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(54) Title: A COMPOSITION FOR PREVENTION OR TREATMENT OF BONE MARROW DAMAGE

(57) Abstract: Disclosed herein are a composition for prevention or treatment of bone marrow damage comprising Substance-P as an active ingredient; a use of Substance-P for the preparation of a medicament for prevention or treatment of bone marrow damage; a method for prevention or treatment of bone marrow damage comprising administering a therapeutically effective amount of Substance-P to a mammal; an anticancer supplement comprising Substance-P as an active ingredient; a use of Substance-P for the preparation of an anticancer supplement; and a method for prevention or treatment of cancer comprising administering a therapeutically effective amount of Substance-P as an anticancer supplement to a mammal. Substance-P stimulates proliferation of mesenchymal stem cells (MSCs) within the bone marrow to thereby facilitate protection and regeneration of bone marrow cells and hematopoietic stem cells. Therefore, the composition of the present invention can be therapeutically used for treatment and/or prevention of bone marrow damage. Further, the composition of the present invention can be used as an anticancer supplement for anticancer therapy.

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A COMPOSITION FOR PREVENTION OR TREATMENT OF BONE MARROW DAMAGE

TECHNICAL FIELD

5 The present invention relates to a composition for prevention or treatment of bone marrow damage comprising Substance-P as an active ingredient; a use of Substance-P for the preparation of a medicament for prevention or treatment of bone marrow damage; a method for prevention or treatment of bone marrow damage comprising administering a therapeutically effective amount of Substance-P to a mammal; an anticancer supplement
10 comprising Substance-P as an active ingredient; a use of Substance-P for the preparation of an anticancer supplement; and a method for prevention or treatment of cancer comprising administering a therapeutically effective amount of Substance-P as an anticancer supplement to a mammal.

15 BACKGROUND ART

Bone marrow damage, which is caused by various factors such as radiation exposure, administration of anticancer drugs, trauma, and the like, may result in the damage of hematopoietic stem cells (HSCs) as well as mesenchymal stem cells (MSCs) which are bone marrow stromal cells (BMSCs). MSCs are known to support the proliferation of HSCs.
20 Further, it has been reported that it is possible to effectively facilitate *ex vivo* expansion of HSCs when MSCs derived from human placenta, bone marrow or umbilical cord blood are used as a cell feeder layer (Zhang Y, et al., Exp Hematol 32:657-664, 2004; and Wang JF, et al., Haematologica 89:837-844, 2004). Therefore, MSCs can play an important role in spontaneous recovery of HSCs in damaged bone marrow or engraftment of transplanted HSCs.

25 Substance P (SP) is an 11-amino acid neuropeptide, which is expressed in sensory neurons, macrophages, eosinophils, corneal cells including endothelium, epithelium and keratocytes, and granulation tissues. Several reports have suggested implication of Substance-P in neuro-immune communication on hematopoietic regulation. Substance-P nerve fibers are distributed in the bone marrow stroma, and Substance-P binds to the neurokinin-1 receptor
30 (NK-1) to thereby stimulate bone marrow stromal cells, resulting in production of stem cell factors and interleukin-1 which may be favorable for hematopoietic stimulation as feeders.

In a previous study as set forth by the present inventors, which addresses the role of

Substance-P in mobilization and repopulation of mesenchymal stem cells (MSCs), Korean Patent No. 10-593397 discloses a use of Substance-P for the manufacture of a medicament for wound-healing or facilitating wound-healing, and a use of Substance-P for the manufacture of a medicament for mobilization or proliferation of MSCs from the bone marrow, or facilitating the mobilization or proliferation of MSCs.

Based on results of the above-mentioned previous study, the present inventors made an attempt to investigate whether Substance-P is capable of exhibiting therapeutic effects on bone marrow damage through stimulation of the mesenchymal stem cell repopulation to thereby facilitate proliferation of bone marrow cells and hematopoietic stem cells, in bone marrow damage with accompanying cellular destruction of bone marrow cells and hematopoietic stem cells.

DISCLOSURE OF THE INVENTION

TECHNICAL PROBLEM

Therefore, the present invention has been made in view of the above problems, and it is an object of the present invention to provide a composition for prevention or treatment of bone marrow damage comprising Substance-P as an active ingredient.

It is another object of the present invention to provide a use of Substance-P for the preparation of a medicament for prevention or treatment of bone marrow damage.

It is a further object of the present invention to provide a method for prevention or treatment of bone marrow damage comprising administering a therapeutically effective amount of Substance-P to a mammal.

It is another object of the present invention to provide an anticancer supplement comprising Substance-P as an active ingredient.

It is a still further object of the present invention to provide a use of Substance-P for the preparation of an anticancer supplement.

It is yet another object of the present invention to provide a method for prevention or treatment of cancer comprising administering a therapeutically effective amount of Substance-P as an anticancer supplement to a mammal.

TECHNICAL SOLUTION

In accordance with an aspect of the present invention, the above and other objects can be accomplished by the provision of a composition for prevention or treatment of bone marrow damage comprising Substance-P as an active ingredient; a use of Substance-P for the preparation of a medicament for prevention or treatment of bone marrow damage; and a method for prevention or treatment of bone marrow damage comprising administering a therapeutically effective amount of Substance-P to a mammal.

In accordance with another aspect of the present invention, there is provided an anticancer supplement comprising Substance-P as an active ingredient; a use of Substance-P for the preparation of an anticancer supplement; and a method for prevention or treatment of cancer comprising administering a therapeutically effective amount of Substance-P as an anticancer supplement to a mammal.

ADVANTAGEOUS EFFECTS

The composition of the present invention can be therapeutically used for treatment and/or prevention of bone marrow damage. Further, the composition of the present invention can be used as an anticancer supplement for anticancer therapy.

DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph comparing changes in the number of viable bone marrow cells between a group with administration of Substance-P prior to irradiation and a group without administration.

FIG. 2 is a graph comparing changes in the number of viable bone marrow cells between a group with administration of Substance-P after irradiation and a group without administration.

FIG. 3 is a graph comparing changes in the number of viable blood cells between a group with administration of Substance-P after irradiation and a group without administration.

FIG. 4 is a micrograph showing colony morphology after 2-week culture of bone

marrow cells in HSC-CFU media, for a group with administration of Substance-P prior to irradiation and a group without administration.

FIG. 5 is a graph showing changes in colony counts after 2-week culture of bone marrow cells in HSC-CFU media, for a group with administration of Substance-P prior to irradiation and a group without administration.

FIG. 6 is a micrograph showing colony morphology after 2-week culture of bone marrow cells in HSC-CFU media, for a group with administration of Substance-P after irradiation and a group without administration.

FIG. 7 is a graph showing changes in colony counts after 2-week culture of bone marrow cells in HSC-CFU media, for a group with administration of Substance-P after irradiation and a group without administration.

MODE FOR INVENTION

Hereinafter, the present invention will be described in more detail.

The present invention provides a composition for prevention or treatment of bone marrow damage comprising Substance-P as an active ingredient. In addition, the present invention provides a use of Substance-P for the preparation of a medicament for prevention or treatment of bone marrow damage.

In the present invention, bone marrow damage may be caused by various factors such as irradiation (radiotherapy), anticancer drug administration (chemotherapy), trauma, and the like. Irradiation may include radiation application for cancer radiotherapy, as well as accidental radiation exposure. Bone marrow damage caused due to other causal factors also falls within the scope of the present invention.

In order to demonstrate prophylactic and therapeutic effects of Substance-P on bone marrow damage in the present invention, bone marrow damage was induced by radiation in mice. Then, for comparison, observation was made of the number of bone marrow cells and blood cells of the Substance-P administered group and the non-administered group, and a colony count was also performed according to colony-forming unit (CFU) assay for each group. As a result, the Substance-P administered group was significantly higher in numbers of

bone marrow cells and blood cells as well as in the colony count, as compared to the non-administered group, thus confirming that Substance-P stimulates mesenchymal stem cells to thereby activate the production of bone marrow cells and hematopoietic stem cells. Not only when Substance-P was administered to animals following induction of bone marrow damage, but also when animals were pretreated with Substance-P prior to induction of bone marrow damage, both exhibited significantly greater numbers of bone marrow cells and blood cells in conjunction with a significantly higher colony count, as compared to the non-administered group.

Therefore, it is possible to achieve treatment of bone marrow damage as well as effective prevention of bone marrow damage, when the composition of the present invention comprising Substance-P as an active ingredient is used therapeutically for bone marrow damage.

When the occurrence of bone marrow damage is inevitable due to radiotherapy or chemotherapy, for example, pretreatment of a subject with Substance-P prior to application of anticancer therapy can lead to significant reduction in the extent of bone marrow damage. Further, administration of Substance-P in combination with conventional anticancer therapy can prevent decreases of blood cells due to the anticancer therapy, which then enables continuous chemotherapy regimens.

Consequently, prevention, treatment or alleviation of bone marrow damage resulting from conventional anticancer therapy can be accomplished via administration of the composition or medicament for prevention or treatment of bone marrow damage according to the present invention, concurrently with, before or after radiotherapy or chemotherapy.

Further, the composition of the present invention comprising Substance-P as an active ingredient can be used as an anticancer supplement. Therefore, the present invention provides an anticancer supplement comprising Substance-P as an active ingredient and a use of Substance-P for the preparation of an anticancer supplement.

The composition or medicament comprising Substance-P as an active ingredient or the anticancer supplement comprising Substance-P as an active ingredient may comprise one or more pharmaceutically acceptable carriers known in the art. After selection of the pharmaceutically acceptable carriers which are suitable for the administration of Substance-P to a subject, Substance-P may be suspended or dissolved in pharmaceutically acceptable carriers by a conventional method known in the art. Preferred is a water-soluble carrier.

As the incidence of bone marrow damage leads to a decreased number of mesenchymal stem cells in bone marrow, it is obvious that therapeutic effects on bone marrow damage will significantly increase by co-administration of mesenchymal stem cells capable of supporting production of hematopoietic stem cells in conjunction with Substance-P.

5 The composition or medicament of present invention for prevention or treatment of bone marrow damage or the anticancer supplement of present invention may further comprise mesenchymal stem cells in addition to Substance-P.

As used herein, the term "MSC" or "mesenchymal stem cell" designates a cell which is capable of proliferating and differentiating into chondrogenic, osteogenic, adipogenic,
10 stromogenic (marrow stromal), myogenic, and neural lineages. Mesenchymal stem cells may be derived from, e.g., bone marrow, umbilical cord blood, peripheral blood and other tissues.

Further, the present invention provides a method for prevention or treatment of bone marrow damage comprising administering a therapeutically effective amount of Substance-P to a mammal.

15 Further, the present invention provides a method for prevention or treatment of cancer comprising administering a therapeutically effective amount of Substance-P as an anticancer supplement to a mammal.

As used herein, the term "mammal" refers to any mammalian species that is in need of treatment, examination or experiment, preferably human.

20 As used herein, the term "therapeutically effective amount" refers to an amount of an active ingredient or pharmaceutical composition that will elicit the biological or medical response of a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or clinician, and encompasses an amount of the active ingredient or pharmaceutical composition which will relieve the symptoms of the disease or disorder being
25 treated. As will be apparent to those skilled in the art, the therapeutically effective dose and administration times of the active ingredient in accordance with the present invention may vary depending upon desired therapeutic effects. Therefore, an optimal dose of the active drug to be administered can be easily determined by those skilled in the art. For example, an effective dose of the active drug is determined taking into consideration various factors such
30 as kinds of disease, severity of disease, contents of active ingredients and other components contained in the composition, kinds of formulations, age, weight, health status, sex and dietary habits of patients, administration times and routes, release rates of the composition, treatment

duration, and co-administered drugs.

In the present invention, an effective dose (ED) of Substance-P may be in a range of 0.1 to 100 $\mu\text{g/kg}$.

Further, an effective dose (ED) of mesenchymal stem cells, which are used in combination with Substance-P, may be in a range of 3×10^4 to 3×10^7 cells/kg, particularly 1×10^6 to 1×10^7 cells/kg.

In the method for prevention or treatment of bone marrow damage in accordance with the present invention, Substance-P may be administered in the form of a composition or medicament for prevention or treatment of bone marrow damage or in the form of an anticancer supplement.

The composition, medicament or anticancer supplement of the present invention can be administered to a subject (including human) via parenteral or topical routes, such as intravenous injection, subcutaneous injection, endothelial injection, intramuscular injection, etc. Particularly preferred is intravenous injection.

These and other objects, advantages and features of the present invention will become apparent from the detailed embodiments given below which are made in conjunction with the following Examples. The present invention may be embodied in different forms and should not be misconstrued as being limited to the embodiments set forth herein, and those skilled in the art will appreciate that various modifications, additions and substitutions are possible without departing from the scope and spirit of the invention as disclosed in the accompanying claims. Therefore, it should be understood that the embodiments disclosed herein are provided only for illustrating the present invention and should not be construed as limiting the scope and spirit of the present invention.

Example 1: Effects of Substance-P on protection and regeneration of bone marrow

(1) Administration of Substance-P to bone marrow lesions

In order to ascertain protective and regenerative effects of Substance-P on bone marrow, 8-week-old C57bl/6 mice were purchased as experimental animals and divided into three groups, each consisting of 6 animals ($n=6$): two experimental groups (administration of a test drug before and after induction of bone marrow damage) and a control group. For this purpose, bone marrow damage was induced by radiation in animals.

For the group used to confirm bone marrow-protective effects of Substance-P, 0.1 nmol/g of Substance-P was injected into caudal vein of mice, 1 day prior to radiation. 24 hours later, animals were irradiated with a gamma irradiator at a dose of 4 Gy. 4 hours after irradiation, 0.1 nmol/g of Substance-P diluted in PBS was injected once more into caudal vein of mice. Substance-P was diluted in PBS prior to use thereof.

For the group used to confirm bone marrow-regenerative effects of Substance-P, 0.1 nmol/g of Substance-P was intravenously administered to caudal veins of mice immediately after animals were irradiated with gamma rays. 24 hours later, Substance-P was intravenously administered once more to animals.

(2) Isolation of bone marrow cells

Bone marrow cells were isolated from animals 3 and 7 days after irradiation. For this purpose, femurs were isolated from mice and defatted to obtain the femoral bones only. A medium was allowed to flow from one end of the bone to the other end thereof using a 26-gauge syringe. This procedure was repeated five times to ensure that bone marrow cells were completely extracted from the bone. The cells were pooled in a tube, and centrifuged at 1500 rpm for 5 min and washed two times with PBS. The viable cell count was performed and compared between the drug-administered groups (administration of Substance-P before and after irradiation) and the non-administered group.

FIG. 1 is a graph showing numerical changes in viable bone marrow cells in the group to which Substance-P was administered prior to exposure of animals to radiation. Even though there was no significant difference between the irradiated and non-irradiated groups on the 3rd post-irradiation day, the animal group with administration of Substance-P prior to irradiation exhibited about two-fold higher viable cell count after 7 days, as compared to the non-administered group. From these results, it can be seen that pretreatment of animals with Substance-P can result in stimulation of MSC proliferation which then brings about the prevention of bone marrow damage.

FIG. 2 is a graph showing numerical changes in viable bone marrow cells in the group to which Substance-P was administered after exposure of animals to radiation. Even though there was no significant difference between the irradiated and non-irradiated groups on the 3rd post-irradiation day, the animal group with administration of Substance-P after irradiation was about 2.5-fold higher in the viable cell count after 7 days, as compared to the non-administered

group. Therefore, it can be seen that administration of Substance-P after bone marrow damage can also result in stimulation of MSC proliferation which then brings about the treatment of bone marrow damage.

(3) Isolation of blood cells

Blood cells were isolated from animals 3 and 7 days after irradiation treatment was complete. For this purpose, whole blood (WB) was isolated from abdominal vena cava using a 26-gauge syringe. The isolated blood was placed in a 15 mL tube and then diluted two times with addition of PBS (WelGENE Inc., Korea). For isolation of blood cells, each 2 mL of Ficoll plaque (Amersham) was placed in fresh tubes and the diluted blood was gently put on the Ficoll layer. Care was taken to ensure that the Ficoll layer was not mixed with the blood layer. After the blood layer was completely placed, centrifugation was carried out at 2200 rpm for 25 min. Once centrifugation was complete, separation of layers took place with formation of a total of four layers. These layers correspond to a plasma layer, a blood cell layer with exclusion of erythrocytes, a Ficoll layer, and an erythrocyte layer in the order of from the uppermost layer to the lowermost layer. Only the blood cell layer was separated from among them and placed in a tube to which PBS was then added, followed by centrifugation. The viable cell count was performed and compared between the drug-administered groups (administration of Substance-P before and after irradiation) and the non-administered group.

FIG. 3 shows that a rapid irreversible decrease of viable blood cells after irradiation takes place with no recovery of a normal blood cell level even after one week.

(4) CFU assay

When bone marrow cells and blood cells were prepared, the cells were inoculated onto 35 mm plates at a density of 3×10^3 bone marrow cells/plate and 5×10^6 blood cells/plate, respectively and cultured in hematopoietic stem cell-colony forming unit media (HSC-CFU media, available from Miltenyi). The cells were cultured without change of the culture medium for two weeks while a colony count was performed daily.

FIG. 4 is a microscopic image showing colony morphology after cell culture of bone marrow cells in HSC-CFU media, for a group with administration of Substance-P prior to exposure of animals to radiation and a group without administration. A left panel of FIG. 4 shows colony formation of the non-administered group. As can be confirmed from FIG. 4, a

myriad of colonies were observed prior to irradiation, whereas the microscopic image taken on the 3rd post-irradiation day showed a very low colony count and the colony number on the 7th post-irradiation day increased due to regenerative function of the bone marrow itself. The group with administration of Substance-P prior to irradiation exhibited higher colony counts immediately after irradiation as well as on the 3rd post-irradiation day, as compared to the non-administered group. Further, the Substance P-administered group exhibited higher colony counts on the 7th post-irradiation day, as compared to the non-administered group.

FIG. 5 is a graph showing changes in colony counts after 2-week culture of bone marrow cells in HSC-CFU media, for a group with administration of Substance-P prior to exposure of animals to radiation and a group without administration. At the early stage of cell culture, there was a slight difference in the colony count between the Substance P-administered group and the non-administered group. However, the colony count in the Substance-P pretreatment group significantly increased over time and was about 9-fold higher on the 14th post-irradiation day, as compared to the non-administered group.

FIG. 6 is a microscopic image showing colony morphology after cell culture of bone marrow cells in HSC-CFU media, for a group with administration of Substance-P after exposure of animals to radiation and a group without administration. A left panel of FIG. 6 shows colony formation of the non-administered group. As can be confirmed from FIG. 6, the number of colonies prior to irradiation was countless, whereas the microscopic image taken on the 3rd post-irradiation day exhibited no colony formation and the microscopic image on the 7th post-irradiation day showed slight formation of colonies at a very insignificant number due to regenerative function of the bone marrow itself. On the other hand, the group with administration of Substance-P after irradiation exhibited no colony formation on the 3rd post-irradiation day, but colony formation was observable from the 5th post-irradiation day and the colony count significantly increased on the 7th post-irradiation day.

FIG. 7 is a graph showing changes in colony counts after 2-week culture of bone marrow cells in HSC-CFU media, for a group with administration of Substance-P after exposure of animals to radiation and a group without administration. At the early stage of cell culture, there was a slight difference in the colony count between the Substance P-administered group and the non-administered group. However, the colony count in the Substance P-administered group gradually increased over time and was about 3-fold higher on the 14th post-irradiation day, as compared to the non-administered group.

INDUSTRIAL APPLICABILITY

As apparent from the above description, Substance-P stimulates proliferation of mesenchymal stem cells (MSCs) within the bone marrow to thereby facilitate protection and
5 regeneration of bone marrow cells and hematopoietic stem cells. Therefore, it is possible to achieve treatment of bone marrow damage as well as effective prevention of bone marrow damage, when the composition of the present invention comprising Substance-P as an active ingredient is therapeutically used for bone marrow damage. Further, the composition of the present invention can be used as an anticancer supplement for anticancer therapy.

WHAT IS CLAIMED IS:

1. A composition for prevention or treatment of bone marrow damage comprising Substance-P as an active ingredient.

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2. The composition according to claim 1, wherein the bone marrow damage is caused by radiotherapy, chemotherapy, or trauma.

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3. The composition according to claim 2, wherein the composition is administered concurrently with, before or after radiotherapy or chemotherapy.

4. The composition according to any one of claims 1 to 3, further comprising mesenchymal stem cells (MSCs).

15

5. An anticancer supplement comprising Substance-P as an active ingredient.

6. A use of Substance-P for the preparation of a medicament for prevention or treatment of bone marrow damage.

20

7. The use according to claim 6, wherein the bone marrow damage is caused by radiotherapy, chemotherapy, or trauma.

25

8. The use according to claim 7, wherein the medicament is administered concurrently with, before or after radiotherapy or chemotherapy.

9. The use according to any one of claims 6 to 8, wherein the medicament further comprises mesenchymal stem cells (MSCs).

30

10. A use of Substance-P for the preparation of an anticancer supplement.

11. A method for prevention or treatment of bone marrow damage comprising administering a

therapeutically effective amount of Substance-P to a mammal.

12. The method according to claim 11, wherein the bone marrow damage is caused by radiotherapy, chemotherapy or trauma.

5

13. The method according to claim 12, wherein Substance-P is administered concurrently with, before or after radiotherapy or chemotherapy.

14. The method according to any one of claims 11 to 13, further comprising administering
10 mesenchymal stem cells (MSCs).

15. A method for prevention or treatment of cancer comprising administering a therapeutically effective amount of Substance-P as an anticancer supplement to a mammal.

1/4

FIGURES

Fig. 1

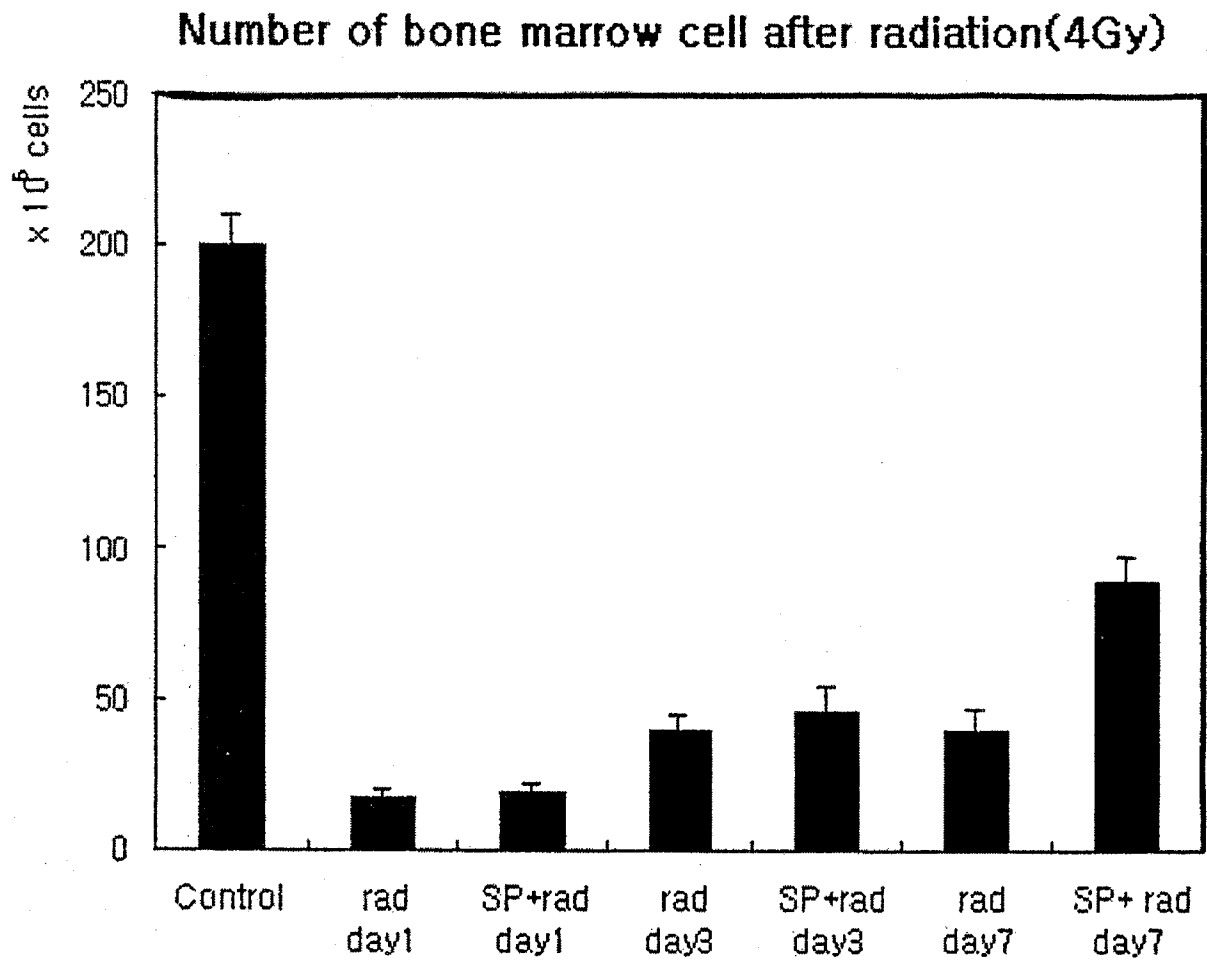


Fig. 2

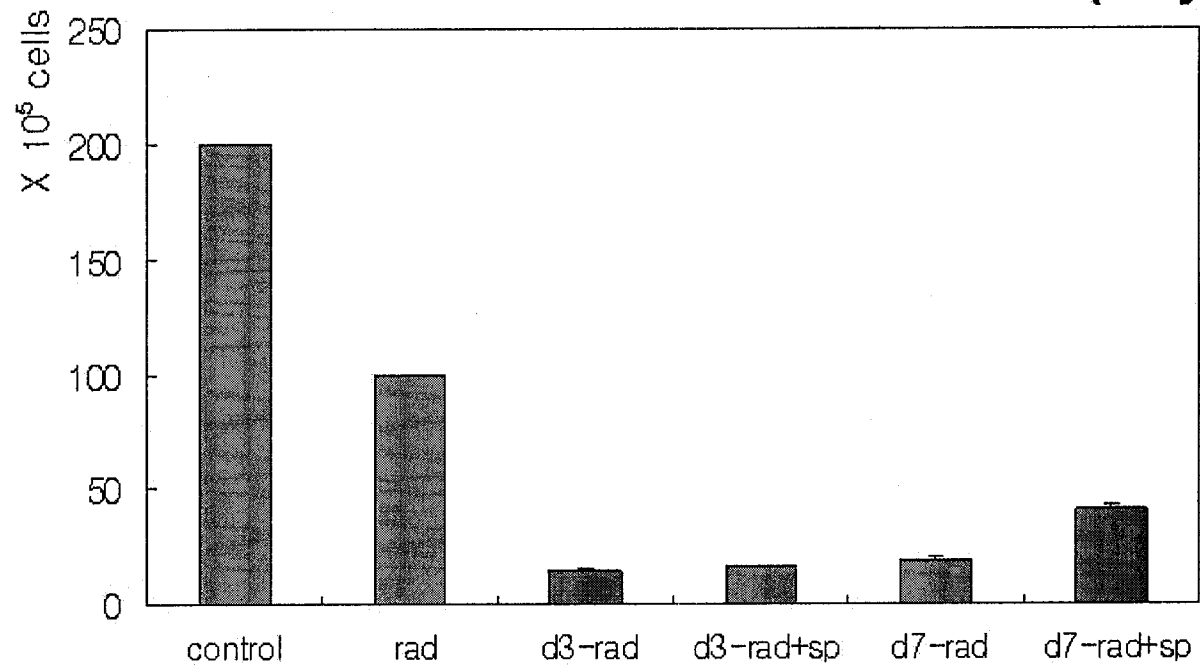
Number of bone marrow cell after radiation(4Gy)

Fig. 3

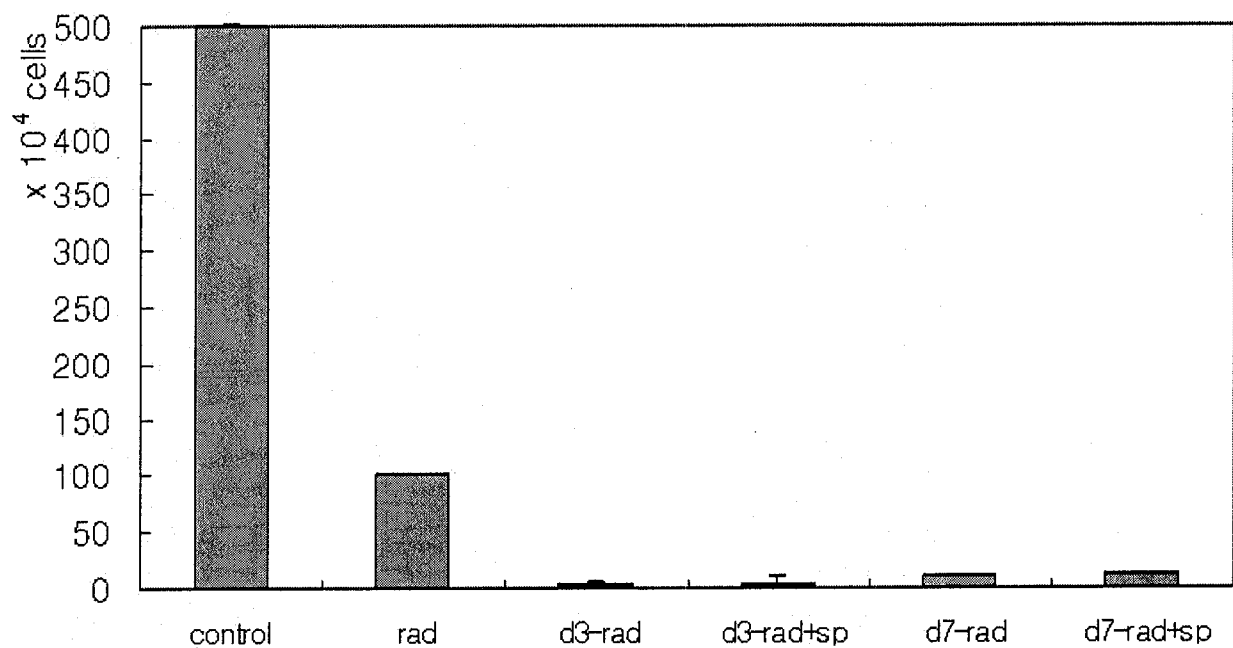
Number of peripheral blood cell after radiation(4Gy)

Fig. 4

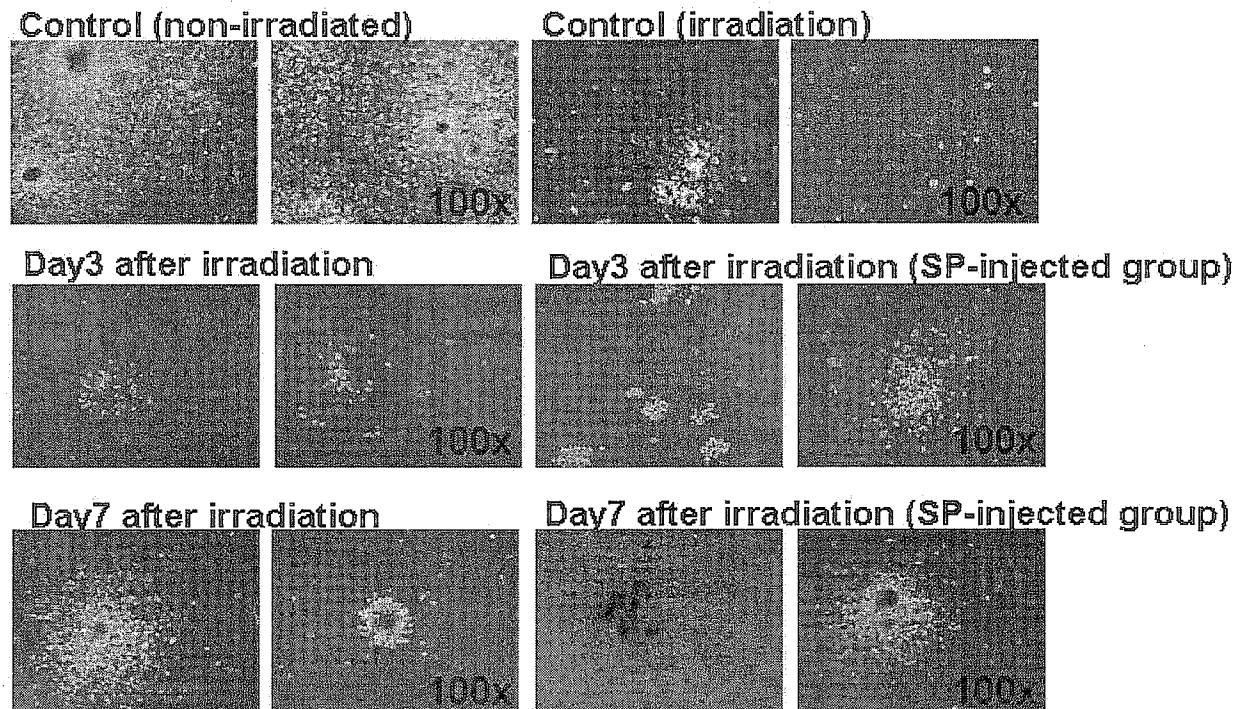


Fig. 5

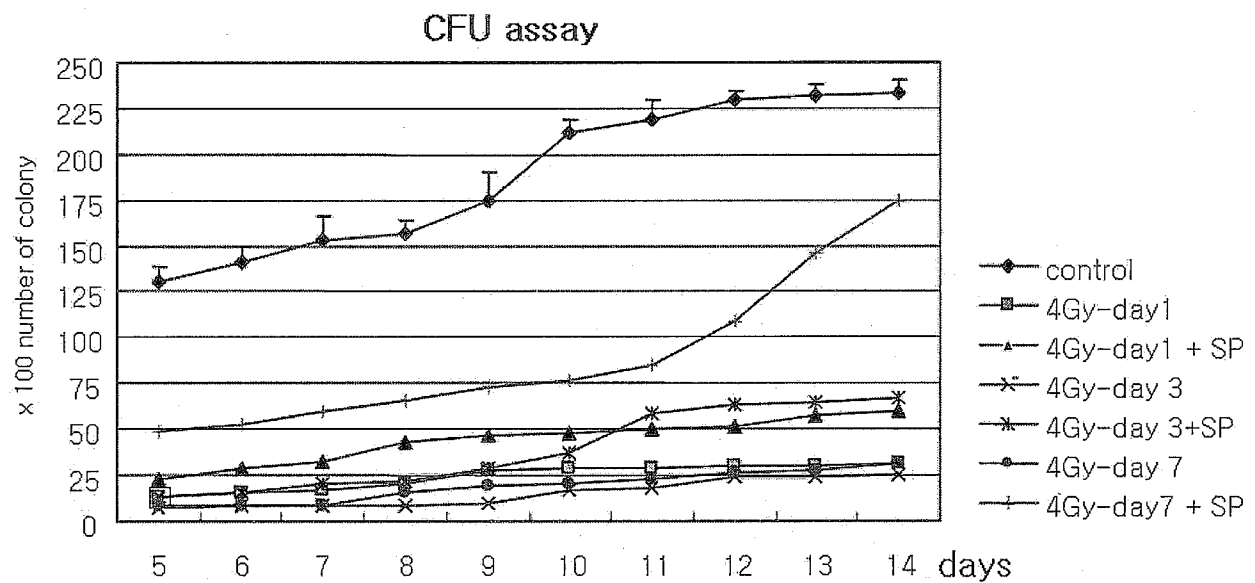


Fig. 6

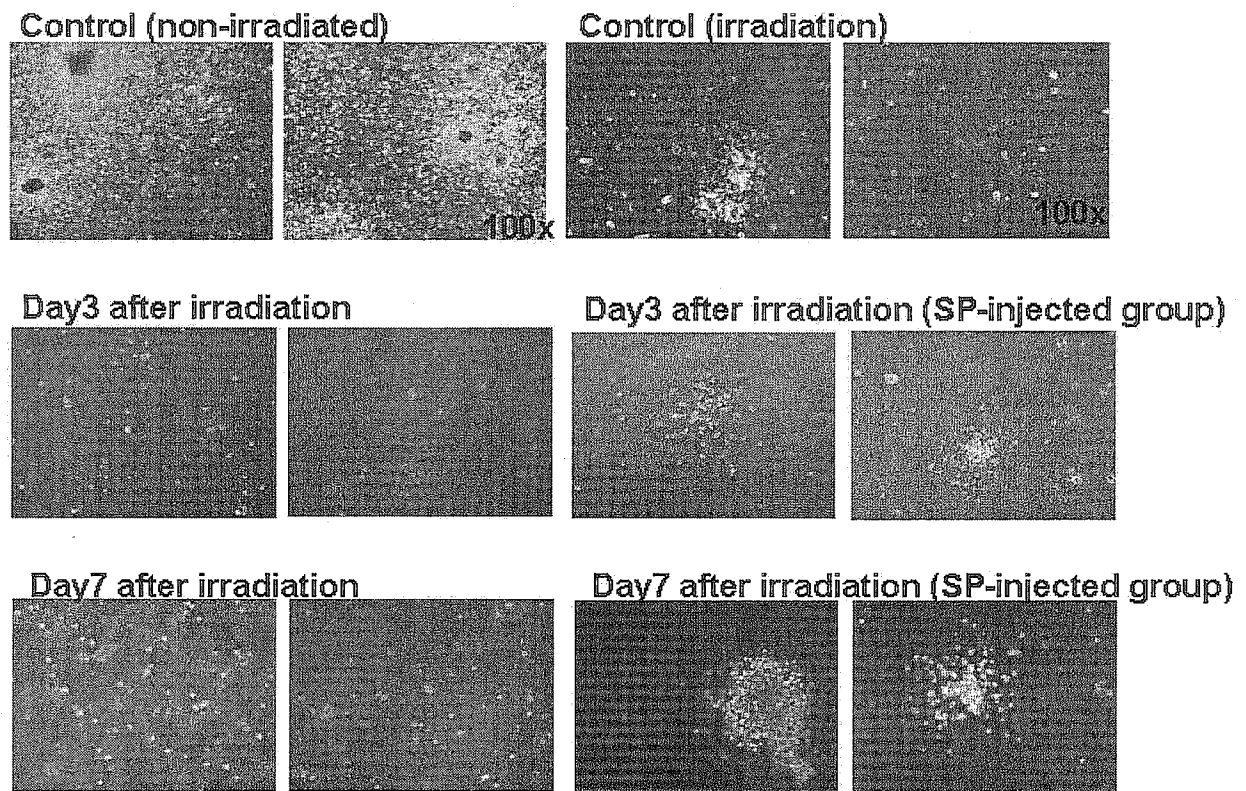
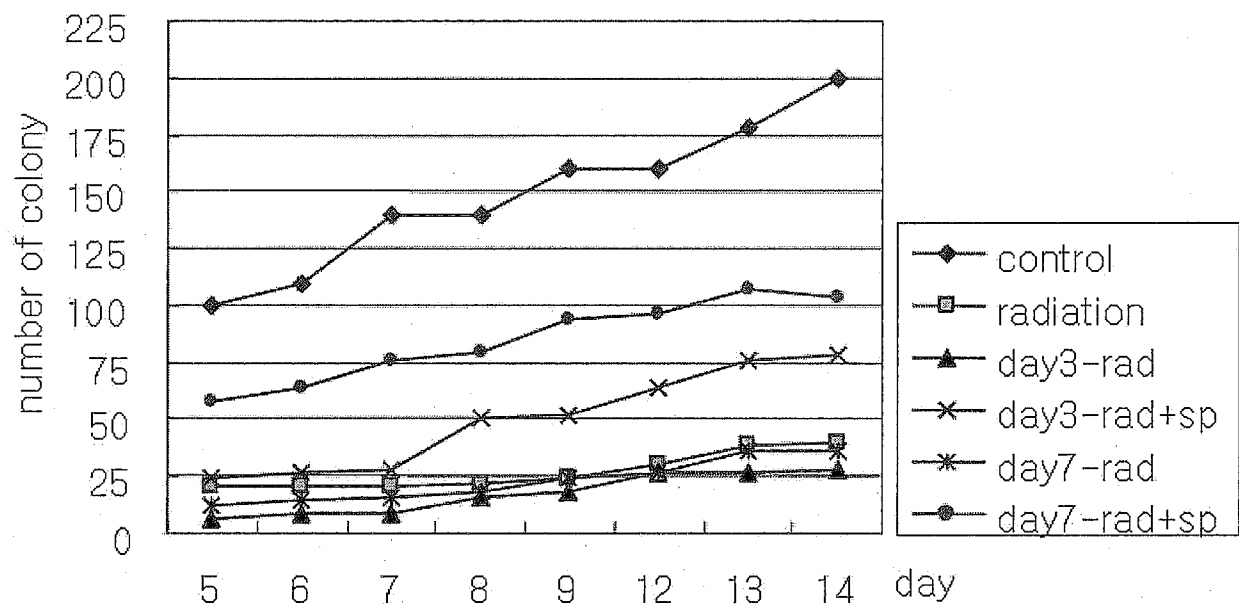


Fig. 7



VIII-5-1	Declaration: Non-prejudicial disclosure or exceptions to lack of novelty Declaration as to non-prejudicial disclosures or exceptions to lack of novelty (Rules 4.17(v) and 51bis.1(a)(v)): Name (LAST, First)	in relation to this international application SON, Youngsook declares that the subject matter claimed in this international application was disclosed as follows:
VIII-5-1(i)	Kind of disclosure:	publication
VIII-5-1(i)	Date of disclosure:	09 December 2006 (09.12.2006)
VIII-5-1(i)	Title of disclosure:	Stimulating Effect of Substance-P on the Recovery from Radiation-induced Bone Marrow Suppression
VIII-5-1(i)	Place of disclosure:	

INTERNATIONAL SEARCH REPORT

International application No.

PCT/KR2007/002762**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 11-15
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 11-15 pertain to method for treatment of the human body therapy, as well as diagnostic method, and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

A. CLASSIFICATION OF SUBJECT MATTER*A61K 38/14(2006.01)i, A61P 19/00(2006.01)i*

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 8 : A61K 38/14, 38/04, 35/28, A61P 19/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PubMed, eKIPASS(KIPO internal), STN, Data base of ASCB 46th Annual Meeting

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Son, Y. et al., 'Stimulating effect of substance-P on the recovery from radiation-induced bone marrow suppression' In: ASCB 46th Annual Meeting, 2006 See abstract	1-10
X	EP 1658855 A2 (KOREA ATOMIC ENERGY RESEARCH INSTITUTE) 24 May 2006 See abstract, paragraphs 2-15	1-10
A	Human placenta-derived mesenchymal progenitor cells support culture expansion of long-term culture-initiating cells from cord blood CD34+ cells. Experimental hematology. July 2004, Vol. 32, No. 7, pp.657-664. See abstract, pages 663-664.	1-10
A	Mesenchymal stem/progenitor cells in human umbilical cord blood as support for ex vivo expansion of CD34(+) hematopoietic stem cells and for chondrogenic differentiation. Hematologica. July 2004. Vol. 89, No. 7, pp. 837-844. See abstract, pages 842-843.	1-10



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

16 OCTOBER 2007 (16.10.2007)

Date of mailing of the international search report

16 OCTOBER 2007 (16.10.2007)

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2007/002762Patent document
cited in search reportPublication
datePatent family
member(s)Publication
date

EP 1658855 A2

24.05.2006

CN 1824289 A

30.08.2006

EP 1658855 A3

31.05.2006

JP 18124389 A

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KR 2006037176 A

03.05.2006

US 2006127373 A

15.06.2006