the cancer stem cell is regulated by the balance between the symmetric and asymmetric divisions and the deregulation of the mechanisms controlling said self-renewal is most likely involved in the onset of the tumor.

Glioma is the most common primary tumor of the brain and can be classified in four clinical grades depending on its histology and prognosis. Grade IV gliomas (glioblastoma multiforme) are highly aggressive and resistant to both radiotherapy and chemotherapy. Despite progress in understanding the molecular mechanisms involved in the genesis and progression of glioma, the prognosis and the treatment of this type of tumor continues to be ineffective. The treatment of choice for glioma is surgical intervention. Nevertheless, surgical treatment is usually accompanied by a pharmacological adjuvant treatment or by means of radiotherapy. The drugs of choice for the treatment of glioma include the combination referred to as PCV which comprises procarbazine, CCNU (lomustine) and vincristine, temozolomide in combination with radiotherapy.

It is considered that GICs are responsible for the onset, propagation and recurrence of tumors, indicating that the most effective therapies will come from therapies directed at compartmentalizing glioma stem cells. A tumor will not be eradicated if GICs are not eliminated.

Therefore, it is necessary to have alternative treatments which prevent the drawbacks of treatments known in the state of the art and which can efficiently eliminate GICs.

Summary ~~of the Invention~~

In a first ~~aspect~~embodiment, the ~~invention~~present disclosure relates to an inhibitory agent of the expression and/or the activity of an IL-6 type cytokine for the treatment of diseases associated with unwanted cell proliferation.

In another ~~aspect~~embodiment, the ~~invention~~present disclosure relates to a pharmaceutical composition comprising a therapeutically effective amount of an inhibitory agent according to the

~~invention~~present disclosure and a pharmaceutically acceptable carrier for the treatment of diseases associated with unwanted cell proliferation.

In another ~~aspect~~embodiment, the ~~invention~~present disclosure relates to an *in vitro* method for the identification of compounds capable of blocking/inhibiting the cell proliferation of tumor cells induced by an IL-6 type cytokine or a functionally equivalent variant thereof comprising the steps of:

(i) contacting a cell expressing the receptor for an IL-6 type cytokine with an IL-6 type cytokine and a candidate compound, and

(ii) identifying those compounds blocking the cell proliferation of said cell.

In another ~~aspect~~embodiment, the ~~invention~~present disclosure relates to an *in vitro* method for the diagnosis of diseases associated with unwanted cell proliferation in a subject or for determining the predisposition of a subject to suffer said disease associated with unwanted cell proliferation, or for determining the stage or severity of said disease associated with unwanted cell proliferation in a subject, or for monitoring the effect of the therapy administered to a subject with said disease associated with unwanted cell proliferation, which comprises quantifying the expression levels of the gene encoding an IL-6 type cytokine or of the protein encoded by said gene or functionally equivalent variant of said protein in a biological sample from said subject, in which an increase of the expression of the gene encoding an IL-6 type cytokine or of the protein encoded by said gene or functionally equivalent variant of said protein, with respect to the expression of the gene encoding an IL-6 type cytokine or of the protein encoded by said gene or functionally equivalent variant of said protein in a control sample, is indicative of a disease associated with unwanted cell proliferation, or of greater predisposition of said subject to suffer from a disease associated with unwanted cell proliferation or of the non-

response to the therapy administered to said subject.

In an aspect, there is provided the use of an inhibitory anti-LIF antibody in the manufacture of a medicament for the treatment of cancer, wherein the cancer is characterized by presenting a concentration of LIF which is at least 5% greater than that occurring in a control sample, and wherein said cancer is glioma.

In another aspect, there is provided an *in vitro* method for the identification of compounds capable of blocking/inhibiting the cell proliferation of tumor cells induced by LIF, comprising the steps of:

(i) contacting a cell expressing the receptor for LIF with LIF and a candidate compound, and

(ii) identifying those compounds blocking the cell proliferation of said cell,

wherein the cell expressing the receptor for LIF is a glioma initiating cell (GIC).

In another aspect, there is provided an *in vitro* method for selecting patients suffering from cancer to be treated with an inhibitory agent of LIF, comprising:

a) quantifying the expression levels of LIF in said patient, and

b) comparing said expression level with a control level,

wherein if the expression level of LIF is greater than the control level, then the patient is selected to receive treatment with an inhibitory agent of LIF, and wherein the cancer is glioma.

In another aspect, there is provided an *in vitro* method for the prognosis of life expectancy of subjects suffering from cancer, comprising quantifying the expression levels of the gene encoding LIF or of the protein encoded by said gene in a biological sample from said subject, wherein an increase of the expression of the gene encoding LIF or of the protein encoded by said gene, with respect to the expression of the gene encoding LIF or of the protein encoded by said gene in a control sample, is indicative of a reduced life expectancy,

wherein the patient is selected to receive treatment with an inhibitory agent of LIF, and wherein the cancer is glioma.

In another ~~aspect~~embodiment, the ~~invention~~present disclosure relates to the use of a kit comprising reagents for the quantification of the expression levels of the gene encoding an IL-6 type cytokine or of the protein encoded by said gene or functionally equivalent variant of said protein for the diagnosis of cancer in a subject or for determining the predisposition of a subject to suffer said cancer, or for determining the stage or severity of said cancer in a subject, or for predicting the probability of survival and/or of the average expected life time of a subject suffering from said cancer, or for monitoring the effect of the therapy administered to a subject with said cancer, in which if the reagents detect an increase in the expression of said gene or said protein or functionally equivalent variant thereof with respect to a control sample, then said subject can suffer from a disease associated with unwanted cell proliferation, or presents a greater predisposition to suffer said disease associated with unwanted cell proliferation, or presents greater severity of said disease, or the administered therapy is not being effective.

Claims

1. Use of an inhibitory anti-LIF antibody in the manufacture of a medicament for the treatment of cancer, wherein said cancer is glioma.

2. An *in vitro* method for the identification of compounds capable of blocking/inhibiting the cell proliferation of tumor cells induced by LIF, comprising the steps of:
   (i) contacting a cell expressing the receptor for LIF with LIF and a candidate compound, and
   (ii) identifying those compounds blocking the cell proliferation of said cell,
   wherein the cell expressing the receptor for LIF is a glioma initiating cell (GIC).

3. An *in vitro* method for designing a customized therapy for a patient suffering from cancer, or for selecting patients suffering from cancer, or for the prognosis of life expectancy of subjects suffering from cancer, comprising quantifying the expression levels of the gene encoding LIF or of the protein encoded by said gene in a biological sample from said subject, wherein an increase of the expression of the gene encoding LIF or of the protein encoded by said gene, with respect to the expression of the gene encoding LIF or of the protein encoded by said gene in a control sample, is indicative of a reduced life expectancy, wherein the patient is selected to receive treatment with an inhibitory agent of LIF, and wherein the cancer is glioma.

4. An *in vitro* method for designing a customized therapy for a patient suffering from cancer according to claim 3 comprising:
   (a) quantifying the expression levels of LIF in said patient, and
   (b) comparing said expression levels with control levels,

wherein if the expression levels of LIF in said patient are greater than the control values, then an inhibitory agent of LIF is administered to said patient, wherein the inhibitory agent is an inhibitory antibody specific to LIF or an antibody blocking the LIF receptors.

5. An *in vitro* method for selecting patients suffering from cancer according to claim 3, to be treated with an inhibitory agent of LIF comprising

(a) quantifying the expression levels of LIF in said patient, and

(b) comparing said expression levels with control levels,

wherein if the expression levels of LIF in said patient are greater than the control values, then said patient is selected to receive treatment with an inhibitory agent of LIF, wherein the inhibitory agent is an inhibitory antibody specific to LIF or an antibody blocking the LIF receptors.

6. The method according to claim 3, wherein the quantification of the expression levels of the gene encoding LIF comprises the quantification of the messenger RNA (mRNA) of said gene, a fragment of said mRNA, complementary DNA (cDNA) of said gene, a fragment of said cDNA, or mixtures thereof.

7. The method according to claim 4, wherein the quantification of the expression levels of the gene encoding LIF is performed by means of a quantitative polymerase chain reaction (PCR).

8. The method according to claim 3, wherein the quantification of the levels of protein is performed by means of Western blot, immunohistochemistry, ELISA or by means of the determination of the activity of said protein.

9. The use according to claim 1, or the method according to any one of claims 3 to 8, wherein said glioma is grade IV glioma.

10. The use according to claims 1 or 9, or the method according to claim 3, wherein the cancer tumor forming cells are characterized by presenting a concentration of LIF which is at least 5% greater than those occurring in a control sample.

11. A pharmaceutical composition comprising a therapeutically effective amount of an antibody referred to in any of claims 1, or 7 to 9 together with a pharmaceutically acceptable carrier.

Claims

1. Use of an inhibitory anti-LIF antibody in the manufacture of a medicament for the treatment of cancer, wherein the cancer is characterized by presenting a concentration of LIF which is at least 5% greater than that occurring in a control sample, and wherein said cancer is glioma.

2. An *in vitro* method for the identification of compounds capable of blocking/inhibiting the cell proliferation of tumor cells induced by LIF, comprising the steps of:
   (i) contacting a cell expressing the receptor for LIF with LIF and a candidate compound, and
   (ii) identifying those compounds blocking the cell proliferation of said cell,
   wherein the cell expressing the receptor for LIF is a glioma initiating cell (GIC).

3. An *in vitro* method for selecting patients suffering from cancer to be treated with an inhibitory agent of LIF, comprising:
   a) quantifying the expression levels of LIF in said patient, and
   b) comparing said expression level with a control level, wherein if the expression level of LIF is greater than the control level, then the patient is selected to receive treatment with an inhibitory agent of LIF, and wherein the cancer is glioma.

4. An *in vitro* method for the prognosis of life expectancy of subjects suffering from cancer, comprising quantifying the expression levels of the gene encoding LIF or of the protein encoded by said gene in a biological sample from said subject, wherein an increase of the expression of the gene encoding LIF or of the protein encoded by said gene, with respect to the expression of the gene encoding LIF or of the protein encoded by said gene in a control sample, is indicative of a reduced life expectancy,

wherein the patient is selected to receive treatment with an inhibitory agent of LIF, and wherein the cancer is glioma.

5. The method according to any one of claims 3-4, wherein the quantification of the expression levels of the gene encoding LIF comprises the quantification of the messenger RNA (mRNA) of said gene, a fragment of said mRNA, complementary DNA (cDNA) of said gene, a fragment of said cDNA, or mixtures thereof.

6. The method according to claim 5, wherein the quantification of the expression levels of the gene encoding LIF is performed by means of a quantitative polymerase chain reaction (PCR).

7. The method according to any one of claims 3-4, wherein the quantification of the levels of protein is performed by means of Western blot, immunohistochemistry, ELISA or by means of the determination of the activity of said protein.

8. The use according to claim 1, or the method according to any one of claims 3 to 7, wherein said glioma is grade IV glioma.