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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