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The Survey on Cellular and Engineered Tissue Therapies in Europe in 2013

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Following the coordinated efforts of five established scientific organizations, this report, the sixth of its kind, describes activity in Europe for the year 2013 in the area of *cellular and engineered tissue therapies*, excluding hematopoietic stem cell (HSC) treatments for the reconstitution of hematopoiesis. Three hundred eighteen teams from 31 countries responded to the cellular and engineered tissue therapy survey; 145 teams from 25 countries reported treating 2187 patients, while a further 173 teams reported no activity. Indications were musculoskeletal/rheumatological disorders (45%; 89% autologous), cardiovascular disorders (20%; 99% autologous), hematology/oncology, predominantly prevention or treatment of graft versus host disease (GvHD) and HSC graft enhancement, (19%; <1% autologous), neurological disorders (3%; 100% autologous), gastrointestinal disorders (2%; 32% autologous), and other indications (11%; 67% autologous). The majority of autologous cells (88%) were used to treat musculoskeletal/rheumatological (57%) and cardiovascular (27%) disorders, whereas allogeneic cells were used mainly for hematology/oncology (64%). The reported cell types were mesenchymal stem/stromal cells (MSC) (49%), HSC (28%), chondrocytes (11%), dendritic cells (2%), keratinocytes (1%), and others (9%). In 46% of the grafts, cells were delivered following *ex vivo* expansion, sorted in 17% of the reported cases and transduced in only 3%. Thirty three percent of treatments were delivered intravenously or intra-arterially, and of the remaining 67%, 37% used a membrane/scaffold, 28% a suspension, and 2% a gel. The data are compared to those previously collected to identify trends in a still unpredictably evolving field.

Introduction

CELL- AND TISSUE-BASED therapeutic approaches are progressively gaining ground in the clinics, in part, due to renewed interest shown by public bodies, for example, government-sponsored programs and public charities, together with increasing attention from private funders.[1] In Europe, the main drivers in this arena have been academic institutions and small–medium enterprises that have been able to progressively ''GMPify'' cellular and tissue-engineered therapy approaches to make them compliant with the 2007 regulatory framework and the subsequent national and EU-guidelines.[2] This development is still ongoing and it has been of fundamental importance in allowing an understanding of the safety and clinical relevance of cells and tissues as therapeutic tools. Moreover, it represents a fundamental learning phase for process setup, manufacturing and delivery of cells and tissues from the laboratories to the patients, thereby creating a basis for individualized therapies and, simultaneously, identifying limitations that need to be overcome. Mapping this scenario is of the utmost importance for the progression of the field, which currently involves thousands of patients affected by different conditions and impacts clinical, biomedical, regulatory as well as commercial stakeholders.

Against a background of innovations in science, together with the above-mentioned regulatory environment concerning the use of cellular and engineered tissue therapies, the European sections of the Tissue Engineering and Regenerative Medicine International Society (TERMIS-EU),

For the Joint Survey Committee of the Tissue Engineering and Regenerative Medicine International Society (TERMIS)-Europe, the International Cartilage Repair Society (ICRS), the International Society for Cellular Therapy (ISCT)-Europe, the International Federation for Adipose Therapeutics (IFATS) and the European Group for Blood and Marrow Transplantation (EBMT).
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of the International Society for Cellular Therapy (ISCT), of the International Federation for Adipose Therapeutics (IFATS), and of the International Cartilage Repair Society (ICRS), in a joint initiative with the European group for Blood and Marrow Transplantation (EBMT), established a survey of cellular and engineered tissue therapies. Since 2008, the number of patients treated in Europe with cells or engineered tissues has been collected and sorted by specific therapeutic indications, cell/tissue and donor types and, together with the processing and delivery modes, analysed to describe the evolving situation at the European level.[3–7] It is thanks to the continued efforts of the different working groups that this yearly collection of data represents a means of monitoring changes and capturing trends in a complex and still rather unpredictably developing field.

In this study, we report the results of the sixth survey for the activity, related to patients treated in 2013. The information presented is generally available ahead of published studies, since safety/efficacy data are not required and is complementary to that available in public databases (e.g., www.clinicaltrials.gov), the survey specifying the number of treatments effectively conducted opposed to those planned.

Patients and Methods

Definitions

For the purpose of this survey, *cellular and engineered tissue therapy* is any clinical treatment based on living cells, excluding donor lymphocyte infusions and nonmanipulated hematopoietic cells, for hematological reconstitution.

Data collection and validation

Participating teams were, as in previous years, requested to report their data for 2013 by indication, cell type and source, donor type, processing method, and delivery mode. Some modifications were made to the survey form: dendritic cells were added to the cell type and source, the delivery mode was amended (intravenous/intra-arterial [i.v./i.a.] and intra-organ—either suspension, gel or membrane/scaffold), and a new question included to identify the number of patients treated as part of a clinical trial, as individualized/single cases or as a routine therapy.

The survey followed the traditional principles of the EBMT transplant activity survey, which concentrates on numbers of patients with a first cellular therapy. Six hundred eighty-seven teams known to be actively transplanting in 48 countries (39 European and 9 affiliated countries) were contacted for the 2013 EBMT survey, to which were added members of the other participating societies and teams who 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 1 (Supplementary Data are available online at www.liebertpub.com/tea), were received in paper form and electronically.

Transplant rates

Transplant rates, defined as the reported numbers of patients receiving cellular or engineered tissue 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 2013 US census office database (www.census.gov).

Results

Participating teams

Three hundred eighteen teams from 31 countries (28 European, 3 EBMT affiliated countries) responded to the *cellular and engineered tissue therapy survey of patients treated in 2013*. One hundred forty-five teams (25 countries: 23 European, 2 EBMT affiliated—Iran, Israel) reported performing cellular or tissue-engineered therapies: 142 of these teams provided detailed information on indication, cell source and type, donor type, cell/tissue processing, and delivery mode. A further 173 teams reported no activity. Teams who reported treating patients for the previous survey edition (treatments in 2012) and did not respond this year were directly contacted with repeated personal messages. Teams that responded with detailed information on their activity are listed in Appendix 1 in alphabetical order of country, then city. In addition, their EBMT CIC code (if applicable), the total number of reported cellular or tissue-engineered therapies, and the split between allogeneic and autologous donors is included.

Number of cellular or tissue-engineered therapies and disease indications

According to the received reports, 2187 patients were treated with cellular or engineered tissue therapies: data on six patients were excluded from the analysis due to the absence of complete information. Of the remaining 2181 patients, 1552 (71%) were treated with autologous cells and 629 (30%) with allogeneic cells (Table 1). Indications were musculoskeletal/rheumatological disorders (45%; 89% autologous), cardiovascular disorders (20%; 99% autologous), hematology/oncology (predominantly prevention or treatment of graft versus host disease [GvHD], and hematopoietic stem cell [HSC] graft enhancement) (19%; <1% autologous), neurological disorders (3%; 100% autologous), gastrointestinal disorders (2%; 32% autologous), and other indications (11%; 67% autologous).

As in the previous year, cartilage and bone repair were by far the most frequently reported indications among the *musculoskeletal/rheumatological disorders*, comprising almost half of all treatments in this group, followed by reconstructive surgery/tissue enhancement (21% of treatments). Treatments for decubitus and leg ulcers were the main reasons for a cellular or engineered tissue therapy among the *cardiovascular disorders*, closely followed by peripheral artery disease, together accounting for 62% of treatments in this group of indications. The number of patients treated for *neurological and gastrointestinal indications* was fairly small (114) and mostly confined to Crohn's disease (*gastrointestinal*) followed by multiple sclerosis and amyotrophic lateral sclerosis (*neurological*). Among the remaining indications, most patients were treated for skin reconstruction (burns) or for solid tumor excision (Table 1). One hundred eighteen patients were reported under miscellaneous, that is, they were treated for indications other

Table 1. Number of Reported Cellular and Engineered Tissue Therapy Treatments in Europe in 2013 Sorted by Indication, Cell Source, and Donor Type

	Cell type and source													
	Autologous						*Allogeneic*							
Indication	*HSC*	*MSC*	*Chondrocyte*	*Keratinocyte*	*Dendritic cells*	*Other*	*HSC*	*MSC*	*Keratinocyte*	*Dendritic cells*	*Other*	*Autologous*	*Allogeneic*	*Total*
Cardiovascular														
Peripheral artery disease	131											131		131
Cardiomyopathy	61						2					61	2	63
Heart failure	26	11										37		37
Myocardial ischemia	41	16										57		57
Decubitus and leg ulcers	113	18									4	131	4	135
Other/unspecified	3											3		3
Musculoskeletal/rheumatological														
Bone repair (maxillofacial)	75											75		75
Bone repair (orthopedics)	18	39	13					1				70	1	71
Osteogenesis imperfecta								1					1	1
Cartilage repair (orthopedics)		159	224					98			4	383	102	485
Muscle repair	2	2						2				4	2	6
Tendon/ligament	3	36				12						51		51
Reconstructive surgery/ tissue enhancement		200		6								206		206
Scleroderma	14	8										22		22
Arthritis	39	23			6							68		68
Other/unspecified	2	4										6		6
Neurological														
Multiple sclerosis	4	18										22		22
Amyotrophic lateral sclerosis	11	9										20		20
Parkinson's	3											3		3
Peripheral nerve regeneration (trauma)	4											4		4
Other/unspecified	8	10										18		18
Gastrointestinal														
Crohn's disease	5							28				5	28	33
Liver insufficiency	2				4	4		4				10	4	14
Hematology/oncology														
GvHD prevention or treatment							23	333					356	356
HSC graft enhancement	1						15	32				1	47	48
Miscellaneous														
Skin reconstruction—burns									23		42		65	65
Cornea repair						1						1		1
Diabetes						1					5	1	5	6
Solid tumor	9				26	18				3		53	3	56
Other	3	13			1	92		9				109	9	118
Total	578	566	237	6	37	128	40	508	23	3	55	1552	629	2181

HSC, hematopoietic stem cell; MSC, mesenchymal stromal/stem cell; GvHD, graft versus host disease.

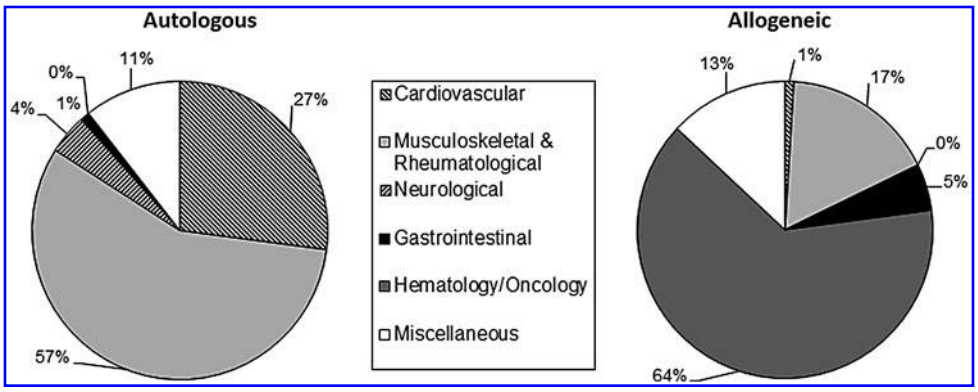

FIG. 1. Percentage of indications for cellular and engineered tissue therapies in Europe in 2013, sorted by donor type. Data used for this chart were derived from the extended questionnaire and the standard European Group for Blood and Marrow Transplantation (EBMT) survey sheet.

than those mentioned in the form, for example, for hemorrhagic cystitis.

Cell type, source, and donor type

The reported cell types were mesenchymal stem/stromal cells (MSC) (49%), HSC (28%), chondrocytes (11%), dendritic cells (2%), keratinocytes (1%), and others (9%). This year, no treatments were reported using dermal fibroblasts. From 1074 MSC-based therapies, 53% were autologous transplants, and of the 618 HSC treatments, 94% were autologous transplants (Table 1). Of the remaining cell sources, all chondrocyte transplants, 93% of dendritic cells, 21% of keratinocytes and 70% of other cell sources, were autologous.

The majority of autologous cells (88%) were used to treat musculoskeletal/rheumatological, cardiovascular, or neurological indications (57%, 27%, and 4%, respectively). Although only a small number of patients (67) had neurological disorders, all treatments used autologous cells. The main uses of allogeneic cells were, as in previous years, for hematology/oncology (64%) and for musculoskeletal/rheumatological indications (17%), almost all of which were for cartilage repair (Fig. 1). The trends for the various therapy areas over the last 5 years are shown in Figure 2.

In 2013, MSC were mostly obtained from bone marrow (69%) or adipose tissue (30%). MSC were used mainly for GvHD (32%) or for two musculoskeletal indications, namely cartilage repair (24%) and reconstructive surgery/tissue enhancement (19%). For the HSC treatments, cells were derived from peripheral blood (70%) or bone marrow (29%): 61% of them were used to treat cardiovascular disorders, mainly periperhal artery disease or decubitus and leg ulcers, and 25% for musculoskeletal/rheumatological indications, mainly bone repair. All chondrocyte preparations were for cartilage and bone repair. Keratinocytes were almost exclusively used for either skin reconstruction or reconstructive surgery/tissue enhancement. Only a small number of patients (40) were treated with dendritic cells, here identified as a cell source for the first time. These cells were used for solid tumor (29 patients), arthritis and liver insufficiency. The cell source ''other'' (i.e., not among those foreseen in the form) was reported for 183 (8%) patients. The teams also reported the use of combinational treatments, for example, fat cells augmented with monocytes from peripheral blood cells (in reconstructive surgery/tissue enhancement or chondrocytes with allogeneic MSC for cartilage repair). These could not be consistently captured by the format of the questionnaire and data display, but are worth being qualitatively mentioned here since they are in line with recently published trends.[8,9] The use of hybrid products such as these, combining cell types or combining cells with bone marrow fraction or blood-derived additives, is clearly on the rise and will need to be monitored in a revised survey edition in future years.

Cell processing and delivery mode

Of all the grafted products, just under half underwent cell expansion (46%), 3% (55 patients only) were transduced, and 17% were sorted (Table 2). Ninety-two percent of cardiovascular, 53% of musculoskeletal/rheumatological, and 45% of neurological indications were treated with nonexpanded cells, while gastrointestinal indications were mainly treated (60%) with expanded cells. Expanded cells

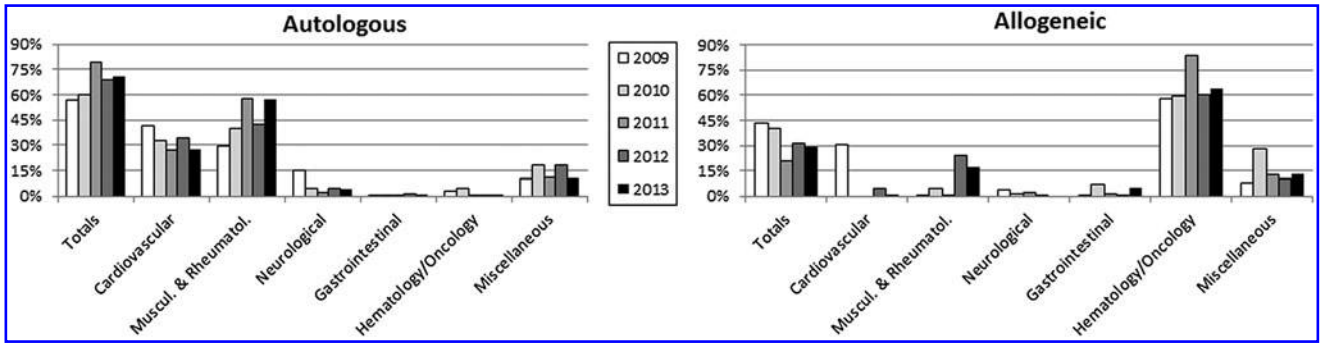

FIG. 2. Comparative analysis of indications for cellular and engineered tissue therapies in Europe from 2009 to 2013, sorted by donor type. Data used for this chart were derived from the current study and four previous reports.[3–7]

Table 2. Number of Reported Cellular and Engineered Tissue Therapy Treatments in Europe in 2013 Sorted by Processing Mode

	Cell processing							
Indications	*Nonexp.*	*Expanded*	*Untransduced*	*Transduced*	*Unsorted*	*Sorted*	*Automated*	*Manual*
Cardiovascular								
Peripheral artery disease	131		131		130	1	119	12
Cardiomyopathy	63		63		7	56	58	5
Heart failure	26	11	14	23	37			37
Myocardial ischemia	41	16	57		45	12	16	41
Decubitus + leg ulcers	129	6	135		135		129	6
Other/unspecified	3		3		3		3	
Musculoskeletal/rheumatological								
Bone repair (maxillofacial)	75		75		75		75	
Bone repair (orthopedics)	48	23	71		56	15	45	26
Osteogenesis imperfecta		1	1		1			1
Cartilage repair (orthopedics)	112	373	483	2	284	201	87	398
Muscle repair	4	2	6		4	2	2	4
Tendon/ligament	11	40	51		48	3	5	46
Reconstructive surgery/ tissue enhancement	200	6	206		206		154	52
Scleroderma	14	8	22		22			22
Arthritis	62	6	68		27	41	45	23
Other/unspecified	2	4	6		4	2	2	4
Neurological								
Multiple sclerosis	4	18	22		21	1	7	15
Amyotrophic lateral sclerosis	11	9	20		20		11	9
Parkinson's	3		3			3		3
Peripheral nerve regeneration (trauma)	4		4			4		4
Other/unspecified	8	10	18		10	8		18
Gastrointestinal								
Crohn's disease	13	20	33		33			33
Liver insufficiency	6	8	10	4	12	2		14
Hematology/oncology								
GvHD prevention or treatment	23	333	353	3	354	2		356
HSC graft enhancement	1	47	48		44	4	1	47
Miscellaneous								
Skin reconstruction—burns	42	23	65		65		42	23
Cornea repair		1	1		1			1
Diabetes	6		6		6			6
Solid tumor	38	18	45	11	44	12	11	45
Other	95	23	106	12	106	12	13	105
Total	1175	1006	2126	55	1800	381	825	1356

nonexp, nonexpanded.

were also used for 94% of hematology/oncology treatments and 35% of treatments for skin reconstruction.

Cell sorting was applied predominantly for musculoskeletal/rheumatological (69% of all sorted cells) and cardiovascular indications (18% of all sorted cells). 264 patients with musculoskeletal/rheumatological indications (27% of all patients in this group), of whom 201 were treated for cartilage repair, received treatment with sorted cells as did 69 patients with cardiovascular indications (16% of all patients in this group).

Of the 39% of cells reported to be processed using an automated device, most were used to treat musculoskeletal/rheumatological (50%) and cardiovascular (39%) indications.

Thirty-three percent of the cells were delivered intravenously or intra-arterially. Of the remaining 67% (intra-organ delivery), 37% used a membrane/scaffold, 28% a suspension, and 2% a gel (Table 3). Intravenous (i.v.) or intra-arterial (i.a.) delivery was reported for all hematology/oncology treatments (56% of all i.v. and i.a. treatments) and for 74% of gastrointestinal indications. Eighty-five percent of treatments delivered through a gel were for musculoskeletal/rheumatological indications (for either bone and cartilage repair or scleroderma). The use of a suspension for cell delivery was reported mainly for musculoskeletal/rheumatological (55%) and cardiovascular (28%) indications, while the use of a membrane/scaffold was split between musculoskeletal/rheumatological

Table 3. Number of Reported Cellular and Engineered Tissue Therapy Treatments in Europe in 2013 Sorted by Delivery Mode

	Cell delivery mode			
		Intra-organ		
Indications	*i.v. or i.a*	*Suspension*	*Gel*	*Membrane/scaffold*
Cardiovascular				
Peripheral artery disease	17	26		88
Cardiomyopathy	2	61		
Heart failure	3	34		
Myocardial ischemia	9	48		
Decubitus + leg ulcers		2		133
Other/unspecified	3			
Musculoskeletal/rheumatological				
Bone repair (maxillofacial)				75
Bone repair (orthopedics)		16	13	42
Osteogenesis imperfect		1		
Cartilage repair (orthopedics)	70	166	18	231
Muscle repair	2	4		
Tendon/ligament	12	14		25
Reconstructive surgery/tissue enhancement		65		141
Scleroderma	14		8	
Arthritis		64		4
Other/unspecified		2		4
Neurological				
Multiple sclerosis	18	4		
Amyotrophic lateral sclerosis	9	11		
Parkinson's		3		
Peripheral nerve regeneration (trauma)		4		
Other/unspecified	5	13		
Gastrointestinal				
Crohn's disease	25	8		
Liver insufficiency	10	4		
Hematology/oncology				
GvHD prevention or treatment	356			
HSC graft enhancement	48			
Miscellaneous				
Skin reconstruction—burns		5		60
Cornea repair				1
Diabetes	6			
Solid tumor	14	36		6
Other	94	17	7	
TOTAL	717	608	46	810

i.a, intra-arterial; i.v., intravenous.

(64%), decubitus and leg ulcers (16%), peripheral artery disease (11%), and skin reconstruction (burns) (7%).

Treatments for both musculoskeletal/rheumatological and cardiovascular indications were predominantly delivered through membrane/scaffold (53% and 52%, respectively) or suspension (40% and 34%, respectively), with 92% of treatments for skin reconstruction (burns) administered through membrane/scaffold. No neurological or gastrointestinal indications were treated using a gel or membrane/scaffold. As this revised approach to recording the mode of delivery was introduced with this survey, no identification of trends is possible.

Transplant rates and active teams

Reported cellular and engineered tissue therapies were performed in a limited number of countries and with different intensity. Figure 3 displays the reported transplants per 10 million inhabitants in the different European and EBMT-associated countries. The highest transplant rates (i.e., >40 per 10 million population) were reported in (in decreasing order) Slovenia, the Netherlands, Italy, Spain, Belgium, Denmark, the Czech Republic, Norway, and Switzerland.

The number of teams reporting cellular and tissue-engineered therapies were also mapped in the different European and EBMT-associated countries after normalization to the inhabitant numbers (Fig. 4). The number of reporting teams per 10 million inhabitants were higher than 4 in Slovenia, Finland, Belgium, Lithuania, the Netherlands, Switzerland, and Spain (again in decreasing order).

As of last year, the top 10 countries (out of 31 total) accounted for 85% of all patients treated.

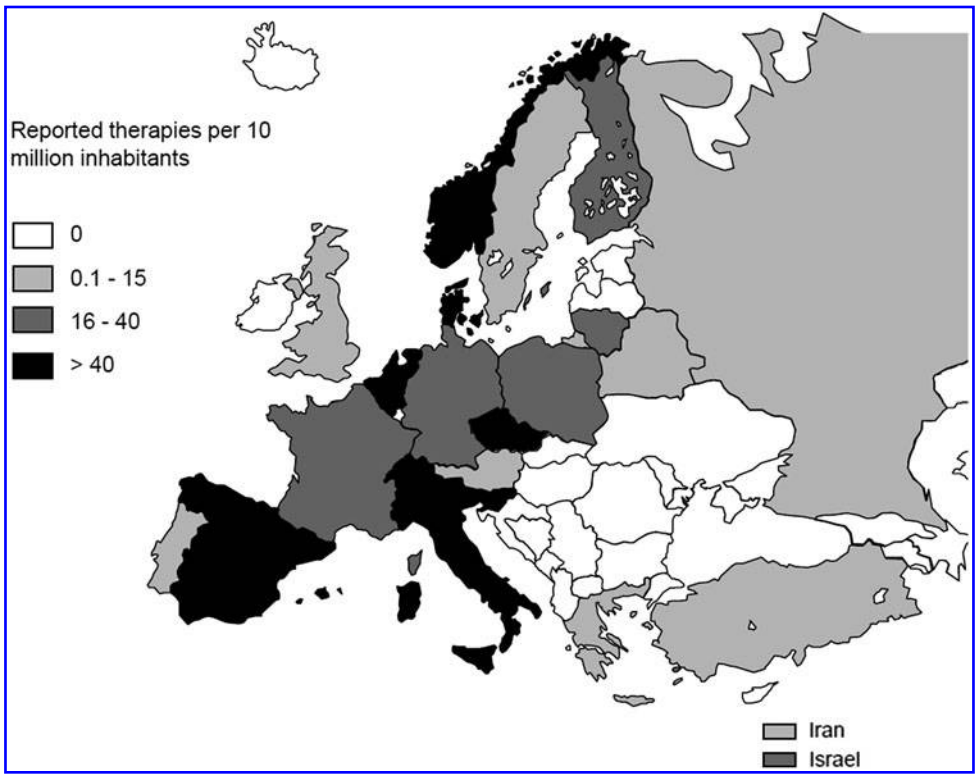

FIG. 3. Number of cellular and engineered tissue therapies per 10 million inhabitants reported in Europe in 2013.

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

With this survey, teams were asked for the first time to report if patients were treated with cells/engineered tissues in the context of a clinical trial, as individualized/single case treatment, or as a routine therapy. Where information was provided (from 77 teams for 1479 patients, 70% of total patient number), 46% of patients were treated as routine therapy, 34% as part of a clinical trial, and 20% as

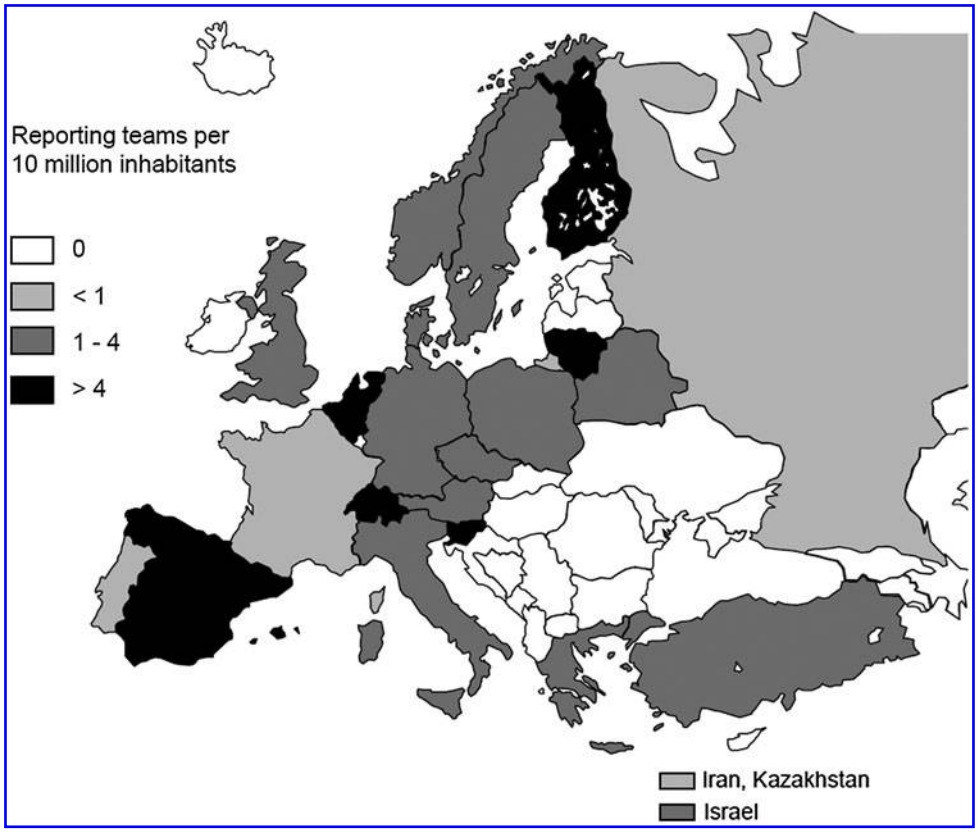

FIG. 4. Number of teams per 10 million inhabitants reporting cellular and engineered tissue therapies in Europe in 2013.

individualized/single cases. Fourteen teams reported treating 675 patients with routine therapies: most (58%) were treated for musculoskeletal and rheumatological indications (of which 38% for reconstructive surgery/tissue enhancement and 50% for cartilage and bone repair), followed by cardiovascular disorders (32%, of which 60% for decubitus and leg ulcers and 40% for peripheral artery disease) and 6% for skin reconstruction following burns. Importantly, 64% of the treatments reported as ''routine therapy'' involved the use of fat- and/or peripheral blood-derived cells. Of the 33 teams who reported treating 502 patients as part of a clinical trial, most (59%) were treated for musculoskeletal and rheumatological indications (of which 53% for cartilage repair), followed by cardiovascular disorders (15%).

Discussion

The data collected for this sixth edition of the cellular and engineered tissue therapy survey show a modest increase from the previous year in both the number of reporting teams and number of patients treated. Since the survey's inception, the total number of teams reporting the use of cellular and engineered tissue therapies has risen from 143 in 2008 to 318 in 2013, with the number of teams reporting full data rising from 33 in 2008 to 142 in 2013. At the same time, the total number of patients treated has risen from 1040 in 2008 to 2187 in 2013 (Fig. 5).

We have compared the results obtained from patients treated in 2013 for specific indications with previous years and found few significant differences. Although no patients were treated for bypass graft in 2013, numbers in previous years were also rather limited (six in 2012 and nine in 2011). The treatments for patients with heart failure accounted for 9% of all cardiovascular ones, compared to 13% and 17%, in 2011 and 2012 respectively. This reduction can most likely be attributed to changes in a limited number of highly active teams, who did not respond to the survey this time.

As in the previous 2 years, the most used cell source in 2013 was MSC, accounting again for around 50% of the treatments. The most represented indication for their use was again GvHD prevention or treatment (15% of all patients, 333 in all). The use of dermal fibroblasts, employed almost exclusively for skin reconstruction in previous surveys, was not reported in 2013, indicating that the promise of bilayered or composite tissue-engineered skin[10,11] is still not reflected in the clinical scenario, which is dominated by the more conventional use of keratinocytes only. The primary use of dendritic cells, although for a small number of patients (29 patients), was related to solid tumor, consistent with last year's report, followed by arthritis and liver insufficiency.

Analysis of treatments reported as being carried out in the context of clinical trials or as a routine therapy was combined with data on associated indications and cells used. Collectively, such assessments indicate that intra-operative isolation and use of cells, predominantly in the context of plastic and reconstructive surgery, are considered a routine treatment, while procedures employing cell expansion, and therefore subject to registry under ATMP (Advanced Therapy Medicinal Product) regulations, are prevalently considered experimental and thus part of a clinical trial. This trend is consistent with the fact that ATMPs are only allowed in the routine clinical practice after having passed cell quality and efficacy indicator checks, to assure patient, provider, payer, and policy maker of the safe and effective application of expensive and personalized treatments. In the specific context of cell-based cartilage repair, we received reports indicating a roughly 50-50 split between the use within a clinical trial or as a routine therapy. Underlying this dichotomy could be the fact that cartilage cell therapy is part of the reimbursement system only in some European countries. There is currently no way to predict the development of reimbursement of cell therapy for specific indications (e.g., cartilage repair) in individual EU regions and/or countries. This will have a considerable influence on the field and affect the number of patients who can be treated in future. Such considerations indicate that treatment selection and growth, or decline of treatment choice, is greatly influenced by both political and local economic factors and related to the social healthcare systems.

The fact that 66% of patients were treated as either individualized/single cases or part of routine therapy rather than as part of a clinical trial indicates that data from clinical trials represent a subset of those presented here. Nevertheless, analysis of trends from registered clinical studies (e.g., www.clinicaltrials.gov) and of market data from companies providing expansion of cells intended for cell therapy as a service would, although challenging, be highly informative to complement the yearly survey reports. We are aware that centers where cellular therapy treatments are performed likely in significant numbers did not participate in the survey and a personalized team-hunting strategy (e.g., toward previously active or publishing teams) is only partially effective. However, the program is based on answers supplied on a voluntary basis. The most convincing incentive for active teams to report through our survey will be (1)

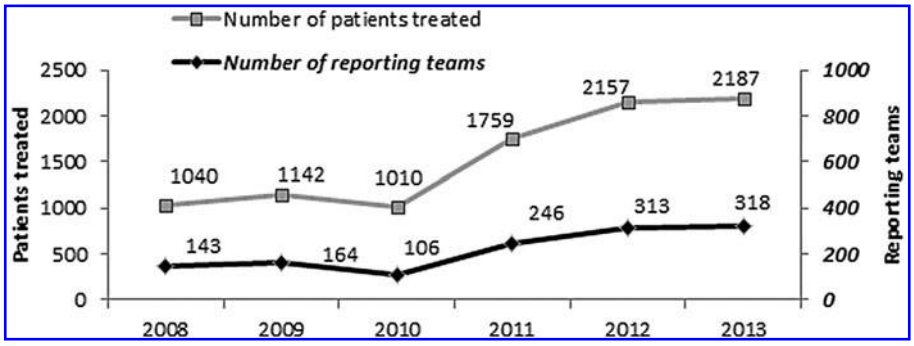

FIG. 5. Number of reporting teams and patients treated using cellular and engineered tissue therapies from 2008 to 2013. Data used for this chart were derived from the current study and previous reports.[3–7]

to demonstrate the increased recognition of the initiative by the field and (2) to convey the importance to further develop it through contributions which are transparently acknowledged without compromising opportunities to publish or protect clinical data.

Toward the end of 2014, IFATS, the International Federation for Adipose Therapeutics and Science, became a supporting society. This addition underlines that the survey program is continuing to receive growing recognition as a reference platform for the collection and dissemination of information that is not available in public databases or scientific publications. ISCT with its other sister societies has also been increasingly supportive of this European initiative since its inception. The international nature of most of the involved societies represents a push for widening the data collection to other world regions, with global repository of data, as well as for accelerating the process of data collection and analysis, toward more timely dissemination of the information to the Regenerative Medicine and Tissue Engineering Community. Indeed a larger collective effort will be necessary to guarantee that cell-based and tissue-engineered therapies, despite the challenges to be overcome, will seriously develop into global opportunities to counteract still lethal diseases and unmet clinical needs.

Acknowledgments

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Disclosure statement

No competing financial interests exist.

References

1. Schachter, B. Therapies of the state: what can governmental agencies do to lower the risk of cell therapies and the enterprises commercializing them? Nat Biotechnol **32,** 736, 2014.
2. European Medicines Agency. Guideline on human cell-based medicinal products. EMEA/CHMP/410869/2006. 2008.
3. Martin, I., Baldomero, H., Tyndall, A., Niederwieser, D., and Gratwohl, A. A survey on cellular and engineered tissue therapies in Europe in 2008. Tissue Eng Part A **16,** 2419, 2010.
4. Martin, I., Baldomero, H., Bocelli-Tyndall, C., Slaper-Cortenbach, I., Passweg, J., and Tyndall, A. The survey on cellular and engineered tissue therapies in Europe in 2009. Tissue Eng Part A **17,** 2221, 2011.
5. Martin, I., Baldomero, H., Bocelli-Tyndall, C., Passweg, J., Saris, D., and Tyndall, A. The survey on cellular and engineered tissue therapies in Europe in 2010. Tissue Eng Part A **18,** 2268, 2012.
6. Martin, I., Baldomero, H., Bocelli-Tyndall, C., Emmert, M.Y., Hoerstrup, S.P., Ireland, H., Passweg, J., and Tyndall, A. The survey on cellular and engineered tissue therapies in Europe in 2011. Tissue Eng Part A **20,** 842, 2014.
7. Martin, I., Ireland, H., Baldomero, H., and Passweg, J. The survey on cellular and engineered tissue therapies in Europe in 2012. Tissue Eng Part A **21,** 1, 2015.
8. De Angelis, B., Gentile, P., Orlandi, F., Bocchini, I., Di Pasquali, C., Agovino, A., Gizzi, C., Patrizi, F., Scioli, M.G., Orlandi, A., and Cervelli, V. Limb rescue: a new autologous-peripheral blood mononuclear cells technology in critical limb ischemia and chronic ulcers. Tissue Eng Part C **21,** 423, 2015.
9. Bekkers, J.E., Tsuchida, A.I., van Rijen, M.H., Vonk, L.A., Dhert, W.J., Creemers, L.B., and Saris, D.B. Single-stage cell-based cartilage regeneration using a combination of chondrons and mesenchymal stromal cells: comparison with microfracture. Am J Sports Med **41,** 2158, 2013.
10. Idrus, R.B., Rameli, M.A., Low, K.C., Law, J.X., Chua, K.H., Latiff, M.B., and Saim, A.B. Full-thickness skin wound healing using autologous keratinocytes and dermal fibroblasts with fibrin: bilayered versus single-layered substitute. Adv Skin Wound Care **27,** 171, 2014.
11. Böttcher-Haberzeth, S., Biedermann, T., Klar, A.S., Widmer, D.S., Neuhaus, K., Schiestl, C., Meuli, M., and Reichmann, E. Characterization of pigmented dermo-epidermal skin substitutes in a long-term in vivo assay. Exp Dermatol **24,** 16, 2015.

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(*Appendix follows* →)

Appendix: List of Centers Reporting Use of Cellular and Engineered Tissue Therapy in Europe in 2013

Format: City, Hospital, Department, Centre Identification Code (CIC—as used for EBMT teams in the EBMT standard survey), Physicians (Total treatments: allogeneic/autologous)

Austria

Krems, University Krems, Regenerative Medicine and Orthopaedics, S. Nehrer, T. Luksch, P. Holzmann, M. Gruber (5:0/5)

Vienna, Medical University Hospital, Traumatology, S. Aldrian, C. Albrecht (4:4/0)

Vienna, Universitätsklinik für Innere Medizin-AKH, CIC 227, H. Greinix, P. Kalhs (1:1/0)

Belarus

Minsk, Belorussian Centre, CIC 591, N. Minakovskaya, Y. Mareika, A. Alexeichik, O. Aleinikova (15:15/0)

Belgium

Antwerp, Antwerp University Hospital (UZA), CIC 996, W. Schroyens, Z. Berneman (24:0/24)

Brussels, Military Hospital Queen Astrid, Burn Wound Centre, G. Verbeken (23:23/0)

Gent, University Hospital, CIC 744, L.A. Noens (1:1/0)

Leuven, University Hospital Gasthuisberg, CIC 209, J. Maertens, G. Verhoef, M. Renard (1:1/0)

Liège, CHU Liege, Gastrology, E. Louis (10:10/0)

Liège, CHU Liege, Surgery and Transplantation, M. Meurice (2:2/0)

Liège, University Hospital Sart-Tilman, CIC 726, Y. Béguin, B. de Prijck (22:22/0)

Czech Republic

Prague, Academy of Sciences, Institue of Experimental Medicine, E. Sykova, S. Konradova, Z. Koci, P. Markova (27:0/27)

Znojmo, General Hospital Znojmo, Orthopaedics and Traumatology, R. Hart, P. Smid, M. Komzak (29:0/29)

Denmark

Copenhagen, The Heart Centre Rigshospitalet, Cardiac Catherization Lab., J. Kastrup (32:0/32)

Copenhagen, University Hospital, Clinical Immunology, A. Fischer-Nielsen, E. Haastrup, R. Oliveri (6:0/6)

Finland

Helsinki, Children's Hospital, CIC 219, K. Vettenranta (2:2/0)

Helsinki, Helsinki University Central Hospital, CIC 515, L. Volin (1:1/0)

Helsinki, HUCH Jorvi Hospital, Orthopaedics, Traumatology, T. Paatela (1:0/1)

Turku, University Central Hospital, CIC 225, M. Itälä-Remes, M. Kauppila, M. Putkonen, U. Salmenniemi, K. Remes (10:10/0)

France

Clermont Ferrand, CHU Estaing, Centre de Biotherapie d'Auvergne, CIC 273, J. Kanold, P. Halle, J.-O. Bay (6:0/6)

Grenoble, CHU de Grenoble (St. Ismier), Unite de Therapie et d-Ingenierie Cellulaire, A. Moisan, V. Persoons, H. Egelhofer, O. Detante (14:8/6)

Marseille, Arthosport Centre, Knee Institute, M. Assor (85:85/0)

Nantes, CHU Nantes, UTCG, Institut de Biologie, CIC 253, B. Dreno, S. Saïagh, S. Bercegeay, D. Heymann, P. Chevallier (8:6/2)

Paris, Hôpital St. Louis, CIC 960, H. Dombret, L. Degos, P. Rousselot (1:0/1)

Germany

Chemnitz, Klinikum Chemnitz GmbH, Innere Medizin III, CIC 104, M. Hänel, A. Morgner (7:7/0)

Darmstadt, Agaplesion Elisabethenstift, Klinik für Orthopädie, Unfallchirurgie und Sportmedizin, T. Schreyer (0:0/14)

Dinslaken, St. Vinzenz Hospital, Orthopädie und Unfallchirurgie, W. Zinser, F. Glahn, M. Rüter (36:0/36)

Dresden, Universitätsklinikum Carl Gustav Carus, Medizinische Klinik und Poliklinik I, CIC 808, G. Ehninger, M. Bornhäuser, M. Gahr (22:22/0)

Essen, Universitätsklinikum, CIC 259.1, O. Basu, B. Kremens (2:2/0)

Frankfurt, J. W. Goethe Universität, CIC 138, T. Klingebiel, P. Bader (3:3/0)

Frankfurt, Klinikum Frankfurt Oder, CIC 190, M. Kiehl (20:20/0)

Halle, BG-Clinic Bergmannstrost, Neurosurgery, H.J. Meisel (13:0/13)

Hannover, Hannover Medical School (MHH), Haematology, Haemostasis, Oncology and Stem Cell Transplantation, CIC 295.1, A. Ganser, J. Krauter (7:1/6)

Hannover, Medizinische Hochschule, CIC 295.2, C. Kratz, K.W. Sykora (1:1/0)

Homburg/Saar, Universitätsklinikum Saarlandes, Experimental Orthopädie, H. Madry (8:0/8)

Munich, Klinikum Schwabing, C.M. Wendtner, N. Fischer (1:1/0)

Munich, Technische Universität München, Paediatrics, CIC 189, S. Burdach, A. Wawer, I. Teichert- von Lüttichau (2:2/0)

Münster, Universitätklinikum Münster, CIC 505, H. Jürgens, K. Ehlert (1:1/0)

Tübingen, Universitätsklinikum, CIC 535, R. Handgretinger, P. Lang (6:3/3)

Würzburg, Universitätsklinikum, CIC 196, P. Schlegel (1:1/0)

Greece

Athens, Academy of Athens Biomedical Research Foundation, Hellenic Cord Blood Bank, A.C. Papassavas, T.T. Chatzistamatiou, E. Michalopoulos, C. Stavropoulos-Giokas (15:0/15)

Athens, University of Athens, CIC 604, P. Tsirigotis (1:1/0)

Iran, Islamic Rep.

Shiraz, Nemazee Hospital, Shiraz University Medical Sciences, CIC 188, M. Ramzi (15:0/15)

Teheran, Shariati Hospital, CIC 633, A. Ghavamzadeh, M. Jahani (7:7/0)

Israel

Jerusalem, Hadassah University Hospital, CIC 258, R. Or, S. Slavin (16:16/0)

Petach-Tikva, Children's Medical Centre, CIC 755, J. Stein (1:1/0)

Tel Hashomer, Edmond and Lily Safra Children's Hospital, Sheba Medical Centre, CIC 572, A. Toren, B. Bielorai, G. Goldstein, D. Hutt (11:11/0)

Italy

Bologna, 6th div Rizzoli Orth. Institute, RIT- Cell Factory, L. Roseti, A. Bassi, A. Maso (5:0/5)

Bologna, Hospital St. Orsola, CIC 240, G. Bandini, M. Cavo, F. Bonifazi (2:0/2)

Bologna, Istituto Ortopedico Rizzoli, 3rd Orthopaedic and Traumatology Clinic, D. Donati (24:0/24)

Cagliari, Ospedale per le Microcitemie, CIC 811.2, M. Orofino (1:1/0)

Florence, AOU Careggi, BMT Unit, CIC 304, A. Bosi, R. Saccardi, S. Guidi (4:0/4)

Genova, Istituto Giannina Gaslini, CIC 274, G. Dini, E. Lanino (1:1/0)

Milan, Istituto Scientifico H.S. Raffaele; Univ. Milan*, Stem Cells Research Centre; Dept Neurological Sciences*, CIC 813, G. Cossu, F. Ciceri; Y. Torrente* (2:2/0)

Milan, OASI Bio-research Foundation, Ortho. Arthro. Surgery Int., A. Gobbi, D. Lad (47:0/47)

Milan, University of Milan IRCCS, CIC 265, A. Cortelezzi, E. Tagliaferri (1:1/0)

Monza, Ospedale San Gerardo, CIC 279, A. Rovelli (5:5/0)

Rome, Università ''La Sapienza,'' Experimental Medicine, C. Marchese, E. Vescarelli, S. Ceccarelli, C. Nodale (21:0/21)

Rome, University Tor Vergata, Reconstructive Surgery, V. Cervelli, D.J. Bottini, B. De Angelis (473:42/431)

Kazakhstan

Astana, National Research Centre for Oncology and Transplantation, I. Pivovarova (2:2/0)

Lithuania

Vilnius, Santariskiu Klinikos, CIC 644, L. Griskevicius, I. Trociukas (11:11/0)

Vilnius, University Children's Hospital, CIC 508, J. Rascon (2:1/1)

Netherlands

Amsterdam, Antoni Van Leeuwenhoek Cancer Institute, CIC 976, S. Rodenhuis, J. Baars (1:0/1)

Amsterdam, VU Medical Centre, Dermatology, S. Gibbs (4:4/0)

Amsterdam, VU University Medical Centre, CIC 588, E. Meijer, G.J. Ossenkoppele (6:6/0)

Groningen, University Hospital, CIC 546, G. van Imhoff (2:2/0)

Leiden, University Hospital, CIC 203, J.H. Veelken, M. Egeler, P.A. von dem Borne (51:14/37)

Rotterdam, Erasmus Medical University Centre, Orthopaedics, S. de Jonge, R.-J. de Vos, J.A.N. Verhaar, J.L. Tol (12:0/12)

Utrecht, UMC, Orthopaedic Surgery, D. Saris (70:6/64)

Utrecht, UMCU/WKZ, CIC 239.2, M. Bierings, N.M. Wullffraat (7:7/0)

Utrecht, University Hospital UMCU, CIC 239.1, E. Petersen (23:23/0)

Norway

Oslo, Oslo University Hospital, *Ex vivo* cell lab, Dept. Immunology, CIC 235, J. Brinchmann (2:0/2)

Tromso, University Hospital North Norway, Orthopaedic Surgery, G. Knutsen (20:0/20)

Poland

Bydgoszcz, Nicolaus Copernicus University, CIC 764, M. Wysocki, J. Styczynski, R. Debski (2:2/0)

Cracow, University Children's Hospital JUMC, Transplantation, CIC 507, J. Gozdzik, W. Czogala, O. Wiecha, S. Skoczen (3:3/0)

Katowice, Regional Blood Centre, Tissue Bank Department, H. Bursig, A. Wysocka–Wycisk, P. Sitek, A. Kurzak (13:0/13)

Lublin, Children's University Hospital, Haematology, Oncology, Transplantation, CIC 678, J. Kowalczyk, K. Drabko, A. Zaucha-Prazmo (1:1/0)

Warsaw, Carolina Medical Centre, R. Smigielski, Z. Pojda (51:0/51)

Warsaw, Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, CIC 800, S. Mazur, Z. Pojda (27:0/27)

Wroclaw, Lower Silesian Centre, BM Donor Registry, CIC 538, A. Lange (2:0/2)

Portugal

Lisbon, Instituto Portugues de Oncologia, CIC 300, M. Abecasis (1:1/0)

Russian Federations

Moscow, Federal Research Centre, Pediatric Haematology, CIC 694, A. Maschan, D. Balachov (22:22/0)

Moscow, Research Haematology Centre of RAS, CIC 930, V.G. Savtchenko (30:30/0)

Moscow, The Russian Children's Research Hospital, CIC 411, E. Skorobogatova (3:3/0)

St. Petersburg, Pavlov Medical University, CIC 725, B.V. Afanasyev, L. Zubarovskaya (32:6/26)

St. Petersburg, Russian Research Institute of Haematology, BMTU, K.M. Abdulkadyerov, S. Voloshin, A. Kuzyaeva, I. Iapreeya (9:0/9)

Slovenia

Ljublijana, Educell d.o.o, N. Kregar-Velikonja (3:0/3)

Ljublijana, UMC Ljubljana, Advanced Heart Failure and Transplantation Centre, B. Vrtovec, G. Poglajen, M. Sever, G. Zemljic (38:0/38)

Ljublijana, University Medical Centre, Haematology, CIC 640, S. Zver, J. Pretnar (30:0/30)

Spain

Barcelona, Hospital Clinic, CIC 214, M. Rovira (6:1/5)

Barcelona, Hospital Quirón Teknon, ITRT, Institut de Teàpia Regenerativa Tissular, L. Orozco, A. Munar, R. Soler, F. Soler (116:7/109)

Cadiz, Hospital de Jérez, CIC 612, S. Garzon (1:1/0)

Cordoba, Hospital Reina Sofia, CIC 238, A. Torres-Gomez, I. Herrera (26:2/24)

Granada, Hospital Virgen de la Nieves, Serv. Hematologia y Hemoterapia, CIC 559, M. Jurado Chacon, L. Moratalla López, A. Romero Aguilar, E. López Fernández (1:1/0)

Leon, Hospital Universitario de Leon, CIC 426, F. Ramos, N. de las Heras (1:0/1)
Madrid, Clinica CEMTRO, Traumatology and Orthopaedics, P. Guillén-García, I. Guillen-Vicente, M. Guillen-Vicente, S. Arauz de Robles (20:0/20)
Madrid, Fundacion Jimenez Diaz, CIC 309, J.L. Lopez-Lorenzo (0:0/0)
Madrid, Hospital de la Princesa, CIC 236, A. Figuera, A. Alegre (3:3/0)
Madrid, Hospital Doce de Octubre, CIC 382, J.J. Lahuerta, J. de la Serna (3:0/3)
Madrid, Hospital General Universitario Gregorio Maranon, CIC 819, J.L. Diez-Martin (14:6/8)
Madrid, Hospital Uni Materno Infantil Gregorio Maranon, CIC 410, C. Belendez (3:0/3)
Madrid, Hospital Universitario Puerta de Hierro, CIC 728, J.R. Cabrera Martin (8:8/0)
Murcia, Hospital Virgen de la Arrixaca, CIC 323, J.M. Moraleda (19:0/19)
Palma de Mallorca, USP Clinica Palmaplanas, Stem Centre SL, S. Dos Anjos Vilaboa (18:0/18)
Pamplona, Clinica Universitaria de Navarra, Cell Therapy Area, F. Prosper Cardoso, E.J. Andreu, S. Inoges, A. Lopez (143:7/136)
Pamplona, Clinica Universitaria de Navarra, CIC 737, J. Rifon (1:1/0)
Pamplona, Hospital de Navarra, CIC 577, E. Olavarria (6:6/0)
Salamanca, Complejo Hospital, CIC 727, D. Caballero (18:18/0)
Santiago de Compostela, Hospital Clinico Universitario, CIC 570, J.L. Bello Lopez (2:2/0)
Valencia, Hospital Clinico Universitario, CIC 282, C. Solano (1:1/0)

Sweden

Linköping, RIL, University Hospital, CIC 740, A. Sandstedt, K. Le Blanc (1:1/0)
Uppsala, University Hospital, CIC 266, K. Carlson (3:3/0)

Switzerland

Basel, University Hospital, Traumatology, M. Jakob, F. Saxer, M. Mumme (10:0/10)
Geneva, Concept Clinic, K.-U. Schlaudraff (19:0/19)
Lugano, Cardiocentro Ticino, Cardiology, D. Sürder, T. Moccetti, L. Turchetio, M. Radrizzahi (3:0/3)
Zurich, Universitäts Kinderklinik, CIC 334, T. Güngör, F. Scherer (1:1/0)

Turkey

Adana, Baskent University of Adana, CIC 589, H. Ozdogu, C. Boga, S. Asma, S. Yuce (2:2/0)
Ankara, Children's Hospital, B. Tunc, F.M. Azik (1:1/0)
Ankara, Gazi University, Besevler, CIC 169, G. Sucak (1:1/0)
Ankara, University of Ankara, CIC 620, E. Unal, M. Ertem (5:5/0)
Antalya, Medical Park Antalya Hospital, Pediatric Stem Cell Transplantation Unit, CIC 911, A. Yesilipek (5:5/0)
Antalya, Medical Park Hospitals, CIC 919, Y. Koc (1:1/0)
Gaziantep, Gaziantep University Medical School, CIC 402, M. Pehlivan (3:3/0)
Istanbul, Acibadem University Atakent Hospital, CIC 457, G. Öztürk, F. Erbey (6:6/0)
Istanbul, Cerrahpasa Medical School Istanbul University, BMT Unit, CIC 761, T. Soysal, S.O. Aydin (1:1/0)
Istanbul, Medical Park Goztepe Hospital, CIC 929, G. Karasu, O. Dogru (5:5/0)
Istanbul, University of Istanbul, CIC 760, M. Aktan (4:4/0)
Kayseri, Erciyes University Faculty of Medicine, CIC 627.2, M. Karakukcu (1:1/0)
Kocaeli, Anadolu Saglik Merkezi, CIC 440, Z. Gülbas (2:2/0)
Kozyatagi, Istanbul, Acibadem Kozyatagi Hospital, S. Ratip (2:2/0)

United Kingdom

Birmingham, Heartlands Hospital, CIC 284, E. Nikolousis, S. Paneesha (3:3/0)
Birmingham, The Birmingham Children's Hospital, CIC 781, S. Lawson (8:8/0)
London, Hammersmith Hospitals NHS Trust, CIC 205, J. Apperley, E. Olavarria, E. Kanfer, A. Rahemtulla, R. Szydlo (9:9/0)
London, King's College Hospital, CIC 763, G. Mufti, A. Pagliuca (1:1/0)
London, London Chest Hospital, Cardiac Research, A. Mathur, S. Hamshere (3:0/3)
London, St Mary's Hospital, CIC 866, J. de La Fuente (3:3/0)
London, The Royal Free Hospital, CIC 216, S. Mackinnon (2:2/0)
Manchester, Royal Children's Hospital, CIC 521, R. Wynn (2:2/0)
Manchester, University Manchester, CT Unit, R. Guest (7:0/7)
Newcastle upon Tyne, Newcastle-upon-Tyne Hospitals Foundation Trust, Cellular Therapy Facility, A.M. Dickinson, D. Bradley (13:0/13)
Oswestry, RJAH Oswestry Orthopaedic Hospital, P. Harrison (29:0/29)
Sheffield, Sheffield Teaching Hospitals NHS Foundation Trust, Haematology, CIC 778, J. Snowden, A. Vora (7:4/3)
Southampton, CRC Wessex, CIC 704, A. Duncombe, D. Richardson (2:2/0)

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Invited Submission

The Survey on Cellular and Engineered Tissue Therapies in Europe in 2012*

Ivan Martin, PhD,[1,2] Hilary Ireland, MSc,[1,2] Helen Baldomero, MSc,[3] and Jakob Passweg, MD[3]

Following the coordinated efforts of five established scientific organizations, this report describes activity in Europe for the year 2012 in the area of *cellular and engineered tissue therapies*, excluding hematopoietic stem cell (HSC) treatments for the reconstitution of hematopoiesis. Three hundred thirteen teams from 33 countries responded to the cellular and engineered tissue therapy survey: 138 teams from 27 countries provided data on 2157 patients, while a further 175 teams reported no activity. Indications were musculoskeletal/rheumatological disorders (36%; 80% autologous), cardiovascular disorders (25%; 95% autologous), hematology/oncology, predominantly prevention or treatment of graft versus host disease and HSC graft enhancement (19%; 1% autologous), neurological disorders (3%; 99% autologous), gastrointestinal disorders (1%; 71% autologous), and other indications (16%; 79% autologous). Autologous cells were predominantly used for musculoskeletal/rheumatological (42%) and cardiovascular (34%) disorders, whereas allogeneic cells were mainly used for hematology/oncology (60%). The reported cell types were mesenchymal stem/stromal cells (49%), HSC (28%), chondrocytes (11%), dermal fibroblasts (4%), keratinocytes (1%), and others (7%). In 51% of the grafts, cells were delivered after *ex vivo* expansion, whereas cells were transduced or sorted in 10% and 16%, respectively, of the reported cases. Cells were delivered intra-organ (35%), intravenously (31%), on a membrane or gel (15%), or using 3D scaffolds (19%). The data are compared with those collected since 2008 to identify trends in the field and discussed in the light of recent publications and ongoing clinical studies.

Introduction

There is a large and relevant clinical demand for cell-based therapies to induce tissue or organ regeneration, as well as to modulate the immune system. Nonetheless, progression from first-in-human experiences in a few patients to full integration into routine clinical practice involves many steps and is often an uphill struggle.[1] To penetrate mainstream healthcare processes, critical scientific challenges must be addressed and acceptable standards of safety and potency must be achieved. This requires the development of new knowledge and the design of clinical studies that can teach on human cell biology. In addition, the translational pathway needs to overcome a series of non-scientific barriers, based on financing, regulatory, and public perception issues. Ultimately, healthcare systems are likely to struggle to meet the associated costs and it is unclear how priorities will be set with regard to reimbursement decisions.[2]

Against this background of innovations in science and the emerging regulatory environment, the European sections of the Tissue Engineering and Regenerative Medicine International Society-Europe (TERMIS-EU), of the International Society of Cellular Therapy (ISCT), and of the International Cartilage Repair Society (ICRS), in a joint initiative with the European Group for Blood and Marrow Transplantation (EBMT) and the European League Against Rheumatism (EULAR), established a survey on novel cellular therapies, now referred to as a survey of cellular and engineered tissue therapies. Since 2008, the number of patients treated in Europe with cells or engineered tissues has been collected and sorted by specific therapeutic indications, cell/tissue and donor types, along with the processing and delivery modes.[3–6]

Here, we report the results of the fifth survey for the activity in 2012, along with a comparison to previous years. The information presented is generally available ahead of

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published studies, because safety/efficacy data are not required for the report, and complementary to that available in public databases (e.g., www.clinicaltrials.gov) as the survey specifies the number of treatments effectively conducted as opposed to planned. Thanks to the continued efforts of the different working groups, the yearly availability of collected data represents a means of monitoring changes and capturing trends in a complex and still rather unpredictably developing field.

Patients and Methods

Definitions

For the purpose of this survey, *cellular and engineered tissue therapy* is any clinical treatment based on living cells excluding donor lymphocyte infusions and nonmanipulated hematopoietic cells for hematological reconstitution.

Data collection and validation

Participating teams were, as in previous years, requested to report their data for 2012 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. Six hundred eighty teams known to be actively transplanting in 48 countries (38 European and 10 affiliated countries) were contacted for the 2012 EBMT survey, to which were added members of the other four participating societies and teams who had contributed to any earlier survey. The non-European countries affiliated with the EBMT activity survey are Algeria, Iran, Israel, Jordan, Kazakistan, Lebanon, Nigeria, Saudi Arabia, South Africa, and Tunisia. Extended questionnaires, in the format displayed in Supplementary Table S1 (Supplementary Data are available online at www.liebertpub.com/tea), were received in paper form and electronically.

Transplant rates

Transplant rates, defined as the reported numbers of patients receiving cellular or engineered tissue 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 2012 US census office database (www.census.gov).

Results

Participating teams

Three hundred thirteen teams from 33 countries (26 European, 7 EBMT affiliated countries) responded to the *cellular and engineered tissue therapy* survey. One hundred thirty-eight teams (27 countries: 23 European, 4 EBMT affiliated—Iran, Israel, Saudi Arabia, and South Africa) reported performing cellular or tissue-engineered therapies and provided detailed information on indication, cell source and type, donor type, cell/tissue processing, and delivery mode. A further 175 teams reported no activity. Teams that responded with 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 tissue-engineered therapies and the split between allogeneic and autologous donor is included.

Number of cellular or tissue-engineered therapies and disease indications

According to the received reports, 2157 patients were treated with cellular or engineered tissue therapies, 672 (31%) with allogeneic and 1485 (69%) with autologous cells (Table 1). Indications were musculoskeletal/rheumatological disorders (36%; 80% autologous), cardiovascular disorders (25%; 95% autologous), hematology/oncology (predominantly prevention or treatment of graft versus host disease [GvHD], hematopoietic stem cell [HSC] graft enhancement) (19%; 1% autologous), neurological disorders (3%; 99% autologous), gastrointestinal disorders (1%; 71% autologous), and other indications (16%; 79% autologous).

Among the *musculoskeletal/rheumatological disorders*, cartilage and bone repair were the most frequently reported indications, followed by reconstructive surgery/tissue enhancement. Treatments for decubitus and leg ulcers were the main reasons for a cellular or engineered tissue therapy among the *cardiovascular disorders*, followed by peripheral artery disease and then heart failure. The number of patients treated for *neurological and gastrointestinal indications* was rather limited (88) and mostly confined to multiple sclerosis, amyotrophic lateral sclerosis (*neurological*), and Crohn's disease (*gastrointestinal*). Among the remaining indications, most patients were treated for solid tumor or skin reconstruction (Table 1).

Cell type, source, and donor type

The reported cell types were mesenchymal stem/stromal cells (MSC) (49%), HSC (28%), chondrocytes (11%), dermal fibroblasts (4%), keratinocytes (1%), and others (7%). Of the 614 HSC treatments, 93% were autologous transplants (Table 1). From 1055 MSC-based therapies, 53% were autologous. Of the remaining cell sources, 70% of chondrocytes, 71% of keratinocytes, and all dermal fibroblast transplants were autologous.

Autologous cells were predominantly used for musculoskeletal/rheumatological (42%) or cardiovascular (34%) disorders and for solid tumors (10%), whereas the main uses of allogeneic cells were for hematology/oncology (60%) and, for the first time in any significant numbers, for musculoskeletal/rheumatological indications (24%). Of these, cartilage repair was the main indication (comprising 19% of the total and 81% within the musculoskeletal/rheumatological grouping) (Fig. 1).

The percentage of treatments using autologous versus allogeneic cells steadily increased from 36% in 2008 to 69% in 2012, with the actual number of patients treated with autologous cells more than doubling in this period (from 664 to 1485 patients). The number of patients treated with allogeneic cells also increased year on year (from 376 to 672), although the percentage of treatments in hematology/oncology was reasonably stable at around 60%, with a peak at more than 80% in 2011. The trends for the various therapy areas are reflected in Figure 2.

In 2012, MSC were mostly obtained from bone marrow (74%; of which 42% were autologous) or adipose tissue

Table 1. Number of Reported Cellular and Engineered Tissue Therapy Treatments in Europe in 2012 Sorted by Indication, Cell Source, and Donor Type

	Cell type and source														
	Autologous						*Allogeneic*								
Indication	*HSC*	*MSC*	*Chondrocyte*	*Keratinocyte*	*Dermal fibroblast*	*Other*	*HSC*	*MSC*	*Chondrocyte*	*Keratinocyte*	*Dermal fibroblast*	*Other*	*Autologous*	*Allogeneic*	*Total*
Cardiovascular															
Peripheral artery disease	103											7	103	7	110
Cardiomyopathy	55						2						55	2	57
Heart failure	73	19											92	0	92
Myocardial ischemia	46	10					19						56	19	75
Bypass graft	6												6	0	6
Decubitus and leg ulcers	150	45											195	0	195
Other/unspecified													0	0	0
Musculoskeletal/rheumatological															
Bone repair (maxillofacial)	19	5											24	0	24
Bone repair (orthopaedics)	3	11						7					14	7	21
Osteogenesis imperfect		12						1					12	1	13
Cartilage repair (orthopedics)		224	165					57	72				389	129	518
Muscle repair						8							8	0	8
Tendon/ligament													0	0	0
Reconstructive surgery/tissue enhancement		151	1					23					152	23	175
Sclerodoma	11	4											15	0	15
Arthritis	3	5											8	0	8
Other/unspecified		1											1	0	1
Neurological															
Multiple sclerosis	3	22											25	0	25
Amyotrophic lateral sclerosis	11	14											25	0	25
Parkinson's	1												1	0	1
Peripheral nerve regeneration (trauma)	3												3	0	3
Other/unspecified	5	7										1	12	1	13
Gastrointestinal															
Crohn's disease	4	7						6					11	6	17
Liver insufficiency	4												4	0	4
Hematology/oncology															
GvHD prevention or treatment							17	360					0	377	377
HSC graft enhancement		4					2	27					4	29	33
Miscellaneous															
Skin reconstruction				51	9			3		23			60	26	86
Cornea repair						1						3	1	3	4
Diabetes	15	3										3	18	3	21
Solid tumor	41	1				100							142	0	142
Other	14	11		4	3	17	4	15				20	49	39	88
Total	570	556	166	55	12	126	44	499	72	23	0	34	1485	672	2157

GvHD, graft versus host disease; HSC, hematopoietic stem cells; MSC, mesenchymal stromal/stem cells.

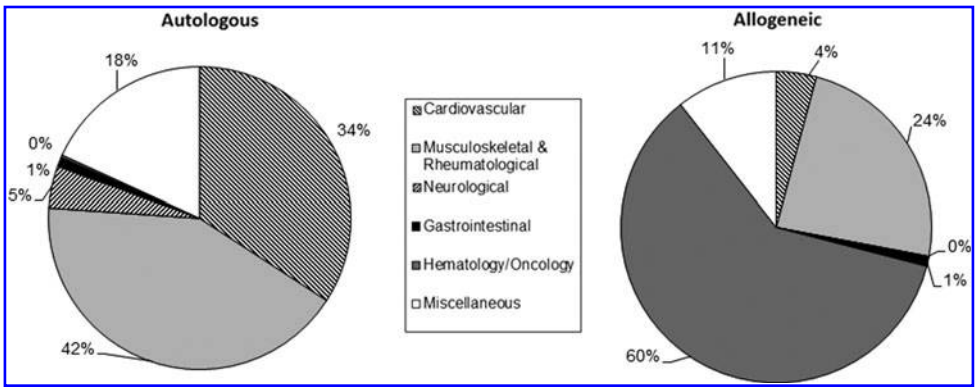

FIG. 1. Percentage of indications for cellular and engineered tissue therapies in Europe in 2012, sorted by donor type.

(25%; of which 87% were autologous), whereas in 2011 they were obtained from adipose tissue and bone marrow in almost equal amounts. MSC were mainly used for GvHD (34%) and for two musculoskeletal indications, namely cartilage repair (26%) and reconstructive surgery/tissue enhancement (16%). For the HSC treatments, cells were derived from peripheral blood (60%) or bone marrow (40%) and 71% of them were used to treat cardiovascular disorders. All chondrocyte preparations were for cartilage repair, while keratinocytes and dermal fibroblasts were almost exclusively used for skin reconstruction. The use of combinational treatments, for example, fat and peripheral blood cells in reconstructive surgery/tissue enhancement, was also reported but could not be consistently captured by the format of the questionnaire.

Cell processing and delivery mode

Of all the grafted products, just more than half underwent cell expansion (51%), 10% were transduced, and 16% were sorted (Table 2). Ninety-three percent of cardiovascular, 50% of musculoskeletal/rheumatological and 36% of neurological indications were treated with nonexpanded cells, while gastrointestinal indications were predominantly (62%) treated with expanded cells. Expanded cells were also used for 97% of hematology/oncology treatments and 80% of treatments for skin reconstruction.

Cell sorting was applied predominantly for musculoskeletal/rheumatological (51% of all sorted cells) and cardiovascular indications (18% of all sorted cells). One hundred seventy patients with musculoskeletal/rheumatological indications (22% of all patients in this group), of whom 161 were treated for cartilage repair, received treatment with sorted cells as did 59 patients with cardiovascular indications (11% of all patients in this group).

Transplanted cells were genetically transduced for 71% of diabetic cases, 27% of heart failure, 23% of cartilage repairs, 21% of solid tumors, and 3% of hematology/oncology cases. Fifty-six percent of all transduced cells were used for cartilage repair. This is the first year that transduced cells were used in any number for this indication (120 of 508 cartilage repair patients treated).

Of the 41% of cells reported to be processed using an automated device, most were used to treat cardiovascular (46%) and musculoskeletal/rheumatological (43%) indications. The previous year, we introduced the topic of whether cells were processed manually or by automated means (when at least one step of cell isolation or culture is performed with an automated device, i.e., a specifically designed instrument beyond a centrifuge or sorter). For patients treated in 2011, manual techniques were almost 4 times as likely to have been used (1377 manual vs. 382 automated) whereas for 2012 patients the ratio reduced significantly (1269 manual vs. 888 automated). The highest use of automated processing in both years was to treat patients for cardiovascular and musculoskeletal/rheumatological indications.

Thirty-five percent of the cell grafts were delivered intra-organ, 31% intravenously, 15% on a membrane or gel, and 19% using a 3D scaffold (Table 3). Cells were delivered intra-organ for 57% of cardiovascular, 48% of neurological, and 39% of musculoskeletal/rheumatological indications. Intravenous (i.v.) delivery was reported for all hematology/oncology treatments and for about half (48%) of gastrointestinal indications. The use

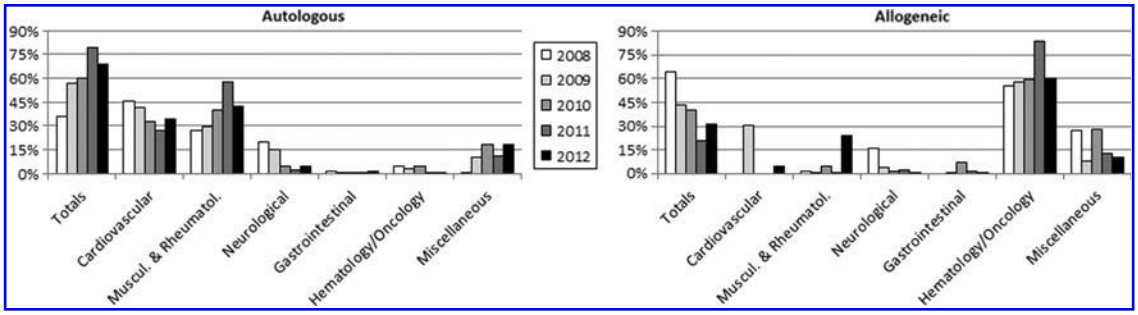

FIG. 2. Comparative analysis of indications for cellular and engineered tissue therapies in Europe from 2008 to 2012, sorted by donor type. Data used for this chart were derived from this study and the four previous reports.[3–6]

Table 2. Number of Reported Cellular and Engineered Tissue Therapy Treatments in Europe in 2012 Sorted by Processing Mode

	Cell processing							
Indications	*Nonexpanded*	*Expanded*	*Untransduced*	*Transduced*	*Unsorted*	*Sorted*	*Automated*	*Manual*
Cardiovascular								
Peripheral artery disease	103	7	109	1	100	10	77	33
Cardiomyopathy	57		57		32	25	52	5
Heart failure	74	18	67	25	88	4	48	44
Myocardial ischemia	65	10	75		61	14	29	46
Bypass graft	6		6			6	6	
Decubitus + leg ulcers	195		195		195		195	
Musculoskeletal/rheumatological								
Bone repair (maxillofacial)	24		24		24		22	2
Bone repair (orthopaedics)	11	10	21		17	4	9	12
Osteogenesis imperfecta	12	1	13		13		12	1
Cartilage repair (orthopaedics)	177	341	398	120	357	161	167	351
Muscle repair		8	8		8			8
Reconstructive surgery/tissue enhancement	162	13	175		175		162	13
Scleroderma	6	9	15		10	5	5	10
Arthritis	3	5	8		8		3	5
Other		1	1		1			1
Neurological								
Multiple sclerosis	3	22	25		23	2	1	24
Amyotrophic lateral sclerosis	11	14	25		25			25
Parkinson's	1		1			1		1
Peripheral nerve regeneration (trauma)	3		3		2	1	2	1
Other	6	7	13		8	5		13
Gastrointestinal								
Crohn's disease	4	13	17		17		1	16
Liver insufficiency	4		4		1	3		4
Hematology/oncology								
GvHD prevention or treatment	12	365	366	11	377		11	366
HSC graft enhancement	2	31	33		31	2	2	31
Miscellaneous								
Skin reconstruction	18	68	86		86			86
Cornea repair		4	4		4			4
Diabetes	3	18	6	15	18	3	15	6
Solid tumor	66	76	112	30	65	77	39	103
Other	37	51	76	12	76	12	30	58
Total	1065	1092	1943	214	1822	335	888	1269

of a membrane or a gel for cell delivery was mainly reported for skin reconstruction (76% of cases), for treatment of decubitus and leg ulcers (54% of cases), or for musculoskeletal/rheumatological (17% of cases) indications. A 3D scaffold was used for 42% of musculoskeletal/rheumatological treatments, in particular for cartilage or bone repair (37%). Other uses of a scaffold were for treating peripheral artery disease (42% of cases).

Over the 5 years of the survey, most cells were delivered intra-organ, followed by i.v. and membrane or 3D scaffold delivery (Fig. 3). There was some use of i.v. delivery in all indication groups over the 5 years, although to varying degrees: i.v. not only was the only delivery mode for GvHD treatments but also was used in treating musculoskeletal/rheumatological indications. While all gastrointestinal indications were treated via i.v. in 2008 and 2009, intra-organ delivery was introduced in 2010 (10% of patients), rising to about 50% in 2011 and 2012. The highest use of intra-organ delivery in 2012 was for cardiovascular indications (57%) and Crohn's disease (52% of gastrointestinal [GI] indications), followed by neurological (48%) and musculoskeletal/rheumatological indications (39%).

Transplant rates and active teams

Reported cellular and engineered tissue therapies were performed in a limited number of countries and with a different intensity. Figure 4 displays the reported transplants per 10 million inhabitants in the different European and EBMT-associated countries. High transplant rates (i.e., >100 per 10 million population) were reported in the Netherlands and Slovenia. 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 (Fig. 5). The number of reporting teams per 10 million inhabitants was higher than four in Austria, Belgium, The Netherlands, Slovenia, and Switzerland. Interestingly, the top 10 countries (out of 27 total) accounted for 86% of all patients treated.

Discussion

The data collected in this fifth edition of the cellular and engineered tissue therapy survey indicate a further increase in the number of reporting teams (+27%) and of total

Table 3. Number of Reported Cellular and Engineered Tissue Therapy Treatments in Europe in 2012 Sorted by Delivery Mode

	Cell delivery mode			
Indications	*Intravenous*	*Intra-organ*	*Membrane/gel*	*3D scaffold*
Cardiovascular				
Peripheral artery disease	28	29	7	46
Cardiomyopathy	6	51		
Heart failure	5	87		
Myocardial ischemia	31	44		
Bypass graft		6		
Decubitus + leg ulcers		90	105	
Musculoskeletal/rheumatological				
Bone repair (maxillofacial)			17	7
Bone repair (orthopaedics)		2	3	16
Osteogenesis imperfecta	1			12
Cartilage repair (orthopaedics)		114	115	289
Muscle repair		8		
Reconstructive surgery/tissue enhancement		172		3
Scleroderma	11	4		
Arthritis		5		3
Other	1			
Neurological				
Multiple sclerosis	18	7		
Amyotrophic lateral sclerosis	9	16		
Parkinson's		1		
Peripheral nerve regeneration (trauma)		1	2	
Other	6	7		
Gastrointestinal				
Crohn's disease	6	11		
Liver insufficiency	4			
Hematology/oncology				
GvHD prevention or treatment	377			
HSC graft enhancement	33			
Miscellaneous				
Skin reconstruction	3		65	18
Cornea repair			4	
Diabetes	3	18		
Solid tumor	66	76		
Other	67	14		7
Total	675	763	318	401

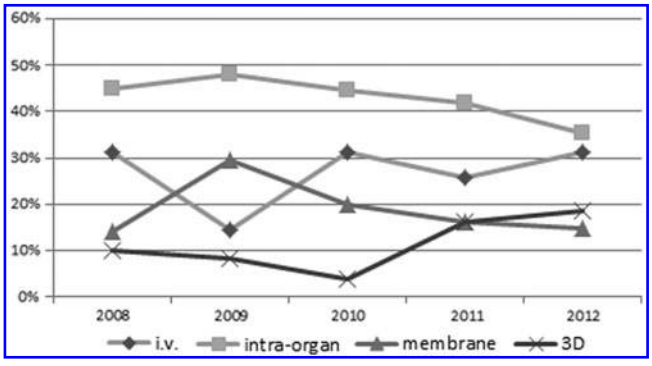

FIG. 3. Percentage comparison of cell delivery modes 2008 to 2012. Data used for this chart were derived from this study and the four previous reports.[3–6]

treatments reported (+23%) as compared with the previous year. Over the 5 years, the total number of reporting teams has more than doubled from 143 in 2008 to 313 in 2012, with the number reporting full data rising fourfold from 33 in 2008 to 138 in 2012 (Fig. 6). At the same time, the total number of patients treated has risen from 1040 in 2008 to 2159 in 2012.

These results indicate that, thanks to the networks of the involved societies, the follow up of teams who have previously reported, and the strategy of head-hunting for known active teams, the program is receiving a growing recognition as a reference platform for the collection and dissemination of information that is not available in public databases or scientific publications. Moreover, analysis of data generated in the five surveys[3–6] allows the identification of some established features.

We have compared the results obtained for patients treated in 2011 and 2012 for specific indications and have found that the largest differences can be attributed in most cases to additional reporting teams or to one or two teams

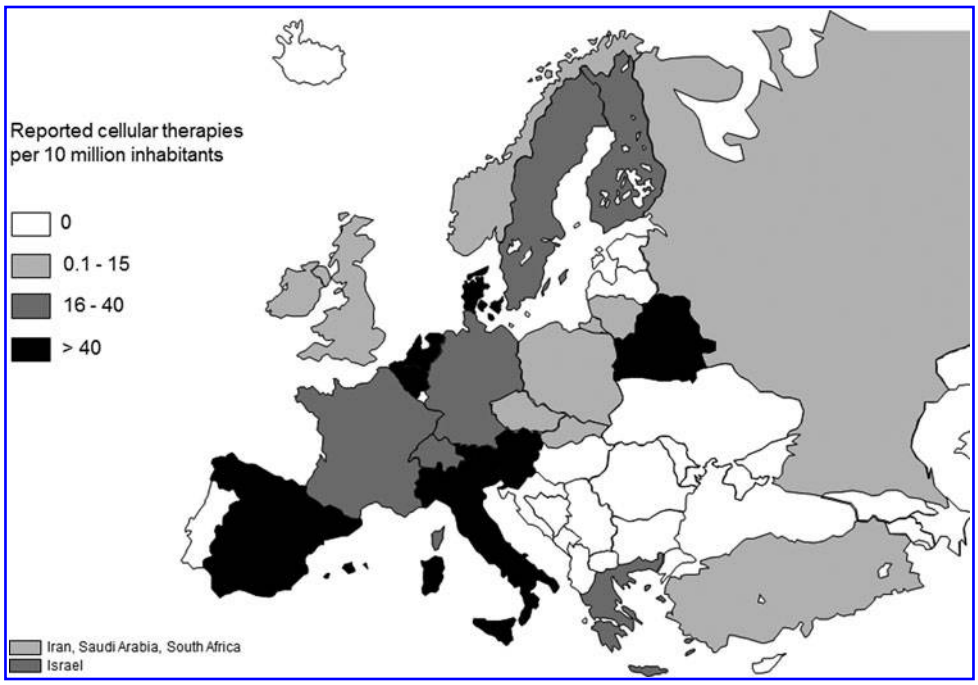

FIG. 4. Number of cellular and engineered tissue therapies per 10 million inhabitants reported in Europe in 2012.

reporting the treatment of a higher number of patients. For example, for solid tumors, there were two newly reporting teams who between them accounted for 89 patients and therefore for most of the increase (38 in 2011, 142 in 2012). Conversely, the increase in the number of patients treated for decubitus and leg ulcers (58 in 2011, 195 in 2012) as well as for heart failure (51 in 2011, 92 in 2012) was predominantly due to the increased activity of one or two teams. This consideration prompts for a degree of caution in the interpretation of developing trends, as the data are possibly affected by fluctuations and ''noise'' driven by a restricted number of teams.

The most used cell source in 2012 was MSC (1055 treatments), and the most represented indication for their use was GvHD prevention or treatment (360 patients). In the 4 years 2008–2011, the average number of patients treated for GvHD (268, range 240–298) was consistently one of the largest. Enthusiasm for the use of MSC for treating GvHD has been built on the evidence from phase II clinical trial data published by European collaborative groups in recent years.[7] This is despite the failure of a large, predominantly US-based multicenter phase III trial, examining the use of an industrial MSC product to treat acute GvHD, to meet the primary endpoint.[8–10] The product, Prochymal®, initially

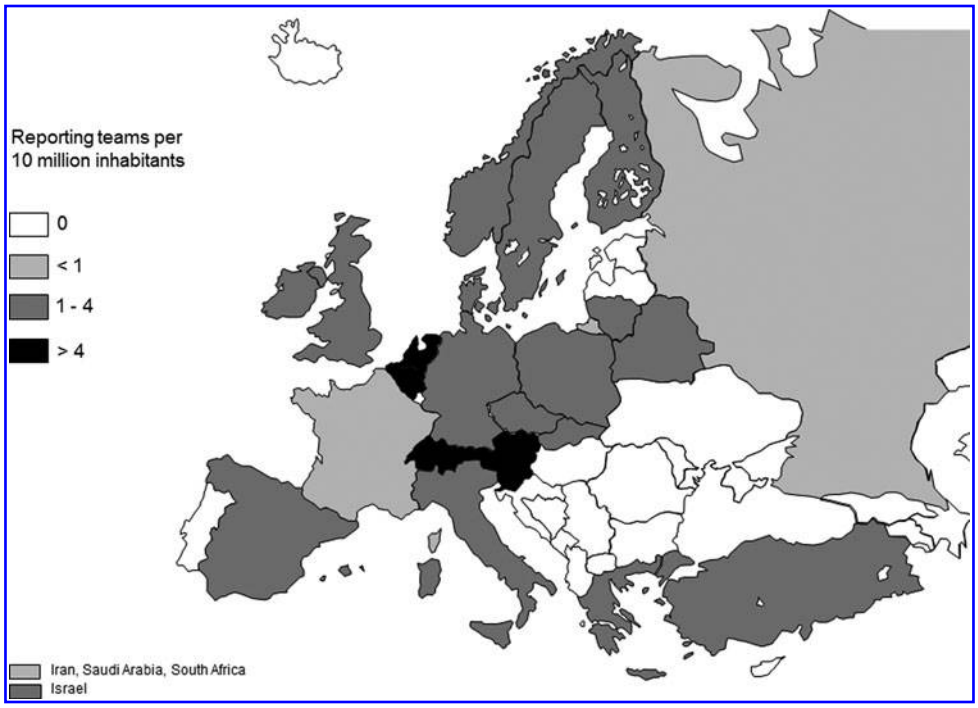

FIG. 5. Number of teams per 10 million inhabitants reporting cellular and engineered tissue therapies in Europe in 2012.

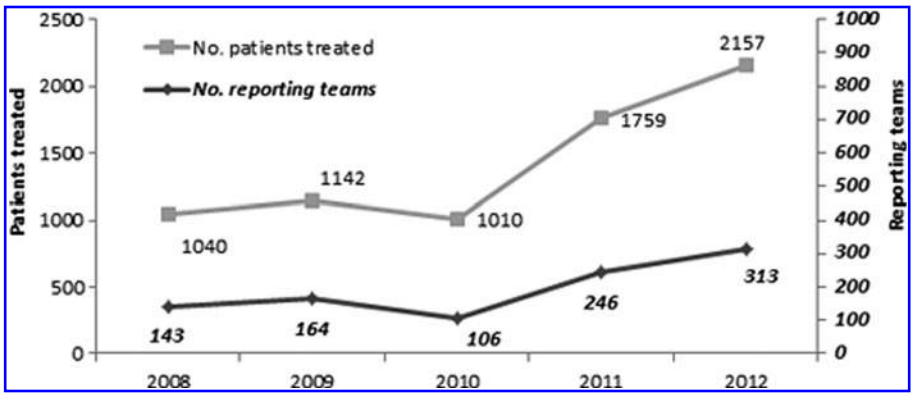

FIG. 6. Number of reporting teams and number of patients treated using cellular and engineered tissue therapies from 2008 to 2012. Data used for this chart were derived from this study and the four previous reports.[3–6]

owned by Osiris Therapeutics Inc. and acquired by the Mesoblast Group in October 2013,[11] is the world's first approved allogeneic stem cell therapeutic for the treatment of acute GvHD in children. According to a recent expert opinion article,[12] the negative trial results and availability of alternative therapies means that the product in its current form is unlikely to find widespread use in the treatment of acute GvHD. However, publication of the results of the Phase III study is needed to provide clarity on the clinical activity and to derive any conclusion.

The apparent discrepancy between the European experience (MSC mainly manufactured by academic centers)[7] and that of the industry-sponsored study (industrial MSC) is discussed by Galipeau[13] and could be explained by variance in donor characteristics, responsiveness to interferon-γ activation, the scale of cellular product expansion, inducible immunogenicity of the cells, and/or changes after cryopreservation. Indeed, interest in the area remains high and several clinical trials in Europe are ongoing.[12] A search on clinicaltrials.gov for open studies on GvHD and MSC in European Centers yielded three phase I trials, five phase II trials, and a double-blind placebo-controlled randomized phase III trial comparing steroids and MSC as first-line therapy against steroids alone.[14] The results of the current survey reflect the continuing clinical activity of participating centers, distributed throughout Europe.

In 2008 and 2009, all skin reconstruction treatments were performed using keratinocytes (36 patients in 2008, 51 in 2009). Dermal fibroblasts were introduced in 2010 as an alternative cell source for this indication (50 out of 104 patients), followed in 2011 by MSC (29 out of 96 patients although only 3 out of 86 patients in 2012). The identified trends are consistent with the developing scientific literature. In fact, it is increasingly recognized that both fibroblasts and keratinocytes have a role in healing chronic wounds,[15,16] and that tissue-engineered skin with superficial fibroblasts and keratinocytes holds promise for the treatment of patients with basement membrane disorders and other skin blistering diseases.[17] A review focusing on the benefits of MSC in skin wound healing and tissue regeneration indicated a possible contribution of MSC to reconstituting skin in cutaneous wounds.[18] Although the mechanism of action is far from being understood, the reported clinical activity reflects the possible trophic role by MSC in skin wound closure by affecting both dermal fibroblast and keratinocyte migration, along with a contribution to the deposition of extracellular matrix.[19]

The number of patients treated for solid tumor rose from 38 in 2011 to 142 in 2012. The primary source of cells in both years was ''other'' (28 in 2011 and 100 in 2012). A review of the results of a search on clinicaltrials.gov for nondrug treatments for solid tumors shows a current interest in the use of dendritic cells.[20,21] These two trials, taking place in Belgium and Spain, correspond to the locations of the most active reporting groups for this indication. We would, therefore, assume that the ''other'' is likely to be dendritic cells and that the increase in patient numbers relates to current trials. We expect to confirm this assumption in the next survey edition, as the form for patients treated in 2013 was revised to include dendritic cells as a specific cell source.

Throughout the 5-year period of the survey, the use of cells for cartilage repair has displayed a number of developing trends. Despite some yearly fluctuations, the introduction of MSC along with chondrocytes is being consolidated, as 54% of the total treatments in 2012 used MSC. The data are consistent with ongoing clinical studies, including the injection of autologous adipose-derived MSC in patients with moderate or severe osteoarthritis of the knee.[22] It is also worth highlighting that in 2012 we received the first reports of transduced cells being used for cartilage repair (23%). Based on the available literature,[23,24] these treatments are likely to be targeting degenerative as opposed to traumatic cartilage pathologies. Finally, while all reported cartilage repair treatments in 2011 used autologous cells, in 2012, 20% of MSC (57 of 281 patients) and 30% of chondrocytes (72 of 237 patients) were from allogeneic sources. The trend may be a direct consequence of previous studies indicating safety and feasibility of allogeneic cells for cartilage lesions[25] and reflect ongoing clinical trials.[26,27]

The earlier assessments for a few representative indications confirm that cellular and engineered tissue therapies, outside the field of hematological malignancies, are still in their infancy and predominantly embedded in the context of clinical trials. Challenges for the routine clinical translation of laboratory investigations, beyond the initial assessment of safety, are of a different nature. From a scientific standpoint, in most cases there is still a limited understanding of the biological processes initiated by implanted cells or engineered tissues and of their mechanisms of therapeutic function. This knowledge is critical to derive predictive

assays of potency, which is, in turn, necessary to define relevant in-process controls and release criteria to guarantee repeatable quality of the graft.[28,29] From an engineering and economic perspective, an increased robustness in manufacturing, cost-effectiveness for the service provider and sustainability for the healthcare system will likely require an introduction of technological innovations to automate and streamline production processes.[30] From a clinical and regulatory standpoint, the organization of multicenter trials will be important to increase the level of evidence for clinical effectiveness. To this end, the fact that within Europe different national organs are in charge to implement Good Manufacturing Practice (GMP) guidelines or to approve clinical trials adds to the intrinsic complexity of the strict framework in the field of Advanced Therapy Medicinal Products (ATMP).[29] In all these regards, analyses of trends in cellular and engineered tissue therapies, based on an early and open communication of patient treatments, will be critical to guide future initiatives and coordinate efforts of the different working parties.

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Disclosure Statement

No competing financial interests exist.

References

1. Birchall, M.A., and Seifalian, A.M. Tissue engineering's green shoots of disruptive innovation. Lancet **384,** 288, 2014.
2. Pirnay, J.-P., Vanderkelen, A., de Vos, D., Draye, J.-P., Rose, T., Ceulemans, C., Ectors, N., Hays, I., Jennes, S., and Verbeken, G. Business oriented EU human cell and tissue product legislation will adversely impact Member States' health care systems. Cell Tissue Bank **14,** 525, 2013.
3. Martin, I., Baldomero, H., Tyndall, A., Niederwieser, D., and Gratwohl, A. A survey on cellular and engineered tissue therapies in Europe in 2008. Tissue Eng Part A **16,** 2419, 2010.
4. Martin, I., Baldomero, H., Bocelli-Tyndall, C., Slaper-Cortenbach, I., Passweg, J., and Tyndall, A. The survey on cellular and engineered tissue therapies in Europe in 2009. Tissue Eng Part A **17,** 2221, 2011.
5. Martin, I., Baldomero, H., Bocelli-Tyndall, C., Passweg, J., Saris, D., and Tyndall, A. The survey on cellular and engineered tissue therapies in Europe in 2010. Tissue Eng Part A **18,** 2268, 2012.
6. Martin, I., Baldomero, H., Bocelli-Tyndall, C., Emmert, M.Y., Hoerstrup, S.P., Ireland, H., Passweg, J., and Tyndall, A. The survey on cellular and engineered tissue therapies in Europe in 2011. Tissue Eng Part A **20,** 842, 2014.
7. Lin, Y., and Hogan, W.J. Clinical application of mesenchymal stem cells in the treatment and prevention of graft-versus-host disease. Adv Hematol **2011,** 427863, 2011.
8. Osiris Press Release via Business Wire. Osiris Therapeutics announces preliminary results for Prochymal® phase III GvHD trials. 8 September 2014.
9. TrialsUnited.com. Efficacy and safety of adult human mesenchymal stem cells to treat steroid refractory acute graft versus host disease. ClinicalTrials.gov Identifier: NCT00366145, 2013.
10. US National Institutes of Health. Efficacy and safety of adult human mesenchymal stem cells to treat steroid refractory acute graft versus host disease. ClinicalTrials.gov Identifier: NCT00366145, 2011.
11. Mesoblast Ltd. News Release, Reported via Globe Newswire. Mesoblast acquires Osiris' culture expanded stem cell therapeutic business. 10 October 2013.
12. Chen, G.L., Paplham, P., and McCarthy, P.L. Remestemcel-L for acute graft-versus-host disease therapy. Expert Opin Biol Ther **14,** 261, 2014.
13. Galipeau, J. The mesenchymal stromal cells dilemma—does a negative phase III trial of random donor mesenchymal stromal cells in steroid-resistant graft-versus-host disease represent a death knell or a bump in the road? Cytotherapy **15,** 2, 2013.
14. HOVON Studies SCT. Stem cell transplantation and cellular therapies. HOVON 112 MSC, 2013.
15. Werner, S., Krieg, T., and Smola, H. Keratinocyte–fibroblast interactions in wound healing. J Invest Dermatol **127,** 998, 2007.
16. Wojtowicz, A.M., Oliveira, S., Carlson, M.W., Zawadzka, A., Rousseau, C.F., and Baksh, D. The importance of both fibroblasts and keratinocytes in a bilayered living cellular construct used in wound healing. Wound Repair Regen **22,** 246, 2014.
17. Varkey, M., Ding, J., and Tredget, E.E. Superficial dermal fibroblasts enhance basement membrane and epidermal barrier formation in tissue-engineered skin: implications for treatment of skin basement membrane disorders. Tissue Eng Part A **20,** 540, 2014.
18. Fu, X., and Li, H. Mesenchymal stem cells and skin wound repair and regeneration: possibilities and questions. Cell Tissue Res **335,** 317, 2009.
19. Walter, M.N., Wright, K.T., Fuller, H.R., MacNeil, S., and Johnson, W.E. Mesenchymal stem cell-conditioned medium accelerates skin wound healing: an *in vitro* study of fibroblast and keratinocyte scratch assays. Exp Cell Res **316,** 1271, 2010.
20. US National Institutes of Health. Dendritic cell vaccination for patients with solid tumors. ClinicalTrials.gov Identifier: NCT01291420, 2013.

21. US National Institutes of Health. Phase II study with hiltonol and dendritic cells in solid tumors. ClinicalTrials.gov Identifier: NCT01734564, 2013.
22. US National Institutes of Health. ADIPOA–clinical study. ClinicalTrials.gov Identifier: NCT01585857, 2014.
23. Madry, H., and Cucchiarini, M. Advances and challenges in gene-based approaches for osteoarthritis. J Gene Med **15,** 343, 2013.
24. Evans, C.H., Ghivizzani, S.C., and Robbins, P.D. Arthritis gene therapy and its tortuous path into the clinic. Transl Res **161,** 205, 2013.
25. Almqvist, K.F., Dhollander, A.A., Verdonk, P.C., Forsyth, R., Verdonk, R., and Verbruggen, G. Treatment of cartilage defects in the knee using alginate beads containing human mature allogeneic chondrocytes. Am J Sports Med **37,** 1920, 2009.
26. Evans, C.H., Kraus, V.B., and Setton, L.A. Progress in intra-articular therapy. Nat Rev Rheumatol **10,** 11, 2014.
27. US National Institutes of Health. Reparation of cartilage injuries in the human knee by implantation of fresh human allogeneic chondrocytes. ClinicalTrials.gov Identifier: NCT00263432, 2013.
28. European Medicines Agency. Guideline on human cell-based medicinal products EMEA/CHMP/410869/2006. www.ema.europa.eu/pdfs/human/cpwp/41086906enfin.pdf, 2008.
29. The Committee for Advanced Therapies (CAT) and the CAT Scientific Secretariat. Challenges with advanced therapy medicinal products and how to meet them. Nat Rev Drug Discov **9,** 195, 2010.
30. Martin, I., Simmons, P.J., and Williams, D.F. Manufacturing challenges in regenerative medicine. Sci Transl Med **6,** 232fs16, 2014.

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Appendix: List of Reporting Cellular Therapy/Tissue Engineering Centers in Europe in 2012

Format: City, Hospital, Department, CIC (EBMT teams), Physicians (Total treatments: allogeneic/autologous)

CIC = Center Identification Code (as used in the standard EBMT survey)

Austria

Krems, University Krems, Regenerative Medicine and Orthopedics, S. Nehrer (9: 9/0)

Linz, AO Krankenhaus, 3. Medizinische Abteilung, M.A. Fridrik, S. Hennerbichler (20: 4/16)

Vienna, Medical University Hospital, Traumatology, S. Marlovits, Ch. Albrecht (2: 0/2)

Vienna, Universitätsklinik für Innere Medizin-AKH, CIC 227, H. Greinix, P. Kalhs (1: 1/0)

Belarus

Minsk, Belorussian Center, CIC 591, O. Aleinikova (29: 24/5)

Minsk, Hospital No. 9, Belorussian Transplant Center, N. Milanovich (17: 2/15)

Belgium

Antwerp, Orthopaedic Center, Knee Surgery and Sports Traumatology, P. Verdonk (10: 10/0)

Antwerp, Stuivenberg ZH, CIC 339, P. Zachee (2: 2/0)

Antwerp, University Antwerpen, Hematology, CIC 996, W. Schroyens, Z. Berneman (42: 3/39)

Brussels, Clinique Universitaire St. Luc, CIC 234, X. Poiré, C. Vermylen (2: 2/0)

Brussels, Institut Jules Bordet, Children's Hospital, CIC 215, D. Bron, C. Devalck, A. Ferster (2: 0/2)

Brussels, Military Hospital Queen Astrid, Burn Wound Center, G. Verbeken (24: 23/1)

Brussels, U.L.B. Hôpital Erasme, Hematology, CIC 596, B. Bailly, A. Kentos, M. Lambermont (1: 0/1)

Leuven, University Hospital Gasthuisberg, CIC 209, J. Maertens, G. Verhoef, M. Renard (1: 1/0)

Liège, CHU Liège, Gastrology, E. Louis (1: 1/0)

Liège, CHU Liège, Surgery and Transplantation, M. Meurice (6: 6/0)

Liège, University Hospital Sart-Tilman, CIC 726, Y. Béguin, B. de Prijck (8: 8/0)

Czech Republic

Prague, Academy of Sciences, Institue of Experimental Medicine, Z. Kollarova (9: 0/9)

Denmark

Copenhagen, The Heart Center Rigshospitalet, Cardiac Catherization Lab., J. Kastrup (33: 0/33)

Finland

Helsinki, HUCH Jorvi Hospital, Orthopedics, Traumatology, T. Paatela (10: 0/10)

Kuopio, University Hospital, Orthopedics, Traumatology and Hand Surgery, A. Joukainen (1: 0/1)

France

Grenoble, CHU de Grenoble, Pathology, Neurovascular, O. Detante, A. Moisan (2: 0/2)

Grenoble, CHU Grenoble, Hôpital A. Michallon, Hematology, Oncology, CIC 270, J.Y. Cahn, P. Drillat, C.E. Bulabois (9: 3/6)

Marseille, Arthosport Center, Knee Institute, M. Assor (120: 0/120)

Paris, Hôpital St. Antoine, CIC 775, N.C. Gorin, L. Fouillard (1: 1/0)

Paris, Hôpital St. Louis, Cell Therapy Unit, J. Larghero (40: 7/33)

Germany

Chemnitz, Klinikum Chemnitz GmbH, Innere Medizin Lll, CIC 104, M. Hänel, A. Morgner (2: 2/0)

Dinslaken, St. Vinzenz Hospital, Unfall und Orthopädie, W. Zinser (61: 0/61)

Dresden, Universitätsklinikum Carl Gustav Carus, CIC 808, G. Ehninger, M. Bornhäuser, M. Gahr (31: 31/0)

Essen, Universitätsklinikum, KMT Klinik, CIC 2591, D.W. Beelen (2: 2/0)

Frankfurt, J. W. Goethe Universität, Kinderheilkunde lll, CIC 138, T. Klingebiel, P. Bader (5: 5/0)

Frankfurt, Klinikum Frankfurt Oder, Innere Medizin, CIC 190, M. Kiehl (12: 11/1)

Halle, Clinic Bergmannstrost, Neurosurgery, H.J. Meisel (8: 0/8)

Hannover, Medizinische Hochschule, Hematology, Oncology, CIC 295, A. Ganser, J. Krauter (3: 0/3)

Hannover, Medizinische Hochschule, Pediatric Hematology and Oncology, CIC 295, C. Kratz, K.W. Sykora (2: 2/0)

Munich, Klinikum Rechts der Isar, lll. Med Klinik, CIC 558, C. Peschel, M. Verbeek (1: 1/0)

Regensburg, Universitätsklinikum, Hematology, Oncology, CIC 787, R. Andreesen, S. Corbacioglu (1: 1/0)

Tübingen, Universitätsklinikum, Pediatrics, CIC 535, R. Handgretinger, P. Lang (9: 8/1)

Würzburg, Universitätsklinikum, Pediatric Hematology and Oncology, CIC 196, P. Schlegel (3: 3/0)

Greece

Athens, Academy of Athens, Hellenic Cord Blood Bank, A. Papassavas, C. Stavropoulos-Giokas (18: 0/18)

Athens, Aghia Sophia Children's Hospital, Pediatrics, CIC 752, S. Graphakos (2: 2/0)

Thessaloniki, Sports Clinic, E.T. Papacostas (2: 0/2)

Iran, Islamic Rep.

Shiraz, Nemazee Hospital, CIC 188, M. Ramzi (9: 0/9)

Teheran, Shariati Hospital, Hematology, Oncology, CIC 633, A. Ghavamzadeh, M. Jahani (3: 3/0)

Ireland

Galway, University College Hospital, Hematology, CIC 408, A. Hayat (2: 0/2)

Israel

Jerusalem, Hadassah University Hospital, CIC 258, R. Or, S. Slavin (18: 18/0)

Petach-Tikva, Beilinson Hospital, Adult Hematology, CIC 409, M. Yeshurun (1: 1/0)

Petach-Tikva, Children's Medical Center, Pediatrics, CIC 755, J. Stein (1: 1/0)

Italy

Bergamo, Ospedale Riuniti, CIC 658, A. Rambaldi (6: 6/0)

Bologna, Hospital St. Orsola, Inst. Hematology, CIC 240, G. Bandini, M. Baccarani, F. Bonifazi (3: 0/3)

Bologna, 6th div, Istituto Ortopedico Rizzoli (IOR), RIT-Cell Factory, L. Roseti (17: 0/17)

Bologna, Istituto Ortopedico Rizzoli (IOR), Orthopedic Pathology, Osteoarticular TR, D. Donati (14: 0/14)

Bolzano, Ospedale S. Maurizio, CIC 299, S. Cortelazzo, M. Casini, I. Cavattoni (2: 2/0)

Florence, Policlinico di Careggi, CIC 304, A. Bosi, S. Guidi (4: 1/3)

Genoa, Istituto Giannina Gaslini, Hematology, Oncology, CIC 274, G. Dini, E. Lanino (1: 1/0)

Milan, OASI Bio-research Foundation, Orthopedic Arthroscopic Surgery International, A. Gobbi, D. Lad (6: 0/6)

Milan, University of Milan IRCCS, CIC 265, A. Cortelezzi, E. Tagliaferri (1: 1/0)

Monza, L'Università di Milano-Bicocca, Ospedale San Gerardo del Tintori, CIC 544, E. Pogliani, P. Pioltelli, M. Parma (3: 2/1)

Monza, Ospedale San Gerardo, CTMO-Clinica Pediatrica, CIC 279, A. Rovelli (7: 7/0)

Padua, Centro Leucemie Infantili, CIC 285, C. Messina, M. Pillon, E. Calore (2: 2/0)

Pavia, Policlinico IRCCS St. Matteo, Pediatrics, CIC 557, M. Zecca (4: 4/0)

Piemonte, Ospedale degli infermi di Biella, Orthopedics, A. Siclari (52: 52/0)

Rome, Università ''La Sapienza,'' Plastic Surgery, A. Conversi, N. Scuderi (27: 0/27)

Rome, Università degli Studi di Roma ''Tor Vergata,'' Reconstructive Surgery, V. Cervelli, D.J. Bottini, B. De Angelis (425: 0/425)

Lithuania

Vilnius, University Children's Hospital, Hematology, Oncology, CIC 508, J. Rascon (3: 2/1)

Netherlands

Amsterdam, University Medical Center VUMC, Orthopedic Surgery, M. Helder (5: 0/5)

Amsterdam, VU Medical Center, Dermatology, S. Gibbs (13: 0/13)

Amsterdam, VU University Medical Center, Pediatric Hematology and Oncology, CIC 588, E. Meijer, G.J. Ossenkoppele (3: 3/0)

Groningen, University Hospital, Hematology, CIC 546, G. van Imhoff (8: 8/0)

Leiden, University Hospital, CIC 203, J.H. Veelken, M. Egeler (63: 13/50)

Utrecht, UMC, Orthopedic Surgery, D. Saris (58: 58/0)

Utrecht, UMCU/WKZ, Pediatrics, CIC 2392, M. Bierings, N.M. Wullffraat (6: 6/0)

Utrecht, University Hospital UMCU, CIC 239, E. Petersen (47: 47/0)

Norway

Oslo, Rikshospitalet-Radiumhospitalet, G. Lauritzen, S. Kvaloy (1: 0/1)

Poland

Bydgoszcz, Nicolaus Copernicus University, Pediatrics, CIC 764, M. Wysocki, J. Styczynski, R. Debski (10: 0/10)

Cracow, University Children's Hospital JUMC, CIC 507, J. Gozdzik (1: 1/0)

Katowice, Regional Blood Center, Tissue Bank Department, A. Wysocka-Wycisk (21: 0/21)

Warsaw, Carolina Medical Center, R. Smigielski, Z. Pojda (2: 0/2)*

Warsaw, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, S. Mazur, Z. Pojda (28: 0/28)*

Wroclaw, University of Medicine, Pediatrics, CIC 817, A. Chybicka, J. Owoc-Lempach (3: 3/0)

Russian Federation

Moscow, Federal Research Center, Pediatric Hematology, CIC 694, A. Maschan, D. Balachov (7: 7/0)

Moscow, Research Hematology Center of RAS, CIC 930, V.G. Savtchenko (21: 21/0)

Moscow, The Russian Children's Research Hospital, CIC 411, E. Skorobogatova (3: 3/0)

Novosibirsk, Research Institute for Clinical Immunology, CIC 376, V. Sergeevuicheva (5: 2/3)

St. Petersburg, Pavlov Medical University, Hematology, CIC 725, B.V. Afanasyev, L. Zubarovskaya (32: 5/27)

St. Petersburg, Research Institute of Hematology, Hematology, K.M. Abdulkadirov (9: 0/9)

Saudi Arabia

Riyadh, King Faisal Specialist Hospital, Hematology, Oncology, CIC 397, M. Al Jurf (1: 0/1)

Slovak Republic

Bratislava, 2nd. Children's Clinic, University Hospital, CIC 684, J. Horàkovà, S. Sufliarska, I. Bodova (1: 1/0)

Slovenia

Ljublijana, Educell d.o.o, N. Kregar-Velikonja (9: 0/9)

Ljublijana, UMC Ljubljana, Cardiology, B. Vrtovec (78: 0/78)

Ljublijana, University Medical Center, Hematology, CIC 640, S. Zver, J. Pretnar (39: 0/39)

South Africa

Cape Town, Constantiaberg Medical Clinic, Hematology, CIC 772, A. Abayomi, M. Du Toit (13: 13/0)

Spain

Barcelona, Institut de Teàpia Regenerativa Tissular, F. Soler, C.M. Teknon (92: 0/92)

Barcelona, University Hospital Dexeus, J. Monllau (7: 7/0)

Cordoba, Hospital Reina Sofia, Hematology, CIC 238, A. Torres-Gomez (30: 0/30)

Granada, Hospital Virgen de la Nieves, Hematology, CIC 559, J.M. De Pablos Gallego, M. Jurado Chacon (2: 2/0)

Madrid, Hospital de la Princesa, Hematology, CIC 236, A. Figuera, A. Alegre (2: 1/1)

Madrid, Hospital General La Paz, CIC 734, R. Arrieta (1: 0/1)

Madrid, Hospital General Universitario Gregorio Marañón, Materno Infantil, Oncology, CIC 410, C. Belendez (1: 0/1)

Madrid, Hospital Universitario Puerta de Hierro, CIC 728, J.R. Cabrera Martin (8: 8/0)

Madrid, Hospital Universitario San Carlos, Hematology, J. Diaz-Mediavilla, L. Llorente, R. Martinez (3: 0/3)

Malaga, Carlos Haya Hospital, Hematology, CIC 576, M. Gonzalez, M. Pascual (13: 13/0)

Murcia, Hospital Virgen de la Arrixaca, CIC 323, J.M. Moraleda (18: 2/16)

Palma de Mallorca, Hospital Universitari Son Espases (Son Dureta), CIC 722, J. Besalduch, M. Canaro (2: 0/2)

Pamplona, Clínica Universidad de Navarra, Cell Therapy Area, F. Prosper Cardoso (113: 5/108)

Pamplona, Clínica Universidad de Navarra, Hematology, CIC 737, J. Rifon (1: 1/0)

Pamplona, Hospital de Navarra, Hematology, CIC 577, E. Olavarria (4: 4/0)

Salamanca, Complejo Hospital, Hematology, CIC 727, D. Caballero (25: 18/7)

Seville, Hospital Universitario Virgen del Rocio, Hematology, CIC 769, I. Espigado, F. Marquez (2: 0/2)

Sweden

Stockholm, Karolinska University Hospital, Huddinge, CIC 212, P. Ljungman, O. Ringden (29: 24/5)

Stockholm, Sports Trauma Reseach Center, CapioArtroClinic AB, P. Wange, L. Ekström (3: 0/3)

Switzerland

Basel, Bruderholzspital, Orthobiologie und Knorpelersatz, M. Arnold (1: 0/1)

Basel, University Hospital, Traumatology, M. Jakob (3: 0/3)

Basel, University Hospital, Reconstructive Surgery, D. Schäfer (1: 0/1)

Geneva, Concept Clinic, K.-U. Schlaudraff (23: 23/0)

Lugano, Cardiocentro Ticino, Cardiology, D. Sürder (3: 2/1)

Turkey

Adana, Baskent University Adana, Hematology, CIC 589, H. Ozdogu, C. Boga, S. Asma, S. Yuce (2: 0/2)

Ankara, Ankara Research and Education Hospital, Hematology, CIC 423, F. Altuntas, M. Yüksel (8: 8/0)

Ankara, Gazi University, Besevler, Hematology, CIC 169, G. Sucak (1: 1/0)

Ankara, University of Ankara, Pediatrics, CIC 620, E. Unal, M. Ertem (4: 4/0)

Antalya, Akdeniz University Hospital, Pediatrics, CIC 618, M.A. Yesilipek, V. Hazar, A. Kupesiz (5: 5/0)

Antalya, Medical Park Hospitals, Hematology, Oncology, CIC 919, Y. Koc (9: 9/0)

Antalya, Medstar Antalya-Cakirlar Hospital, CIC 864, I. Karadogan (2: 2/0)

Gaziantep, Gaziantep University Medical School, Hematology, CIC 402, M. Pehlivan (2: 2/0)

Istanbul, Acibadem Kozyatagi Hospital, Hematology, S. Ratip (5: 5/0)

Istanbul, Cerrahpasa Medical School, CIC 761, B. Ferhanoglu, T. Soysal, M. Cem Ar (1: 1/0)

Istanbul, Medical Park Bahcelievler Hospital, Pediatrics, CIC 457, G. Öztürk, F. Erbey (8: 8/0)

Istanbul, Medical Park Goztepe Hospital, Pediatrics, CIC 929, G. Karasu, O. Dogru (6: 6/0)

Istanbul, University of Istanbul, Hematology, CIC 760, D. Sargin, S. Kalayoglu-Besisik (4: 4/0)

Izmir, Dokuz Eylul University, Pediatrics, Hematology, CIC 688, H. Özsan, H. Ören (1: 1/0)

* = Late report, not included in the analysis and tables

Izmir, Ege University, Bornova, Hematology, CIC 628, F. Vural, G. Saydam, N. Soyer (7: 0/7)

Samsun, Ondokuz Mayis University, Pediatrics, M. Elli (4: 4/0)

United Kingdom

Birmingham, The Birmingham Children's Hospital, Pediatrics, CIC 781, S. Lawson (4: 4/0)

Bristol, Royal Hospital for Sick Children, CIC 386, J.M. Cornish, D. Marks, C. Steward (6: 0/6)

London, Great Ormond Street Hospital, Pediatrics, CIC 243, P. Veys (1: 1/0)

London, Hammersmith Hospitals NHS Trust, CIC 205, J. Apperley, E. Olavarria, E. Kanfer, A. Rahemtulla, R. Szydlo (3: 3/0)

London, St Mary's Hospital, Pediatrics, CIC 866, J. de la Fuente (6: 6/0)

London, St. Bartholomew's and the Royal London Hospital, CIC 768, J. Gribben, J. Cavenagh, S. Agrawal, T. Lister (19: 19/0)

Manchester, School of Cancer and Enabling Sciences, CT Unit, R. Guest (2: 0/2)

Oswestry, Oswestry Orthopedic Hospital, P. Harrison (28: 0/28)

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Invited Submission

The Survey on Cellular and Engineered Tissue Therapies in Europe in 2011

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Following the coordinated efforts of five established scientific organizations, this report describes the "novel cellular therapy" activity (i.e., cellular treatments excluding hematopoietic stem cells [HSC] for the reconstitution of hematopoiesis) in Europe for the year 2011. Two hundred forty-six teams from 35 countries responded to the cellular therapy survey, 126 teams from 24 countries provided data on 1759 patients using a dedicated survey and 120 teams reported no activity. Indications were musculoskeletal/rheumatological disorders (46%; 99% autologous), cardiovascular disorders (22%; 100% autologous), hematology/oncology, predominantly including the prevention or treatment of graft-versus-host disease (18%; 2% autologous), neurological disorders (2%; 83% autologous), gastrointestinal (1%; 68% autologous), and other indications (12%; 77% autologous). Autologous cells were used predominantly for musculoskeletal/rheumatological (58%) and cardiovascular (27%) disorders, whereas allogeneic cells were used mainly for hematology/oncology (84%). The reported cell types were mesenchymal stem/stromal cells (56%), HSC (23%), chondrocytes (12%), dermal fibroblasts (3%), keratinocytes (2%), and others (4%). In 40% of the grafts, cells were delivered following *ex vivo* expansion, whereas cells were transduced or sorted, respectively, in 3% and 10% of the reported cases. Cells were delivered intraorgan (42%), intravenously (26%), on a membrane or gel (16%), or using 3D scaffolds (16%). Compared to last year, the number of teams participating in the dedicated survey doubled and, for the first time, all European Group for Blood and Marrow Transplantation teams reporting information on cellular therapies completed the extended questionnaire. The data are compared with those collected since 2008 to identify trends in the field. This year's edition specifically focuses on cardiac cell therapy.

Introduction

The clinical use of the so-called "novel cellular therapies," namely those not aimed at the reconstitution of the hematopoietic system, is not only a challenging target for the scientific community, but also the subject of intense public debate.[1,2] The landscape includes not only the scientific and clinical community together with the patients, their families, and the lay public, but also health regulators, national health services/health insurance companies, and service providers. Despite the direct interest by a broad set of involved parties, transparent access to accurate data on clinical use of cell therapies is extremely limited and confined within specific sectors.

In 2008, the European sections of the Tissue Engineering and Regenerative Medicine International Society-Europe (TERMIS-EU), of the International Society of Cellular Therapy (ISCT), and of the International Cartilage Repair Society (ICRS), in a joint initiative with the European group for Blood and Marrow Transplantation (EBMT) and the European League Against Rheumatism (EULAR), established a survey on novel cellular therapies. This has allowed the number of patients treated in Europe with cells or engineered tissues to be collected and to be sorted by specific therapeutic indications, cell types used, and cell processing/delivery modes.[3–5] The survey aims to offer a transparent and unbiased update on the constructive work carried out, thanks to the coordinated efforts

For the Joint Survey Committee of the Tissue Engineering and Regenerative Medicine International Society (TERMIS)-Europe, the International Cartilage Repair Society (ICRS), the European League Against Rheumatism (EULAR), the International Society for Cellular Therapy (ISCT)-Europe, and the European Group for Blood and Marrow Transplantation (EBMT).
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[5]Swiss Center for Regenerative Medicine, Zurich, Switzerland.

of the different stakeholders, including scientists, clinicians, and their patients, in compliance with the required authorizations.

Here, we report the results of the fourth survey for the activity in 2011, with a comparison to the previously identified trends and a specific discussion on cell-based treatments in the field of cardiovascular therapy. The information presented is complementary to that available in published studies and public databases (e.g., www.clinicaltrials.gov), as it does not include safety/efficacy data and specifies the conducted as opposed to planned numbers of treatments.

Patients and Methods

Definitions

For the purpose of this survey, novel cellular therapies include the use of cells other than hematopoietic stem cells (HSC) or of HSC for uses other than reconstitution of the hematopoietic system. The term HSC, which is often ambiguously used in the field of novel cellular therapies, here indicates a mixture of stem and progenitor cells predominantly of the hematopoietic lineage. Donor lymphocyte infusions often used in relapsing patients after HSC transplantation are considered to be an integral part of the HSC transplant procedure and are excluded.

Data collection and validation

Participating teams were requested to report their data for 2011 by indication, cell type and source, donor type, processing method, and delivery mode. The survey followed the traditional principles of the EBMT, concentrating on numbers of patients with a first cellular therapy. EBMT teams from 49 countries (39 European and 10 affiliated countries) were contacted for the 2011 report (EBMT survey), as were members of the 4 participating societies, teams who had reported activity to previous surveys, together with 118 additional contacts identified either through the clinicaltrials.gov database or literature search. The non-European countries affiliated with the EBMT were Algeria, Azerbaijan, Iran, Israel, Jordan, Lebanon, Nigeria, Saudi Arabia, South Africa, and Tunisia. Extended questionnaires, in the format displayed in Supplementary Table S1 (Supplementary Data are available online at www.liebertpub.com/tea), were received in paper form or electronically. Quality control measures, for EBMT members only, included several established independent systems: confirmation of validity of the entered data by the reporting team, selective comparison of the survey data with MED-A data sets in the EBMT ProMISE data system, cross-checking with the National Registries, and onsite visits of selected teams. No quality control system could be applied to the non-EBMT reporting teams as yet.

For this survey, a number of changes in the data collection sheet were introduced (i) to better capture and group the disease indications and (ii) to distinguish between automated and manual cell processing. In the accompanying guidelines, automated cell processing was described as being appropriate when the cell isolation or culture was performed using an automated device.

Transplant rates

Transplant rates, defined as the reported numbers of patients receiving cellular therapies or 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 2011 US census office database (www.census.gov).

Results

Participating teams

Two hundred forty-six teams in 35 countries (29 European and 6 EBMT affiliated countries) responded to the novel cellular therapy survey, 126 teams (24 countries) reported performing novel cellular therapies providing detailed information on indication, cell source and type, donor type, processing, and delivery mode, whereas 120 teams reported no activity. In previous years, a number of teams have reported using the standard EBMT transplant activity survey sheet, allowing the inclusion of limited information. This year, for the first time, all EBMT teams reporting information on cellular therapies completed the extended questionnaire. Teams that responded to the activity are listed in Appendix in alphabetical order by country, city, EBMT CIC code (if applicable), along with the total numbers of reported novel cellular therapies.

Number of novel cellular therapies and disease indications

According to the received reports, 1759 patients were treated with novel cellular therapies, 373 (21%) with allogeneic, and 1386 (79%) with autologous cells (Table 1). Indications were musculoskeletal/rheumatological disorders (46%; 99% autologous), cardiovascular disorders (22%; 100% autologous), HSC graft enhancement/prevention or treatment of graft-versus-host disease (GvHD), herewith grouped using the term "hematology/oncology" (18%; 2% autologous), neurological disorders (2%; 83% autologous), gastrointestinal (1%; 68% autologous), and other indications (12%; 77% autologous).

Among the musculoskeletal/rheumatological disorders, the reconstructive surgery/tissue enhancement was the most frequently reported indication, followed by cartilage and bone repair. Among the cardiovascular disorders, myocardial ischemia and peripheral artery disease were the main reasons for a cellular therapy, followed by cardiomyopathy and heart failure. The number of patients treated for neurological and gastrointestinal indications was rather limited and mostly confined to multiple sclerosis (neurological) and Crohn's disease (gastrointestinal). Among the remaining indications, most patients were treated for skin reconstruction or for solid tumor (Table 1).

Cell type, source, and donor type

The reported cell types were mesenchymal stem/stromal cells (MSC) (56%), HSC (23%), chondrocytes (12%), dermal fibroblasts (3%), keratinocytes (2%), and others (4%). Of the 411 HSC treatments, 97% were autologous transplants and 74% of these were for cardiovascular diseases (Table 1). All 214 chondrocyte and 49 dermal fibroblast transplants were autologous, whereas all 31 keratinocytes transplants were allogeneic. From 979 MSC-based therapies, 67% were autologous. The donor type was associated with the disease

Table 1. Number of Reported Novel Cellular Therapy Treatments in Europe in 2011 Sorted by Indication, Cell Source, and Donor Type

	Cell type and source											
	Autologous					*Allogeneic*						
Indication	*HSC*	*MSC*	*Chondrocyte*	*Dermal fibroblast*	*Other*	*HSC*	*MSC*	*Keratinocyte*	*Other*	*Autologous*	*Allogeneic*	*Total*
Cardiovascular												
Peripheral artery disease	70	6								76	0	76
Cardiomyopathy	49	4								53	0	53
Heart failure	51									51	0	51
Myocardial ischemia	89	1			5					95	0	95
Bypass graft	9									9	0	9
Decubitus and leg ulcers		58								58	0	58
Other/unspecified	25	4			6					35	0	35
Musculoskeletal/rheumatological												
Bone repair (maxillofacial)	19	5								24	0	24
Bone repair (orthopaedics)	24	36								60	0	60
Osteogenesis imperfecta		2					2			2	2	4
Cartilage repair (orthopaedics)		40	207							247	0	247
Muscle repair	9									9	0	9
Tendon/ligament		8								8	0	8
Reconstructive surgery/tissue enhancement		382	7		3					392	0	392
Scleroderma	4	3								7	0	7
Arthritis		38								38	0	38
Other/unspecified		12		1						13	0	13
Neurological												
Multiple sclerosis	2	8				1	2			10	3	13
Parkinson's	1									1	0	1
Other/unspecified	19	4							4	23	4	27
Gastrointestinal												
Crohn's disease		13					2			13	2	15
Liver insufficiency							4			0	4	4
Hematology/oncology												
GvHD prevention or treatment						13	252			0	265	265
HSC graft enhancement	7	1					47			8	47	55
Miscellaneous												
Skin reconstruction		29		36	0			31		65	31	96
Cornea repair					4					4	0	4
Diabetes									4	0	4	4
Solid tumor	10				28					38	0	38
Other	9	5		12	21		11			47	11	58
Total	397	659	214	49	67	14	320	31	8	1386	373	1759

HSC, hematopoietic stem cells; MSC, mesenchymal stromal/stem cells; GvHD, graft-versus-host disease.

indication: autologous cells were used predominantly for musculoskeletal/rheumatological (58%) and cardiovascular (27%) disorders, whereas the main use of allogeneic cells was for hematology/oncology (84%) (Fig. 1). MSC were mainly obtained from adipose tissue (50%) or bone marrow (49%) and mostly used for the reconstructive surgery/tissue enhancement within the area of musculoskeletal/rheumatological disorders (54%) or for hematology/oncology (31%). For the HSC treatments, cells were derived from bone marrow (65%) or peripheral blood (35%).

The percentage of treatments using autologous versus allogeneic cells steadily increased from 36% in 2008 to 79% in

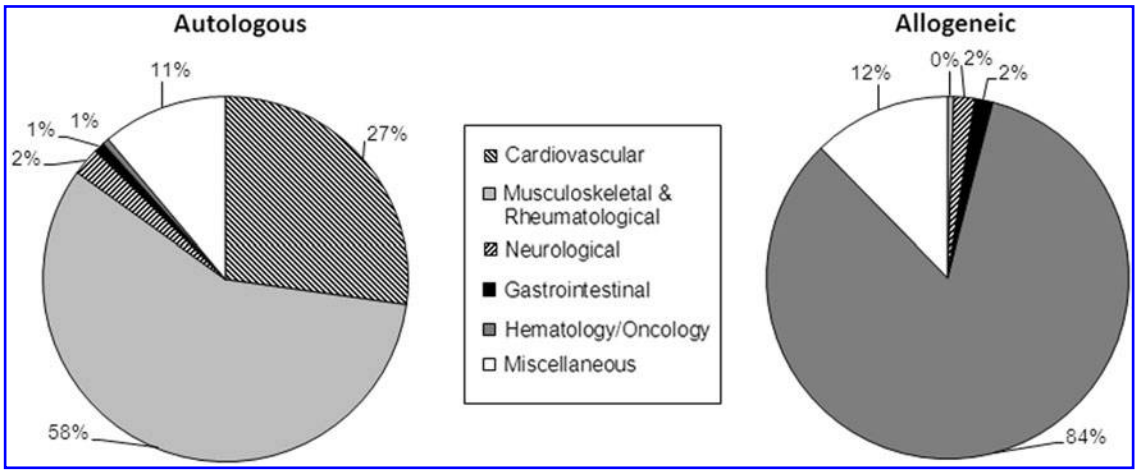

FIG. 1. Percentage of indications for novel cellular therapies in Europe in 2011, sorted by donor type.

2011. This was reflected in the trends for the various therapy areas, with the exception of hematology/oncology (Fig. 2).

Cell processing and delivery mode

Of all the grafted products, 65% required cell expansion, 3% were transduced cells, and 10% were sorted (Table 2). Nonexpanded cells were used to treat 95% of cardiovascular, 70% of musculoskeletal/rheumatological, and 63% of neurological indications, while gastrointestinal indications were exlusively treated with expanded cells. Expanded cells were also used for 97% of hematology/oncology treatments. Cell sorting was applied predominantly for musculoskeletal/rheumatological (10%) and cardiovascular (10%) disorders. Transplanted cells were genetically transduced for 58% of solid tumor cases, 21% of gastrointestinal (all liver insufficiency), and 6% of cardiovascular diseases. Twenty-four percent of cells were reported to be processed using an automated device. These cells were mostly used to treat cardiovascular (39%), musculoskeletal/rheumatological (25%), or gastrointestinal (21%) diseases.

Just under one half (42%) of the cell grafts was delivered intra-organ, 26% intravenously, 16% on a membrane or gel, and 16% using a 3D scaffold (Table 3). Cells were delivered intra-organ for 66% of cardiovascular, 58% of neurological, and 50% of musculoskeletal/rheumatological disorders. Intravenous delivery was reported for all hematology/oncology treatments and about half (47%) for gastrointestinal disorders. The use of a membrane or a gel for cell delivery was reported almost exclusively for musculoskeletal/rheumatological (33%) treatments. A 3D scaffold was used for musculoskeletal/rheumatological indications (16%), in particular for cartilage or bone repair (42%) and for cardiovascular (21%) disorders—within this mainly for decubitus and leg ulcers (74%).

Transplant rates and active teams

Reported cellular therapies were performed in a limited number of countries and with different intensity. Figure 3 displays the reported cellular therapy transplants per 10 million inhabitants in the different European- and EBMT-associated countries. High transplant rates (i.e., >100 per 10 million population) were reported in Italy and Slovenia. The number of teams reporting novel cellular therapies was also mapped in the different European- and EBMT-associated countries after normalization to the inhabitant numbers (Fig. 4). The number of reporting teams per 10 million inhabitants was higher than four in Belgium, Israel, The Netherlands, Slovenia, Spain, and Switzerland.

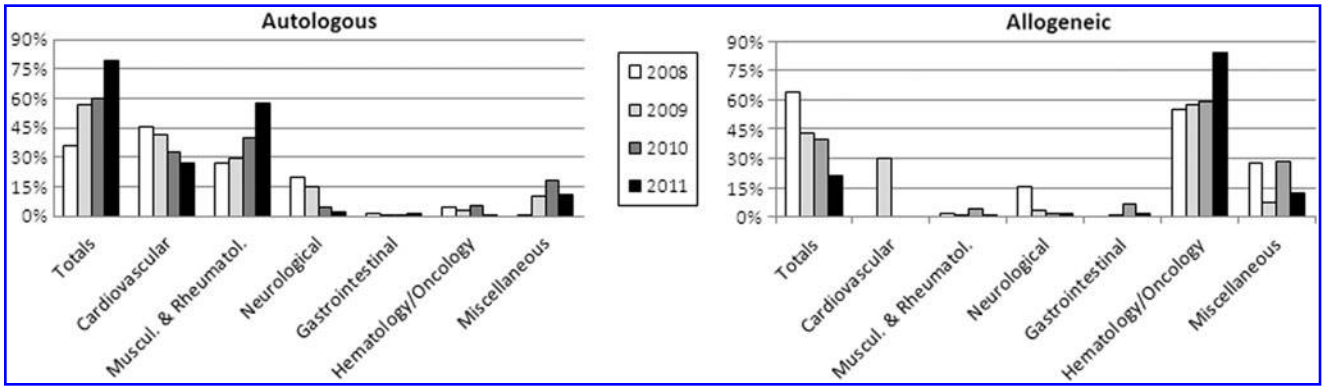

FIG. 2. Comparative analysis of indications for novel cellular therapies in Europe from 2008 to 2011, sorted by donor type. Data used for this chart were derived from the current study and the three previous reports.[3–5]

Table 2. Number of Reported Novel Cellular Therapy Treatments in Europe in 2011 Sorted by Cell Processing Mode

	Cell processing							
Indications	*Nonexpanded*	*Expanded*	*Untransduced*	*Transduced*	*Unsorted*	*Sorted*	*Automated*	*Manual*
Cardiovascular								
Peripheral artery disease	70	6	52	24	62	14	43	33
Cardiomyopathy	53		53		52	1	1	52
Heart failure	51		51		46	5	13	38
Myocardial ischemia	90	5	95		89	6	3	92
Bypass graft	9		9			9	9	
Valve replacement								
Decubitus + leg ulcers	58		58		58		58	
Other	29	6	35		31	4	20	15
Musculoskeletal/rheumatological								
Bone repair (maxillofacial)	24		24		24		5	19
Bone repair (orthopaedics)	51	9	60		51	9	31	29
Osteogenesis imperfecta		4	4		3	1	1	3
Cartilage repair (orthopaedics)	86	161	247		219	28	21	226
Muscle repair	9		9		9		9	
Tendon/ligament	8		8		8		8	
Reconstructive surgery/tissue enhancement	377	15	392		387	5	126	266
Scleroderma	4	3	7		4	3	1	6
Arthritis		38	38			38		38
Other		13	13		13			13
Neurological								
Multiple sclerosis	2	11	13		13		1	12
Parkinson's	1		1			1		1
Other	23	4	27		27			27
Gastrointestinal								
Crohn's disease		15	15		15		0	15
Liver insufficiency		4		4	4		4	
Hematology/oncology								
GvHD prevention or treatment	11	254	264	1	263	2	9	256
HSC graft enhancement		55	55		54	1		55
Miscellaneous								
Skin reconstruction	37	59	96		70	26	8	88
Cornea repair		4	4		4			4
Diabetes	4		4			4		4
Solid tumor	32	6	16	22	14	24	2	36
Other	21	37	58		58		9	49
Total	1050	709	1708	51	1578	181	382	1377

Discussion

The data collected in the fourth edition of the novel cellular therapy survey indicate a further increase compared to the previous year in the number of reporting teams (+19%), of total treatments reported (+39%), and of total treatments reported using the dedicated form (+74%). These results indicate that, thanks to the networks of the involved societies and the introduced strategy of head-hunting for known active teams, the program is receiving a growing recognition as a reference platform to collect and disseminate information that is not available in public databases or scientific publications. Moreover, the comparative analysis of data generated in the four surveys[3–5] allows the identification of some established features and developing trends.

The steady increase in the percentage of treatments using autologous versus allogeneic cells is possibly due to a combination of cultural, regulatory, and/or commercial issues. Due to the oft claimed "minimal manipulation" and "homologous use" of the cells, the use of nonexpanded autologous MSC for reconstructive surgery/tissue enhancement is considered by some as "tissue transplantation" rather than "biological drug," and therefore not subject to the same rigorous regulatory framework as are expanded MSC. This distinction may become somewhat artificial, as shown recently in the Celltex case.[6] The number of treatments for GvHD prevention or treatment remained relatively stable throughout the 4 years (from 240 in 2008 to 265 in 2011), possibly due to the combination of increasing encouraging phase I/II data,[7] but there is a lack of conclusive data from adequately powered, prospective randomized controlled (PRC) trials.

The most obvious changes in the indications addressed were in the important introduction of nonexpanded MSC (predominantly freshly harvested from autologous adipose

Table 3. Number of Reported Novel Cellular Therapy Treatments in Europe in 2011 Sorted by Delivery Mode

Indications	*Cell delivery mode*			
	Intravenous	*Intra-organ*	*Membrane/gel*	*3D scaffold*
Cardiovascular				
Peripheral artery disease	7	69		
Cardiomyopathy	1	52		
Heart failure	20	31		
Myocardial ischemia	11	84		
Decubitus + leg ulcers				58
Other	10	5		20
Musculoskeletal/rheumatological				
Bone repair (maxillofacial)				24
Bone repair (orthopaedics)	14	34		12
Osteogenesis imperfecta		2		2
Cartilage repair (orthopaedics)		47	120	80
Muscle repair		9		
Tendon/ligament			8	
Reconstructive surgery/tissue enhancement		268	118	6
Scleroderma	3		3	1
Arthritis		38		
Other			13	
Neurological				
Multiple sclerosis	13			
Parkinson's		1		
Peripheral nerve regeneration (trauma)				
Other	4	23		
Gastrointestinal				
Crohn's disease	7	8		
Liver insufficiency	3	1		
Hematology/oncology				
GvHD prevention or treatment	265			
HSC graft enhancement	55			
Miscellaneous				
Skin reconstruction		29		67
Cornea repair			4	
Diabetes		4		
Solid tumor	14	24		
Other	25		21	12
Total	452	729	287	282

3D, three-dimensional.

tissue) for plastic and reconstructive surgery, as well as for decubitus and leg ulcers (total of 440 treatments). In this regard, evidence of efficacy is still limited to case reports and small series at this stage.[8,9] It is thus vital that PRC clinical trials are carried out in the next years to demonstrate a statistical superiority of outcome for the cell-based versus cell-free treatments. The trend in the cell delivery mode was rather stable: the exception is of a fourfold increase in the percentage of use of 3D scaffolds, mostly associated with cartilage/bone repair treatments, skin reconstruction, and ulcers.

This year, for the first time, the data collection for cell processing included a query of whether cell graft manufacturing included a step performed with an automated system. Although the definition of "automation" could be interpreted differently by the responding teams, and respondents did not specify whether the system was closed or streamlined with the rest of the manufacturing line, it is nonetheless remarkable that 22% of the total treatments were claimed to involve an automated process. A closer analysis of the associated cell sources indicates that an automated device was introduced predominantly for the direct implantation of freshly harvested, autologous cells. The collected data are consistent with the commercial availability of systems for the device-assisted isolation or concentration of HSC (e.g., Sepax; Biosafe SA, www.biosafe.ch), of adipose-derived cells (e.g., Celution®; Cytori, www.cytori.com) or of bone marrow-derived MSC (e.g., Reamer Irrigator Aspirator; Synthes, www.synthes.com).

This year's edition offers a perspective on cardiac cell therapy, in an attempt to complement the collected data with those available from other sources. Cardiovascular disease represents a leading disease worldwide associated with a high morbidity and mortality.[10] Current therapeutic options for patients suffering from heart failure due to myocardial infarction or other cardiomyopathies comprise medical treatment, ventricular assist devices, and heart transplantation. However, although heart transplantation has emerged as the standard of care and the only curative treatment for these patients, the key problem of organ shortage—while

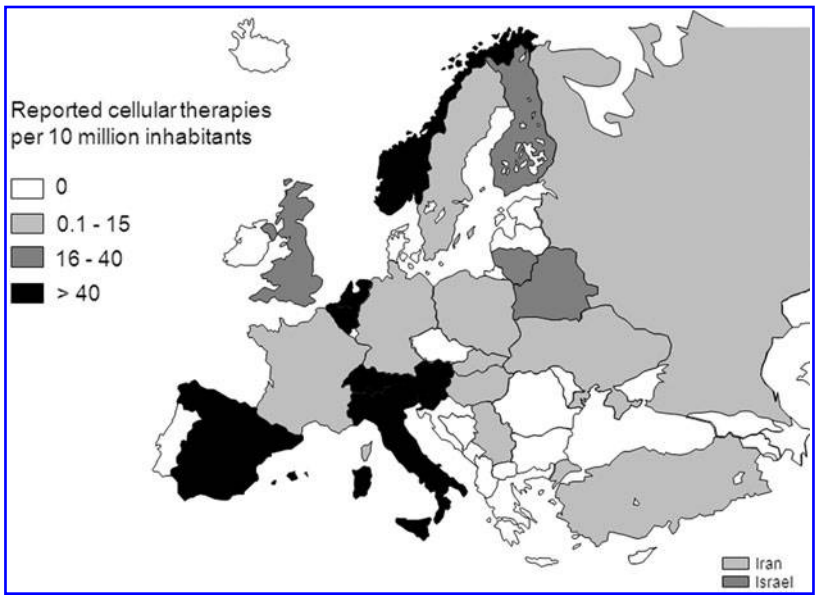

FIG. 3. Number of novel cellular therapies per 10 million inhabitants reported in Europe in 2011.

patient numbers continually rise—remains. In line with regenerative strategies in other medical fields, the concept of cardiac stem cell therapy has created substantial hope for the treatment of heart failure due to myocardial infarction and other cardiomyopathies.[11] Therefore, numerous experimental and preclinical animal studies have been performed in the past decade[12] utilizing a wide range of different adult stem cells. These include different subpopulations of bone marrow-derived progenitors, skeletal myoblasts, adipose-tissue derived MSC, prenatal progenitors, blood-derived progenitors as well as the recently discovered cardiac-resident stem cells.[13–19] In addition, embryonic stem cells or induced pluripotent cells have been shown to be able to differentiate into functional cardiomyocytes and are in the focus as a potential cell source.[20] Based on promising preclinical data, various cell types have already progressed into use in clinical pilot studies primarily aiming at demonstrating feasibility and safety in patients suffering from acute myocardial infarction, chronic heart disease/refractory angina, as well as ischemic cardiomyopathy.[18,21–25]

Bone marrow-derived progenitors represent the most frequently used cell source. Historically, Prof. Bodo Strauer from the University of Düsseldorf was, in 2001, the first to treat patients with acute myocardial infarction with intracoronary-infused bone marrow mononuclear cells (BMMC).[26] Based on this study, numerous cohort studies and randomized trials such as the BOOST study and the REPAIR-AMI trial have been performed, testing intracoronary infusion of bone marrow-derived progenitor cells for cardiac cell therapy.[21,25,27] While all study groups reported a sufficient safety profile for these cells, the results with regard to efficacy (i.e., improvement of ventricular function) are still under controversial discussion. A recent meta-analysis of 50 studies (with a total of 2625 patients) comprising mixed results of cohort studies and PRC trials demonstrated a significant, but still relatively limited (~4%)

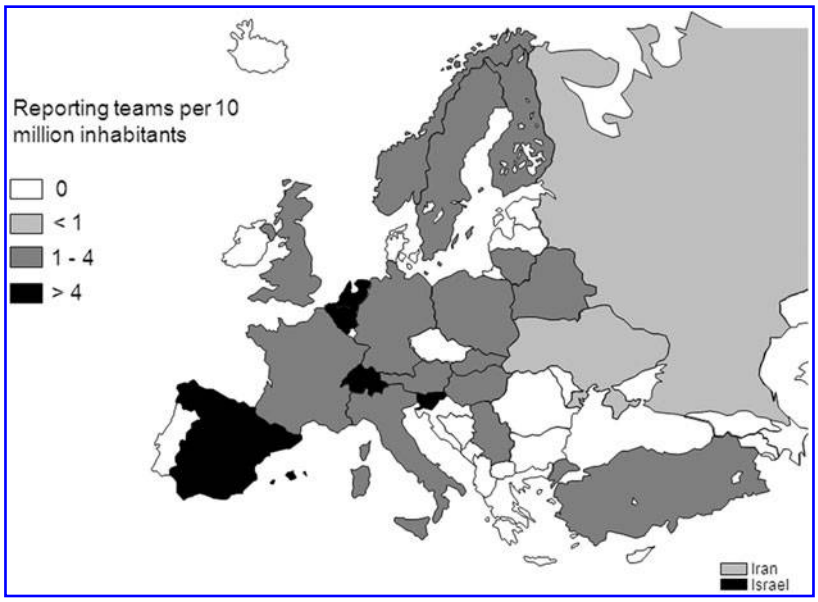

FIG. 4. Number of teams per 10 million inhabitants reporting novel cellular therapies in Europe in 2011.

improvement of left ventricular ejection fraction (LVEF) after BMMC therapy when compared to control patients.[28]

In line with the collected data (Table 1), the application of one subpopulation of BMMC, namely MSC, has been reported to be a valid and safe option for cardiac cell therapy. In contrast to BMMC, the use of MSC in smaller cohort studies has demonstrated a more pronounced effect on LVEF; this, however, needs to be confirmed in current PRC trials such as the TAC-HFT (TAC-HFT/ClinicalTrials.gov Identifier: NCT00768066). In parallel, the utilization of adipose tissue-derived MSC has been investigated in several preclinical studies and has lead to the initiation of first clinical trials such as the APOLLO study (APOLLO/ClinicalTrials.gov Identifier: NCT00442806).

An interesting concept to enhance the efficacy and the cardiogenic potential of bone marrow-derived MSC is the concomitant application of a cardiopoietic cocktail. This has been shown to be feasible in a preclinical study[29] and has recently led to a pilot clinical study, the C-Cure trial, where the safety and importantly beneficial effect of cardiopoietic MSC could be demonstrated (C-Cure/ClinicalTrials.gov Identifier: NCT00810238) and was the basis for a randomized multicenter trial to be initiated.

Besides the utilization of BMMC or subpopulations thereof, the use of skeletal myoblasts has also been proposed as a potential cell source for myocardial repair and has advanced into numerous clinical studies such as the MAGIC trial[30] and others (MYOHEART/ClinicalTrials.gov Identifier: NCT00054678). However, while preclinical and initial clinical data showed promising results, the major problem with these cells is the lack of electrical coupling with the hosting myocardium. Due to a lack of gap junctions and connexins, the skeletal myoblast therapy led to severe arrhythmia in some individuals and raised significant safety concerns. However, to ensure patient safety, systematic antiarrhythmic medical therapy or implantable cardioverter-defibrillator implantation represent valid tools to treat affected patients.[31]

Following the compelling evidence on the preclinical use of cardiac resident stem cells, two pilot clinical trials employing cardiac progenitors were recently initiated[22,24] (CADUCEUS/ClinicalTrials.gov Identifier: NCT00893360; SCIPIO/ClinicalTrials.gov Identifier: NCT00474461). The promising preliminary results will need to be confirmed, in both the longer term and larger patient series.

Ten years after the first intracoronary clinical application of BMMC was reported,[32] the concept of cardiac cell therapy has continuously evolved over time utilizing different cell types and application routes (intracoronary vs. intramyocardial) in different clinical scenarios. While most of these studies have focused on feasibility and safety, more recently initiated trials are targeting assessment of the efficacy of cardiac cell therapy concepts. Although the body of clinical experience is continuously growing, several key issues and questions are pending. These include not only the definition of appropriate product release criteria and clinical endpoints but also of a suitable cell type, route, and time of application. In this regard, the reported data here offer the unique opportunity to capture trends and monitor changes in the field, in a way which reflects the conducted (as opposed to planned) number of treatments and which can be communicated before a full report is published and publicly available.

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Disclosure Statement

No competing financial interests exist.

References

1. Abbott, A. Stem-cell ruling riles researchers. Nature **495,** 418, 2013.
2. Editorial. Smoke and mirrors. Nature **496,** 269, 2013.
3. Martin, I., Baldomero, H., Tyndall, A., Niederwieser, D., and Gratwohl, A. A survey on cellular and engineered tissue therapies in Europe in 2008. Tiss Eng Part A **16,** 2419, 2010.
4. Martin, I., Baldomero, H., Bocelli-Tyndall, C., Slaper-Cortenbach, I., Passweg, J., and Tyndall., A. The survey on cellular and engineered tissue therapies in Europe in 2009. Tiss Eng Part A **17,** 2221, 2011.
5. Martin, I., Baldomero, H., Bocelli-Tyndall, C., Passweg, J., Saris, D., and Tyndall., A. The survey on cellular and engineered tissue therapies in Europe in 2010. Tiss Eng Part A **18,** 2268, 2012.
6. Cyranoski, D. Cowboy culture. Nature **494,** 166, 2013.
7. Le Blanc, K., Frassoni, F., Ball, L., Locatelli, F., Roelofs, H., Lewis, I., Lanino, E., Sundberg, B., Bernardo, M.E., Remberger, M., Dini, G., Egeler, R.M., Bacigalupo, A., Fibbe, W., and Ringdén, O. Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study. Lancet **371,** 1579, 2008.
8. Cervelli, V., Gentile, P., De Angelis, B., Calabrese, C., Di Stefani, A., Scioli, M.G., Curcio, B.C., Felici, M., and Orlandi, A. Application of enhanced stromal vascular fraction and fat grafting mixed with PRP in post-traumatic lower extremity ulcers. Stem Cell Res **6,** 103, 2011.
9. Doi, K., Tanaka, S., Iida, H., Eto, H., Kato, H., Aoi, N., Kuno, S., Hirohi, T., and Yoshimura, K. Stromal vascular fraction isolated from lipo-aspirates using an automated processing system: bench and bed analysis. J Tissue Eng Regen Med. Doi: 10.1002/term.1478 2012.
10. Weir, R.A., McMurray, J.J., and Velazquez, E.J. Epidemiology of heart failure and left ventricular systolic dysfunction after acute myocardial infarction: prevalence, clinical char-

acteristics, and prognostic importance. Am J Cardiol **97,** 13F, 2006.
11. Segers, V.F., and Lee, R.T. Stem-cell therapy for cardiac disease. Nature **451,** 937, 2008.
12. van der Spoel, T.I., Jansen of Lorkeers, S.J., Agostoni, P., van Belle, E., Gyongyosi, M., Sluijter, J.P., *et al.* Human relevance of pre-clinical studies in stem cell therapy: systematic review and meta-analysis of large animal models of ischaemic heart disease. Cardiovasc Res **91,** 649, 2011.
13. Asahara, T., and Kawamoto, A. Endothelial progenitor cells for postnatal vasculogenesis. Am J Physiol Cell Physiol **287,** C572, 2004.
14. Emmert, M.Y., Emmert, L.S., Martens, A., Ismail, I., Schmidt-Richter, I., Gawol, A., *et al.* Higher frequencies of BCRP+cardiac resident cells in ischaemic human myocardium. Eur Heart J **34,** 2830, 2013.
15. Pfister, O., Mouquet, F., Jain, M., Summer, R., Helmes, M., Fine, A., *et al.* CD31- but not CD31+cardiac side population cells exhibit functional cardiomyogenic differentiation. Circ Res **97,** 52, 2005.
16. Menasche, P. Skeletal myoblasts for cardiac repair: Act II? J Am Coll Cardiol **52,** 1881, 2008.
17. Valina, C., Pinkernell, K., Song, Y.H., Bai, X., Sadat, S., Campeau, R.J., *et al.* Intracoronary administration of autologous adipose tissue-derived stem cells improves left ventricular function, perfusion, and remodelling after acute myocardial infarction. Eur Heart J **28,** 2667, 2007.
18. Williams, A.R., and Hare, J.M. Mesenchymal stem cells: biology, pathophysiology, translational findings, and therapeutic implications for cardiac disease. Circ Res **109,** 923, 2011.
19. Messina, E., De Angelis, L., Frati, G., Morrone, S., Chimenti, S., Fiordaliso, F., *et al.* Isolation and expansion of adult cardiac stem cells from human and murine heart. Circ Res **95,** 911, 2004.
20. Haase, A., Olmer, R., Schwanke, K., Wunderlich, S., Merkert, S., Hess, C., *et al.* Generation of induced pluripotent stem cells from human cord blood. Cell Stem Cell **5,** 434, 2009.
21. Assmus, B., Honold, J., Schachinger, V., Britten, M.B., Fischer-Rasokat, U., Lehmann, R., *et al.* Transcoronary transplantation of progenitor cells after myocardial infarction. N Engl J Med **355,** 1222, 2006.
22. Bolli, R., Chugh, A.R., D'Amario, D., Loughran, J.H., Stoddard, M.F., Ikram, S., *et al.* Cardiac stem cells in patients with ischaemic cardiomyopathy (SCIPIO): initial results of a randomised phase 1 trial. Lancet **378,** 1847, 2011.
23. Hare, J.M., Traverse, J.H., Henry, T.D., Dib, N., Strumpf, R.K., Schulman, S.P., *et al.* A randomized, double-blind, placebo-controlled, dose-escalation study of intravenous adult human mesenchymal stem cells (prochymal) after acute myocardial infarction. J Am Coll Cardiol **54,** 2277, 2009.
24. Makkar, R.R., Smith, R.R., Cheng, K., Malliaras, K., Thomson, L.E., Berman, D., *et al.* Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS): a prospective, randomised phase 1 trial. Lancet **379,** 895, 2012.
25. Schachinger, V., Erbs, S., Elsasser, A., Haberbosch, W., Hambrecht, R., Holschermann, H., *et al.* Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. N Engl J Med **355,** 1210, 2006.
26. Strauer, B.E., Brehm, M., Zeus, T., Gattermann, N., Hernandez, A., Sorg, R.V., *et al.* [Intracoronary, human autologous stem cell transplantation for myocardial regeneration following myocardial infarction]. Dtsch Med Wochenschr **126,** 932, 2001.
27. Wollert, K.C., Meyer, G.P., Lotz, J., Ringes-Lichtenberg, S., Lippolt, P., Breidenbach, C., *et al.* Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial. Lancet **364,** 141, 2004.
28. Jeevanantham, V., Butler, M., Saad, A., Abdel-Latif, A., Zuba-Surma, E.K., and Dawn, B. Adult bone marrow cell therapy improves survival and induces long-term improvement in cardiac parameters: a systematic review and meta-analysis. Circulation **126,** 551, 2012.
29. Behfar, A., Yamada, S., Crespo-Diaz, R., Nesbitt, J.J., Rowe, L.A., Perez-Terzic, C., *et al.* Guided cardiopoiesis enhances therapeutic benefit of bone marrow human mesenchymal stem cells in chronic myocardial infarction. J Am Coll Cardiol **56,** 721, 2010.
30. Menasche P, Alfieri O, Janssens S, McKenna W, Reichenspurner H, Trinquart L, *et al.* The myoblast autologous grafting in ischemic cardiomyopathy (MAGIC) trial: first randomized placebo-controlled study of myoblast transplantation. Circulation **117,** 1189, 2008.
31. Menasche, P. Stem cell therapy for heart failure: are arrhythmias a real safety concern? Circulation **119,** 2735, 2009.
32. Strauer, B.E., and Steinhoff, G. 10 years of intracoronary and intramyocardial bone marrow stem cell therapy of the heart: from the methodological origin to clinical practice. J Am Coll Cardiol **58,** 1095, 2011.

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(*Appendix follows*)

Appendix: List of Reporting Novel Cellular Therapy Centres in Europe in 2011

Format: City, Hospital, Department, Centre Identification Code (EBMT teams), Physicians (Total treatments; allogenic/autologous)
CIC, Centre Identification Code (as used for the standard EBMT survey)

Austria
Krems, University Krems, Regenerative Medicine and Orthopedics, S. Nehrer (18; 0/18)
Linz, AO Krankenhaus, 3. Medizinische Abteilung, M. A. Fridrik (11; 0/11)
Vienna, Medical University Hospital, Traumatology, S. Marlovits, Ch. Albrecht (7; 0/7)

Belarus
Minsk, Belorussian Center, CIC 591, O. Aleinikova (18; 18/0)
Minsk, Hospital No. 9, Belorussian Transplant Centre, N. Milanovich (9; 6/3)

Belgium
Antwerp, University Antwerpen, Haematology, CIC 996, W. Schroyens (50; 0/50)
Bruges, AZ Sint Jan, CIC 506, D. Selleslag, T. Lodewyck, A.v. Hoof, J.v. Droogenbroeck, K.v. Eygen (2; 2/0)
Brussels, Clinique Universitaire St. Luc, CIC 234, X. Poiré, C. Vermylen (1; 1/0)
Brussels, Institut Jules Bordet, Children's Hospital, CIC 215, D. Bron, C. Devalck, A. Ferster (1; 0/1)
Brussels, Military Hospital Queen Astrid, Burn Wound Centre, G. Verbeken (31; 31/0)
Brussels, U.L.B. Hôpital Erasme, Haematology, CIC 596, B. Bailly, A. Kentos, M. Lambermont (1; 0/1)
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Florence, Policlinico di Careggi, CIC 304, A. Bosi, S. Guidi (10; 4/6)

Genoa, Istituto Giannina Gaslini, Haematology, Oncology, CIC 274, G. Dini, E. Lanino (1; 1/0)
Genoa, Ospedale Villa Scassi, Plastic Surgery, F. Casabona (251; 0/251)
Milan, Orthopaedic Arthroscopic Surgery International Bioresearch Foundation, Gobbi NPO, A. Gobbi, G. Karnatzikos (14; 0/14)
Monza, L'Università di Milano-Bicocca, Ospedale San Gerardo dei Tintori, CIC 544, E. Pogliani, P. Pioltelli, M. Parma (1; 1/0)
Monza, Ospedale San Gerardo, CTMO–Clinica Pediatrica, CIC 279, A. Rovelli (3; 3/0)
Padua, Centro Leucemie Infantili, CIC 285, C. Messina, M. Pillon, E. Calore (2; 2/0)
Rome, Rome Transplant Network, CIC 756, W. Arcese, P. De Fabritiis (3; 3/0)
Rome, Università "La Sapienza," Plastic Surgery, A. Conversi, N. Scuderi (21; 0/21)
Rome, Università degli Studi di Roma "Tor Vergata," Reconstructive Surgery, V. Cervelli, D.J. Bottini, B. De Angelis (258; 0/258)

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Amsterdam, University Medical Center VUMC, Orthopaedic Surgery, M. Helder (5; 0/5)
Groningen, University Hospital, Haematology, CIC 546, G. van Imhoff (1; 1/0)
Leiden, University Hospital, CIC 203, J.H. Veelken, M. Egeler (76; 19/57)
Utrecht, UMC, Orthopaedic Surgery, D. Saris (55; 0/55)
Utrecht, UMCU/WKZ, Paediatrics, CIC 239.2, M. Bierings, N.M. Wullffraat (5; 5/0)
Utrecht, University Hospital UMCU, CIC 239, E. Petersen (7; 7/0)

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Ankara, University of Ankara, Paediatrics, CIC 620, E. Unal, M. Ertem (2; 2/0)
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The Survey on Cellular and Engineered Tissue Therapies in Europe in 2010

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Following the coordinated efforts of five established scientific organizations, this report describes the *novel cellular therapy* activity in Europe for the year 2010. One hundred six teams from 27 countries responded to the cellular therapy survey, 69 teams from 21 countries provided data on 1010 patients using a dedicated survey; 37 teams reported no activity. These data were combined with an additional 260 records reported by 37 teams in 15 countries to the standard European group for Blood and Marrow Transplantation (EBMT) database. Indications were graft-vs.-host-disease (GvHD; 26%; 11% autologous), musculoskeletal disorders (25%; 93% autologous), cardiovascular disorders (20%; 100% autologous), epithelial disorders (16%; 44% autologous), autoimmune diseases (11%; 55% autologous), and neurological disorders (2%; 62% autologous). Autologous cells were predominantly used for musculoskeletal (39%) and cardiovascular (32%) disorders, whereas allogeneic cells were mainly used for GvHD (58%) and epithelial disorders (23%). The reported cell types were mesenchymal stem/stromal cells (MSC; 49%), hematopoietic stem cells (28%), chondrocytes (10%), dermal fibroblasts (4%), keratinocytes (1%), and others (8%). In 63% of the grafts, cells were delivered following *ex vivo* expansion, whereas cells were transduced or sorted respectively in 10% or 28% of the reported cases. Cells were delivered intraorgan (45%), intravenously (31%), on a membrane or gel (20%) or using 3D scaffolds (4%). Compared with last year, the number of teams adopting the dedicated survey was 1.25-fold higher and, with few exceptions, the collected data confirmed the captured trends. This year's edition specifically discusses scientific, clinical, regulatory, and commercial aspects related to the use of cell therapy for the repair of cartilage defects.

Introduction

Despite the compelling clinical needs in regenerative medicine, the so-called *novel cellular therapies*, namely those not targeting the reconstitution of the hematopoietic system, have yet to result in products with a documented clinical benefit. It is worthwhile considering that in the field of bone marrow transplants, which represents the pioneering cellular therapy, it took almost 30 years from the first scattered clinical tests in the 1950s until hematopoietic stem cell (HSC) transplantation became the standard of treatment for hematologic malignancies, and refinements of the procedure continue to be investigated to improve the success rates. This short historical perspective indicates that clinical implementation of cellular therapy requires time and long-term efforts and that *novel cellular therapies* are still at an infancy stage. As for the field of bone marrow transplantation, progress in the field of *novel cellular therapies* is expected to require an open and coordinated communication of the ongoing trials, as a platform to carry out analyses of trends, successes, and failures.[1–4]

Information available in public databases (e.g., www.clinicaltrial.gov) is critical to establish a map of the planned or ongoing trials, but does not allow identifying the precise number of patients treated with specific cells at a defined point in time. Published results of clinical studies are keys to evaluate the primary endpoints, but only marginally represent the total number of performed trials. Databases organized by working groups on specific areas (e.g., by the European group for Blood and Marrow Transplantation [EBMT]) have the main advantage of including data on the patient outcome, but can hardly be extended to the public domain, where

For the Joint Survey Committee of the Tissue Engineering and Regenerative Medicine International Society (TERMIS)-Europe, the International Cartilage Repair Society (ICRS), the European League Against Rheumatism (EULAR), the International Society for Cellular Therapy (ISCT)-Europe, and the European Group for Blood and Marrow Transplantation (EBMT).
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sharing of critical information may conflict with confidentiality issues or commercial interests.

Since 2008, a complementary program has been established by the European sections of the Tissue Engineering and Regenerative Medicine International Society (TERMIS-EU), the International Society of Cellular Therapy (ISCT), and the International Cartilage Repair Society (ICRS) in a joint initiative with the EBMT and the European League Against Rheumatism (EULAR).[5,6] The program is organized in the form of a survey, collecting the number of patients being treated in Europe by *novel cellular therapies*, sorted by specific therapeutic indications, cell types used, and cell processing/delivery modes. The absence of patient assessment data, the yearly publication of the data, and the possibility offered to the participating teams to query more specific information offers an open and flexible platform to establish and disseminate the status in the field of *novel cellular therapies* in Europe.

Here, we report the results of the third survey edition for the activity in 2010, with a comparison to the previously identified trends and a specific discussion on the field of cell-based cartilage repair procedures.

Patients and Methods

Definitions

For the purpose of this survey, *novel cellular therapies* include the use of cells other than HSC or of HSC for uses other than reconstitution of the hematopoietic system. The term HSC, which is often ambiguously used in the field of *novel cellular therapies*, indicates a mixture of stem and progenitor cells predominantly of the hematopoietic lineage. Donor lymphocyte infusions, often used in relapsing patients after HSC transplantation, are considered to be an integral part of the HSC transplant procedure and are excluded. The term "Epithelial disorders" is also used to include parenchymal diseases, as for example, diabetes or liver insufficiency.

Data collection and validation

Participating teams were requested to report their data for 2010 by indication, cell type and source, donor type, processing method, and delivery mode. The survey followed the traditional principles of the EBMT, concentrating on numbers of patients with a first cellular therapy. Members of the four participating societies from 47 countries (39 European and 8 affiliated countries) were contacted for the 2010 report (EBMT survey). The non-European countries affiliated with the EBMT were Algeria, Iran, Israel, Jordan, Lebanon, Saudi Arabia, South Africa, and Tunisia. For EBMT teams not using the extended questionnaire, information on cellular therapies was limited to numbers of HSC for nonhematopoietic use, mesenchymal stem/stromal cell (MSC)-based therapies (later identified to be almost exclusively related to treatment of graft-vs.-host-disease [GvHD]), and donor type. Extended questionnaires, in the format displayed in Supplementary Figure S1(Supplementary Data are available online at www.liebertpub.com/tea), were collected by paper forms or electronically. Quality control measures, for EBMT members only, included several established independent systems: confirmation of validity of the entered data by the reporting team, selective comparison of the survey data with MED-A data sets in the EBMT ProMISE data system, cross-checking with the National Registries, and onsite visits of selected teams. No quality control system could be yet applied for the non-EBMT reporting teams.

Transplant rates

Transplant rates, defined as the reported numbers of patients receiving cellular therapies or 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 2010 U.S. census office database (www.census.gov).

Results

Participating teams

One hundred six teams in 27 countries (24 European and 3 affiliated countries) responded to the *novel cellular therapy* survey; 69 teams (21 countries) reported performing *novel cellular therapies* with detailed information on indication, cell source and type, donor type, processing, and delivery mode, while 37 teams reported no activity. The remaining 37 teams from 15 countries (13 European and 2 affiliated countries) reported using the standard EBMT transplant activity survey, allowing to include only limited information. Data were thus received from a total of 23 countries. Teams that responded with activity are listed in the Appendix in alphabetical order by country, city, and EBMT center code (if applicable), along with the total number of reported *novel cellular therapies*.

Number of novel cellular therapies and disease indications

According to the received reports, 1142 patients were treated with *novel cellular therapies*, 504 (40%) with allogeneic and 766 (60%) with autologous cells (Table 1). Main indications were GvHD (26%; 11% autologous), musculoskeletal disorders (25%; 93% autologous), cardiovascular disorders (20%; 100% autologous), epithelial disorders (16%; 44% autologous), autoimmune diseases (11%; 55% autologous), and neurological disorders (2%; 62% autologous).

More detailed information on specific indications was obtained from 1010 patients. Among the musculoskeletal disorders, cartilage and bone repair were the most frequently reported indications. Among the cardiovascular disorders, peripheral artery disease, myocardial ischemia, and heart failure were the main reasons for a cellular therapy. Skin reconstruction, diabetes, and cornea repair were the three main reported indications for epithelial/parenchymal disorders. Among autoimmune disorders, gastrointestinal diseases and multiple sclerosis represented the predominant indications. The number of patients treated for neurological indications was rather limited and mostly confined to Huntington's disease. The number of reports of patients treated for GvHD needs to be combined with that reported in the EBMT standard form, for a total of 336 cases (Table 1).

Cell type, source and donor type

Of the 353 HSC treatments, 93% were autologous transplants and 59% were used to treat cardiovascular

Table 1. Number of Reported *Novel Cellular Therapy* Treatments in Europe in 2010 Sorted by Indication, Cell Source, and Donor Type

	Cell type and source											
	Autologous				*Allogeneic*							
Indication	*HSC*	*MSC*	*Chondrocyte*	*Other*	*HSC*	*MSC*	*Keratinocyte*	*Fibroblast*	*Other*	*Autologous*	*Allogeneic*	*Total*
Cardiovascular												
Peripheral artery disease	70	8								78	0	78
Cardiomyopathy	25									25	0	25
Heart failure	33	15								48	0	48
Myocardial ischemia	38	9		6						53	0	53
Bypass graft	6									6	0	6
Ulcer										0	0	0
Other/unspecified	38									38	0	38
Musculoskeletal										0	0	0
Bone repair (maxillofacial)	1			1	1					2	1	3
Bone repair (orthopedics)	26	19				10				45	10	55
Osteogenesis imperfecta										0	0	0
Cartilage repair	12	86	125			10				223	10	233
Muscle repair										0	0	0
Tendon/ligament		2								2	0	2
Reconstructive surgery										0	0	0
Other/unspecified	30									30	0	30
Neurological										0	0	0
Huntington's									7	0	7	7
Peripheral nerve regeneration (trauma)	3									3	0	3
Other/unspecified	8	2			1					10	1	11
Epithelial										0	0	0
Skin reconstruction				20			19	50	15	20	84	104
Cornea repair				6	24				2	6	26	32
Organ failure										0	0	0
Diabetes	25	5							3	30	3	33
Liver insufficiency	1									1	1	2
Other	11	11		10						32	0	32
Autoimmune										0	0	0
Rheumatological		1				1				1	1	2
Gastrointestinal		1				33				1	33	34
Multiple Sclerosis		24								24	0	24
Other		24		26		29				50	29	79
GvHD		38				298				38	298	336
Total	327	245	125	69	26	382	19	50	27	766	504	1270

HSC, hematopoietic stem cells; MSC, mesenchymal stem/stromal cell; GvHD, graft-vs.-host-disease.

diseases (Table 1). All 125 chondrocyte transplants were autologous, whereas all 19 keratinocytes and 50 dermal fibroblasts transplants were allogeneic. Of 627 MSC-based therapies, 61% were allogeneic. The donor type was associated with the disease indication: autologous cells were predominantly used for musculoskeletal (39%) and cardiovascular (32%) disorders, whereas allogeneic cells were mainly used for GvHD (58%) and epithelial (23%) disorders (Fig. 1). In the detailed survey, MSC were mainly obtained from bone marrow (63%) or adipose tissue (25%) and mostly used to treat GvHD (38%), musculoskeletal (31%), and autoimmune disorders (14%). For the HSC treatments, cells were derived from the bone marrow (90%) or peripheral blood (10%).

Cell processing and delivery mode

Of all the grafted products reported in detailed form, 63% required cell expansion, 10% were transduced cells, and 28% were sorted (Table 2). Nonexpanded cells were used to treat 83% of neurological, 82% of cardiovascular, 37% of

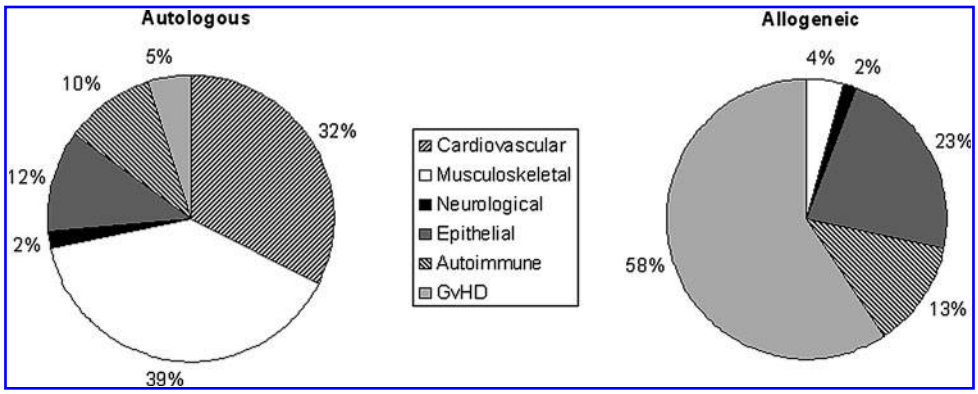

FIG. 1. Percentage of indications for *novel cellular therapies* in Europe in 2010, sorted by donor type. Data used for this chart were derived from the extended questionnaire and the standard European group for Blood and Marrow Transplantation (EBMT) survey sheet. GvHD, graft-vs.-host-disease.

musculoskeletal, 26% of epithelial, and 30% of autoimmune disorders, while GvHD was exclusively treated with expanded cells. Cell sorting was applied for 70% of autoimmune, 44% of epithelial, 42% of cardiovascular, and 14% of musculoskeletal disorders. Transplanted cells were genetically transduced for 69% of autoimmune, 18% of epithelial, 3% of cardiovascular diseases, and 1% of the GvHD treatments.

About one half (45%) of the cell grafts was delivered intraorgan, 31% intravenously, 20% on a membrane or gel, and 4% using a 3D scaffold (Table 3). Cells were delivered

Table 2. Number of Reported *Novel Cellular Therapy* Treatments in Europe in 2010 Sorted by Cell Processing Mode

	Cell processing					
Indications	*Nonexpanded*	*Expanded*	*Untransduced*	*Transduced*	*Unsorted*	*Sorted*
Cardiovascular						
Peripheral artery disease	70	8	78		40	38
Cardiomyopathy	25		25		10	15
Heart failure	33	15	48		15	33
Myocardial ischemia	38	15	47	6	50	3
Bypass graft	6		6		6	
Valve replacement						
Ulcer						
Other						
Musculoskeletal						
Bone repair (maxillofacial)	1	2	3		3	
Bone repair (orthopedics)	48	7	55		55	
Osteogenesis imperfecta						
Cartilage repair	49	184	233		189	44
Muscle repair						
Tendon/ligament	2		2		2	
Reconstructive surgery						
Other	13		13		13	
Neurological						
Huntington's	7		7		7	
Peripheral nerve regeneration	3		3		3	
Other		2	2		2	
Epithelial						
Skin reconstruction	15	89	104		34	70
Cornea repair	24	8	32		32	
Organ failure						
Diabetes	3	30	8	25	25	8
Liver insufficiency		2	1	1	1	1
Other	11	21	21	11	21	11
Autoimmune						
Rheumatological		2	2		1	1
Gastrointestinal		34	1	33	1	33
Multiple Sclerosis		24	24		24	
Other	26			26		26
GvHD		193	191	2	193	
Total	374	636	906	104	727	283

Data only from extended questionnaire.

Table 3. Number of Reported *Novel Cellular Therapy* Treatments in Europe in 2010 Sorted by Delivery Mode

	Cell delivery mode			
Indications	*Intravenous*	*Intraorgan*	*Membrane/gel*	*3D scaffold*
Cardiovascular				
Peripheral artery disease	1	73	4	
Cardiomyopathy		25		
Heart failure		48		
Myocardial ischemia	26	27		
Bypass graft		6		
Valve replacement				
Ulcer				
Other				
Musculoskeletal				
Bone repair (maxillofacial)			1	2
Bone repair (orthopedics)		29	5	21
Osteogenesis imperfecta				
Cartilage repair		109	107	17
Muscle repair				
Tendon/ligament			2	
Reconstructive surgery				
Other		13		
Neurological				
Huntington's		7		
Peripheral nerve regeneration			3	
Other	2			
Epithelial				
Skin reconstruction		70	34	
Cornea repair			32	
Organ failure				
Diabetes	30	3		
Liver insufficiency	2			
Other	11	7	14	
Autoimmune				
Rheumatological	2			
Gastrointestinal		34		
Multiple Sclerosis	24			
Other	26			
GvHD	193			
Total	317	451	202	40

Data only from extended questionnaire.

intraorgan for 85% of cardiovascular, 58% of neurological, 49% of musculoskeletal, 40% of autoimmune, and 39% of epithelial disorders. Intravenous delivery was reported for all GvHD treatments and predominantly for autoimmune (60%), epithelial/parenchymal (21%), and cardiovascular (13%) disorders. The use of a membrane or a gel for cell delivery was reported almost exclusively for epithelial (39%) or musculoskeletal (38%) treatments. A 3D scaffold was used only for musculoskeletal indications (13%), in particular cartilage or bone repair.

Transplant rates and active teams

Reported cellular therapies were performed in a limited number of countries and with different intensity. Figure 2 displays the reported cellular therapy transplants per 10 million inhabitants in the different European and EBMT-associated countries. High transplant rates (i.e., >100 per 10 million population) were reported in Belgium, the Republic of Belarus, Slovenia, and Switzerland. The number of teams reporting *novel cellular therapies* was also mapped in the different European and EBMT-associated countries after normalization to the inhabitant numbers (Fig. 3). The number of reporting teams per 10 million inhabitants was higher than 4 in Belgium, Finland, Israel, Slovenia, and Switzerland.

Discussion

Compared with the data collected for patients treated in the previous years,[5,6] the present report confirms the main identified trends, with a few remarkable differences. Although the percentages of treatments using autologous versus allogeneic cells were almost identical to those from 2008 and 2009, comparative analysis of specific categories indicates that the distribution of autologous or allogeneic cell transplantation for different indications has not yet reached a consolidated trend (Fig. 4). The discrepancies are more

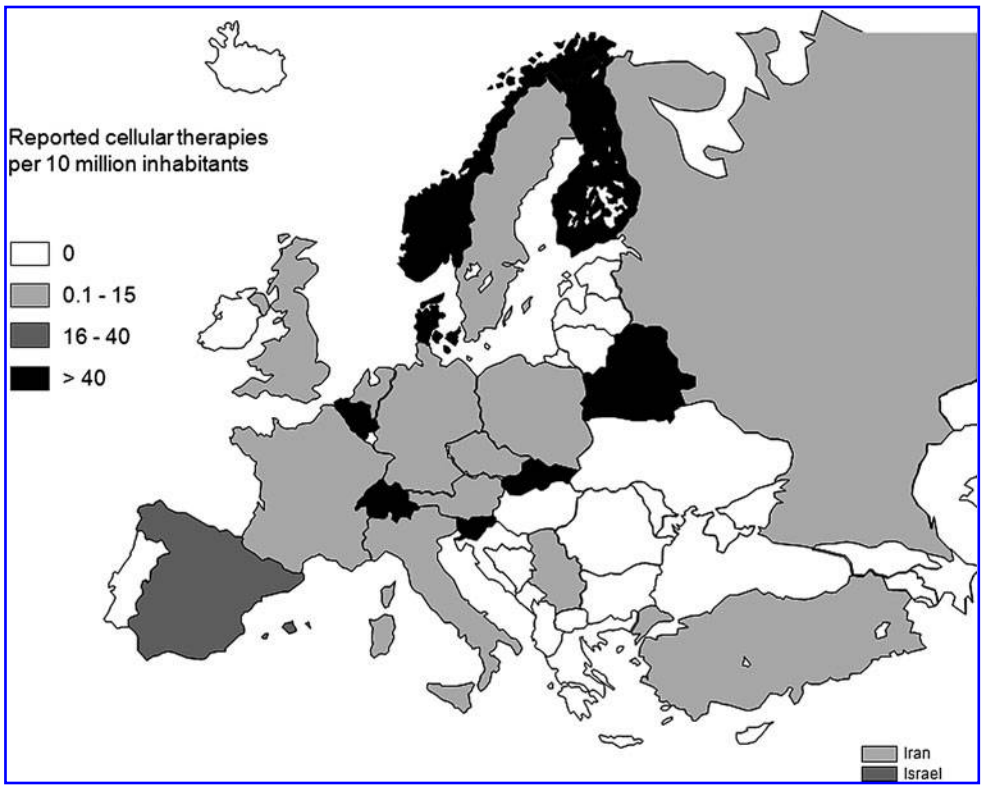

FIG. 2. Number of *novel cellular therapies* per 10 million inhabitants reported in Europe in 2010. Data used for this chart were derived from the extended questionnaire or the standard EBMT survey sheet.

evident in the field of cardiovascular diseases, due to the predominant treatment of ulcers with allogeneic cells in 2009, and of epithelial/parenchymal disorders, due to the variable source of cells used for skin reconstruction. The remarkable absence of reports on the use of allogeneic cells for cardiac-related disorders in Europe is in line with the list of ongoing trials officially registered at www.clinicaltrials .gov and summarized in a recent study.[7] The fact that most ongoing trials for cardiac-related disorders outside Europe use allogeneic cells[7] highlights that the present report may be not representative of a geographically global scenario for what concerns donor types within specific categories, probably due to a combination of cultural, regulatory, and/ or commercial issues.

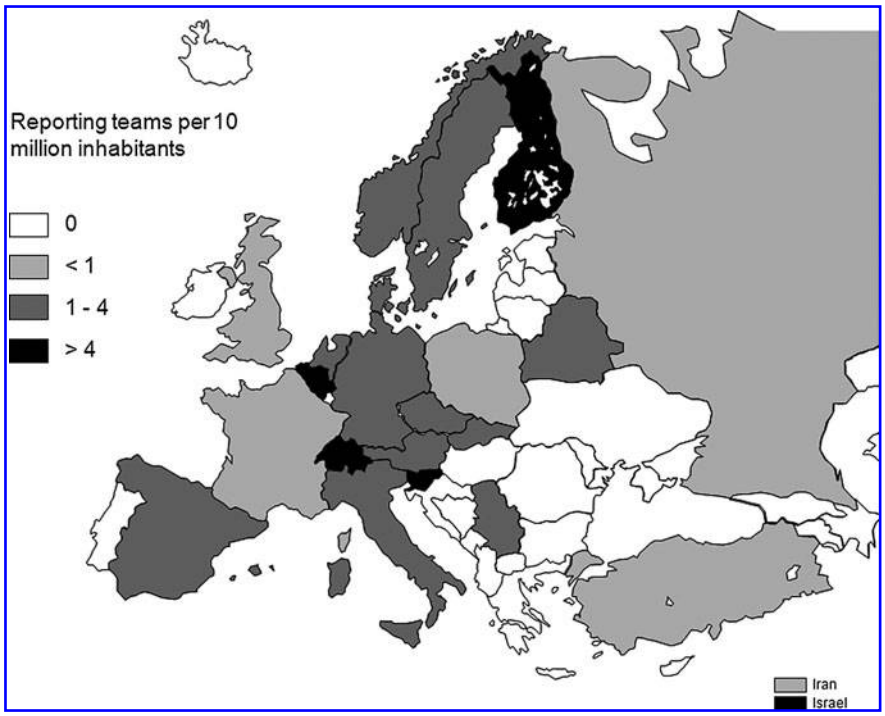

FIG. 3. Number of teams per 10 million inhabitants reporting *novel cellular therapies* in Europe in 2010. Data used for this chart were derived from the extended questionnaire or the standard EBMT survey sheet.

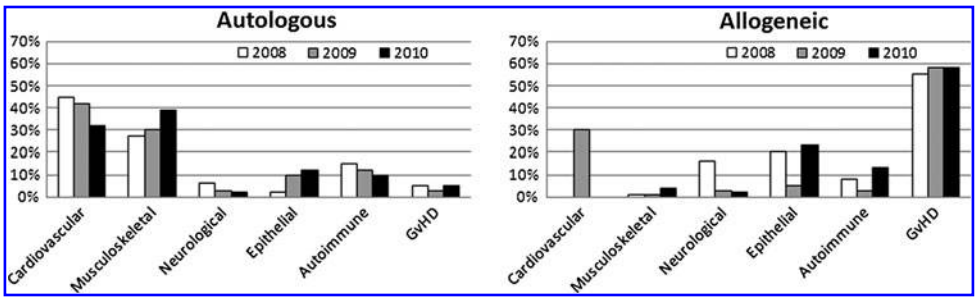

FIG. 4. Comparative analysis of indications for *novel cellular therapies* in Europe from 2008 to 2010, sorted by donor type. Data used for this chart were derived from the current study and the two previous reports.[5,6]

The percentage of cases treated with expanded cells, requiring dedicated Good Manufacturing Practice facilities and compliance to a rigorously defined quality management system, slightly but steadily increased from 51% in 2008 and 59% in 2009 to 63% in 2010. This may indicate that the manufacturing groups are positively reacting to the tighter regulatory framework for Advanced Therapy Medicinal Products introduced in 2008 by the European Medicines Agency (EMA; www.ema.europa.eu). The use of transduced or sorted cells progressively increased from 2008, possibly reflecting the recognition that specific biological processes need to be targeted by enhancing expression of defined genes or implanting more homogeneous cell phenotypes. With regard to the cell delivery modes, the 2010 data confirmed that the use of a 3D scaffold remains confined within the field of musculoskeletal diseases, although in this area the percentage of use decreased by 50% from 2009. This figure is in line with the higher challenges in establishing "tissue engineering" procedures in the clinical practice, compared with the more conventional cell delivery modes.

This year's focus: cell therapy for cartilage repair

In cartilage regeneration, the use of cell therapy has been established for over 20 years.[8,9] This extensive experience has been beneficial to the cell therapy field as a whole to recognize the importance of identifying proper clinical indications and of validating the tools for outcome evaluation, and to experience the challenges of the treatments that are mainly economical and logistical. In Europe, cellular therapies were placed under the guidance of advanced therapeutical medicinal products by the EMA. The necessary trial data for registration have increased the current clinical knowledge and allowed more evidence-based treatment selection and development of well-established algorithms for patient profiling.[10,11] The time between cartilage damage, the occurrence of symptoms and initiation of treatment is of direct influence on treatment outcome.[12] So-called "old defects" in a chronic stage, treated in an environment of disturbed joint homeostasis, show significantly worse clinical outcome at 5-year follow-up. Thus, the initial concept of applying cell therapy after failure of other treatments is being replaced by earlier intervention with application of advanced imaging methods for more active early diagnosis.

Since the new regulatory pathway and framework have been established in 2008, the first product has been approved (ChondroCelect; Tigenix, Leuven, Belgium) and others are in the process of acquiring such approval (MACI, Genzyme; Sanofi, Kopenhagen, Denmark). The next step will be to place these products within a clinical setting that most effectively exploits them. Given the general economic challenges in Europe, it seems clear that innovative healthcare solutions need to take into account the economic downturn and associated financial restrictions of healthcare systems. More and more we will be asked to apply innovative solutions in an initially limited market, to generate well designed prospective cost benefit and risk analyses. This will be most likely applied in selected cell therapy centers and should be providing data to a central European prospective registry (i.e., ICRS EuroCart), which will allow for reporting collaboratively on the outcome of these essential developments.

The data from the current survey indicate a rise from 7% in 2009 to 21% in 2010 in the use of nonexpanded cells. This seems to be a signal of the desire to limit the complexity and the morbidity of two-stage surgical procedures. The development of one-stage procedures alleviates the need for double surgery and extensive waiting time between biopsy and graft delivery. Currently, only autologous chondrocyte-based therapy has a clinically proven track record. However, the focus is shifting toward the use of MSCs from diverse sources to be applied in one-stage procedures with or without addition of growth factors, bone marrow concentrates, and other cell types and/or biomaterials.[13]

Another interesting observation from this survey is the use of membranes or gels as delivery substances. Their rise from 12% in 2009 to 38% in 2010 clearly demonstrates the increased acceptance of biomaterials but may also reflect the demand for higher reliability of delivery, appropriate cell dosing, and possibly arthroscopic or minimally invasive graft delivery, for which injectables or synthetic carriers are essential. These changes will progress most likely to a level where injectable and malleable biomaterials will be used in all procedures, replacing the need for additional harvesting of patient's own tissue (e.g., periosteal flap) for the application of the cell product.

What will be the next developments in cell-based cartilage repair? The application of cell therapy to the treatment of critically sized defects or in osteoarthritis is a great challenge and would have considerable impact on the field.[14,15] Another challenge is the need to establish registered products for specific indications based on multiple prospective randomized trials and in turn to address the large financial and regulatory burden these trials produce. The associated risk is to slow down the implementation of innovation and to exclude the smaller initiatives, thus creating a bias toward large pharmaceutical companies, which may or may not be desirable. Broader and more standardized clinical trials/use of cell-based grafts will require to introduce manufacturing paradigms inspired from other well-established biotechnology sectors, for example an automated production within

closed bioreactor systems.[16] Finally, a European harmonization of guidelines of eligibility for reimbursement by health insurances will have to be targeted. Most professional orthopedic organizations agree on a clinical treatment algorithm for cartilage defects and this professional consensus should be the guide for policy makers and healthcare providers.[17–19]

Conclusions

The progressive increase in the number of reporting teams using the dedicated form and the number of total treatments being claimed (respectively 25% and 11% from the previous year) indicates that the inter-society program of the survey on *novel cellular therapies* is becoming a reference platform for access to information that is not available in public databases or scientific publications. Nevertheless, we are aware that several active teams in Europe have not reported treatments and therefore, the data in this survey represent an underestimation of the actual number of *novel cellular therapies* and groups involved. The use of a more organically structured query form, which has been introduced for the collection of 2011 data, together with the planned headhunting for active teams not yet reporting treatments, are expected to further consolidate the program. Moreover, while published and registered studies provide a complementary type of information, released with a different timing as compared with this survey, we expect that only an integrated use of the different instruments will allow to effectively monitor changes and trends in cell-based therapeutic strategies.

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Disclosure Statement

There are no conflicts of interest to declare. Writing of the article was the sole responsibility of the authors.

References

1. Gratwohl, A. Bone marrow transplantation activity in Europe 1990. Report from the European Group for Bone Marrow Transplantation (EBMT). Bone Marrow Transplant **8,** 197, 1991.
2. Gratwohl, A., Baldomero, H., Horisberger, B., Schmid, C., Passweg, J., and Urbano-Ispizua, A. Accreditation Committee of the European Group for Blood and Marrow Transplantation (EBMT). Current trends in haematopoietic stem cell transplantation in Europe. Blood **100,** 2374, 2002.
3. Gratwohl, A., Baldomero, H., Schwendener, A., Gratwohl, M., Apperley, J., Niederwieser, D., Frauendorfer, K., and Joint Accreditation Committee of the International Society for Cellular Therapy; European Group for Blood and Marrow Transplantation; European Leukemia Net. Predictability of hematopoietic stem cell transplantation rates. Haematologica **92,** 1679, 2007.
4. Tyndall, A. Successes and failures of stem cell transplantation in autoimmune diseases. Hematol Am Soc Hematol Educ Program **2011,** 280, 2011.
5. Martin, I., Baldomero, H., Tyndall, A., Niederwieser, D., and Gratwohl, A. A survey on cellular and engineered tissue therapies in Europe in 2008. Tiss Eng A **16,** 2419, 2010.
6. Martin, I., Baldomero, H., Bocelli-Tyndall, C., Slaper-Cortenbach, I., Passweg, J., and Tyndall, A. The survey on cellular and engineered tissue therapies in Europe in 2009. Tiss Eng A **17,** 2221, 2011.
7. Richardson, J.D., Nelson, A.J., Zannettino, A.C.W., Gronthos, S., Worthley, S.G., and Psaltis, P.J. Optimization of the cardiovascular therapeutic properties of mesenchymal stromal/stem cells–taking the next step. Stem Cell Rev Rep 2012 [Epub ahead of print]; DOI: 10.1007/s12015-012-9366-7.
8. Peterson, L., Vasiliadis, H.S., Brittberg, M., and Lindahl, A. Autologous chondrocyte implantation: a long-term follow-up. Am J Sports Med **38,** 1117, 2010.
9. Brittberg, M., Lindahl, A., Nilsson, A., Ohlsson, C., Isaksson, O., and Peterson, L. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. N Engl J Med **331,** 889, 1994
10. Bekkers, J.E., Inklaar, M., and Saris, D.B. Treatment selection in articular cartilage lesions of the knee: a systematic review. Am J Sports Med **37,** 148S, 2009.
11. de Windt, T.S., Bekkers, J.E., Creemers, L.B., Dhert, W.J., and Saris, D.B. Patient profiling in cartilage regeneration: prognostic factors determining success of treatment for cartilage defects. Am J Sports Med **37,** 58S, 2009.
12. Vanlauwe, J., Saris, D.B., Victor, J., Almqvist, K.F., Bellemans, J., and Luyten, F.P. Five-year outcome of characterized chondrocyte implantation versus microfracture for symptomatic cartilage defects of the knee: early treatment matters. Am J Sports Med **39,** 2566, 2011.
13. Acharya, C., Adesida, A., Zajac, P., Mumme, M., Jakob, M., Riesle, J., Martin, I., and Barbero, A. Enhanced chondrocyte proliferation and mesenchymal stromal cells chondrogenesis in coculture pellets mediate improved cartilage formation. J Cell Physiol **227,** 88, 2011.
14. Gomoll, A.H., Filardo, G., de Girolamo, L., Espregueira-Mendes, J., Marcacci, M., Rodkey, W.G., Steadman, J.R., Zaffagnini, S., and Kon, E. Surgical treatment for early osteoarthritis. Part I: cartilage repair procedures. Knee Surg Sports Traumatol Arthrosc **20,** 450, 2012
15. Gomoll, A.H., Filardo, G., Almqvist, F.K., Bugbee, W.D., Jelic, M., Monllau, J.C., Puddu, G., Rodkey, W.G., Verdonk, P., Verdonk, R., Zaffagnini, S., and Marcacci, M. Surgical treatment for early osteoarthritis. Part II: allografts and concurrent procedures. Knee Surg Sports Traumatol Arthrosc **20,** 468, 2012.
16. Martin, I., Smith, T., and Wendt, D. A roadmap for the bioreactor-based translation of tissue engineering strategies into clinical products. Trends Biotech **27,** 495, 2009

17. Saris, D.B., Buma, P., and Bulstra, S.K. Advies van de Nederlandse Orthopaedische Vereniging; Chirurgische behandelingen van kraakbeendefecten in de knie. Available at www.orthopeden.org, 2011.
18. Behrens, P., Bosch, U., Bruns, J., *et al.* [Indications and implementation of recommendations of the working group "Tissue Regeneration and Tissue Substitutes" for autologous chondrocyte transplantation (ACT)]. Z Orthop Ihre Grenzgeb **142,** 529, 2004.
19. Vanlauwe, J., Almqvist, F., Bellemans, J., Huskin, J.P., Verdonk, R., and Victor, J. Repair of symptomatic cartilage lesions of the knee: the place of autologous chondrocyte implantation. Acta Orthop Belg **73,** 145, 2007.

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(Appendix follows →)

Appendix: List of Reporting *Novel Cellular Therapy* Centers in Europe in 2010

List of reporting *novel cellular therapy* centers in Europe in 2010

Format: City, Hospital, Center Identification Code number (if data were imported from the standard EBMT survey sheet), Physicians (Total treatments; allogeneic/autologous)

CIC = Center Identification Code (if data were imported from the standard EBMT survey sheet)

Austria

Graz, Childrens University Hospital, CIC 593, CH. Urban (1; 1/0)
Innsbruck, University Hospital, CIC271, G. Gastl, D. Nachbaur (1; 1/0)

Belarus

Minsk, Belorussian Center, CIC 591, O Aleinikova (36; 36/0)
Minsk, Hospital No.9, N. Milanovich (37; 11/26)
Minsk, Hospital No.9, N. Milanovich (40; 16/24)

Belgium

Brussels, University Hospital, CIC 630, R. Schots, F. Trullemans (1; 1/0)
Brugge, A.Z. St. Jan, CIC 506, D.Selleslag, A.v.Hoof, J.v.Droogenbroeck, K.v.Eygen (11; 11/0)
Brussels, Institut Jules Bordet, Childrens Hospital, CIC 215, d. Bron, C. Devalck, A. Ferster (4; 4/0)
Antwerpen, University Antwerpen, CIC 996, W. Schroyens (36; 3/33)
Leuven, University Hospital Gasthuisberg, CIC 209, G. Verhoef, M. Delforge,J. Maertens (4; 4/0)
Leuven, University Hospital Leuven, N. Ectors (19; 19/0)
Liège, University Hospital Sart-Tilman, CIC 726, Y. Béguin, B de Prijck (32; 32/0)

Czech Republic

Prague, Charles University, E. Sykova (4; 0/4)

Denmark

Copenhagen, The Heart Centre Rigshospitalet, J. Kastrup (24; 0/24)

Finland

Helsinki, HUCH Jorvi Hospital, T. Paatela (13; 0/13)
Helsinki, Helsinki University Central Hospital, CIC 515, L. Volin (3; 0/3)
Jyväskylä, Jyväskylä central hospital, I. Kiviranta (8; 0/8)
Kuopio, University Hospital, a. Joukainen (2: 0/2)

France

Clermont Ferrand, CRCTCP, CHU Estaing, CIC273, J.-O. Bay, F. Deméocq, P. Travade (33; 24/9)
Grenoble, Hospitalier A. Michallon, CIC 270, J.Y. Cahn, F.Garban, P. Drillat, D. Plantaz (8; 3/5)
Paris, Hôpital Cochin, M. Quarre (1; 0/1)

Germany

Berlin, Universitäts-Klinik Charlottenburg, CIC 336, W. Ebell, G. Gaedicke (1; 1/0)
Dresden, Universitätsklinikum Carl Gustav Carus, CIC 808, G. Ehninger, H. Bornhäuser (22; 22/0)
Frankfurt, Klinikum Frankfurt Oder, CIC 190, M. Kieshl (6; 6/0)
Frankfurt, Universitätsklinikum d. J. W. Goethe, CIC 138, T. Klingebiel, P. Bader (4; 4/0)
Hannover, Medizinische Hochschule, CIC 295, A. Ganser, M. Eder (4; 0/4)
Hannover, Medizinische Hochschule, CIC 295, A. Ganser, M. Eder (2 2/0)
Halle, Clinic Bergmannstrost, H.J. Meisel (16: 0/16)
Köln, Universitäts-Klinik, CIC 534, M. Hallek, Ch. Scheid, F. Berthold, T. Simon (3 0/3)
München, Tech, Universität Munich, M. Kessling (15; 15/0)
München, KK München Schwabing, CIC 189, S. Burdach, A. Wawer, M. Nathrath (1; 1/0)
Regensburg, Universitäts Klinikum, CIC 787, E. Holler, A. Reichle, R. Andreesen (1; 1/0)
Tübingen, Medizinische Universitäts-Klinik, CIC 223, L. Kanz, C. Faul (2; 2/0)
Tübingen, Medizinische Universitäts-Klinik, CIC 535, R. Handgretinger, P. Lang (4; 4/0)

Iran, Islamic Rep.

Teheran, Shariati Hospital, CIC 633, M. Jahani (26; 26/0)
Teheran, Shariati Hospital, CIC 633, M. Jahani (37; 5/32)
Teheran, Taleghani General hospital, M. Mehdizadeh (5; 0/5)

Israel

Jerusalem, Hadassah University Hospital, CIC 258, R. Or, S. Slavin (24; 24/0)
Tel Hashomer, Sheba Medical Center, CIC 754, A. Nagler, A. Shimoni (1; 1/0)
Tel Hashomer, Chaim Sheba Medical Cebter, CIC 572, A. Toren (1; 1/0)

Italy

Bergamo, Ospedale Riuniti, CIC 658, A. Rambaldi (5; 5/0)
Bologna, 6th div Rizzoli Orthopedic Institute, CIC 453, L. Roseti, S. Giannini, R. Buda, E. Kon (12; 0/12)
Cagliari, Ospedale per le Microcitemie, CIC 8112, M. Orofino (1; 1/0)
Cagliari, Centro Trapianti di Midollo Osseo, CIC 8111, G. La Nasa (1; 1/0)
Firenze, Policlinico di Careggi, CIC 304, A. Bosi, S. Guidi (1; 0/1)
Firenze, Policlinico di Careggi, CIC 304, A. Bosi, S. Guidi (15; 7/8)
Milano, Gobbi NPO, G. Karnatzikos (16; 0/16)

Milano, University of Milan, CIC265, G. Lambertenghi Deliliers (2; 2/0)
Monza, Uni. di Milano-Bicocca, CIC 544, E. Pogliani, P. Pioltelli, G. Corneo (1; 1/0)
Modena, University of Modena, CIC 543, F. Narni, A. Cuoghi, P. Bresciani (4; 0/4)
Monza, Ospedale San Gerardo, CIC 279, A. Rovelli (5; 5/0)
Pavia, Policlinico IRCCS St. Matteo, CIC 557, M. Zecca (2; 2/0)
Palermo, Ospedale "La Maddalena," CIC 692, M. Musso, F. Porretto, A. Crescinanno (1; 0/1)
Palermo, ARNAS Civico Di Christina, CIC853, G. Pagnucco (8; 0/8)
Pesaro, Ospedale San Salvatore, CIC 529, G. Visani (3; 3/0)
Reggio di Calabria, Azienda Ospedale "Riuniti e Morelli," Bianchi- Melacrino, CIC 587, P. Iacopino (2; 0/2)
Roma, Rome Transplant, Network, CIC 756, W. Arcese, P. De Fabritiis (2; 2/0)
Roma, Uni Campus Bio-Medico, G. Vadala (6; 0/6)

Netherlands

Groningen, University Hospital, CIC 546, G. van Imhoff (1; 1/0)
Utrecht, UMCU/WKZ, CIC 2392, M. Bierings, NM. Wullffraat (5; 5/0)
Utrecht, Wilhelmina Childrens Hospital, CIC 2392, E.R. de Graeff-Meeder (5; 5/0)

Norway

Oslo, Oslo University Hospital, CIC 235, D. Albrechtsen, L. Brinch (21; 0/21)

Poland

Cracow, University Children's Hospital JUMC, CIC 507, J. Gozdzik (1; 1/0)
Cracow, University Children's Hospital JUMC, CIC 507, J. Gozdzik (3; 0/3)
Wroclaw, Lower Silesian Cent./BM Donor Registry, CIC 538, A. Lange (4; 0/4)

Portugal

Lisbon, Instituto Portugues de Oncologia, CIC 300, M. Abecasis (3; 3/0)

Russian Fed.

Moscow, Center of Cell Technologies, K. Ekaterina (117; 62/55)
Moscow, Cancer Research centre, G. Mentrevich (6; 0/6)
Moscow, Research Haematology Center of RAS, V.G. Savtchenko (11; 11/0)
Novosibirsk, Inst. Clinical Immunolgy, CIC 376, I. Lisukov (21; 3/18)
St. Petersburg, Pavlov Medical University, CIC 725, B.V. Afanassiev, L. Zubarovskaya (8; 0/8)
St. Petersburg, Pavlov Medical University, CIC 725, B.V. Afanassiev, L. Zubarovskaya (31; 0/31)
Moscow, Russian Children's Hospital, CIC 694, A. Maschan, E. Skorobogato, E. Pachanov (12; 11/1)

Serbia

Belgrade, Military Medical Academy, CIC 582, D. Stamatovic (4; 0/4)

Slovak Republic

Bratislava, National Cancer Institute, J. Lakota (4; 3/1)
Bratislava, University Hospital,CIC 610, M. Mistrik (31; 0/31)

Slovenia

Ljublijana, Educell d.o.o, N. Kregar-Velikonja (7; 0/7)
Ljublijana, University Medical Centre, CIC 640, J. Pretnar (15; 0/15)

Spain

Barcelona, Hospital Clinic, CIC 214, M. Rovira (1; 1/0)
Barcelona, ITRT Inst. de Terapia Regenerativa Tissular, C.M. Teknon (26; 0/26)
Cordoba, Hospital Reina Sofia, CIC 238, A. Torres-Gomez (34; 0/34)
Madrid, Cellerix, J. Bravo (44; 33/11)
Madrid, Hospital Universitario San Carlos, J. Diaz-Mediavilla, L. Llorente, R. Martinez (3; 0/3)
Madrid, Hospital General Universitario Gregorio Marañon, CIC 819, J.L. Diez-Martin (1; 1/0)
Madrid, Hospital Niño Jesus, CIC732, M.A. Diaz (1; 1/0)
Murcia, Hospital Virgen de la Arrixaca, CIC 323, JM. Moraleda, A. Morales Lazaro (16; 0/16)
Murcia, Hospital General Universitario Morales Meseguer, CIC 735, V. Vicente-Garcia, I. Heras (6; 0/6)
Palma de Mallorca, Hospital Uni. Son Espases (Son Dureta), CIC 722, J. Besalduch, M. Canaro (4; 0/4)
Pamplona, Clinica Uni de Navarra, F. Prosper Cardoso (18; 1/17)
Salamanca, Complejo Hospital, CIC 727, D. Caballero (13; 13/0)
Valencia, Hospital Clinico Universitario, CIC 282, c. Solano (1; 1/0)

Sweden

Lund, University Hospital, CIC 283, S. Lenhoff (2; 2/0)

Switzerland

Basel, University Hospital Basel, D. Schaefer (1: 0/1)
Geneva, Hôpital Cantonal Universitarie, CIC 261, J. Passweg, Y. Chalandon, M. Ansari (1; 1/0)
Geneva, Hôpital Cantonal Universitarie, CIC 261, J. Passweg, Y. Chalandon, M. Ansari (7; 0/7)
Zürich, Universitäts Kinderklinik, CIC 334, R. Seger, F. Scherer (1; 1/0)
Zürich, Schulthess Klinik, M. Steinwachs (76; 10/66)

Turkey

Ankara, University Faculty of Medicine, A.R. Akar (61; 0/61)
Ankara, Ihsan Dogramaci Children's Hospital (Hacettepe), CIC 399, A.Tuncer, D. Uckan (3; 3/0)
Ankara, Stem Cell Transplant Center, CIC 436, D. Uvkan-Cetinkaya, N. Günes (2; 2/0)
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Antalya, Medical Park Hospitals, CIC 919, Y. Koc (7; 7/0)

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London, Hammersmith Hospitals NHS Trust, CIC 205, J. Apperley, E. Olavarria, E.
Kanfer, A. Rahemtulla, R. Szydlo (7; 7/0)
London, Great Ormond Street Hospital, CIC 243, P. Veys (4; 4/0)
Manchester, Royal Children's Hospital, CIC 521, R. Wynn (2; 2/0)
Oswestry, Oswestry Orthopaedic Hospital, P. Harrison (30; 0/30)