The survey on cellular and engineered tissue therapies in Europe in 2013

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ABSTRACT

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 treatments for the reconstitution of hematopoiesis. 318 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 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%), hematopoietic stem cells (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%. 33% 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.

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INTRODUCTION

Cell- and tissue-based therapeutic approaches are progressively gaining ground in the clinics in part due to renewed interest shown by public bodies, e.g. 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 set-up, 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), 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.

Here 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 as 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 (DLIs) and non-manipulated 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 (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. 687 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, 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

318 teams from 31 countries (28 European, 3 EBMT affiliated countries) responded to the *cellular and engineered tissue therapy survey of patients treated in 2013*. 145 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 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 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 6 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 (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 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 amongst 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 amongst 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*). Amongst the remaining indications, most patients were treated for skin reconstruction (burns) or for solid tumor excision (Table 1). 118 patients were reported under miscellaneous, i.e. they were treated for indications other than those mentioned in the form, e.g. 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%), 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 and 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 (Figure 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 2 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 use of combinational treatments, e.g. 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 of the 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). 92% of cardiovascular, 53% of musculoskeletal/rheumatological and 45% of neurological indications were treated with non-expanded cells, while gastrointestinal indications were mainly treated (60%) with expanded cells. Expanded cells 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.

33% 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. 85% of treatments delivered via 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 (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 via membrane/scaffold (53% and 52% respectively) or suspension (40% and 34% respectively), with 92% of treatments for skin reconstruction (burns) administered via 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 (Figure 4). The number of reporting teams per 10 million inhabitants was higher than 4 in Slovenia, Finland, Belgium, Lithuania, The Netherlands, Switzerland and Spain (again in decreasing order).

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

Treatments as part of a clinical trial vs. 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 individualized/single cases. 14 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 (Figure 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 by-pass graft in 2013, numbers in previous years were also rather limited (6 in 2012 and 9 in 2011). The treatments for patients with heart failure accounted for 9% of all cardiovascular ones, as 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, is 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, in order 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 individualised/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 that a personalized team-hunting strategy (e.g., towards 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 (i) to demonstrate the increased recognition of the initiative by the field and (ii) to convey the importance to further develop it through contributions which are transparently acknowledged without compromising opportunities to publish or protect clinical data.

Towards 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, towards more timely dissemination of the information to the Regenerative Medicine and Tissue Engineering Community. Indeed a larger collective effort will be necessary in order 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.

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Disclosure statement

No competing financial interests exist.

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Appendix: List of centres reporting use of cellular and engineered tissue therapy in Europe in 2013

Legend to the Tables

Table 1

Number of reported cellular and engineered tissue therapy treatments in Europe in 2013 sorted by indication, cell source and donor type.

Abbreviations: HSC = hematopoietic stem cells; MSC = mesenchymal stromal/stem cells, GvHD = graft versus host disease

Table 2

Number of reported cellular and engineered tissue therapy treatments in Europe in 2013 sorted by processing mode.

Abbreviation: non exp = non expanded, GvHD = graft versus host disease, HSC = hematopoietic stem cells.

Table 3

Number of reported cellular and engineered tissue therapy treatments in Europe in 2013 sorted by delivery mode.

Abbreviation: i.v. = intravenous

Supplementary Table 1

Extended questionnaire used to collect data on cellular and engineered tissue therapy treatments in Europe in 2013.

Legend to the Figures

Figure 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 EBMT survey sheet.

Figure 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).

Figure 3

Number of cellular and engineered tissue therapies per 10 million inhabitants reported in Europe in 2013. Data used for this map were derived from the extended questionnaire or the standard EBMT survey sheet.

Figure 4

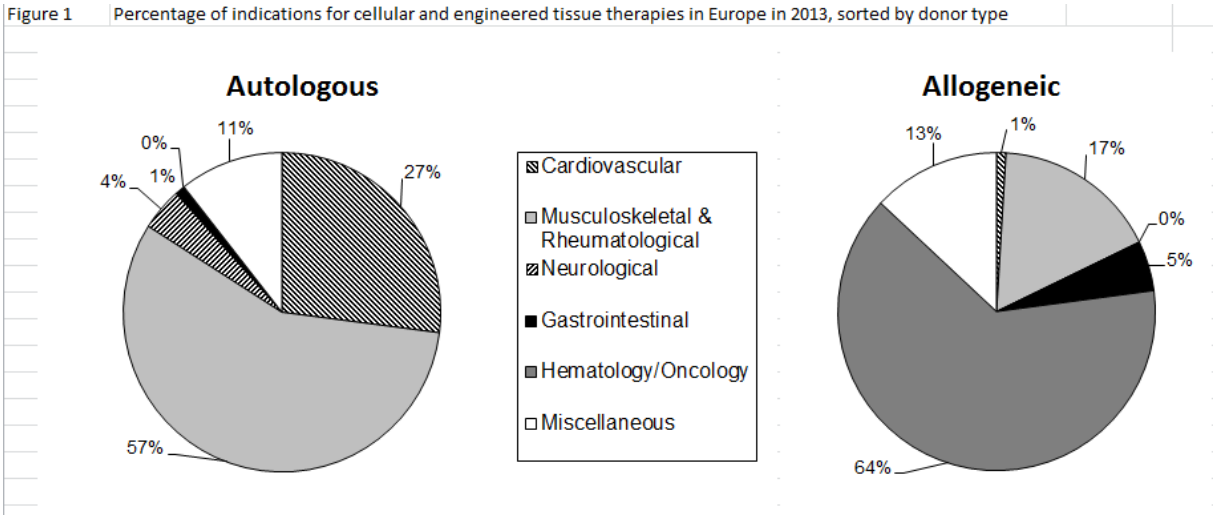
Number of teams per 10 million inhabitants reporting cellular and engineered tissue therapies in Europe in 2013. Data used for this map were derived from the extended questionnaire or the standard EBMT survey sheet.

Figure 5

Number of reporting teams and number of 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).

The survey on cellular and engineered tissue therapies in Europe in 2013

Legend to the Figures



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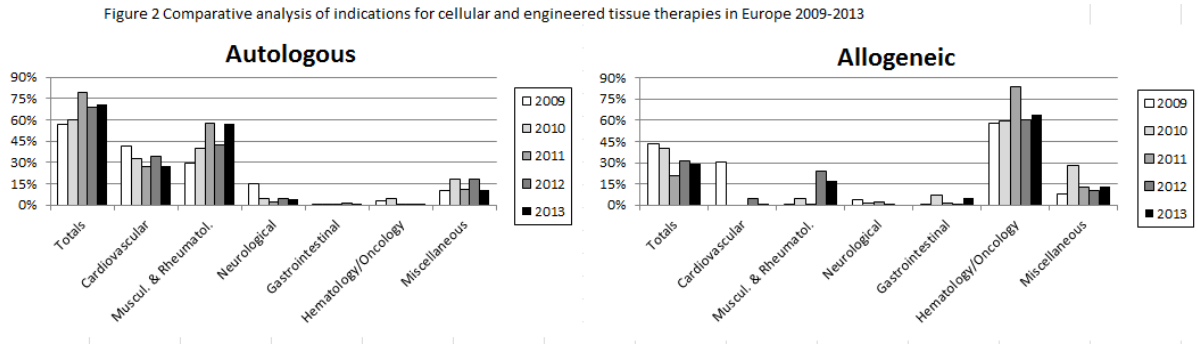

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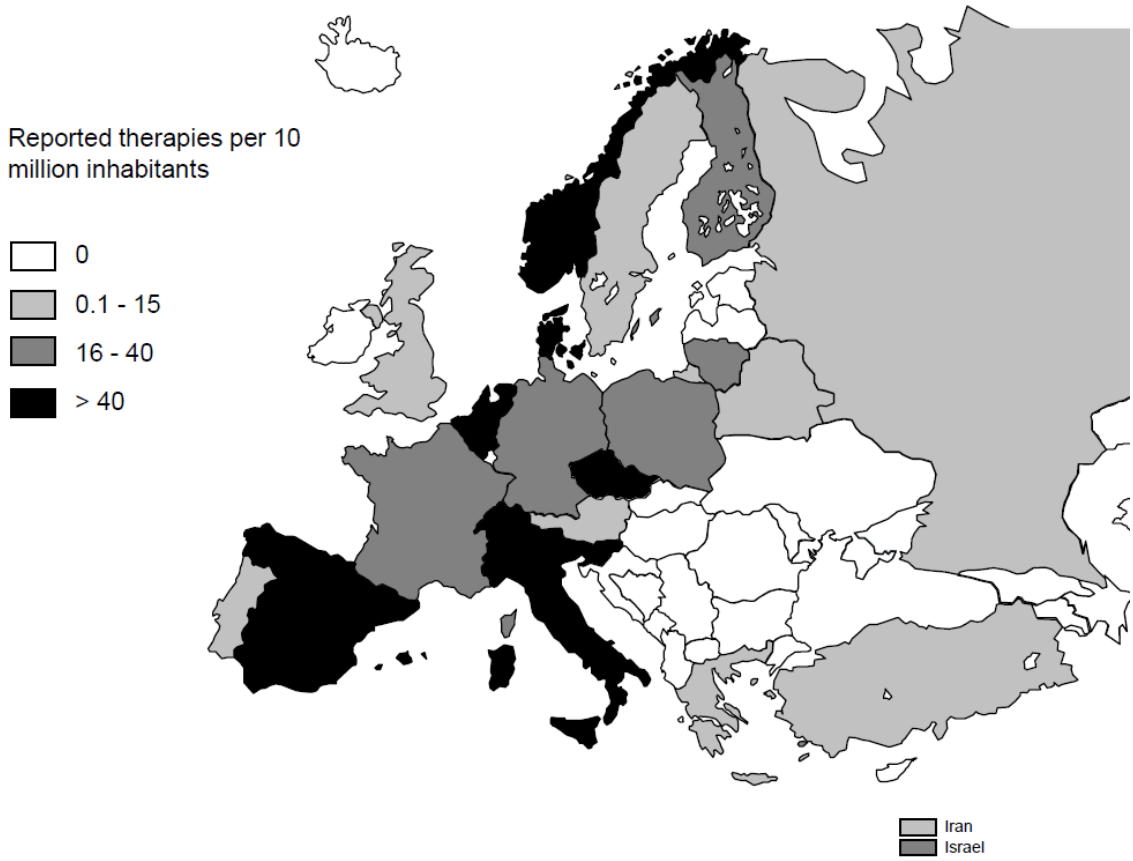

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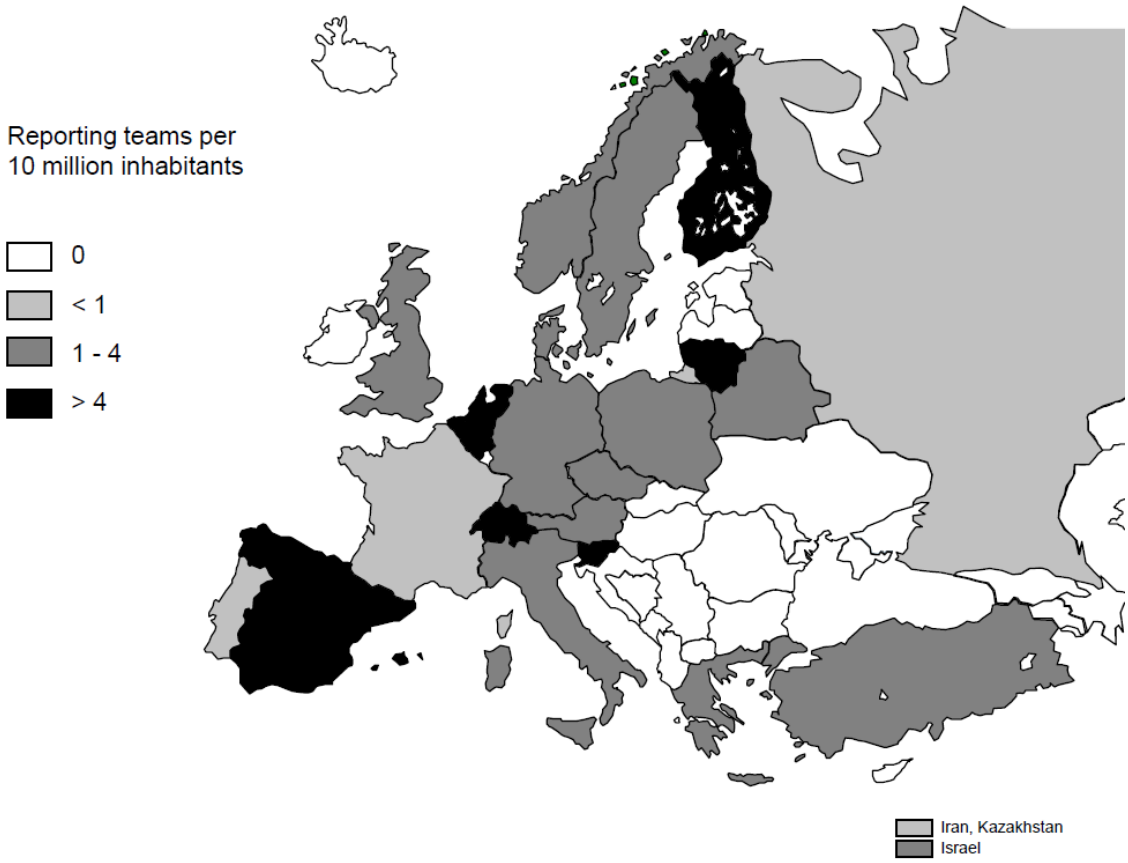
Figure 4



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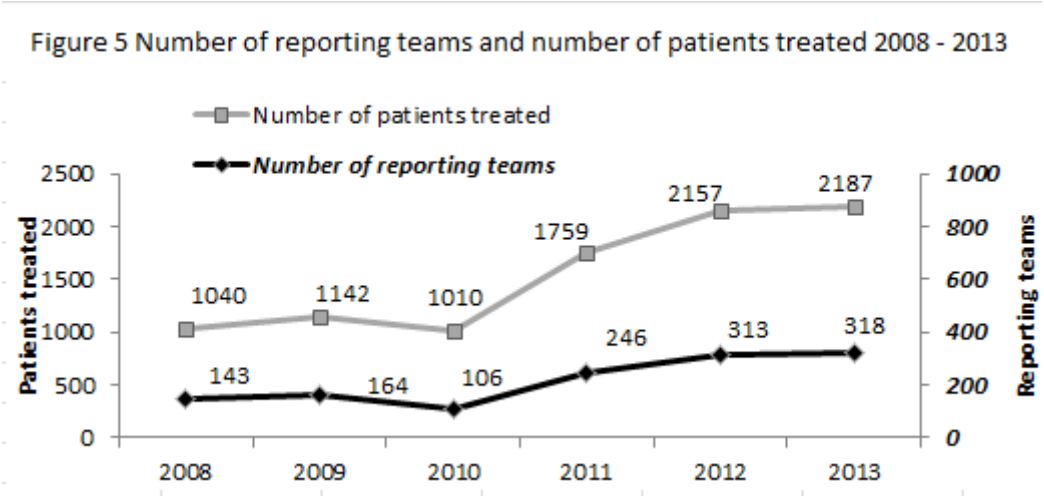

Figure 5

Number of reporting teams and number of 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).

Table 1

	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

Table 2

Indications	**Cell processing**							
	non exp.	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

Table 3

Indications	Cell delivery mode			
	i.v. or i.a.	intra-organ		
		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 imperfecta		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

Appendix: List of European Centres Reporting Cellular and Tissue Engineered Therapies 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)

2013 SURVEY OF NOVEL CELL THERAPIES / TISSUE ENGINEERING

2013 Activity	Donor Type	Part A: Cell type and source															Part B: Processing								Part C: Delivery mode			
		Hematopoietic cells				Mesenchymal stromal cells					Chon-dro-cytes	Kera-tino-cytes	Dermal-fibro-blasts	Panc-reatic islets	Muscle cells	Dend-ritic	Other	B1		B2		B3		B4		I.V. or I.A.	Intra-organ		
		BM	CB	PB	Other	BM	Plac	CB	Fat	Other								Nonex-panded	Expand-ed	Untrans-duced	Trans-duced	Un-sorted	Sorted	Auto-mated	Manual		Sus-pension	Gel	Membrane/ scaffold
Cardiovascular																													
Peripheral artery disease	Allogeneic																												
	Autologous																												
Cardiomyopathy	Allogeneic																												
	Autologous																												
Heart failure	Allogeneic																												
	Autologous																												
Myocardial ischemia	Allogeneic																												
	Autologous																												
Bypass graft	Allogeneic																												
	Autologous																												
Valve replacement	Allogeneic																												
	Autologous																												
Decubitus + leg ulcers	Allogeneic																												
	Autologous																												
Other	Allogeneic																												
	Autologous																												
Musculoskeletal/Rheumatological																													
Bone repair (maxillofacial)	Allogeneic																												
	Autologous																												
Bone repair (orthopaedics)	Allogeneic																												
	Autologous																												
Osteogenesis imperfecta	Allogeneic																												
	Autologous																												
Cartilage repair (maxillofacial)	Allogeneic																												
	Autologous																												
Cartilage repair (orthopaedics)	Allogeneic																												
	Autologous																												
Muscle repair	Allogeneic																												
	Autologous																												
Tendon / ligament	Allogeneic																												
	Autologous																												
Reconstructive surgery/	Allogeneic																												
tissue enhancement	Autologous																												
Systemic lupus erythematosus	Allogeneic																												
	Autologous																												
Scleroderma	Allogeneic																												
	Autologous																												
Arthritis	Allogeneic																												
	Autologous																												
Other	Allogeneic																												
	Autologous																												

2013 Activity	Donor Type	Part A: Cell type and source															Part B: Processing								Part C: Delivery mode			
		Hematopoietic cells				Mesenchymal stromal cells					Chon-dro-cytes	Kera-tino-cytes	Dermal-fibro-blasts	Panc-reatic islets	Muscle cells	Dend-ritic	Other	B1		B2		B3		B4		I.V. or I.A.	Intra-organ		
		BM	CB	PB	Other	BM	Plac	CB	Fat	Other								Nonex-panded	Expand-ed	Untrans-duced	Trans-duced	Un-sorted	Sorted	Auto-mated	Manual		Sus-pension	Gel	Membrane/ scaffold
Neurological																													
Multiple Sclerosis	Allogeneic																												
	Autologous																												
Amyotrophic lateral sclerosis	Allogeneic																												
	Autologous																												
Parkinson's	Allogeneic																												
	Autologous																												
Peripheral nerve regeneration (trauma)	Allogeneic																												
	Autologous																												
Other	Allogeneic																												
	Autologous																												
Gastrointestinal																													
Crohn's disease	Allogeneic																												
	Autologous																												
Liver insufficiency	Allogeneic																												
	Autologous																												
Miscellaneous																													
Skin reconstruction - burns	Allogeneic																												
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Cornea repair	Allogeneic																												
	Autologous																												
Diabetes	Allogeneic																												
	Autologous																												
Solid tumor	Allogeneic																												
	Autologous																												
Other	Allogeneic																												
	Autologous																												
Hematology/Oncology																													
GvHD prevention or treatment	Allogeneic																												
HSC graft enhancement	Allogeneic																												
	Autologous																												
TOTALS																													

How many of the patients were treated as part of a clinical trial, as an individualized/single case or as a routine therapy? Please enter the number in the relevant box	Clinical trial		Individualized/single case		Routine therapy		Comments:

Tick relevant organisation EBMT CIC No: ……. EULAR ☐ ICRS ☐ ISCT ☐ TERMIS ☐

Team members (up to 4 names), name and address of unit

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