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(54) **Title**: METHODS AND COMPOSITIONS FOR TREATMENT OF BONE, SKIN, SUBCUTANEOUS, MUCOSAL AND/OR SUBMUCOSAL CANCER BY PERCUTANEOUS AND/OR TRANSMUCOSAL ADMINISTRATION OF INTERFERON

(57) **Abstract**: The invention provides a method and/or composition for the treatment of bone cancer including primary bone cancer and secondary bone cancer, breast cancer, skin cancer, nasopharyngeal carcinoma, oral cancer, vulva cancer, prostate cancer, cervical cancer, melanoma including melano carcinoma by percutaneous and/or transmucosal administration of the interferon. Further, the invention provides a method and/or composition for the treatment of skin, subcutaneous, mucosal and/or submucosal primary cancer and cancer metastatic lesions by percutaneous and/or transmucosal administration of the interferon, especially a method and/or composition for the treatment of bone cancer pain including pain resulted by secondary bone cancer.

WO 2014/106492 A2

METHODS AND COMPOSITIONS FOR TREATMENT OF BONE, SKIN, SUBCUTANEOUS, MUCOSAL AND/OR SUBMUCOSAL CANCER BY PERCUTANEOUS AND/OR TRANSMUCOSAL ADMINISTRATION OF INTERFERON

FIELD OF THE INVENTION

[1] This invention relates to methods and products for treatment of cancer in subjects.

BACKGROUND

[2] Cancer, such as cancer in the bones, is a debilitating and painful disease and is often associated with metastases from primary tumors originating from other tissues or organs, but can also arise as primary tumors. As yet, there is no good, easily administered, effective treatment to alleviate the pain or treat the disease or give the people suffering from this disease any encouragement that their conditions could improve. Similarly, there is as yet no good, effective, easily administered treatment for skin cancer, subcutaneous cancer, mucosal and/or other submucosal cancers. Hence, there is an unmet medical need for the provision of methods, compositions and products for treatment of such diseases and the side effects of such diseases, such as bone pain.

SUMMARY OF THE INVENTION

[3] The invention herein provides one or more methods and/or compositions and/or other products for the treatment of primary and/or secondary cancer in a subject, including for example cancer in the bone or bones (hereafter, "bone"), as well as skin cancer, subcutaneous cancer or carcinoma, mucosal cancer or carcinoma and/or other submucosal cancer or carcinoma, including metastasized lesions, and treatment of pain arising from the cancer, especially from bone cancer, in each instance, whether the cancer is primary or secondary, where secondary cancer refers to cancer from metastases originating from a primary tumor.

[4] The invention provides a method and/or composition for the treatment of bone cancer including primary bone cancer and secondary bone cancer, breast cancer, skin cancer, nasopharyngeal carcinoma, oral cancer, vulva cancer, prostate cancer, cervical cancer, melanoma including melanocarcinoma by percutaneous and/or transmucosal administration of the interferon. Further, the invention provides a method and/or composition for the treatment of skin, subcutaneous, mucosal and/or submucosal primary cancer and cancer metastatic lesions by percutaneous and/or transmucosal administration of the interferon, especially a method and/or composition for the treatment of bone cancer pain including pain resulted by secondary bone cancer.

[5] The invention provides one or more methods for the treatment of primary bone cancer or secondary bone cancer in a subject, comprising administering the interferon to an area of a bone of the subject where the bone is affected by cancer or comprises cancer cells.

[6] The invention also provides one or more methods for the treatment of skin, subcutaneous, mucosal and/or submucosal cancer in a subject, comprising administering the interferon to a skin, subcutaneous, mucosal and/or submucosal area of the subject where the area is affected by cancer or comprises cancer cells, wherein such cancers are primary cancers or secondary cancers metastatic from primary cancers.

[7] In some embodiments, the invention provides administering to the subject an effective amount of a consensus interferon alpha that comprises an amino acid sequence of SEQ ID NO: 1 and having anti-cancer activity. In some embodiments, the amino acid sequence is encoded by a polynucleotide comprising a polynucleotide sequence of SEQ ID NO:2

[8] In some embodiments of the invention, the interferon is administered by local administration, such as to an area affected by cancer or comprising cancer cells.

[9] In some embodiments of the invention, the interferon is administered by local administration and at least one of inhalation administration and systemic administration.

[10] In some embodiments, the invention provides methods and compositions for

treating bone cancer (including primary bone cancer and secondary bone cancer), breast cancer, skin cancer, nasopharyngeal carcinoma, oral cancer, carcinoma of the vulva, prostatic carcinoma, cervical carcinoma and melanoma (including melanocarcinoma) by percutaneous and/or transmucosal administration.

[11] In some embodiments, the invention provides methods and compositions for treating primary skin cancer, subcutaneous carcinoma, mucosal carcinoma and/or submucosal carcinoma as well as metastasized lesions, including methods and compositions for treating pain caused by bone cancer (including secondary bone cancer).

[12] In some embodiments, the invention provides methods and compositions as any described herein, where the interferon is administered by local administration, inhalation administration, or systemic administration, where systemic administration includes subcutaneous administration and intramuscular administration, such as subcutaneous injection and intramuscular injection.

[13] In some embodiments, the invention provides methods and compositions as any described herein, further comprising administering the interferon by at least one of injection and inhalation of aerosolized interferon.

[14] In some embodiments, the invention provides methods and compositions for treating cancer as any described herein, where the interferon is administered by local administration, or optionally by percutaneous administration and/or transmucosal administration.

[15] The skin cancer herein includes cancer involving the epidermal cells such as basal cell carcinoma, epidermoid carcinoma, squamous cell carcinoma, including melanoma (including melanocarcinoma) cervical carcinoma, and carcinoma of the vulva. The subcutaneous cancer herein involves cancer of the subcutaneous tissues or cells and includes breast and prostatic cancer or carcinoma and the like. The mucosal cancer herein involves cancer of the mucosal cells and includes nasopharyngeal carcinoma, oral cancer, and rectal carcinoma. The submucosal tumor includes cancer of the submucosal tissues including bone cancer.

[16] In some embodiments, the invention provides methods, compositions and/or

other products for treating bone cancer, skin cancer, subcutaneous cancer; mucosal cancer and/or submucosal cancer and/or cancer pain by local administration of the interferon, and local administration includes percutaneous administration and/or transmucosal administration.

[17] The invention provides, in some embodiments, administering the interferon to an area of a bone of the subject where the bone is affected by cancer or comprises cancer cells. The cancer in the bone can be primary bone cancer or can be secondary bone cancer, that is, a cancer that has metastasized to the bone from a primary tumor that originates from another tissue or organ.

[18] The invention also provides methods and compositions for treatment of cancer in a subject comprising administering to the subject an effective amount of a consensus interferon alpha that comprises anti-cancer activity and an amino acid sequence of SEQ ID NO: 1, wherein the interferon is administered by local administration to the skin and/or to the mucosa of the subject.

[19] The invention additionally provides a method as any of the foregoing methods, where the interferon is administered by percutaneous administration or systemic administration.

[20] In some embodiments, systemic administration includes subcutaneous administration and intramuscular administration.

[21] The invention moreover provides a method as any of the foregoing methods, further providing administering the interferon to the subject systemically by injection, such as subcutaneous injection and intramuscular injection.

[22] The invention additionally provides a method as any of the foregoing methods, further comprising administering the interferon to the subject by inhalation. In some embodiments, inhalation administration includes administration of a dried interferon powder. In some embodiments, inhalation administration includes administration of an aqueous solution of the interferon. In some embodiments, inhalation administration includes administration of an aerosolized form of the interferon.

[23] The invention also provides a method of treatment of cancer in bone in a subject comprising administering to the subject an effective amount of a consensus

interferon alpha that comprises anti-cancer activity and an amino acid sequence of SEQ ID NO: 1, wherein the interferon is administered percutaneously to the subject.

[24] The invention additionally provides a method as the foregoing method of application of the interferon percutaneously, on or to the skin of the subject, and/or transmucosally, to or on the mucosa of the subject.

[25] The invention further provides a method percutaneously and/or transmucosally as the foregoing, further comprising administering the interferon by at least one of: injection and inhalation, optionally, by both injection and inhalation administration, where the inhalation administration includes administration of an aerosolized form of the interferon, a dry powder and/or an aqueous solution of the interferon.

[26] The invention further provides a method as any of the foregoing methods, wherein application of interferon to an area of the bone includes at least one of: application of the interferon directly or indirectly to or on the bone.

[27] The invention also provides a method as any of the foregoing methods, wherein application of interferon to the skin comprises application to or on the skin in proximity to the bone affected by cancer, that is, that part of the bone that comprises cancer cells or application to or on the skin surrounding the bone affected by cancer.

[28] In some embodiments, the administration to the skin includes application of the interferon to the skin surrounding the bone affected by cancer.

[29] The invention further provides a method as any of the foregoing methods, where the interferon is administered to the mucosa. In some embodiments, application to the mucosa includes application to the mucosa in proximity to the bone affected by cancer, that is, that part of the bone comprising cancer cells, or to the mucosa surrounding the bone affected by cancer.

[30] The invention also provides a method as any of the foregoing methods, wherein application of the interferon to the skin includes application of the interferon subcutaneously.

[31] The invention further provides a method as any of the foregoing methods, wherein application of the interferon to the mucosa includes submucosal administration.

[32] The invention moreover provides a method as any of the foregoing methods, wherein application of the interferon to the skin comprises at least one of: spraying an aqueous solution of the interferon on skin, applying a cream comprising the interferon on skin, applying a membrane, such as a transdermal patch comprising the interferon, or any other membrane comprising the interferon that allows for controlled-release or permeation or diffusion of the interferon to and through skin of subject, or creating a depot effect such that interferon is deposited under the skin and produces a slow-release or controlled release effect, and/or other closed drug delivery systems.

[33] The invention further provides a method as any of the foregoing methods, wherein administering the interferon by inhalation comprises at least one of: delivering the interferon intranasally and to the lungs.

[34] The invention also provides a method as any of the foregoing methods, wherein the interferon is formulated as a solution or a suspension.

[35] The invention provides a method as any of the foregoing methods wherein the interferon is formulated in the form of at least one of: nanoparticles, microspheres, liposomes or other controlled release single or composite material.

[36] The invention also provides a method as any of the foregoing methods, wherein the interferon administered by injection is administered in at least two or more dosages, each dosage being higher than or the same as the previous dose.

[37] The invention provides a method as any of the foregoing methods, wherein the first dose of injection of the interferon comprises about 2 microgram to about 15 microgram of the interferon.

[38] The invention provides a method as any of the foregoing methods, wherein the first dose of injection of the interferon comprises 9 microgram or 15 microgram of interferon.

[39] The invention also provides a method as any of the foregoing methods, where the second dose of injection of the interferon comprises about 15 microgram to about 50 microgram of the interferon.

[40] The invention also provides a method of any of the foregoing embodiments, wherein the second dose of injection of the interferon comprises 15 microgram or 18

microgram or 21 microgram of the interferon.

[41] The invention provides a method as any of the foregoing methods, wherein the third dose and/or any subsequent dose of injection of the interferon is higher or the same as the second dose.

[42] The invention further provides a method as any of the foregoing methods, wherein administering the interferon by application to the skin or the bone or the mucosa comprises spraying thereon at least 1 – 12 times a day, optionally 2 – 10 times a day, still optionally, 3 – 8 times a day, further optionally 4 or 5 or 6 times per day.

[43] The invention still further provides a method as any of the foregoing methods, wherein administering the interferon to the subject by inhalation comprises administering the interferon by inhalation every day or every few days, such as every 2 days or every 3 days.

[44] The invention provides a method as any of the foregoing methods, wherein administering the interferon to the subject to or on the bone or skin or mucosa or other local administration comprises applying a formulation of the interferon at a concentration in the range of about 0.01 mg/ml to about 5 mg/ml optionally, in the range of about 0.03 mg/ml to about 2 mg/ml and further optionally, in the range of about 0.05 mg/ml to about 1 mg/ml, and still further optionally, in the range of about 0.1 mg/ml to about 0.5 mg/ml.

[45] The invention provides a method as any of the foregoing methods, wherein the primary tumor comprises at least one of: a solid tumor and a non-solid tumor.

[46] Further, the invention provides that the primary tumor that metastasized can be cancer of the respiratory system, cancer of the digestive system, cancer of the urinary system, breast cancer, skin cancer, cancer of the reproductive system, head and neck cancer, cancer of the hormonal system, and cancer of the nervous system. The cancer of the digestive system includes: oral cancer, tongue cancer, laryngeal carcinoma, esophageal cancer, gall bladder cancer, liver cancer, gastrointestinal cancer, and pancreatic cancer. The cancer of the reproductive system includes: carcinoma of the external genitalia, cervical cancer, endometrial cancer, uterine cancer, ovarian cancer,

and prostate cancer. The cancer of the respiratory system includes: lung cancer and nasopharyngeal carcinoma. The cancer of the urinary system includes: kidney cancer and bladder cancer. The cancer of the hormonal system includes: adrenal cancer and thyroid cancer. The head and neck cancer comprises nasopharyngeal carcinoma. The skin cancer includes: epithelial and subcutaneous cancer such as prostatic carcinoma, breast cancer, basal cell carcinoma, epidermoid carcinoma, squamous cell carcinoma, carcinoma of the external genitalia such as carcinoma of the vulva, and melanoma including melanocarcinoma. The cancer of the nervous system includes: neuroma, malignant neuroma, glioma, and astrocytoma.

[47] The invention provides that the lung cancer includes: small cell lung cancer and non-small cell lung cancer. The gastrointestinal cancer includes: gastrointestinal interstitial cell tumor, stomach cancer, colon cancer, rectal cancer, and colorectal cancer. The gall bladder cancer includes cholangiocarcinoma. The liver cancer includes hepatocellular carcinoma. The kidney cancer includes renal cell carcinoma. The bladder cancer includes superficial bladder cancer.

[48] The invention further provides that the primary tumor that metastasized can be: a carcinoma, a sarcoma, and a rhabdomyosarcoma.

[49] The invention further provides that the primary tumor that metastasized can also be one of: abdominal tumor, myoepithelial carcinoma, synovial sarcoma, hemangioma, lymphoma and Kaposi's sarcoma.

[50] The invention also provides that the mucosal cancer includes oral cancer, nasopharyngeal carcinoma, rectal cancer, laryngeal carcinoma and tongue cancer.

[51] The invention provides a method as any of the foregoing methods, where the bone cancer, skin cancer, subcutaneous carcinoma, mucosal carcinoma and/or submucosal carcinoma includes bone cancer (including primary bone cancer and secondary bone cancer), breast cancer, skin cancer, nasopharyngeal carcinoma, oral cancer, carcinoma of the vulva, prostatic carcinoma, cervical carcinoma and melanoma, including melanocarcinoma.

[52] The invention provides a method as any of the foregoing methods, wherein injection of the interferon comprises injection before, after, or at about the same time

as the administration of the interferon to or on the skin and/or bone, and/or mucosa, and/or submucosa.

[53] The invention further provides a method as any of the foregoing methods, wherein application of the interferon by inhalation comprises such application before, after or approximately at the same time as application of the interferon to or on the skin and/or bone, and/or mucosa, and/or submucosa.

[54] The invention provides a method as any of the foregoing methods, wherein administration of the interferon to or on the skin, bone, mucosa, and/or submucosa comprises such administration before, after, or at the same time as administration of the interferon by injection and/or administration of the interferon by inhalation, and the administration of the interferon by injection comprises such administration before, after, or at about the same time as administration of the interferon by inhalation, if any.

[55] The invention provides that for local administration, the interferon can be applied to or on the cancerous lesion. Further, application to or on the cancerous lesion can be by: at least one of infiltration administration, percutaneous administration, transdermal administration, epidermal administration, and transmucosal administration. Percutaneous administration can also be achieved by spraying the interferon.

[56] The invention also provides that local administration of the interferon comprises administration of interferon in a range of about 2 microgram to about 2100 microgram, optionally, in a range of about 4 microgram to about 1800 microgram, further optionally, in a range of about 9 microgram to about 1500 microgram, still optionally, in a range of about 12 microgram to about 1200 microgram, still further optionally, in a range of about 15 microgram to about 1000 microgram, yet further optionally, in a range of about 18 microgram to about 900 microgram, still yet optionally, in a range of about 21 microgram to about 750 microgram, and still further optionally, in a range of about 24 microgram to about 600 microgram.

[57] The invention provides that when the interferon is administered locally to the subject, it can be administered in a range of about 1 – 12 times per day, optionally, 2 –

10 times per day, still optionally, 3 – 8 times per day, and still further optionally, 4 – 6 times per day.

[58] In some embodiments, the invention provides that when the interferon is administered to the subject locally, it can be administered at least 1, 2, 3, 4, 5, 6, 7, 8, or more times per day.

[59] The invention additionally provides that when the interferon is administered to the subject by local administration, the interferon can be administered every day, or every other day, or every 2nd, 3rd, 4th, 5th, 6th, 7th, 8th, 9th, 10th, 11th, 12th, 13th, 14th, 15th, 16th, 17th, 18th, 19th, 20th, or 21st day, or every month, or every 2, or 3, or 4, or 5, or 6 or 7, or 8, or 9, or 10, or 11, or 12 months or longer.

[60] The invention moreover provides a method as of the foregoing, where administration of the interferon can be by spraying, and the spray can be in an amount in a range of about 6 microgram to about 100 microgram, optionally, in a range of about 10 microgram to about 80 microgram, further optionally, in a range of about 20 microgram to about 60 microgram, and still further optionally, in a range of about 30 microgram to about 40 microgram per spray administration and at a concentration in a range of about 0.01 mg/ml to about 5 mg/ml, optionally, about 0.03 mg/ml to about 2 mg/ml, further optionally, about 0.05 mg/ml to about 1 mg/ml, and still optionally, about 0.1 to 0.5 mg/ml.

[61] The invention further provides a method as any of the foregoing, where the interferon can be administered by spraying 1 – 10 times per day, optionally, 2 – 9 times per day, further optionally, 3 – 8 times per day, still optionally 4 – 7 times per day, yet still optionally 5 – 6 times per day.

[62] The invention also provides a method as any of the foregoing, where the interferon for local administration can be formulated as at least one of: an aqueous solution, such as for spraying, a membrane permeation or diffusion drug delivery system, a controlled release drug delivery system, a closed drug delivery system, a patch such as a transdermal patch, or a depot comprising the interferon injected under the skin, producing a slow-release effect.

[63] The invention also provides a method as any of the foregoing, where the

interferon administered by systemic administration is administered before, at about the same time, and/or after the percutaneous administration of the interferon. The systemic administration includes subcutaneous administration and intramuscular administration. Optionally, the systemic administration includes subcutaneous injection and intramuscular injection.

[64] The invention further provides a method as any of the foregoing, where the interferon when administered by systemic administration, can be administered in an amount in a range of about 2 microgram to about 70 microgram, optionally in a range of about 4 microgram to about 50 microgram, further optionally, in a range of about 9 microgram to about 30 microgram, still optionally, in a range of about 15 microgram to about 24 microgram, still further optionally, in a range of about 18 microgram to about 21 microgram, per injection.

[65] The invention moreover provides a method as any of the foregoing, when the interferon is administered by systemic administration, it is administered at least once every 1 – 8 days, optionally, at least once every 2 – 7 days, still optionally, at least once every 3 – 6 days, further optionally, at least once every 4 – 5 days. Still optionally, the interferon can be administered every 1 – 2 days.

[66] The invention further provides a method as any of the foregoing, where the duration of the systemic interferon administration is at least for: 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year, 2 years, 3 years, 4 years, 5 years, and 6 years.

[67] The invention also provides a method as any of the foregoing methods, wherein the duration of the interferon administration is for a period of time in a range of 1 day to 6 years, optionally, 1 week to 4 years, still optionally, 2 weeks to 3 years, further optionally, 1 month to 1 year, still further optionally, 2 months to 9 months, or longer, or throughout the remaining life of the subject.

[68] The invention also provides a method as any of foregoing methods, wherein the interferon is administered by subcutaneous or intramuscular injection at least 2

times, optionally, at least 4 times, further optionally, at least 6 times, still optionally, at least 8 times, still further optionally, at least 10 times.

[69] The invention further provides a method as any of the foregoing systemic administration or injection methods, wherein the interferon is administered in at least one initial induction dose in a range of about 2 microgram to about 15 microgram, optionally, about 3 microgram to about 10 microgram, still optionally about 4.5 microgram to about 9.5 microgram, further optionally, about 4 microgram to about 9 microgram, and still further optionally, at about 4.5 microgram or 9 microgram.

[70] The invention also provides a method of any of the foregoing systemic administration or injection methods, wherein, the interferon is further administered in at least one subsequent therapeutic dose in a range of about 10 microgram to about 70 microgram each time, optionally in a range of about 12 microgram to about 50 microgram each time, further optionally in a range of about 15 microgram to about 30 microgram each time.

[71] The invention additionally provides a method of any of the foregoing systemic administration or injection methods, wherein the time interval between the induction dose and the therapeutic dose of the interferon is in a range of about 1 day to about 1 month, optionally or preferably, in a range of about 1 days to about 3 week, including a range of about 1 day to about 3 days, or is 1, day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 1 week, 2 weeks and 3 weeks.

[72] The invention also provides a method as any of the foregoing systemic administration or injection methods, wherein the interferon is administered to the subject at a frequency of about once every day or about once every 2, 3, 4, 5, 6, 7, 8, 9, or 10 days, optionally, in a range of about once every 1 – 7 days, further optionally, about once every 1 – 2 days, at the induction dose.

[73] The invention further provides a method as any of the foregoing systemic administration or injection methods, wherein the interferon is administered to the subject at a frequency of about once every day or about once every 2, 3, 4, 5, 6, 7, 8, 9, or 10 days, optionally, in a range of about once every 1 – 7 days, further optionally, about once every 1 – 2 days, at the therapeutic dose.

[74] The invention also provides a method as any of the foregoing systemic administration or injection methods, wherein the duration of administration of the induction dose and the therapeutic dose is at least: 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year, 2 years, 3 years, 4 years, 5 years, or 6 years, or optionally over the remaining life of the subject.

[75] The invention moreover provides a method as any of the foregoing inhalation administration methods, wherein the inhalation administration comprises at least one of: pulmonary inhalation and nasal inhalation.

[76] The invention further provides a method as any of the foregoing inhalation administration methods, wherein the interferon for inhalation administration comprises at least one of: dry powder and aerosolized interferon.

[77] The invention also provides a method as any of the foregoing inhalation administration methods, wherein the interferon is administered in an amount in a range of about 100 microgram to about 2000 microgram, optionally, about 120 microgram to about 1500 microgram, further optionally, about 150 microgram to about 1200 microgram, still optionally, about 200 microgram to about 900 microgram, yet further optionally, about 450 microgram to about 750 microgram, still further optionally, about 500 microgram to about 650 microgram, still yet further optionally, at 600 microgram, by one inhalation administration.

[78] The invention also provides a method as any of the foregoing inhalation administration methods, wherein the interferon is administered by inhalation administration about once every 1 or 2 or 3 days, optionally, every day.

[79] The invention also provides a method as any of the foregoing inhalation administration methods, wherein the duration of inhalation administration is in a range of about 1 day to about 6 years, optionally, about 1 week to about 4 years, further optionally, about 2 weeks to about 3 years, still optionally, about 3 weeks to about 2 years, still further optionally, about 1 month to about 1 year, or yet further optionally, about 2 months to about 9 months.

[80] The invention also provides a method as any of the foregoing inhalation

administration methods, wherein the duration of inhalation administration is at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year, 2 years, 3 years, 4 years, 5 years, or 6 years, or optionally for a long time, such as over the remaining life of the subject.

[81] The invention additionally provides a method as any of the foregoing methods, wherein the interferon is administered as a monotherapy.

[82] The invention also provides a method as any the foregoing methods, further including administering to the subject at least one other anti-cancer therapy.

[83] The invention also provides a method as any of the foregoing methods, wherein the at least one other anti-cancer therapy is administered to the subject before, simultaneously or at about the same time, and/or after administration of the interferon.

[84] The invention also provides a method as any of the foregoing methods, wherein the at least one other anti-cancer therapy comprises at least one of: chemotherapy, radiotherapy, surgical therapy, interventional therapy, biotherapy, targeted therapy, and Traditional Chinese medicine.

[85] The invention further provides a method as any of the foregoing methods, wherein the biotherapy comprises at least one of gene therapy and immunotherapy, and the surgical therapy comprises ablation therapy.

[86] The invention also provides a method as any of the foregoing methods, wherein the treatment achieves at least one of: elimination of at least one cancer lesion, reduction in size of at least one cancer lesion, and non-progression of growth of at least one cancer lesion, as compared to before treatment.

[87] The invention further provides a method as any of the foregoing methods, wherein the at least one anti-cancer therapy is a non-surgical therapy.

[88] The invention additionally provides a sprayer for administering an interferon that comprises anti-cancer activity and an amino acid sequence of SEQ ID NO: 1, wherein the interferon is formulated in an amount for administering at least 1 – 12 times, optionally, 2 – 10 times, further optionally, 3 – 8 times, still optionally, 4 or 5

or 6 times.

[89] The invention provides a sprayer as the foregoing sprayer, wherein the amount of interferon comprises a concentration in a range of at least about 0.01 mg/ml to about 5 mg/ml, optionally, about 0.03 mg/ml to about 2 mg/ml, still optionally, about 0.05 mg/ml to about 1 mg/ml, further optionally, about 0.1 mg/ml to about 0.5 mg/ml.

[90] In some embodiments, the amount of interferon in any of the foregoing sprayer can include about 0.1 mg/ml, about 0.2 mg/ml, about 0.3 mg/ml, about 0.4 mg/ml or about 0.5 mg/ml of the interferon.

[91] The invention also provides a sprayer as any of the foregoing sprayer, wherein the sprayer is a single use sprayer comprising one day's supply of the interferon.

[92] The invention further provides a sprayer as any of the foregoing sprayer, wherein the sprayer is a multiple use sprayer comprising at least a one-week supply of the interferon.

[93] The invention provides a sprayer for administration of a consensus interferon alpha to a subject, wherein the interferon comprises anti-cancer activity and an amino acid sequence of SEQ ID NO: 1, and is formulated at a concentration of 300 microgram/ml.

[94] The invention additionally provides a sprayer as fore-mentioned, wherein the interferon is formulated in an aqueous solution in a volume of 2 ml.

[95] The invention also provides a sprayer as any of the foregoing sprayer, wherein the interferon is encoded by a polynucleotide comprising the sequence of SEQ ID NO:2.

[96] The invention moreover provides a measured or metered dose of an interferon comprising a single use amount of the interferon, wherein the interferon comprises anti-cancer activity and an amino acid sequence of SEQ ID NO: 1.

[97] The invention also provides a metered dose as the foregoing metered dose, wherein the metered dose comprises the interferon in an amount in a range of about 100 microgram to about 2000 microgram, optionally, about 120 microgram to about 1500 microgram, further optionally or preferably, about 150 microgram to about 1200 microgram, still optionally or more preferably, about 200 microgram to about 900

microgram, yet optionally or further preferably, about 450 microgram to about 750 microgram, still further optionally or still more preferably, about 500 microgram to about 650 microgram, and yet optionally or preferably, 600 microgram of the interferon.

[98] The invention provides a metered dose as any of the foregoing metered dose, further comprising an additional amount of the interferon, sufficient for at least one week of treatment.

[99] The invention provides a metered dose as any of the foregoing metered dose, wherein the metered dose is formulated for inhalation.

[100] The invention provides a metered dose for inhalation as above, wherein the metered dose is formulated for inhalation via the nose or for inhalation via the lungs.

[101] The invention provides a metered dose as any of the foregoing metered dose, wherein the interferon was aerosolized.

[102] The invention moreover provides a transdermal patch comprising an interferon, wherein the interferon comprises anti-cancer activity and an amino acid sequence of SEQ ID NO: 1, and wherein the patch allows diffusion or permeation of the interferon to the skin of a subject.

[103] The invention also provides a sprayer as any of the foregoing sprayers, wherein the sprayer comprises at least a two-week supply of the interferon.

[104] The invention also provides a sprayer as any of the foregoing sprayers, wherein the sprayer is configured and formulated for delivery of the interferon to the nose.

[105] The invention also provides a sprayer as any of the foregoing sprayers, wherein the sprayer is configured and formulated for delivery of the interferon to or on at least one of: the subject's skin or bone or mucosa.

[106] The invention additionally provides a sprayer as any of the foregoing sprayers, wherein the sprayer is configured and formulated for delivery of the interferon by inhalation for delivery to the lungs of the subject, such as an inhaler.

[107] The invention also provides a metered dose of a consensus interferon alpha that comprises anti-cancer activity for inhalation, wherein the metered dose comprises

interferon in an amount in the range of about 100 microgram to about 2000 microgram, optionally, about 200 microgram to about 1000 microgram, still optionally about 300 microgram to about 900 microgram, further optionally, about 400 microgram to about 800 microgram, still further optionally, about 500 microgram to about 700 microgram, yet further optionally, about 600 microgram.

[108] The invention provides a metered dose as any of the foregoing embodiments, wherein the metered dose is formulated for intranasal application.

[109] The invention moreover provides a method of preparation of a medicament, wherein the medicament comprises consensus interferon alpha that comprises anti-cancer activity for administration to a subject who has cancer in bone, wherein the interferon is formulated in at least two distinct formulations, one for injection and one for percutaneous application to or on the skin or bone of the subject.

[110] The invention also provides a method of preparation of a medicament as of the foregoing embodiment, wherein the interferon is further formulated in a third formulation, for inhalation administration.

[111] The invention further provides use of a consensus interferon alpha having an amino acid sequence of SEQ ID NO: 1 and anti-cancer activity in the preparation of medicaments for treatment of bone cancer, skin cancer, subcutaneous carcinoma, mucosal carcinoma and/or submucosal carcinoma in subjects.

[112] The invention additionally provides use of a consensus interferon alpha having an amino acid sequence of SEQ ID NO: 1 and anti-cancer activity in the preparation of medicaments for treatment of pain associated with cancer, including bone cancer, in subjects.

[113] The invention also provides a drug composition for treatment of bone cancer, skin cancer, subcutaneous carcinoma, mucosal carcinoma and/or submucosal carcinoma in subjects, where the composition contains a consensus interferon alpha having an amino acid sequence of SEQ ID NO:1 and anti-cancer activity.

[114] The invention further provides a drug for treatment of pain associated with cancer, such as bone cancer, in subjects. This composition contains a consensus interferon alpha that has an amino acid sequence of SEQ ID NO: 1 and anti-cancer

activity.

DETAILED DESCRIPTION OF THE INVENTION

[115] The terms used in this application are intended to have their ordinary meaning as understood by persons skilled in the art, unless specifically indicated otherwise. In addition, the following terms have the additional meanings, as specified herein.

[116] The term "anti-cancer activity" as used herein includes any activity that arrests or suspends the growth of cancer cells or the progression of the disease, including causing apoptosis or necrosis of cancer cells, stopping the progression of their growth or cell cycle, or inducing tumor shrinkage or disappearance of tumor.

[117] The term "biotherapy" as used herein includes any and all biologics that are or can be used for treatment of cancer or side effects of cancer treatment and includes but is not limited to: antibodies, recombinant proteins, microRNA, siRNA, gene therapy, viral therapy, and cell therapy. Endostar and antibodies such as Rituxin, Herceptin, Avastin are examples drugs having anti-cancer effects that can be used herein. NK cell therapy is an example of cell therapy that can be used herein.

[118] The term "bone pain" or "pain associated with cancer" as used herein includes sensation of pain recognized by a subject as being related to cancer, including cancer in the bone.

[119] The term "cancer" as used herein includes primary cancer as well as secondary cancer that metastasized from a primary tumor arising from another tissue or organ.

[120] The term "cancer-affected bone" as used herein means a bone or an area of the bone that contains cancer cells.

[121] The term "cancer in bone" as used herein means the presence of cancer cells in one or more bones in reference to a subject. Such cancer cells may arise from a primary bone cancer or secondary bone cancer, that is, cancer that have metastasized from a primary tumor, such as originating from another tissue or organ in the body.

[122] The term "comprises" or "comprising" as used herein means has/have or having, contains or containing, includes or including, and/or is or being, and is not to be interpreted as limiting to the specified element or elements, but may encompass

unspecified element or elements.

[123] The term "consensus interferon alpha" as used herein means a polypeptide having the amino acid sequence of the interferon as described in US Patent No. 7,364,724, US Patent No. 7,585,647, US Patent No. 8,114,395 and US Patent No. 8,287,852. The amino acid sequence is shown as SEQ ID NO:1. The amino acid sequence can be encoded by a polynucleotide having the sequence of SEQ ID NO:2. In one aspect, the amino acid sequence of the interferon, such as that made by recombinant techniques, as well as the nucleotide sequence encoding the same (together with a termination codon), are shown below as SEQ ID NO:1 and SEQ ID NO:2, respectively. These sequences are also referenced in U.S. Patent Nos. 7,585,647; 7,364,724; 8,114,395 and 8,287,852:

M C D L P Q T H S L G N R R A L I L L A

1 ATGTGCGACC TGCCGCAGAC CCACTCCCTG GGTAACCGTC GTGCTCTGAT CCTGCTGGCT

TACACGCTGG ACGGCGTCTG GGTGAGGGAC CCATTGGCAG CACGAGACTA GGACGACCGA

Q M R R I S P F S C L K D R H D F G F P

61 CAGATGCGTC GTATCTCCCC GTTCTCCTGC CTGAAAGACC GTCACGACTT CGGTTTCCCG

GTCTACGCAG CATAGAGGGG CAAGAGGACG GACTTTCTGG CAGTGCTGAA GCCAAAGGGC

Q E E F D G N Q F Q K A Q A I S V L H E

121 CAGGAAGAAT TCGACGGTAA CCAGTTCCAG AAAGCTCAGG CTATCTCCGT TCTGCACGAA

GTCCTTCTTA AGCTGCCATT GGTCAAGGTC TTTCGAGTCC GATAGAGGCA AGACGTGCTT

M I Q Q T F N L F S T K D S S A A W D E

181 ATGATCCAGC AGACCTTCAA CCTGTTCTCC ACCAAAGACT CCTCCGCTGC TTGGGACGAA

TACTAGGTCG TCTGGAAGTT GGACAAGAGG TGGTTTCTGA GGAGGCGACG AACCCTGCTT

S L L E K F Y T E L Y Q Q L N D L E A C

241 TCCCTGCTGG AAAAATTCTA CACCGAACTG TACCAGCAGC TGAACGACCT GGAAGCTTGC

AGGGACGACC TTTTTAAGAT GTGGCTTGAC ATGGTCGTCG ACTTGCTGGA CCTTCGAACG

V I Q E V G V E E T P L M N V D S I L A

301 GTTATCCAGG AAGTTGGTGT TGAAGAAACC CCGCTGATGA ACGTTGACTC CATCCTGGCT

CAATAGGTCC TTCAACCACA ACTTCTTTGG GGCGACTACT TGCAACTGAG GTAGGACCGA

V K K Y F Q R I T L Y L T E K K Y S P C

361 GTTAAAAAAT ACTTCCAGCG TATCACCCTG TACCTGACCG AAAAAAAATA CTCCCCGTGC

CAATTTTTTA TGAAGGTCGC ATAGTGGGAC ATGGACTGGC TTTTTTTTAT GAGGGGCACG

A W E V V R A E I M R S F S L S T N L Q

421 GCTTGGGAAG TTGTTCGTGC TGAAATCATG CGTTCCTTCT CCCTGTCCAC CAACCTGCAG

CGAACCCTTC AACAAGCACG ACTTTAGTAC GCAAGGAAGA GGGACAGGTG GTTGGACGTC

E R L R R K E (SEQ ID NO:1)

481 GAACGTCTGC GTCGTAAAGA ATAA (SEQ ID NO:2)

CTTGCAGACG CAGCATTTCT TATT (SEQ ID NO:3)

[124] The term "effective amount" as used herein means an amount that can produce a desired, beneficial or therapeutic effect.

[125] The term "in proximity to the bone" as used herein means in close contact with the bone, including but not limited to the skin covering protrusions such as the clavicle, the ribs, the joints, etc., or the mucosa surrounding a bone, such as a bone affected by cancer.

[126] The term "inhalation" as used herein includes inhalation by breathing in through the nose, such as by intranasal administration, or breathing in through the lungs, such as via the throat or nasopharynx by pulmonary administration.

[127] The term "injection" as used herein means delivery of a substance such as a drug, for example, the interferon herein, by puncturing the skin, and includes injection into one or more of a tissue or organ or a body cavity, such as injection into the

muscle (intramuscular injection), the peritoneal cavity (intraperitoneal injection), a blood vessel (intravenous injection), a tumor (intratumoral injection), under the skin (subcutaneous injection), or into a lymph node, or the thoracic cavity, and the like.

[128] The term "local administration" in reference to the interferon as used herein means administering or applying the interferon to a specified area of the body. Local administration can be administration to an area of a tissue, such as the skin, the bone, the nasal cavity, the throat or nasopharynx, the lungs (as when exposed during surgery), or to an area of an organ (as when exposed during surgery). Local administration may be topical or percutaneous, such as applying to or on the surface of the skin, or transmucosal, such applying to or on the surface of the mucosa, such as the oral cavity. Local administration can include the deposition of a drug depot for slow- or controlled release under the skin.

[129] The term "pharmaceutically acceptable carrier or excipients" means any and all dry or aqueous ingredients that are conventionally approved by regulatory authorities for use to formulate medicines for administration to human subjects. Each such carrier or excipient may, by itself, not have any therapeutic value, but may also be used as an adjunct, enhancing the therapeutic value of the interferon to be administered.

[130] The term "sprayer" as used herein means a device for delivery of a drug by spraying, such as by spraying the interferon, into the nose or throat of the subject for inhalation administration or by spraying the drug onto the skin or bone or mucosa of the subject for local, percutaneous or transmucosal administration. The sprayer herein can deliver an aqueous solution of the interferon, or a dry lyophilized form of the interferon. The formulation in the sprayer can be aerosolized or not.

[131] The term "systemic administration" as used herein means a form of administration of a drug that is intended for systemic circulation. Systemic administration includes injection into a blood vessel, injection into the lymphatic system, subcutaneous injection, intramuscular injection, intraperitoneal injection, or injection into a body cavity.

[132] The term "treatment" shall include amelioration or relief of symptoms of a

disease or illness or side effects thereof, or arrest of disease progression, as in inducing complete remission, partial remission, and stabilization of disease. In some instances, treatment includes prevention of recurrence or prolongation of tumor-free survival.

[133] As used herein, the singular includes the plural and vice versa unless the context indicates otherwise. Also, the ranges of numbers provided herein include the specified beginning number and the specified ending number of each range and any number in between such ranges as if each such number in between has been specifically mentioned.

[134] The invention is more particularly described as follows. These embodiments, however, are not intended to limit the scope of the claims, but serve to explain the invention to one of ordinary skill in the art to which this field applies. All references, patents, and other printed documents cited herein are incorporated herein by reference.

[135] The inventors herein have discovered that cancers such as bone, skin, subcutaneous, mucosal and/or submucosal cancers, as well as bone pain arising from cancer in the bone, can be treated and the pain relieved by administration of a consensus interferon alpha that comprises anti-cancer activity and an amino acid sequence of SEQ ID NO:1.

[136] In some embodiments, the consensus interferon alpha is encoded by a polynucleotide sequence of SEQ ID NO: 2. In some embodiments, the interferon comprises the super compound interferon, SIFN (also be refered to as recombinant super-compound interferon (rSIFN-co)), as prepared and as described in US Patent No. 7,364,724, US Patent No. 7,585,647, US Patent No. 8,114,395 and US Patent No. 8,287,852.

[137] In some embodiments, the present interferon has the amino acid sequence of SEQ ID NO: 1. In some embodiments, the present interferon is encoded by the nucleotide sequence of SEQ ID NO: 2. In some embodiments, the present interferon has the amino acid sequence of SEQ ID NO: 1, and is encoded by the nucleotide sequence of SEQ ID NO: 2. Further, the interferon comprises the amino acid sequence

of SEQ ID NO: 1, and is encoded by the nucleotide sequence of SEQ ID NO: 2.

[138] In some embodiments, in comparison with interferon such as interferon alfacon-1 (INFERGEN®), which has the amino acid sequence of SEQ ID NO: 1, but is not encoded by the nucleotide sequence of SEQ ID NO: 2, the present interferon has a changed spatial configuration and/or enhanced biologic activities and/or different pharmacokinetics characteristics. For example, the present interferon has a changed spatial configuration and enhanced biologic activities, changed spatial configuration and different pharmacokinetics characteristics, or changed spatial configuration, enhanced biologic activities and different pharmacokinetics characteristics. The enhanced biological activities include: enhanced antiviral activity, enhanced tumor cell growth inhibition or proapoptotic effect, less side effects and/or could be used in large dose (e.g. each dose > 10 million IU). For example, the enhanced biological activities can be enhanced antiviral activity and/or enhanced tumor cell (such as breast cancer cell or cervical cancer cell) growth inhibition or proapoptotic effect (see Zheng, J. et al. J Sichuan Univ (Med Sci Edi), 2010, 41(1), 29-34; Chen, Y, et al. J Sichuan Univ (Med Sci Edi), 2008, 39(5), 715-718). The different pharmacokinetics characteristics include: after intramuscular injection of the interferon in subjects whose BMI ranged from about 18 to about 23, the time of blood sample collection was plotted against the concentration of 2-5Aoligonucleotidase in the serum of the subjects, and the resulting area under the curve of this chart is significantly greater and/or the half-life of this interferon in the body is longer than those of the interferon such as interferon alfacon-1 (INFERGEN®), which has the amino acid sequence of SEQ ID NO: 1, but is not encoded by the nucleotide sequence of SEQ ID NO: 2after injection under the same conditions.

[139] In some embodiments, the present interferon has the amino acid sequence of SEQ ID NO: 1, and is encoded by the nucleotide sequence of SEQ ID NO: 2, wherein the interferon has increased inhibitory activities on the expression of hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) of Hepatitis B

Virus as compared to an interferon such as interferon alfacon-1 (INFERGEN®), which has the amino acid sequence of SEQ ID NO: 1, but is not encoded by the nucleotide sequence of SEQ ID NO: 2.

[140] In some embodiments, the invention provides one or more methods and compositions for treatment of bone cancer in a subject, including primary or secondary bone cancer, where cancer cells are present in at least one bone or a part of a bone in a subject, using the fore-mentioned interferon.

[141] In some embodiments, the invention provides one or more methods and compositions for treatment of skin or epithelial cancer in a subject, including primary and/or secondary skin cancer, using the fore-mentioned interferon. In some embodiments, the skin or epithelial cancer includes cervical carcinoma, basal cell carcinoma, epidermoid carcinoma, squamous cell carcinoma, carcinoma of the external genitalia, and melanoma, including melanocarcinoma.

[142] In some embodiments, the invention provides one or more methods and compositions for treatment of subcutaneous cancer in a subject, including primary and/or secondary subcutaneous cancer, using the forementioned interferon. In some embodiments, the subcutaneous cancer includes prostatic carcinoma and breast cancer.

[143] In some embodiments, the invention provides one or more methods and compositions for treatment of mucosal cancer in a subject, including primary and/or secondary mucosal cancer, using the fore-mentioned interferon. In some embodiments, mucosal cancer includes oral cancer, nasopharyngeal carcinoma, rectal cancer, laryngeal carcinoma and tongue cancer.

[144] In some embodiments, the invention provides for methods and compositions for treatment of submucosal cancer in a subject, including primary and/or secondary submucosal cancer, using the fore-mentioned interferon.

[145] In some embodiments, the invention provides methods and compositions for treating at least one of: bone cancer (primary or secondary), breast cancer, skin cancer, nasopharyngeal carcinoma, oral cancer, carcinoma of the vulva, prostatic carcinoma, cervical carcinoma and melanoma, including melanocarcinoma in a subject by

administration of the interferon. In some embodiments, the interferon is administered to the subject by percutaneous administration. In some embodiments, the interferon is administered to the subject by transmucosal administration.

[146] In some embodiments, the invention provides one or more methods and compositions for treatment of pain in a subject, such as pain arising from or associated with the presence of cancer, such as bone cancer pain, using the fore-mentioned interferon.

[147] In some embodiments, the invention provides administering to the subject an effective amount of the interferon by administering the interferon locally such as on a cancer lesion, such as to or on the bone for cancer in the bones, the skin for skin cancer, the subcutaneous tissue for subcutaneous cancer, the mucosa for mucosal cancer, and the submucosa, for submucosal cancer, either directly or indirectly.

[148] Such application can be direct, such as by perfusion when the bone, the subcutaneous tissue, or the submucosa is partially or totally exposed during surgery, or indirect, by application on the skin covering or in proximity to the bone (such as a cancer-affected bone) or the skin covering the subcutaneous cancer or on the mucosa surrounding the submucosa comprising a tumor, and allowing the interferon to pass through the skin or the mucosa.

[149] In some embodiments, local administration of the interferon to a subject includes: percutaneous administration and/or transmucosal administration.

[150] For local administration of the interferon by percutaneous administration, the interferon can be sprayed on the skin, such as the skin covering the cancer-affected tissue. In the case of bone cancer, the interferon can be sprayed on that part of the skin covering or in close proximity to the bone, such as the skin covering the humerus, the femur, the clavicle, etc., in which tumor cells, including metastatic tumor cells, can be found. In some embodiments, the interferon can be administered locally by transmucosal administration, where the interferon is applied to a mucosal surface affected by cancer, as the oral cavity for oral cancer.

[151] In some embodiments, the interferon for percutaneous or transmucosal administration may be formulated as an aqueous solution, or a cream that can be

applied to the skin or mucosa, or a membrane permeation or diffusion drug delivery system, or a controlled release drug delivery system, or a closed drug delivery system, or a patch such as a transdermal patch, or a depot comprising the interferon for injection under the skin to produce a slow- or controlled-release effect, as desired.

[152] In some embodiments, interferon for percutaneous administration or transmucosal administration can be in the form of a solution or a suspension. The solution or suspension will comprise an amount of the interferon and other pharmaceutically acceptable agents or excipients conventionally used, such as water, phosphate buffered saline, EDTA, Tween 80, trisodium citrate, glycerol, sodium chloride, phenylmethanol, HSA and the like. Such a solution can be made, for example, as described in US Patent No. 7,585,647.

[153] The interferon herein for local administration or for inhalation can be formulated as a spray, such as one that can be sprayed on the skin, or on the mucosa, or on an exposed cancer-affected tissue, or into the nose for intranasal delivery, or into the nasopharynx for pulmonary delivery.

[154] The interferon herein can also be formulated as a dry, lyophilized powder. The dry powder can be used in an aerosolized spray for administration to the nose or to the lungs such as through the nasopharynx.

[155] The interferon herein can further be applied in the form of a transdermal patch comprising a solution or suspension of the interferon for either fast or slow or controlled release of the interferon. The transdermal patch herein can be made using standard or extant technology, for example, as described in US Patent No. 8,158,145, US Patent No. 8,095,213 and US Patent No. 8,071,125, and the like. The transdermal patch can be placed on the cancer-affected skin, or on the skin covering the cancer-affected tissue.

[156] In some embodiments, the transdermal patch that can be applied to the skin covering the affected area of the bone and can be left in place over a period of time, such as for several hours, for one or a few days.

[157] The interferon herein can further be formulated as encapsulated particles, whether made from a single or composite material. Examples of such particles are

nanoparticles, microparticles, microspheres, liposomes and the like, using extant technology. Such particles can be made, for example, as described in US Patent No. 7,537,803, US Patent No. 8,389,493 and US Patent No. 7,829,113.

[158] In some embodiments, the cancer in the bone, or skin or subcutaneous cancer, or mucosal cancer or submucosal cancer can be a primary cancer or a metastasized tumor originating from a primary tumor arising from another tissue or organ.

[159] In some embodiments, the primary tumor herein can be any one or more of: a solid tumor and a non-solid tumor.

[160] In some embodiments, the primary tumor herein includes at least one of: cancer of the respiratory system, cancer of the digestive system, cancer of the urinary system, breast cancer, skin cancer, subcutaneous cancer, mucosal cancer, submucosal cancer, cancer of the reproductive system, head and neck cancer, cancer of the hormonal system, and cancer of the nervous system.

[161] In some embodiments, the cancer of the digestive system includes at least one of: oral cancer, tongue cancer, laryngeal carcinoma, esophageal cancer, gall bladder cancer, liver cancer, gastrointestinal cancer, and pancreatic cancer; the cancer of the reproductive system includes at least one of: carcinoma of the external genitalia, cervical cancer, endometrial cancer, uterine cancer, ovarian cancer, and prostate cancer; the cancer of the respiratory system includes at least one of: lung cancer and nasopharyngeal carcinoma; the cancer of the urinary system includes at least one of: kidney cancer and bladder cancer; the cancer of the hormonal system includes at least one of: adrenal cancer and thyroid cancer; the head and neck cancer includes nasopharyngeal carcinoma; the skin cancer includes at least one of: basal cell carcinoma, epidermoid carcinoma, squamous cell carcinoma, carcinoma of the external genitalia, and malignant melanoma; the subcutaneous cancer includes prostatic carcinoma and breast cancer; the mucosal cancer includes cancer involving the mucosa, such as oral cancer, tongue cancer, gastrointestinal cancer, and colorectal cancer; the submucosal cancer includes bone cancer; and the cancer of the nervous system includes at least one of: neuroma, malignant neuroma, glioma, and astrocytoma.

[162] In some embodiments, the lung cancer includes at least one of: small cell lung cancer and non-small cell lung cancer; the gastrointestinal cancer includes at least one of: gastrointestinal interstitial cell tumor, stomach cancer, colon cancer, rectal cancer, and colorectal cancer; the gall bladder cancer includes cholangiocarcinoma; the liver cancer includes hepatocellular carcinoma; the kidney cancer includes renal cell carcinoma; the bladder cancer includes superficial bladder cancer; and the subcutaneous cancer includes at least one of: prostatic carcinoma and breast cancer .

[163] In some embodiments, the primary tumor herein comprises at least one of: a carcinoma, a sarcoma, and a rhabdomyosarcoma.

[164] In some embodiments, the primary tumor herein can be at least one of: abdominal tumor, myoepithelial carcinoma, synovial sarcoma, hemangioma, lymphoma and Kaposi's sarcoma.

[165] In some embodiments of the invention, the interferon can be administered both locally, such as percutaneously and/or transmucosally and systemically to the subject.

[166] In some embodiments, the invention provides methods and compositions for the treatment of cancer in the bone, skin cancer, subcutaneous cancer, mucosal cancer and/or submucosal cancer in a subject comprising administering to the subject an effective amount of a consensus interferon alpha that comprises anti-cancer activity, wherein the interferon is administered both by systemic administration, and by percutaneous administration.

[167] In some embodiments, the systemic administration includes injection into the subject. Injection herein includes injection in at least one of the following modes: intramuscularly, intratumorally, intraperitoneally, intravenously, subcutaneously, into the thoracic cavity, and into one or more lymph nodes.

[168] In some embodiments, the invention provides methods and compositions for the treatment of cancer as any of the foregoing methods and compositions which, besides administering the interferon by systemic administration, such as by injection, and such as by intramuscular injection, and by percutaneous administration, such as by spraying on a cancer-affected tissue, the interferon is additionally administered by inhalation.

[169] In some embodiments, the invention provides methods and compositions for the treatment of cancer in bone, skin cancer, subcutaneous cancer, mucosal cancer, and/or submucosal cancer in a subject comprising administering to the subject an effective amount of a consensus interferon alpha that comprises anti-cancer activity, wherein the interferon is administered both by inhalation and by percutaneous administration to the cancer-affected tissue.

[170] In some embodiments, inhalation includes inhalation through the nose or through the throat/nasopharynx to the lungs. Administration by inhalation through the nose can be accomplished with an intranasal spray. Administration by inhalation through the throat/nasopharynx to the lungs can be accomplished by use of inhaler. Such intranasal spray or inhaler can be in the form of an aerosolized formulation of the interferon or an aqueous solution containing the interferon, for example.

[171] In some embodiments, the invention provides methods and compositions as any described herein, where the interferon administered locally includes applying the interferon to one or more cancerous lesions. Further, application to the cancerous lesion can be by infiltration administration, percutaneous administration, transdermal administration, epidermal administration, and transmucosal administration. Local administration can be achieved by spraying the interferon locally.

[172] In some embodiments, the invention provides methods and compositions as any described herein, where the interferon formulated for local administration can be formulated as at least one of: an aqueous solution, a dry powder, or a cream.

[173] In some embodiments, the invention provides any one or more of the methods and compositions described herein, wherein application of the interferon by percutaneous administration, in combination with application of the interferon by systemic administration, such as by injection, and such as by intramuscular injection, and/or administration by inhalation, can be administered on the same day or on separate days.

[174] In some embodiments, application of the interferon by percutaneous administration can be before, simultaneously or at about the same time as, or after administration of the interferon by injection or by inhalation, if any.

[175] In some embodiments, the invention provides any one or more of the methods and compositions as described herein, where application of the interferon to the mucosa comprises submucosal administration.

[176] In some embodiments, the interferon that is applied locally, percutaneously or transmucosally, such as by spraying, can be applied in a range of about 1 to 12 times a day, optionally in a range of about 2 – 10 times a day, still optionally, in a range of about 3 – 8 times a day, further optionally, in a range of about 4 – 7 times a day. In some embodiments, the interferon that is applied locally, percutaneously or transmucosally is applied 4 or 5 or 6 times a day.

[177] In some embodiments, the interferon that is applied locally, percutaneously or transmucosally, such as by spraying, can be applied at least 1, 2, 3, 4, 5, 6, 7, or 8, or more times per day.

[178] In some embodiments, the invention provides methods and compositions as any described herein, where local administration, administration to the bone, skin, mucosal or submucosa comprises applying a formulation of the interferon at a concentration in a range of about 0.01 mg/ml to about 5 mg/ml, optionally, in a range of about 0.03 mg/ml to about 2 mg/ml, further optionally in a range of about 0.05 mg/ml to about 1 mg/ml, and still further optionally, in a range of about 0.1 mg/ml to about 0.5 mg/ml. In some embodiments, the interferon for local administration comprises interferon in a range of about 2 microgram to about 2100 microgram, optionally, in a range of about 4 microgram to about 1800 microgram, still optionally, in a range of about 9 microgram to about 15 microgram, further optionally, in a range of about 12 microgram to about 1200 microgram, yet still optionally, in a range of about 15 microgram to about 1000 microgram, yet further optionally, in a range of about 18 microgram to about 900 microgram, yet still optionally, in a range of about 21 microgram to about 750 microgram, and still further optionally, in a range of about 24 microgram to about 600 microgram.

[179] The invention additionally provides, in some embodiments, administration of the interferon locally every day or every other day. In some embodiments, the interferon, for local administration, is administered every 2^{nd}, 3^{rd}, 4^{th}, 5^{th}, 6^{th}, 7^{th}, 8^{th},

9th, 10th, 11th, 12th, 13th, 14th, 15th, 16th, 17th, 18th, 19th, 20th, or 21st day. In some embodiments, the interferon administered locally is administered every month, every 2, or 3, or 4, or 5, or 6, or 7, or 8, or 9, or 10, or 11, or 12 months, or longer, such as for the remaining life of the subject.

[180] In some embodiments, the invention provides methods and compositions as any described herein, where the interferon is applied by spraying, and the interferon in the spray can be in an amount in a range of about 6 microgram to about 100 microgram, optionally, in a range of about 10 microgram to about 80 microgram, still optionally, in a range of about 20 microgram to about 60 microgram, further optionally, in a range of about 30 microgram to about 40 microgram per spray administration.

[181] In some embodiments, the interferon for spray administration comprises a concentration in a range of about 0.01 mg/ml to about 5 mg/ml, optionally in a range of about 0.03 mg/ml to about 2 mg/ml, further optionally, in a range of about 0.05 mg/ml to about 1 mg/ml, and still further optionally, in a range of about 0.1 mg/ml to about 0.5 mg/ml.

[182] In some embodiments, the interferon that is formulated for injection can be injected every day or every other day or every few days, such as every 2 or every 3 days. In some embodiments, the interferon is administered systemically is administered at least once every 1 – 8 days, optionally, at least once every 2 – 7 days, still optionally, at least once every 3 – 6 days, further optionally, at least once every 4 – 5 days, still further optionally, at least once every 1 – 2 days.

[183] In some embodiments, the interferon to be administered by systemic administration, such as by injection, and such as by intramuscular injection, is administered in an amount in a range of about 2 microgram to about 70 microgram, optionally in a range of about 4 microgram to about 50 microgram, further optionally, in a range of about 9 microgram to about 30 microgram, still optionally, in a range of about 15 microgram to about 24 microgram, still further optionally, in a range of about 18 microgram to about 21 microgram, per injection.

[184] In some embodiments, the second dose of interferon that is injected can be at a

higher dosage than the first dose. In some embodiments, the third dose of interferon for injection can be the same as the second dose or can be higher than the second dose.

[185] In some embodiments, for systemic administration, the interferon is administered in at least one initial dose, that is, an induction dose, in a range of about 2 microgram to about 15 microgram, optionally, about 3 microgram to about 12 microgram, still optionally about 4 microgram to about 9 microgram, further optionally, about 5 microgram to about 6 microgram. In some embodiment, the induction dose has about 9 microgram or about 15 microgram of the interferon. The induction dose can be used for one or more subsequent administrations to the subject as well.

[186] In some embodiments, for systemic administration, the interferon is further administered in at least one subsequent therapeutic dose in a range of about 10 microgram to about 50 microgram each time, optionally in a range of about 12 microgram to about 30 microgram each time, further optionally in a range of about 15 microgram to about 24 microgram each time, and still optionally, in a range of about 18 microgram to about 21 microgram each time. In some embodiments, the therapeutic dose has about 15, or 18, or 21 microgram of the interferon.

[187] In some embodiments, the interferon to be administered by systemic administration is administered at least for: 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year, 2 years, 3 years, 4 years, 5 years, and 6 years.

[188] In some embodiments, the interferon to be administered by systemic administration is administered for a duration in a range of about 1 day to about 6 years, optionally, about 1 week to about 4 years, still optionally, about 2 weeks to about 3 years, further optionally, about 1 month to about 1 year, still further optionally, about 2 months to about 9 months, or longer, such as throughout the remaining life of the subject.

[189] In some embodiments, the interferon for systemic administration is

administered to the subject at a frequency in a range of about once every 1 – 7 days, further optionally, about once every 1 – 2 days, at the induction dose. In some embodiments, the interferon for systemic administration is administered at a frequency of about once every day or about once every other day at the induction dose. Optionally, the interferon for systemic administration is administered every 2, 3, 4, 5, 6, 7, 8, 9, or 10 days at the induction dose.

[190] In some embodiments, for systemic administration, the interferon is administered to the subject at a frequency in a range of about once every 1 – 7 days, further optionally, about in a range of about once every 1 – 2 days, at the therapeutic dose.

[191] In some embodiments, for systemic administration, the interferon is administered to the subject at a frequency of about once every day, or about once every 2, 3, 4, 5, 6, 7, 8, 9, or 10 days, at the therapeutic dose.

[192] In some embodiments, the interferon is administered by subcutaneous or intramuscular injection at least 2 times, optionally, at least 4 times, further optionally, at least 6 times, still optionally, at least 8 times, still further optionally, at least 10 times.

[193] In some embodiments, for systemic administration, the time interval between administration of the induction dose and the administration of the therapeutic dose of the interferon is in a range of about 1 day to about 1 month, optionally or preferably, in a range of about 1 day to about 1 week, still optionally or more preferably, in the range of about 1 day to 3 days. In some embodiments, the time interval between the induction dose and the therapeutic dose is 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 1 week, 2 weeks, 3 weeks, or 1 month.

[194] In some embodiments, the time interval between injection of the first dose and injection of the second dose of interferon is in a range of about 1 day – 1 month, optionally, in a range of about 2 days to about 3 weeks, further optionally, in a range of about 3 days to about 2 weeks, still optionally, in a range of about 4 days to about 10 days, still further optionally, in a range of about 5 days to about 9 days, yet further optionally, in a range of about 6 – 8 days, and still further optionally, about 7 days.

[195] In some embodiments, the duration of administration of the induction dose and the therapeutic dose is at least: 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year, 2 years, 3 years, 4 years, 5 years, or 6 years, or optionally longer or over the remaining life of the subject.

[196] In some embodiments, the inhalation administration of the interferon includes at least one of: pulmonary inhalation and nasal inhalation.

[197] In some embodiments, the interferon for inhalation administration includes at least one of: dry powder and aerosolized interferon.

[198] In some embodiments, the interferon to be applied by inhalation is administered in an amount in a range of about 100 microgram to about 2000 microgram, optionally, about 120 microgram to about 1500 microgram, further optionally, about 150 microgram to about 1200 microgram, still optionally, about 200 microgram to about 900 microgram, yet further optionally, about 450 microgram to about 750 microgram, still further optionally, about 500 microgram to about 650 microgram, in one inhalation administration. In some embodiments, the interferon to be applied by inhalation is administered in an amount of 600 microgram in one inhalation administration.

[199] In some embodiments, the interferon for inhalation administration is administered by inhalation administration about once every 1 or 2 or 3 days, optionally, every day.

[200] In some embodiments, the duration of inhalation administration is in a range of about 1 day to about 6 years, optionally, about 1 week to about 4 years, further optionally, about 2 weeks to about 3 years, still optionally, about 3 weeks to about 2 years, still further optionally, about 1 month to about 1 year, or yet further optionally, about 2 months to about 9 months.

[201] In some embodiments, the duration of inhalation administration is at least for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year, 2 years, 3 years, 4 years,

5 years, or 6 years, or optionally for a long time, such as over the remaining life of the subject.

[202] In general, the duration and frequency of administration of the interferon herein can be determined by one or more attending physicians or medical staff depending on the typical criteria such as the need of the subject for further treatment, the health of the subject, the tolerance of the subject to the interferon, the presence of adverse side effects, and the like.

[203] In some embodiments, the interferon administration is the sole anti-cancer therapy administered to the subject. In some embodiments, the interferon administration is combined with at least one other anti-cancer therapy.

[204] The at least one other anti-cancer therapy can be administered to the subject before, at about the same time, and/or after administration of the interferon.

[205] In some embodiments, the at least one other anti-cancer therapy includes at least one of: chemotherapy, radiotherapy, surgical therapy, interventional therapy, biotherapy, targeted therapy, and Traditional Chinese medicine.

[206] In some embodiments, the biotherapy includes the use of any type of biologics for treatment and includes recombinant proteins, antibodies, gene therapy, cell therapy, use of targeted antibodies, or other immunotherapy.

[207] In some embodiments, the surgical therapy comprises ablation therapy. In some embodiments, the at least one anti-cancer therapy is a non-surgical therapy.

[208] In some embodiments, the invention provides treatment which achieves at least one of: elimination of at least one cancer lesion, reduction in size of at least one cancer lesion, and non-progression of growth of at least one cancer lesion, as compared to before treatment.

[209] The invention provides in some embodiments, a sprayer for administering an interferon that comprises anti-cancer activity and an amino acid sequence of SEQ ID NO: 1.

[210] In some embodiments, the interferon in the sprayer is formulated in an amount for administering the interferon at least 1 – 12 times, optionally, 2 – 10 times, further optionally, 3 – 8 times. In some embodiments, the sprayer herein contains an

amount of the interferon for administering the interferon at least 4 or 5 or 6 times.

[211] In some embodiments, the amount of interferon in the sprayer has a concentration in a range of at least about 0.01 mg/ml to about 5 mg/ml, optionally, about 0.03 mg/ml to about 2 mg/ml, still optionally, about 0.05 mg/ml to about 1 mg/ml. In some embodiments, the sprayer contains the interferon at a concentration of about 0.1 mg/ml, about 0.2 mg/ml, about 0.3 mg/ml, about 0.4 mg/ml, or 0.5 mg/ml.

[212] In some embodiments, the sprayer is described herein and is a single use sprayer containing one day's supply of the interferon. In some embodiments, the sprayer is a multi-use sprayer and contains interferon sufficient for use for at least 2 days, or 3 days, or 4 days, or 5 days, or a week, or 2 weeks.

[213] In some embodiments, the invention provides a sprayer as any described herein, where the sprayer is configured and the interferon therein is formulated for delivery of the interferon to the nose of the subject.

[214] In some embodiments, the sprayer herein is configured and the interferon therein is formulated for delivery of the interferon to or on at least the subject's skin, or bone, or mucosa of the subject.

[215] In some embodiments, the sprayer herein is configured and the interferon therein is formulated for delivery of the interferon by inhalation to the lungs of the subject.

[216] The invention further provides a measured or metered dose of an interferon comprising an amount of the interferon, wherein the interferon comprises anti-cancer activity and an amino acid sequence of SEQ ID NO: 1.

[217] A metered dose allows the subject to self-administer the interferon and/or allows administration by non-medical, lay staff, such as by one of the patient's family members, thus, reducing the number of visits to the hospital or to the doctor's office, and cutting down costs of treatment. The inventors' discovery of the effectiveness of local administration of the interferon, such as by percutaneous or transmucosal administration, such as by spraying on a cancer-affected area, with or without additional systemic administration of the interferon, and with or without additional inhalation administration of the interferon, makes such delivery and such

administration feasible.

[218] In some embodiments, the metered dose contains the interferon in an amount in a range of about 100 microgram to about 2000 microgram, optionally, about 120 microgram to about 1500 microgram, further optionally, about 150 microgram to about 1200 microgram, still optionally, about 200 microgram to about 900 microgram. In some embodiments, the metered dose optionally or preferably contains the interferon in an amount in a range of about 450 microgram to about 750 microgram, still optionally or preferably, in a range of about 500 microgram to about 650 microgram. In some embodiments, the metered dose contains the interferon herein in an amount of about 600 microgram.

[219] In some embodiments, the metered dose contains a single use amount of the interferon. In some embodiments, the metered dose contains an amount of the interferon that is sufficient for 2 treatments, 3 treatments, 4 treatments or 5 treatments. Optionally, the metered dose contains at least a one-week supply of the interferon.

[220] In some embodiments, the metered dose is formulated for percutaneous administration, such as for local spraying. In some embodiments, the metered dose is formulated for inhalation. In some embodiments, the metered dose is formulated for inhalation via the nose. In some embodiments, the interferon is formulated for inhalation via the lungs.

[221] In some embodiments, the metered dose contains the interferon in lyophilized powder form. In some embodiments, the interferon in the metered dose is aerosolized. In some embodiments, the interferon in the metered dose contains an aqueous formulation of the interferon, or interferon in the form of nanoparticles, microparticles, or microspheres and the like.

[222] The invention further provides a transdermal patch comprising the consensus interferon alpha that comprises anti-cancer activity, and having an amino acid sequence of SEQ ID NO: 1.

[223] The invention also provides a method of preparation of a medicament for administration to a subject, where the medicament contains the consensus interferon alpha that has anti-cancer activity and an amino acid sequence of SEQ ID NO: 1. The

medicament containing the interferon can be used for treatment of cancer in the bones, skin cancer, subcutaneous cancer, mucosal cancer, and submucosal cancer, as described herein. The medicament can be formulated in at least 2 distinct formats, one for systemic administration, such as by injection and the other for local administration, such as application to the skin, bone, or mucosa of the subject.

[224] In some embodiments, the fore-mentioned medicament can be formulated in a third format for inhalation administration, such as a nasal spray or an aerosolized form for pulmonary delivery.

[225] The invention further provides, in some embodiments use of a consensus interferon alpha that comprises anti-cancer activity and an amino acid sequence of SEQ ID NO; 1, in the preparation of a medicament for treatment of bone cancer, skin cancer, subcutaneous carcinoma, mucosal carcinoma and/or submucosal carcinoma in subjects. In some embodiments, the invention provides the use of such interferon in preparation of a medicament for treatment of pain, such as that associated with or arising from cancer in the bones, such as in bone cancer.

[226] The invention moreover provides a pharmaceutical composition that contains the fore-mentioned interferon and at least one pharmaceutically acceptable carrier or excipient, where the composition is formulated for local administration, for systemic administration, and/or for inhalation administration, for the treatment of bone cancer, skin cancer, subcutaneous carcinoma, mucosal carcinoma and/or submucosal carcinoma in subjects.

[227] In some embodiments, the invention provides a pharmaceutical composition that contains the fore-mentioned interferon and at least one pharmaceutically acceptable carrier or excipient, where the composition is formulated for treatment of pain, such as bone pain associated with or arising from cancer, such as bone cancer.

[228] In some embodiments, the interferon herein is encoded by a polynucleotide comprising the sequence of SEQ ID NO: 2.

[229] The invention herein is further exemplified by the following examples which are for illustrative purposes and are not to be construed as limiting the invention in any way.

[230] EXAMPLE 1. Treatment of Patient #1 with non-small-cell lung cancer (NSCLC) and multiple bone metastases.

[231] Summary. Patient #1 was a 39 year old male who was diagnosed with NSCLC with multiple lymph node metastases in the mediastinum, the left segment of his neck, the right and root segment of his neck, left supraclavicular fossa. Patient #1 also had left-sided pleural effusion and multiple bone metastases in the vertebral column, bilateral ribs, right clavicular joint, sternum, left sacrum, etc. Patient #1 was given intramuscular injection and aerosol inhalation of SIFN (or recombinant super-compound interferon (rSIFN-co)) and local spraying of the SIFN on bony lesions, in combination with chemotherapy treatment, a GP regimen, and Gefinitib therapy. After treatment, the primary lesions on the left lung disappeared as well as the multiple lymph node metastases in the left supraclavicular fossa and left-sided pleural effusion. Also, metastatic bone lesions around the whole body shrank or disappeared.

[232] Treatment with SIFN began on October 12, 2011 with aerosol inhalation of 600ug every day. Intramuscular injection of SIFN started on December 12, 2011, once every other day at 9μg dose for the first time, 15μg dose for the second time and 18μg dose for the third time and thereafter. Local spraying on bone metastases (vertebral column, ribs, sternum, sacrum, etc.), by spraying on the skin over the bone metastases, began on March 12, 2012 at about 4 to 6 times per day.

[233] A second cycle of GP Regimen started on October 14, 2011 (each cycle lasting 21 days) at 1000mg/m^2 of Gemcitabine on days 1 and 8 and 75 mg/m^2 of Cisplatin on day 1. Gefinitib was administered from November 2011 at 1 pill each time (250 mg/pill) and once per day.

[234] Diagnosis before administration of SIFN. A chest CT scan on September 21, 2011 showed a high-density blocky shadow (9 cm x 3.5 cm) around the left mediastinum with a CT value of 39Hu. The boundaries between this shadow and part of the great vessels in the mediastinum superius, left hilum and left posterior pleura were obscure. Patchy shadow of inflammatory exudates with high density could be seen in the lungs. Enlarged lymph nodes were found in the mediastinum.

A few patchy shadows with high density were seen inhomogeneously in the upper segment of the right hilum portion, where the boundaries were clear. Arched effusions were found on left posterior side. Diagnosis conclusion: Patient #1 had lung cancer in left mediastinum combined with left sided pleural effusion and obstructive pneumonia. Multiple patchy shadows were present in the hilum, suggesting the possible occurrence of metastases.

[235] Biopsy was conducted with fibro-bronchoscopy on September 27, 2011. A biopsy was done in the bronchus of the left upper lobe. Three grey soft tissues were found with about 0.1 cm x 0.1 cm x 0.1 cm in size. Diagnosis conclusion: Patient #1 might have poorly or moderately differentiated adenocarcinoma.

[236] The whole body bone ECT scan on September 29, 2011 showed multiple lesions with high radioactivity concentration in the vertebral column, bilateral ribs, right-sided sternoclavicular joints, sternum, left-sided sacroiliac joints and left-sided ilium. Radioactivity distribution was normal in the skull and limb long bones. Diagnosis conclusion: Systemic bone lesions with high radioactivity concentration were found, suggesting possible occurrence of systemic bone metastases.

[237] Color Doppler ultrasound was conducted on September 30, 2011. Multiple hypoechoic nodules were found at the left segment of the neck, which had clear boundaries without any hilum of lymph node. Larger hypoechoic nodule was 1.0 cm x 0.7 cm in size. One hypoechoic nodule of about 1.2 cm x 0.8 cm was found at the left supraclavicular fossa, which had clear boundary but had no hilum of the lymph node. One hypoechoic nodule of about 1.4 cm x 1.1 cm was seen at the root segment of right-sided neck, which had clear boundary but had no hilum of the lymph node. No abnormal lymph nodes were found in the right-sided supraclavicular fossa. Diagnosis conclusion: hypoechoic nodules and abnormal lymph nodes were found at left segment of neck, left supraclavicular fossa and root segment of the right-sided neck.

[238] Diagnosis after administration of SIFN.

[239] The CT scan on November 15, 2011 showed shadows of soft tissues of about 3.6 cm x 4.2 cm in the left upper lung. High density patchy shadows were scattered and had obscure boundaries. No enlarged lymph nodes were seen in the

mediastinum.

[240] A bone scan was conducted on December 6, 2011. Multiple spot-like, mass-like and sheet-like shadows with abnormal radioactivity concentration could be seen in right sternoclavicular joints, ribs, vertebral column and pelvis. Radioactivity distributions of other parts were substantially uniform and symmetrical. Diagnosis conclusion: partial lesions shrank and were reduced as compared to the previous CT result (September 29, 2011).

[241] PET/CT scan was conducted on December 29, 2011. A nodule with a diameter of about 8 mm was observed at the apex of the left lung and the radioactivity distribution was slightly increased. Small sheet-like shadows with slightly higher density and fibrous lesions were found in surrounding area of the lung and radioactivity distribution was slightly increased. Scattered, patchy shadows with slightly higher density were found in the lung and no significant abnormalities were found in the radioactivity distribution.

[242] Conclusion: (1) after treatment, no obvious increase in FDG metabolism was found on or at lesions of the apex of the left lung, suggesting inactivation of most of the tumor cells; (2) asymmetric hyperosteogeny was found in several parts of the whole body and FDG metabolism in some lesions was inhomogeneous with a few increased. After treatment for 2 months, the patient had lesions in his lungs disappeared and the systemic bone metastases shrank in size.

[243] PET/CT scan on May 31, 2012 only indicated that, the bone density changed in several vertebrae of the spinal column and shadows with abnormal radioactivity concentrations were found, while the bone metastases disappeared.

[244] EXAMPLE 2. Treatment of Patient #2 with melanoma and bone metastases.

[245] Patient #2 was a 43 year old female who had melanoma at the nose (recurrence after surgery) and bone metastases at the bilateral hip joints, bilateral femurs, bilateral humeri, ribs and bilateral shoulder joints. Intramuscular injection of SIFN and local spraying of SIFN on lesions (on the skin over the bone metastases) were administered. After treatment, the lesions disappeared, including those involving

the bilateral shoulder joints, the multiple enlarged lymph nodes in the armpits, the recurrent and metastatic lesions at residual cavity after surgery of the right paranasal sinus and nasal cavity. The multiple abnormal signals at the bilateral hip joints and upper segment of the femur also disappeared.

[246] Treatment regimens before administration of SIFN.

[247] Two cycles of administration of Endostar and temozolomide were applied on October 30, 2011 and November 30, 2011. Endostar at 15 mg was given per day on days 1 – 10 and 200mg of temozolomide was given per day on days 1 – 5orally.

[248] Targeted radiotherapy (50Gy/25f) began on November 2, 2011 and the target regions included right maxillary sinus and ¼ of the left maxillary sinus, bilateral ethmoid sinuses, bilateral frontal sinuses and the adjacent tissues of the right eyeball. Radiotherapy ended on December 7, 2011.

[249] Administration of SIFN.

[250] Treatment with SIFN began on December 21, 2011. Intramuscular injection of SIFN was administered every other day (9μg for the first time, 15μg for the second time, 18μg for the third time and thereafter) combined with local spraying to the skin surface of the right shoulder for 4 to 5 times per day. Spraying was applied to the skin surfaces of the left shoulder and other regions of bone metastases from February 27, 2012 at 4 to 5 times per day.

[251] Diagnosis before administration of SIFN.

[252] Surgery for the right sinus was provided using an endoscope and the neoplasm in the nasal cavity was resected on August 23, 2011. Biopsy after surgery showed that tumors were found in the polyp-like matter in the middle nasal meatus and the mass inside the right maxillary sinus. Malignant melanoma was diagnosed by immunohistochemistry: HMB45 (partly+), MART1 (-), S100 (-), CD63(+), NSE(-), PCK (-), EMA (+), CD56(-), and KI671(25%). Subtotal resection of right maxillary bone and resection of the tumor in the nasal cavity and paranasalsinus was conducted again on October 8, 2011.

[253] MRI of paranasalsinus was conducted on December 8, 2011. 1. Compared with the imaging taken on October 26, 2011, soft tissues surrounding residual cavity

were thickened and significantly enhanced, suggesting a possibility of recurrence. 2. Several lymph nodes at the neck were enlarged. 3. Hypertrophy was found at the left-sided inferior nasal concha and inflammation was seen at the left maxillary sinus, sphenoid sinus and ethmoid sinus. 4. Otitis media and mastoiditis were found at the right side.

[254] The MRI scan of the hip joints on December 8, 2011 showed that a lesion with long T1 and long T2 signal was seen at the left acetabulum and extended to the left ischium. High signals in fat suppression sequences and significant enhancement were found. Significantly enhanced long T1 and long T2 nodular lesion were seen at the lower portions of bilateral ilia and right anterior acetabulum. Conclusion: multiple abnormal signals were found in the bone substance of the bilateral hip joints and bone metastases probably occurred.

[255] MRI of shoulder joints on December 8, 2011showed that, patchy shadows with long T1 and long T2 signals, inhomogeneous enhancement and obscure boundaries were found at the bilateral acromial ends of the clavicles, infraglenoid bone substance of the right scapula, peripheral margin of the bilateral scapulae, the upper parts of the bilateral humeri and bilateral multiple ribs. Multiple lymph nodes appeared at bilateral axilla with part of them enlarged. Conclusion: considering the medical history, the description above indicated multiple metastases to bilateral shoulder joints and axilla.

[256] Bone imaging on December 12, 2011 showed that, bones of the whole body were displayed clearly and dense radioactive patchy shadows were found in the nasopharyngeal region, maxillary sinus region, T8 vertebra and the lower segment of the left acetabulum. Diagnosis conclusion: multiple lesions with elevated bone metabolism were found, suggesting possible occurrence of bone metastases.

[257] Diagnosis after administration of SIFN.

[258] MRI scan of the shoulder joint on May 2, 2012 showed no obvious bone destruction at the left shoulder. Spot-like shadows with long T2 and long T1 signals were seen in the humeral head, probably indicating small cystic lesions.

[259] Pelvic MRI on May 2, 2012showedshadows with long T1 and long T2 signals

at the upper branch of the left pubis with significant enhancement. No obvious abnormality was seen in the remaining part of the pelvis.

[260] Brain MRI on May 2, 2012 showed 1) no intracranial abnormality; 2) bilateral otitis media and mastoiditis;3) the middle and inferior turbinates, the inner wall of maxillary sinus at the right side were missing, leading to a cavity formed by connecting sinus cavity and nasal cavity; 4)left maxillary sinusitis; 5) sphenoid sinusitis and frontal sinusitis.

[261] MRI of lumbar, head and shoulder joints on June 26, 2012 showed that: 1) fat deposition was found on rear and upper portion of the second lumbar vertebra with the remaining corpus vertebrae and intervertebral disc being normal; 2) intracranial brain tissue was normal; 3) the lack of nasal conchae at the right nasal cavity and inner wall of the right maxillary sinus was as above; 4) bilateral ethmoiditis and sphenoid sinusitis and bilateral mastoiditis were found; 5) no lymph nodes enlargement or enhancement was found on either side of the neck.; 6) bilateral caput humeralis and bilateral shoulder joints were normal. After treatment, the lesions disappeared, including those involving the bilateral shoulder joints, the multiple enlarged lymph nodes insubaxillary area, the recurrent and metastatic lesions at residual cavity after surgery of right paranasal sinus and nasal cavity. The multiple abnormal signals at bilateral hip joints and upper segment of the femur also disappeared.

[262] EXAMPLE 3. Treatment of Patient #3 with small cell lung cancer (SCLC) and multiple metastases.

[263] Patient #3 was a 47 year old female. She was diagnosed with small-cell lung cancer at the right lung accompanied by multiple metastases in the liver, mediastinal lymph nodes, left humerus, left clavicle, vertebrae, right femur, pelvis, etc. Intramuscular injection and aerosol inhalation of SIFN and local spraying (on the skin over the bone metastases) of SIFN on lesions combined with chemotherapy were administered. After treatment, the primary lesions in the lung and the liver metastases apparently shrank. Also, part of the bone metastases was eliminated, such as those in the left humerus, left clavicle, C2 vertebra and left T9processustransversus.

[264] Regimens before administration of SIFN.

[265] The first cycle of chemotherapy, Regimen CE, began on May 7, 2012, with each cycle lasting for 28 days: carboplatin (CBP), 300mg/m^2 on day 1; etoposide (VP-16) at 100 mg/m^2 on days 3 – 7. Six cycles were completed by December 2012.

[266] Administration of SIFN.

[267] Treatment with SIFN began on May 28, 2012. Intramuscular injection of SIFN was applied every other day with 9μgfor the first time, 15μgfor the second time, and 18μgfor the third time and thereafter. Meanwhile, aerosol inhalation was administered at 600μgeach time per day. SIFN was simultaneously sprayed locally onto the skin surface of the left humerus, left clavicle, C2 vertebra, left T9 processus transversus and pelvis from September 20, 2012, for 4 – 5 times per day. By December 2012, myelosuppression became apparent since SIFN treatment was applied in combination with chemotherapy. Hence, intramuscular injection and aerosol inhalation of SIFN was periodically provided, but local spraying of SIFN continued for another 3 months.

[268] Diagnosis before administration of SIFN.

[269] Chest CT scans on May 4, 2012 showed atelectasis in the upper lobe of the right lung, indicating a space-occupying lesion. A mass lesion was also seen in the right lobe of the liver with the maximum section area of 5.1 cm x 6.7 cm. The boundary of the mass was obscure.

[270] Test on tumor markers on May 7, 2012 displayed 171.40 ng/ml of CEA, 17.10 ng/ml of carbohydrate antigen 211 and 58.30 ng/ml of NSE.

[271] Abdomen CT scan on May 8, 2012 showed multiple (at least 6) mass-like and nodular space-occupying lesions in both lobes of the liver. The biggest one among them was in the right anterior lobe, 54 mm x 72 mm in size, heterogeneously enhanced, and made part of the liver capsule bulged. Other lesions had a diameter ranging from9 mmto12 mm. A small quantity of effusion existed around the liver. Diagnosis conclusion: multiple space-occupying masses were present in the liver, suggesting the possible occurrence of malignancy and metastases. A small amount of effusion was found around the liver.

[272] PET/CT scans on May 9, 2012 showed FDG metabolism increased

abnormally in multiple bones, left humerus, left clavicle, C2 vertebra, left T9 processus transversus, several segments of the pelvis and right femur were involved. The average SUV was 3.0 to 9.6. CT scan showed the structure disorder of the osseous substances in part of the lesions. The bilateral thoracic cavities were symmetrical, with the trachea in the middle. Consolidation were observed in the upper lobe of the right lung and partial of the consolidation region near the hilus of the lung showed mass-like shadow with elevated FDG metabolism having an average SUV of 7.8. The FDG metabolism in the consolidation region near the pleura appeared to be normal. Shadows of enlarged lymph nodes were seen at the mediastinum in front of the right side of the trachea, with relatively high FDG metabolism, which fused with shadow in the consolidation region, resulting an average SUV of 6.9. Diagnosis conclusion: 1) consolidation were found in the upper lobe of the right lung and the FDG metabolism in a portion near the hilus was abnormally high, suggesting the existence of a central lung cancer accompanied by atelectasis of the upper lobe of the right lung. Metastases of lymph nodes occurred at the mediastinum in front of the right side of the trachea. Multiple metastases were found in the liver and in the bones; 2) FDG metabolism was normal in the brain.

[273] Diagnosis after administration of SIFN.

[274] Color Doppler ultrasound scan on abdomen on August 24, 2012 showed that the liver had regular shapes and the liver capsule was smooth. A solid mass of about 3.5 cm x 2.8 cm (the previous size of which was 7.5 cm x 5.9 cm) was found in the right lobe of the liver.

[275] PET/CT scan on October 9, 2012 showed: 1) the chest appeared to be symmetrical and the lung markings were clear. A lobulated mass of about 1.9 cm x 1.8 cm in size was found in the rear segment of the right upper lobe, wherein the FDG intake was increased and the maximum value of SUV was 14.8. Abnormal shadows or metabolisms were not found in other parts of the lungs. The lymph nodes at the mediastinum and the right-sided hilum were enlarged with elevated FDG intakes (SUV_{max}=5.6). 2) the liver had normal shape, smooth edges, and normal ratio of the lobes. A low-density shadow of about 1.9 cm x 2.7 cm (the previous size of which

was 7.5 cm x 5.9 cm) was found in the lower segment of the anterior lobe of the right liver. The FDG intakes at outer margins were increased with SUV_{max} being 3.5. 3) The cervical vertebrae, thoracic vertebrae and lumbar vertebrae were well arranged. Bone substances were destroyed focally in the left ilium and the right femoral intertrochanter, wherein the FDG intakes were elevated with SUV_{max} being 4.5.(Bone metastases previously existed in the left humerus, left clavicle, C2 vertebra, left T9 processus transversus, several segments of the pelvis and the right-sided femur.) After treatment with SIFN, the primary lesions in lung and the metastases in the liver evidently shrank. Also, bone metastases were eliminated in the left humerus, left clavicle, C2 vertebra and the left T9 processus transversus.

[276] EXAMPLE 4. Treatment of Patient #4 with adenocarcinoma and multiple bone metastases.

[277] Patient #4 was a 30 year old female diagnosed with adenocarcinoma of the left lung, accompanied by multiple bone metastases including the eighth rear rib on the right side, right-sided sacroiliac joint, left-sided ilium, etc. SIFN administration by intramuscular injection, aerosol inhalation and local spraying on lesions combined with chemotherapy and radiotherapy were provided. After treatment, lesions in lung evidently shrank and the SUV value decreased according to PET/CT. Lesion in the left pubis turned better after local spraying of the interferon. Bone metastases in the fifth and eighth thoracic vertebrae disappeared.

[278] Regimens before administration of SIFN.

[279] Chemotherapy was carried out from June 28, 2011 (GP regimen): 1.6 g of Gemzar on days 1 and 8 and 60 mg of Cisplatin on days 1 and 2.

[280] Regimens for administration of SIFN in combination with chemotherapy and radiotherapy.

[281] Treatment of SIFN began on July 1, 2011. Intramuscular injection of SIFN was provided every other day with 15μg for the first time and 18μg for the second time and thereafter. Meanwhile, aerosol inhalation was administered every day, once per day with 600μg for each time. Spraying was locally applied to the skin surfaces of the left pubis, the fifth and eighth thoracic vertebrae and the eighth rear rib on the

right side from June 12, 2012, at 4 to 5 times per day. Surgery with Cyberknife was performed to the right ilium near the sacroiliac joint on July 17, 2012.

[282] Diagnosis before administration of SIFN.

[283] The physical examination result of May 2011 showed shadows in the lungs. Chest CT scan on June 16, 2011displayed a round-shaped space-occupying shadow in the rear segment of the left lower lobe. The shadow was slightly enhanced with a size of 31.8 mm x 36.8 mm. Needle biopsy of the left lung on June 22, 2011 showed a few abnormal cells. Liquid based cytology demonstrated the existence of adenocarcinoma cells. Bone scan on June 27, 2011 showed abnormal radioactive concentrations in the eighth rear rib on the right side, the right-sided sacroiliac joint and the left-sided ilium, suggesting possible metastases in the pelvis and ribs.

[284] Diagnosis after administration of SIFN.

[285] PET/CT scans on September 22, 2011 showed a shadow of a lobulated soft tissue at the lower lobe of the left lung, 3.2 cm x 2.5 cm in size. FDG intakes were increased with an average value of SUV of 4.7 and a maximum value of 5.3. Chest CT scan on February 1, 2012 showed that the exudate shadows in both lungs disappeared as compared to the images taken on August 23, 2011. The lesions on the rear segment of the right upper lobe disappeared and a mass of 21 mm x 15 mm was found in the posterior segment of the left lower lobe. The lesions at the lower lobe of the left lung evidently shrank in size, compared to those on August 23, 2011.

[286] PET/CT scans on July 14, 2012 showed an irregular low-density shadow of 3.3 cm x 2.1 cm at the left lower lobe adjacent to the pleura, in which spot-like calcification could be seen. FDG intakes were slightly and unevenly elevated, with the maximum value of SUV 2.1. Bone scan on September 14, 2012 showed that the radioactive concentration did not change much in eighth rear rib on the right side, right-sided sacroiliac joints, left-sided ilium, left pubis and right-sided iliac joint, compared to the images taken on June 11, 2012. However, the metastatic lesions at the fifth and eighth thoracic vertebrae disappeared as shown in the images of June 11, 2012.

[287] MR of sacroiliac joints on September 21, 2012 showed that the lesions in the

left pubis turned better as compared to the images taken on June 27, 2011. The lesions in the right ilium adjacent to the sacroiliac joint, the right-sided femoral head and neck further progressed.

[288] The treatment lasted for more than one year until December 2012. The lesions in the lungs evidently shrank in size and the SUV values decreased according to PET/CT. As for the bone metastases, the lesions at the right ilium adjacent to the sacroiliac joint worsened after radiotherapy. However, lesions in the left pubis and the fifth and eighth thoracic vertebrae exhibited obvious improvement after 3 months of local spraying of SIFN.

[289] EXAMPLE 5. Treatment of Patient #5 with nasopharyngeal carcinoma.

[290] Patient #5 was a 48 year old female who was first diagnosed as having low-differentiated squamous nasopharyngeal carcinoma, IVa (T4N3M0) on December 27, 2007.

[291] Administration of SIFN began on: SIFN was administered on October 30, 2012, at a dose of 15 μg each time, every other day (subcutaneous or intramuscular injection). Patient did not have any surgery or any adjuvant therapy. Treatment regimen included nasopharyngeal spraying of the SIFN administered as of November 24, 2012. The injecting dosage of SIFN-co increased to 21 μg as of November 25, 2012.

[292] The medical history of Patient #5 was collected on October 30, 2012, as follows:

[293] Patient's chief complaints: Nasopharyngeal carcinoma was diagnosed more than 4 years ago, followed by radiotherapy and chemotherapy more than 3 years ago. Recurrence of the tumor had been found for more than 1 week ago.

[294] Patient's Medical History: A mass was found at the neck in 2007 when the patient referred to Jinshan Hospital affiliated to Fudan University, to get further examination. The pathological examination on December 27, 2007 revealed an undifferentiated type of non-keratinizing carcinoma in the nasopharynx, with immunohistochemistry results showing CK+, EMA+, LCA-, CD68-, 34β E12+, CK5/6+. No other relevant examination and treatment was performed thereafter. The

mass relapsed at the neck in 2009 and the patient had an examination in Mianyang Central Hospital on May 8, 2009. A few atypical hyperplastic squamous epithelia were found in nasopharyngeal mucosa. The patient was suggested to have a biopsy again. Examination on May 12, 2009 showed chronic inflammation with few suspected cancer cells at the margin. Another examination was made in West China Hospital on May 16, 2009, which showed hyperplasia of squamous epithelia acompanied with focal coagulative necrosis, slight to moderate atypical hyperplasia of squamous epithelia, and some inflammatory exudate. After diagnosis, the patient went to Mianyang Tumor Hospital and had 35 courses of radiotherapy and 5 doses of chemotherapy in total. The lesions at nasopharynx and the mass at the neck disappeared after the treatment, suggesting clinical remission.

[295] The patient complained of head discomfort again in March, 2012, with no obvious abnormality found after examinations. A CT scan was performed on June 11, 2012 due to the recurrent headache. The results showed that the right-sided wall was thickened in nasopharynx and local ulcers were likely developed. No treatment was given at the time. The biopsy examination on October 23, 2012 showed a few degenerated atypical cells amidst the chronically inflammated mucous, suggesting the possibility of low differentiated squamous cell carcinoma. The CT scan imaging on October 26, 2012 showed irregular mass of soft tissues density at the left side of the top wall of the nasopharynx.

[296] The main symptoms of this patient currently related to the headache at the right side and difficulty in moving joints of her jaw. She had to stay at home. The patient and her relatives volunteered to use SIFN as of October 30, 2012.

[297] The course of SIFN treatment: On October 31, 2012, the patient had her first intramuscular injection of SIFN of 15 μg at 10:00 am on October 30, 2012. One hour after the administration, the patientshivered, and her body temperature reached 37.8°C after 4 hours. The temperature then decreased and became normal about 7 hours after the drug administration. Her waist and lower extremities began to ache more than 8 hours after the drug administration, which disappeared the next morning. She had no other complaints.

[298] The patient had her second intramuscular injection of SIFN of 15 μg at 14:00 pm on November 1, 2012. The patient shivered about 6 hours after the drug administration. The highest body temperature as measured was 38.0°C (the specific time was not recorded). The body temperature then decreased and finally became normal, without any drug administration or other solutions to reduce the body temperature. Meanwhile, headache was reported, which was ameliorated the next morning. She had no other complaints.

[299] The patient had her fourth intramuscular injection of SIFN of 15 μg on November 6, 2012. The patient shivered about 3 hours after the drug administration. Then, her body temerature began to increase and reached the highest (38.0°C) after 5 hours since the drug administration. The temperature become normal 2 hours later without any attempts to decrease the body temperature. Meanwhile, a headache, a toothache, an earache and a stomach discomfort were reported, which were ameliorated the next morning. She had no other complaints.

[300] The patient had her ninth intramuscular injection of SIFN of 15 μg on November 15, 2012. The patient shivered for about 3 hours after the drug administration. Then, her body temerature reached 37.4°C after about 6 hours since the drug administration and began to decrease later. Meanwhile, a headache, a toothache and an earache were reported, which were ameliorated the next morning. No other discomforts were reported.

[301] A blood routine on October 26, 2012 the following results: WBC, 5.1 x 10^9/L; PLT, 353 x 10^9/L; percentage of lymphocyte, 28.5 %; percentage of neutrophilic granulocyte, 59.4 %; and percentage of monocytes, 8.3 %. A blood routine on November 6, 2012 showed the following results: WBC, 4.1×10^9/L; PLT, 234×10^9/L; percentage of lymphocyte, 40.7%; percentage of neutrophils, 50.6%. A liver function test on November 13, 2012 showed that ALT was 18 U/L and AST was 17 U/L. A CT scan on November 19, 2012 showed that the mass at the top wall of nasopharynx was a little bit larger in size, compared to one found in CT scan on October 26, 2012. The patient reported that her persistent headache was evidently relieved, while she still had difficulty in moving joints of her jaw and neck pain. She had no other complaints.

The therapeutic regimen was adjusted as follows based on her situation. Specifically, the intramuscular injection of rIFN was adjusted to 21 μg each time, every other day, combined with local spraying of SIFN on the nasopharynx.

[302] Spraying was applied to the nasopharynx from November 24, 2012 for 5 – 6 times per day. The right-side teeth ached about 2 to 3 minutes after the drug administration and the pain was ever severer than before. The pain persisted for about 2 hours and then substantially disappeared. Intramuscular injection of SIFN of 21 μg began on November 25, 2012. No chills, fever or headache was reported.

[303] The patient had an intramuscular injection of SIFN of 21 μg for the fourth time on December 1, 2012, combined with nasopharyngeal spraying. She shivered for about 4 hours after the drug administration but the body temperature remained normal. The toothache still existed but was much better than before. The secretion of the nasopharynx contained a little blood. No obvious headache occurred. The patient was suggested to have a blood routine and a liver function test.

[304] The patient had an intramuscular injection of SIFN of 21 μg for the tenth time on December 13, 2012, combined with nasopharyngeal spraying. Toothache and earache were still reported after the drug administration but not as bad as before. Her waist ached sometimes and the secretion of the nasopharynx contained a little blood. No other discomfort was reported. The patient was suggested to pay attention to the secretion of the nasopharynx and prevent the debris from blocking the airway.

[305] The blood routine on December 4, 2012 showed the following results: WBC, 4.4×10^9/L; PLT, 201×10^9/L. The liver function test on December 5, 2012 showed that ALT was 48 U/L and AST was 49 U/L. The patient still had a toothache and paroxysmal pains appeared at the left ear 7 days ago (the ache appeared at the right ear before). The secretion of the nasopharynx remained the same. No headache was reported.

[306] January 23, 2013: The patient said the headache and toothache were gone and felt that she was able to move her jaw better. The secretion of the nasopharynx remained the same. She had no other complaints.

[307] EXAMPLE 6. The use of a transdermal patch in the treatment of

melanocarcinoma.

[308] A transdermal patch having an effective amount of SIFN in the range of about 200 microgram to about 600 microgram per patch is applied on a subject's cancerous skin lesions, such as a melanocarcinoma lesion. The subject has no metastasis. No other anti-tumor therapy is provided. Subcutaneous injection and/or intramuscular injection of SIFN are/is administered combined with the application of the transdermal patch on the cancerous lesions. Specifically, the subcutaneous injection and/or intramuscular injection are/is provided every other day at 15 microgram to 24 microgram of interferon per dose. The transdermal patch is replaced with a new one every day. This treatment regimen is continued for a duration of 2 months. Tumor shrinkage is expected.

[309] EXAMPLE 7. The use of a spray in the treatment of tongue cancer.

[310] SIFN is administered to a subject who has a projecting mass at his tongue which can be highly to moderately differentiated squamous cell carcinoma. The subject can have enlarged lymph nodes at his neck. No other anti-tumor therapy is provided. Briefly, the SIFN is administered by subcutaneous injection and/or intramuscular injection as well as local administration by spraying on the projecting mass. The subcutaneous injection and/or intramuscular injection are/is provided every other day with 9 microgram to 24 microgram of the interferon per dose. The spray containing an effective amount of interferon of in the range of about 200 microgram/ml to about 600 microgram/ml is applied to the lesions on his tongue 2 to 4 times per day. Also, interferon can be injected to the lymph nodes at the neck once every three days at about 80 microgram to about 200 microgram of interferon per dose. Administration of the SIFN is continued for about 20 days. The mass on the tongue is expected to fall off and the enlarged lymph nodes are expected to shrink in size.

What is Claimed is:

1. A method of treatment of cancer in bone in a subject, comprising administering to the subject an effective amount of an interferon that comprises anti-cancer activity, wherein the interferon comprises an amino acid sequence of SEQ ID NO: 1.

2. A method of treatment of bone pain in a subject who has cancer in bone, comprising administering to the subject an effective amount of an interferon that comprises anti-cancer activity and an amino acid sequence of SEQ ID NO: 1.

3. The method of any of claims 1 and 2, wherein the cancer in bone is a primary bone cancer.

4. The method of any of claims 1 and 2, wherein the cancer in bone is a secondary bone cancer that metastasized from a primary tumor.

5. A method of treatment of skin cancer in a subject, comprising administering to the subject an effective amount of an interferon that comprises anti-cancer activity, wherein the interferon comprises an amino acid sequence of SEQ ID NO: 1.

6. A method of treatment of subcutaneous cancer and/or mucosal carcinoma or submucosal carcinoma in a subject, comprising administering to the subject an effective amount of an interferon that comprises anti-cancer activity, wherein the interferon comprises an amino acid sequence of SEQ ID NO: 1.

7. The method of claim 5 or 6, wherein the skin cancer and/or subcutaneous cancer and/or mucosal or submucosal carcinoma is a primary tumor.

8. The method of claim 5 or 6, wherein the skin cancer and/or subcutaneous cancer and/or mucosal or submucosal carcinoma is a secondary tumor that metastasized from a primary tumor.

9. The method of any of claims 3, 4, 7 and 8, wherein the primary tumor comprises at least one of: a solid tumor and a non-solid tumor.

10. A method of treatment of cancer and/or pain associated with cancer in a subject, comprising administering to the subject an effective amount of an interferon that comprises anti-cancer activity and an amino acid sequence of SEQ ID NO: 1, wherein

the cancer comprises at least one of primary or secondary: bone cancer, breast cancer, skin cancer, nasopharyngeal carcinoma, oral cancer, carcinoma of the vulva, prostatic carcinoma, cervical carcinoma and melanoma, including melanocarcinoma, wherein the interferon is administered by percutaneous and/or transmucosal administration.

11. The method of claim 9 or 10, wherein the primary tumor comprises at least one of: bone cancer, cancer of the respiratory system, cancer of the digestive system, cancer of the urinary system, skin cancer, subcutaneous cancer, mucosal cancer, submucosal cancer, cancer of the reproductive system, head and neck cancer, cancer of the hormonal system, and cancer of the nervous system.

12. The method of claim 11, wherein the cancer of the digestive system comprises at least one of: oral cancer, tongue cancer, laryngeal carcinoma, esophageal cancer, gall bladder cancer, liver cancer, gastrointestinal cancer, and pancreatic cancer; wherein the cancer of the reproductive system comprises at least one of: carcinoma of the external genitalia, including the vulva, cervical cancer, endometrial cancer, uterine cancer, ovarian cancer, and prostate cancer; wherein the cancer of the respiratory system comprises at least one of: lung cancer and nasopharyngeal carcinoma; wherein the cancer of the urinary system comprises at least one of: kidney cancer and bladder cancer; wherein the cancer of the hormonal system comprises at least one of: adrenal cancer and thyroid cancer; wherein the head and neck cancer comprises nasopharyngeal carcinoma; wherein the subcutaneous cancer comprises at least one of: prostatic carcinoma and breast cancer; wherein skin cancer comprises at least one of: basal cell carcinoma, epidermoid carcinoma, squamous cell carcinoma such as carcinoma of the external genitalia, such as the vulva, and melanoma, including melanocarcinoma; wherein mucosal cancer comprises cancer involving mucosal cells including oral cancer, tongue cancer, esophageal cancer, nasopharyngeal cancer, gastrointestinal cancer, and colorectal cancer; and wherein the cancer of the nervous system comprises at least one of: neuroma, malignant neuroma, glioma, and astrocytoma.

13. The method of claim 12, wherein the lung cancer comprises at least one of: small cell lung cancer and non-small cell lung cancer; wherein the gastrointestinal cancer

comprises at least one of: gastrointestinal interstitial cell tumor, stomach cancer, colon cancer, rectal cancer, and colorectal cancer; wherein the gall bladder cancer comprises cholangiocarcinoma; wherein the liver cancer comprises hepatocellular carcinoma; wherein the kidney cancer comprises renal cell carcinoma; wherein bladder cancer comprises superficial bladder cancer.

14. The method of claim 10, wherein the primary tumor comprises at least one of: a carcinoma, a sarcoma, and a rhabdomyosarcoma.

15. The method of claim 10, wherein the primary tumor comprises at least one of: abdominal tumor, myoepithelial carcinoma, synovial sarcoma, hemagioma, lymphoma and Kaposi's sarcoma.

16. The method of any of claims 6 – 9, subcutaneous cancer comprises prostatic carcinoma and breast cancer; the mucosal cancer comprises oral cancer, nasopharyngeal carcinoma, rectal cancer, laryngeal carcinoma and tongue cancer; and the submucosal cancer comprises bone cancer.

17. The method of any of claims 1 -16, wherein administering the interferon to the subject comprises administering the interferon by local administration.

18. The method of any of claims 1 – 17, wherein administering the interferon to the subject further comprises administering the interferon by systemic administration.

19. The method of any of claims 1 – 18, wherein administering the interferon to the subject further comprises administering the interferon by inhalation administration.

20. The method of any of claims 17 – 19, wherein the local administration of the interferon comprises administering the interferon to the cancerous lesion.

21. The method of any of claims 17 – 20, wherein local administration of the interferon comprises at least one of: infiltration administration, percutaneous administration, transdermal administration, epidermal administration, and transmucosal administration.

22. The method of any of claims 17 – 21, wherein the local or percutaneous or transmucosal administration of the interferon comprises administration by spraying.

23. The method of any of claims 17 – 22, wherein local or percutaneous or transmucosal administration of the interferon comprises administration of interferon

in a range of about 2 microgram to about 2100 microgram.

24. The method of claim 23, wherein administration of the interferon comprises administration of the interferon in a range of about 4 microgram to about 1800 microgram.

25. The method of claim 24, wherein administration of the interferon comprises administration of the interferon in a range of about 9 microgram to about 1500 microgram.

26. The method of claim 25, wherein administration of the interferon comprises administration of the interferon in a range of about 12 microgram to about 1200 microgram.

27. The method of claim 26, wherein administration of the interferon comprises administration of the interferon in a range of about 15 microgram to about 1000 microgram.

28. The method of claim 27, wherein administration of the interferon comprises administration of the interferon in a range of about 18 microgram to about 900 microgram.

29. The method of claim 28, wherein administration of the interferon comprises administration of the interferon in a range of about 21 microgram to about 750 microgram.

30. The method of claim 29, wherein administration of the interferon comprises administration of the interferon in a range of about 24 microgram to about 600 microgram.

31. The method of claim 30, wherein administration of the interferon comprises administration of the interferon at a dose of about 600 microgram.

32. The method of any of claims 17 – 31, wherein the interferon is administered to the subject locally at least 1 – 12 times per day.

33. The method of claim 32, wherein the interferon is administered to the subject locally at least 2 – 10 times per day.

34. The method of claim 33, wherein the interferon is administered to the subject locally at least 3 – 8 times per day.

35. The method of claim 34, wherein the interferon is administered to the subject at least 4 – 6 times per day.

36. The method of claim 35, wherein the interferon is administered to the subject for 4 or 5 or 6 times per day.

37. The method of any of claims 17 - 36, wherein the interferon is administered locally at least every other day.

38. The method of claim 37, wherein the interferon is administered locally every day.

39. The method of any of claims 22 – 38, wherein the administration of the interferon by spraying comprises administration of the interferon in an amount in a range of about 6 microgram to about 100 microgram per spray administration.

40. The method of claim 39, wherein the interferon is in an amount in a range of about 10 microgram to about 80 microgram per spray administration.

41. The method of claim 40, wherein the interferon is in an amount in a range of about 20 microgram to about 60 microgram per spray administration.

42. The method of claim 41, wherein the interferon is in an amount in a range of about 30 microgram to about 40 microgram per spray administration.

43. The method of any of claims 17 - 42, wherein the interferon is at a concentration in a range of about 0.01 mg/ml to about 5 mg/ml.

44. The method of claim 43, wherein the interferon is at a concentration of about 0.03 mg/ml to about 2 mg/ml.

45. The method of claim 44, wherein the interferon is at a concentration of about 0.05 mg/ml to about 1 mg/ml.

46. The method of claim 45, wherein the interferon is at a concentration of about 0.1 to 0.5 mg/ml.

47. The method of any of claims 17 – 46, wherein administration of the interferon to the subject comprises administration of the interferon to or on the bone, the skin, the mucosa, and/or the submucosa of the subject, wherein the interferon comprises a concentration in a range of about 0.01 mg/ml to about 5 mg/ml, optionally, in a range of about 0.03 mg/ml to about 2 mg/ml, further optionally, in a range of about 0.05 mg/ml to about 1 mg/ml, and still further optionally, in a range of about 0.1 to about

0.5 mg/ml.

48. The method of any of claim 22 – 47, wherein the administration of the interferon by spraying comprises administration of the interferon to the subject at least 1 – 12 times per day.

49. The method of claim 48, wherein the spray administration of the interferon comprises spraying the interferon on the subject at least 2 – 10 times per day.

50. The method of claim 49, wherein the spray administration of the interferon comprises administration by spraying at least 3 – 8 times per day.

51. The method of claim 50, wherein the spray administration of the interferon comprises administration by spraying at least 4 – 7 times per day.

52. The method of claim 51, wherein the spray administration of the interferon comprises administration by spraying4 or 5 or 6 times per day.

53. The method of any of claims 17 – 52, wherein the interferon for local administration is formulated as at least one of: a dry powder, an aqueous solution, a cream, a membrane permeation or diffusion drug delivery system, a controlled release drug delivery system, a closed drug delivery system, a transdermal patch, or a depot comprising the interferon injected under the skin, producing a slow-release effect.

54. The method of any of claims 17 – 53, wherein the interferon comprises interferon formulated as nanoparticles, microparticles, microsphere, liposomes or a controlled release single or composite material.

55. The method of any of claims 18 – 54, wherein the interferon administered by systemic administration is administered before, and/or at about the same time, and/or after the local, such as percutaneous administration of the recombinant interferon.

56. The method of any of claims 18 – 55, wherein systemic administration comprises at least one of: subcutaneous administration and intramuscular administration.

57. The method of any of claims 18 – 56, wherein the systemic administration comprises injection.

58. The method of claim 57, wherein the interferon is administered in an amount in a range of about 2 microgram to about 70 microgram per injection.

59. The method of claim 58, wherein the interferon is administered in an amount in a

range of about 4 microgram to about 50 microgram per injection.

60. The method of claim 59, wherein the interferon is administered in a range of about 9 microgram to about 30 microgram per injection.

61. The method of claim 60, wherein the interferon is administered in a range of about 15 microgram to about 24 microgram per injection.

62. The method of claim 61, wherein the interferon is administered in a range of about 18 microgram to about 21 microgram, per injection.

63. The method of claims 18 – 62, wherein the interferon is administered by systemic administration at least once every 1 – 8 days.

64. The method of claim 63, wherein the interferon is administered by systemic administration at least once every 2 – 7 days.

65. The method of claim 64, wherein the interferon is administered by systemic administration at least once every 3 – 6 days.

66. The method of claim 65, wherein the interferon is administered by systemic administration at least once every 4 – 5 days.

67. The method of claim 63, wherein the interferon is administered by systemic administration every 1 – 2 days.

68. The method of any of claims 17 – 67, wherein the duration of the interferon administration per course of treatment is at least for: 1 day – 12 month or optionally, for more than a year.

69. The method of claim 68, wherein the duration of the interferon administration of the interferon is at least for 2 days – 10 months per course of treatment.

70. The method of claim 69, wherein the duration of the administration of the interferon is at least for 3 days – 8 months per course of treatment.

71. The method of claim 70, wherein the duration of the administration of the interferon is at least for 4 days – 6 months per course of treatment.

72. The method of claim 71, wherein the duration of the administration of the interferon is at least for 5 days – 5 months per course of treatment.

73. The method of claim 72, wherein the duration of the administration of the interferon is at least for 6 days – 4 months per course of treatment.

74. The method of claim 73, wherein the duration of the administration of the interferon is at least for 7 days – 2 months per course of treatment.

75. The method of claim 74, wherein the duration of the administration of the interferon is at least for 8 days – 1 month per course of treatment.

76. The method of claim 75, wherein the duration of the administration of the interferon is at least for 9 days – 3 weeks per course of treatment.

77. The method of claim 76, wherein the duration of the administration of the interferon is at least for 10 days – 2 weeks per course of treatment.

78. The method of claim 77, wherein the duration of the administration of the interferon is at least for 11 days – 1 week per course of treatment.

79. The method of any of claims 57 – 78, wherein the interferon when administered by subcutaneous injection or intramuscular injection is administered at least 2 – 10 times per course of treatment.

80. The method of claim 79, wherein the interferon is administered by subcutaneous or intramuscular injection at least 4 – 8 times per course of treatment.

81. The method of claim 80, wherein the interferon is administered by subcutaneous or intramuscular injection at least 6– 7 times per course of treatment.

82. The method of any of claims 18 - 81, wherein the interferon administered systemically is administered in at least one initial induction dose comprising the interferon in a range of about 2 microgram to about 18 microgram.

83. The method of claim 82, wherein the at least one induction dose comprises the interferon in a range of about 3 microgram to about 15 microgram.

84. The method of claim 83, wherein the at least one induction dose comprises the interferon in a range of about 4 microgram to about 9 microgram.

85. The method of claim 84, wherein the at least one induction doses comprises interferon in a range of about 5 microgram to about 8 microgram.

86. The method of claim 82, wherein the at least one induction dose comprises interferon at about 9 microgram or about 15 microgram.

87. The method of any of claims 82 – 86, wherein, the interferon administered systemically is further administered in at least one subsequent therapeutic dose in a

range of about 10 microgram to about 70 microgram each time.

88. The method of claim 87, wherein the therapeutic dose of the interferon is in a range of about 12 microgram to about 50 microgram each time.

89. The method of claim 88, wherein the therapeutic dose of the interferon is in a range of about 15 microgram to about 30 microgram each time.

90. The method of claim 89, wherein the therapeutic dose of the interferon is in a range of about 18 microgram to about 24 microgram each time.

91. The method of any of claims 87– 90, wherein the time interval between the induction dose and the therapeutic dose of the interferon is in a range of about 1 day to about 1 month, optionally, in a range of about 2 days to about 3 weeks, further optionally, in a range of about 3 days to about 2 weeks, still optionally, in a range of about 4 days to about 10 days, still further optionally, in a range of about 5 days to about 9 days, yet further optionally, in a range of about 6 to about 8 days, and still further optionally, about 7 days.

92. The method of any of claims 82 – 91, wherein the interferon administered systemically is administered to the subject at a frequency of about once every 1 to10 days at the induction dose.

93. The method of claim 92, wherein the interferon is administered to the subject systemically at a frequency of about once every 1 – 2 days at the induction dose.

94. The method of claim 92, wherein the interferon is administered to the subject systemically at a frequency of about once every 3 – 9 days at the induction dose .

95. The method of claim 94, wherein the interferon is administered to the subject at a frequency of about 4 – 8 days at the induction dose.

96. The method of claim 95, wherein the interferon is administered to the subject at a frequency of about once every 5 – 7 days at the induction dose.

97. The method of any claim 87 – 96, wherein the interferon is administered to the subject at a frequency of about once 1 – 10 days at the therapeutic dose.

98. The method of claim 97, wherein the interferon is administered to the subject every day or about once every other day at the therapeutic dose.

99. The method of claim 97, wherein the interferon is administered to the subject

every 1 – 7 days at the therapeutic dose.

100. The method of any of claims 19 – 99, wherein the inhalation administration comprises at least one of: pulmonary inhalation and nasal inhalation.

101. The method of any of claims 19 – 100, wherein the interferon for inhalation administration comprises at least one of: dry powder and/or aerosolized interferon and/or an aqueous solution.

102. The method of any of claims 19 – 101, wherein the interferon for inhalation is administered in an amount in a range of about 100 microgram to about 2000 microgram in one inhalation administration.

103. The method of claim 102, wherein the interferon for inhalation is administered in an amount in a range of about 120 microgram to about 1500 microgram in one inhalation administration.

104. The method of claim 103, wherein the interferon for inhalation is administered in an amount in a range of about 150 microgram to about 1200 microgram in one inhalation administration.

105. The method of claim 104, wherein the interferon for inhalation is administered in an amount in a range of about 200 microgram to about 900 microgram in one inhalation administration.

106. The method of claim 105, wherein the interferon for inhalation is administered in an amount in a range of about 450 microgram to about 750 microgram in one inhalation administration.

107. The method of claim 106, wherein the interferon for inhalation is administered in an amount in a range of about 500 microgram to about 650 microgram in one inhalation administration.

108. The method of claim 107, wherein the interferon for inhalation is administered in an amount of about 600 microgram, in one inhalation administration.

109. The method of any of claims 19 – 108, wherein the interferon is administered by inhalation administration about once every 1 or 2 or 3 days, optionally, every day.

110. The method of any of claims 1 – 109, wherein the interferon is administered as a monotherapy.

111. The method of any of claims 1 – 110, further comprising administering to the subject at least one other anti-cancer therapy.

112. The method of claim 111, wherein the at least one other anti-cancer therapy is administered to the subject before, at about the same time, and/or after administration of the interferon.

113. The method of any of claims 111 or 112, wherein the at least one other anti-cancer therapy comprises at least one of: chemotherapy, radiotherapy, surgical therapy, interventional therapy, biotherapy, targeted therapy, and Traditional Chinese medicine.

114. The method of claim 113, wherein the biotherapy comprises at least one of gene therapy and immunotherapy, and the surgical therapy comprises ablation therapy.

115. The method of any of claims 1 – 114, wherein the treatment achieves at least one of: elimination of at least one cancer lesion, reduction in size of at least one cancer lesion, and non-progression of growth of at least one cancer lesion, as compared to before treatment.

116. The method of any of claims 111 -115, wherein the at least one anti-cancer therapy is a non-surgical therapy.

117. A sprayer for administering an interferon that comprises anti-cancer activity and an amino acid sequence of SEQ ID NO:1, wherein the sprayer comprises the interferon formulated in an amount for administering the interferon at least 4 or 5 or 6 times.

118. The sprayer of claim 117, wherein the interferon is formulated at a concentration in a range of at least about 0.01 mg/ml to about 5 mg/ml.

119. The sprayer of claim 117 or 118, wherein the interferon is formulated at a concentration in a range of about 0.03 mg/ml to about 3 mg/ml.

120. The sprayer of claim 119, wherein the interferon is formulated at a concentration in a range of about 0.05 mg/ml to about 2 mg/ml.

121. The sprayer of claim 120, wherein the interferon is formulated at a concentration in a range of about 0.1 mg/ml to about 1 mg/ml.

122. The sprayer of claim 121, wherein the interferon is formulated at a concentration

in a range of about 0.15 mg/ml to about 0.5 mg/ml.

123. The sprayer of claim 122, wherein the interferon is formulated at a concentration in a range of about 0.2 mg/ml to about 0.4 mg/ml.

124. The sprayer of claim 123, wherein the interferon is formulated at a concentration of about 0.3 mg/ml.

125. The sprayer of any of claim 117 – 124, wherein the sprayer is a single use sprayer comprising one day's supply of the interferon.

126. The sprayer of any of claims 117 - 124, wherein the sprayer is a multiple use sprayer comprising at least a one-week supply of the interferon.

127. A sprayer for administration of a consensus interferon alpha that comprises anti-cancer activity and an amino acid sequence of SEQ ID NO: 1, wherein the sprayer comprises the interferon, wherein the interferon is formulated at a concentration of 300 microgram/ml.

128. The sprayer of claim 127, wherein the interferon is formulated in a volume of 2 ml.

129. The sprayer of any of claims 117 – 128, wherein the interferon encoded by a polynucleotide comprising the sequence of SEQ ID NO: 2.

130. A metered dose of an interferon comprising a single use amount of the interferon, wherein the interferon comprises anti-cancer activity and an amino acid sequence of SEQ ID NO: 1.

131. The metered dose of claim 130, wherein the metered dose comprises the interferon in an amount in a range of about 100 microgram to about 2000 microgram.

132. The metered dose of claim 131, wherein the interferon is in an amount in a range of about 200 microgram to about 1000 microgram.

133. The metered dose of claim 132, wherein the interferon is in an amount in a range of about 300 microgram to about 900 microgram.

134. The metered dose of claim 133, wherein the interferon is in an amount in a range of about 400 microgram to about 800 microgram.

135. The metered dose of claim 134, wherein the interferon is in an amount in a range of about 500 microgram to about 700 microgram.

136. The metered dose of claim 135, wherein the metered dose comprises about 600 microgram of the interferon.

137. The metered dose of any of claims130 – 136, wherein the metered dose comprises the interferon in an amount sufficient for at least one week of treatment.

138. The metered dose of any of claims 130 – 137, wherein the metered dose is formulated for inhalation.

139. The metered dose of claim 138, wherein the metered dose is formulated for inhalation via the nose.

140. The metered dose of claim 138, wherein the metered dose is formulated for inhalation via the lungs.

141. The metered dose of any of claims 138 – 140, wherein the interferon is in an aerosolized form.

142. A method for preparation of a medicament, wherein the medicament comprises a consensus interferon alpha that comprises anti-cancer activity and an amino acid sequence of SEQ ID NO: 1, for administration to a subject who has cancer in bone, wherein the interferon is formulated in at least two distinct formulations, one for injection and one for local application to the bone, skin, mucosa or submucosa of the subject.

143. The method for preparation of a medicament as in claim 142, wherein the interferon is further formulated for inhalation administration.

144. Use of a consensus interferon alpha that comprises an amino acid sequence of SEQ ID NO:1 and anti-cancer activity in the preparation of a medicament for treating bone cancer, skin cancer, subcutaneous carcinoma, mucosal carcinoma and/or submucosal carcinoma in subjects.

145. Use of a consensus interferon alpha that comprises an amino acid sequence of SEQ ID NO:1 and anti-cancer activity in the preparation of a medicament for treating pain associated with cancer.

146. The use of claim 145, wherein the pain associated with cancer comprises pain in the bones.

147. A pharmaceutical composition for treatment of bone cancer, skin cancer,

subcutaneous carcinoma, mucosal carcinoma and/or submucosal carcinoma in a subject, wherein the composition comprises a consensus interferon alpha that comprises an amino acid sequence of SEQ ID NO: 1 and anti-cancer activity and a pharmaceutically acceptable carrier or excipient, wherein the composition is formulated for delivery by local administration.

148. A pharmaceutical composition for treatment of pain associated with cancer in a subject, wherein the composition comprises a consensus interferon alpha that comprises an amino acid sequence of SEQ ID NO: 1 and anti-cancer activity and a pharmaceutically acceptable carrier or excipient, wherein the composition is formulated for local administration.

149. The pharmaceutical compositions of any of claims 147 and 148, wherein the local administration comprises percutaneous and/or transmucosal administration.

150. A method of treatment of cancer in a subject, comprising administering an effective amount of an interferon to an area of the subject where the area is affected by cancer or comprises cancer cells by percutaneous and/or transmucosal administration, wherein the interferon comprises anti-cancer activity and an amino acid sequence of SEQ ID NO:1.

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(54)发明名称

通过干扰素的经皮和/或经粘膜给药治疗骨癌、皮肤癌、皮下癌、粘膜癌和/或粘膜下癌的方法和组合物

(57)摘要

本发明提供通过干扰素的经皮和/或经粘膜给药用于治疗骨癌包括原发性骨癌和继发性骨癌、乳腺癌、皮肤癌、鼻咽癌、口癌、外阴癌、前列腺癌、宫颈癌、黑色素瘤包括黑色素癌的方法和/或组合物。此外,本发明提供了通过干扰素的经皮和/或经粘膜给药用于治疗皮肤、皮下、粘膜、和/或粘膜下原发癌及癌症转移病灶的方法和/或组合物,尤其是用于治疗骨癌疼痛包括继发性骨癌所引起疼痛的方法和/或组合物。

CN 104902917 A

1.一种治疗受试者骨中的癌症的方法，包括向所述受试者施用有效量的包含抗癌活性的干扰素，其中所述干扰素包含 SEQ ID NO :1 的氨基酸序列。

2.一种治疗具有骨中的癌症的受试者的骨痛的方法，包括向所述受试者施用有效量的包含抗癌活性以及 SEQ ID NO :1 的氨基酸序列的干扰素。

3.根据权利要求 1 和 2 任一项的方法，其中所述骨中的癌症是原发性骨癌。

4.根据权利要求 1 和 2 任一项的方法，其中所述骨中的癌症是由原发性肿瘤转移的继发性骨癌。

5.一种治疗受试者中皮肤癌的方法，包括向所述受试者施用有效量的包含抗癌活性的干扰素，其中所述干扰素包含 SEQ ID NO :1 的氨基酸序列。

6.一种治疗受试者中皮下癌和 / 或粘膜癌或粘膜下癌的方法，包括向所述受试者施用有效量的包含抗癌活性的干扰素，其中所述干扰素包含 SEQ IDNO :1 的氨基酸序列。

7.根据权利要求 5 或 6 的方法，其中所述皮肤癌和 / 或皮下癌和 / 或粘膜癌或粘膜下癌是原发性肿瘤。

8.根据权利要求 5 或 6 的方法，其中所述皮肤癌和 / 或皮下癌和 / 或粘膜癌或粘膜下癌是由原发性肿瘤转移的继发性肿瘤。

9.根据权利要求 3、4、7 和 8 任一项的方法，其中所述原发性肿瘤包括如下至少一种 ：实体瘤和非实体瘤。

10.一种治疗受试者中癌症和 / 或与癌症相关的疼痛的方法，包括向所述受试者施用有效量的包含抗癌活性以及 SEQ ID NO :1 的氨基酸序列的干扰素，其中所述癌症包括如下的至少一种原发性或继发性癌症 ：骨癌、乳腺癌、皮肤癌、鼻咽癌、口癌、外阴癌、前列腺癌、宫颈癌、以及黑色素瘤，包括黑色素癌，其中通过经皮和 / 或粘膜给药施用所述干扰素。

11.根据权利要求 9 或 10 的方法，其中所述原发性肿瘤包括如下的至少一种 ：骨癌、呼吸系统癌症、消化系统癌症、泌尿系统癌症、皮肤癌、皮下癌、粘膜癌、粘膜下癌、生殖系统癌症、头颈癌、内分泌系统癌症、和神经系统癌症。

12.根据权利要求 11 的方法，其中所述消化系统癌症包括如下的至少一种 ：口癌、舌癌、喉癌、食道癌、胆囊癌、肝癌、胃肠道癌、和胰腺癌 ；其中所述生殖系统癌症包括如下的至少一种 ：外生殖器癌，包括外阴癌，宫颈癌、子宫内膜癌、子宫癌、卵巢癌、和前列腺癌 ；其中所述呼吸系统癌症包括如下的至少一种 ：肺癌和鼻咽癌 ；其中所述泌尿系统癌症包括如下的至少一种 ：肾癌和膀胱癌 ；其中所述内分泌系统癌症包括如下的至少一种 ：肾上腺癌和甲状腺癌 ；其中所述头颈癌包括鼻咽癌 ；其中所述皮下癌包括如下的至少一种 ：前列腺癌和乳腺癌 ；其中所述皮肤癌包括如下的至少一种 ：基底细胞癌、表皮样癌、鳞状细胞癌例如外生殖器癌，例如外阴癌，和黑色素瘤，包括黑色素癌 ；其中所述粘膜癌包括累及粘膜细胞的癌症，包括口癌、舌癌、食道癌、鼻咽癌、胃肠道癌、和结直肠癌 ；以及其中所述神经系统癌症包括如下的至少一种 ：神经瘤、恶性神经瘤、神经胶质瘤、和星形细胞瘤。

13.根据权利要求 12 的方法，其中所述肺癌包括如下的至少一种 ：小细胞肺癌和非小细胞肺癌 ；其中所述胃肠道癌包括如下的至少一种 ：胃肠道间质细胞瘤、胃癌、结肠癌、直肠癌、和结直肠癌 ；其中所述胆囊癌包括胆管癌 ；其中所述肝癌包括肝细胞癌 ；其中所述肾癌包括肾细胞癌 ；其中所述膀胱癌包括浅表性膀胱癌。

14.根据权利要求 10 的方法，其中所述原发性肿瘤包括如下的至少一种 ：癌、肉瘤、和

横纹肌肉瘤。

15. 根据权利要求 10 的方法，其中所述原发性肿瘤包括如下的至少一种 ：腹部肿瘤、肌上皮癌、滑膜肉瘤、血管瘤、淋巴瘤和卡波济氏肉瘤。

16. 根据权利要求 6 ～ 9 任一项的方法，所述皮下癌包括前列腺癌和乳腺癌 ；所述粘膜癌包括口癌、鼻咽癌、直肠癌、喉癌和舌癌 ；和所述粘膜下癌包括骨癌。

17. 根据权利要求 1 ～ 16 任一项的方法，其中向所述受试者施用干扰素包括通过局部给药施用所述干扰素。

18. 根据权利要求 1 ～ 17 任一项的方法，其中向所述受试者施用干扰素进一步包括通过全身给药施用所述干扰素。

19. 根据权利要求 1 ～ 18 任一项的方法，其中向所述受试者施用干扰素进一步包括通过吸入给药施用所述干扰素。

20. 根据权利要求 17 ～ 19 任一项的方法，其中所述干扰素的局部给药包括向癌病灶施用所述干扰素。

21. 根据权利要求 17 ～ 20 任一项的方法，其中所述干扰素的局部给药包括如下的至少一种 ：浸润给药、经皮给药、透皮给药、表皮给药和粘膜给药。

22. 根据权利要求 17 ～ 21 任一项的方法，其中所述干扰素的局部或经皮或粘膜给药包括通过喷雾给药。

23. 根据权利要求 17 ～ 22 任一项的方法，其中所述干扰素的局部或经皮或粘膜给药包括施用约 2 微克至约 2100 微克的干扰素。

24. 根据权利要求 23 的方法，其中所述干扰素的给药包括施用约 4 微克至约 1800 微克的干扰素。

25. 根据权利要求 24 的方法，其中所述干扰素的给药包括施用约 9 微克至约 1500 微克的干扰素。

26. 根据权利要求 25 的方法，其中所述干扰素的给药包括施用约 12 微克至约 1200 微克的干扰素。

27. 根据权利要求 26 的方法，其中所述干扰素的给药包括施用约 15 微克至约 1000 微克的干扰素。

28. 根据权利要求 27 的方法，其中所述干扰素的给药包括施用约 18 微克至约 900 微克的干扰素。

29. 根据权利要求 28 的方法，其中所述干扰素的给药包括施用约 21 微克至约 750 微克的干扰素。

30. 根据权利要求 29 的方法，其中所述干扰素的给药包括施用约 24 微克至约 600 微克的干扰素。

31. 根据权利要求 30 的方法，其中所述干扰素的给药包括施用约 600 微克剂量的干扰素。

32. 根据权利要求 17 ～ 31 任一项的方法，其中向所述受试者每天局部施用至少 1 ～ 12 次所述干扰素。

33. 根据权利要求 32 的方法，其中向所述受试者每天局部施用至少 2 ～ 10 次所述干扰素。

34. 根据权利要求 33 的方法，其中向所述受试者每天局部施用至少 3 ～ 8 次所述干扰素。

35. 根据权利要求 34 的方法，其中向所述受试者每天局部施用至少 4 ～ 6 次所述干扰素。

36. 根据权利要求 35 的方法，其中向所述受试者每天施用 4 或 5 或 6 次所述干扰素。

37. 根据权利要求 17 ～ 36 任一项的方法，其中至少隔日局部施用所述干扰素。

38. 根据权利要求 37 的方法，其中每日局部施用所述干扰素。

39. 根据权利要求 22 ～ 38 任一项的方法，其中通过喷雾施用所述干扰素包括以每次喷雾给药约 6 微克至约 100 微的量施用所述干扰素。

40. 根据权利要求 39 的方法，其中以每次喷雾给药约 10 微克至约 80 微克的量施用所述干扰素。

41. 根据权利要求 40 的方法，其中以每次喷雾给药约 20 微克至约 60 微克的量施用所述干扰素。

42. 根据权利要求 41 的方法，其中以每次喷雾给药约 30 微克至约 40 微克的量施用所述干扰素。

43. 根据权利要求 17 ～ 42 任一项的方法，其中所述干扰素的浓度为约 0.01mg/ml 至约 5mg/ml。

44. 根据权利要求 43 的方法，其中所述干扰素的浓度为约 0.03mg/ml 至约 2mg/ml。

45. 根据权利要求 44 的方法，其中所述干扰素的浓度为约 0.05mg/ml 至约 1mg/ml。

46. 根据权利要求 45 的方法，其中所述干扰素的浓度为约 0.1 至 0.5mg/ml。

47. 根据权利要求 17 ～ 46 任一项的方法，其中向所述受试者施用干扰素包括将所述干扰素施用在受试者的骨、皮肤、粘膜、和 / 或粘膜下，或施用在受试者的骨、皮肤、粘膜、和 / 或粘膜下之上，其中所述干扰素包括约 0.01mg/ml 至约 5mg/ml，任选地，约 0.03mg/ml 至约 2mg/ml，进一步任选地，约 0.05mg/ml 至约 1mg/ml，和更进一步任选地，约 0.1 至约 0.5mg/ml 的浓度。

48. 根据权利要求 22 ～ 47 任一项的方法，其中通过喷雾施用所述干扰素包括向所述受试者每天施用至少 1 ～ 12 次所述干扰素。

49. 根据权利要求 48 的方法，其中所述干扰素的喷雾给药包括每天对所述受试者喷雾至少 2 ～ 10 次所述干扰素。

50. 根据权利要求 49 的方法，其中所述干扰素的喷雾给药包括每天喷雾给药至少 3 ～ 8 次。

51. 根据权利要求 50 的方法，其中所述干扰素的喷雾给药包括每天喷雾给药至少 4 ～ 7 次。

52. 根据权利要求 51 的方法，其中所述干扰素的喷雾给药包括每天喷雾给药 4 或 5 或 6 次。

53. 根据权利要求 17 ～ 52 任一项的方法，其中将用于局部给药的所述干扰素配制为如下的至少一种 ：干粉、水溶液、霜剂、膜渗透或扩散药物递送系统、控释药物递送系统、封闭药物递送系统、透皮贴剂、或包含在皮肤下注射的干扰素而产生缓释效果的储库型制剂。

54. 根据权利要求 17 ～ 53 任一项的方法，其中所述干扰素包括被配制为如下的干扰

素：纳米颗粒、微米颗粒、微球、脂质体或控释的单一或复合材料。

55. 根据权利要求 18 ～ 54 任一项的方法，其中在局部给药，例如经皮给药所述重组干扰素之前、和 / 或大约同时、和 / 或之后施用通过全身给药施用的所述干扰素。

56. 根据权利要求 18 ～ 55 任一项的方法，其中所述全身给药包括如下的至少一种：皮下给药和肌肉给药。

57. 根据权利要求 18 ～ 56 任一项的方法，其中所述全身给药包括注射。

58. 根据权利要求 57 的方法，其中所述干扰素以每次注射约 2 微克至约 70 微克的量施用。

59. 根据权利要求 58 的方法，其中所述干扰素以每次注射约 4 微克至约 50 微克的量施用。

60. 根据权利要求 59 的方法，其中所述干扰素以每次注射约 9 微克至约 30 微克的量施用。

61. 根据权利要求 60 的方法，其中所述干扰素以每次注射约 15 微克至约 24 微克的量施用。

62. 根据权利要求 61 的方法，其中所述干扰素以每次注射约 18 微克至约 21 微克的量施用。

63. 根据权利要求 18 ～ 62 任一项的方法，其中每 1 ～ 8 天通过全身给药施用至少一次所述干扰素。

64. 根据权利要求 63 的方法，其中每 2 ～ 7 天通过全身给药施用至少一次所述干扰素。

65. 根据权利要求 64 的方法，其中每 3 ～ 6 天通过全身给药施用至少一次所述干扰素。

66. 根据权利要求 65 的方法，其中每 4 ～ 5 天通过全身给药施用至少一次所述干扰素。

67. 根据权利要求 63 的方法，其中每 1 ～ 2 天通过全身给药施用所述干扰素。

68. 根据权利要求 17 ～ 67 任一项的方法，其中每疗程干扰素给药的持续时间为至少：1 天～ 12 个月，或任选地，持续超过 1 年。

69. 根据权利要求 68 的方法，其中每疗程干扰素给药的持续时间为至少 2 天～ 10 个月。

70. 根据权利要求 69 的方法，其中每疗程干扰素给药的持续时间为至少 3 天～ 8 个月。

71. 根据权利要求 70 的方法，其中每疗程干扰素给药的持续时间为至少 4 天～ 6 个月。

72. 根据权利要求 71 的方法，其中每疗程干扰素给药的持续时间为至少 5 天～ 5 个月。

73. 根据权利要求 72 的方法，其中每疗程干扰素给药的持续时间为至少 6 天～ 4 个月。

74. 根据权利要求 73 的方法，其中每疗程干扰素给药的持续时间为至少 7 天～ 2 个月。

75. 根据权利要求 74 的方法，其中每疗程干扰素给药的持续时间为至少 8 天～ 1 个月。

76. 根据权利要求 75 的方法，其中每疗程干扰素给药的持续时间为至少 9 天～ 3 周。

77. 根据权利要求 76 的方法，其中每疗程干扰素给药的持续时间为至少 10 天～ 2 周。

78. 根据权利要求 77 的方法，其中每疗程干扰素给药的持续时间为至少 11 天～ 1 周。

79. 根据权利要求 57 ～ 78 任一项的方法，其中当通过皮下注射或肌肉注射给药时，每疗程施用至少 2 ～ 10 次所述干扰素。

80. 根据权利要求 79 的方法，其中当通过皮下注射或肌肉注射给药时，每疗程施用至少 4 ～ 8 次所述干扰素。

81. 根据权利要求 80 的方法，其中当通过皮下注射或肌肉注射给药时，每疗程施用至少 6 ～ 7 次所述干扰素。

82. 根据权利要求 18 ～ 81 任一项的方法，其中以至少一个包含约 2 微克至约 18 微克的干扰素的初始诱导剂量施用全身给药的干扰素。

83. 根据权利要求 82 的方法，其中所述至少一个诱导剂量包含约 3 微克至约 15 微克的干扰素。

84. 根据权利要求 83 的方法，其中所述至少一个诱导剂量包含约 4 微克至约 9 微克的干扰素。

85. 根据权利要求 84 的方法，其中所述至少一个诱导剂量包含约 5 微克至约 8 微克的干扰素。

86. 根据权利要求 82 的方法，其中所述至少一个诱导剂量包含约 9 微克或约 15 微克的干扰素。

87. 根据权利要求 82 ～ 86 任一项的方法，其中以至少一个每次约 10 微克至约 70 微克的随后治疗剂量进一步施用全身给药的干扰素。

88. 根据权利要求 87 的方法，其中所述干扰素的治疗剂量为每次约 12 微克至约 50 微克。

89. 根据权利要求 88 的方法，其中所述干扰素的治疗剂量为每次约 15 微克至约 30 微克。

90. 根据权利要求 89 的方法，其中所述干扰素的治疗剂量为每次约 18 微克至约 24 微克。

91. 根据权利要求 87 ～ 90 任一项的方法，其中所述干扰素的诱导剂量和治疗剂量之间的时间间隔为约 1 天至约 1 个月，任选地，约 2 天至约 3 周，进一步任选地，约 3 天至约 2 周，更任选地，约 4 天至约 10 天，还更任选地，约 5 天至约 9 天，还进一步任选地，约 6 至约 8 天，和更进一步任选地，约 7 天。

92. 根据权利要求 82 ～ 91 任一项的方法，其中以每 1 至 10 天约一次的频率向所述受试者施用诱导剂量的全身给药的干扰素。

93. 根据权利要求 92 的方法，其中以每 1 ～ 2 天约一次的频率向所述受试者施用诱导剂量的全身给药的干扰素。

94. 根据权利要求 92 的方法，其中以每 3 ～ 9 天约一次的频率向所述受试者施用诱导剂量的全身给药的干扰素。

95. 根据权利要求 94 的方法，其中以约 4 ～ 8 天的频率向所述受试者施用诱导剂量的干扰素。

96. 根据权利要求 95 的方法，其中以每 5 ～ 7 天约一次的频率向所述受试者施用诱导剂量的干扰素。

97. 根据权利要求 87 ～ 96 任一项的方法，其中以 1 ～ 10 天约一次的频率向所述受试者施用治疗剂量的干扰素。

98. 根据权利要求 97 的方法，其中每天或每隔一天约一次向所述受试者施用治疗剂量的干扰素。

99. 根据权利要求 97 的方法，其中每 1 ～ 7 天向所述受试者施用治疗剂量的干扰素。

100. 根据权利要求 19 ～ 99 任一项的方法，其中所述吸入给药包括如下的至少一种：经肺吸入和经鼻吸入。

101. 根据权利要求 19 ～ 100 任一项的方法，其中用于吸入给药的干扰素包括如下的至少一种：干粉和 / 或雾化的干扰素和 / 或水溶液。

102. 根据权利要求 19 ～ 101 任一项的方法，其中在一次吸入给药中以约 100 微克至约 2000 微克的量施用用于吸入的干扰素。

103. 根据权利要求 102 的方法，其中在一次吸入给药中以约 120 微克至约 1500 微克的量施用用于吸入的干扰素。

104. 根据权利要求 103 的方法，其中在一次吸入给药中以约 150 微克至约 1200 微克的量施用用于吸入的干扰素。

105. 根据权利要求 104 的方法，其中在一次吸入给药中以约 200 微克至约 900 微克的量施用用于吸入的干扰素。

106. 根据权利要求 105 的方法，其中在一次吸入给药中以约 450 微克至约 750 微克的量施用用于吸入的干扰素。

107. 根据权利要求 106 的方法，其中在一次吸入给药中以约 500 微克至约 650 微克的量施用用于吸入的干扰素。

108. 根据权利要求 107 的方法，其中在一次吸入给药中以约 600 微克的量施用用于吸入的干扰素。

109. 根据权利要求 19 ～ 108 任一项的方法，其中每 1 或 2 或 3 天约一次，任选地，每天约一次通过吸入给药施用所述干扰素。

110. 根据权利要求 1 ～ 109 任一项的方法，其中所述干扰素作为单一疗法施用。

111. 根据权利要求 1 ～ 110 任一项的方法，进一步包括向所述受试者施用至少一种其他抗癌疗法。

112. 根据权利要求 111 的方法，其中在施用所述干扰素之前、大约同时和 / 或之后向所述受试者施用至少一种其他抗癌疗法。

113. 根据权利要求 111 或 112 任一项的方法，其中至少一种其他抗癌疗法包括如下的至少一种：化学治疗、放射治疗、手术治疗、介入治疗、生物治疗、靶向治疗和中药治疗。

114. 根据权利要求 113 的方法，其中所述生物治疗包括如下的至少一种：基因治疗和免疫治疗，以及所述手术治疗包括消融治疗。

115. 根据权利要求 1 ～ 114 任一项的方法，其中所述达到如下的至少一种目的：与治疗前相比，消除至少一个癌症病灶、减小至少一个癌症病灶的尺寸以及至少一个癌症病灶的无进展生长。

116. 根据权利要求 111 ～ 115 任一项的方法，其中所述至少一种抗癌疗法是非手术治疗。

117. 一种用于施用包含抗癌活性和 SEQ ID NO：1 的氨基酸序列的干扰素的喷雾剂，其中所述喷雾剂包含以用于施用至少 4 或 5 或 6 次干扰素的量配制的所述干扰素。

118. 根据权利要求 117 的喷雾剂，其中所述干扰素被配制为至少约 0.01mg/ml 至约 5mg/ml 的浓度。

119. 根据权利要求 117 或 118 的喷雾剂，其中所述干扰素被配制为约 0.03mg/ml 至约

3mg/ml 的浓度。

120. 根据权利要求 119 的喷雾剂，其中所述干扰素被配制为约 0.05mg/ml 至约 2mg/ml 的浓度。

121. 根据权利要求 120 的喷雾剂，其中所述干扰素被配制为约 0.1mg/ml 至约 1mg/ml 的浓度。

122. 根据权利要求 121 的喷雾剂，其中所述干扰素被配制为约 0.15mg/ml 至约 0.5mg/ml 的浓度。

123. 根据权利要求 122 的喷雾剂，其中所述干扰素被配制为约 0.2mg/ml 至约 0.4mg/ml 的浓度。

124. 根据权利要求 123 的喷雾剂，其中所述干扰素被配制为约 0.3mg/ml 的浓度。

125. 根据权利要求 117 ～ 124 任一项的喷雾剂，其中所述喷雾剂是包含一天干扰素供应量的单次使用喷雾剂。

126. 根据权利要求 117 ～ 124 任一项的喷雾剂，其中所述喷雾剂是包含至少一周干扰素供应量的多次使用喷雾剂。

127. 一种用于施用包含抗癌活性和 SEQ ID NO :1 的氨基酸序列的复合干扰素 α 的喷雾剂，其中所述喷雾剂包含所述干扰素，其中所述干扰素以 300 微克 /ml 的浓度配制。

128. 根据权利要求 127 的喷雾剂，其中所述干扰素被配制在 2ml 的体积中。

129. 根据权利要求 117 ～ 128 任一项的喷雾剂，其中所述干扰素为包含 SEQ ID NO :2 的序列的多核苷酸编码。

130. 一种包含单次使用量的干扰素定剂，其中所述干扰素包含抗癌活性和SEQ ID NO : 1 的氨基酸序列。

131. 根据权利要求 130 的定剂，其中所述定剂包含约 100 微克至约 2000 微克的量的干扰素。

132. 根据权利要求 131 的定剂，其中所述干扰素的量为约 200 微克至约 1000 微克。

133. 根据权利要求 132 的定剂，其中所述干扰素的量为约 300 微克至约 900 微克。

134. 根据权利要求 133 的定剂，其中所述干扰素的量为约 400 微克至约 800 微克。

135. 根据权利要求 134 的定剂，其中所述干扰素的量为约 500 微克至约 700 微克。

136. 根据权利要求 135 的定剂，其中所述定剂包含约 600 微克的干扰素。

137. 根据权利要求 130 ～ 136 任一项的定剂，其中所述定剂包含足以进行至少一周治疗的量的干扰素。

138. 根据权利要求 130 ～ 137 任一项的定剂，其中所述定剂被配制用于吸入。

139. 根据权利要求 138 的定剂，其中所述定剂被配制用于经鼻吸入。

140. 根据权利要求 138 的定剂，其中所述定剂被配制用于经肺吸入。

141. 根据权利要求 138 ～ 140 任一项的定剂，其中所述干扰素处于雾化形式。

142. 一种制备药物的方法，其中所述药物包含含有抗癌活性和 SEQ ID NO :1 的氨基酸序列的复合干扰素 α，用于向具有骨中的癌症的受试者施用，其中所述干扰素被配制为至少两个独立的配方，一个用于注射以及另一个用于向受试者的骨、皮肤、粘膜或粘膜下局部施用。

143. 如权利要求 142 中所述的制备药物的方法，其中所述干扰素被进一步配制用于吸

入给药。

144. 包含 SEQ ID NO :1 的氨基酸序列和抗癌活性的复合干扰素 α 在制备用于治疗受试者中骨癌、皮肤癌、皮下癌、粘膜癌和 / 或粘膜下癌的药物中的应用。

145. 包含 SEQ ID NO :1 的氨基酸序列和抗癌活性的复合干扰素 α 在制备用于治疗与癌症相关的疼痛的药物中的应用。

146. 根据权利要求 145 的应用，其中所述与癌症相关的疼痛包括骨中的疼痛。

147. 一种用于治疗受试者中骨癌、皮肤癌、皮下癌、粘膜癌和 / 或粘膜下癌的药物组合物，其中所述组合物包含含有 SEQ ID NO :1 的氨基酸序列和抗癌活性的复合干扰素 α 以及药学上可接受的载体或赋形剂，其中所述组合物被配制用于通过局部给药递送。

148. 一种用于治疗受试者中与癌症相关的疼痛的药物组合物，其中所述组合物包含含有 SEQ ID NO :1 的氨基酸序列和抗癌活性的复合干扰素 α 以及药学上可接受的载体或赋形剂，其中所述组合物被配制用于局部给药。

149. 根据权利要求 147 和 148 任一项的药物组合物，其中所述局部给药包括经皮和 / 或粘膜给药。

150. 一种治疗受试者中癌症的方法，包括通过经皮和 / 或粘膜给药向所述受试者为癌症所影响的区域或包含癌细胞的区域施用有效量的干扰素，其中所述干扰素包含抗癌活性和 SEQ ID NO :1 的氨基酸序列。

通过干扰素的经皮和/或经粘膜给药治疗骨癌、皮肤癌、皮下癌、粘膜癌和/或粘膜下癌的方法和组合物

技术领域

[0001] 本发明涉及在受试者中治疗癌症的方法和产品。

[0002] 发明背景

[0003] 癌症，例如骨中的癌症，是使人衰弱并疼痛的疾病，并且经常与源自其他组织或器官的原发性肿瘤的转移相关，但是也能够作为原发性肿瘤而发生。迄今为止，没有好的、容易给药的有效治疗来减轻该疼痛或治疗该疾病或给予受该疾病之苦的人任何有关他们的症状能够得到改善的鼓励。同样，迄今为止没有好的、有效的、容易给药的用于皮肤癌、皮下癌、粘膜癌和/或其他粘膜下癌的治疗。因此，对于提供治疗这些疾病以及这些疾病的副作用例如骨痛的方法、组合物和产品存在尚未满足的医疗需求。

[0004] 发明概述

[0005] 本发明在此提供一种或多种用于在受试者中治疗原发性癌症和/或继发性癌症以及治疗由癌症特别是骨癌引发的疼痛的方法和/或组合物和/或其他产品，所述原发性癌症和/或继发性癌症包括例如骨中的癌症，以及皮肤癌、皮下癌、粘膜癌和/或其他粘膜下癌，包括转移的病灶，在各个例子中，癌症为原发性或继发性，其中继发性癌症是指从源自原发性肿瘤的转移而来的癌症。

[0006] 本发明提供通过干扰素的经皮和/或经粘膜给药而用于治疗骨癌包括原发性骨癌和继发性骨癌、乳腺癌、皮肤癌、鼻咽癌、口癌、外阴癌、前列腺癌、宫颈癌、黑色素瘤包括黑色素癌的方法和/或组合物。此外，本发明提供通过干扰素的经皮和/或经粘膜给药来治疗皮肤、皮下、粘膜和/或粘膜下原发性癌和癌症转移病灶的方法和/或组合物，特别是用于治疗骨癌疼痛包括由继发性骨癌引起的疼痛的方法和/或组合物。

[0007] 本发明提供一种或多种在受试者中治疗原发性骨癌或继发性骨癌的方法，包括向受试者的受癌症侵袭或包含癌细胞的骨区域施用干扰素。

[0008] 本发明还提供一种或多种在受试者中治疗皮肤癌、皮下癌、粘膜癌和/或粘膜下癌的方法，包括向受试者的受癌症侵袭或包含癌细胞的皮肤、皮下、粘膜和/或粘膜下区域施用干扰素，其中这些癌症是原发性癌症或从原发性癌症转移而来的继发性癌症。

[0009] 在一些实施方式中，本发明提供了向受试者施用有效量的含有 SEQ ID NO:1 的氨基酸序列并具有抗癌活性的复合干扰素 α。在一些实施方式中，所述氨基酸序列由包含SEQ ID NO:2 多核苷酸序列的多核苷酸所编码。

[0010] 在本发明的一些实施方式中，干扰素通过局部给药而施用，例如施用至受癌症侵袭或包含癌细胞的区域。

[0011] 在本发明的一些实施方式中，干扰素通过局部给药以及吸入给药和全身给药中的至少一种而施用。

[0012] 在一些实施方式中，本发明提供通过经皮和/或经粘膜给药用于治疗骨癌（包括原发性骨癌和继发性骨癌）、乳腺癌、皮肤癌、鼻咽癌、口癌、外阴癌、前列腺癌、宫颈癌和黑色素瘤（包括黑色素癌）的方法和组合物。

[0013] 在一些实施方式中，本发明提供用于治疗原发性皮肤癌、皮下癌、粘膜癌和 / 或粘膜下癌以及转移病灶的方法和组合物，包括用于治疗由骨癌（包括继发性骨癌）引起的疼痛的方法和组合物。

[0014] 在一些实施方式中，本发明提供如任何本文描述的方法和组合物，其中所述干扰素通过局部给药、吸入给药或全身给药而施用，其中全身给药包括皮下给药和肌肉给药，例如皮下注射和肌肉注射。

[0015] 在一些实施方式中，本发明提供如任何本文描述的方法和组合物，还包括通过注射和吸入雾化干扰素中的至少一种来施用干扰素。

[0016] 在一些实施方式中，本发明提供如任何本文描述的治疗癌症的方法和组合物，其中干扰素通过局部给药而施用，或者任选地通过经皮给药和 / 或经粘膜给药而施用。

[0017] 本文的皮肤癌包括涉及表皮细胞的癌症，例如基底细胞癌、表皮样癌、鳞状细胞癌，包括黑色素瘤（包括黑色素癌）、宫颈癌和外阴癌。本文的皮下癌涉及皮下组织或细胞的癌症并包括乳腺癌和前列腺癌等。本文的粘膜癌涉及粘膜细胞的癌症并包括鼻咽癌、口癌和直肠癌。粘膜下肿瘤包括粘膜下组织的癌症，包括骨癌。

[0018] 在一些实施方式中，本发明提供通过干扰素的局部给药而治疗骨癌、皮肤癌、皮下癌、粘膜癌和 / 或粘膜下癌和 / 或癌症疼痛的方法、组合物和 / 或其他产品，且所述局部给药包括经皮给药和 / 或经粘膜给药。

[0019] 在一些实施方式中，本发明提供向受试者的受癌症侵袭或包含癌细胞的骨区域施用干扰素。骨中的癌症可以是原发性骨癌或者可以是继发性骨癌，继发性骨癌为已从源自另一组织或器官的原发性肿瘤转移至骨的癌症。

[0020] 本发明还提供在受试者中治疗癌症的方法和组合物，包括向受试者施用有效量的包含抗癌活性以及 SEQ ID NO :1 的氨基酸序列的复合干扰素 α，其中干扰素通过局部给药而施用至受试者的皮肤和 / 或粘膜。

[0021] 本发明还提供如任何上述方法的方法，其中干扰素通过经皮给药或全身给药而施用。

[0022] 在一些实施方式中，全身给药包括皮下给药和肌肉给药。

[0023] 本发明还提供如任何上述方法的方法，还提供通过注射（例如皮下注射和肌肉注射）向受试者全身性地施用干扰素。

[0024] 本发明还提供如任何上述方法的方法，还包括通过吸入向受试者施用干扰素。在一些实施方式中，吸入给药包括干扰素干粉的给药。在一些实施方式中，吸入给药包括干扰素水溶液的给药。在一些实施方式中，吸入给药包括雾化形式的干扰素的给药。

[0025] 本发明还提供治疗受试者骨中的癌症的方法，包括向受试者施用有效量的包含抗癌活性和 SEQ ID NO :1 的氨基酸序列的复合干扰素 α，其中干扰素经皮施用至受试者。

[0026] 本发明还提供如上述方法的方法，经皮将干扰素应用在受试者皮肤上或应用至受试者皮肤，和 / 或经粘膜应用至受试者粘膜或应用在受试者粘膜上。

[0027] 本发明还提供如前所述的经皮和 / 或经粘膜的方法，还包括通过注射和吸入中的至少一种，任选地，通过注射给药和吸入给药两者施用干扰素，，其中吸入给药包括雾化形式的干扰素、干扰素的干粉和 / 或干扰素水溶液的给药。

[0028] 本发明还提供如任何上述方法的方法，其中向骨区域应用干扰素包括直接或间接

将干扰素应用到骨或骨上的至少一种。

[0029] 本发明也提供如任何上述方法的方法，其中对皮肤应用干扰素包括应用到与受癌症侵袭的骨（即包含癌细胞的骨部分）邻近的皮肤或皮肤上，或者应用到受癌症侵袭的骨周边的皮肤或皮肤上。

[0030] 在一些实施方式中，施用至皮肤包括将干扰素应用至受癌症侵袭的骨的周边的皮肤。

[0031] 本发明还提供如任何上述方法的方法，其中将干扰素施用至粘膜。在一些实施方式中，应用至粘膜包括应用至与受癌症侵袭的骨（即包含癌细胞的骨部分）邻近的粘膜，或应用至在受癌症侵袭的骨周边的粘膜。

[0032] 本发明也提供如任何上述方法的方法，其中将干扰素应用至皮肤包括皮下应用干扰素。

[0033] 本发明还提供如任何上述方法的方法，其中向粘膜应用干扰素包括粘膜下给药。

[0034] 本发明还提供如任何上述方法的方法，其中向皮肤应用干扰素包括如下的至少一种：向皮肤上喷干扰素的水溶液、在皮肤上涂覆包含干扰素的霜剂、敷膜例如包含干扰素的透皮贴剂或任何其他使得干扰素可以控释或渗透或扩散至受试者皮肤或通过受试者皮肤的包含干扰素的膜、或产生使干扰素沉积在皮肤下并产生缓释或控释效果的储库（depot）效果、和 / 或其他封闭药物递送系统。

[0035] 本发明还提供如任何上述方法的方法，其中通过吸入而施用干扰素包括经鼻递送干扰素和递送至肺中的至少一种。

[0036] 本发明也提供如任何上述方法的方法，其中干扰素配制成溶液或混悬液。

[0037] 本发明提供如任何上述方法的方法，其中干扰素配制成如下的至少一种：纳米颗粒、微球、脂质体或其他控释的单一或复合材料。

[0038] 本发明也提供如任何上述方法的方法，其中通过注射给药的干扰素以至少两个或更多个剂量进行施用，各个剂量高于前一剂量或与前一剂量相同。

[0039] 本发明提供如任何上述方法的方法，其中干扰素注射的第一剂量包含约 2 微克至约 15 微克的干扰素。

[0040] 本发明提供如任何上述方法的方法，其中干扰素注射的第一剂量包含 9 微克或 15 微克的干扰素。

[0041] 本发明也提供如任何上述方法的方法，其中干扰素注射的第二剂量包含约 15 微克至约 50 微克的干扰素。

[0042] 本发明也提供任何上述实施方式的方法，其中干扰素注射的第二剂量包含 15 微克或 18 微克或 21 微克的干扰素。

[0043] 本发明提供如任何上述方法的方法，其中干扰素注射的第三剂量和 / 或任何随后剂量要高于第二剂量或与第二剂量相同。

[0044] 本发明还提供如任何上述方法的方法，其中通过应用至皮肤或骨或粘膜的干扰素给药包括在其上喷雾一天至少 1 ～ 12 次，任选地为一天 2 ～ 10 次，再任选地为一天 3 ～ 8 次，更任选地为每天 4 或 5 或 6 次。

[0045] 本发明还提供如任何上述方法的方法，其中通过吸入向受试者施用干扰素包括每天或每几天（例如每 2 天或每 3 天）经吸入而施用干扰素。

[0046] 本发明提供如任何上述方法的方法，其中将干扰素施用至受试者骨或皮肤或粘膜或者施用至骨或皮肤或粘膜上、或者其他局部给药包括以约 0.01mg/ml 至约 5mg/ml，任选地为约 0.03mg/ml 至约 2mg/ml，更任选地为约 0.05mg/ml 至约 1mg/ml，还更任选地为约 0.1mg/ml 至约 0.5mg/ml 的浓度应用干扰素制剂。

[0047] 本发明提供如任何上述方法的方法，其中原发性肿瘤包括实体瘤和非实体瘤中的至少一种。

[0048] 此外，本发明提供，转移的原发性肿瘤可以是呼吸系统癌症、消化系统癌症、泌尿系统癌症、乳腺癌、皮肤癌、生殖系统癌症、头颈癌、内分泌系统癌症、和神经系统癌症。消化系统癌症包括：口癌、舌癌、喉癌、食道癌、胆囊癌、肝癌、胃肠道癌、和胰腺癌。生殖系统癌症包括：外生殖器癌、宫颈癌、子宫内膜癌、子宫癌、卵巢癌、和前列腺癌。呼吸系统癌症包括：肺癌和鼻咽癌。泌尿系统癌症包括：肾癌和膀胱癌。内分泌系统癌症包括：肾上腺癌和甲状腺癌。头颈癌包括鼻咽癌。皮肤癌包括：上皮癌和皮下癌，例如前列腺癌、乳腺癌、基底细胞癌、表皮样癌、鳞状细胞癌、外生殖器癌例如外阴癌、和黑色素瘤包括黑色素癌。神经系统癌症包括：神经瘤、恶性神经瘤、神经胶质瘤、和星形细胞瘤。

[0049] 本发明提供，肺癌包括：小细胞肺癌和非小细胞肺癌。胃肠道癌包括：胃肠道间质细胞瘤、胃癌、结肠癌、直肠癌、和结直肠癌。胆囊癌包括胆管癌。肝癌包括肝细胞癌。肾癌包括肾细胞癌。膀胱癌包括浅表性膀胱癌。

[0050] 本发明还提供，转移的原发性肿瘤可以是癌、肉瘤、和横纹肌肉瘤。

[0051] 本发明还提供，转移的原发性肿瘤也可以是腹部肿瘤、肌上皮癌、滑膜肉瘤、血管瘤、淋巴瘤和卡波济氏肉瘤。

[0052] 本发明也提供，粘膜癌包括口癌、鼻咽癌、直肠癌、喉癌和舌癌。

[0053] 本发明提供如任何上述方法的方法，其中骨癌、皮肤癌、皮下癌、粘膜癌和 / 或粘膜下癌包括骨癌（包括原发性骨癌和 / 或继发性骨癌）、乳腺癌、皮肤癌、鼻咽癌、口癌、外阴癌、前列腺癌、宫颈癌和黑色素瘤包括黑色素癌。

[0054] 本发明提供如任何上述方法的方法，其中干扰素注射包括在干扰素施用至皮肤和 / 或骨和 / 或粘膜和 / 或粘膜下之中或者施用至皮肤和 / 或骨和 / 或粘膜和 / 或粘膜下之上的之前、之后、或大约同时进行注射。

[0055] 本发明还提供如任何上述方法的方法，其中通过吸入的干扰素应用包括在将干扰素应用到皮肤和 / 或骨和 / 或粘膜和 / 或粘膜下之中或者应用到皮肤和 / 或骨骼和 / 或粘膜和 / 或粘膜下之上的之前、之后或大约同时的这样的应用。

[0056] 本发明提供如任何上述方法的方法，其中向皮肤、骨、粘膜和 / 或粘膜下或者向皮肤、骨骼、粘膜和 / 或粘膜下之上施用干扰素包括在通过注射的干扰素给药和 / 或通过吸入的干扰素给药之前、之后或大约同时进行的这样的给药，且通过注射的干扰素给药包括在通过吸入的干扰素给药（如果有的话）之前、之后或大约同时进行的这样的给药。

[0057] 本发明提供，对于局部给药，干扰素可以施用至癌病灶中或癌病灶上。此外，应用到癌病灶中或癌病灶上可以通过：浸润给药、经皮给药、透皮给药、表皮给药和粘膜给药中的至少一种来进行。经皮给药也可以通过喷干扰素来实现。

[0058] 本发明也提供，干扰素的局部给药包括以约 2 微克至约 2100 微克，任选地，约 4 微克至约 1800 微克，更任选地，约 9 微克至约 1500 微克，任选地，约 12 微克至约 1200 微克，

更任选地，约 15 微克至约 1000 微克，进一步任选地，约 18 微克至约 900 微克，更任选地，约 21 微克至约 750 微克，还更任选地，约 24 微克至约 600 微克的干扰素给药。

[0059] 本发明提供，当干扰素局部施用至受试者时，可以以每天约 1 ～ 12 次，任选地，每天 2 ～ 10 次，更任选地，每天 3 ～ 8 次，进一步任选地，每天 4 ～ 6 次进行给药。

[0060] 在一些实施方式中，本发明提供，当干扰素局部给药至受试者时，可以以每天至少 1、2、3、4、5、6、7、8 或更多次进行给药。

[0061] 本发明还提供，当干扰素通过局部给药施用至受试者时，干扰素的施用可以为每天或每隔一天，或每 2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20 或 21 天，或每个月，或每 2 或 3 或 4 或 5 或 6 或 7 或 8 或 9 或 10 或 11 或 12 个月或更长时间。

[0062] 本发明还提供如上述的方法，其中干扰素给药可以通过喷雾进行，且每次喷雾给药的喷雾可以为约 6 微克至约 100 微克，任选地，为约 10 微克至约 80 微克，更任选地，约 20 微克至约 60 微克，还更任选地，约 30 微克至约 40 微克的量，且浓度为约 0.01mg/ml 至约 5mg/ml，任选地，为约 0.03mg/ml 至约 2mg/ml，更任选地，约 0.05mg/ml 至约 1mg/ml，还更任选地，为约 0.1 至 0.5mg/ml。

[0063] 本发明还提供如任何上述的方法，其中干扰素可以通过每天喷雾 1 ～ 10 次，任选地，每天 2 ～ 9 次，更任选地，每天 3 ～ 8 次，还更任选地，每天 4 ～ 7 次，进一步更任选地，每天 5 ～ 6 次来给药。

[0064] 本发明也提供如任何上述的方法，其中用于局部给药的干扰素可以配制成如下的至少一种 :水溶液（例如用于喷雾）、膜渗透或扩散药物递送系统、控释药物递送系统、封闭药物递送系统、贴剂例如透皮贴剂、或注射在皮肤下的包含干扰素以产生缓释效果的储库型制剂。

[0065] 本发明也提供如任何上述的方法，其中通过全身给药的干扰素给药在干扰素的经皮给药之前、大约同时和 / 或之后进行。全身给药包括皮下给药和肌肉给药。任选地，全身给药包括皮下注射和肌肉注射。

[0066] 本发明还提供如任何上述的方法，其中当通过全身给药而施用时，干扰素可以以每次注射约 2 微克至约 70 微克，任选地，约 4 微克至约 50 微克，更任选地，约 9 微克至约 30 微克，还更任选地，约 15 微克至约 24 微克，进一步更任选地，约 18 微克至约 21 微克的量施用。

[0067] 本发明还提供如任何上述的方法，当通过全身给药施用干扰素时，每 1 ～ 8 天给药至少一次，任选地，每 2 ～ 7 天给药至少一次，更任选地，每 3 ～ 6 天给药至少一次，还更任选地，每 4 ～ 5 天给药至少一次。更任选地，干扰素可以每 1 ～ 2 天进行给药。

[0068] 本发明还提供如任何上述的方法，其中，干扰素全身给药的持续时间为至少 1 天、2 天、3 天、4 天、5 天、6 天、7 天、8 天、9 天、10 天、1 周、2 周、3 周、4 周、1 个月、2 个月、3 个月、4 个月、5 个月、6 个月、7 个月、8 个月、9 个月、10 个月、11 个月、1 年、2 年、3 年、4 年、5 年和 6 年。

[0069] 本发明也提供如任何上述方法的方法，其中干扰素给药的持续时间为 1 天至 6 年的时间段，任选地，为 1 周至 4 年，更任选地，为 2 周至 3 年，还更任选地，为 1 个月至 1 年，进一步更任选低，为 2 个月至 9 个月，或更长时间，或贯穿受试者的剩余寿命。

[0070] 本发明也提供如任何上述方法的方法，其中干扰素通过皮下注射或肌肉注射至少

2 次，任选地，为至少 4 次，更任选地，为至少 6 次，还更任选地，为至少 8 次，进一步更任选地，为至少 10 次来施用。

[0071] 本发明还提供如任何上述全身给药或注射方法的方法，其中干扰素以约 2 微克至约 15 微克，任选地，约 3 微克至约 10 微克，更任选地，约 4.5 微克至约 9.5 微克，还更任选地，约 4 微克至约 9 微克，进一步更任选地，约 4.5 微克或 9 微克的至少一次初始诱导剂量进行给药。

[0072] 本发明也提供任何上述全身给药或注射方法的方法，其中，干扰素还以每次约 10 微克至约 70 微克，任选地，每次约 12 微克至约 50 微克，更任选地，每次约 15 微克至约 30 微克的至少一次随后治疗剂量进行给药。

[0073] 本发明还提供任何上述全身给药或注射方法的方法，其中干扰素的诱导剂量和治疗剂量之间的时间间隔为约 1 天至约 1 个月，任选地或优选地为约 1 天至约 3 周，包括约 1 天至约 3 天，或为 1 天、2 天、3 天、4 天、5 天、6 天、7 天、8 天、9 天、10 天、1 周、2 周和 3 周。

[0074] 本发明也提供如任何上述全身给药或注射方法的方法，其中以约每天一次或约每 2、3、4、5、6、7、8、9 或 10 天一次，任选地，约每 1 ～ 7 天一次，更任选地，约每 1 ～ 2 天一次的频率向受试者施用诱导剂量的干扰素。

[0075] 本发明也提供如任何上述全身给药或注射方法的方法，其中以约每天一次或约每 2、3、4、5、6、7、8、9 或 10 天一次，任选地，约每 1 ～ 7 天一次，更任选地，约每 1 ～ 2 天一次的频率向受试者施用治疗剂量的干扰素。

[0076] 本发明也提供如任何上述全身给药或注射方法的方法，其中诱导剂量和治疗剂量的给药的持续时间为至少 1 周、2 周、3 周、1 个月、2 个月、3 个月、4 个月、5 个月、6 个月、7 个月、8 个月、9 个月、10 个月、11 个月、1 年、2 年、3 年、4 年、5 年或 6 年，或任选贯穿受试者的剩余寿命。

[0077] 本发明还提供如任何上述吸入给药方法的方法，其中吸入给药包括经肺吸入和经鼻吸入中的至少一种。

[0078] 本发明还提供如任何上述吸入给药方法的方法，其中用于吸入给药的干扰素包括干粉干扰素和雾化干扰素中的至少一种。

[0079] 本发明还提供如任何上述吸入给药方法的方法，其中干扰素在一次吸入给药中以约 100 微克至约 2000 微克，任选地，约 120 微克至约 1500 微克，更任选地，约 150 微克至约 1200 微克，更任选地，约 200 微克至约 900 微克，更任选地，约 450 微克至约 750 微克，还更任选地，约 500 微克至约 650 微克，进一步更任选地，600 微克的量施用。

[0080] 本发明也提供如任何上述吸入给药方法的方法，其中以约每 1 或 2 或 3 天（任选为每天）一次地通过吸入给药施用干扰素。

[0081] 本发明也提供如任何上述吸入给药方法的方法，其中吸入给药的持续时间为约 1 天至约 6 年，任选为约 1 周至约 4 年，更任选为约 2 周至约 3 年，更任选为约 3 周至约 2 年，还更任选为约 1 个月至约 1 年，或进一步更任选为约 2 个月至约 9 个月。

[0082] 本发明也提供如任何上述吸入给药方法的方法，其中吸入给药的持续时间为至少 1 天、2 天、3 天、4 天、5 天、6 天、7 天、8 天、9 天、10 天、1 周、2 周、3 周、1 个月、2 个月、3 个月、4 个月、5 个月、6 个月、7 个月、8 个月、9 个月、10 个月、11 个月、1 年、2 年、3 年、4 年、5 年或 6 年、或任选为长期，例如贯穿受试者的剩余寿命。

[0083] 本发明还提供如任何上述方法的方法，其中干扰素作为单一疗法而给药。

[0084] 本发明也提供如任何上述方法的方法，还包括向受试者施用至少一种其他抗癌疗法。

[0085] 本发明也提供如任何上述方法的方法，其中至少一种其他抗癌疗法在干扰素给药之前、同时或大约同时和 / 或之后施用给受试者。

[0086] 本发明也提供如任何上述方法的方法，其中至少一种其他抗癌疗法包括如下的至少一种 :化学治疗、放射治疗、手术治疗、介入治疗、生物治疗、靶向治疗和中药治疗。

[0087] 本发明还提供如任何上述方法的方法，其中生物治疗包括基因治疗和免疫治疗中的至少一种，且手术治疗包括消融治疗。

[0088] 本发明也提供如任何上述方法的方法，其中治疗达到如下的至少一种目的 :与治疗前相比，消除至少一个癌症病灶、减小至少一个癌症病灶的尺寸以及至少一个癌症病灶的无进展生长。

[0089] 本发明还提供如任何上述方法的方法，其中至少一种抗癌疗法是非手术治疗。

[0090] 本发明还提供用于施用包含抗癌活性和SEQ ID NO :1 的氨基酸序列的干扰素的喷雾剂，其中干扰素配制成施用至少 1 ～ 12 次，任选地，2 ～ 10 次，更任选地，3 ～ 8 次，还更任选地，4 或 5 或 6 次的量。

[0091] 本发明提供如上述喷雾剂的喷雾剂，其中干扰素的量包括至少约 0.01mg/ml 至约 5mg/ml，任选地，约 0.03mg/ml 至约 2mg/ml，更任选地，为约 0.05mg/ml 至约 1mg/ml，还更任选地，约 0.1mg/ml 至约 0.5mg/ml 的浓度。

[0092] 在一些实施方式中，在任何上述喷雾剂中的干扰素的量可以包括约 0.1mg/ml、约 0.2mg/ml、约 0.3mg/ml、约 0.4mg/ml 或约 0.5mg/ml 的干扰素。

[0093] 本发明也提供如任何上述喷雾剂的喷雾剂，其中喷雾剂是含有一天的干扰素供应量的单次使用喷雾剂。

[0094] 本发明还提供如任何上述喷雾剂的喷雾剂，其中喷雾剂是含有至少一周干扰素供应量的多次使用喷雾剂。

[0095] 本发明提供用于向受试者施用复合干扰素 α 的喷雾剂，其中干扰素包含抗癌活性和 SEQ IDNO :1 的氨基酸序列，并配制为 300 微克 /ml 的浓度。

[0096] 本发明还提供如上所述的喷雾剂，其中干扰素配制在体积 2ml 的水溶液中。

[0097] 本发明也提供如任何上述喷雾剂的喷雾剂，其中干扰素由含有 SEQ ID NO :2 的序列的多核苷酸所编码。

[0098] 本发明还提供包含单次使用量的干扰素的干扰素定剂 (measured or metered dose)，其中干扰素包含抗癌活性和 SEQ ID NO :1 的氨基酸序列。

[0099] 本发明也提供如上述定剂的定剂，其中定剂包含约 100 微克至约 2000 微克的量的干扰素，任选地为约 120 微克至约 1500 微克，还任选地或优选地为约 150 微克至约 1200 微克，更任选地或更优选地为约 200 微克至约 900 微克，更任选地或更优选地为约 450 微克至约 750 微克，更任选地或更优选地为约 500 微克至约 650 微克，更任选地或优选地为 600 微克干扰素。

[0100] 本发明提供如任何上述定剂的定剂，还包含足以用于至少一周治疗的额外量的干扰素。

[0101] 本发明提供如任何上述定剂的定剂，其中定剂配制为用于吸入。

[0102] 本发明提供如上所述用于吸入的定剂，其中定剂配制成经鼻吸入或经肺吸入。

[0103] 本发明提供如任何上述定剂的定剂，其中干扰素被雾化。

[0104] 本发明还提供包含干扰素的透皮贴剂，其中干扰素包含抗癌活性和 SEQ ID NO :1 的氨基酸序列，其中贴剂使得干扰素可以扩散或渗透至受试者的皮肤。

[0105] 本发明也提供如任何上述喷雾剂的喷雾剂，其中喷雾剂包含至少两周供应量的干扰素。

[0106] 本发明也提供如任何上述喷雾剂的喷雾剂，其中喷雾剂被设置并配制成将干扰素递送至鼻子。

[0107] 本发明也提供如任何上述喷雾剂的喷雾剂，其中喷雾剂被设置并配制成将干扰素递送至受试者的皮肤或骨或粘膜中的至少一种之中或之上。

[0108] 本发明还提供如任何上述喷雾剂的喷雾剂，其中喷雾剂被设置或配制成用于通过递送用吸入（例如吸入器）将干扰素递送至受试者的肺。

[0109] 本发明也提供用于吸入的包含抗癌活性的复合干扰素 α 的定剂，其中定剂包含约 100 微克至约 2000 微克，任选地，约 200 微克至约 1000 微克，更任选地，约 300 微克至约 900 微克，更任选地，约 400 微克至约 800 微克，还更任选地，约 500 微克至约 700 微克，进一步更任选地，约 600 微克的量的干扰素。

[0110] 本发明提供如任何上述实施方式的定剂，其中定剂配制为用于鼻内应用。

[0111] 本发明还提供制备药物的方法，其中药物包含复合干扰素 α，该复合干扰素 α 含有抗癌活性，以施用给患有骨中的癌症的受试者，其中干扰素配制在至少两个分开的制剂中，一个用于注射且一个用于经皮应用至受试者的皮肤或骨之中或之上。

[0112] 本发明还提供制备如上述实施方式的药物的方法，其中干扰素还配制在第三制剂中用于吸入给药。

[0113] 本发明还提供具有 SEQ ID NO :1 的氨基酸序列和抗癌活性的复合干扰素 α 在制备用于在受试者中治疗骨癌、皮肤癌、皮下癌、粘膜癌和 / 或粘膜下癌的药物中的用途。

[0114] 本发明还提供具有 SEQ ID NO :1 的氨基酸序列和抗癌活性的复合干扰素 α 在制备用于在受试者中治疗与癌症包括骨癌相关的疼痛的药物中的用途。

[0115] 本发明也提供用于在受试者中治疗骨癌、皮肤癌、皮下癌、粘膜癌和 / 或粘膜下癌的药物组合物，其中所述组合物包含具有 SEQ ID NO :1 氨基酸序列和抗癌活性的复合干扰素 α。

[0116] 本发明还提供用于在受试者中治疗与癌症例如骨癌相关的疼痛的药物。该组合物包含具有 SEQ ID NO :1 氨基酸序列和抗癌活性的复合干扰素 α。

[0117] 发明详述

[0118] 在本申请中使用的术语意在具有被本领域技术人员所理解的普通含义，除非另外具体指出。此外，以下术语具有在本文中指明的额外含义。

[0119] 在本文中使用的术语“抗癌活性”包括任何阻止或推迟癌细胞生长或癌症进展的活性，包括引起癌细胞的凋亡或坏死、使它们的生长进程或细胞周期停止、或引起肿瘤缩小或肿瘤消失。

[0120] 在本文中使用的术语“生物治疗”包括任何和所有用于或者能够用于治疗癌

症或癌症治疗的副作用的生物制剂(biologics),包括但不限于:抗体、重组蛋白、微RNA(microRNA)、siRNA、基因治疗、病毒治疗和细胞治疗。恩度(Endostar)以及例如利妥昔(Rituxin)、赫赛汀(Herceptin)、阿瓦斯丁(Avastin)的抗体是可以在此处使用的具有抗癌效果的药物实例。NK细胞治疗是可在此处使用的细胞治疗的实例。

[0121] 本文中使用的术语“骨痛”或“与癌症相关的疼痛”包括由与癌症包括骨中的癌症相关的受试者意识到的疼痛感。

[0122] 本文中使用的术语“癌症”包括原发性癌症以及从源自另一组织或器官的原发性肿瘤转移而来的继发性癌症。

[0123] 本文中使用的术语“受癌症侵袭的骨”是指含有癌细胞的骨或骨骼区域。

[0124] 本文中使用的术语“骨中的癌症”是指在受试者的一处或多处骨中存在癌细胞。这些癌细胞可以是由原发性骨癌或继发性骨癌(即,从原发性肿瘤比如起源于身体另一组织或器官的原发性肿瘤转移的癌)引起。

[0125] 本文中使用的术语“包含”或“包括”(comprises、comprising)是指具有、包含、包括和/或是,并不应被解读为局限于指定元素,而是可以包括非指定的元素。

[0126] 本文中使用的术语“复合干扰素α”是指具有在美国专利第7,364,724号、美国专利第7,585,647号、美国专利第8,114,395号和美国专利第8,287,852号中描述的干扰素的氨基酸序列的多肽。氨基酸序列示为SEQ ID NO:1。氨基酸序列可以由具有SEQ ID NO:2的序列的多核苷酸编码。在一个方面,干扰素(例如由重组技术制得的干扰素)的氨基酸序列、以及编码这些干扰素的核苷酸序列(连同终止密码子)在以下分别示为SEQ ID NO:1和SEQ ID NO:2。这些序列也参见美国专利第7,585,647号、第7,364,724号、第8,114,395号和第8,287,852号:

[0127]

M C D L P Q T H S L G N R R A L I L L A

1 ATGTGCGACC TGCCGCAGAC CCACTCCCTG GGTAACCGTC GTGCTCTGAT CCTGCTGGCT

TACACGCTGG ACGGCGTCTG GGTGAGGGAC CCATTGGCAG CACGAGACTA GGACGACCGA

Q M R R I S P F S C L K D R H D F G F P

61 CAGATGCGTC GTATCTCCCC GTTCTCCTGC CTGAAAGACC GTCACGACTT CGGTTTCCCG

GTCTACGCAG CATAGAGGGG CAAGAGGACG GACTTTCTGG CAGTGCTGAA GCCAAAGGGC

Q E E F D G N Q F Q K A Q A I S V L H E

121 CAGGAAGAAT TCGACGGTAA CCAGTTCCAG AAAGCTCAGG CTATCTCCGT TCTGCACGAA

[0128]

GTCCTTCTTA AGCTGCCATT GGTCAAGGTC TTTCGAGTCC GATAGAGGCA AGACGTGCTT

M I Q Q T F N L F S T K D S S A A W D E

181 ATGATCCAGC AGACCTTCAA CCTGTTCTCC ACCAAAGACT CCTCCGCTGC TTGGGACGAA

TACTAGGTCG TCTGGAAGTT GGACAAGAGG TGGTTTCTGA GGAGGCGACG AACCCTGCTT

S L L E K F Y T E L Y Q Q L N D L E A C

241 TCCCTGCTGG AAAAATTCTA CACCGAACTG TACCAGCAGC TGAACGACCT GGAAGCTTGC

AGGGACGACC TTTTTAAGAT GTGGCTTGAC ATGGTCGTCG ACTTGCTGGA CCTTCGAACG

V I Q E V G V E E T P L M N V D S I L A

301 GTTATCCAGG AAGTTGGTGT TGAAGAAACC CCGCTGATGA ACGTTGACTC CATCCTGGCT

CAATAGGTCC TTCAACCACA ACTTCTTTGG GGCGACTACT TGCAACTGAG GTAGGACCGA

V K K Y F Q R I T L Y L T E K K Y S P C

361 GTTAAAAAAT ACTTCCAGCG TATCACCCTG TACCTGACCG AAAAAAAATA CTCCCCGTGC

CAATTTTTTA TGAAGGTCGC ATAGTGGGAC ATGGACTGGC TTTTTTTTAT GAGGGGCACG

A W E V V R A E I M R S F S L S T N L Q

421 GCTTGGGAAG TTGTTCGTGC TGAAATCATG CGTTCCTTCT CCCTGTCCAC CAACCTGCAG

CGAACCCTTC AACAAGCACG ACTTTAGTAC GCAAGGAAGA GGGACAGGTG GTTGGACGTC

E R L R R K E （SEQ ID NO:1）

481 GAACGTCTGC GTCGTAAAGA ATAA （SEQ ID NO:2）

CTTGCAGACG CAGCATTTCT TATT （SEQ ID NO:3）

[0129] 本文中使用的术语“有效量”是指能够产生所期望的、有益的或治疗效果的量。

[0130] 本文中使用的术语“与骨邻近”是指与骨紧密接触，包括但不限于覆盖凸出物(protrusions)例如锁骨、肋骨、关节等的皮肤、或包围骨（例如受癌症侵袭的骨）的粘膜。

[0131] 本文中使用的术语“吸入”包括经鼻吸气的吸入，例如通过鼻内给药，或者经肺吸气，例如通过经肺给药经由喉或鼻咽吸入。

[0132] 本文中使用的术语“注射”是指通过在皮肤上穿刺而进行的物质例如药物（例如本文的干扰素）的递送，并且包括注射到组织或器官或体腔的一个或多个中，例如注射到

肌肉（肌肉注射）、腹腔（腹膜内注射）、血管（静脉注射）、肿瘤（瘤内注射）、皮下（皮下注射），或注射到淋巴结或胸腔等中。

[0133] 本文中使用的有关于干扰素的术语“局部给药”是指将干扰素施用或应用到身体的特定区域。局部给药可以施用至组织区域，组织为例如皮肤、骨、鼻腔、喉或鼻咽、肺（当在手术中暴露时），或施用至器官区域（当在手术中暴露时）。局部给药可以是表面(topical)或经皮给药，例如应用到皮肤表面或之上，或者经粘膜给药，例如应用在粘膜（例如口腔）表面或之上。局部给药可以包括药物储库型制剂的沉积，以在皮肤下进行缓释或控释。

[0134] 术语“药学上可接受的载体或赋形剂”是指常规由管理机构批准的用于配制对人类受试者给药的药物的任何和所有干燥或水性成分。各个这些载体或赋形剂自身可以不具有任何治疗价值，但是可以用作辅剂，以增强待施用的干扰素的治疗价值。

[0135] 本文使用的术语“喷雾剂”是指通过喷雾递送药物的装置，例如通过将干扰素喷雾到受试者的鼻或喉以用于吸入给药，或者通过将药物喷雾到受试者的皮肤或骨或粘膜之上以用于局部给药、经皮给药或经粘膜给药。本文的喷雾剂可以递送干扰素的水溶液、或冻干形式的干扰素。喷雾剂中的制剂可以是雾化的或非雾化的。

[0136] 本文中使用的术语“全身给药”是指意在全身循环的药物施用形式。全身给药包括注射到血管中，注射到淋巴系统中，皮下注射、肌肉注射、腹膜注射或注射到体腔中。

[0137] 术语“治疗”将包括，疾病或病症或其副作用的症状改善或减轻、或疾病进程的停止，如引起完全的缓解、部分缓解和使疾病稳定。在一些实例中，治疗包括防止复发或延长无瘤存活期。

[0138] 本文中使用的单数包括复数，反之亦然，除非上下文中另外指明。而且，本文中的数值范围包括各个范围的具体开始数字和具体结尾数位以及任何在该范围之间的数字，就如同这之间的各个数字均被具体指明一样。

[0139] 下面更具体地描述本发明。然而，这些实施方式并不意在限制权利要求的范围，而是用来向本领域普通技术人员解释本发明。本文中引用的所有参考文献、专利和其他印刷档并入本文以作参考。

[0140] 本发明人已经发现，癌症例如骨癌、皮肤癌、皮下癌、粘膜癌和 / 或粘膜下癌，以及源自骨中的癌症的骨痛可以通过施用包含抗癌活性和SEQ ID NO :1的氨基酸序列的复合干扰素 α 得以治疗，并使疼痛得到缓解。

[0141] 在一些实施方式中，复合干扰素 α 由SEQ ID NO :2的多核苷酸序列编码。在一些实施方式中，干扰素包括高效复合干扰素SIFN（也称为重组高效复合干扰素 (rSIFN-co)），如在美国专利第7,364,724号、美国专利第7,585,647号、美国专利第8,114,395号和美国专利第8,287,852号中制备并记载的。

[0142] 在一些实施方式中，本发明的干扰素具有SEQ ID NO :1的氨基酸序列。在一些实施方式中，本发明的干扰素由SEQ ID NO :2的核苷酸序列编码。在一些实施方式中，本发明的干扰素具有SEQ 1D NO :1的氨基酸序列，并由SEQ ID NO :2的核苷酸序列编码。此外，所述干扰素包含SEQ ID NO :1的氨基酸序列，并由SEQ ID NO :2的核苷酸序列编码。

[0143] 在一些实施方式中，与具有SEQ ID NO :1的氨基酸序列而不由SEQ ID NO :2的核苷酸序列编码的干扰素例如干扰素alfacon-1（干复津，INFERGEN®）相比，本发明的干

扰素具有改变的空间构象和/或增强的生物学活性和/或不同的药物代谢动力学特性。例如，本发明的干扰素具有改变的空间构象和增强的生物学活性，改变的空间构象和不同的药物代谢动力学特性，或改变的空间构象、增强的生物学活性和不同的药物代谢动力学特性。增强的生物学活性包括：增强的抗病毒活性、增强的肿瘤细胞生长抑制或促凋亡作用、更小的副作用和/或可以以大剂量使用（例如，每个剂量＞1千万IU）。例如，增强的生物学活性可以是增强的抗病毒活性和/或增强的肿瘤细胞（例如乳腺癌细胞或宫颈癌细胞）生长抑制或促凋亡作用（参见：郑洁等，四川大学学报（医学版），2010，41(1)，29-34；陈研等，四川大学学报（医学版），2008，39(5)，715-718）。不同的药物代谢动力学特性包括：在肌肉注射给体重指数(BMI)为约18-约23范围内的受试者后，以采血时间对受试者血清中的2-5A寡聚核苷酸酶浓度作图，所得曲线的曲线下面积显著大于在同一条件下注射具有SEQ ID NO:1的氨基酸序列但不为SEQ ID NO:2的核苷酸序列编码的干扰素例如干扰素alfacon-1（干复津，INFERGEN®）所获得的曲线下面积和/或与之相比更长的半衰期。

[0144] 在一些实施方式中，本发明的干扰素具有SEQ ID NO:1的氨基酸序列，并由SEQ ID NO:2的核苷酸序列编码，其中与具有SEQ ID NO:1的氨基酸序列而不由SEQ ID NO:2的核苷酸序列编码的干扰素例如干扰素alfacon-1（干复津，INFERGEN®）相比，所述干扰素对乙型肝炎病毒的乙型肝炎表面抗原(HBsAg)和乙型肝炎e抗原(HBeAg)的表达具有增强的抑制活性。

[0145] 在一些实施方式中，本发明提供一种或多种使用上述干扰素在受试者中治疗骨癌包括原发性骨癌或继发性骨癌的方法和组合物，其中癌细胞存在于受试者的至少一个骨中或骨的一部分中。

[0146] 在一些实施方式中，本发明提供一种或多种使用上述干扰素在受试者中治疗皮肤癌或上皮癌包括原发性和/或继发性皮肤癌的方法和组合物。在一些实施方式中，所述皮肤癌或上皮癌包括宫颈癌、基底细胞癌、表皮样癌、鳞状细胞癌、外生殖器癌、和黑色素瘤，包括黑色素癌。

[0147] 在一些实施方式中，本发明提供一种或多种使用上述干扰素在受试者中治疗皮下癌包括原发性和/或继发性皮下癌的方法和组合物。在一些实施方式中，所述皮下癌包括前列腺癌和乳腺癌。

[0148] 在一些实施方式中，本发明提供一种或多种使用上述干扰素在受试者中治疗粘膜癌包括原发性和/或继发性粘膜癌的方法和组合物。在一些实施方式中，所述粘膜癌包括口癌、鼻咽癌、直肠癌、喉癌和舌癌。

[0149] 在一些实施方式中，本发明提供使用上述干扰素在受试者中治疗粘膜下癌包括原发性和/或继发性粘膜下癌的方法和组合物。

[0150] 在一些实施方式中，本发明提供通过干扰素的给药在受试者中治疗如下至少一种：骨癌（原发性或继发性）、乳腺癌、皮肤癌、鼻咽癌、口癌、外阴癌、前列腺癌、宫颈癌和黑色素瘤（包括黑色素癌）的方法和组合物。在一些实施方式中，干扰素通过经皮给药而施用至受试者。在一些实施方式中，干扰素通过经粘膜给药而施用至受试者。

[0151] 在一些实施方式中，本发明提供一种或多种使用上述干扰素在受试者中治疗疼痛的方法和组合物，疼痛为例如源于癌症存在或与癌症存在相关的疼痛，例如骨癌痛。

[0152] 在一些实施方式中，本发明提供，通过直接地或间接地在例如癌病灶上局部施用

干扰素，例如在骨中癌症的骨、皮肤癌的皮肤、皮下癌的皮下组织、粘膜癌的粘膜以及粘膜下癌的粘膜下层之中或之上施用干扰素，向受试者施用有效量的干扰素。

[0153] 这些应用可以是直接的，例如当手术中骨、皮下组织或粘膜下部分地或全部地暴露时通过灌注进行，或者是间接的，通过在覆盖或邻近骨（例如受癌症侵袭的骨）的皮肤或覆盖皮下癌的皮肤上或在包围含肿瘤粘膜下层的粘膜上施用，并使得干扰素穿过皮肤或粘膜。

[0154] 在一些实施方式中，向受试者的干扰素局部给药包括：经皮给药和/或经粘膜给药。

[0155] 对于通过经皮给药的干扰素局部给药，干扰素可以喷在皮肤上，例如覆盖受癌症侵袭组织的皮肤上。在骨癌的情况下，干扰素可以喷在覆盖或紧邻骨的皮肤部分上，例如覆盖肱骨、股骨、锁骨等的皮肤，在这些细胞中可发现肿瘤细胞，包括转移的肿瘤细胞。在一些实施方式中，干扰素可以通过经粘膜给药而局部施用，其中干扰素应用在受癌症感染的粘膜表面，例如口癌的口腔。

[0156] 在一些实施方式中，如果需要的话，用于经皮或经粘膜给药的干扰素可以配制成能够应用至皮肤或粘膜的水溶液或霜剂、或膜渗透或扩散药物递送系统、或控释药物递送系统、或封闭药物递送系统、或贴剂例如透皮贴剂、或包含用于在皮肤下注射的干扰素而产生缓释或控释效果的储库型制剂。

[0157] 在一些实施方式中，用于经皮给药或经粘膜给药的干扰素可以是溶液或混悬液的形式。所述溶液或混悬液将包含一定量的干扰素以及其他传统使用的药学可接受的试剂或赋形剂，例如水、磷酸盐缓冲盐水、EDTA、吐温 80、柠檬酸三钠、甘油、氯化钠、苯甲醇、HSA 等。这些溶液可以如例如在美国专利第 7,585,647 中所述的那般制备。

[0158] 本文中用于局部给药或用于吸入的干扰素可以配制为喷雾，例如能够喷在皮肤上或粘膜上或暴露的受癌症侵袭的组织上，或喷入鼻子以用于鼻内递送或喷入鼻咽以用于经肺递送的喷雾。

[0159] 本文的干扰素也可以配制为干燥的冻干的粉末。干粉可以用在例如经鼻咽而对鼻子或肺给药的雾化喷雾中。

[0160] 本文的干扰素还可以以含有干扰素的溶液或混悬液的透皮贴剂的形式应用，以用于快速的或缓慢的或受控的干扰素释放。本文的透皮贴剂可以使用标准技术或现有技术制备，如美国专利第 8,158,145 号、美国专利第 8,095,213 号和美国专利第 8,071,125 号等所述。该透皮贴剂可以放置在受癌症侵袭的皮肤上或覆盖受癌症侵袭的组织的皮肤上。

[0161] 在一些实施方式中，所述透皮贴剂可应用至覆盖受侵袭骨区域的皮肤并且可停留一段时间例如数个小时、一天或数天。

[0162] 本文的干扰素还可以配制成包封颗粒，不管由单一材料或复合材料制得。这些颗粒的实例是使用现有技术得到的纳米颗粒、微米颗粒、微球、脂质体等。这些颗粒可以如例如美国专利第 7,537,803 号、美国专利第 8,389,493 号和美国专利第 7,829,113 号中所述般进行制备。

[0163] 在一些实施方式中，骨中的癌症、或皮肤癌或皮下癌、或粘膜癌或粘膜下癌可以是原发性癌症或源自于从另一组织或器官发生的原发性肿瘤的转移肿瘤。

[0164] 在一些实施方式中，本文的原发性肿瘤可以是实体瘤和非实体瘤中的任一种或多

种。

[0165] 在一些实施方式中，本文的原发性肿瘤包括如下的至少一种：呼吸系统癌症、消化系统癌症、泌尿系统癌症、乳腺癌、皮肤癌、皮下癌、粘膜癌、粘膜下癌、生殖系统癌症、头颈癌、内分泌系统癌症、和神经系统癌症中。

[0166] 在一些实施方式中，消化系统癌症包括如下的至少一种：口癌、舌癌、喉癌、食道癌、胆囊癌、肝癌、胃肠道癌、和胰腺癌；生殖系统癌症包括如下的至少一种：外生殖器癌、宫颈癌、子宫内膜癌、子宫癌、卵巢癌、和前列腺癌；呼吸系统癌症包括肺癌和鼻咽癌中的至少一种；泌尿系统癌症包括肾癌和膀胱癌中的至少一种；内分泌系统癌症包括肾上腺癌和甲状腺癌中的至少一种；头颈癌包括鼻咽癌；皮肤癌包括如下的至少一种：基底细胞癌、表皮样癌、鳞状细胞癌、外生殖器癌、和恶性黑色素瘤；皮下癌包括前列腺癌和乳腺癌；粘膜癌包括涉及粘膜的癌症，例如口癌、舌癌、胃肠道癌、和结直肠癌；粘膜下癌包括骨癌；以及神经系统癌症包括如下的至少一种：神经瘤、恶性神经瘤、神经胶质瘤、和星形细胞瘤。

[0167] 在一些实施方式中，肺癌包括小细胞肺癌和非小细胞肺癌中的至少一种；胃肠道癌包括如下的至少一种：胃肠道间质细胞瘤、胃癌、结肠癌、直肠癌、和结直肠癌；胆囊癌包括胆管癌；肝癌包括肝细胞癌；肾癌包括肾细胞癌；膀胱癌包括浅表性膀胱癌；皮下癌包括前列腺癌和乳腺癌中的至少一种。

[0168] 在一些实施方式中，本文的原发性肿瘤包括如下的至少一种：癌、肉瘤、和横纹肌肉瘤。

[0169] 在一些实施方式中，本文的原发性肿瘤可以是如下的至少一种：腹部肿瘤、肌上皮癌、滑膜肉瘤、血管瘤、淋巴瘤和卡波济氏肉瘤。

[0170] 在本发明的一些实施方式中，干扰素可以同时局部地（例如经皮地和/或经粘膜地）以及全身性地施用至受试者。

[0171] 在一些实施方式中，本发明提供在受试者中治疗骨中的癌症、皮肤癌、皮下癌、粘膜癌和/或粘膜下癌的方法和组合物，包括向受试者施用有效量的含有抗癌活性的复合干扰素 α，其中干扰素同时通过全身性给药以及通过经皮给药而施用。

[0172] 在一些实施方式中，全身给药包括向受试者注射。本文的注射包括以肌肉内、肿瘤内、腹膜内、静脉内、皮下中的至少一种模式注射到胸腔中以及注射到一个或多个淋巴结中。

[0173] 在一些实施方式中，本发明提供如任何上述方法和组合物的用于治疗癌症的方法和组合物，除通过全身给药（例如通过注射以及例如通过肌肉注射）以及通过皮下给药（例如通过喷在癌症侵袭的组织上）施用干扰素外，干扰素还另外通过吸入而施用。

[0174] 在一些实施方式中，本发明提供在受试者中治疗骨中的癌症、皮肤癌、皮下癌、粘膜癌、和/或粘膜下癌的方法和组合物，包括向受试者施用有效量的含有抗癌活性的复合干扰素 α，其中干扰素同时通过吸入和通过皮下给药而施用至受癌症侵袭的组织中。

[0175] 在一些实施方式中，吸入包括经鼻或经喉/鼻咽到肺的吸入。通过经鼻吸入的给药可以用鼻内喷雾完成。通过经喉/鼻咽到肺的吸入的给药可以通过吸入器的使用而完成。这些鼻内喷雾或吸入器可以是例如雾化配方的干扰素或含有干扰素的水溶液的形式。

[0176] 在一些实施方式中，本发明提供如任何本文所述的方法和组合物，其中局部给药的干扰素包括将干扰素应用至一个或多个癌性病灶。此外，应用到癌性病灶可以通过浸润

给药、经皮给药、透皮给药、表皮给药和粘膜给药。局部给药可以通过局部干扰素喷雾而实现。

[0177] 在一些实施方式中，本发明提供如任何本文所述的方法和组合物，其中配制用于局部给药的干扰素可以配制成水溶液、干粉或霜剂中的至少一种。

[0178] 在一些实施方式中，本发明提供本文所述的方法和组合物中的任一种或多种，其中通过经皮给药的干扰素应用，联合通过全身给药的干扰素应用（例如通过注射和例如通过肌肉注射）和/或通过吸入的给药可以在同一天或在分开几天中施用。

[0179] 在一些实施方式中，通过经皮给药的干扰素应用可以在通过注射或通过吸入（如果有的话）施用干扰素之前、同时或大约同时、或之后进行。

[0180] 在一些实施方式中，本发明提供如本文所述的方法和组合物中的任一种或多种，其中干扰素应用到粘膜包括粘膜下给药。

[0181] 在一些实施方式中，局部地、经皮地或经粘膜地应用干扰素（例如通过喷雾）可以按以下进行，一天应用约 1 ～ 12 次，任选地，一天约 2 ～ 10 次，还更任选地，一天约 3 ～ 8 次，进一步更任选地，一天约 4 ～ 7 次。在一些实施方式中，局部地、经皮地或经粘膜地施用的干扰素为一天应用 4 或 5 或 6 次。

[0182] 在一些实施方式中，例如通过喷雾进行的局部地、经皮地或经粘膜地施用的干扰素，可以每天施用至少 1、2、3、4、5、6、7 或 8 或更多次。

[0183] 在一些实施方式中，本发明提供如任何本文所述的方法和组合物，其中局部施用至骨、皮肤、粘膜或粘膜下包括以约 0.01mg/ml ～约 5mg/ml，任选地，约 0.03mg/ml ～约 2mg/ml，更任选地，约 0.05mg/ml ～约 1mg/ml，还更任选地，约 0.1mg/ml ～约 0.5mg/ml 的浓度施用干扰素制剂。在一些实施方式中，用于局部给药的干扰素包括约 2 微克～约 2100 微克，任选地，约 4 微克～约 1800 微克，更任选地，约 9 微克～约 15 微克，更任选地，约 12 微克～约 1200 微克，更任选地，约 15 微克～约 1000 微克，更任选地，约 18 微克～约 900 微克，还更任选地，约 21 微克～约 750 微克，进一步更任选地，约 24 微克～约 600 微克的干扰素。

[0184] 在一些实施方式中，本发明还提供每天或每隔一天的局部干扰素给药。在一些实施方式中，用于局部给药的干扰素每 2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20 或 21 天施用。在一些实施方式中，局部给药的干扰素每个月，每 2 或 3 或 4 或 5 或 6 或 7 或 8 或 9 或 10 或 11 或 12 个月施用，或更长时间例如受试者的剩余寿命进行施用。

[0185] 在一些实施方式中，本发明提供如任何本文所述的方法和组合物，其中干扰素通过喷雾施用，喷雾中的干扰素可以为每次喷雾给药约 6 微克至约 100 微克，任选地，约 10 微克至约 80 微克，更任选地，约 20 微克至约 60 微克，还更任选地，约 30 微克至约 40 微克的量。

[0186] 在一些实施方式中，用于喷雾给药的干扰素包括约 0.01mg/ml 至约 5mg/ml，任选地，约 0.03mg/ml 至约 2mg/ml，更任选地，约 0.05mg/ml 至约 1mg/ml，还更任选地，约 0.1mg/ml 至约 0.5mg/ml 的浓度。

[0187] 在一些实施方式中，配制用于注射的干扰素可以每天或每隔一天或每几天例如每 2 天或每 3 天进行注射。在一些实施方式中，干扰素全身施用，每 1 ～ 8 天施用至少一次，任选地，每 2 ～ 7 天施用至少一次，更任选地，每 3 ～ 6 天施用至少一次，还更任选地，每 4 ～

5 天施用至少一次，进一步更任选地，每 1 ～ 2 天施用至少一次。

[0188] 在一些实施方式中，通过全身给药例如通过注射以及例如通过肌肉注射而施用的干扰素以每次注射约 2 微克至约 70 微克，任选地，约 4 微克至约 50 微克，更任选地，约 9 微克至约 30 微克，还更任选地，约 15 微克至约 24 微克，进一步更任选地，约 18 微克至约 21 微克的量施用。

[0189] 在一些实施方式中，注射的干扰素的第二剂量可以高于第一次给药的剂量。在一些实施方式中，注射的干扰素的第三剂量可以与第二剂量相同或者可以高于第二剂量。

[0190] 在一些实施方式中，对于全身给药，干扰素以至少一个初始剂量（即诱导剂量）施用，具体为约 2 微克至约 15 微克，任选地为约 3 微克至约 12 微克，更任选地为约 4 微克至约 9 微克，还更任选地为约 5 微克至约 6 微克。在一些实施方式中，诱导剂量具有约 9 微克或约 15 微克的干扰素。诱导剂量也可以用于对受试者的一次或多次随后给药。

[0191] 在一些实施方式中，对于全身给药，干扰素还以每次约 10 微克至约 50 微克的至少一次后续治疗剂量进行施用，任选地为每次约 12 微克至约 30 微克，更任选地为每次约 15 微克至约 24 微克，还更任选地为每次约 18 微克至约 21 微克。在一些实施方式中，治疗剂量具有约 15 或 18 或 21 微克的干扰素。

[0192] 在一些实施方式中，通过全身给药而施用的干扰素至少施用 1 天、2 天、3 天、4 天、5 天、6 天、7 天、8 天、9 天、10 天、1 周、2 周、3 周、4 周、1 个月、2 个月、3 个月、4 个月、5 个月、6 个月、7 个月、8 个月、9 个月、10 个月、11 个月、1 年、2 年、3 年、4 年、5 年和 6 年。

[0193] 在一些实施方式中，通过全身给药而施用的干扰素施用约 1 天至约 6 年的时间，任选地为约 1 周至约 4 年，更任选地为约 2 周至约 3 年，还更任选地为约 1 个月至约 1 年，进一步更任选地为约 2 个月至约 9 个月或更长，例如贯穿受试者的剩余寿命。

[0194] 在一些实施方式中，用于全身给药的干扰素以约每 1 ～ 7 天一次的频率以诱导剂量向受试者施用，更任选地为约每 1 ～ 2 天一次。在一些实施方式中，用于全身给药的干扰素以约每天一次的频率或每隔一天一次的频率以诱导剂量施用。任选地，用于全身给药的干扰素以诱导剂量每 2、3、4、5、6、7、8、9 或 10 天进行施用。

[0195] 在一些实施方式中，对于全身给药，干扰素以约每 1 ～ 7 天一次的频率以治疗剂量对受试者施用，更任选地，以约每 1 ～ 2 天一次的频率以治疗剂量对受试者施用。

[0196] 在一些实施方式中，对于全身给药，干扰素以约每天一次或约每 2、3、4、5、6、7、8、9 或 10 天一次的频率以治疗剂量施用给受试者。

[0197] 在一些实施方式中，干扰素通过皮下注射或肌肉注射施用至少 2 次，任选地为至少 4 次，更任选地为至少 6 次，还更任选地为至少 8 次，进一步更任选地为至少 10 次。

[0198] 在一些实施方式中，对于全身给药，干扰素的诱导剂量给药与治疗剂量给药之间的时间间隔为约 1 天至约 1 个月，任选地或优选地为约 1 天至约 1 周，更任选或更优选地为约 1 天至 3 天。在一些实施方式中，诱导剂量与治疗剂量之间的时间间隔为 1 天、2 天、3 天、4 天、5 天、6 天、7 天、8 天、9 天、10 天、1 周、2 周、3 周或 1 个月。

[0199] 在一些实施方式中，干扰素的第一剂量注射与第二剂量注射之间的时间间隔为约 1 天至 1 个月，任选地为约 2 天至约 3 周，更任选地为约 3 天至约 2 周，更任选地为约 4 天至约 10 天，更任选地为约 5 天至约 9 天，还更任选地为约 6 ～ 8 天，进一步更任选地为约 7 天。

[0200] 在一些实施方式中，诱导剂量和治疗剂量的给药持续时间为至少 1 周、2 周、3 周、1 个月、2 个月、3 个月、4 个月、5 个月、6 个月、7 个月、8 个月、9 个月、10 个月、11 个月、1 年、2 年、3 年、4 年、5 年或 6 年，或任选地为更长或贯穿受试者的剩余寿命。

[0201] 在一些实施方式中，干扰素的吸入给药包括经肺吸入和经鼻吸入中的至少一种。

[0202] 在一些实施方式中，用于吸入给药的干扰素包括干粉和雾化干扰素中的至少一种。

[0203] 在一些实施方式中，通过吸入应用的干扰素在一次吸入给药中以约 100 微克至约 2000 微克，任选地，约 120 微克至约 1500 微克，更任选地，约 150 微克至约 1200 微克，更任选地，约 200 微克至约 900 微克，还更任选地，约 450 微克至约 750 微克，进一步更任选地，约 500 微克至约 650 微克的量施用。在一些实施方式中，通过吸入应用的干扰素在一次吸入给药中以 600 微克的量施用。

[0204] 在一些实施方式中，用于吸入给药的干扰素通过吸入给药约每 1 或 2 或 3 天，任选地为每天一次地进行施用。

[0205] 在一些实施方式中，吸入给药的持续时间为约 1 天至约 6 年，任选地为约 1 周至约 4 年，更任选地为约 2 周至约 3 年，更任选为约 3 周至约 2 年，还更任选地为约 1 个月至约 1 年，或进一步更任选地为约 2 个月至约 9 个月。

[0206] 在一些实施方式中，吸入给药的持续时间为至少 1 天、2 天、3 天、4 天、5 天、6 天、7 天、8 天、9 天、10 天、1 周、2 周、3 周、1 个月、2 个月、3 个月、4 个月、5 个月、6 个月、7 个月、8 个月、9 个月、10 个月、11 个月、1 年、2 年、3 年、4 年、5 年、或 6 年，或任选地为更长时间，例如贯穿受试者的剩余寿命。

[0207] 通常而言，本文中干扰素给药的持续时间和频率可以由一个或多个主治医师或医务人员根据常规标准例如受试者对于进一步治疗的需求、受试者的健康、受试者对干扰素的耐受、不良副作用的存在等而确定。

[0208] 在一些实施方式中，干扰素给药是对受试者施用的单一抗癌疗法。在一些实施方式中，干扰素给药与至少一种其他抗癌疗法联用。

[0209] 至少一种其他抗癌疗法可以在干扰素给药之前、大约同时和 / 或之后施用给受试者。

[0210] 在一些实施方式中，至少一种其他抗癌疗法包括如下的至少一种 :化学治疗、放射治疗、手术治疗、介入治疗、生物治疗、靶向治疗和中药治疗。

[0211] 在一些实施方式中，生物治疗包括使用任何类型的生物制品用于治疗，并且包括重组蛋白、抗体、基因治疗、细胞治疗、靶向抗体的使用或其他免疫治疗。

[0212] 在一些实施方式中，手术治疗包括消融治疗。在一些实施方式中，所述至少一种抗癌治疗是非手术治疗。

[0213] 在一些实施方式中，本发明提供达到如下的至少一种目的的治疗 :与治疗前相比，消除至少一个癌症病灶、减小至少一个癌症病灶的尺寸以及至少一个癌症病灶的无进展生长。

[0214] 在一些实施方式中，本发明提供用于施用含有抗癌活性和 SEQ ID NO :1 的氨基酸序列的干扰素的喷雾剂。

[0215] 在一些实施方式中，喷雾剂中的干扰素配制成施用干扰素至少 1 ～ 12 次，任选地，

2 ～ 10 次，更任选地，3 ～ 8 次的量。在一些实施方式中，本文的喷雾剂包含用于施用干扰素至少 4 或 5 或 6 次的干扰素的量。

[0216] 在一些实施方式中，喷雾剂中的干扰素的量具有至少约 0.01mg/ml ～约 5mg/ml，任选地，约 0.03mg/ml 至约 2mg/ml，更任选地，约 0.05mg/ml 至约 1mg/ml 的浓度。在一些实施方式中，喷雾剂包含浓度约 0.1mg/ml、约 0.2mg/ml、约 0.3mg/ml、约 0.4mg/ml 或 0.5mg/ml 的干扰素。

[0217] 在一些实施方式中，喷雾剂在本文中描述，并且是含有一天的干扰素供应量的单次使用喷雾剂。在一些实施方式中，喷雾剂是多次使用喷雾剂并包含足以使用至少 2 天、或 3 天、或 4 天、或 5 天、或 1 周、或 2 周的干扰素。

[0218] 在一些实施方式中，本发明提供如任何本文所述的喷雾剂，其中配置喷雾剂且本文的干扰素配制成用于将干扰素递送至受试者鼻子。

[0219] 在一些实施方式中，配置本文的喷雾剂，其中的干扰素配制成将干扰素至少递送至受试者的皮肤或受试者的骨或粘膜之中或之上。

[0220] 在一些实施方式中，配置本文的喷雾剂，其中的干扰素配制成通过吸入而将干扰素递送至受试者的肺。

[0221] 本发明还提供含有一定量干扰素的干扰素定剂，其中干扰素包含抗癌活性和 SEQ ID NO :1 的氨基酸序列。

[0222] 定剂使得受试者可以自行施用干扰素和 / 或使得非医疗、非专业人员可以给药，例如通过患者家庭成员之一进行给药，因此，减少对医院或对医生办公室的访问次数，并削减治疗费用。本发明人对于干扰素局部给药的有效性的发现，例如通过经皮给药或经粘膜给药，例如通过喷雾到受癌症侵袭的区域，伴有或不伴有额外的干扰素全身给药，伴有或不伴有额外的干扰素吸入给药，使得这种递送和这种给药切实可行。

[0223] 在一些实施方式中，定剂以约 100 微克至约 2000 微克，任选地，约 120 微克至约 1500 微克，更任选地，约 150 微克至约 1200 微克，还更任选地，约 200 微克至约 900 微克的量包含干扰素。在一些实施方式中，定剂任选地或优选地含有约 450 微克至约 750 微克，更任选地或优选地，约 500 微克至约 650 微克的量的干扰素。在一些实施方式中，定剂在其中含有约 600 微克的量的干扰素。

[0224] 在一些实施方式中，定剂包含单次使用量的干扰素。在一些实施方式中，定剂含有足以用于 2 次治疗、3 次治疗、4 次治疗或 5 次治疗的干扰素的量。任选地，定剂含有至少一周供应量的干扰素。

[0225] 在一些实施方式中，定剂配制成用于经皮给药，例如用于局部喷雾。在一些实施方式中，定剂配制成用于吸入。在一些实施方式中，定剂配制成经鼻吸入。在一些实施方式中，干扰素配制成用于经肺吸入。

[0226] 在一些实施方式中，定剂含有冻干粉末形式的干扰素。在一些实施方式中，定剂中的干扰素是雾化的。在一些实施方式中，定剂中的干扰素包含干扰素的水性制剂、或纳米颗粒、微米颗粒或微球等形式的干扰素。

[0227] 本发明还提供含有复合干扰素 α 的透皮贴剂，复合干扰素 α 含有抗癌活性并具有 SEQ ID NO :1 的氨基酸序列。

[0228] 本发明也提供制备用于对受试者给药的药物的方法，其中药物包含具有抗癌活性

和 SEQ ID NO :1 的氨基酸序列的复合干扰素 α 。含有干扰素的药物可以用于治疗骨中的癌症、皮肤癌、皮下癌、粘膜癌和粘膜下癌，如本文所述。药物可以配制成至少 2 个分开的制剂，一个用于全身给药，例如通过注射，另一个用于局部给药，例如应用至受试者的皮肤、骨或粘膜。

[0229] 在一些实施方式中，上述药物可以配制用于吸入给药的第三制剂，例如用于肺递送的鼻喷雾或雾化形式。

[0230] 在一些实施方式中，本发明还提供含有抗癌活性和 SEQ ID NO :1 的氨基酸序列的复合干扰素 α 在制备用于在受试者中治疗骨癌、皮肤癌、皮下癌、粘膜癌和 / 或粘膜下癌的药物中的用途。在一些实施方式中，本发明提供这些干扰素在制备用于治疗疼痛例如与骨中的癌症（例如骨癌）相关或源自骨中的癌症（例如骨癌）的疼痛的药物中的用途。

[0231] 本发明还提供含有上述干扰素和至少一种药学上可接受的载体或赋形剂的药物组合物，其中组合物配制成用于局部给药、用于全身给药、和 / 或用于吸入给药，以在受试者中治疗骨癌、皮肤癌、皮下癌、粘膜癌和 / 或粘膜下癌。

[0232] 在一些实施方式中，本发明提供含有上述干扰素和至少一种药学上可接受的载体或赋形剂的药物组合物，其中组合物配制成用于治疗疼痛，例如与癌症例如骨癌相关或源自癌症例如骨癌的骨痛。

[0233] 在一些实施方式中，本文的干扰素由包括 SEQ ID NO :2 序列的多核苷酸编码。

[0234] 本文的发明还通过以下实施例来示例说明，这些实施例用于示例说明的目的，而不以任何形式构成对本发明的限制。

[0235] 实施例 1. 患有非小细胞肺癌 (NSCLC) 和多发骨转移的患者 #1 的治疗

[0236] 概要患者 #1 是 39 岁男性，诊断有 NSCLC 伴纵膈内、左侧颈部，右侧颈根部、左侧锁骨上窝多发淋巴结转移。患者 #1 也患有左侧胸腔积液以及脊柱、双侧肋骨、右侧锁骨关节、胸骨、左侧骶骨等多发骨转移。给予患者 #1 以 SIFN（或重组高效复合干扰素 (rSIFN-co)）的肌肉注射和雾化吸入以及骨转移病灶处 SIFN 的局部喷雾，并联合化疗 (GP 方案）和吉非替尼治疗。在治疗之后，消除了左肺原发病灶以及左侧锁骨上窝多发转移淋巴结和左侧胸腔积液。同时，消除或缩小了全身多处骨转移病灶。

[0237] 2011 年 10 月 12 日开始 SIFN 的治疗，每天 600 μg 雾化吸入。2011 年 12 月 12 日开始肌肉注射 SIFN，隔天 1 次，其中第 1 次 9 μg，第 2 次 15 μg，第 3 次及之后 18 μg。2012 年 3 月 12 日开始，通过在骨转移上的皮肤表面喷雾，给予骨转移（脊柱、肋骨、胸骨、骶骨等）局部喷雾，每天约 4 ～ 6 次。

[0238] 2011 年 10 月 14 日开始第 2 周期的 GP 方案（每周期 21 天），第 1 天和第 8 天，吉西他滨 1000mg/m^2，且第 1 天顺铂 75mg/m^2。2011 年 11 月开始吉非替尼给药，每天 1 次，1 次 1 片 (250mg/ 片）。

[0239] SIFN 给药前的诊断 :2011 年 9 月 21 日的胸部 CT 扫描示出左侧纵膈周边的块状高密度影 (9cm×3.5cm)，CT 值 39Hu。在该高密度影与上纵膈部分大血管、左肺门及左后胸膜之间的分界欠清晰。肺部组织可见斑片状高密度炎性渗出影。纵膈内可见肿大的淋巴结。右上肺门区可见不均匀的少量斑片状高密度影，边界清晰。左后侧可见弧形积液。诊断结论 :患者 #1 患有左侧纵膈型肺癌，伴有左侧胸腔积液及阻塞性肺炎。肺门多发斑片影，表明可能存在转移。

[0240] 2011 年 9 月 27 日用纤维支气管镜进行活检。对左上叶固有支进行活检。发现三个灰白色软质组织，大小约 0.1cm×0.1cm×0.1cm。诊断结论 :患者 #1 可能患有中 - 低分化腺癌。

[0241] 2011 年 9 月 29 日的全身 ECT 骨扫描示出，脊柱、双侧肋骨、右侧胸锁关节、胸骨、左侧骶髂关节和左侧髂骨的多发放射性浓聚灶。颅骨和四肢长骨中的放射性分布为正常。诊断结论 :全身多发放射性骨浓聚灶，表明可能发生全身骨转移。

[0242] 2011 年 9 月 30 日进行彩色多普勒超声。在左侧颈部见多发低回声结节，边界清楚，未见淋巴门。大低回声结节的大小为约 1.0cm×0.7cm。左侧锁骨上窝见一低回声结节，大小约 1.2cm×0.8cm，其边界清楚，未见淋巴门。右侧颈根部见一低回声结节，大小约 1.4cm×1.1cm，其边界清楚，未见淋巴门。右侧锁骨上窝未见异常淋巴结。诊断结论 :在左颈部、左锁骨上窝和右侧颈根部见低回声结节和异常淋巴结。

[0243] SIFN 给药之后的诊断。

[0244] 2011 年 11 月 15 日的 CT 扫描示出，左上肺见大小约 3.6cm×4.2cm 的软组织影。分散有片状密度影，边界模糊。纵膈未见肿大的淋巴结。

[0245] 2011 年 12 月 6 日进行骨扫描。在右侧胸锁骨关节、肋骨、脊椎骨和骨盆可见多处点状、团状和片状的异常放射性浓聚影。其他部位的放射性分布基本均匀和对称。诊断结论 :相比于之前的 CT 结果 (2011 年 9 月 29 日)，部分病灶范围缩小，程度减轻。

[0246] 2011 年 12 月 29 日进行 PET/CT 扫描。在左肺尖可见直径约 8mm 的结节，放射性分布轻度升高。肺的周围区域可见小片状略高密度影和纤维灶，放射性分布稍升高。在肺中可见分散的斑片状略高密度影，放射性分布未见明显异常。

[0247] 结论 :(1) 治疗后，在左肺尖的病灶 FDG 代谢未见明显增高，表明大部分肿瘤细胞已灭活 ;(2) 在全身一些部位见不匀称骨质增生，部分病灶的 FDG 代谢不均匀增高。治疗两个月后，患者肺部病灶消失，且全身骨转移缩小。

[0248] 2012 年 5 月 31 日的 PET/CT 扫描仅仅指出，脊椎的多个椎体可见骨密度改变，可见异常放射性浓聚影，而骨转移消失。

[0249] 实施例 2. 患有黑色素瘤和骨转移的患者 #2 的治疗

[0250] 患者 #2 是患有鼻部黑色素瘤 (术后复发) 并伴有双侧髋关节、双侧股骨、双侧肱骨、肋骨和双侧肩关节骨转移的 43 岁女性。施行 SIFN 的肌肉注射以及对病灶的 SIFN 局部喷雾 (在骨转移部位的皮肤表面)。经治疗后，病灶消失，包括涉及双侧肩关节、腋窝多发肿大淋巴结、右侧鼻窦及鼻腔肿瘤术后残腔内的复发转移病灶的那些。双侧髋关节以及股骨上段的多发异常信号消失。

[0251] SIFN 给药之前的治疗方案。

[0252] 在 2011 年 10 月 30 日和 11 月 30 日进行两个周期的恩度和替莫唑胺给药。在第 1 ～ 10 天每天口腔施用恩度 15mg，第 1 ～ 5 天每天口腔施用替莫唑胺 200mg。

[0253] 2011 年 11 月 2 日开始靶向放射治疗 (50Gy/25f)，靶标区域包括右侧上颌窦和左侧 1/4 上颌窦、双侧筛窦、双侧额窦、右侧眼球球旁组织。放射治疗结束于 2011 年 12 月 7 日。

[0254] SIFN 的给药。

[0255] 2011 年 12 月 21 日开始 SIFN 治疗。隔天进行 SIFN 的肌肉注射 (第 1 次 9μg，第

2 次 15 μg，第 3 次及以后 18 μg)，同时给予右肩部皮肤表面局部喷雾，每天 4 ～ 5 次。2012 年 2 月 27 日开始，给予左肩及其他骨转移区域的皮肤表面喷雾，每天 4 ～ 5 次。

[0256] SIFN 给药之前的诊断。

[0257] 2011 年 8 月 23 日，使用内窥镜提供对右侧鼻窦的手术，切除鼻腔中新生物。术后活检示出 :在中鼻道息肉样物和右上颌窦内新生物中均发现肿瘤。通过免疫组织化学诊断出恶性黑色素瘤 :HMB45(部分 +)，MART1(-)，S100(-)，CD63(+)，NSE(-)，PCK(-)，EMA(+)，CD56(-)，K1671(25％)。2011 年 10 月 8 日再次进行右上颌骨的次全切除术以及鼻腔和鼻副窦的肿瘤切除术。

[0258] 2011 年 12 月 8 日进行鼻副窦的 MRI。1. 与 2011 年 10 月 26 日拍摄的图像相比，残腔周围的软组织增厚，明显强化，表明可能复发。2. 颈部多枚淋巴结肿大。3. 左侧下鼻甲肥大，左侧上颌窦、蝶窦和筛窦见炎症。4. 右侧发现中耳乳突炎。

[0259] 2011 年 12 月 8 日的髋关节 MRI 扫描示出，左侧髋臼可见长 T1 和长 T2 信号的病灶，并延伸到左侧坐骨。脂肪抑制序列呈高信号，并发现明显强化。双侧髂骨下部及右髋臼前柱均见显著增强的结节样长 T1 长 T2 病灶。结论 :在双侧髋关节的骨质内多发异常信号，可能发生骨转移。

[0260] 2011 年 12 月 8 日的肩关节 MRI 示出，在双侧锁骨肩峰端、右肩胛盂下骨质、双侧肩胛骨周边、双侧肱骨上段和双侧多根肋骨发现长 T1 长 T2 信号的片状影、不均匀强化和模糊边界。双侧腋窝见多个淋巴结，且部分肿大。结论 :考虑到医学史，以上说明表明双侧肩关节和腋窝多发转移。

[0261] 2012 年 12 月 12 日的骨影像示出，全身骨骼显示清晰，在鼻咽区、上颌窦区、T8 椎体和左侧髋臼下区见片状放射性增浓影。诊断结论 :发现多处骨代谢增高病灶，表明可能发生骨转移。

[0262] SIFN 给药之后的诊断

[0263] 2012 年 5 月 2 日的肩关节 MRI 扫描示出，在左肩未见明显骨质破坏。在肱骨头中见点状的长 T2 长 T1 信号影，可能是小囊性灶。

[0264] 2012 年 5 月 2 日骨盆 MRI 示出左侧耻骨上支的长 T1 长 T2 信号影，明显强化。骨盆其余部分未见明显异常。

[0265] 2012 年 5 月 2 日的头部 MRI 示出，(1) 颅内无异常 ;(2) 双侧中耳乳突炎 ;(3) 右侧中、下鼻甲和右上颌窦内壁缺失，引起由窦腔与鼻腔形成的腔 ;(4) 左上颌窦炎 ;(5) 蝶窦炎和额窦炎。

[0266] 2012 年 6 月 26 日的腰椎、头部和肩关节 MRI 示出，1) 在腰椎 2 后上发现脂肪沉积，其余椎体骨质和椎间盘为正常 ;2) 颅内脑组织为正常 ;3) 右侧鼻腔鼻甲和右侧上颌窦内侧壁的缺失如上 ;4) 发现双侧筛窦、蝶窦炎症和双侧乳突炎 ;5) 双侧颈部未见淋巴结肿大或强化 ;6) 双侧肩关节股骨头为正常。在治疗后，病灶消失，包括涉及双侧肩关节、腋窝多发肿大淋巴结、右侧鼻窦和鼻腔肿瘤术后残腔内复发和转移的那些。双侧髋关节和股骨上段骨的多发异常信号也消失。

[0267] 实施例 3. 患有小细胞肺癌 (SCLC) 和多处转移的患者 #3 的治疗

[0268] 患者 #3 是 47 岁女性。其诊断有右肺小细胞肺癌，伴有肝、纵膈淋巴结、左肱骨、左锁骨头、椎体、右股骨和骨盆等多处转移。施行 SIFN 的肌肉注射和雾化吸入以及 SIFN 对病

灶的局部喷雾（骨转移部位皮肤表面），并联合化学治疗。经治疗后，肺部原发病灶和肝脏转移明显缩小。同时，消除部分骨转移，如在左肱骨、左锁骨头、C2 椎体和 T9 左侧横突的骨转移。

[0269] SIFN 给药之前的方案。

[0270] 2012 年 5 月 7 日开始第一个周期的化学治疗 (CE 方案)，各个循环持续 28 天，其中第一天施用卡铂 (CBP)300mg/m^2，在第 3 ～ 7 天施用依托泊甙 (VP-16)100mg/m^2。至 2012 年 12 月，完成 6 个循环。

[0271] SIFN 的给药。

[0272] 2012 年 5 月 28 日开始用 SIFN 治疗。SIFN 的肌肉注射隔天施用 1 次，第 1 次 9μg，第 2 次 15μg，第 3 次及以后为 18μg。同时，施行喷雾吸入，每天 1 次，1 次 600μg。从 2012 年 9 月 20 日开始，同时给予左肱骨、左锁骨头、C2 椎体、T9 左侧横突和骨盆的皮肤表面以 SIFN 局部喷雾，每天 4 ～ 5 次。至 2012 年 12 月，因联合化学治疗施行 SIFN 治疗，骨髓抑制变得明显。因此，间断性地提供 SIFN 的肌肉注射和雾化吸入，但是 SIFN 的局部喷雾再持续 3 个月。

[0273] SIFN 给药之前的诊断。

[0274] 2012 年 5 月 4 日的胸部 CT 扫描示出，右肺上叶不张，表明占位病灶的可能性。肝右叶见团块灶，最大横截面积为 5.1cm×6.7cm。团块的边缘模糊。

[0275] 2012 年 5 月 7 日对肿瘤标志物的测试显示出 171.40ng/ml 的 CEA、17.10ng/ml 的糖类抗原 211 以及 58.30ng/ml 的 NSE。

[0276] 2012 年 5 月 8 日的腹部 CT 扫描示出，在肝脏左右叶见多发（至少 6 处）团块和结节状占位病灶。其中最大的占位位于右前叶，大小 54mm×72mm，不均匀强化，且局部肝包膜向外膨隆。其余病灶的直径为 9mm ～ 12mm。肝周围存在少量积液。诊断结论 :肝脏多发占位团块，表明可能发生恶性肿瘤和转移。肝的周围见少量积液。

[0277] 2012 年 5 月 9 日的 PET/CT 扫描示出，多处骨骼中的 FDG 代谢异常增高，涉及左肱骨、左锁骨头、C2 椎体、T9 左侧横突、骨盆多处和右侧股骨。平均 SUV 为 3.0 ～ 9.6。CT 扫描示出在部分病灶中的骨质结构紊乱。双侧胸腔对称，气管居中。在右肺上叶观察到实变，近肺门的部分实变区域示出团块状 FDG 代谢增高影，平均 SUV 为 7.8。近胸膜的实变区域中的 FDG 代谢似乎是正常的。纵隔气管右前可见肿大淋巴结影，FDG 代谢相当高，并与实变影融合，使得平均 SUV 为 6.9。诊断结论 :1) 右肺上叶中可见实变影，近肺门的部分中的 FDG 代谢异常高，提示存在中央型肺癌伴右肺上叶的肺不张。在纵隔气管右前淋巴结发生转移。在肝和骨骼中发现多发转移 ;2) 脑内 FDG 代谢为正常。

[0278] SIFN 给药之后的诊断。

[0279] 2012 年 8 月 24 日腹部多普勒彩超扫描显示，肝脏形态规则，包膜光整。肝右叶可见约 3.5cm×2.8cm(其之前大小为 7.5cm×5.9cm) 的囊实性肿块。

[0280] 2012 年 10 月 9 日的 PET/CT 扫描示出 :1) 胸部对称，肺纹理清晰。右肺上叶后段见分叶状肿块，大小约 1.9cm×1.8cm，其中 FDG 摄取增高 SUV 最大值为 14.8。在肺的其他部分未见异常影或代谢。纵膈和右侧肺门的淋巴结肿大，伴有 FDG 摄取增高 (SUV_{max} = 5.6)。2) 肝脏具有正常形态、光整轮廓和正常比例的肝叶。肝右前叶下段可见约 1.9cm×2.7cm 低密度影（之前大小为 7.5cm×5.9cm)。外缘的 FDG 摄取增高，SUV_{max} = 3.5。3) 颈椎、胸椎

和腰椎序列齐。左侧髂骨和右侧股骨粗隆间现局限性骨质破坏，其中 FDG 摄取增高，SUV_{max} ＝ 4.5。（之前骨转移存在于左肱骨、左锁骨头、C2 椎体、T9 左侧横突、骨盆多处和右侧股骨。）在用 SIFN 治疗之后，肺部的原发病灶和肝脏转移均明显缩小。同时，左肱骨、左锁骨头、C2 椎体和 T9 左侧横突的骨转移均消除。

[0281] 实施例 4. 患有腺癌和多发骨转移的患者 #4 的治疗

[0282] 患者 #4 是 30 岁女性，诊断有左肺腺癌伴右后第 8 肋、右侧骶髂关节、左侧髂骨等多处骨转移。提供通过肌肉注射、雾化吸入和对病灶的局部喷雾的 SIFN 给药，并联合化学治疗和放疗治疗。经过治疗，肺部病灶明显缩小，PET/CT 显示 SUV 值下降。左侧耻骨病灶在干扰素的局部雾化后好转。第 5 和第 8 胸椎的骨转移消失。

[0283] SIFN 给药之前的方案。

[0284] 2011 年 6 月 28 日执行化学治疗 (GP 方案)，在第 1 和第 8 天施用健择 1.6g，并在第 1 和第 2 天施用顺铂 60mg。

[0285] 联合化学治疗和放射治疗的 SIFN 给药方案。

[0286] 2011 年 7 月 1 日开始 SIFN 治疗。SIFN 的肌肉注射隔天提供，第 1 次 15μg，第 2 次及以后 18μg。同时，每天施行喷雾吸入，每天一次，一次 600μg。从 2012 年 6 月 12 日开始，给予左侧耻骨、第 5 和第 8 胸椎和右后第 8 肋骨的皮肤表面以局部喷雾，每天 4 ～ 5 次。于 2012 年 7 月 17 日对近骶髂关节的右侧髂骨进行射波刀手术。

[0287] SIFN 给药之前的诊断。

[0288] 2011 年 5 月的身体检查结果显示出肺部阴影。2011 年 6 月 16 日的胸部 CT 扫描示出左肺下叶背段中的类圆形占位影。该占位影的大小为 31.8mm×36.8mm，轻度强化。2011 年 6 月 22 日的左肺穿刺活检示出一些异常细胞。液基细胞学显示存在腺癌细胞。2011 年 6 月 27 日的骨扫描示出右后第 8 肋、右侧骶髂关节部位和左侧髂骨的异常放射性浓聚，表明盆骨和肋骨有转移可能。

[0289] SIFN 给药之后的诊断。

[0290] 2011 年 9 月 22 日的 PET/CT 扫描示出左肺下叶的分叶状软组织密度影，大小为 3.2cm×2.5cm。FDG 摄取增高，SUV 平均值为 4.7，最大值为 5.3。2012 年 2 月 1 日的胸部 CT 扫描显示，相比于 2011 年 8 月 23 日拍摄的图像，两肺的渗出影消失。右肺上叶后段的病灶消失，左下肺背段见 21mm×15mm 的肿块。左肺下叶的病灶，与 2011 年 8 月 23 日相比，明显缩小。

[0291] 2012 年 7 月 14 日的 PET/CT 扫描示出左下肺近胸膜处的 3.3cm×2.1cm 的不规则低密度影，其中可见点状钙化灶。FDG 摄取轻微并不均匀上升，最大 SUV 值为 2.1。2012 年 9 月 14 日的骨扫描显示，与 2012 年 6 月 11 日拍摄的图像相比，右后第 8 肋、右侧骶髂关节、左侧髂骨、左侧耻骨和右侧髋骨关节的放射性浓聚影的变化不明显。然而，在 2012 年 6 月 11 日图像中示出的第 5 和第 8 胸椎的转移病灶消失。

[0292] 2012 年 9 月 21 日的骶髂关节 MR 示出，与 2011 年 6 月 27 日拍摄的图像相比，左侧耻骨的病灶有好转。右侧髂骨近骶髂关节处、右侧股骨头和股骨颈的病灶有所进展。

[0293] 至 2012 年 12 月，治疗持续 1 年多。根据 PET/CT，肺部病灶的大小明显缩小，SUV 值下降。对于骨转移，右侧髂骨近骶髂关节处的病灶在放疗治疗后病情进展。然而，左侧耻骨以及第 5 和第 8 胸椎的病灶在 3 个月 SIFN 局部喷雾之后表现出明显好转。

[0294] 实施例 5. 患有鼻咽癌的患者 #5 的治疗

[0295] 患者 #5 是 48 岁女性，在 2007 年 12 月 27 日初次诊断为低分化鼻咽鳞癌 IVa(T4N3M0)。

[0296] SIFN 给药 :2012 年 10 月 30 日开始隔天施用 SIFN,剂量为每次 15μg(皮下注射或肌肉注射)。患者没有任何手术或任何相关治疗。治疗方案包括开始于 2012 年 11 月 24 日的 SIFN 鼻咽喷雾。SIFN-co 的注射剂量从 2012 年 11 月 25 日增加到 21μg。

[0297] 患者 #5 的医学史收集于 2012 年 10 月 30 日,如下 :

[0298] 患者主诉 :4 年多前诊断为鼻咽癌,3 年多前开始放射治疗和化学治疗。肿瘤复发在 1 周多之前。

[0299] 患者病史 :患者于 2007 年发现颈部包块,在复旦大学附属金山医院检查,以进一步检查。2007 年 12 月 27 日的病理检查显示鼻咽部非角化性未分化癌,免疫组化结果示出 CK+、EMA+、LCA-、CD68-、34βE12+、CK5/6+。之后未进行其他相关检查和治疗。2009 年再次颈部包块复发,患者在 2009 年 5 月 8 日在绵阳中心医院做检查。在鼻咽部粘膜中找到少许非典型增生鳞状上皮。患者被建议再做活检。2009 年 5 月 12 日的检查示出慢性发炎,边缘部见极少可疑癌细胞。2009 年 5 月 16 日在华西医院做另一检查,显示鳞状上皮增生伴有灶性区组织凝固性坏死,鳞状上皮的轻 - 中度非典型增生,以及少许炎性渗出物。在诊断之后,患者去往绵阳肿瘤医院,并共计放射治疗 35 次,化学治疗 5 次。治疗后鼻咽部病灶和颈部包块消失,表明临床缓解。

[0300] 2012 年 3 月患者再次诉头痛不适,在之后的检查中未见明显异常。于 2012 年 6 月 11 日再次因头痛复发而进行 CT 扫描。结果显示,鼻咽部右侧壁增厚,且有可能发生局部溃疡。此时未进行治疗。2012 年 10 月 23 日的活检显示,粘膜慢性炎内见少量退变非典型细胞,表明可能是低分化鳞状细胞癌。2012 年 10 月 26 日的 CT 扫描图像示出在鼻咽顶部壁偏左侧的不规则软组织密度影。

[0301] 该患者的当前主要症状涉及右侧头痛和颌关节活动困难。她必须在家休养。该患者和其亲属自愿从 2012 年 10 月 30 日开始使用 SIFN。

[0302] SIFN 治疗过程 :2013 年 10 月 31 日,患者于 2012 年 10 月 30 日 10:00am 第一次肌肉注射 SIFN 15μg。给药一个小时后,患者出现寒战,4 小时后体温达最高 37.8℃。之后,体温下降,于给药后约 7 小时恢复正常。在给药 8 小时多后,腰部和双下肢开始酸痛,此症状于次日早晨消失。患者未诉其他不适。

[0303] 患者于 2012 年 11 月 1 日 14:00pm 第二次肌肉注射 SIFN 15μg。患者在用药后约 6 小时开始寒战。最高体温测量为 38.0℃ (具体时间未记录)。之后,体温下降,最终恢复正常,没有任何给药或其他降低体温的措施。同时,患者报告头痛,于次日早晨缓解。患者未诉其他不适。

[0304] 患者于 2012 年 11 月 6 日第四次肌肉注射 SIFN 15μg。患者在给药后约 3 小时开始出现寒战。之后,其体温开始上升,并于给药后 5 小时达到最高 (38.0℃)。未给予任何降温处理,体温在 2 小时后恢复正常。同时,患者报告有头痛、牙龈痛、耳痛和胃部不适,于次日早晨缓解。患者未诉其他不适。

[0305] 患者于在 2012 年 11 月 15 日第九次肌肉注射 SIFN 15μg。患者在给药后约 3 小时出现寒战。之后,体温在给药约 6 小时后达到 37.4℃,并开始下降。同时,患者诉头痛、牙

龈痛和耳痛，于次日早晨缓解。患者未诉其他不适。

[0306] 2012 年 10 月 26 日的血常规示出以下结果 :WBC 为 5.1×10^9/L、PLT 为 353×10^9/L、淋巴细胞比率为 28.5％、中性粒细胞比率为 59.4％以及单核细胞比率为 8.3％。2012 年 11 月 6 日的血常规示出以下结果 :WBC 为 4.1×10^9/L、PLT 为 234×10^9/L、淋巴细胞比率为 40.7％、中性粒细胞比率为 50.6％。2012 年 11 月 13 日的肝功能检查示出，ALT 为 18U/L，且 AST 为 17U/L。2012 年 11 月 19 日的 CT 扫描显示，与 2012 年 10 月 26 日的 CT 扫描相比，鼻咽部顶壁肿块稍有增大。患者诉，持续性头疼症状明显缓解，但仍有颌关节活动困难和颈部疼痛。患者未诉其他不适。基于其情况，治疗方案调整如下，具体将 SIFN 肌肉注射调整为隔日，每次 21μg，联合对鼻咽部的 SIFN 局部喷雾。

[0307] 从 2012 年 11 月 24 日开始，施行鼻咽部喷雾每天 5 ～ 6 次。在用药后约 2 ～ 3 分钟开始出现右侧牙痛，且疼痛较之前严重。疼痛持续约 2 小时，之后基本消失。2012 年 11 月 25 日开始行肌肉注射 SIFN 21μg。患者未诉寒战、发热或头痛。

[0308] 患者于 2012 年 12 月 1 日第四次肌肉注射 SIFN 21μg，并配合鼻咽部喷雾。给药后约 4 小时出现寒战，但是体温保持正常。牙痛仍存在但是较之前减轻。鼻咽部分泌物含少量血丝。无明显头痛。建议患者到医院进行血常规和肝功检查。

[0309] 患者于 2012 年 12 月 13 日第十次肌肉注射 SIFN 21μg，并配合鼻咽部喷雾。给药后患者仍有牙痛和耳痛但较之前减轻。其偶有腰部酸痛，且鼻咽部分泌物含少量血丝。患者未诉其他不适。建议患者注意鼻咽部分泌物，并防止鼻咽部脱落物堵塞呼吸道。

[0310] 2012 年 12 月 4 日的血常规示出以下结果 :WBC 为 4.4×10^9/L，PLT 为 201×10^9/L。2012 年 12 月 5 日的肝功能检查显示，ALT 为 48U/L，且 AST 为 49U/L。患者仍有牙痛，且在 7 天前出现左耳阵发性疼痛（在此之前为右耳疼痛）。鼻咽部分泌物与之前相同。患者未诉头痛。

[0311] 2013 年 1 月 23 日 :患者诉无头痛且无牙痛，并感觉能够更好地移动其颌关节。鼻咽部分泌物与之前相同。患者未诉其他不适。

[0312] 实施例 6. 透皮贴剂在黑色素癌治疗中的用途

[0313] 将每贴剂 SIFN 有效量为约 200 微克至约 600 微克的透皮贴剂施用在受试者的癌性皮肤病灶上，例如黑色素癌病灶。受试者没有癌转移。不提供其他抗癌疗法。联合透皮贴剂在癌病灶上的应用来施行 SIFN 的皮下注射和 / 或肌肉注射。具体而言，皮下注射和 / 或肌肉注射隔天提供，每剂量 15 微克至 24 微克干扰素。透皮贴剂每天换新。治疗方案持续 2 个月时期。预期肿瘤萎缩。

[0314] 实施例 7. 喷雾在舌癌治疗中的用途

[0315] 对在舌部具有突出团块的受试者施用 SIFN，该突出团块可以是中高度分化鳞状细胞癌。受试者可以在其颈部具有肿大淋巴结。不提供其他抗肿瘤疗法。简而言之，通过皮下注射和 / 或肌肉注射以及通过对突出团块喷雾而进行的局部给药，来施用 SIFN。皮下注射和 / 或肌肉注射隔天提供，每剂量为 9 微克至 24 微克的干扰素。将含有约 200 微克 /ml 至约 600 微克 /ml 的有效量的干扰素的喷雾施用至舌部病灶，每天 2 ～ 4 次。同时，可将干扰素注射至颈部淋巴结，每三天一次，每剂量约 80 微克至约 200 微克干扰素。SIFN 的给药持续约 20 天。预期舌部的团块掉落，并预期肿大淋巴结的大小缩小。

[0001]

序列表

<110> 远东超级实验室有限公司

<120> 通过干扰素的经皮和/或经粘膜给药治疗骨癌、皮肤癌、皮下癌、粘膜癌和/或粘膜下癌的方法和组合物

<130> 1662-PCT-CN

<140>
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<170> PatentIn version 3.5

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Leu Glu Ala Cys Val Ile Gln Glu Val Gly Val Glu Glu Thr Pro Leu
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Thr Leu Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val
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caggaagaat tcgacggtaa ccagttccag aaagctcagg ctatctccgt tctgcacgaa 180

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cttgcagacg cagcatttct tatt 504

摘要

本发明提供通过干扰素的经皮和/或经粘膜给药用于治疗骨癌包括原发性骨癌和继发性骨癌、乳腺癌、皮肤癌、鼻咽癌、口癌、外阴癌、前列腺癌、宫颈癌、黑色素瘤包括黑色素癌的方法和/或组合物 。此外，本发明提供了通过干扰素的经皮和/或经粘膜给药用于治疗皮肤、皮下、粘膜、和/或粘膜下原发癌及癌症转移病灶的方法和/或组合物，尤其是用于治疗骨癌疼痛包括继发性骨癌所引起疼痛的方法和/或组合物 。