinical scientists. Around 500 research groups were selected based on their track record to form 18 Thematic Networks of Cooperative Health Research (RETICS). Stem cell research is explicitly covered in the Cell Therapy Network (TERCEL). Similarly, almost 400 groups were selected to create nine virtual Networking Centers of Biomedical Research (CIBER), which are legal entities that provide additional administrative and operational flexibility. In addition, to capitalize on the strength of clinical research in Spain, the Carlos III Health Institute has initiated a process to accredit hospitals of excellence with Health Research Institutes, which will be eligible for additional funding. Five such institutes have been sanctioned so far, nucleated around Hospital Clínic, Hospital Vall d'Hebrón, Hospital Bellvitge, and Hospital Germans Trias i Pujol (all of them in the Barcelona area), as well as Hospital Virgen del Rocío in Seville.

The Challenge Ahead

While collaborative research among Spanish groups has become the norm, international collaboration is, unfortunately, still the exception, and even more so when private companies are involved. The 2008 edition of the Eurostat report on "Science, technology and innovation in Europe" places Spain as the country with the least innovation cooperation at European and international levels. This trend must be corrected if Spanish research initiatives and networks are to succeed in the worldwide biomedical picture. While the Cooperation Programme of the European Commission (EC) has drastically changed the collaboration patterns in many areas of biomedical research, this impact has yet to be seen in human pluripotent stem cell research, due to the traditionally timid approach of the EC toward hESCs, given the diversity in national legislation and sensibilities (Winston, 2007). On the other hand, Spain is beginning to attract significant numbers of foreign researchers to conduct postdoctoral studies, but the positive results of these interactions in terms of international collaborations will take several years to realize. In the meantime, it is imperative that specific policies are put in place to foster international collaborative research projects. An important initiative in this direction has been taken very recently by the Spanish Ministry of Science and Innovation (MICINN), which has allocated 10 million euro to a joint funding call with the California Institute for Regenerative Medicine (CIRM) to support collaborative projects between Spanish and Californian groups. This venture is allegedly the first in a series of international collaboration agreements that will comprise the MICINN's ambitious

International Program of Research on Regenerative Medicine.

We can only hope that the necessary steps to secure Spain's position in the biomedical research landscape are not deterred this time by the current worldwide situation of economic and financial crisis. This risk, in combination with Spain's track record, is the inspiration for the title of this article. This is certainly a generalization, but the Spanish approach to problem-solving tends to swing between two extremes: an unwavering and almost heroic determination to resolve a situation (real or otherwise) that is seemingly unsolvable, and the complete and unashamed neglect of problems that prove to be difficult to solve. These extremes are epitomized by, on the one hand, Don Quixote's ferocious attacks on the windmills that he perceived to be giants, and on the other, by the infamous exclamation by renowned Spanish writer Miguel de Unamuno, in reference to the national technological impasse: "Let others invent!" Peculiar to Spain is that both extremes are often pursued, alternatively, by a given individual or community with respect to the same problem. Indeed, this duality is more troubling when exhibited by policymakers, a situation that is not infrequent. All too often, the priority of modernizing Spanish biomedical research has been put aside in favor of more urgent needs (the consolidation of the "national spirit" under Franco's dictatorship, the economic crisis of the 1970s, the efforts to enter the European Community, the economic crisis of 1991–92, and the adaptation of the common European currency, to name a few). This time, we really are facing giants. A giant effort has been made in the past 10 years to modernize Spanish biomedical research. Giant results may be achieved if the different strategic initiatives are given time to come to fruition. Giant benefits for society at large can come by developing safe and efficient strategies of regenerative medicine. Since we are not likely to change the Spanish habit of running away from true giants, let us pretend, just for this situation, that they are only windmills.

ACKNOWLEDGMENTS

We thank M. Edel and all the members of the Center for Regenerative Medicine in Barcelona for fruitful discussion and input. We apologize to the many excellent Spanish researchers whose work could not be cited here due to formatting space constraints.

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