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The survey on cellular and tissue-engineered therapies in Europe and neighboring Eurasian countries in 2014 and 2015

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Abstract

Background aims. With the support of five established scientific organizations, this report, the seventh of its kind, describes activity in Europe for the years 2014 and 2015 in the area of cellular and tissue-engineered therapies, excluding hematopoietic stem cell (HSC) treatments for the reconstitution of hematopoiesis. *Methods.* In 2015 [respectively 2014], 205 [276] teams from 32 countries responded to the cellular and tissue-engineered therapy survey; 178 [126] teams reported treating 3686 [2665] patients. *Results.* Indications were musculoskeletal/rheumatological disorders (32% [33%]), cardiovascular disorders (12% [21%]), hematology/oncology (predominantly prevention or treatment of graft versus host disease and HSC graft enhancement; 20% [20%]), neurological disorders (4% [6%]), gastrointestinal disorders (<1% [1%]) and other indications (31% [20%]). The majority of autologous cells (60% [73%]) were used to treat musculoskeletal/rheumatological (44% [36%]) disorders, whereas allogeneic cells were used mainly for hematology/oncology (61% [68%]). The reported cell types were mesenchymal stromal cells (40% [49%]), chondrocytes (13% [6%]), hematopoietic stem cells (12% [23%]), dermal fibroblasts (8% [3%]), dendritic cells (2% [2%]), keratinocytes (1% [2%]) and others (24% [15%]). Cells were expanded *in vitro* in 63% [40%] of the treatments, sorted in 16% [6%] of the cases and rarely transduced (<1%). Cells were delivered predominantly as suspension 43% [51%], intravenously or intra-arterially (30% [30%]), or using a membrane/scaffold (25% [19%]). *Discussion.* The data are compared with those from previous years to identify trends in a still unpredictably evolving field. Perspectives of representatives from plastic surgery practitioners, Iran and ISCT are presented (contributing authors D.A. Barbara, B. Hossein and W.L. Mark, respectively).

Key Words: *cellular therapy, clinical trial, regenerative medicine, tissue engineering*

Introduction

The numerous opportunities offered by emerging cellular and tissue-engineered therapies are being increasingly presented in the public media as if they will be routine medical procedures in the near future [1]. As these treatments become more widespread and visible to the public, it is beholden upon clinicians, researchers and the health care industry to raise awareness of the risks and benefits through communication of outcomes from official clinical trials [2,3]. In this context, results published in the scientific press and public databases (e.g., clinicaltrials.gov) provide insight into prospective and ongoing trials. However, these disclosures represent only a small number of the total interventions performed, and they do not specify the precise number of patients treated for separate indications with specific cells in a defined period. In fact,

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they exclude the majority of patients who are treated outside of formal clinical trials and patients treated with non-substantially modified, "homologous" cell/tissue therapies that are not regulated as medicines and not subject to formal clinical trials. Moreover, it is crucial to map the cell/tissue donor types, along with the modes of cell processing and delivery, and match them with the use for specific therapeutic indications. These data are of substantial significance in providing transparent safety reporting, predicting developing trends and possibly advances in the field.

Since 2008, this survey has aimed to offer an unbiased update on the number of patients treated using cellular and tissue-engineered therapies in Europe and Eurasian countries associated with the European group for Blood and Marrow Transplantation (EBMT) [4–9]. This has been made possible by support from the International Society for Cellular Therapy (ISCT), the European Chapter of the Tissue Engineering and Regenerative Medicine International Society (TERMIS-EU), the International Federation for Adipose Therapeutics (IFATS), the International Cartilage Repair Society (ICRS), and the EBMT. The survey comprises data of treated patients sorted by specific therapeutic indications, cell/tissue donor types, together with the processing and delivery modes, without reference to the clinical outcome, thus avoiding infringement of the publication rights for the clinical teams themselves.

In this article, we report the combined results of the seventh and eighth activity survey, covering treatments in 2014 and 2015 together with a description of some recent trends. The report includes a specific discussion on the use of fat-derived cells in plastic and reconstructive surgery, on the clinical translation of cellular therapies in Iran and on the ISCT perspective for this program.

Methods

Definitions

For the purpose of this survey, "cellular and tissue-engineered therapy" is any clinical treatment based on living cells excluding donor lymphocyte infusions (DLIs) and non-manipulated hematopoietic cells for hematological reconstitution. Data regarding DLIs and non-manipulated hematopoietic cells for hematological reconstitution are collected and reported independently by the EBMT [10,11].

Data collection and validation

Participating teams were, as in previous years, requested to report their data for 2014 and 2015 by indication, cell type and source, donor type, processing method and delivery mode. The survey followed the traditional principles of the EBMT transplant activity survey, which concentrates on numbers of patients with a first cellular therapy. For the 2014 survey, more than 600 teams known to be actively transplanting in 48 countries (39 European and 9 affiliated countries) were contacted, to which were added members of the other participating societies, who distributed the survey directly to their members in Europe by e-mail, and teams that had contributed to any earlier survey. The non-European countries affiliated with the EBMT activity survey are Algeria, Iran, Israel, Jordan, Lebanon, Nigeria, Saudi Arabia, South Africa and Tunisia. Extended questionnaires, in the format displayed in Supplementary Table SI, were received in paper form and electronically.

For the 2015 survey, due to changes in the data being collected by the EBMT for its survey, only EBMT teams that had previously reported treating patients with a cell or tissue-engineered therapy were automatically sent the extended questionnaire. During the year, EBMT teams that reported treatments with regenerative medicine were also sent the extended questionnaire, as were contributors to all past surveys. The supporting societies distributed the survey directly to their members in Europe by e-mail and/or published the survey and documents on their websites. New teams identified either through their contribution to published clinical trials or their reports on the platform clinicaltrials.gov (using the search terms "Tissue-engineer" and "Cell" associated with either "Transplant" or "Treatment" in the relevant countries) were contacted and invited to report their data.

Treatment rates

Treatment rates, defined as the reported numbers of patients receiving cellular or tissue-engineered therapies and the number of teams reporting treatments per 10 million inhabitants, were computed for each country, without adjustments for patients who crossed borders or received treatment in a foreign country. Population numbers were obtained from the 2014 and 2015 eurostat database (ec.europa.eu/eurostat).

Results

Unless described otherwise, all the reported data are displayed simultaneously for the years 2015 and 2014 (format: *number declared* 2015 [*number declared* 2014]), as this report encompasses the survey data for both the years 2014 and 2015.

Participating teams

Two hundred and five [276] teams from 32 countries (26 European, 6 EBMT-affiliated countries) responded to the cellular and tissue engineered therapy

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survey of patients treated in 2015 [2014]. One hundred seventy-eight [126] teams (from 21 [25] countries: 19 [23] European, 2 [2] EBMT affiliated—Iran, Israel [Iran, Israel]) reported performing cellular or tissue-engineered therapies. All of these teams provided detailed information on the indication, cell source and type, donor type, cell/tissue processing and delivery mode. A further 27 [150] teams reported no activity.

Teams that replied with detailed information on their activity are listed in the appendix in alphabetical order of country, then city. In addition, their EBMT CIC code (if applicable), the total number of reported cellular or engineered therapies and the split between allogeneic and autologous donors are included.

Number of cellular or tissue-engineered therapies and disease indications

According to the received reports for 2015 [2014], respectively 3686 [2665] patients were treated with cellular or tissue-engineered therapies. Of these patients, 2513 (68%) [1884 (71%)] were treated with autologous cells and 1173 (32%) [781 (29%)] with allogeneic (Table I). Indications were musculoskeletal/rheumatological disorders (32%; 92% autologous [33%; 77% autologous]), cardiovascular disorders (12%; 69% autologous [21%; 99% autologous]), hematology/oncology (predominantly prevention or treatment of graft versus host disease [GVHD] and HSC graft enhancement) (20%; 1% autologous [20%; 2% autologous]), neurological disorders (4%; 69% autologous [6%; 100% autologous]), gastrointestinal disorders (<1%; 0% autologous [1%; 0% autologous]) and other indications (31%; 86% autologous [20%; 94% autologous]).

As in previous years, cartilage and bone repair were by far the most frequently reported indications among the *musculoskeletal/rheumatological disorders*, comprising 69% [46%] of all treatments in this group. In 2014, this was followed by reconstructive surgery/tissue enhancement with 21% similar to preceding years. Subsequently, however, treatments for reconstructive surgery/tissue enhancement decreased to 7% in 2015 in this category, while treatments for arthritis increased from 9% in 2014 to 19% in 2015.

In 2014, the three top reasons for a cellular or tissue-engineered therapy among the *cardiovascular disorders* were treatments for decubitus and leg ulcers (27%), peripheral artery disease (27%) and heart failure (19%), accounting for almost three-quarters of the treatments. By contrast, in 2015, treatments for all three indications decreased (respectively to 19%, 12% and 15%), making up less than half (46%) of the therapies. This decline was paralleled by an increase in treatments for miscellaneous indications (rising from 15% in 2014 to 36% in 2015), implying a more diversified use of cells than in the past.

Similar to previous surveys, the number of patients treated for *neurological and gastrointestinal indications* was relatively small for both years (166 [174]). Approximately two-thirds (64% [63%]) of neurological indications in both years were restricted to multiple sclerosis (35% [46%]) and amyotrophic lateral sclerosis (29% [17%]). The low number of treatments for *gastrointestinal indications* (16 [15] patients) was mostly confined to Crohn's disease in 2014 (87%) and liver insufficiency in 2015 (88%).

Remaining indications were designated to the category *miscellaneous*, in which 526 patients were reported in 2014 and 1150 patients in 2015. In this group, the number of patients being treated for solid tumor excision (186 [56] patients) was prevalent for both years. Among this enlarging faction, the increase of patients undergoing cellular or tissue-engineered therapy for cornea repair was most prominent, from 4 patients in 2014 to 84 the following year. Within this grouping, *other* encompasses indications not included on the survey form, such as acute respiratory distress syndrome, atrophic scars, chronic tissue toxicity, Parry-Romberg syndrome, rectal fistula and hemorrhagic cystitis. The fact that the number of patients reported in this group increased from 456 in 2014 to 835 in 2015 suggests that the listed indications need to be revised for future versions of the survey.

Cell type, source and donor type

The reported cell types were mesenchymal stromal cells (MSCs) (40% [49%]), chondrocytes (13% [6%]), HSCs (12% [23%]), dermal fibroblasts (8% [3%]), dendritic cells (2% [2%]) and others (25% [18%]) (Table I). The types of "other" cells (where specified) include melanocytes, amniotic membrane, keratinocytes, limbal epithelial cells, endothelial cells, glioblastoma cells, cardiac stem cells and a combination of keratinocytes, melanocytes and fibroblasts (Supplementary Table SII). However, as we observe the increasing use of a variety of other cell sources, the future surveys will be adapted accordingly.

From 1492 [1319] MSC-based therapies, less than half (45% [48%]) were autologous transplants, whereas of the 428 [602] HSC treatments almost all (97% [95%]) were autologous transplants (Table I). Of the remaining cell sources, 88% [96%] of chondrocyte transplants, 87% [96%] of dendritic cells, 95% [100%] of dermal fibroblasts 94% [100%] of keratinocytes and 67% [95%] of other cell sources were autologous.

The majority of autologous cells (60% [73%]) were used to treat musculoskeletal/rheumatological (44% [36%]), cardiovascular (13% [29%]) or neurological (4% [8%]) disorders. However, an increasing amount

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Table I. Number of reported cell and tissue-engineered therapy treatments in Europe in 2014 and 2015 sorted by indication, cell source and donor type.

Cell type and source	Autologous						Allogeneic								
Indication	HSC	MSC	Chondrocyte	Dendritic cells	Dermal fibroblast	Other	HSC	MSC	Chondrocyte	Dendritic cells	Dermal fibroblast	Other	Autologous	Allogeneic	Total
Cardiovascular															
Peripheral artery disease	55 [143]					[6]							55 [149]		55 [149]
Cardiomyopathy	44 [50]	2 [0]				6 [0]							52 [50]		52 [50]
Heart failure	48 [67]	5 [0]				2 [37]		14 [0]				1 [0]	55 [104]	15 [0]	70 [104]
Myocardial ischemia	30 [19]							1 [0]					30 [19]	1 [0]	31 [19]
Decubitus and leg ulcers	68 [138]	10 [0]				1 [3]						4 [6]	79 [141]	4 [6]	83 [147]
Other/unspecified	44 [81]	2 [0]						120 [1]					46 [81]	120 [1]	166 [82]
Musculoskeletal/rheumatological															
Bone repair (maxillofacial)	[1]	15 [0]				3 [0]							18 [1]		18 [1]
Bone repair (orthopedics)	3 [2]	59 [58]	55 [0]			28 [0]		6 [0]				8 [0]	145 [60]	14 [0]	159 [60]
Osteogenesis imperfecta	[2]							2 [0]					0 [2]	2 [0]	2 [2]
Cartilage repair (maxillofacial)		10 [0]	9 [18]										19 [18]		19 [18]
Cartilage repair (orthopedics)		118 [180]	325 [126]			125 [6]		5 [0]	57 [6]				568 [312]	62 [6]	630 [318]
Muscle repair		4 [1]						10 [153]					4 [1]	10 [153]	14 [154]
Tendon/ligament		4 [9]						[41]					4 [9]	0 [41]	4 [50]
Reconstructive surgery/tissue enhancement		78 [129]			[56]			2 [0]				1 [0]	78 [185]	3 [0]	81 [185]
Scleroderma	6 [2]							2 [0]					6 [2]	2 [0]	8 [2]
Arthritis		209 [81]				12 [0]							221 [81]		221 [81]
Other/unspecified		13 [1]	20 [0]										33 [1]		33 [1]
Neurological															
Multiple sclerosis	[10]	44 [63]						6 [0]		3 [0]			44 [73]	9 [0]	53 [73]
Amyotrophic lateral sclerosis	19 [3]	10 [25]						15 [0]					29 [28]	15 [0]	44 [28]
Parkinson's disease	[7]												0 [7]		0 [7]
Peripheral nerve regeneration (trauma)	[4]	1 [0]											1 [4]		1 [4]
Other/unspecified	2 [23]	27 [2]				[22]		23 [0]					29 [47]	23 [0]	52 [47]
Gastrointestinal															
Crohn's disease								2 [13]						2 [13]	2 [13]
Liver insufficiency								14 [2]						14 [2]	14 [2]
Hematology/oncology															
GVHD prevention or treatment							9 [20]	470 [462]				150 [10]		629 [492]	629 [492]
HSC graft enhancement	[12]	1 [0]		3 [0]			2 [10]	44 [28]				45 [0]	4 [12]	91 [38]	95 [50]
Miscellaneous															
Skin reconstruction—burns		8 [0]			5 [4]	[2]		5 [0]			10 [0]	3 [2]	13 [6]	18 [2]	31 [8]
Cornea repair						22 [1]		[3]				62 [0]	22 [1]	62 [3]	84 [4]
Diabetes		7 [0]				3 [0]						4 [2]	10 [0]	4 [2]	14 [2]
Solid tumor	88 [5]			61 [49]		28 [0]				7 [2]	1 [0]	1 [0]	177 [54]	9 [2]	186 [56]
Other	10 [3]	82 [47]		7 [3]	285 [10]	387 [373]		42 [20]		1 [0]	5 [0]	16 [0]	771 [436]	64 [20]	835 [456]
Total	417 [572]	709 [596]	409 [144]	71 [52]	290 [70]	617 [450]	11 [30]	783 [723]	57 [6]	11 [2]	16 [0]	295 [20]	2513 [1884]	1173 [781]	3686 [2665]

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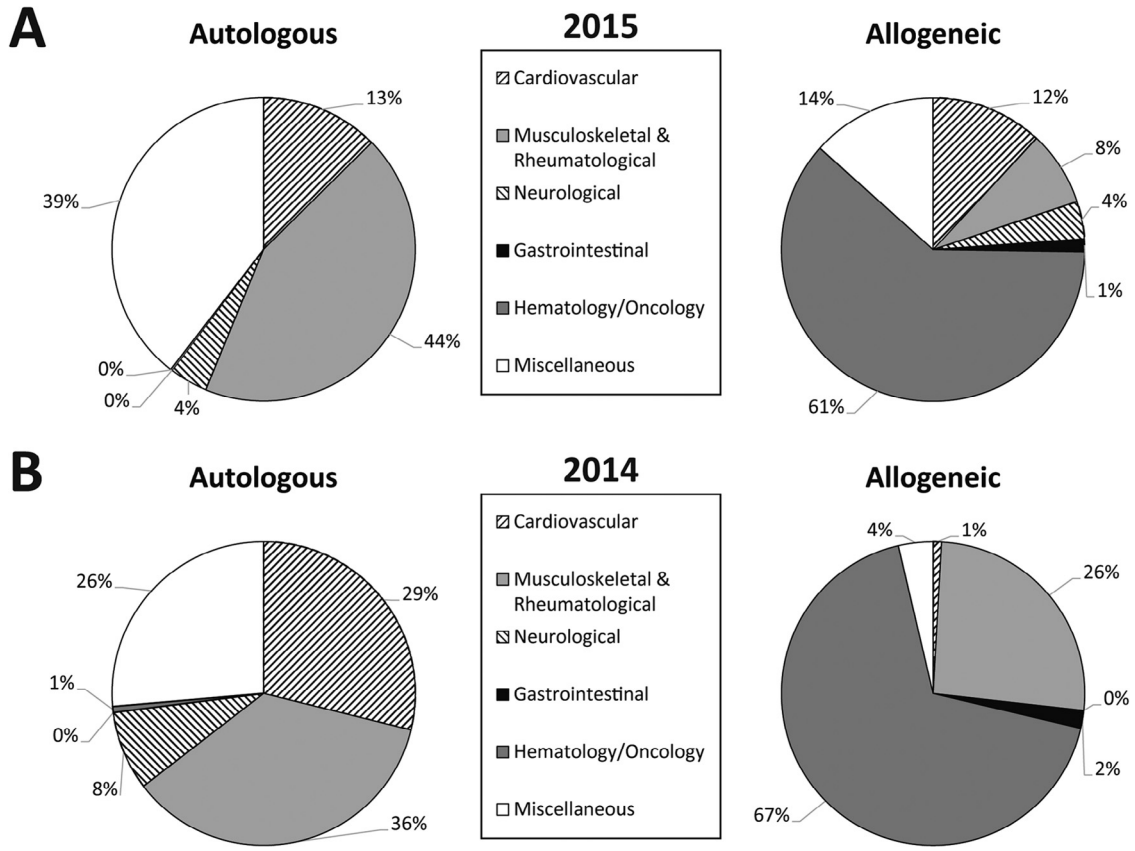

Figure 1. Percentage of indications for cell and tissue-engineered therapies in Europe in 2015 (top) and 2014 (bottom), sorted by donor type.

of autologous cells (40% [26%]) were used for the treatment of miscellaneous indications.

As in previous years, the primary use of allogeneic cells was for hematology/oncology indications (61% [68%]). The percentage of allogeneic cells for musculoskeletal/rheumatological indications for 2014 (26%) remained similar to past reports, although surprisingly declined to 8% in 2015. The majority of allogeneic cell use for musculoskeletal/rheumatological indications was for muscle repair ([77%]) in 2014 and for cartilage repair (67%) in 2015. Interestingly in 2015, in contrast to the previous 4 years, frequent use of allogeneic cells for cardiovascular indications (12%) was reported (data were collected from six independent teams) (Figure 1). The trends for the various therapy areas over the past 5 years are shown in Figure 2.

As in past years, most MSC preparations were obtained from bone marrow (70% [75%]) or adipose tissue

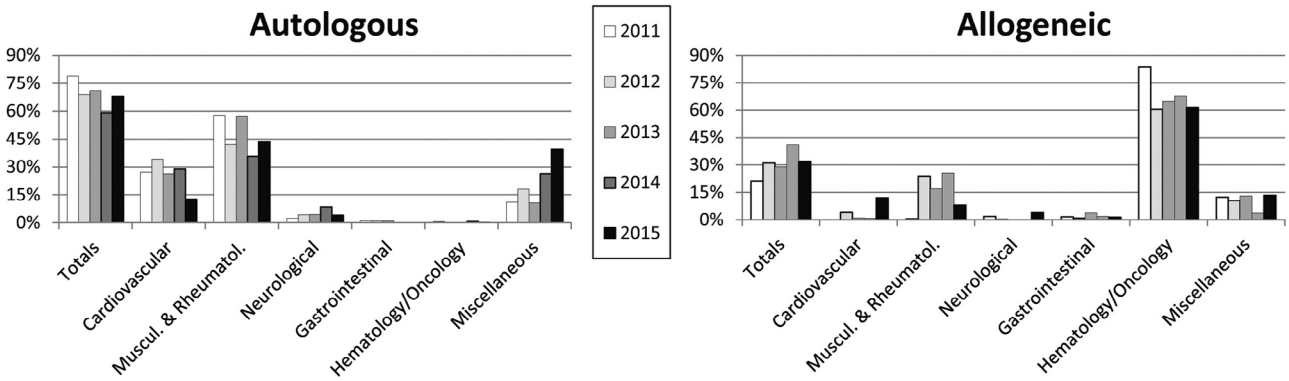

Figure 2. Comparative analysis of indications for cell and tissue-engineered therapies in Europe from 2011 to 2015, sorted by donor type. Data used for this chart were derived from the current study and three previous reports [4,8,9].

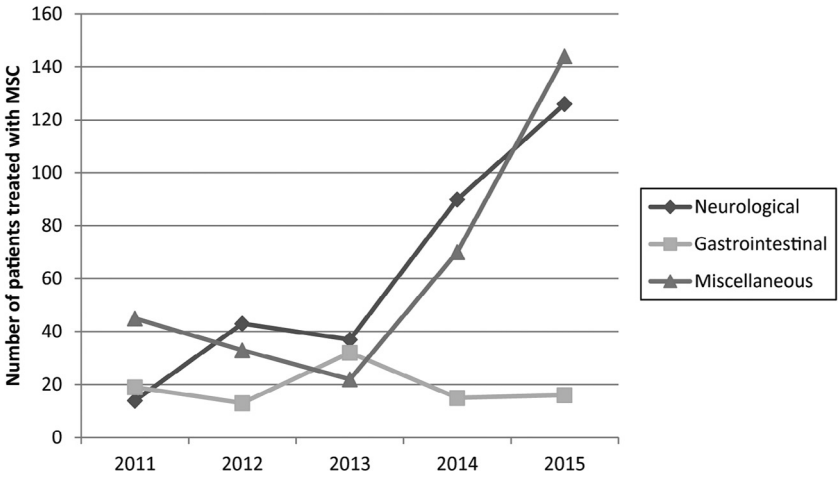

Figure 3. Number of patients treated with MSCs for neurological, gastrointestinal and miscellaneous indications from 2011 to 2015. Data used for this chart were derived from the current study and two previous reports [4,8,9].

(24% [24%]). MSCs were mainly used for musculoskeletal indications (36% [50%]) and GVHD (32% [35%]) in both years (Table I). Interestingly, the number of patients being treated with MSCs has increased by almost two-thirds (66%) since 2011. This increase of MSC is due to the increasing use in hematology/oncology over the years, from 300 patients in 2011 [4] to 515 in 2015 (Table I) and a recent (past 2 years) gain in their usage for other indications such as neurological and miscellaneous (Figure 3). Nonetheless, MSC use for the treatment of musculoskeletal indications remained relatively constant over the past 5 years. This trend may reflect the scientific recognition of the rather limited direct contribution of MSCs in tissue repair, typically targeted in the musculoskeletal field, and instead their modulatory role of inflammatory/immunological processes through their secretome [12].

For the HSC treatments, cells were derived from peripheral blood (47% [72%]) or bone marrow (40% [23%]); 68% [83%] of HSC preparations were used to treat cardiovascular disorders, mainly peripheral artery disease or decubitus and leg ulcers, and in 2015 21% for solid tumor. Almost all chondrocyte preparations were for cartilage and bone repair. Dendritic cells were included in the survey as a cell source for the first time in the survey of patients treated in 2013. Since then the number of patients increased from 40 in 2013 to 82 in 2015. The majority of these cells were used for the treatment of solid tumors (83% [94%]). The cell source "other" (i.e., not among those separately listed in the form) almost doubled from 470 patients (18% of all patients in 2014) to 912 in 2015 (25% of all patients).

Some teams also reported use of combination treatments, for example, fat cells augmented with monocytes from peripheral blood cells in reconstructive surgery/tissue enhancement or chondrocytes with allogeneic MSCs for cartilage repair. These could not be consistently captured by the format of the questionnaire and of the data display but are worth being qualitatively mentioned here because they are in line with recently published trends [8,9].

Cell processing and delivery mode

Of all the grafted products, non-transduced (99.5% [99%]) and unsorted (84% [94%]) cells were predominantly used. The small number of transduced cell therapies (18 [21] patients) was limited to the treatment of hematology/oncology, solid tumor and miscellaneous indications. In 2014, more than 85% of the sorted cells were used for the treatment of cardiovascular and neurological indications, whereas in 2015, these two groups barely made up one-third (32%), even though the amount of patients treated in both years were similar. This development probably arises due to an increased use of sorted cells for the treatment of miscellaneous indications, which make up half of the sorted cells in 2015. Additionally, in 2015 14% of the sorted cells were also being used for musculoskeletal/rheumatological treatments, mainly for cartilage repair (73%) (Table II).

In 2014, 60% of the cells were non-expanded, whereas in 2015 the trend appears reversed with expanded cells used in 62% of treatments. The main contributors to this increase were in the cardiovascular, musculoskeletal/rheumatological and miscellaneous indications. In 2014, these conditions were treated with expanded cells in 1%, 36% and 20% of cases, respectively, whereas in 2015, the values increased to 35%, 67% and 49%. Additionally, the use of expanded cells for neurological treatments increased from 61% in 2014 to 81% in 2015. For the treatment of gastrointestinal indications, expanded cells were used in 100%

Table II. Number of reported cell and tissue-engineered therapy treatments in Europe in 2014 and 2015 sorted by processing mode.

	Cell processing							
Indications	Non expanded	Expanded	Untransduced	Transduced	Unsorted	Sorted	Automated	Manual
Cardiovascular								
Peripheral artery disease	55 [149]		55 [149]		55 [148]	[1]	53 [142]	2 [7]
Cardiomyopathy	50 [50]	2 [0]	52 [50]		13 [18]	39 [32]	38 [33]	14 [17]
Heart failure	48 [101]	22 [3]	70 [104]		68 [70]	2 [34]	48 [34]	22 [70]
Myocardial ischemia	30 [19]	1 [0]	31 [19]		31 [11]	[8]	4 [13]	27 [6]
Decubitus and leg ulcers	72 [144]	11 [3]	83 [147]		83 [147]		68 [138]	15 [9]
Other/unspecified	44 [81]	122 [1]	166 [82]		46 [62]	120 [20]	164 [61]	2 [21]
Musculoskeletal/rheumatological								
Bone repair (maxillofacial)	[1]	18 [0]	18 [1]		10 [1]	8 [0]	[1]	18 [0]
Bone repair (orthopedics)	49 [41]	110 [19]	159 [60]		155 [60]	4 [0]	6 [35]	153 [25]
Osteogenesis imperfecta		2 [2]	2 [2]		2 [2]			2 [2]
Cartilage repair (maxillofacial)	19 [18]		19 [18]		19 [18]		9 [18]	10 [0]
Cartilage repair (orthopedics)	207 [167]	423 [151]	630 [318]		569 [305]	61 [13]	217 [106]	413 [212]
Muscle repair	4 [151]	10 [3]	14 [154]		14 [154]		4 [150]	10 [4]
Tendon/ligament	4 [50]		4 [50]		4 [50]			4 [50]
Reconstructive surgery/tissue enhancement	75 [128]	6 [57]	81 [185]		77 [185]	4 [0]	73 [98]	8 [87]
Scleroderma	[2]	8 [0]	8 [2]		2 [0]	6 [2]		8 [2]
Arthritis	33 [2]	188 [79]	221 [81]		221 [81]		15 [0]	206 [81]
Other/unspecified		33 [1]	33 [1]		33 [1]			33 [1]
Neurological								
Multiple sclerosis	7 [25]	46 [48]	53 [73]		50 [71]	3 [2]	[4]	53 [69]
Amyotrophic lateral sclerosis	19 [3]	25 [25]	44 [28]		44 [26]	[2]	19 [1]	25 [27]
Parkinson's disease	[7]		[7]			[7]		[7]
Peripheral nerve regeneration (trauma)	[4]	1 [0]	1 [4]		1 [0]	[4]		1 [4]
Other/unspecified	2 [23]	50 [24]	52 [47]		25 [24]	27 [23]	29 [0]	23 [47]
Gastrointestinal								
Crohn's disease		2 [13]	2 [13]		2 [13]			2 [13]
Liver insufficiency	2 [0]	12 [2]	14 [2]		14 [2]		2 [0]	12 [2]
Hematology/oncology								
GVHD prevention or treatment	59 [0]	570 [492]	622 [484]	7 [8]	608 [492]	21 [0]	8 [14]	621 [478]
HSC graft enhancement	3 [16]	92 [34]	93 [45]	2 [5]	93 [50]	2 [0]	4 [8]	91 [42]
Miscellaneous								
Skin reconstruction—burns	3 [2]	28 [6]	31 [8]		31 [8]			31 [8]
Cornea repair	61 [0]	23 [4]	84 [4]		84 [4]			84 [4]
Diabetes	7 [2]	7 [0]	14 [2]		8 [2]	6 [0]	7 [2]	7 [0]
Solid tumor	93 [51]	93 [5]	183 [51]	3 [5]	153 [51]	33 [5]	1 [5]	185 [51]
Other	426 [366]	409 [90]	829 [453]	6 [3]	579 [453]	256 [3]	82 [74]	753 [382]
Total	1372 [1603]	2314 [1062]	3668 [2644]	18 [21]	3094 [2509]	592 [156]	851 [937]	2835 [1728]

of cases in 2015 and 88% in 2014. Fifty percent of the expanded cells were used for the treatment of hematology/oncology indications in 2014: only 29% were used a year later, even though more than 90% of the hematology/oncology treatments were performed with expanded cells in both years (Table II). Of the cells reported as processed using an automated device in at least one step (23% [35%]), most were used to treat musculoskeletal/rheumatological (38% [44%]) and cardiovascular (44% [45%]) indications (Table II).

In both years, 30% of the cells were delivered intravenously (IV) or intra-arterially (IA). Of the remaining 70%, which were administered via intraorgan delivery, 25% [19%] used a membrane/scaffold, 43% [51%] a suspension and 1% [>1%] a gel. IV or IA delivery was reported for almost all (99% [98%]) hematology/oncology treatments, these indications making up 64% [67%] of all IV and IA treatments. Cells for neurological indications were delivered either IV or IA (39% [52%]) or locally in a suspension (61% [48%]). The use of a suspension for cell delivery was reported mainly for musculoskeletal/rheumatological (28% [32%]), cardiovascular (18% [30%]) and miscellaneous (49% [29%]) indications. The leading use for suspension delivery in musculoskeletal/rheumatological treatments was for reconstructive surgery/tissue enhancement in 2014 (42% of musculoskeletal/rheumatological treatments) and for arthritis in 2015 (49%) (Table III).

Only 9 patients (<0.5% of all patients) were treated using a gel as a mode of cell delivery in 2014. In 2015,

Table III. Number of reported cell and tissue-engineered therapy treatments in Europe in 2014 and 2015 sorted by delivery mode.

	Cell delivery mode			
		Intra-organ		
Indications	IV or IA	Suspension	Gel	Membrane/scaffold
Cardiovascular				
Peripheral artery disease	10 [12]	45 [137]		
Cardiomyopathy	7 [43]	45 [7]		
Heart failure	24 [66]	14 [38]		32 [0]
Myocardial ischemia	15 [14]	16 [5]		
Decubitus and leg ulcers		68 [138]		15 [9]
Other/unspecified	12 [1]	94 [81]		60 [0]
Musculoskeletal/rheumatological				
Bone repair (maxillofacial)				18 [1]
Bone repair (orthopedics)	10 [0]	31 [12]	[1]	118 [47]
Osteogenesis imperfecta	2 [0]	[2]		
Cartilage repair (maxillofacial)	10 [0]	9 [18]		
Cartilage repair (orthopedics)	3 [0]	71 [81]	35 [0]	521 [237]
Muscle repair	10 [3]	[1]	4 [0]	[150]
Tendon/ligament		4 [50]		
Reconstructive surgery/tissue enhancement		80 [180]	[1]	1 [4]
Scleroderma	8 [0]	[2]		
Arthritis		221 [79]		[2]
Other/unspecified	[1]	32 [0]		1 [0]
Neurological				
Multiple sclerosis	49 [54]	4 [19]		
Amyotrophic lateral sclerosis	21 [6]	23 [22]		
Parkinson's disease		[7]		
Peripheral nerve regeneration (trauma)		1 [4]		
Other/unspecified	8 [2]	44 [45]		
Gastrointestinal				
Crohn's disease	2 [3]	[10]		
Liver insufficiency	14 [2]			
Hematology/oncology				
GVHD prevention or treatment	620 [480]	9 [12]		
HSC graft enhancement	92 [49]	3 [1]		
Miscellaneous				
Skin reconstruction—burns		1 [0]	9 [6]	21 [2]
Cornea repair	[3]			84 [1]
Diabetes	14 [0]	[2]		
Solid tumor	105 [7]	79 [49]		2 [0]
Other	68 [47]	697 [344]	4 [1]	66 [64]
Total	1104 [793]	1591 [1346]	52 [9]	939 [517]

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this number rose to 52 patients of whom most (84%) were treated for cartilage repair (35 patients) and skin reconstruction for burns (9 patients).

The use of a membrane/scaffold was split between musculoskeletal/rheumatological (70% [85%]), cardiovascular (12% [2%]) and miscellaneous (18% [13%]) indications. Membrane/scaffolds for musculoskeletal/rheumatological treatments were mainly used for cartilage and bone repair (>99% [65%]) in both years. In 2014, 34% of musculoskeletal/rheumatological treatments using a membrane/scaffold were devoted to therapies for muscle repair. Of the miscellaneous group, the predominant use for treatments with membrane/scaffold in 2015 was cornea repair (49%) and skin reconstruction for burns (12%).

Transplant rates and active teams

Reported cellular and engineered tissue therapies were performed in a limited number of countries and with different intensity. Figure 4 displays the reported transplants per 10 million inhabitants in the European and EBMT associated countries. The highest transplant rates (i.e., >40 per 10 million population) were reported in (in decreasing order) Slovenia, Denmark, Iran, Spain, Italy, Germany, Turkey and the Netherlands in 2015 and in Slovenia, Italy, Iran, Lithuania, Denmark and Spain in 2014.

The number of teams reporting cellular and tissue-engineered therapies was also mapped in the different European and EBMT associated countries after normalization to the inhabitant numbers (Figure 5). The number of reporting teams per 10 million inhabitants was greater than four (in decreasing order) in Slovenia, Denmark, Norway and Belgium in 2015 and in Slovenia, Belgium, the Netherlands, Switzerland, Finland, Denmark, Lithuania, Ireland, Israel, Italy, France, Slovak Republic, Sweden, Czech Republic and Spain in 2014.

The top 10 countries (of 21 [25] countries reporting data) accounted for 91% [88%] of all patients treated.

The decrease in reporting countries from 2014 (25) to 2015 (21) is likely because we had only one or two responding centers in the four countries of Belarus, Czech Republic, Finland and Ireland, which reported low numbers of patients treated in 2014 (13, 6, 3 and 2, respectively) to the EBMT survey and therefore were out of scope for the 2015 survey.

Treatments as part of a clinical trial versus individualized treatment or routine therapy

Teams were asked to report whether patients were treated with cells or engineered tissues in the context of a clinical trial, as individualized or single case treatment or as a routine therapy. Where information was provided (3039 patients, 82% of total patient numbers, [808 patients, 30% of total patient number]), 29% [18%] of patients were treated as routine therapy, 37% [60%] as part of a clinical trial and 34% [22%] as individualized/single cases.

In 2015, 22 teams reported treating 883 patients with cells as routine therapies, 37 teams treated 1030 individualized/single cases and 1126 patients were part of a clinical trial, conducted by a total of 65 teams.

Discussion

The data collected for the seventh and eighth editions of the cellular and engineered-tissue therapy survey show an increase from the previous years in the number of patients treated. The increasing trend of reporting teams, as in previous years, could be observed in 2015 (178), despite a deflection witnessed in 2014 (126). Since the survey's inception, the total number of teams reporting full data has risen from 33 in 2008 to 178 in 2015. At the same time, the total number of patients treated has risen from 1040 in 2008 to 3686 in 2015 (Figure 6).

The data and legitimate differences are reported and discussed in the results section. There have been some shifts in the data from 2014 to 2015, which are prominent but not thoroughly discussed (e.g., the 21-fold increase of patients undergoing cellular or tissue-engineered therapy for cornea repair). There have been single "spikes" like this in the past in which one or two clinical trials of a specific indication or using specific cells push the corresponding numbers up for the year of the trial. However, we have to follow these indications in the following years to see how they progress and whether they really are the precursors for a developing trend or if they are one-time trials. Such investigations further underline the importance of documenting, comparing and analyzing the results of our annual survey.

A perspective from ISCT

The power of data collection to inform the development of novel therapies, independently of whether treatments are offered within or outside of formal clinical trials, has been well demonstrated in the field of hematopoietic stem cell transplantation by the EBMT [10,11,13] and the Center for International Blood and Marrow Transplant Research (CIBMTR) databases. ISCT, as one of the lead societies behind the current survey on cellular and tissue-engineered therapies, recognizes this and sees reporting of clinical treatments in a standardized format across multiple centers as a responsible approach to the development of cell and gene therapies. Looking forward, the current program is a relevant starting point to possibly extend reporting to clinical outcome. Such a data set might produce statistically relevant conclusions about safety and

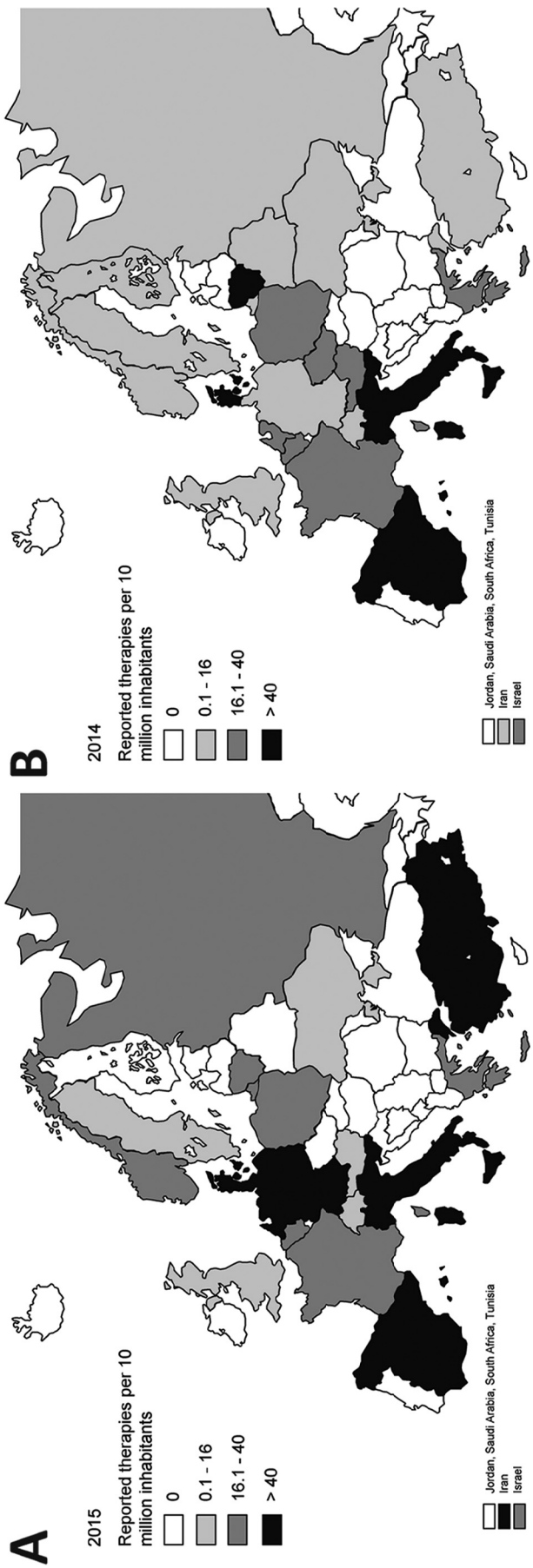

Figure 4. Number of cell and tissue-engineered therapies per 10 million inhabitants reported in Europe in (A) 2015 and (B) 2014.

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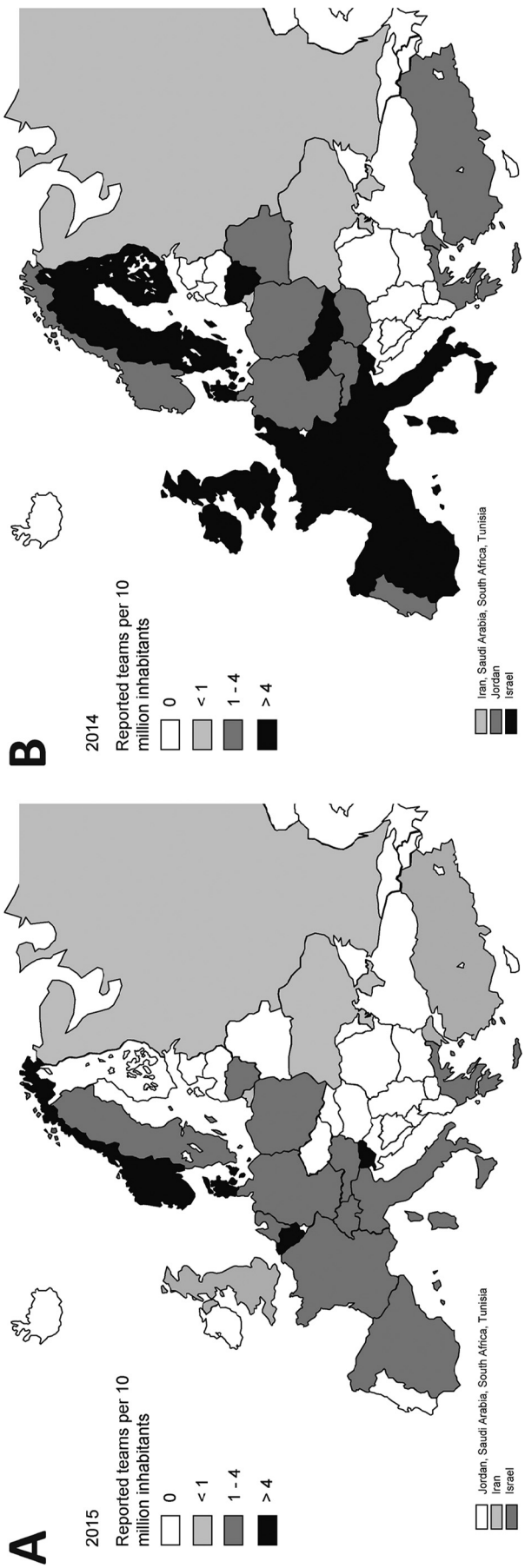

Figure 5. Number of teams per 10 million inhabitants reporting cell and tissue-engineered therapies in Europe in (A) 2015 and (B) 2014.

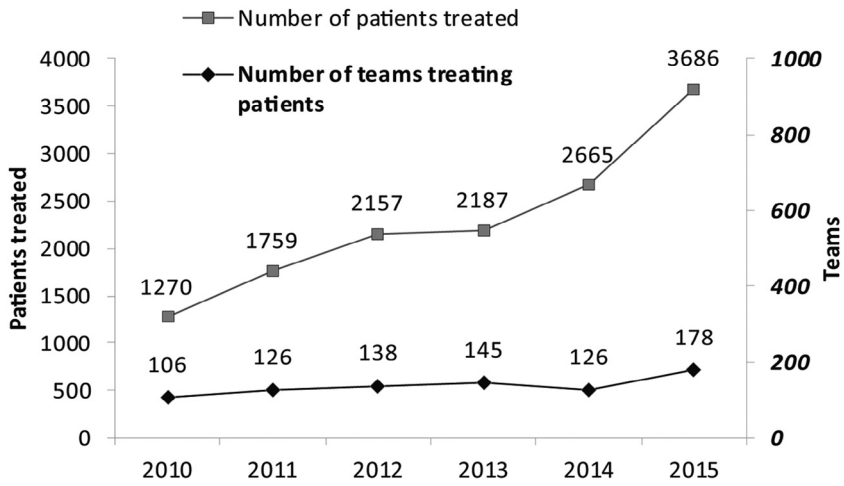

Figure 6. Number of reporting teams and number of patients treated using cell and tissue-engineered therapies from 2010 to 2015. Data used for this chart were derived from the current study and previous reports [4,5,8,9].

clinical efficacy and become an important reference point in discussions of untested cell and gene therapies that currently dominate the field and are the focus of the ISCT Presidential Task Force on the Use of Unproven Cellular Therapies. Such a registry should combine clinical data with technical details of the cell product specification and the manufacturing process. A recent survey by Knut Niss on behalf of the ISCT Process and Product Development Committee identified more than 1000 peer-reviewed articles on human mesenchymal stromal cells in 2011 alone, analysis of which showed enormous variability in production techniques and final product definition [14]. Thus, patients receiving "MSC" therapies across multiple centers are not receiving the same treatments, and a suitable registry needs to record the details of manufacture and release criteria to be truly informative.

A perspective from plastic surgery

For the purposes of this more detailed analysis, fat-derived MSCs include both the stromal vascular fraction (SVF) of cells freshly harvested from adipose tissue and the expanded progeny, adipose stromal cells (ASCs). The use of fat-derived MSCs, initially not reported in the first survey edition of patients treated in 2008, has markedly increased, and for the recent surveys of 2012 to 2015, made up 24% to 30% of the total MSC use (Figure 7A). Autologous fat grafting, introduced more than 100 years ago and refined at the end of the 20th century to achieve better consistency and reproducibility, has become a popular procedure for abnormality contouring, breast reconstruction and cosmetic surgery [15]. The definition and characterization of the SVF and ASCs at the beginning of the 21st century opened new possibilities for the use of adipose tissue–derived material: isolated fat-derived cells are now typically used in plastic and reconstructive surgery for the treatment of ischemic injuries, wound healing, breast and facial tissue filling, post-traumatic or congenital tissue deficits or recurrent scars [16]. The survey series reflects this trend because the highest percentages (ranging from 40% to 80%) of treatments based on fat-derived MSCs have consistently been within the domain of reconstructive surgery (Figure 7B).

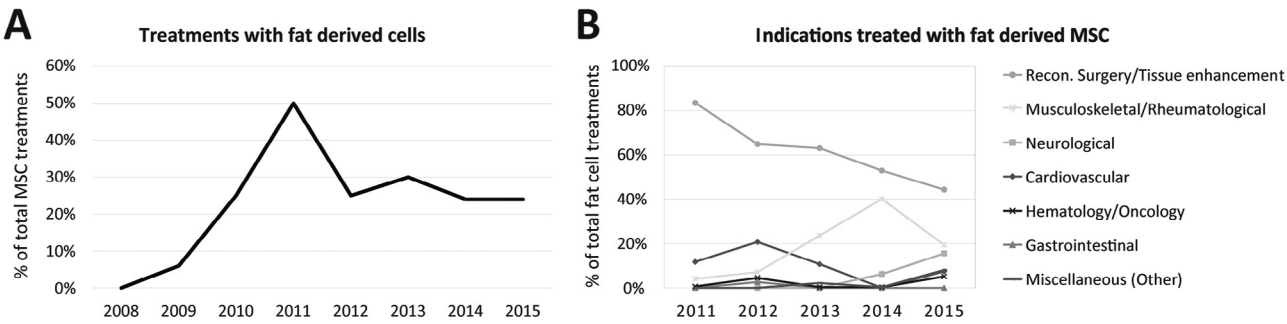

Figure 7. (A) Treatments with fat-derived cells, expressed as a percentage of those based on mesenchymal stromal cells (MSCs) from any source. (B) Comparative, percentual analysis of indications treated with fat-derived cells. Data used for this chart were derived from the current study and previous reports [4–9].

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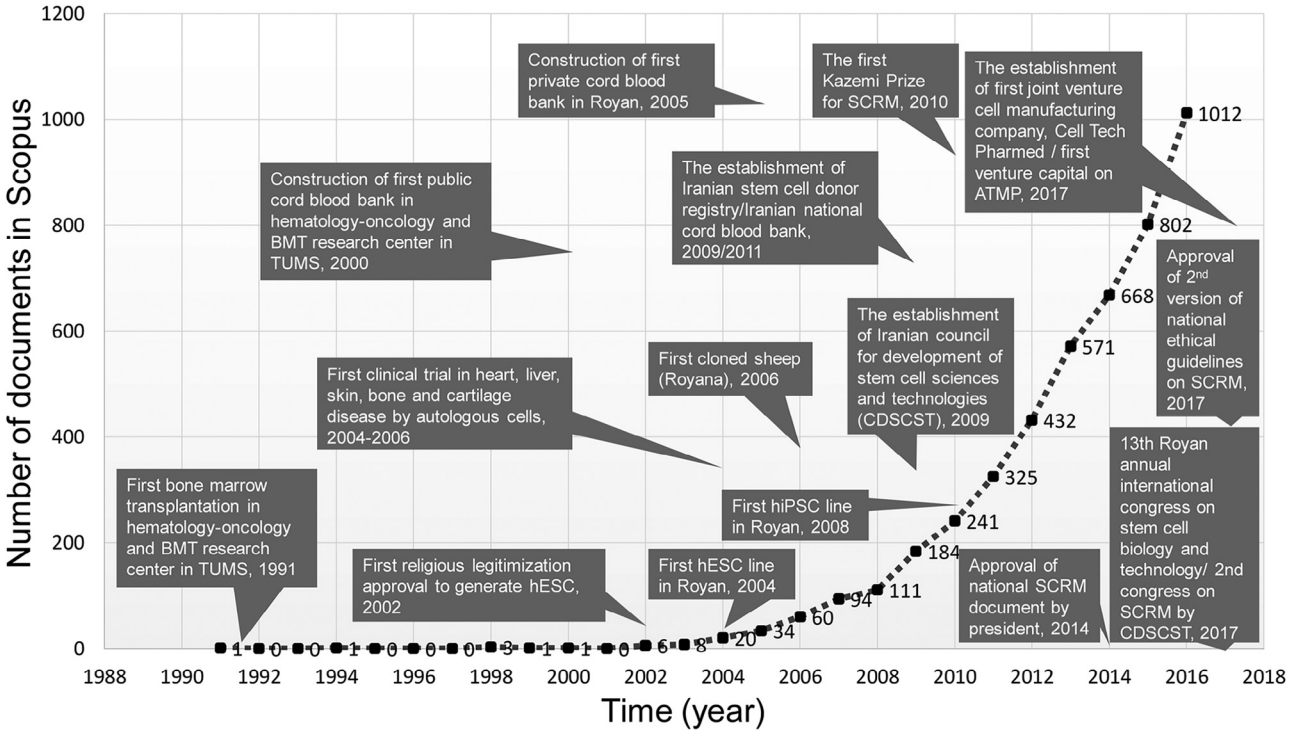

Figure 8. Publications in the field of stem cells and regenerative medicine of Iran shown in chronological order, based on search in Scopus. ATMP, advanced therapy medicinal product; BMT, bone marrow transplantation; hESC, human embryonic stem cell; hiPSC, human pluripotent stem cell; SCRM, stem cells and regenerative medicine; TUMS, Tehran University of Medical Sciences.

Studies of the past decade have shown that the use of SVF cells from adipose tissue, which include preadipocytes, stromal fibroblasts, vascular endothelial cells and a variety of immune cells, may accelerate tissue healing thanks to the angiogenic properties and the capacity to regulate inflammatory processes [17]. The graft function seems to be driven predominantly by the cell secretory profile, sharing similarities with that of bone marrow–derived MSCs, with the additional direct contribution of endothelial lineage cells to new vasculature formation [18].

Even though SVF cells and ASCs hold great promise in "regenerative surgery" and are being used increasingly in various treatments, clinical results often remain variable, and many open questions still need to be addressed. First, there are many procedural variations with respect to cell harvesting, processing techniques and reinjection methods [19]. Would these alter effectiveness of the procedure and account for the observed variability in the rates of graft resorption [20]? Moreover, is the therapeutic potential related to the dose/proportion of specific cell sub-populations that constitute the highly heterogeneous preparations? Or is the predictability of results related to the ability of the recipient to create an adequate vascular support after grafting? Answers to such critical questions would determine the potential need for more targeted patient selection, for more stringent release criteria (e.g., number of cells with a defined phenotype) or for introduction of combinatorial treatments (e.g., platelet-rich plasma), which would enable these procedures to be considered as "routine therapies."

A perspective from Iran

The Royan Institute for Stem Cell Biology and Technology in Tehran, Iran, was one of the main contributors to the survey of 2014 and 2015 in respect to treated patients. The institute currently treats more than 600 patients a year using autologous or allogeneic cells for patients affected by myocardial infarction, diabetes, vascular, liver, skin, eye, bone, cartilage and neurological disorders. This is mirrored by the 119 Iranian clinical trials in the field of cellular therapy registered in clinicaltrials.gov. This proficiency is attributed to coordinated scientific, technological, political, regulatory and social programs.

The history of cell therapies in Iran dates back to 1991, when bone marrow transplantation started in the Hematology-Oncology Research Center in Tehran University of Medical Sciences (Figure 8). Since then, translational research, at the interface between discovery science and clinical application, has relied on cell and developmental biology, nanobiotechnology and tissue engineering, cellular reprograming, bioinformatics, small molecules, gene therapy, immunotherapy

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and cell therapy in regenerative medicine. In 2009, after the first report on the generation of human embryonic stem cells from pre-implantation embryos by the Royan Institute [21], under the auspices of the Vice President for Science and Technology, the Council for Development of Stem Cell Sciences and Technologies (CDSCST) was established to draft the national stem cell research policy document [22]. Cell-based products in Iran are now subject to the laws and regulations governing conventional drugs and medicinal products of the Food and Drug Organization and following in most cases the European regulations for advanced therapy medicinal products.

From a financial standpoint, CDSCST and the National Institute for Medical Research Development (NIMAD) (affiliated to the Ministry of Health and Medical Education) support interdisciplinary projects and networks between centers of excellence toward the development of high value translational technology platforms and innovative technologies in regenerative medicine and tissue engineering. Remarkably, the first joint ventures between the Royan Institute and major pharmaceutical companies or private banks were established to support the translation of knowledge and cutting-edge scientific discovery into commercial products. This endeavor, combined with the generous contribution of charities for health and sustained by the CDSCST, resulted in the registration of about 40 companies to develop and commercialize cell-based products.

To raise awareness in the public and gain the interest of the youth, the Royan Institute, with support of the Tehran municipality and CDSCST, developed several outreach programs, including the establishment of a "stem cell adventure mobile lab," "Stem cells for all" and the national Olympiad of stem cells and regenerative medicine for high school students. The main challenge currently experienced toward further scientific and clinical development in the field of cellular therapies in Iran is related to the need for open exchanges of materials and scientists with Western countries. To promote cross-border connections with international pioneers, the Royan Institute and the CDSCST organize international congresses on stem cells and regenerative medicine each year, awarding the Kazemi Prize to the most influential scientists in the field. However, only a political resolution of the current segregation status will enable effective networking and further promote Iran as one of the most progressive countries in the translation of cell and tissue-engineered therapies to the bedside. By bringing together the efforts and translational outcome of institutions from European and Eurasian countries, this survey offers an opportunity for exchange, cooperation and integration beyond political barriers. In this context, despite the expected challenges, we envision an extension of the program to other geographic regions, across continental and cultural borders, in the years to come.

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haploidentical donors but fewer cord blood transplants. Bone Marrow Transplant 2015;50(4):476–82.
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Appendix A: List of centers reporting use of cellular and engineered tissue therapy in Europe in 2014 and 2015

EBMT data for teams treating GVHD or HSC enhancement in 2015 are not included and listed in the supplementary appendix to Bone Marrow Transplant [11].

Format: City, Hospital, Department, Center Identification Code (CIC, as used for EBMT teams in the EBMT standard survey), Physicians (Total treatments: allogeneic/autologous in 2015), [Total treatments: allogeneic/autologous in 2014]

Austria

Krems, Danube University Krems, Regenerative Medicine and Orthopedics, S. Nehrer, T. Luksch, P. Holzmann, M. Gruber, (7; 0/7), [8; 0/8]

Vienna, Medical University Hospital, Traumatology, Ch. Albrecht, S. Aldrian, (5; 5/0), [6; 6/0]

Belarus

Minsk, Belorussian Center, CIC 591, N. Minakovskaya, Y. Mareika, A. Alexeichik, O. Aleinikova, (0), [13; 9/4]

Belgium

Antwerp, Antwerp University Hospital (UZA), Hematology; Center for Cellular Therapy and Regenerative Medicine, CIC 996, Z. Berneman, N. Zakaria, J. Behaegel, S. Ni Dhubhgaill, C. Koppen, E. Melsbach, (25; 0/25), [10; 2/8]

Antwerp, University Hospital, Center for Regenerative Medicine, N. Zakar, (11; 0/11), [0]

Bruges, AZ. Sint Jan, CIC 506, D. Selleslag, T. Lodewyck, A. v. Hoof, J. v. Droogenbroeck, (0), [2; 2/0]

Ghent, University Hospital, CIC 744, L. A. Noens, (0), [4; 4/0]

Leuven, University Hospital Gasthuisberg, CIC 209, J. Maertens, G. Verhoef, M. Delforge, T. De Vos, A. Van Campanhout, (2; 2/0), [2; 2/0]

Liège, University Liège, CHU Sart-Tilman, Gastrology, E. Louis, (0), [4;4/0]

Liège, University Liège, CHU Sart-Tilman, Hematology, CIC 726, Y. Béguin, B. de Prijck, (3; 3/0), [17; 17/0]

Liège, University Liège, CHU Sart-Tilman, Surgery and Transplantation, M. Meurice, (1; 1/0), [6; 6/0]

Czech Republic

Brno, Masaryk University Hospital, Pediatric Oncology, CIC 597, J. Sterba, (0), [34; 34/0]

Pilsen, Charles University Hospital, Hematology/Oncology, CIC 718, P. Jindra, A. Jungova, D. Lysak, K. Steinerova, (0), [6; 6/0]

Denmark

Copenhagen, Herlev University Hospital, CIC 568, P. Andersen, P. Josefsson, I. Svane, (56; 0/56), [0]

Copenhagen, Rigshospitalet, Copenhagen University Hospital, Cardiology Stem Cell Center, J. Kastrup, A. Ekblond, (17; 13/4), [0]

Copenhagen, Rigshospitalet, Copenhagen University Hospital, Cell Therapy Facility, Clinical Immunology, A. Fischer-Nielsen, E. Haastrup, and R. Oliveri (2014), L. M. Fog (2015), (13; 0/13), [13; 0/13]

Odense, Odense University Hospital[1] and University of Southern Denmark[3], Danish Centre for Regenerative Medicine[1], Lab Molecular and Cellular Cardiology, Dep Clinical Biochemistry and Pharmacology[2], M. K. Haahr[1,3], C. Harken Jensen[1,2], S. P. Sheikh[2,3], (5; 0/5), [16; 0/16]

Finland

Helsinki, Children's Hospital, Pediatrics, CIC 219, K. Vettenranta, (0), [2; 2/0]

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Turku, University Central Hospital, Medicine, CIC 225, M. Itälä-Remes, M. Kauppila, M. Putkonen, U. Salmenniemi, K. Remes, (0), [3; 3/0]

France

Clermont Ferrand, CRCTCP, CHU Estaing, Centre de Biotherapie d'Auvergne, CIC 273, J-O. Bay, P. Travade, J. Kanold, P. Halle, (0), [22; 16/6]

Lille, Hospital Claude Huriez, Endocrinology, M. Vantyghem, A. Lemapihan-Paranthoen, (7; 4/3), [0]

Marseille, Arthosport Center, Knee Institute, Chirurgie prothétique et régénérative du genou, M. Assor, (165; 0/165), [95; 0/95]

Montpellier, CHRU de Montpellier, Rheumatology, C. Jorgensen, Y. Pers, R. Ferreira, L. Sensebe, (3; 0/3), [0]

Nantes, CHU Nantes, Hematology, CIC 253, P. Chevallier, (0), [9; 8/1]

Nantes, CHU Nantes, Institute of Biology, Cell and Gene Therapy Facility, B. Dreno, A. Khammari, S. Saiagh, M. Benjelloun-Zahar, S. Bercegeay, D. Heymann, (25; 13/12), [0]

Paris, Hôpital Robert Debré, Pediatric Hematology and Immunology, CIC 631, J.-H. Dalle, A. Baruchel, (0), [1; 1/0]

Paris, Hôpital St. Antoine, CIC 775, M. Mohty, F. Giannotti, N.-C. Gorin, (0), [67; 67/0]

Paris, Hôpital St. Louis, Cell Therapy Unit, J. Larghero, (1; 1/0), [0]

Paris, Hôpital St. Louis, CIC 207, G. Socié, E. Gluckman, H. Esperou, (2; 2/0), [0]

Paris, UMR Inserm, Clinic of Cardiology, G. Lamirault, (1; 0/1), [0]

St. Ismier, CTI Cell (was CHU Grenoble), H. Egelhofer, A. Moisan, V. Persoons, O. Detante, (0), [6; 4/2]

Germany

Chemnitz, Klinikum Chemnitz GmbH, Klinik für Innere Medizin III, CIC 104, M. Hänel, A. Morgner, (0), [3; 3/0]

Darmstadt, Agaplesion Elisabethenstift, Evangelisches Krankenhaus, Klinik für Orthopädie, Unfallchirurgie und Sportmedizin, T. Schreyer, M. Schneider, (18; 0/18), [0]

Dinslaken, St. Vinzenz Hospital, Orthopädie und Unfallchirurgie mit Sportmedizin und Alterstraumatologie, W. Zinser, F. Glahn, M. Rüter, (55; 0/55), [56; 0/56]

Dresden, Universitätsklinikum, Medizinische Klinik und Poliklinik I, CIC 808, G. Ehninger, M. Bornhäuser, M. Gahr, (26; 26/0), [29; 29/0]

Halle, BG-Clinic Bergmannstrost, Neurosurgery, H. J. Meisel, (32; 0/32), [8; 0/8]

Halle, Martin-Luther-Universität Halle-Wittenburg, Klinik für Innere Medizin IV, CIC 338, H.-J. Schmoll, L. Müller, T. Weber, (0), [1; 1/0]

Homburg/Saar, Universitätsklinikum Saarlandes, Center for Experimental Orthopedics, H. Madry, (9; 0/9), [8; 0/8]

Kelkheim, Gemeinschaftspraxis, Orthopedic Sports Medicine, H. Kniffler, K.-W. Richter, (23; 0/23), [0]

Munich, KH München Schwabing, Pediatrics, CIC 189, S. Burdach, A. Wawer, I. Teichert-von Lüttichau, M. Nathrath, (2; 2/0), [0]

Straubing, Sporthopaedicum Straubing, P. Angele, S. Fickert, (162; 0/162), [0]

Tübingen, Universitätsklinikum, Gemeinsames Stammzell-Labor der Kinderklinik und der Medizinischen Klinik II, CIC 535, R. Handgretinger, P. Lang, (10; 7/3), [5; 3/2]

Tübingen, University Hospital, Rheumatology, D. Henes, (6; 0/6), [0]

Greece

Athens, Biomedical Research Foundation Academy of Athens (BRFAA), Hellenic Cord Blood Bank, A. C. Papassavas, T. K. Chatzistamatiou, E. Michalopoulos, C. Stavropoulos-Giokas, (24; 6/18), [27; 0/27]

Athens, St. Sophia Children's Hospital, Oncology Center "Marianna V. Vardinoyannis-ELPIDA," CIC 752, S. Graphakos, (0), [1; 1/0]

Thessaloniki, MIS Orthopedic Center, E. T. Papacostas, M. Papasoulis, A. Sideridis, I. Terzidis, (7; 0/7), [5; 0/5]

Iran

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Shiraz, Nemazee Hospital, Shiraz University of Medical Sciences, Hematology-Oncology and BMT, CIC 188, M. Ramzi, (0), [40; 0/40]

Teheran, Royan Institute of Stem Cell Biology and Technology, H. Baharvand, (696; 41/655), [611; 3/608]

Teheran, Shariati Hospital, Hematology-Oncology and BMT Research, CIC 633, A. Ghavamzadeh, M. Jahani, (0), [10; 10/0]

Teheran, Taleghani Hospital, Blood and Marrow Transplantation Center, CIC 916, M. Mehdizadeh, A. Hajifathali, (0), [4; 4/0]

Ireland

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Israel

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Italy

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Bologna, Istituto Ortopedico Rizzoli, 3rd Orthopedic and Traumatology Clinic, prevalently Oncology, D. Donati, N. Baldini, G. Ciapetti, (2; 0/2), [39; 0/39]

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Milan, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Cell Factory, Center for Cellular Therapy and Cryobiology, R. Giordano, L. Lazzari, (7; 5/2), [0]

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Lithuania

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Norway

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Moscow, Human Stem Cell Institute PJSC, Z. Vadim, A. Pulin, G. Volozhin, I. Eremin, (233; 0/233), [0]

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Pamplona, Hospitalario de Navarra, Complejo, Hematology CTU, CIC 577, T. Zudaire, M. Rodriguez, (0), [4; 4/0]

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Switzerland

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Lugano, Cardiocentro Ticino, Cell Therapy Unit/Cardiology, D. Sürder, T. Moccetti, L. Turchetto, M. Radrizzan, (1; 0/1), [1; 0/1]

Zurich, University Children's Hospital Zurich, Tissue Biology Research Unit, E. Reichmann, M. Meuli, C.Schiestl, (5; 0/5), [6; 0/6]

Turkey

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Istanbul, Istanbul Medipol University, Pediatric Hematology, CIC 446, S. Anal, (0), [1; 1/0]

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Appendix B: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.jcyt.2017.08.009.