Impaired Functions of Bone Marrow Mesenchymal Stromal Cells in Patients with Hematological Malignancies are Partially Improved by Fibroblast Growth Factor

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Abstract

Mesenchymal stromal cells (MSCs) possess a multi-lineage potential and immunoregulatory activities which provides them a great potential in cell-oriented technologies. However, their biologic properties may be impaired in various pathologies, so approaches to improving the ability of MSCs to expand and express the expected immunoregulatory properties represent one of the challenges for this novel therapy. In the present study, we characterized bone marrow-derived MSC expansion along with their functional properties in patients with hematological malignancies, and designed a strategy of ex vivo pretreatment with the basic fibroblast growth factor (FGFb) to improve MSC activities. Our results demonstrated those patients MSCs are generally consistent with the Minimal criteria proposed by International Society for Cellular Therapy to design MSCs, and, moreover, possess a well-defined ability to maintain hematopoiesis. At the same time MSC growth, immunosuppressive and osteogenic potential are significantly diminished in patients. Nevertheless, MSC generation in FGFb-enriched conditions was accompanied by a decrease of cultivation until confluence, increase in the cell yield and the number of cycling MSCs. In addition, similar to intact MSCs, FGF-treated MSCs exhibited a significant secretory activity but lowered immunosuppressive and osteogenic potential. These data indicate FGFb ability to correct impaired MSC expansion and note FGFb using is feasible to optimize MSC-based protocols in the treatment of some hematological malignancies.

Keywords: Mesenchymal stromal cell; Immunoregulation; Hemoblastoses; Fibroblast growth factor

Abbreviations: MSCs: Mesenchymal Stromal Cells; FGFb: Basic Fibroblast Growth Factor; HL: Hodgkin’s Lymphoma; NHL: Non-Hodgkin’s Lymphoma; MM: Multiple Myeloma; AA: Aplastic Anemia; AL: Acute Leukemia; CFU-F: Fibroblast Colony-forming Units

Introduction

Mesenchymal stromal cells (MSCs) as bone marrow cells of non-hematopoietic origin are rated as somatic stem cells characterized by self-renewal and multipotent differentiation [1,2,3]. Further, MSCs play an important role in creation of microenvironment which is necessary for maturation, differentiation and survival of hematopoietic progenitor cells [4]. Moreover, another important feature of these cells considered to be their immunoregulatory activity [5,6,7]. In last decade biological activity of MSC was actively discussed for their potential use to suppress autoimmune and transplantation reactions, along with the aim of speeding up of hematopoiesis recovery after bone marrow transplantation [8,9,10]. Due to low immunogenicity of MSCs, many existing protocols suppose the use of allogeneic MSCs [11,12,13]. Undoubtedly, the transplantation of allogeneic cells has some advantages including the absence of need for ex vivo expansion of cells, which are also lack of possible disabilities as may occur in pathology, as well as an easy standardization of a pre-prepared “off-the-shelf” cell product (with known potency and defined characteristics). The use of allogeneic cells, however, has “the dark side” as well. Obviously, the application of allogeneic cells may require immunosuppression. Besides, disadvantages of allogeneic cells are related to the possibility of infection, the need for cryopreservation and material storage, and immunogenicity revealed by some authors. To this end, there are some data demonstrated allogeneic MSCs may not only fail to weaken, but rather worsen the disease [14,15]. Despite these cells are considered to be low immunogenic, MSCs when administered may cause so-called instant blood-mediated inflammatory reaction (BMIR) which significantly limits the survival, engraving and efficiency of donor MSCs [16].

All aforesaid explains why many protocols designed to use autologous MSCs which are devoid of many shortcomings of allogeneic cells. The only obstacle may be considered an insufficient and sometimes inconsistent knowledge on the functional competence of immunosuppressive and hematopoietic-supporting potential of these cells in different pathologies. According to literature and our own data, the number of clonogenic progenitors (or CFU-F) in the bone marrow as well as MSC expansion was shown to be significantly decreased in patients with hematological malignancies [17,18,19,20]. At the same time, the clinical efficiency assumes the use of sufficient quantities of MSCs which could be achieved as a result of prolonged culturing MSCs in vitro. However, long-lasting culture expansion of MSCs has a high risk of replicative senescence of cells [21]. In this regard, the most preferable (bearing in mind potential clinical use of MSCs) way of getting sufficient quantities of MSCs is the cultivation of MSCs under the influence of mediators with growth-promoting properties.
activity. Such an effect is known to be typical for a number of factors including platelet-derived growth factor (PDGF), epidermal growth factor (EGF), basic fibroblast growth factor (FGFβ), transforming growth factor β (TGF-β), insulin-like growth factor 1 (IGF-1) and others [22,23,24,25]. However, little is known on whether these factors influence the growth capacity of cells in the pathology, and how it may change the functional activity of patient MSCs.

Here, we evaluated the expansion characteristics and functional activities of MSCs derived from the bone marrow of patients with hematological malignancies, and investigated whether the FGFβ could influence these activities in patient MSCs.

**Design and Methods**

Human bone marrow samples were obtained from donors and patients after obtaining written informed consent. The patient group consisted of 62 patients with hemoblastoses (27 males and 35 females, with average age 35 ± 2.8 years), including those with Hodgkin’s lymphoma (HL; n=16; 28 ± 1.5 years), non-Hodgkin’s lymphoma (NHL; n=12; 37 ± 3.9 years), acute leukemia (AL; n=7; including those with acute lymphoblastic, n=4; 24 ± 2.9 years, and acute myeloblastic leukemia, n=3; 35 ± 3.0 years), multiple myeloma (MM; n=6; 32 ± 1.5 years) and aplastic anemia (AA; n=21; 29 ± 2.6 years). At a point of research all patients were given high-dose chemotherapy. Bone marrow aspirates were also obtained from 24 healthy volunteers with comparable age/gender.

Bone marrow aspirates were obtained from iliac crest trepanobiopsies. Bone marrow mononuclear cells (BMMNCs) were obtained routinely by density gradient centrifugation and incubated in plastic culture flasks (75 cm², Nunc, Denmark), at cell density of 50-100 x 10⁵, in aMEM (Sigma-Aldrich) containing 100 μg/mL gentamycin and 20% fetal calf serum (FCS, ICN) at 37°C in CO₂ incubator. After 72 h non-adherent cell were removed while adherent fraction was cultivated in the presence or absence of basic fibroblast growth factor (FGFβ, at a dose of 10 ng/ml; Sigma-Aldrich, Germany) to reach 80-90% confluence. MSCs were passaged with 0.25% trypsin/0.02% EDTA solution and used after 1-2 passages.

Information on MSC clonogenic precursors, immunophenotype and cell cycle analysis, osteogenic differentiation, MSC effect on T-cell proliferation and cytokine detection assays is available in the Online Supplementary Appendix.

Statistical analysis was performed using GraphPad Prism 5 Demo and Statistica 6.0 package (StatSoft). Data are presented as mean ± SEM or the median value and interquartile range where appropriate. Statistical comparison of the data was performed using the Mann-Whitney U- and Wilcoxon test (for related pairs). Probability values of p < 0.05 were considered statistically significant and those between 0.05 and 0.1 as indicative of a trend.

**Results**

**MSC clonogenicity and expansion**

Bone marrow of all hematological patients contained the adherent, fibroblast-like cells capable of forming colonies (CFU-F; Figure 1). The mean number of CFU-F in donor group was 37±2.7 colonies per 10⁶ BMMNCs (min-max range 19 – 73, median 34). CFU-F number in patients with hematological malignancies was significantly decreased – 21±3.1 (p<0.05). The range of values in patient group was widely varied (from 1 to 80 CFU-F), and 48% of samples showed CFU-F numbers were below the lower percentile value of donors (<21 CFU-F). The most significant decrease of CFU-F number was revealed in patients with NHL (17±5, p<0.01) and HL (26±5, p<0.05).

At the same time, the number of CFU-F in bone marrow of patients with MM, AL and AA was similar to or even higher than the appropriate donor value. Importantly, these patients were found to be highly heterogeneous within the group, and the amount of MSC precursors in a significant proportion of patients (30% of cases for MM, 33% - in AA, 43% - in AL) was reduced and did not exceed the lower percentile values of donors.

Analysis of MSC growth rate revealed that regardless of the number of MSC precursors in the bone marrow, fibroblast-like cells in all cultures have proliferated forming a monolayer (Table 1). In healthy donors, confluent growth in MSC cultures was reached by day 15±4.06 (median 14; range 11-22 days). Meanwhile, in patients the 80-90% confluence took on average 26±2 days (range 10-50) with the highest value of this parameter in patients with NHL (p<0.01) and MM (p<0.01). Moreover, in 33% of AA patients with low CFU-F the time until subconfluence was found to be increased up to 24±3±9.5 days (p<0.05). Of interest is the fact that a significant prolongation of primary cultures was also observed at high levels of MSC precursors as was seen in MSC cultures of patients with MM and AA.

These data suggest the slow MSC growth in patients with hematological malignancies may be a result of decrease in the number

![Figure 1: The number of MSC clonogenic precursors (CFU-F) in donor and patient bone marrow.](https://example.com/figure1.png)

<table>
<thead>
<tr>
<th>Groups (number)</th>
<th>CFU-F (per 10⁶ MNC)</th>
<th>Primary cultivation (days)</th>
<th>MSC yield (per 1 CFU-F)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Donors (n=12)</strong></td>
<td>34 (26-51)</td>
<td>14 (12-17)</td>
<td>1400</td>
</tr>
<tr>
<td><strong>Lymphoma (n=28)</strong></td>
<td>16 (5-43)*</td>
<td>26 (17-34)**</td>
<td>970 (606-3630)</td>
</tr>
<tr>
<td><strong>NHL (n=12)</strong></td>
<td>14 (7-29)**</td>
<td>29 (20-35)**</td>
<td>884 (545-1800)</td>
</tr>
<tr>
<td><strong>AL (n=7)</strong></td>
<td>18 (7-46)*</td>
<td>23 (11-30)</td>
<td>970 (688-2380)</td>
</tr>
<tr>
<td><strong>AA (n=21)</strong></td>
<td>43 (8-60)</td>
<td>18 (13-24)*</td>
<td>695 (422-1940)</td>
</tr>
</tbody>
</table>

Note: Data are presented as median and interquartile range. * - p <0.05, ** - p <0.01 - significance of differences between patients and donors by U-Mann-Whitney test.

**Table 1: CFU-F number and the efficiency of MSC expansion.**
of clonogenic precursors. This assumption is confirmed by the fact that the period of primary cultivation (until first confluence) in patients with HL correlated inversely with the number of CFU-F ($r_c = -0.54$ and $r_s = -0.65$; $p < 0.05$). On the other hand, the increase in primary culturing of MSCs in patients with NHL and AA was not correlated with reduced CFU-F ($r_c = -0.04$ and $r_s = 0.01$, respectively), and thus could be caused by inhibition of proliferation activity of MSCs.

The decrease in MSC proliferative activity is also confirmed when analyzing MSC yield in primary cultures (Table 1). The data suggest that a single MSC precursor generates a 1.4 - 1.9 times less "daughter" cells in patients with hematological malignancies (NHL, HL, AL, AA) than in donor cultures ($p > 0.05$). In addition, the analysis of a cell cycle in CD73+ cells showed that the number of patient MSCs in S+G2/M-phase was lower than that of the donor (3.5±1.2 vs 13.6±3.7%, $p = 0.57$).

**MSC immunophenotype and differentiation**

In general, MSCs of patients with hemoblastoses at the first passaging were found to express a similar to donor MSC immunophenotype (Figure 3, top line). However, CD73, CD90 and CD105-positive cells were lowered (82±2.4, 70±7.7 and 76±9.8%, respectively; $p > 0.05$) with a valid decrease in patients with AA. In contrast to healthy donors, patient MSCs showed a two-fold increased number of HLA-DR-positive cells (22±3.3 vs 11.1±1.6%, $p < 0.05$). Interesting that MSC immunophenotype in patients with low (below the lower percentile of donor value, <21 CFU-F) and high (greater than the upper percentile of donor value, > 51 CFU-F) content of MSC precursors showed no significant differences.

As for differentiation potential, the ability of patient MSCs to differentiate into osteoblasts was found to be significantly less pronounced (Online Supplementary Figure S1). Actually, the large fragments of mineralized matrix painted black on von Kossa/safranin can be seen in the experimental cultures of donor MSCs whereas similar mineralization islets are rare and smaller in size in MSC cultures of lymphoma patient (see Supplemental material, Figure S1).

**MSC secretory activity**

To answer whether the reduced growth capacity and phenotype peculiarities of patient MSCs are associated with the changed secretory activity of these cells, concentrations of secreted mediators were determined by using the Bio-Plex Protein Array System and ELISA (Online Supplementary Table S1). The data obtained demonstrated that patient MSCs actively produce cytokines (IFN-γ, IL-1b, IL-6), chemokines (IL-8, MCP-1, MIP-1b) and growth factors (G-CSF, GM-CSF, VEGF, IGF-1, FGF-b and EPO) during expansion. Moreover, patient MSCs were found to express a similar to donor MSC immunophenotype and differentiation activity of these cells.

**MSC immunosuppression**

Evaluation of MSC immunoregulatory activity have showed (Figure 2) that in patients with hemoblastoses the significant suppressive effect of MSCs was registered mainly at the high concentrations of MSCs in culture (MSC:MNC ratios of 1:1 and 1:2). However, even in this case, the immunosuppressive activity of MSCs was lower than in donor group - by more than 50%. Decrease in MSC numbers in MLC resulted in a further reduction of their ability to inhibit T-cell proliferative response. Moreover, at ratios of 1:5 - 1:100 patient MSCs demonstrated stimulatory activity which was manifested in their ability to increase the response of T cells in MLC as evidenced by the index of suppressive activity greater than 1.0 (gray horizontal line in Figure 2).

The stimulatory effect of MSCs was revealed in 28-33% of AL and AA and in 70% of lymphoma patients. Importantly, this phenomenon has never been observed in the cultures of donor MSCs that were suppressive up to ratio of 1:100.

**FGFb improves patient MSC expansion**

Based on the known data on the positive effect of basic fibroblast growth factor (FGFb) on donor MSC expansion [23,29], we tested whether FGFb is also mitogenic for patient MSCs. For this, MSCs were cultured in the presence of FGFb (at a dose 10 ng/ml) until confluence followed by the estimation of immunophenotype and functional activity of these cells.

Our results showed that FGFb did not affect the adhesiveness of MSC precursors and the number of CFU-F in cultures of MNCs isolated from bone marrow of donors (n=3) and patients with hematological malignancies (n=3). In fact, the number of CFU-F did not change when FGFb was added to the culture medium (24.0±7.2 vs 24.3±6.9 under standard conditions; $p > 0.05$). However, the fibroblast colonies in FGFb-supplemented cultures were more cellular, and, therefore, had the larger size. The increase in the CFU-F size was typical both to the donor and patient MSCs.

Analysis of MSC expansion showed that the culturing of patient MSCs (which are originally distinguished by slow growth) upon FGFb resulted in a significantly decrease of primary cell cultivation (until the first passage; from 25.4 ± 1.52 to 18.6 ± 1.21 days; n=16, $p = 0.041$). Moreover, the evaluation of MSC numbers obtained at the first passage showed FGFb enhanced patient MSC yield – from 30100 ± 3200 to 52350 ± 7980 MSCs/10⁶ MNCs (n=16, $p=0.009$) indicating a more effective cell growth. However, the growth promoting effect of FGFb was obvious mainly in the MSC cultures of lymphoma (n = 8, p=0.023) and acute leukemia (n = 2) patients whereas in patients with aplastic anemia (n = 6) MSC yield remained virtually unchanged (33350 ± 4100 and 38680 ± 3930). These data indicate the different MSC sensitivity to the stimulating action of FGF-b in various hematologic malignancies.

The mitogenic effect of FGFb on patient MSCs was also confirmed by a threefold increase in the cycling cell numbers (in S+G2/M phase; Figure 2). The stimulatory effect of MSCs was revealed in 28-33% of AL and AA and in 70% of lymphoma patients. Importantly, this phenomenon has never been observed in the cultures of donor MSCs that were suppressive up to ratio of 1:100.

**Figure 2:** Immunosuppressive activity of donor and patient MSCs in mixed lymphocyte culture. MNC – peripheral blood mononuclear cells. The data are presented as M ± SE of suppressor activity index (the ratio of T-cell proliferation level in the presence of MSCs to that without MSCs) of donor MSCs (n=7), lymphoma patient MSCs (n=12), AL patient MSCs (n=6), AA patient MSCs (n=9). MSC suppressor activity was tested in mixed lymphocyte culture (MLC; each MSC population was tested in three MLC). * - p < 0.05, ** - p < 0.01 - significant difference in comparison with bone-marrow MSCs from healthy donors (Mann-Whitney test).
from 3.45 ± 1.19 to 10.01 ± 2.91, p = 0.043) in CD73+ MSCs of lymphoma patients (n=3).

**FGFb effect on surface antigen expression and osteogenic differentiation**

The expression of membrane markers showed all tested MSC generated in the presence FGFb, similar to untreated cells, did not express the hematopoietic (CD34) and linear antigens (CD3, CD14, CD20, CD16). At the same time, the number of patient MSCs (n=15) expressed CD73 and HLA-DR was shown to be increased from 89±3.2 up to 93±2.2% (p=0.05) and from 19±5.3 up to 39±7.4 (p=0.018), respectively (Figure 3).

The FGFb effect on differentiation potential was held in donor (n = 5) and patient (n = 8) MSC cultures using a semi-quantitative method developed in our laboratory [27]. As follows from Figure 4, donor MSCs cultured under osteogenic induction medium supplemented with FGFb was differed by a pronounced tendency to increase the calcium production (as seen by 1.5-2 fold increase in osteogenic differentiation indices, IOD). At the same time, FGFb did not affect the initially reduced osteogenic potential of MSCs in patients with hematological malignancies, as evidenced by the low values of IOD both in FGFb(-) and FGFb(+) cultures.

**FGFb effect on secretory activity of patient MSCs**

Next, using multiplex analysis, we investigated the FGFb influence on production of biologically active molecules by MSCs of patients with hematological malignancies (Online Supplementary Table S2). The data demonstrated that FGFb in general did not affect the secretory activity of patient MSCs. Upon FGFb, MSCs more actively produced pro-inflammatory cytokines (IFN-γ and TNF-α (as a trend), IL-2 (p <0.05), as well as some growth factors (GM-CSF). It should be noted that FGFb did not alter the ability of patient MSC to produce IL-10, one of the mediator of MSC immunosuppression.

**FGFb effect on immunosuppressive activity of donor and patient MSCs**

Analysis of FGFb effects on the immunosuppressive properties of MSCs showed (Figure 5) that this factor did not influenced the ability of donor MSCs (n=6) to suppress the proliferation of alloantigen-activated T lymphocytes (p>0.05). As for FGFb impact on the patient MSCs, FGFb did not correct the impaired inhibitory potential of patient MSCs (n=8), so their ability to suppress alloantigen-induced T-cell proliferation still remained lowered.

**Discussion**

The work presented here originated from the question if MSCs derived from bone marrow of patients with hematological malignancies are changed and what alterations are typical for these cells, since data regarding this aspect is few and often contradictory. Our results demonstrated that CFU-F could be isolated consistently from bone marrow aspirates of hematologic patients suggesting patient bone marrow contains a population of precursor cells adhesive to plastic and having fibroblast-like morphology. At the same time, the
Our results showed that, in contrast to donor stromal cells, hematologic patient MSCs displayed a lowered immunosuppressive activity on alloantigen-activated T-cell proliferation. The available data on the immunoregulatory function of MSC in hemoblastoses are controversial [17,38,39]. Arnulf et al. [38] found that MM patient-derived MSCs were unable to sufficiently inhibit T cell proliferation in vitro. In addition, Bacigalupo and coauthors demonstrated significantly lower suppression of T-cell proliferation by MSCs of patients with AA [17]. However, Zhi-Gang et al revealed the inhibitory effect of MSCs was only impaired in patients with AML and myelodysplastic syndromes while in lymphoma patients suppressive properties of MSCs remained unaltered [39].

Another distinction of patient MSCs can be considered the fact that the addition of fewer MSCs led to a less pronounced suppression or even a marked T-cell proliferation. The ability of low numbers of MSCs to stimulate T-lymphocyte proliferation was first reported in donors by Le Blanc [40]. In turn, we demonstrated clearly defined stimulating effect of patient MSCs. The impairment of immunoregulatory activity of patient MSCs may be attributed to changes in cytokine production by these cells. Actually, the stimulatory effect of patient MSCs can be partly explained by increased production of IL-2 (p<0.05) and IL-7 (as a trend), which positively influence on T lymphocyte proliferation. However, we did not find the decrease of cytokines with potential suppressive activity (IL-10, IL-6, VEGF).

Our previous data showed that changed immunomodulatory activity of MSCs did not affect their hematopoiesis-supporting activity that was similar to donor values [41]. Probably that high level of some cytokines (IL-6, IL-8) and colony-stimulating factors produced by patient MSCs to some extent explains a pronounced ability of these cells to stimulate the proliferation and differentiation of hematopoietic progenitor cells [41].

Slow growth rate of MSCs in hematological malignancies may be primarily caused by initially lowered content of MSCs in patient bone marrow. On the other hand, this may be also due to an inhibition of proliferative potential of patient MSCs. Actually, an increased culture period until 70-80% confluence was revealed in MSC cultures of MM and AA patients that are characterized by a high content of MSC clonogenic precursors. These findings allowed us to assume a lowered proliferative capacity of MSCs in patients with hemoblastoses that subsequently was confirmed by the data on reducing the number of cells in S/G2-M phase.

Presently, bone marrow cells are the major source for MSC therapies. Unfortunately, bone marrow-derived MSCs can only be passaged for a limited period, after which they show a marked reduction in proliferation not allowing to get the required cell numbers. Moreover, the decrease in MSC proliferative activity can negatively affect the functional activity of these cells. Recent reports suggest a correlation between MSC proliferation and their
differentiation potential. Indeed, increased proliferative activity of MSCs is associated with chondro-forming processes in vitro [42] as well as bone formation in vivo [43]. Given these and our results on the impaired osteogenic differentiation along with decreased expansion and suppressive activity of MSCs in patients with hemoblastoses, we hypothesized that the use of growth factors would result in higher proliferation of MSCs and, as a consequence – stronger differentiation ability and suppressive properties of patient MSCs. We chose the basic fibroblast growth factor (FGFb) based on its mitogenic effect on donor MSC [23,29,44].

Our results demonstrated that fibroblast colonies in FGF-b-supplemented conditions were more cellular and larger in size indicating a higher proliferative activity of clonogenic precursors [45,29]. Actually, FGFb enhanced the number of patient MSCs in S+G2/M-phase that leads to the increase in the number of cells generated by one clonogenic precursor thus increasing the yield of cells. No less important GFG effect can be considered a significant shortening of culture time until confluence.

The patient MSCs were consistently negative for CD34, CD3 and strongly positive for CD 90 and CD73 - whether they were grown in the presence or in the absence of FGFb. At the same time we found that FGFb induced the expression of HLA-DR in patient MSCs, as has already been described for donor MSCs [29,46]. Boccelli-Tyndal et al. [29] showed that FGFb induced HLA-DR expression only in human MSCs proliferating under its mitogenic effect. Despite the expression of HLA-DR, human MSCs grown in the presence of FGF have shown high suppression of lymphocyte proliferation, but no immunogenicity [47,46]. It is also known that MSCs expressing MHC class II antigens failed to elicit a proliferative response [48]. Our unpublished data revealed no correlation between the expression of HLA-DR in hematological patient MSCs and their immunosuppressive activity.

Previously, we showed that the differentiation potential and immunosuppressive activity of MSCs generated from bone marrow of patients with autoimmune disorders (rheumatoid arthritis) and chronic inflammation (liver cirrhosis) was significantly enhanced upon FGFb (data not shown). Therefore, we expected that the positive FGFb influence on patient MSC proliferation should lead to restoration of their differentiation potential and immunosuppressive properties in hemoblastoses as well. Contrary to our expectations, MSCs from patients with hematological malignancies expanded more effectively under FGFb, but have shown still decreased both osteogenic differentiation and ability to suppress alloantigen-induced T cell proliferation. We assume that the association between increased proliferation of FGF-treated MSCs and the restoration of their suppressive and osteogenic potential in inflammatory diseases, and the absence of such dependence in hemoblastoses could indicate the existence of at least two types of functional MSC dysfunctions – proliferation-dependent and independent. Together, our data on the positive FGFb effect on the impaired proliferative activity of MSCs in some hematologic diseases confirm the potential usefulness of this growth factor for optimizing the protocols of MSC generation thus enabling to optimize clinical application of hematopoietic stem cells co-transplantation with mesenchymal stromal cells in oncohematology.

Competing Interests

The authors declare that they have no competing interests.

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References


