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Spatial and temporal structure of the clinical research based on mesenchymal stromal cells: A network analysis

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Abstract

Background aims. Using innovative tools derived from social network analysis, the aims of this study were (i) to decipher the spatial and temporal structure of the research centers network dedicated to the therapeutic uses of mesenchymal stromal cells (MSCs) and (ii) to measure the influence of fields of applications, cellular sources and industry funding on network topography. *Methods.* From each trial using MSCs reported on ClinicalTrials.gov, all research centers were extracted. Networks were generated using Cytoscape 3.2.2, where each center was assimilated to a node, and one trial to an edge connecting two nodes. *Results.* The analysis included 563 studies. An independent segregation was obvious between continents. Asian, South American and African centers were significantly more isolated than other centers. Isolated centers had fewer advanced phases ($P < 0.001$), completed studies ($P = 0.01$) and industry-supported studies ($P < 0.001$). Various thematic priorities among continents were identified: the cardiovascular, digestive and nervous system diseases were strongly studied by North America, Europe and Asia, respectively. The choice of cellular sources also affected the network topography; North America was primarily involved in bone-marrow–derived MSC research, whereas Europe and Asia dominated the use of adipose-derived MSCs. Industrial funding was the highest for North American centers (90.5%). *Conclusions.* Strengthening of international standards and statements with institutional, federal and industrial partners is necessary. More connections would facilitate the transfer of knowledge, sharing of resources, mobility of researchers and advancement of trials. Developing partnerships between industry and academic centers seems beneficial to the advancement of trials across different phases and would facilitate the translation of research discoveries.

Key Words: *clinical trials as topic, mesenchymal stromal cells, regenerative medicine, social network analysis, stem cells*

Introduction

Collaboration is a necessity in the scientific world, promoting shared resources, funding, facilities and ideas. Knowledge is spread and combined more easily [1]; for example, co-authored papers have been shown to be cited more frequently [2]. This is called "the geography of science," a constantly evolving dynamic between international collaborations and regional issues [2]. Collaborations arise all over the world and form structured networks that could participate to the development and growth of the territories. Their development is under influence of various intrinsic and extrinsic factors, such as private–public partnership (exploiting research competitiveness), history between the partners (including language and colonial past) or government priorities (in terms of science and industrial policies) [2]. In many fields of science, shrinking of financing necessitates finding new ways to optimize existing resources [3,4].

In the connected world of the biomedical sciences, network analyses can be performed, taking advantage of the tools developed in social sciences. Social network analysis (SNA) combines a visualization of relationships both between and within social groups, utilizing the statistical power of graph theory [5]. For SNA, the priority is to analyze the relationships between actors rather than solely individual characteristics. It is possible to measure the influence

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of an individual within the community or the influence of several characteristics or actions on the network evolution [1]. Such analyses would help to identify gaps and reveal necessary and appropriate collaborations or new research opportunities [6]. In biomedicine, networks have been used to describe relationships between metabolic diseases and comorbidities [7], gene–disease associations [8], dynamic of infectious diseases transmission [9] or collaborations in scientific publications [10].

With identification of bone marrow mesenchymal stromal cells (BM-MSCs) by Friedenstein in 1967 [11], regenerative medicine took a new turn. Ethical, biological and technical considerations made these adult cells popular compared with embryonic stem cells, and the first clinical trial with cultured-expanded MSCs was conducted in 1995 [12]. We have previously shown that hundreds of clinical trials are currently registered and running, and some of them already yielded encouraging results in various fields of application, such as amyotrophic lateral sclerosis, graft-versus-host disease, osteoarthritis, refractory Crohn disease, critic limb ischemia or ischemic cardiomyopathy [13,14]. Therapeutic efficacy of these MSCs was mainly based on their paracrine activities, with trophic, immunomodulatory and antimicrobial effects, as well as their differentiation multipotency [15].

MSCs remain a young field of research [16], with few human published results; exploration of clinical trial registers gives a more up-to-date and representative snapshot of the field of stem cells [17]. This is reinforced by the fact the International Committee of Medical Journal Editors has, since 2005, required registration of clinical trials before enrollment of the first patient. It is therefore possible to know the existence of the clinical trials several years before publication, regardless of the outcome of the study. Launched in 2000, concomitantly with the development of stem cell–related trials, the ClinicalTrials.gov database (CTD) so represents an attractive option for aggregation and analyses, to embrace both spatial and temporal complexity of this constantly evolving field [18]. The analysis of clinical trials using tools inspired from SNA seems natural because clinical collaborations are often referred as "networks" (e.g., the Canadian Stem Cell Network SCN or the German Stem Cell Network) [19]. Nevertheless, this approach has not yet been applied to this clinical area, despite some systematic reviews that have been produced [13,20]. A structural analysis would help to understand and optimize the dynamics of the implementation of these trials [21], as well as how the teams work in synergy and share costly resources to develop and complete clinical trials.

The study presented here, is an examination of collaborative networks associated with clinical trials registered at ClinicalTrials.gov about MSCs, using tools derived from social network analysis. The aims of this study were (i) to decipher the spatial and temporal structure of the research network dedicated to the therapeutic uses of MSC and (ii) to measure the influence of fields of applications, cellular sources and industry funding on network topography.

Methods

Data selection

The search strategy in CTD used the keywords "stromal OR stem OR mesenchymal OR progenitor." All trials and their characteristics were exported to be aggregated and computerized using a custom made Perl script. Trials were included if a cell therapy using MSCs was performed (isolated by culture and expansion, or by selection). Trials using cell therapy by the corresponding heterogeneous fraction were also considered. The last search was performed on May 17, 2016.

Unit of analysis

The unit of analysis is the "city," which was assimilated to a research center (with the limit that different units using MSCs within the same city represent a single center). Research centers were extracted from each included trial. If there were several centers, they were linked together in random order to form a ring. Finally, all connected cities formed the MSC network. For each city, its uniqueness was checked. Indeed, some cities may have different names (e.g., Beijin/Beijing), or one denomination may in fact reveal different cities (e.g., the city of Springfield was found in several states across the United States). The population size was recorded according to the latest census available at http://www.citypopulation.de. Centers were classified into six continents: Africa, Asia, Europe, North America, Oceania and South America.

Graphical representation of networks

Graphical representation was generated using Cytoscape 3.2.2 [22], where each city was assimilated to a circle (a node) with a size correlated to the number of trials conducted. One trial represented one tie (an edge) connecting two nodes. A spring-like force was applied between the nodes.

Parameters read-out

Table I summarized the parameters of the social network analysis that may be computed from Cytoscape software [23,24]. Briefly, the node size is the number of trials for a given center. Network density measures the intensity of interaction between cities in the process of participating in clinical trials. The degree

Table I. Parameters of social network analysis that may be computed from Cytoscape software.

Parameter	Description
Degree	Number of studies shared with other cities.
Network density	Density is the number of actual connections between cities divided by the number of possible connections. Higher density indicates a greater degree of interaction between cities in the process of participating in clinical trials. Unconnected centers are isolated nodes.
Network centralization	This percentage indicates the degree of asymmetry in the distribution of connections in the network. A high centralization score indicates that some members are far more central than others within the network.
Network heterogeneity	Variance of the degree. High heterogeneity reflects a great disparity in connectivity between cities.
Clustering coefficient	A density measure of local connections; the likelihood that any two cities that are connected to the same city are also connected (triplicates). This parameter should reflect the degree to which different trials were done in collaborative groups.
Closeness centrality	Indicates the influence of a node on the entire network, the proximity between cities (cohesion of a network).
Betweenness centrality	Reflects the bridge role of a city in the MSC network. It is a measure of the influence of a node over the flow of studies between other nodes. It may also be defined as the number of times a node needs a given node to reach another node.
Neighborhood connectivity	Average number of neighbors of neighbors.
Multiple partners	Proportion of connected partners cities with which at least two studies are shared.

is the number of studies shared with other cities; network heterogeneity represented a dispersion measure of the degree, that is, disparity between cities. A clustering coefficient reflects the manner in which research was done in collaborative groups. Centrality (betweenness and closeness) measures the influence of a trial center's position within a network. Average length path is the mean minimum number of edges that must be crossed to get from one node to another. For each node, the proportion of completed studies were also computed, as was the proportion of studies with a predominantly industrial financing (derived from using Califf *et al.*'s algorithm) [25]. The phase score reflected the progress of the phases of clinical trials (i.e., their maturity). Phase 1 represented safety studies, phase 1/2 or phase 2 were proof-of-concept for efficacy and phase 2/3 or phase 3 were comparison with the standard or best-known treatment [16].

MSC fields of applications

We used the Medical Subject Headings (MeSH), from the U.S. National Library of Medicine, as has been done in other mapping research [14,26,27]. The MeSH is a controlled vocabulary thesaurus used for indexing articles for PubMed. CTD used the "Diseases" branch [C] to describe study conditions. This branch contains 26 sub-branches, corresponding to major disease groupings (e.g., [C06] Digestive System Diseases). If the CTD failed to attribute MeSH keywords to a trial, the most appropriate was added manually.

Statistical analyses

Characteristics across continents were statistically compared using Dunn test with Bonferroni correction to estimate mean differences between groups. Network characteristics were computed using Cytoscape 3.2.2, exported then further analyzed using Stata 13.1 (StataCorp).

Results

On the 6357-screened trials, 563 concerned MSC and 335 concerned their corresponding heterogeneous non-cultured crude fraction. Among MSC sources, bone marrow, adipose and umbilical cord tissues were used in 329, 99 and 128 studies, respectively. Table II shows several features about MSC registered trials involved in a network. Half of the trials were recruiting, half were originated from Asian countries and half were randomized. Studies were small sized with a median interquartile range of 25 [12; 50] patients.

Geographical strategies and temporal evolution of the MSC network

Present network structure is in Figure 1. It clearly demonstrates independent segregation between Asian, European and North America centers. Oceania (Australia and New Zealand) strongly works with both Europe and North America (Supplemental Figure S1). Some relationships between the United States (e.g., Atlanta, Baltimore or Boston), Oxford in the United Kingdom and Pavia and Pesaro in Italy can be observed (Supplemental Figure S1).

That distribution has settled gradually over time (Figure 2a). At first, North American centers were the only ones that were structured for the studies from 1999 to 2005, with few centers (hub nodes) centralizing the connections. In a second step (until 2008), interactions between North American centers intensified,

Table II. Characteristics of the trials included in this study.

		MSCs			
	Heterogeneous fraction	All studies	BM-MSC	ASC	UC-MSC
State of the study	335	563	329	99	128
Not yet recruiting	62 (18.5%)	153 (27.2%)	89 (27.1%)	28 (28.3%)	80 (62.5%)
Recruiting	158 (47.2%)	271 (48.1%)	151 (45.9%)	47 (47.5%)	70 (54.7%)
Enrolling by invitation	15 (4.5%)	16 (2.8%)	7 (2.1%)	2 (2.0%)	4 (3.1%)
Suspended	4 (1.2%)	3 (0.5%)	3 (0.9%)	0 (0.0%)	0 (0.0%)
Withdrawn	3 (0.9%)	4 (0.7%)	2 (0.6%)	0 (0.0%)	2 (1.6%)
Completed	82 (24.4%)	103 (18.3%)	68 (20.7%)	20 (20.2%)	15 (11.7%)
Terminated	10 (3.0%)	11 (2.0%)	7 (2.1%)	2 (2.0%)	2 (1.6%)
No longer available	1 (0.3%)	2 (0.4%)	2 (0.6%)	0 (0.0%)	0 (0.0%)
Study size	332	560	327	98	128
Median (interquartile range)	30 (12–69.5)	25 (12–50)	25 (10–54)	19 (10–41.5)	30 (10–50)
Geographic area	314	527	308	92	120
Asia	104 (33.1%)	268 (50.9%)	119 (38.6%)	48 (52.2%)	91 (75.8%)
Central and South America	43 (13.7%)	22 (4.2%)	9 (2.9%)	3 (3.3%)	9 (7.5%)
North America	80 (25.5%)	107 (20.3%)	86 (27.9%)	10 (10.9%)	10 (8.3%)
Europe	104 (33.1%)	144 (27.3%)	98 (31.8%)	43 (46.7%)	7 (5.8%)
Africa	4 (1.3%)	9 (1.7%)	8 (2.6%)	0 (0.0%)	1 (0.8%)
Oceania	0 (0.0%)	13 (2.5%)	11 (3.6%)	0 (0.0%)	2 (1.7%)
Randomization	331	560	327	98	128
Single arm study	142 (42.9%)	205 (36.6%)	123 (37.6%)	39 (39.8%)	40 (31.3%)
Randomized	140 (42.3%)	267 (47.7%)	153 (46.8%)	49 (50.0%)	63 (49.2%)
Non-randomized	49 (14.8%)	88 (15.7%)	51 (15.6%)	10 (10.2%)	25 (19.5%)
Main sponsor	335	563	329	99	128
National Institutes of Health	4 (1.2%)	8 (1.4%)	8 (2.4%)	0 (0.0%)	0 (0.0%)
Industry	77 (23.0%)	166 (29.5%)	82 (24.9%)	42 (42.4%)	38 (29.7%)
Other	254 (75.8%)	389 (69.1%)	239 (72.6%)	57 (57.6%)	90 (70.3%)
Study phase	335	563	329	99	128
Phase 1	79 (23.6%)	164 (29.1%)	97 (29.5%)	32 (32.3%)	34 (26.6%)
Phase 1/phase 2	118 (35.2%)	224 (39.8%)	116 (35.3%)	37 (37.4%)	66 (51.6%)
Phase 2	63 (18.8%)	109 (19.4%)	72 (21.9%)	19 (19.3%)	17 (13.3%)
Phase 2/phase 3	15 (4.5%)	17 (3.0%)	14 (4.3%)	1 (1.0%)	2 (1.5%)
Phase 3	15 (4.5%)	21 (3.7%)	13 (4.0%)	4 (4.0%)	4 (3.1%)
N/A	45 (12.5%)	28 (5.0%)	14 (4.3%)	6 (6.0%)	5 (3.9%)
Area of expertise	329	557	327	97	126
Bacterial infections and mycoses	0 (0.0%)	5 (0.9%)	3 (0.9%)	1 (1.0%)	1 (0.8%)
Virus diseases	0 (0.0%)	3 (0.5%)	1 (0.3%)	1 (1.0%)	1 (0.8%)
Parasitic diseases	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Neoplasms	2 (0.6%)	8 (1.4%)	5 (1.5%)	1 (1.0%)	2 (1.6%)
Musculoskeletal diseases	42 (12.8%)	78 (14.0%)	45 (13.8%)	17 (17.5%)	14 (11.1%)
Digestive system diseases	15 (4.6%)	67 (12.0%)	31 (9.5%)	17 (17.5%)	20 (15.9%)
Stomatognathic diseases	2 (0.6%)	15 (2.7%)	5 (1.5%)	3 (3.1%)	0 (0.0%)
Respiratory tract diseases	15 (4.6%)	34 (6.1%)	19 (5.8%)	4 (4.1%)	11 (8.7%)
Otorhinolaryngologic diseases	4 (1.2%)	1 (0.2%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Nervous system diseases	76 (23.1%)	112 (20.1%)	68 (20.8%)	17 (17.5%)	27 (21.4%)
Eye diseases	10 (3.0%)	11 (2.0%)	9 (2.8%)	1 (1.0%)	1 (0.8%)
Male urogenital diseases	17 (5.2%)	33 (5.9%)	18 (5.5%)	6 (6.2%)	9 (7.1%)
Female urogenital diseases and pregnancy complications	11 (3.3%)	34 (6.1%)	18 (5.5%)	9 (9.3%)	7 (5.6%)
Cardiovascular diseases	119 (36.2%)	100 (18.0%)	63 (19.3%)	13 (13.4%)	22 (17.5%)
Hemic and lymphatic diseases	2 (0.6%)	15 (2.7%)	10 (3.1%)	1 (1.0%)	4 (3.2%)
Congenital, hereditary, and neonatal diseases and abnormalities	18 (5.5%)	30 (5.4%)	12 (3.7%)	5 (5.2%)	12 (9.5%)
Skin and connective tissue diseases	19 (5.8%)	45 (8.1%)	19 (5.8%)	9 (9.3%)	16 (12.7%)
Nutritional and metabolic diseases	27 (8.2%)	36 (6.5%)	20 (6.1%)	5 (5.2%)	10 (7.9%)
Endocrine system diseases	21 (6.4%)	37 (6.6%)	18 (5.5%)	5 (5.2%)	13 (10.3%)
Immune system diseases	14 (4.3%)	105 (18.9%)	68 (20.8%)	9 (9.2%)	27 (21.4%)
Wounds and injuries	40 (12.2%)	65 (11.7%)	39 (11.9%)	15 (15.5%)	13 (10.3%)

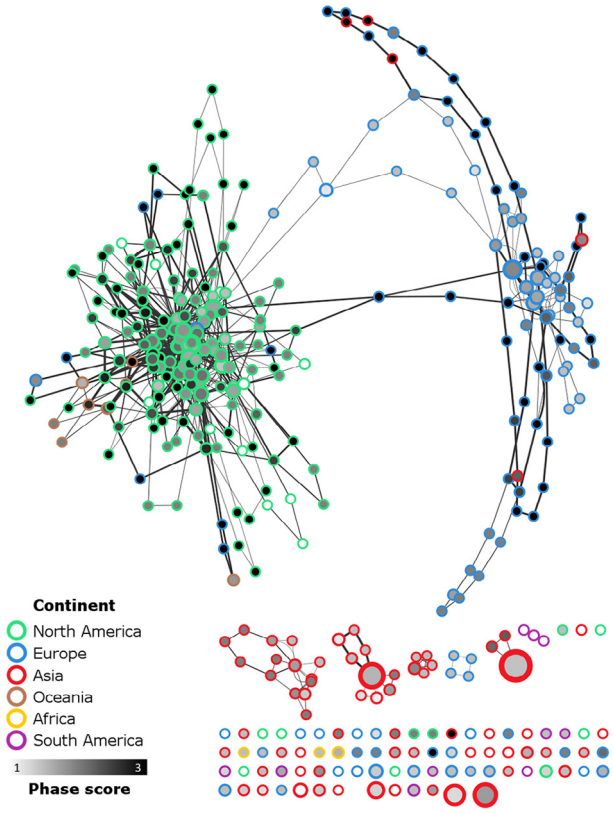

Figure 1. Global network of MSC trials. One circle (node) represents a city, which was assimilated to a research center. Its size is proportional to the number of trials in which the center is involved. The outer color of the circle codes for the continent of the city: green for North America, blue for Europe, red for Asia, brown for Oceania, yellow for Africa and purple for South America. A trial is represented by a line (an edge) between all involved clinical centers, and the line thickness is proportional to the number of trial participants, and a spring-like force was applied between the nodes. The internal color represents the maturity of the studies conducted and is expressed as the score phase ranging between 1 (white, i.e., toward phase 1 studies) and 3 (black, toward phase 3 studies).

while European centers begin to structure themselves around few nodes and were poorly linked to North America. The number of isolated nodes or ring-shape forms increased, illustrating sparse clinical trials initiatives with no to limited interactions. In a third step (until 2012), European and North American networks, respectively, increase their connections within the continent, but there was no evolution between them. The structure until 2015 illustrates the burst of new clinical centers in North America, whereas the network seems more loosely and more centralized for Europe. The number of Asian centers is also increasing, many of them being alone or in small-sized clusters, with four high weighted centers. Over time, the mean node size experienced the strongest growth for Asia, whereas degree and number of new centers increased slightly or even stagnated (Figure 2b–d). North America had the highest values for node degree and number of new centers (Figure 2c,d). Europe exhibited a similar growth curve to North America for node size and new centers, whereas node degree appeared to reach a plateau (Figure 2b–d).

Increasing the connection between the centers improved study completion and maturity

Table III confirms that Asian, South American and African centers are significantly most isolated compared with other centers (48.6%, 70.0% and 100% of isolated nodes, respectively), as reflected by more isolated nodes at the bottom of Figure 1. The degree of North America centers is twofold higher than the European one- and fourfold higher than Asian centers, whereas the number of studies is only significantly lower in European centers (Table III, Figure 2c). Particularly on the Asian continent, different profiles are encountered in the top five countries sorted by mean size (Supplemental Table S1). Iran and South Korea have the greatest number of studies by center but with few centers involved in total, whereas China has a high number of studies in addition to a greater number of centers (20 centers, Supplemental Table S1). Conversely, Table III shows North America centers are more frequently involved into workgroups (higher degree and neighborhood connectivity, lower isolated centers). Isolated centers have significantly lower phase score ($P < 0.001$), fewer completed studies ($P = 0.01$) and fewer industry-supported studies ($P < 0.001$).

Analysis of the phase score showed different levels of involvement among centers

The maturity of the clinical trials conducted by each center was estimated by calculating the phase score that corresponds to the mean phase of the studies in which each clinical center is involved. The phase score ranging from 1 (white, phase 1 only) to 3 (black, phase 3 only) is then represented by a shade of gray inside each circle (Figure 1, Figure 6). Figure 1 shows a differential spatial distribution with the presence of highest and lowest phase scores at the border of the network. By cutting out in tertiles, we categorize these centers according to their maturity: phase score below 1.6, score between 1.6 and 2.2 and score above 2.2, that is, 122, 124 and 123 centers, respectively. Figure 3 statistically confirms the visual impression when centers are gathered according to their score phase into those 3 categories. Compared with centers with a phase score between 1.6 and 2.2, less advanced centers (below 1.6) are more distant from the other centers (significant decrease of betweenness and closeness centralities, increase in isolated nodes number). They also share fewer projects (significant decrease in the degree, clustering coefficient and

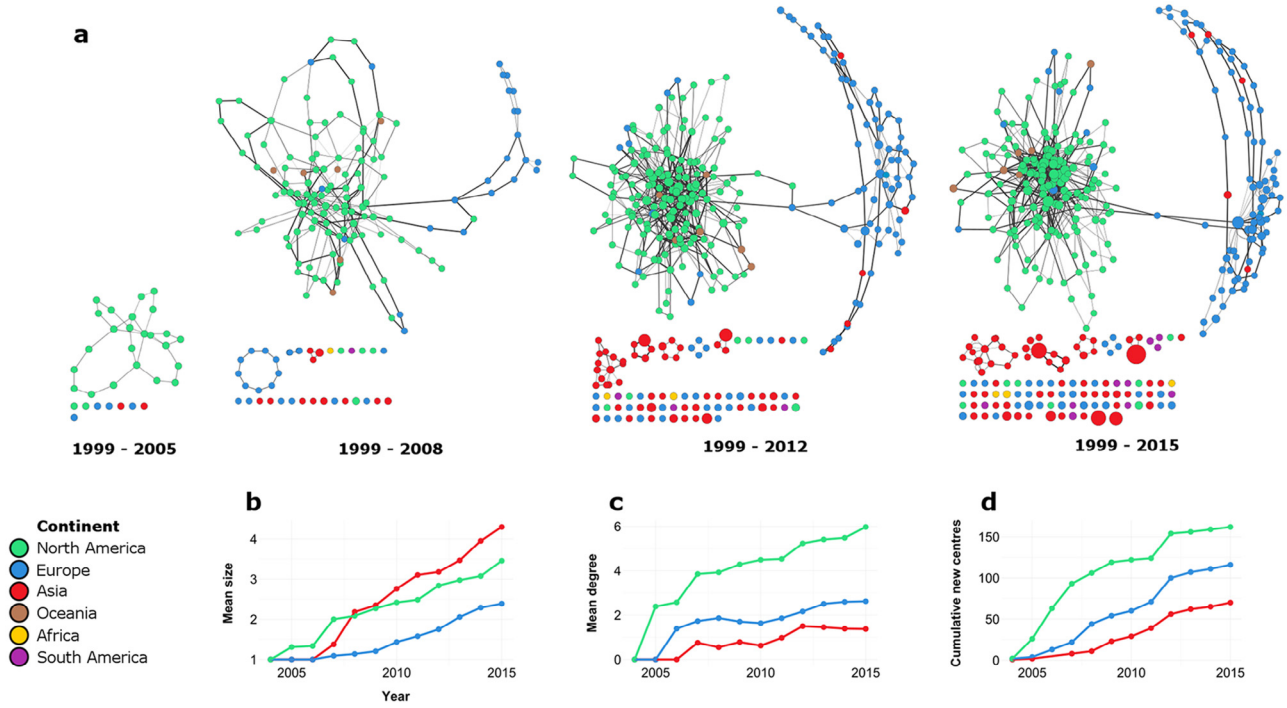

Figure 2. Temporal evolution of the MSC network structuring. (a) One circle (node) represents a city, which was assimilated to a research center. Its size is proportional to the number of trials in which the center is involved. The color of the circle codes for the continent of the city: green for North America, blue for Europe, red for Asia, brown for Oceania, yellow for Africa and purple for South America. A trial is represented by a line (an edge) between all involved clinical centers, the thickness of which is proportional to the number of trial participants, and a spring-like force was applied between the nodes. This structuration was cumulatively presented in four periods 1999–2005, 1999–2008, 1999–2012, 2012–2015. For each year, the structural cumulative characteristics of the network are computed for Asia, North America and Europe. (b) Mean size is the mean number of studies by center. (c) Mean degree is the mean number of studies shared with neighbors. (d) Cumulative number of new centers involved into clinical trials.

neighborhood connectivity). More advanced centers (above 2.2) are also found more distant from the other centers (tendency to decreased closeness centralities), also sharing fewer projects (significant decrease in the clustering coefficient). However, these nodes have more completed trials, are less isolated and their industrial funding is significantly increased.

As depicted in Figure 1 and described in the preceding text, network heterogeneity is both spatial and temporal. We then sought to determine the impact of characteristics of studies and centers on the network topography.

Importance of subjects' recruitment capacities

A significant positive correlation is observed between the number of studies by center and the log-transformed population size of the cities ($r = 0.4$, $P < 0.001$, Supplemental Figure S2a,b). Isolated centers also have a three times larger population than connected centers ($P < 0.001$) even though there is no difference according to the number of studies ($P = 0.15$).

Industrial funding to promote the progression of clinical phases

Progression from early phase 1 to phase 3 clinical trials (score phase) is more advanced in centers from North America and Europe compared with South America or Asia (2.1, 2.1 versus 1.2, 1.6, respectively) as well as study completion (37.5%, 26.4.0% versus 3.3%, 15.2%, respectively). Industrial funding is the highest for North America centers with a mean of 90.5% industrial supporting proportion (Table III).

Various thematic priorities across countries

MSCs are used in various medical applications (Table II), especially in nervous (20.1%), immune system (18.9%), cardiovascular (18.0%) and digestive diseases (12.0%). At a glance, although each major continent is involved into several clinical trials for each field of application, a great disparity in network structuration can be observed (Figure 4). The best developed networks concern digestive (146 nodes), cardiovascular (114 nodes) and immune system diseases (159 nodes).

Table III. Parameters of the social network analysis, computed by geographic area.

Continent	Number of centers	Number of studies	Degree	Isolated centers	Score phase	Completed studies (%)	Industrial support (%)	Neighborhood connectivity
Africa	3	3.0 ± 1.7	0 ± 0 NA,O	3 (100%) O,E,NA	1.5 ± 0.1	6.7 ± 11.5	0 ± 0 NA	0 ± 0 NA
Oceania	8	3.1 ± 2.0	4.0 ± 2.1 A,AF,SA	0 (0%) A,AF,SA	2.3 ± 0.5 A,SA	9.6 ± 14.8	51.1 ± 42.0	6.8 ± 2.4 A,SA
Asia	70	4.3 ± 8.2	1.4 ± 1.8 E,NA,O	34 (48.6%) E,NA,O	1.6 ± 0.5 E,NA,O	15.2 ± 29.9 NA	47.3 ± 45.5 NA	1.6 ± 1.8 O,E,NA
Europe	116	2.4 ± 2.9 NA	2.6 ± 3.1 A,NA	25 (21.6%) A,AF,NA,SA	2.1 ± 0.7 A,SA	26.4 ± 39.1 NA	55.0 ± 45.2 NA	3.8 ± 3.2 A,NA
North America	162	3.5 ± 3.5 E	6.0 ± 5.7 A,AF,E,O	10 (6.2%) A,AF,E,SA	2.1 ± 0.7 A,SA	37.5 ± 35.4 A,E,SA	90.5 ± 23.2 A,AF,E,SA	9.4 ± 4.2 A,AF,E,SA
South America	10	2.3 ± 1.3	0.6 ± 1.0 NA,O	7 (70.0%) E,NA,O	1.2 ± 0.5 E,NA,O	3.3 ± 10.5 NA	25.0 ± 42.5 NA	0.6 ± 1.0 NA,O

Characteristics across continents were statistically compared using Dunn test with Bonferroni correction to estimate mean differences between groups. The codes $^{A,\ AF,\ E,\ O,\ NA}$ and ^{SA} indicate a significant comparison versus Asia, Africa, Europe, Oceania, North America and South America, respectively. NA, not applicable.

Despite its 70 nodes, connected components of nervous system diseases are sparse; studies are performed in isolated centers, and the number of studies by center is clearly superior in Asia. The cardiovascular diseases field is dominated by the North America continent (Figures 4 and 5), particularly the United States (60 centers, 52.6% of the total 114). The network structure on the European continent observed in Figure 1 can be largely explained by the digestive system diseases network topology (Figure 4), suggesting a major pole of competitiveness, with collaborations with Asia (five cities of Israel). Spain includes 18 of the 50 centers in Europe, with 8 studies directed in Madrid. An in-depth analysis reveals that among digestive system diseases, liver diseases are essentially studied by China and gastrointestinal diseases by the United States and Spain (Figure 5b). A similar analyze on immune system diseases reveals that China was particularly concerned with autoimmune diseases, with the United States and Europe focused on graft-versus-host diseases (Figure 5c).

The choice of cellular sources strongly affected the network topology

Table IV shows the differences in the computed parameters between the MSC networks (mainly from placental/umbilical cord [UC-MSCs], BM-MSCs and adipose tissue [ASCs]) and their corresponding heterogeneous fraction (mononuclear and stromal fraction). All parameters from the network using heterogeneous fractions suggest more isolated work of the clinical centers (e.g., lower clustering coefficient, number of neighbors, density and higher isolated nodes). Table IV compares the different network of each of major MSC types: ASCs, BM-MSCs or UC-MSCs. Compared with the BM-MSC network, the ASC network has a lower clustering coefficient and similar isolated nodes; however, the density and centralization are higher. Geographic distribution is obvious because European and Asian centers dominate the field (Figure 6b). Madrid (15 studies) and Seville (11 studies) are the two largest centers, in the middle of the giant graphic. In Asia, Seoul has the largest number of studies using ASCs (23 studies) and was isolated. In contrast, the UC-MSC network exhibits the highest values for isolated nodes and heterogeneity parameters and the lowest values for the mean number of neighbors, multiple partners and centralization parameters. This illustrates that the network of UC-MSCs is essentially composed of clinical centers working in isolation. Such statistics are visually confirmed (Figure 6c). Geographic distribution is also obvious because Asian centers dominated the field with 41% of centers; Seoul and Beijing had the highest number of studies (13 and 28 studies, respectively).

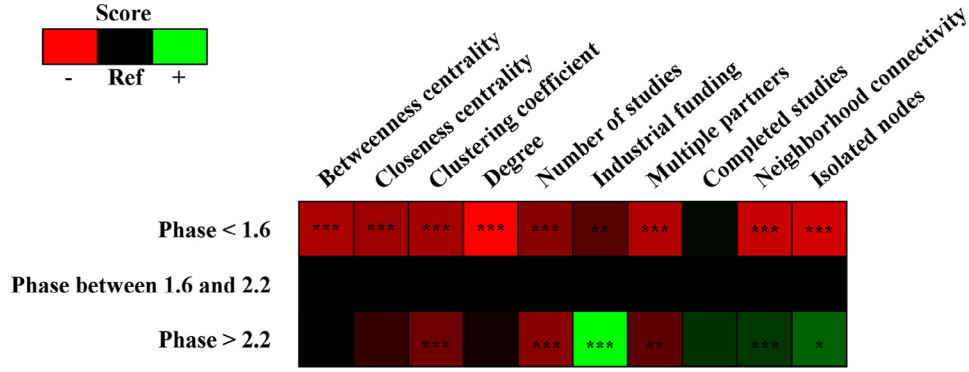

Figure 3. Impact of the phase score on clinical centers position into the MSC network. Clinical centers are split into tertiles of phase categories (score phase <1.6, score phase >2.2 and score phase between 1.6 and 2.2). Different statistical characteristics of the network are presented with a color code referring to the difference compared with the reference group (score between 1.6 and 2.2). Red and green colors indicate a negative and positive impact on the network, respectively. Lighter colors mean stronger difference compared with the reference group. ***$P < 0.001$, **$P < 0.01$.

Finally, evidence suggests that North America and Oceania are strongly involved in BM-MSC research (Figure 6a).

Discussion

Using a methodology adapted from social network analyses, we demonstrate a multifaceted heterogeneity among the clinical trials where MSCs are involved. We point out the necessity of strengthening international collaborations to ensure robustness, efficiency and relevance in the development of MSC research. To this end, several parameters must be considered, such as cell types and public health needs, both at territorial and international levels. The aggregation of industrial funding and the intensification of links between research centers seems beneficial to the advancement of trials across the different phases.

Some limitations of this study should be considered. The registered records did not benefit from the scientific peer-review process and have been considered at the same level of methodological quality, without taking into account the rigor of the recruitment, the randomization process or the blinding management all along the duration of the study [28,29]. Nevertheless, ClinicalTrials.gov provided a more up-to-date vision of this rapidly evolving field, because final publications are often delayed and negative results are less likely to be published [30–32]. Another limitation is semantic: the risk of confusion between expanded cells and heterogeneous fraction cannot be ignored. For example, the term bone marrow–derived mesenchymal stem cells may have sometimes have been used to designate the mononuclear fraction [14]. This could have led to some inaccuracies in our systematic mapping process. Although strongly encouraged, registration was not mandatory for all journals, and it has been shown that one third of clinical trials in PubMed have not been registered [33]. English language can also be a barrier to registration [33]. However, ClinicalTrials.gov regroups 16 registries worldwide, also including Korean, Chinese, Japanese, and Iranian registries.

Each connection is a collaboration between two centers potentially located thousands of kilometers apart. Naturally, the network adopted a "small-word" topology in which the different actors are able to communicate directly despite the physical distance, with the idea that each connected individual can be connected to any other individual with a short chain of relationships [10]. Such structures are economical, tending to minimize wiring costs and increase efficiency while supporting high dynamic complexity [34]. Maximizing small-world-ness would optimize transmission of messages inside the network [35]. The small-world-ness of the MSC network is confirmed as described previously [35]: the clustering coefficient and average short length path of the network are statistically compared with random networks generated using Erdös-Rényi and Watts-Strogatz algorithms from same number of nodes and edges or same number of nodes and mean degree, respectively (data not shown). The fact that this property is confirmed illustrates the importance of sharing resources and the dynamics needed to conduct clinical trials, and researchers naturally tend to meet these principles.

As depicted in Figure 1, separate components reveal little collaboration between continents. For those that do collaborate, such as the United States, Oceania and Europe, this may result from common histories, commonwealths and postwar migration [2,36]. More likely, however, such clustering reveals difficulties in conducting transatlantic studies, as demonstrated in the context of cancer research, due to misunderstandings between the regulatory agencies [37]. Variability due

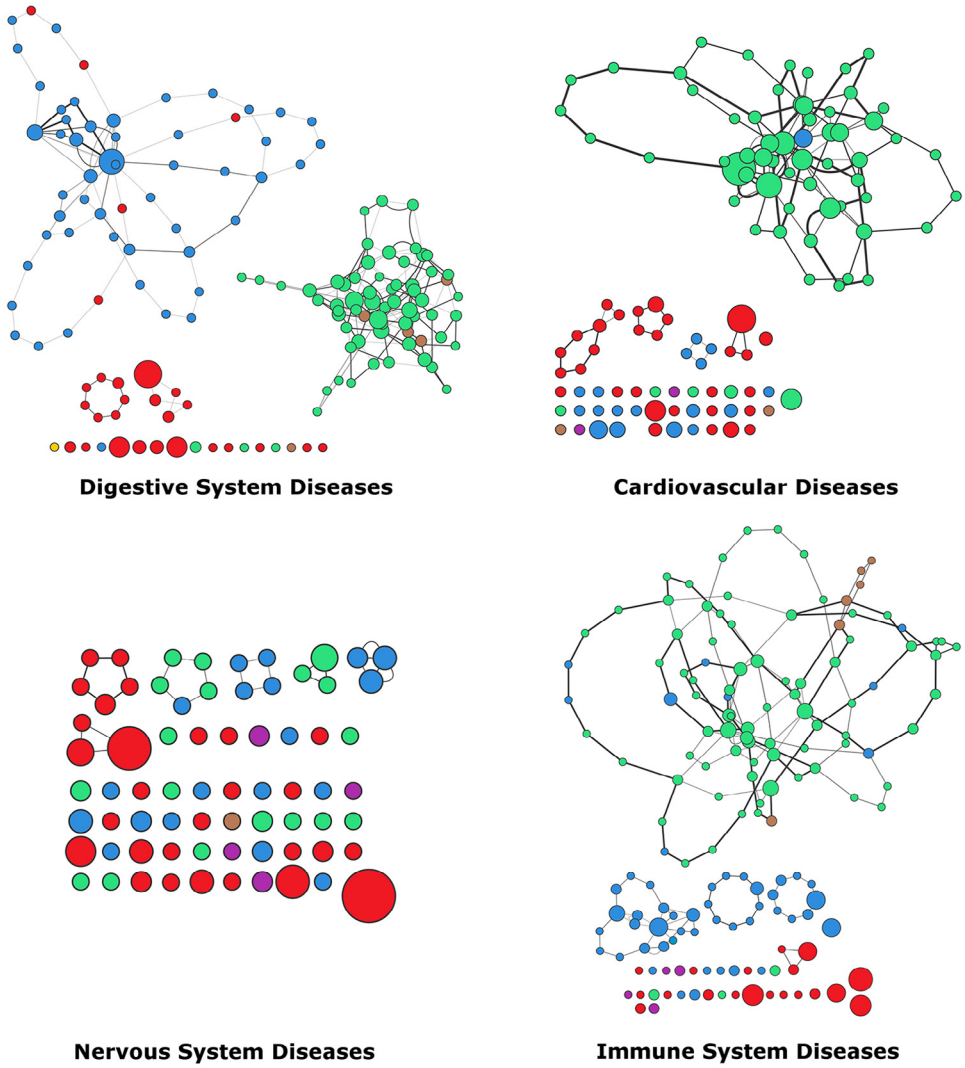

Figure 4. Network of the MSC trials within a field of application. The network of the MSC trials is drawn for four major fields of application (cardiovascular, digestive, nervous system and immune system diseases). One circle (node) represents a city, which is assimilated to a research center. Its size is proportional to the number of trials for each field of application in which the center is involved. The inner color of the circle codes for the continent of the city: green for North America, blue for Europe, red for Asia, brown for Oceania, yellow for Africa and purple for South America. A trial is represented by a line (an edge) between all involved clinical centers, the thickness of which is proportional to the number of trial participants.

to the type of cells on the entire chain of execution from bench to bedside (e.g., building structure, transport, cell-obtaining processes) may generate such segregation [16]. We also point out different strategies across continents. The number of studies by center increased in North America, and new centers were recruited, highly connected to the network. On the contrary, Asia did not diversify many centers, with a high number of studies by centers that were mainly isolated. For Europe, the strategy consisted in increasing the studies shared between centers. This is consistent with the fact that researchers in Asia may not looking for recognition from European and U.S. authors [2].

Recruitment capacity and financing may influence the network topology. Capacity to recruit patients is one element in the choice of the centers involved in clinical trials, both quantitatively and qualitatively [38]. The rapid recruitment with potential cost savings could make Asia attractive [38]. South Korea approved the first stem cell treatments in humans, receiving a funding increase in 2012 to encourage stem cell research [39]. Nevertheless, more permissive regulations (express authority regulation approval), a rapid establishment and execution of clinical trials together with a fast-tracking cellular production may explain the few clinical centers involved with a high number of studies (and with the supremacy of Seoul) [39]. The

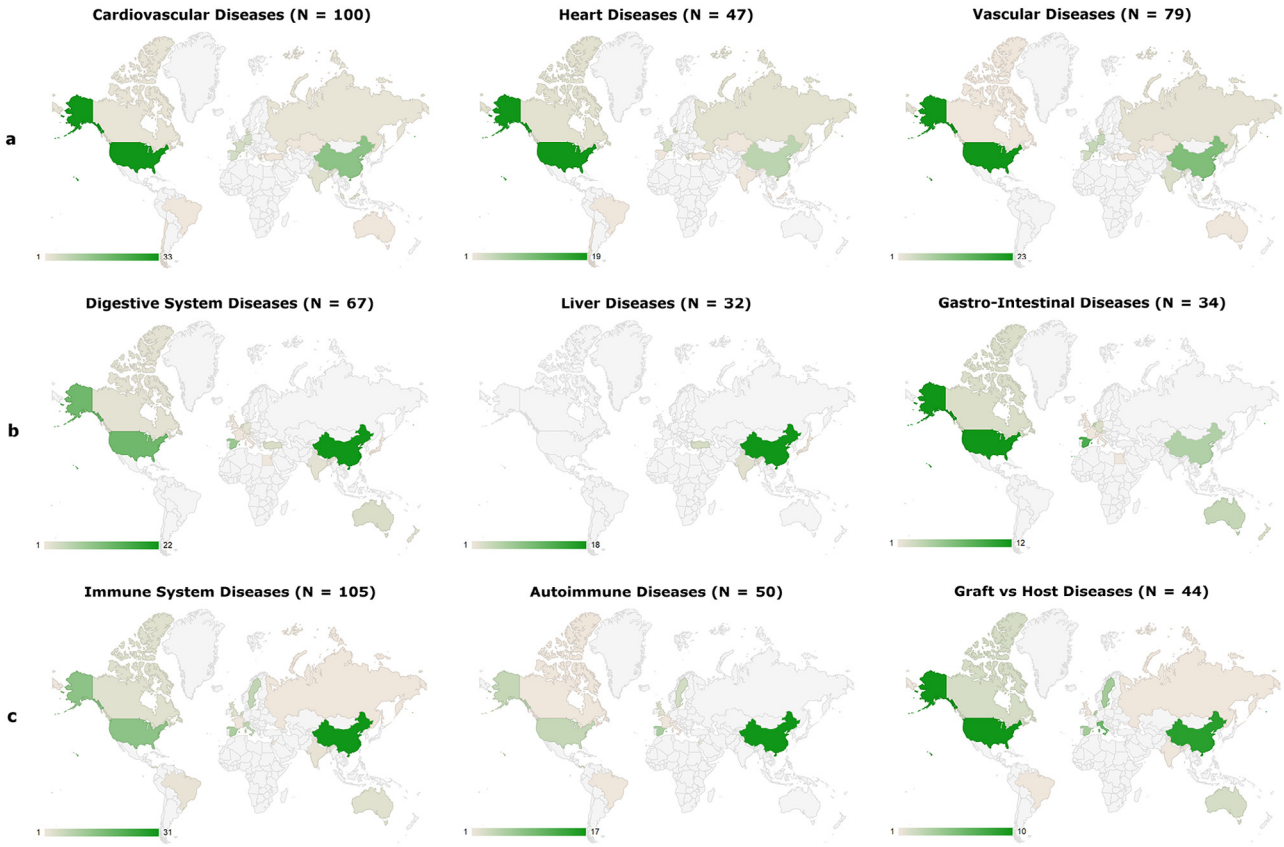

Figure 5. In-depth analysis of some fields of application. (a) Geographic details about cardiovascular diseases (left): heart (middle) and vascular diseases (right). (b) Geographic details about digestive system diseases (left): liver (middle) and gastrointestinal diseases (right). (c) Geographic details about immune system diseases (left): autoimmune (middle) and graft-versus-host (right) diseases. Shades of colors represented the number of studies by country: dark colors mean more studies.

situation in Iran demonstrates the major influence of the Tehran Royan Institute within the country, reported to sponsor 21 of the 26 studies in Iran [40]. The case of China is also striking; despite the large potential of recruitment and the high number of both centers and studies, the proportion of completed studies is only 4% for studies started since 2012. The difficulty to obtain authorization from the health authorities could be responsible for this situation [38].

In the United States, the production of MSCs must comply with Current Good Tissue Practice requirements, under the Code of Federal Regulations (21 CFR 1271, FDA [41]). In Europe, the regulatory framework is mostly derived from the Food and Drug Administration's guiding principles. Cultured MSCs may be considered as "substantially manipulated" and classified as advanced therapy medicinal products, falling under the regulation EC N°1394/2007

Table IV. Parameters of the social network analysis, computed by cellular product type.

	Studies with MSCs	Studies with corresponding heterogeneous fractions	MSC source		
			Bone marrow	Umbilical cord	Adipose tissue
Number of studies	563	335	329	128	99
Clustering coefficient	0.098	0.073	0.139	0.047	0.084
Mean number of neighbors	3.561	1.651	3.706	1.031	2.060
Multiple partners	0.197	0.137	0.181	0.000	0.069
Percentage of isolated nodes	79 (21.4%)	98 (42.8%)	60 (21.0%)	35 (54.7%)	28 (28.3%)
Network density	0.010	0.007	0.013	0.016	0.021
Network centralization	0.056	0.046	0.068	0.049	0.084
Network heterogeneity	1.176	1.127	1.146	1.187	1.107

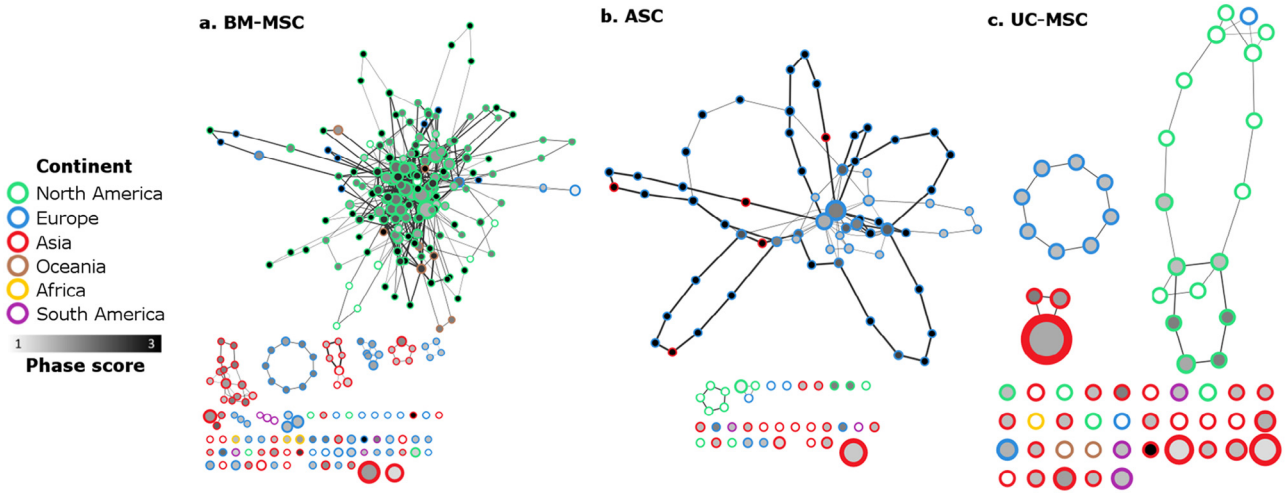

Figure 6. Network of trials using BM-MSC, ASCs and UC-MSCs. (a) BM-MSC network. (b) ASC network. (c) UC-MSC network. One circle (node) represents a city, which was assimilated to a research center. Its size is proportional to the number of trials in which each center is involved. The outer part color of the circle codes for the continent of the city: green for North America, blue for Europe, red for Asia, brown for Oceania, yellow for Africa and purple for South America. A trial is represented by a line (an edge) between all involved clinical centers, the thickness of which is proportional to the number of trial participants. The internal color represented the maturity of studies, expressed between 1 (white, i.e., toward phase 1 studies) and 3 (black, i.e., toward phase 3 studies).

introduced by the European Parliament in 2007 [42] under supervision and control of the European Medicines Agency (EMA). Production and delivery should be in accordance with European GMPs [41]. Japan has a very similar regulatory framework to that of the United States. Since 2012, Japan adopted a new regulatory pathway, classifying therapies as "regenerative medicine products," with an approval system developed for earlier commercialization (entry in the marketplace with provisional approval if phase II studies show efficacy) [32,43]. Since 2012, new regulations have also been put in place in China to attempt to regulate the uncontrolled use of stem cell injection in private clinics and respond to the skepticism about therapeutic efficacy [43–45]. Law is nevertheless complex, and the interpretation of the phrase "minimal manipulation," the need to use autologous therapies, and the potential re-classification MSC infusion as a transplant procedure, have allowed the growth of stem cell clinics that offer unproven therapies, particularly in the United States and Australia [43,46–49].

The industry, through its financing, may facilitate the development of multicenter studies to complete projects and mature more quickly. We suggest it is possible that during phase 1, industry funding is still dispensable. In later phases, industry funding increases, highlighting that more important resources are required for their implementation and the setting of multi-centric studies. The strength of North America in the network may reside in its ability to create links among centers to aggregate industrial financing. This may contribute to a greater ability to complete studies, obtain the necessary authorization from the health regulation authority and implement new studies for later phases. A major difference between Europe and the United States concerns funding; in the United States, federal public funding appears more difficult to obtain but the process of funding seems easier when developed as a financial partnership supported by private institutions, biotech companies or philanthropic organizations [50,51]. Details about funding sources must be part of the careful analysis of published articles and should be considered in future meta-analyses.

On the other hand, strategies at local, regional and national levels; research programs; and industry and state funding influence the evolution of the research topics. The field of cardiovascular disease is dominated by North America: cardiovascular diseases (hypertension, coronary heart disease, congestive heart failure, stroke) are ranked the number one cause of death in the United States (Figure 5a). They kill more than 600 000 people each year, as analyzed by the U.S. Centers for Disease Control and Prevention [52]. The European continent contributes greatly to the digestive system disease network topology, which may reveal the increase of inflammatory bowel diseases in Mediterranean countries [53]. More generally, these figures suggest that local burdens of disease could influence the structuring of the network subtended by the allocation of resources by national and/or regional agencies [54]. In oncology, an analysis of clinical trials demonstrated a significant correlation between the number of trials within geographic regions and local cancer incidence rates [55].

The network using heterogeneous cell fractions is less developed than the MSC network, reflecting that freshly extracted cells from patient tissue at bedside

are more convenient to carry out cell therapy at the individual level. In contrast, the network makes sense when facing the difficulty to manage and comply with the Good Manufacturing Practice. Indeed advanced-therapy medicinal products, cell sorting and MSC culture [16] require specific skills, more important resources, dedicated and qualified structures, and/or distribution of tasks within multicenter studies. The ASC network is still in development, with few weighted centers, which corresponds to the current widespread enthusiasm for this cell source [14].

It is interesting to consider how the network might evolve in the coming years. Network growth is expected to stabilize and the links to become more dense. It would be advisable to develop more collaboration at an international level with more centers connected to the network. On one hand, it seems natural to guide research toward what has not yet been done and open work into new areas. One consequence, in addition to technical and regulatory requirements for centers, is to have a wide variety of practices. Because we still have insufficient knowledge of all factors that are likely to influence the results of MSC therapy, explanations and new research hypotheses may arise from such comparisons. It will help to estimate how differences in trial methodology (comparing studies, protocols, outcomes) may influence the results of therapy. On the other hand, there is interest in developing similar therapeutic approaches in non-connected centers. This may contribute to improving both the safety and robustness of conclusions regarding regenerative medicine treatment. These apparent contradictions are nevertheless complementary, even if equilibrium could be ensured between the two approaches. In parallel, it seems necessary to strive toward the drawing and strengthening of international standards and statements with institutional, federal and industrial partners [51,56,57].

Conclusions

Using an innovative method inspired from social network analyses to map time and space, this study demonstrates that it is possible to consider the dynamics of the regenerative medicine field by MSC. Initially, the network was restricted to North American studies; all geographic areas are now represented. Such study also points to the lack of transatlantic interactions as well as to the isolated work of Asian cities; such segregation may thus reflect the high variability in how cells are prepared and the lack of a comprehensive legislative framework. More connections are needed to facilitate the transfer of knowledge, sharing of resources and mobility of researchers. Developing partnerships between industrial and academic entities would facilitate the translation of research discoveries, while staying attentive to potential conflicts of interest. Some specialization of a continent in a group of diseases or the use of a specific cellular source is also obvious. Local disease burden, policies and funding may be important aspects in the structuring of the territorial network of clinical research.

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Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.jcyt.2016.09.005.