Cell Transplantation, Vol. 19, pp. 1493–1509, 2010
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0963-6897/10 $90.00 + .00
DOI: 10.3727/096368910X540612
E-ISSN 1555-3892
www.cognizantcommunication.com

Editorial Commentary

Stem Cell Research in *Cell Transplantation*: Sources, Geopolitical Influence, and Transplantation

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If the rapidly progressing field of stem cell research reaches its full potential, successful treatments and enhanced understanding of many diseases are the likely results. However, the full potential of stem cell science will only be reached if all possible avenues can be explored and on a worldwide scale. Until 2009, the US had a highly restrictive policy on obtaining cells from human embryos and fetal tissue, a policy that pushed research toward the use of adult-derived cells. Currently, US policy is still in flux, and retrospective analysis does show the US lagging behind the rest of the world in the proportional increase in embryonic/fetal stem cell research. The majority of US studies being on either a limited number of cell lines, or on cells derived elsewhere (or funded by other sources than Federal) rather than on freshly isolated embryonic or fetal material. Neural, mesenchymal, and the mixed stem cell mononuclear fraction are the most commonly investigated types, which can generally be classified as adult-derived stem cells, although roughly half of the neural stem cells are fetal derived. Other types, such as embryonic and fat-derived stem cells, are increasing in their prominence, suggesting that new types of stem cells are still being pursued. Sixty percent of the reported stem cell studies involved transplantation, of which over three quarters were allogeneic transplants. A high proportion of the cardiovascular systems articles were on allogeneic transplants in a number of different species, including several autologous studies. A number of pharmaceutical grade stem cell products have also recently been tested and reported on. Stem cell research shows considerable promise for the treatment of a number of disorders, some of which have entered clinical trials; over the next few years it will be interesting to see how these treatments progress in the clinic.

Key words: Stem cells; Cell transplantation; Regenerative medicine; Allogeneic; Autologous

INTRODUCTION

Stem cell research is rapidly progressing globally toward characterizing their potential use in the treatment of diseases, or use of these cells as a model for disease treatments. There is now a considerable body of work exploring the isolation, preservation, culturing, and the translation of a variety of different stem cell types into the clinical setting. In a recent study of articles published in *Cell Transplantation*, which is one of the top journals in the field of transplantation and can therefore be used as a looking glass to see how regenerative medicine is progressing, manuscripts categorized under the section of stem cells were the second most prominent, and over 100 were related to transplantation studies (47). We, therefore, thought that it would be interesting to explore the upsurge in stem cell manuscripts in more detail, including looking at whether geopolitical influences on stem cell research remain. This commentary does include the "raw" data reported from the American Society for Neural Therapy and Repair (ASNTR) meetings and, as such, highlights the cutting edge of trends of stem cell research within certain fields.

STEM CELL PUBLICATIONS IN *CELL TRANSPLANTATION* BETWEEN 2008 AND 2009

As in the larger study of all manuscripts (47), the 214 stem cell-related articles published in *Cell Transplantation* have first been characterized based on the original

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themes of the section editors and the source or type of stem cells (Table 1).

The largest section was, as expected, shown to be "Neuroscience," with 58 out of 214 articles (27%). However, this was closely followed by the "Stem Cells, Progenitors, and Bone Marrow" section (57 out of 214; 26.6%). Because only 21 of the 52 total neural stem cell papers were classified as "Neuroscience," this confirms that there is considerable overlap between the less specific categories, such as "Stem Cells," "Methods and New Technologies" (third, 26 out of 214; 12.1%), and "Tissue Engineering and Bioartifical Organs" (fourth, 24 out of 214; 11.2%) sections, which are in the same order as in the overall analysis. They predominantly featured the three highest stem cells types (neural, mesenchymal, and mononuclear fraction). Whereas the "Islets and Other Endocrines" section was fifth in the overall analysis, it is last in the stem cell-specific review presented here. This demonstrates how the "Islets and Other Endocrines" section is primarily focused on islet cell or tissue transplantation, rather than on stem cell research.

The next section was "Cardiovascular Systems" (fifth, 18 out of 214; 8.4%). Whereas the top four ranked sections are, in general, fairly equally distributed among the top three stem cell types, this section is predominantly composed of the second and third most widely studied cell types: the mesenchymal stem cell and mononuclear fraction (although the absence of the number one cell type, neural stem cells, is no surprise).

The "Hepatocyes" and "Muscle, Bone, and Cartilage" sections were equal sixth (11 out of 214; 5.1%), followed by the "Skin and Other Tissues" section (6 out of 214; 2.8%).

In previous report on stem cells, we included fetal-derived neural stem cells (NSCs) within the group of fetal stem cells (51). However, the prominence of neuroscience in both this and the larger study (47) suggested that a separate category of NSCs may be more appropriate. This is borne out by "neural stem cells" being the most common type of stem cell studied, with 52 out of 214 articles (24.3 %; see Table 1). This category has been split into two (Fetal and Other) to make it clear how many reports involved cells that were fetal derived. Out of these 52 articles, 27 are derived from a fetal source with six of these being previously derived cell lines (e.g., the CTX0E03 or ReN001 cells generated by ReNeuron, Inc., which are currently being used in a clinical trial to treat stroke in the UK) (170). The "other" subgroup includes neonatal and adult-derived cells as well as another two that were cell lines derived from tumors (178,190). Eight of the "other" articles deal exclusively with endogenous NSCs and how they can be influenced by factors such as age, dietary supplements, growth factors, and stress [e.g. (10,11,127,146)]. An additional four look at how stem cell transplants could affect endogenous NSC activity (18,119,120,147). The two articles listed as "Fetal stem cells" involve the generation and use of stem cell-like hepatocytes (34,179).

The second most commonly studied stem cell is the "mesenchymal stem cell" (MSC; 50 out of 214; 23.4%). This is, in fact, the only type of stem cell to be reported in all nine editorial groups, and their popularity is ranked in a similar order to the overall ranking of these groups (i.e., the three most prominent groups are "Neuroscience," "Stem Cells," and "Methods" with 14, 13, and 6 articles, respectively. The majority of the MSCs were derived from bone marrow (43 out of 50), with four studies using cells derived from placental or amnion tissue [e.g. (20,121)], one from the lung (216), one from the umbilical cord (30), and one from the synovium (184). One study compared bone marrow and amnion-derived MSCs for the treatment of heart injury and observed two similar but different differentiation end products by the cells from the two different sources (81). Three studies looked at factors that affect endogenous production of bone marrow-derived MSCs, including disease (53), growth factors (152), and hypothalmic peptides (60). One of the articles relates to a patented cell line that is preparing to undergo clinical trials in the US [i.e., Athersys' Multistem (73)].

The third largest group of stem cells are "mononuclear stem cells" (MNCs) with 34 articles (15.9%). This is a mixture of stem cells that is generally produced by the differential centrifugation of umbilical cord blood (UCB) or bone marrow using Ficoll and can include stem cells such as MSCs, monocytes, $CD14^+$, $CD34^+$, and $CD133^+$ cells. One of the possible steps for the preparation of MSCs involves the collection of the mononuclear fraction from the source tissue, which is then cultured. The MSCs adhere to the culture flasks while the remaining cells remain in suspension in the media. As shown by the fact that it is the third most common cell type, use of the mixed mononuclear fraction is becoming increasingly prominent. This group has been subdivided into blood- and bone marrow-derived fractions, with the blood-derived MNC being nearly twice as prominent as the bone marrow-derived MNCs (22 and 12 manuscripts, respectively). Inclusion of the bone marrow-derived samples with the MSCs could make this the most investigated stem cell with 62 articles (29%), whereas including the blood-derived mononuclear cells with the blood-derived stem cells could make this the third largest group (31 out of 214; 14.5%). However, because MNCs are increasingly being used and are a more accurate description of the type of stem cells being studied, those reports involving MNCs were collected into their own group. Whereas blood-derived MNCs are dominant in "Neuroscience" (9 of the 10 manuscripts),

Table 1. The Distribution of the Different Forms of Stem Cells Across the Sections of *Cell Transplantation*

	Embryonic Stem Cells	Fetal Stem Cells	Neural Stem Cells		Blood-Derived Stem Cells	Mononuclear Stem Cells		Mesenchymal Stem Cells	Muscle Stem Cells	Fat-Derived Stem Cells	Other Adult Stem Cells	Totals
			Fetal	Other		Blood	Bone Marrow					
Neuroscience	17,37,114, 126, 182,192		1,14,54, 68,84, 86,97, 101,147	7,10,11, 65,116, 117,127, 146,158, 190,191	202	62,63,88, 128,136, 137,139, 160,214	64	24,33,35,40,53, 67,79,107,152, 161,175,181, 183,195		141, 162	99,112, 125,159	58
Islets and other endocrines								30,46				2
Hepatocytes	45,168	179				3,4	157	70		23,212	164,187	11
Tissue engineering and bi-oartifical organs			44,59, 185, 196	178,213	108	39,85, 103		2,22,76,87,135		36,199, 210,211	82,92, 113,143, 189	24
Muscle, bone, and cartilage								80,145,156	15,16,19, 21,41,102, 154,166			11
Stem cells, progenitors and bone marrow	5,13,90,111, 155,177,186, 203, 205		8,9,49, 50,52, 153,170, 173	12,18, 119,120, 130,172, 174,198	26,32,42, 77,149	115,118, 148,167, 200,201	75,110	20,31,57,60, 73,91,95,100, 121,138,184, 188,208		142	55,71, 93,109, 171	57
Methods and new technolo-gies	129,133,134, 193,194	34	43,83, 98,131, 151	25,69, 197,204	94	123		28,72,105,165, 180,217		144,209	140,176	26
Cardiovascular systems						206	6,61,66, 74,96, 106,132, 169	58,81,124,207	104	163	56,78, 150	18
Skin and other tissue					29			122,216	215		27,89	6
Total	22	2	27	25	9	22	12	50	10	12	23	214
			52			34						

bone marrow-derived MNCs are more prominent in "Cardiovascular" studies (8 out of the 9 manuscripts). The "Stem Cells, Progenitors, and Bone Marrow" category is also biased towards the study of blood-derived MNCs (6 out of 8).

Several of the studies are on specific cell types found within the MNC fraction. This includes endothelial progenitor cells derived from the cord blood-derived MNC fraction (115,118) as well as Newman et al. (137), who explored the use of $CD133^+$ neurally induced cells derived from the cord blood MNC fraction.

As with MSCs, one of the articles relates to a patented cell type—Refractory Angina Cell Therapy (ReACT) (75)—an MNC preparation derived from a patient's own bone marrow and it is currently being tested in clinical trials for the treatment of angina in Brazil with favorable results.

The fourth largest stem cell group was the "other adult stem cells" (23 out of 214; 10.7%), which included hepatocyte progenitors [e.g. (164,187)], non-mesenchymal amnion and placental-derived cells (27,56), induced pluripotent stem cells (iPS) (171,176), cancer stem cells (93), and reviews covering genetic manipulation of a multitude of stem cell types [e.g. (55,113)]. The presence of research on iPS cells is of potential interest and may highlight a new source of pluripotent stem cells (previously only obtainable from embryonic tissue), and this could be a rapidly advancing part of stem cell research. We expect to see more research in all of these areas in the future.

Embryonic stem cells (ESCs) were the fifth largest group, with 22 articles out of 214 (10.3%). Eight of these involved the differentiation of the ESCs to neural cells, including dopamine neurons (203), oligodendrocyte progenitors (155), and motor neurons (114) as well as neural precursor or neural stem cells (NPC/NSC) [e.g. (37,191)]. The oligodendrocyte progenitor cells derived from ESCs are the first ESC-derived treatment to be approved for clinical trials by the US FDA and are owned by Geron. Teratoma formation by ESCs was investigated in four studies, including the one by Tanaka et al., who studied this in primates (182), and Matsuda et al., who showed that cotransplantation of ESCs and MSCs reduced the teratoma incidence compared with ESC transplants alone (126). The derivation of hepatocytes from ESCs was also explored by a number of groups [e.g. (177)], as well as insulin-producing cells (133) and MSCs (205).

Fat-derived stem cells were of increasing prominence with 12 reports (5.6%), though it is worth noting that several papers were published from the same groups [e.g. (209,211) and (142,144)].

"Blood-derived stem cell" group (9 out of 214; 4.2%) dropped in prominence, but this is partly due to the removal of the UCB-derived MNC group. Of the nine purely blood-derived studies, four examined hematopoietic stem cells, including their endogenous production during pregnancy (42), and their derivation from umbilical cord blood (94). A further two looked at UCB-derived mesenchymal cells (29,108), whereas one additional study investigated menstrual blood as a source of stem cells (149).

Comparing adult-derived cells to the more controversial embryonic and fetal-derived stem cells (embryonic, fetal and fetal-derived neural cells), we see that research is still predominantly on adult stem cells (163 vs. 51). This may be a reflection on restrictive legislation in some countries, or the fact that adult stem cell research has been ongoing for considerably longer than the relatively new embryonic and fetal stem cell research. We will be comparing stem cell type and location later to examine if restrictive legislation could be a factor. If we compare stem cell manuscripts published in 2008 with those published in 2009, we have 99 versus 115 respectively, suggesting a modest increase in the number of manuscripts. Embryonic versus adult in 2008 and 2009 split 20:79 and 31:84, respectively, showing a greater increase in the number of embryonic compared with adult stem cell research studies.

Source of Stem Cells by Species

A comparison of the species from which the stem cells are derived (Table 2) reveals that the majority of studies are on human (118 out of 214; 55.1%), followed by rat-derived (50 out of 214; 23.4%) and mouse-derived (34 out of 214; 15.8%) stem cells. The majority of the human-derived cells were MSCs (29 out of 118; 24.6%), whereas NSCs were dominant in both rats and mice (24 out of 50; 48% and 9 out of 34; 26.5%, respectively). In both rats and mice, non-fetal-derived neural stem cells were prominent (16 out of 24 and 6 out of 9, respectively), whereas, unsurprisingly, in humans most research was on fetal-derived neural stem cells (as it would not be easy to harvest adult cells!; 16 out of 18). Looking at the different cell types, blood-derived MNCs were almost exclusively human derived (19 out of 22; 86.4%) and the majority of the "other adult stem cells" were also human-derived cells (17 out of 23; 73.9%). This was also true for the blood-derived cell group (7 out of 9; 77.7%). The dominance of human-derived cells may be the logical progression from prior studies using rodent and other mammal-derived species, and may also reflect the early clinical translation of some of these studies, because several reports relate to pharmaceutical company "products" that are either now in, or are preparing to enter, clinical trials. This is discussed below under Stem Cell Transplantation. The "newer" fat-derived stem cells were predominantly rodent based (8 out of 12; 66.7%), which may reflect the relative "new-

Table 2. The Species Source of the Different Types of Stem Cells

	Embryonic Stem Cells	Fetal Stem Cells	Neural Stem Cells		Blood-Derived Stem Cells	Mononuclear Stem Cells		Mesenchymal Stem Cells	Muscle Stem Cells	Fat-Derived Stem Cells	Other Adult Stem Cells	Totals
			Fetal	Other		Blood	Bone Marrow					
Human	5,13,17,37, 111,134,155, 177,192–194, 203	34,179	1,8,14, 44,49, 50,52, 54,68, 86,97, 131,147, 170,185, 196	11,190	26,29,42, 94,108, 149,202	3,4,39, 62,63,85, 88,115, 118,128, 136,137, 139,148, 160,167, 200,201, 214	6,61,64, 75,110, 132,169	2,20,24,30,35, 40,46,53,57, 67,72,73,91, 100,107,121, 124,135,138, 145,175,181, 183,184,188, 195,208,216, 217	16,21, 154,166	23,162, 163	27,55,71, 78,92,93, 99,109, 112,113, 125,150, 159,164, 171,176, 189	118
Primate	90,182			25					102			4
Mouse	45,114,126, 129,133,168, 186,205		9,98, 151	7,10,117, 158,178, 198	32,77	103		22,31,80,152	15,41	142,144, 209–212	140,143	34
Rat			38,43,59, 83,84, 101,153, 173	12,18,65, 69,116, 119,120, 127,130, 146,172, 174,191, 197,204, 213			66,74,96, 106,157	28,33,58,60,70, 76,79,81,95, 122,161,165, 180,207	19,104	36,141	56,82,89	49
Rabbit						123		156	215	199		4
Pig								87,105			187	3
Sheep						206						1
Total	22	2	27	25	9	22	12	50	10	12	23	214
			52			34						

ness" of these cells, and so they are primarily being explored in rodents first before human studies are performed; or this could be a reflection of multiple papers by the same groups (which all feature in the rodent section).

Geographical Distribution of Stem Cell Studies

In several cases, the reports were collaborative efforts between two or more countries. The reports have been categorized based on where the experiments occurred. A study of the geographical location of the reported studies demonstrates that the US is dominant, with 90 out of 214 studies (42.1%; Table 3), followed by Japan, with 32 (15%), and Germany, with 13 (6.1%). In total, 25 different countries were represented. Looking by continent, North America is top, with 97, followed by Asia (60 articles), and then Europe (including Russia/Ukraine/Armenia; 46), with South America contributing another seven and Australasia another four reports. A previous retrospective study in 2007 revealed a bias toward adult stem cell research in the US when compared with fetal and embryonic research (51). The restrictive nature of the US legislation meant that a number of state and alternative sources (from Federal) for funding of ESC research arose. This varied from state to state dependent on their own legislation and a review, published in 2008, provided a summary of the availability of funding across the states (48). The legislation has changed since then, as in 2009 the restrictive use of ESCs was moderated in the US and it will be interesting to see whether this will influence the type of cells studied. An update on the current funding situation by state would be timely, but is not the remit of this report. A summary can be found at http://www.isscr.org/public/regions/ and http://www.ncsl.org/IssuesResearch/Health/EmbryonicandFetalResearchLaws/tabid/14413/Default.aspx.

However, it is likely to be too soon to see whether the changes in legislation have had an effect, but this report will provide a good yardstick against which to measure future reports. It is also important to consider that in 2010 federal funding for embryonic stem cell research was halted by court order, followed by a temporary stay on this decision while the matter is under review.

This report shows that the bias towards adult stem cell research would appear to still be present, with 61 (67.8%) of the 90 US-based manuscripts involving adult stem cells, compared with 29 (32.2%) being embryonic or fetal derived (including over half of the US NSC manuscripts). In fact, the US is top in every category except "fat-derived," "muscle," "other adult stem cells," and bone-marrow-derived MNCs. In both the NSCs (fetal and others) and blood-derived stem cells (general and MNCs) the US has more manuscripts than all the other countries combined. Surprisingly, the US is also top in ESCs, with all but one of the studies being on human-derived ESCs. Six of the studies looked at the generation of NSC/NPCs from these cells [e.g. (5,193)], including the Geron study mentioned earlier (155), whereas Linquist et al. used ESCs to model early neural development (111) and Bakay et al. explored potential problems with hESC transplantation into primates (13). The US-based studies were either on NIH-approved ESC lines, or were privately funded (e.g., by Geron).

Looking at the stem cell types for 2008 and 2009, we can see that ESCs, fetal stem cells, blood-derived stem cells (including general and MNCs), muscle stem cells, and other adult stem cells show little change, whereas MSCs show a 33.3% fall in the number of manuscripts, primarily due to a decrease in Japanese manuscripts on MSCs, whereas China, France, and Germany show a sizeable increase. The number of NSC papers nearly doubles (increasing from 19 to 33) with the largest increase in fetal-derived (increasing from 9 to 18) compared to other sources (increasing from 10 to 15), whereas fat-derived stem cell papers triple (from 3 to 9). The overall number of embryonic/fetal-derived stem cell manuscripts actually showed a greater than 50% increase from 2008 to 2009 (going from 20 to 31, which was predominantly a result of the doubling in fetal-derived NSCs). By comparison, adult stem cells showed a 79:84 split for 2008:2009, respectively, suggesting that while adult stem cells were more popular, ESCs are being studied at an increasing rate. The US split is 12:17 for "embryonic" and 24:37 for "adult" stem cells, suggesting that the US may still be in opposition to the overall worldwide trend with a greater increase in adult stem cell research (54.2%) than embryonic (41.6%)—the increase in non-fetal-derived NSCs being a major contributing factor to this.

STEM CELL TRANSPLANTATION

One of the ultimate aims of stem cell research is to develop new therapies for a number of disorders. This could be either for cell replacement, or to provide specific factors, as a number of studies now suggest. *Cell Transplantation* is one of the top two journals in the field of transplantation, and so a number of its articles relate to stem cell transplantation in either preclinical/clinical trials or in animal models. Consequently, we looked at the stem cell transplantation studies in *Cell Transplantation* in 2008–2009, examining the types of transplants [e.g., allogeneic (same species) or xenogeneic (different species)]. The data primarily cover original articles, but a few reviews of cell transplantation in specific species are also included. Sixty percent of the articles (129 out of 214) involved transplantation and, as Table 4 shows, the majority of the 129 transplantation studies were actually allogeneic (77; 59.7%). In fact, all

Table 3. The Distribution of the Different Types of Stem Cell Research Across the World

	Embryonic Stem Cells	Fetal Stem Cells	Neural Stem Cells		Blood-Derived Stem Cells	Mononuclear Stem Cells		Mesenchymal Stem Cells	Muscle Stem Cells	Fat-Derived Stem Cells	Other Adult Stem Cells	Totals
			Fetal	Other		Blood	Bone Marrow					
USA	5,13,17,37,45, 111,155,193, 194,203	34	8,14,38,44, 49,50,52,54, 59,68,84,97, 101,131,147, 151,153, 173,185,196	7,10–12, 18,65, 116,117, 119,120, 146,158, 172,174, 197,198	26,42,77, 149,202	39,62,63, 88,103, 118,128, 136,137, 139,148, 167,200, 201,214		2,22,24,35,67,72, 73,105,124,152, 175,181,183	41	162	56,71,99, 125,150, 159,171, 176	90
Canada	186			130,213					15,16,102			6
China	205		43			85,123	61	76,156,180,216, 217	215	199		12
Singapore			98									1
Taiwan					32		110	30,31,100			55,78,109, 112,113	10
Japan	90,126,129, 134,182		204			74,106	57,70,80, 91,95,145, 184,207		141,142, 144,209–212	82,89,92,93, 140,143,164, 187,189	32	
Spain						3,4				23,36,163		5
France				190				40,161	19,154			5
Germany	133,168			178		206	6,66,96, 132	58,87,135,138, 165				13
Italy						160		53,81,121,122, 188,208	21		27	9
Austria/Switzerland			83	25	94			20				4
Sweden		179	1									2
UK			86,170	69		115		79				5
Argentina								46				1
Armenia/Ukraine/Russia								60,195				2
Brazil	177						75,157,169	28				5
Ecuador							64					1
South Korea					29,108			33,107	104			5
Australia			9									1
New Zealand	192			127,191								3
Mexico	114											1
Poland									166			1
Total	22	2	27	25	9	22	12	50	10	12	22	214
			52			34						

Table 4. The Type of Transplants Described in *Cell Transplantation* by Species

	Recipient							
Donor	Human	Primate	Mouse	Rat	Rabbit	Sheep	Pig	Total
Human	6,26,35,39,46,64,72, 73,75,78,100,110,132, 137,155,166,169,170, 175,177,188,208	13,44,196	16,21,27,34,62,63,85, 128,139,145,154,160, 179,185,214,217	1–4,14,17,24,29,37, 40,67,86,88,107,124, 131,136,147,148,162, 163,181,183,190,192, 195,200,201			52	70
Primate		25,102	90,182					4
Mouse			7,15,22,41,45,80,126, 151,152,158,168,186, 205,212	114				15
Rat				18,19,28,33,36,43,56, 58,60,66,69,70,79,81, 84,89,95,96,101,104, 106,119,120,122,130, 141,157,161,165,172, 180,191,197,204,207, 213				36
Rabbit					199			1
Sheep						206		1
Pig			105				87	2
Total	22	5	33	65	1	1	2	129

but the human-derived cells were predominantly transplanted in an allogeneic manner. The majority of transplanted cells came from humans (70; 54.3%), followed by the rat (36; 27.9%) and mouse (15; 11.6%), whereas the most common recipient was the rat (65; 50.4%), followed by the mouse (33; 25.6%) and humans (22; 17.1%). No human xenografts were reported, whereas xenogeneic transplantation of human stem cells was more than twice as common as allogeneic transplants (48 vs. 22). The rat, rabbit, and sheep transplants were all allogeneic.

A comparison of the allogeneic transplants by category reveals that the largest section was "Stem Cells, Progenitors, and Bone Marrow" (19/77), followed by "Neuroscience" (15/77), "Cardiovascular Systems" (13/77), and "Methods and New Technologies" (10/77). A detailed study of the more descriptive sections (Stem Cells, Methods, and Tissue Engineering) reveals that the majority were neuroscience related. Country comparison revealed that all five of the Brazilian articles were actually classified as articles involving allogeneic transplants relating to the liver (157,177), heart (75,169), and eye (28), with the cardiac-related articles being human allogeneic transplants and the remainder being allogeneic rat transplants, with three involving bone marrow-derived MNCs, one involving MSCs, and one on ESCs. Nine of the 13 German articles were also allogeneic transplants, with six being cardiovascular related, including two in humans using bone marrow-derived MNCs (6,132). Three other nonhuman studies involved allogeneic transplants of MSCs, whereas another three were of bone marrow-derived MNCs. Also, five of the six Canadian articles were allogeneic transplants. None of these were in humans, two involved muscle stem cells (15,102), and two were neural stem cells (130,213). This compares with the more prominent countries: USA (22 out of 90), Japan (7 out of 32), and China (4 out of 12). Year-by-year comparison revealed a sizeable increase in the number of human allogeneic (6 vs. 16) and human–rat transplants (11 vs. 17), whereas human–primate and human–mouse transplants decreased slightly (2 vs. 1 and 9 vs. 7, respectively). The increase in human allogeneic transplants may reflect that prior animal studies have demonstrated success and that this is the natural progression from these prior studies.

Thirteen of the allogeneic transplantations were also autologous; nine were in humans, with one in primates (25), pigs (87), rabbits (199), and sheep (206). All but one of the human autologous transplants involved bone marrow-derived MNCs (6 out of 9) or MSCs (2 out of

9) for the treatment of cardiovascular disorders (6,75, 132,169), diabetes (46), stroke (110), spinal cord injury (64), and non-musculoskeletal disorders (100). The last human allogeneic transplant used UCB-derived MNCs to enhance vasculogenesis in the potential treatment of ischemic disorders (39). Two reports originated from each of the following countries: Brazil, Taiwan, and Germany. The remaining studies were performed in Argentina, Ecuador, and the US. The Argentina and Ecuador studies, and one of the Brazilian studies, also involved some degree of collaboration with the US, which may just be as consultants or the US may have a greater contribution to the study (46,64,75). For instance, several of the studies, while based in the US, were using fetal-derived stem cells obtained and modified in another country [e.g., ReN001 (or CTX0E03) cells from ReNeuron in the UK] (49,50,131,147,170). These collaborations demonstrate the potential worldwide impact of stem cell research in the treatment of a number of disorders, and by collaborating with other countries this allows the US to be involved in studies that would have been affected by the restrictive legislation if performed in the US.

Whereas this commentary does provide insight into stem cell research, there are certain limitations to be considered. The information is based on publications in one journal, admittedly one of the leading transplantation journals. *Cell Transplantation* publishes manuscripts in a variety of fields that can be translational and do not necessarily relate to stem cells. In addition, the “Neuroscience” and “Islets” fields could be potentially biased because the two coeditors-in-chief of the journal work in these fields. However, because there were only two “Islets” articles, this would suggest that there is no bias. Another consideration is that *Cell Transplantation* has been sponsored by, or is associated with, a number of societies, including the American Society for Neural Therapy and Repair, the Japanese Society of Organ Preservation and Medical Biology, The Pan-Pacific Symposium on Stem Cell Research, and the Annual Cardiac Cell Therapy Meeting. These are all international societies, but they could still lead to some bias towards specific themes or their country of origin. However, because these societies cover different (but potentially overlapping) fields, this should limit any bias. A comprehensive study looking at a number of other journals, all of which could have their own potential biases, could paint a different picture. However, we feel that while this study has its limits it does provide an insight into the current state of stem cell research.

This analysis shows that stem cell research is rapidly advancing worldwide, although there is still a bias towards adult stem cell research, particularly in the US, which may partly relate to the relative newness of embryonic stem cells by comparison or due to geopolitical pressures. Neural stem cells are the most commonly studied single type of stem cell, whereas a combined mesenchymal stem cells and bone marrow-derived mononuclear fraction would be slightly more prominent. This latter group of cells has been studied in several clinical trials currently either on-going or beginning in a number of different countries. Embryonic and fetal-derived stem cells are also being studied clinically, especially with pharmaceutical company backing. The majority of the cardiovascular system-based reports are allogeneic transplant studies of adult stem cells. This highlights the growing importance and potential use of stem cells for a number of disorders and suggests that the next few years could reveal some important advances in the clinic for the treatment of these disorders.

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