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(54) **Title**: COMPOSITIONS AND METHODS FOR TREATING HEART FAILURE

(57) **Abstract**: The present invention provides methods for treating chronic heart failure patients using the medication comprising neuregulin. The methods comprise first performing a companion diagnostic test of each patient before treatment; and then providing a suitable treatment to the patient according to the results of the companion diagnostic test. When the result of the test is within a favorite treatment zone, the patient is suitable for heart failure treatment by administering an effective amount of neuregulin.

COMPOSITIONS AND METHODS FOR TREATING HEART FAILURE

1. FIELD OF THE INVENTION

[0001] The present invention relates to the use of neuregulin protein for the preparation of medication for preventing, treating or delaying heart failure in humans and methods for preventing, treating or delaying heart failure in humans using said medication. Particularly, the present invention provides methods for preventing, treating or delaying heart failure using the medication comprising a neuregulin protein in specific populations of chronic heart failure patients.

2. BACKGROUND OF THE INVENTION

[0002] Heart failure affects approximately five million Americans, and more than 550,000 new patients are diagnosed with the condition each year. Current drug therapy for heart failure is primarily directed to angiotensin-converting enzyme (ACE) inhibitors, which are vasodilators that cause blood vessels to expand, lowering blood pressure and reducing the heart's workload. While the percent reduction in mortality has been significant, the actual reduction in mortality with ACE inhibitors has averaged only 3%-4%, and there are several potential side effects. Additional limitations are associated with other options for preventing or treating heart failure. For example, heart transplantation is clearly more expensive and invasive than drug treatment, and it is further limited by the availability of donor hearts. Use of mechanical devices, such as biventricular pacemakers, are similarly invasive and expensive. Thus, there has been a need for new therapies given the deficiencies in current therapies.

[0003] One promising new therapy involves administration of neuregulin (hereinafter referred to as "NRG") to a patient suffering from or at risk of developing

heart failure. NRGs, a family of EGF-like growth factors, comprises a family of structurally related growth and differentiation factors that include NRG1, NRG2, NRG3 and NRG4 and isoforms thereof, are involed in an array of biological responses: stimulation of breast cancer cell differentiation and secretion of milk proteins; induction of neural crest cell differentiation to Schwann cells; stimulation of skeletal muscle cell synthesis of acetylcholine receptors; and, promotion of myocardial cell survival and DNA synthesis. In vivo studies of neuregulin gene-targeted homozygous mouse embryos with severe defects in ventricular trabeculae formation and dorsal root ganglia development indicate that neuregulin is essential for heart and neural development.

[0004] NRGs bind to the EGF receptor family, which comprises EGFR, ErbB2, ErbB3 and ErbB4, each of which plays an important role in multiple cellular functions, including cell growth, differentiation and survival. They are protein tyrosine kinase receptors, consisting of an extracellular ligand-binding domain, transmenbrane kinase domain and cytoplasmic tyrosine kinase domain. After NRG bind to the extracellular domain of ErbB3 or ErbB4, it induces a conformational change that leads to heterodimer formation between ErbB3, ErbB4 and ErbB2 or homodimer formation between ErbB4 itself, which results in phosphorylation of the receptor's C-terminal domain inside the cell membrane. The phosphorylated intracellular domain then binds additional signal proteins inside the cell, activating the corresponding downstream AKT or ERK signaling pathway, and inducing a series of cell reactions, such as stimulation or depression of cell proliferation, cell differentiation, cell apoptosis, cell migration or cell adhesion. Among these receptors, mainly ErbB2 and ErbB4 are expressed in the heart.

[0005] It has been shown that the EGF-like domains of NRG-1, ranging in size from 50 to 64-amino acids, are sufficient to bind to and activate these receptors. Previous studies have shown that neuregulin-1β (NRG-1β) can bind directly to ErbB3 and ErbB4 with high affinity. The orphan receptor, ErbB2, can form heterdimer with ErbB3 and ErbB4 with higher affinity than ErbB3 or ErbB4 homodimers. Research in

neural development has indicated that the formation of the sympathetic nervous system requires an intact NRG-1β, ErbB2 and ErbB3 signaling system. Targeted disruption of the NRG-1β or ErbB2 or ErbB4 led to embryonic lethality due to cardiac development defects. Recent studies also highlighted the roles of NRG-1β, ErbB2 and ErbB4 in the cardiovascular development as well as in the maintenance of adult normal heart funtion. NRG-1β has been shown to enhance sarcomere organization in adult cardiomyocytes. The administration of a recombinant NRG-1β EGF-like domain significantly improves or protects against deterioration in myocardial performance in distinct animal models of heart failure as well as in clinical trials. These results make NRG-1 promising as a lead compound for the treatment of heart failure. However, there is still a need for more evidences of whether NRG-1 treatment can provide long-term benefits to the heart failure patients and whether the benefits can be provided to all chronic heart failure patients or some subpopulations.

3. SUMMARY OF THE INVENTION

[0006] In human clinical trials of neuregulin for treating heart failure, applicant discovered that evaluating New York Heart Association (NYHA) heart function classification or measuring plasma level of NT-proBNP or BNP in patients allows the selection of heart failure patients who will receive significant treatment benefits from neuregulin. Such benefits include significant reduction in mortality rate.

[0007] It has been discovered by applicant that NRG enhances cardiac muscle cell differentiation and organization of sarcomeric and cytoskeleton structure, as well as cell adhesion. It has been also discovered by applicant that that NRG significantly improves or protects against deterioration in myocardial performance in distinct animal models of heart failure and in clinical trials. Neuregulin, neuregulin polypeptide, neuregulin derivatives, or compounds which mimic the activities of neuregulins, fall within the scope of the present invention.

[0008] Thus, in a first aspect of the invention, a pharmaceutical composition comprise an effective amount of neuregulin is provided for treating chronic heart failure patients, and the patients received significant benefits from the pharmaceutical composition. In some embodiments, the benefit is significant reduction of mortality rate. In some embodiments, the benefit is significant reduction of rehospitalization. In some embodiments, the benefits is the improvement of the biomarkers levels which indicate the improvement of chronic heart failure.

[0009] In a second aspect, the invention provides a method to improve survival or reduce mortality of chronic heart failure patients, comprising administering a pharmaceutical composition comprsing an effective amount of neuregulin to the chronic heart failure patients.

[0010] In a third aspect of the invention, a pharmaceutically effective amount of neuregulin is used for treating chronic heart failure patients whose plasma level of NT-proBNP is within a favorite treatment zone prior to neuregulin treatment. In one embodiment, the favorite treatment zone is no more than 4000 fmol/ml. In another embodiment, the favorite treatment zone is between 1600 fmol/ml and 4000 fmol/ml. In yet another embodiment, the favorite treatment zone is no more than 1600 fmol/ml. In another preferred embodiment, the plasma level is measured by immunoassay.

[0011] In a fourth aspect of the invention, a pharmaceutically effective amount of neuregulin is used for treating chronic heart failure patients who has a specific class of heart function classified by NYHA heart function classification. In some embodiments, the specific class of heart function is NYHA class III.

[0012] In a fifth aspect, the invention features a method of selecting a heart failure patient for treatment by neuregulin. This method comprises measuring the plasma level of NT-proBNP in the patient. In one embodyment, a level of no more than 4000fmol/ml is indicative of the patient being suitable for heart failure treatment by neuregulin. In another embodiment, a level of between 1600 fmol/ml and 4000

fmol/ml is indicative of the patient being suitable for heart failure treatment by neuregulin. In yet another embodiment, a level of no more than 1600 fmol/ml is indicative of the patient being suitable for heart failure treatment by neuregulin.

[0013] In a sixth aspect, the invention features a method of selecting a heart failure patient for treatment by neuregulin. This method comprises evaluating heart function class by NYHA heart function classification. In one embodiment, NYHA class II is indicative of the patient being suitable for heart failure treatment by neuregulin. In another embodiment, NYHA class III is indicative of the patient being suitable for heart failure treatment by neuregulin.

[0014] In a seventh aspect, the invention features a diagnostic kits for selecting a heart failure patient for treatment by neuregulin. In one embodiment, the diagnostic kits comprises immunoassay reagents to measure plasma level of NT-proBNP in a heart failure patient wherein a level of no more than 4000 fmol/ml is indicative of the patient being suitable for heart failure treatment by neuregulin. In another embodiment, a level of between 1600 fmol/ml and 4000 fmol/ml is indicative of the patient being suitable for heart failure treatment by neuregulin. In yet another embodiment, a level of no more than 1600 fmol/ml is indicative of the patient being suitable for heart failure treatment by neuregulin.

[0015] In a eighth aspect of the invention, the use of neuregulin protein for preparation of a medication was provided. The medication can be provided to chronic heart failure patients for long-term benefits. In one embodiment, the long-term benefit is the improvement of survival. In one embodiment, the long-term benefit is the reduction of re-hospitalization. In another embodiment, the long-term benefit is the improvement of biomarkers which indicate the long-term prognosis of chronic heart failure.

[0016] In a ninth aspect of the invention, a companion diagnostic test was provided for the treatment of chronic heart failure by neureguin protein. N-terminal pro-brain natriuretic peptide (NT-proBNP) is used as a biomarker for the companion

diagnostic test. In one embodiment, a level of no more than 4000 fmol/ml is indicative of the patient being suitable for heart failure treatment by neuregulin. In another embodiment, a level of between 1600 fmol/ml and 4000 fmol/ml is indicative of the patient being suitable for heart failure treatment by neuregulin. In yet another embodiment, a level of no more than 1600 fmol/ml is indicative of the patient being suitable for heart failure treatment by neuregulin.

[0017] In a tenth aspect of the invention, a method of treating chronic heart failure using neuregulin is provided. The method comprises an evaluation procedure before treatment and decide whether each patient is suitable to receive neuregulin treatment according to the result of the evaluation. In one embodiment, the evaluation procedure includes NYHA heart function classification of a chronic heart failure patient. In another embodiment, the evaluation procedure includes test of plasma NT-proBNP or BNP for each chronic heart failure patient.

[0018] In a eleventh aspect of the invention, a companion diagnostic kit for deciding whether a chronic heart failure patient is suitable for receiving neuregulin protein treatment is provided. The companion diagnostic kit comprises a test kit for plasma NT-proBNP or BNP and an instruction of how to use the kit and how to judge whether the subject is suitable for neuregulin protein treatment according to the test result.

4. DETAILED DESCRIPTION OF THE INVENTION

[0019] For clarity of disclosure, and not by way of limitation, the detailed description of the invention hereinafter is divided into the subsections that follow. All publications mentioned herein are incorporated by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

A. DEFINITIONS

[0020] Unless defined otherwise, all technical and scientific terms used herein

have the same meaning as is commonly understood by one of ordinary skill in the art to which this invention belongs. All patents, applications, published applications and other publications referred to herein are incorporated by reference in their entirety. If a definition set forth in this section is contrary to or otherwise inconsistent with a definition set forth in the patents, applications, published applications and other publications that are herein incorporated by reference, the definition set forth in this section prevails over the definition that is incorporated herein by reference.

[0021] As used herein, the singular forms "a", "an", and "the" mean "at least one" or "one or more" unless the context clearly dictates otherwise.

[0022] As used herein, "neuregulin" or "NRG" used in the present invention refers to proteins or peptides that can bind and activate ErbB2, ErbB3, ErbB4 or combinations thereof, including but not limited to all neuregulin isoforms, neuregulin EGF-like domain alone, polypeptides comprising neuregulin EGF-like domain, neuregulin mutants or derivatives, and any kind of neuregulin-like gene products that also activate the above receptors as described in detail below. Neuregulin also includes NRG-1, NRG-2, NRG-3 and NRG-4 proteins, peptides, fragments and compounds that mimic the activities of neuregulin. Neuregulin used in the present invention can activate the above ErbB receptors and modulate their biological reactions, e.g., stimulate acetylcholine receptor synthesis in skeletal muscle cell; and/or improve cardiocyte differentiation, survival and DNA synthesis. Neuregulin also includes those variants with conservative amino acid substitutions that do not substantially alter their biological activity. Suitable conservative substitutions of amino acids are known to those of skill in this art and may be made generally without altering the biological activity of the resulting molecule. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity (see, e.g., Watson et al.,Molecular Biology of the Gene, 4th Edition, 1987, The Bejacmin/Cummings Pub.co.,p.224). In preferred embodiments, neuregulin used in the present invention binds to and activates ErbB2/ ErbB4 or ErbB2/ ErbB3 heterodimers, for example, but

not for the purpose of restriction, peptides including the 177-237 residues of NRG-1 β2 isoform containing the amino acid sequence: SHLVKCAEKEKTFCVNGGECF MVKDLSNPSRYLCKCPNEFTGDRCQNYVMASFYKAEELYQ (SEQ ID NO:1). The peptides including the 177-237 residues of NRG-1 β2 isoform comprises the EGF-like domian, which has been proved to be sufficient to bind to and activate the receptors.

[0023] As used herein, "epidermal growth factor-like domain" or "EGF-like domain" refers to a polypeptide motif encoded by the neuregulin gene that binds to and activates ErbB2, ErbB3, ErbB4, or combinations thereof, and bears a structural similarity to the EGF receptor-binding domain as disclosed in WO 00/64400, Holmes et al., Science, 256:1205-1210 (1992); US Patent Nos.5,530,109 and 5,716,930; Hijazi et al., Int. J. Oncol., 13:1061-1067 (1998); Chang et al., Nature, 387:509-512 (1997); Carraway et al., Nature, 387:512-516 (1997); Higashiyama et al., J. Biochem., 122:675-680 (1997); and WO 97/09425, the contents of which are all incorporated herein by reference. In certain embodiments, EGF-like domain binds to and activates ErbB2/ErbB4 or ErbB2/ErbB3 heterodimers. In certain embodiments, EGF-like domain comprises the amino acid sequence of the receptor binding domain of NRG-1. In some embodiments, EGF-like domain comprises the amino acid sequence corresponding to amino acid residues 177-226, 177-237, or 177-240 of NRG-1. In certain embodiments, EGF-like domain comprises the amino acid sequence of the receptor binding domain of NRG-2. In certain embodiments, EGF-like domain comprises the amino acid sequence of the receptor binding domain of NRG-3. In certain embodiments, EGF-like domain comprises the amino acid sequence of the receptor binding domain of NRG-4. In certain embodiments, EGF-like domain comprises the amino acid sequence of Ala Glu Lys Glu Lys Thr Phe Cys Val Asn Gly Gly Glu Cys Phe Met Val Lys Asp Leu Ser Asn Pro, as described in US Patent No.5,834,229.

[0024] The formulation, dosage and route of administration of a neuregulin protein, preferably in the form of pharmaceutical compositions, can be determined

according to the methods known in the art (see e.g., Remington: The Science and Practice of Pharmacy, Alfonso R. Gennaro (Editor) Mack Publishing Company, April 1997; Therapeutic Peptides and Proteins: Formulation, Processing, and Delivery Systems, Banga, 1999; and Pharmaceutical Formulation Development of Peptides and Proteins, Hovgaard and Frkjr (Ed.), Taylor & Francis, Inc., 2000; Medical Applications of Liposomes, Lasic and Papahadjopoulos (Ed.), Elsevier Science, 1998; Textbook of Gene Therapy, Jain, Hogrefe & Huber Publishers, 1998; Adenoviruses: Basic Biology to Gene Therapy, Vol. 15, Seth, Landes Bioscience, 1999; Biopharmaceutical Drug Design and Development, Wu-Pong and Rojanasakul (Ed.), Humana Press, 1999; Therapeutic Angiogenesis: From Basic Science to the Clinic, Vol. 28, Dole et al. (Ed.), Springer-Verlag New York, 1999).

[0025] The neuregulin protein, can be formulated for oral, rectal, topical, inhalational, buccal (e.g., sublingual), parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous), transdemal administration or any other suitable route of administration. The most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular neuregulin protein, which is being used. The neuregulin proteincan be administered alone. Alternatively and preferably, the neuregulin protein, is co-administered with a pharmaceutically acceptable carrier or excipient. Any suitable pharmaceutically acceptable carrier or excipient can be used in the present method (See e.g., Remington: The Science and Practice of Pharmacy, Alfonso R. Gennaro (Editor) Mack Publishing Company, April 1997).

[0026] According to the present invention, the neuregulin protein, alone or in combination with other agents, carriers or excipients, may be formulated for any suitable administration route, such as intracavernous injection, subcutaneous injection, intravenous injection, intramuscular injection, intradermal injection, oral or topical administration. The method may employ formulations for injectable administration in unit dosage form, in ampoules or in multidose containers, with an added preservative. The formulations may take such forms as suspensions, solutions or emulsions in oily

or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, sterile pyrogen-free water or other solvents, before use. Topical administration in the present invention may employ the use of a foam, gel, cream, ointment, transdermal patch, or paste.

[0027] Pharmaceutically acceptable compositions and methods for their administration that may be employed for use in this invention include, but are not limited to those described in U.S. Patent Nos. 5,736,154; 6,197,801 B1; 5,741,511; 5,886,039; 5,941,868; 6,258,374 B1; and 5,686,102.

[0028] The magnitude of a therapeutic dose in the treatment or prevention will vary with the severity of the condition to be treated and the route of administration. The dose, and perhaps dose frequency, will also vary according to age, body weight, condition and response of the individual patient.

[0029] It should be noted that the attending physician would know how to and when to terminate, interrupt or adjust therapy to lower dosage due to toxicity, or adverse effects. Conversely, the physician would also know how to and when to adjust treatment to higher levels if the clinical response is not adequate (precluding toxic side effects).

[0030] Any suitable route of administration may be used. Dosage forms include tablets, troches, cachet, dispersions, suspensions, solutions, capsules, patches, and the like. See, Remington's Pharmaceutical Sciences. In practical use, the neuregulin protein, alone or in combination with other agents, may be combined as the active in intimate admixture with a pharmaceutical carrier or excipient, such as beta-cyclodextrin and 2-hydroxy-propyl-beta-cyclodextrin, a ccording to conventional pharmaceutical compounding techniques. The carrier may take a wide form of preparation desired for administration, topical or parenteral. In preparing compositions for parenteral dosage form, such as intravenous injection or infusion, similar pharmaceutical media may be employed, water, glycols, oils, buffers, sugar,

preservatives, liposomes, and the like known to those of skill in the art. Examples of such parenteral compositions include, but are not limited to dextrose 5% wlv, normal saline or other solutions. The total dose of the neuregulin protein, alone or in combination with other agents to be administered may be administered in a vial of intravenous fluid, ranging from about 1 ml to 2000 ml. The volume of dilution fluid will vary according to the total dose administered.

[0031] The invention also provides for kits for carrying out the therapeutic regimens of the invention. Such kits comprise in one or more containers therapeutically effective amounts of the neuregulin protein, alone or in combination with other agents, in pharmaceutically acceptable form. Preferred pharmaceutical forms would be in combination with sterile saline, dextrose solution, or buffered solution, or other pharmaceutically acceptable sterile fluid. Alternatively, the composition may be lyophilized or dessicated; in this instance, the kit optionally further comprises in a container a pharmaceutically acceptable solution, preferably sterile, to reconstitute the complex to form a solution for injection purposes. Exemplary pharmaceutically acceptable solutions are saline and dextrose solution.

[0032] In another embodiment, a kit of the invention further comprises a needle or syringe, preferably packaged in sterile form, for injecting the composition, and/or a packaged alcohol pad. Instructions are optionally included for administration of composition by a physician or by the patient.

[0033] As used herein, “treat”, “treatment” and “treating” refer to any manner in which the symptoms of a condition, disorder or disease are ameliorated or otherwise beneficailly altered. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof and/or may be therapeutic in terms of a partial or complete cure for a disease and/or adverse effect attributable to the disease. Treament also encompasses any phamaceutical use of the compositions herein.

[0034] As used herein, “heart failure” means an abnormality of cardiac function where the heart does not pump blood at the rate needed for the requirements of

metabolizing tissues. Heart failure includes a wide range of disease states such as congestive heart failure, myocardial infarction, tachyarrhythmia, familial hypertrophic cardiomyopathy, ischemic heart disease, idiopathic dilated cardiomyopathy, myocarditis and the like. The heart failure can be caused by any number of factors, including, without limitation, ischemic, congenital, rheumatic, viral, toxci or idiopathic forms. Chronic cardiac hyperthophy is a significantly diseased state which is a precursor to congestive heart failure and cardiac arrest.

[0035] As used herein, "protein" is synonymous with "polypeptide" or "peptide" unless the context clearly dictates otherwise.

[0036] As used herein, "plasma" is synonymous with "serum" unless the context clearly dictates otherwise.

[0037] As used herein, "long-term benefit" means benefit caused by a treatment or interference which may not be observed in a short period after the treatment or interference. For chronic heart failure patients, long-term benefit may be improvement of survival, reduction of re-hospitalization or improvement of biomarkers which indicate the long-term prognosis. In some embodiments, the time period for observation of the benefit is about 6 months. In some embodiments, the time period for observation of the benefit is about 1 year. In some embodiments, the time period for observation of the benefit is about 1 years. And in other embodiments, the time period for observation of the benefit is about 3 years, 5 years, 10 years or longer.

[0038] As used herein, "survival" means the time or probability one subject may remain alive or living. It could be expressed by survival time or survival rate. Survival time is the time period start from the diagnosis or treatment to the end of the life. Survival rate means the percentage of people who are alive for a given period of time after diagnosis or treatment. For each subject, prolonged survival time caused by a treatment or interference could be regarded as a benefit. For a group of subjects or large populations, prolonged mean survival time or increased survival rate could be regarded as a benefit.

[0039] As used herein, "re-hospitalization" means the times or frequency of the patient admitted to the hospital in a given period of time. The admission to the hospital may caused by all conditions, or only caused by the same condition which is being treated. For each subject, a reduction of times of re-hospitalizations in a given period of time could be regarded as a benefit. And for a group of subjects or large populations, a reduction of total times or mean times of re-hospitalizations could be regarded as a benefit.

[0040] As used herein, "N-terminal brain natriuretic peptide" or "NT-proBNP" means the inactive remnant N-terminal proBNP, the latter is the pro hormone of BNP which is a hormonally active natriuretic peptide that is mainly released from the cardiomyocytes in the left ventricular wall. In reaction to stretch and tension of the myocardial wall the pro hormone proBNP splits into BNP and the hormonally inactive remnant NT-proBNP by proteolytic cleavage.

[0041] BNP and NT-proBNP plasma levels are promising tools in the daily management of suspected or established heart failure. Most studies on the use of BNP and NT-proBNP in clinical practice addressed their diagnostic properties, and an increasingly amount of evidence is available supporting the prognostic value of BNP and NT-proBNP. As NT-proBNP has about 6 times longer of half life in the blood than BNP, it is more widely used as a diagnostic or prognostic marker for heart failure. The plasma NT-proBNP level can be analyzed by commercial kits. For the purpose of example, but not limitation, the commercial kits from Roche or Biomedica. In the examples of the present invention, the NT-proBNP level was detected by kit from Biomedica (Austria).

[0042] Both BNP and NT-proBNP levels in the blood are used for screening, diagnosis of heart failure and are useful to establish prognosis in heart failure, as both markers are typically higher in patients with worse outcome. And, it is discovered in the present invention that plasma level of BNP or NT-proBNP is indicative of the patient being suitable for heart failure treatment by neuregulin. In fact, any diagnostic or prognostic markers for heart failure can be used to determine whether a

patient is suitable for heart failure treatment by neuregulin. The plasma level of NT-proBNP identified in this invention shall be used as guidance rather than a limitation for selection of heart failure patients who will receive significant treatment benefits from neuregulin. For example, using a plasma level of 5000 fmol/ml is still able to select heart failure patients who will receive treatment benefits from neuregulin, but some of these patients will receive treatment benefits in a lesser degree.

[0043] As used herein, "New York Heart Association" or "NYHA" heart function classification is a simple way of classifying the extent of heart failure. It places patients in one of four categories based on how much they are limited during physical activity; the limitations/symptoms are in regards to normal breathing and varying degrees in shortness of breath and/or angina pain: I, no symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.; II, mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity; III, marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m), comfortable only at rest; and IV, severe limitations, experiences symptoms even while at rest, mostly bedbound patients.

[0044] As used herein, "activity unit" or "EU" or "U" means the quantity of standard product that can induce 50% maximal reaction. In other words, to determine the activity unit for a given active agent, the EC50 must be measured. For example, if the EC50 for a batch of product was 0.1 μg, then that would be one unit. Further, if 1μg of that products is being used, then 10 EU (1/0.1) is being used. The EC50 can be determined by any method known in the art, including the method employed by the inventors. This determination of the activity unit is important for quality control of genetically engineered products and clinically used drugs, permits product from different pahrmaceuticals and/or different batch numbers to be quantified with uniform criteria.

[0045] The following is an exemplary, rapid, sensitive, high flux and quantitative method for determination of biological activity of NRG-1 through combining NRG

with cell surface ErbB3/ErbB4 molecule and indirect mediation of ErbB2 phosphorylation (See e.g., Michael D. Sadick et al., 1996, Analytical Biochemistry, 235:207-214 and WO03/099300).

[0046] Briefly, the assay, termed a kinase receptor activation enzyme-linked immunosorbant assay (KIRA-ELISA), consists of two separate microtiter plates, one for cell culture, ligand stimulation, and cell lysis/receptor solubilization and the other plate for receptor capture and phosphotyrosine ELISA. The assay was developed for analysis of NRG-induced ErbB2 activation and utilizes the stimuliation of intact receptor on the adherent breast carcinoma cell line, MCF-7. Membrane proteins are solubilized via Triton X-100 lysis and the receptor is captured in ELISA wells coated with ErbB2-specific antibodies with no cross-reaction to ErbB3 or ErbB4. The degree of receptor phosphorylation is then quantified by antiphosphotyrosine ELISA. A reproducible standard curve is generated with a EC50 of approximately 360pM for heregulin beta 1 (177-244). When identical samples of HRG beta 1 (177-244) are analyzed by both the KIRA-ELISA and quantitative antiphosphotyrosine Western Blot analysis, the results correlate very closely with one another. The assay descibed in this report is able to specifically quantify tyrosine phosphorylation of ErbB2 that results from the interaction of HRG with ErbB3 and/or ErbB4.

[0047] Since most of the genetically engineered medicines are proteins and polypeptides, their activity can be determined by their amino acid sequences or the activity center formed by their spatial structure. Activity titer of protein and polypeptide is not consistent with their absolute quality, therefor cannot be determined with weight unit as that of chemical drugs. However, biological activity of genetically engineered medicines is generally consistent with their pharmacodynamics and titer determination system established through given biological activity can determine its titer unit. Therefore, biological activity determination can be part of a process of titering the substance with biological activity and is an important component of quality control of genetically engineered product. It is important to determine biological activity criteria for quality control of genetically engineered product and

clinically used drugs.

[0048] Quantity of standard product that can induce 50% maximal reaction is defined as an activity unit (1 EU). Accordingly, product from different pharmaceuticals and of different batch numbers can be quantitied with uniform criteria.

B. EXAMPLES

[0049] Example 1: A randomized, double-blinded, multi-center, placebo controlled study to evaluate the efficacy and safety of recombinant human neuregulin 1 in patients with chronic heart failure based on standard treatment

[0050] To evaluate the efficacy of recombinant human neuregulin-1 for injection on chronic heart failure, a phase II, double-blinded, multi-center, placebo controlled, standard treatment based study was carried out in multiple clinical centers in China. A total of 195 patients with NYHA Class II or III stable chronic heart failure were enrolled and randomized into three groups: placebo, or 0.6 μg/kg and 1.2 μg/kg of rhNRG-1. There were no significant variations in demographics or background therapies among groups. According to the schedule, patients were administered the drug for 10 consecutive days in the hospital first, after finishing the day 11 follow up, they were discharged from the hospital. Another two on site follow up were at day 30 and day 90. An telephone interview was conducted one year after the last patient enrolled.

[0051] Investigational product:

[0052] Specification: Neucardin^{TM}, 61 amino acid polypeptide comprises the EGF-like domain of Neuregulin-1 β2 isoform, with the molecular weight of 7054 Dal (1μg=0.14nmol). 250μg (5000 EU)/vial (1μg=20 EU).

[0053] Preparation: For injection.

[0054] Mode of administration: Intravenously drip.

[0055] Storage: in safe place, with limited access and protected from light, at 3-8 ^{o}C.

[0056] Placebo:

[0057] Specification: Excipient for Neucardin^{TM}. 250μg/vial and without active recombinant human neuregulin-1 protein.

[0058] Dosage groups:

Dosage	0μg/kg/day	0.6μg/kg/day	1.2μg/kg/day
Administration	Intravenous infusion		
Volume	50ml		
Course	10 hours per day, for consecutive 10 days		

[0059] Study procedure

[0060] Criteria for participation in the trial included patients with CHF (NYHA class II or III) between the ages of 18 and 65 years old, LVEF ≤40%, in relatively stable clinical condition (including clinical signs, symptoms and accepted standard treatment for CHF at the target dose or maximum tolerance dose for over 1 month). Major exclusion criteria included acute myocardial infarction, hypertrophic cardiomyopathy, constrictive pericarditis, significant valve disease or congenital heart disease, severe pulmonary hypertension, systolic blood pressure <90mmHg or >160mmHg, severe ventricular arrhythmia, cardiac surgery or a cerebrovascular event within the previous six months, claustrophobia or pregnant female subjects. All patients provided witnessed written consent.

[0061] Patients were randomly assigned to three groups, treated with placebo or rhNRG-1 (0.6 or 1.2 μg/kg/day) for 10 consecutive days, after finishing the day 11 follow up, they were discharged from the hospital. Another two on site follow up were at day 30 and day 90. Blood samples of each patient were collected before treatment and at day 11, 30 and 90. Plasma NT-proBNP was tested in the core lab with

NT-proBNP assays (kit from Biomedica). One year after the last patient enrolled, the telephone interview was made for collecting the information of re-hospitalizations, all telephone interviews were recorded in a special form with investigators signature.

[0062] Of the 48 patients with available re-hospitalization information in the placebo group, 12 (25.0%) were rehospitalized for worsening heart failure at least once. For the 0.6 μg/kg group, only 4 (8.7%) of the 46 patients readmitted to the hospital （P=0.05 compare to placebo）; Rehopitalization rate of the 1.2 μg/kg group was 22.0% (11/50). The average times of re-hospitalizations was 0.458 (22/48) per patient in the placebo group, while they were reduced by 57.4% and 17.0% respectively in the 0.6 (8/41) and 1.2 μg/kg group (19/50).

[0063] In the placebo group, the NT-proBNP were almost the same during the study while compare to the baseline. At day 11, the NT-proBNP was significantly increased in rhNRG-1 treated groups (from 1853±1512 to 2399±1841 fmol/ml in 0.6μg/kg group, $P<0.01$; from 1562±1275 to 2774±1926 fmol/ml in 1.2μg/kg group, $P<0.01$). But his increase was transient and was not caused by a worsening heart function as the cardiac function shown to be increased, the NT-proBNP decreased to the baseline level at Day 30 and Day 90 in the 1.2μg/kg group. Moreover, in the 0.6μg/kg group, the NT-proBNP was significantly reduced at day 30 (1323±1124 fmol/ml, P=0.01) and day 90 (1518±1403fmol/ml, P=0.01) while compare to the baseline.

[0064] There results showed that rhNRG-1 treatment can reduce the re-hospitalizations and the plasma level of NT-proBNP, which may indicate rhNRG-1 can provide long-term benefits to chronic heart faiure patients.

[0065] Example 2: A randomized, double-blinded, multi-center, placebo controlled survival study of recombinant human neuregulin 1 in patients with chronic heart failure based on standard treatment

[0066] To evaluate the efficacy of recombinant human neuregulin-1 for injection on chronic heart failure, a phase II, double-blinded, multi-center, placebo controlled,

standard treatment based study was carried out in multiple clinical centers in China. A total of 351 patients with NYHA Class III or IV stable chronic heart failure were enrolled and randomized into placebo group or rhNRG-1 group (0.6 μg/kg). There were no significant variations in demographics or background therapies among groups. According to the schedule, patients were administered with the drug for 10 consecutive days in the hospital, after finishing the day 11 follow up, they were discharged from the hospital, and were administered with the drug once weekly from the 3rd week till the 25th week as out-patient. Blood samplas of each patient were collected before treatment (baseling) and at each follow up. Plasma NT-proBNP level was tested in the core lab with NT-proBNP assays (kit from Biomedica). The survival information was collected at 52th week of the study.

[0067] Investigational product:

[0068] Specification: Neucardin™, 61 amino acid polypeptide comprises the EGF-like domain of Neuregulin-1 β2 isoform, with the molecular weight of 7054 Dal (1μg=0.14nmol). 250μg (5000 EU)/vial (1μg=20 EU).

[0069] Preparation: For injection.

[0070] Mode of administration: Intravenously drip or infusion.

[0071] Storage: in safe place, with limited access and protected from light, at 3-8 °C.

[0072] Placebo:

[0073] Specification: Excipient for Neucardin™. 250μg/vial and without active recombinant human neuregulin-1 protein.

[0074] Dosage and regimens:

	Day1-10	Week 3-25
Dose	0.6μg/kg/day rhNRG-1 or placebo	0.8μg/kg/day rhNRG-1or placebo

Route	Intravenous drip	Intravenous infusion
regimen	10 hours per day for 10 days	10 minures infusion weekly

[0075] Criteria for participation in the trial included patients with CHF (NYHA class III or IV) between the ages of 18 and 80 years old, LVEF ≤40%, in relatively stable clinical condition (including clinical signs, symptoms and accepted standard treatment for CHF at the target dose or maximum tolerance dose for over 1 month). Major exclusion criteria included acute myocardial infarction, hypertrophic cardiomyopathy, constrictive pericarditis, significant valve disease or congenital heart disease, severe pulmonary hypertension, systolic blood pressure <90mmHg or >160mmHg, severe ventricular arrhythmia, cardiac surgery or a cerebrovascular event within the previous six months, claustrophobia or pregnant female subjects. All patients provided witnessed written consent.

[0076] The all-cause mortality of the placebo group at 52 week is 15.91%, with 28 death in 176 patients, while the number is 9.71% in rhNRG-1 group, with 16 death in 175 patients completed the trial (Hazard ratio=0.425, 95%CI 0.222-0.813, p=0.0097). Considering the mortality caused by cardiovasular events, the number of the placebo group at 52 week is 14.77%, with 26 death in 176 patients, and 9.71% in the rhNRG-1 group. So from the results we can find around 40% decrease of the mortality of rhNRG-1 adminstration compared with placebo group, even the placebo group were still maintain their previous standard treatment for chronic heart failure.

[0077] We also analyzed the all-cause mortality based on the stratification of baseline NT-proBNP. When the NT-proBNP level is stratified into 3 stratums as ≤1600fmol/ml, >1600fmol/ml and ≤4000fmol/ml, or >4000fmol/ml, the mortality of rhNRG-1 group vs placebo group are 1.49% vs 8.49%, 8.96% vs 23.33%, and 26.67% vs 28.00%, respectively. And if the NT-proBNP level is stratified as ≤4000fmol/ml or >4000fmol/ml, the mortality of rhNRG-1 group vs placebo group are 5.22% vs 14.89% (p=0.0092), and 26.67% vs 28.00%, respectively. These results show statistical significance that rhNRG-1 can effectively improve the survival of chronic

heart failure patients.

[0078] Further, the patients were stratified with their baseline NYHA heart function class, to be class III or class IV. The all-cause mortality of class III patients in rhNRG-1 group or placebo group is 6.06% (8 death in 132 patients) and 15.49% (22 death in 142 patients), respectively, p=0.0189. While the all-cause mortality of class IV patients in rhNRG-1 group or placebo group is 20.93% (9 death in 43 patients) and 17.65% (6 death in 34 patients), respectively, p=0.7789.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 1

<210> SEQ ID NO 1

<211> LENGTH: 61

<212> TYPE: PROTEIN

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 1

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1 5 10 15

Gly Gly Glu Cys Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr
20 25 30

Leu Cys Lys Cys Pro Asn Glu Phe Thr Gly Asp Arg Cys Gln Asn Tyr
35 40 45

Val Met Ala Ser Phe Tyr Lys Ala Glu Glu Leu Tyr Gln
50 55 60

What is claimed is:

1. A method of treating chronic heart failure, comprising:

a) performing a companion diagnostic test of each patient before treatment; and

b) providing a suitable treatment to the patient according to the results of the companion diagnostic test.

2. The method of claim 1, wherein the companion diagnostic test is the NYHA heart function classification.

3. The method of claim 1, wherein the companion diagnostic test is the test of plasma level of NT-proBNP or BNP.

4. The method of claim 1, wherein the suitable treatment comprising neuregulin treatment.

5. The method of claim 4, wherein the suitable treatment further comprising treating heart failure using one or more anti-heart failure drugs selected from a group consisting of: ACE inhibitors, β-blockers, ARBs, diuretics, and digitalis.

6. The method of claim 2, wherein said suitable treatment is administered when the heart function is NYHA class II or III.

7. The method of claims 3, wherein said suitable treatment is administered when plasma level of NT-proBNP is ≤ 4000 fmol/ml.

8. The method of claim 4 or 5, wherein the neuregulin is neuregulin-1.

9. The method of claim 4 or 5, wherein the neuregulin protein comprises of EGF-like domain of neuregulin-1.

10. The method of claim 4 or 5, wherein the neuregulin comprises of SEQ ID NO:1.

11. Use of neuregulin for the preparation of medications for treating chronic heart failure patients, wherein the patients have a plasma NT-proBNP level of ≤ 4000 fmol/ml before treatment.

12. The use of claim 11, wherein the neuregulin is neuregulin-1.

13. The use of claim 11, wherein the neuregulin comprises of EGF-like domain of

neuregulin-1.

14. The use of claim 11, wherein the neuregulin comprises of SEQ ID NO:1.

15. The use of claim 11, wherein the chronic heart failure is caused by ischaemic, congenital, rheumatic, idiopathic, viral or toxic factors.

16. The use of claim 11, wherein the medication can be used together with anti-heart failure drugs.

17. The use of claim 16, wherein the anti-heart failure drugs is one or more selected from a group consisting of: ACE inhibitors, β-blockers, ARBs, diuretics, and digitalis.

18. Use of neuregulin for the preparation of medications for treating chronic heart failure patients, wherein the patients has a class II or III heart function as classified by NYHA functional classification.

19. The use of claim 18, wherein the neuregulin is neuregulin-1.

20. The use of claim 18, wherein the neuregulin comprises of EGF-like domain of neuregulin-1.

21. The use of claim 18, wherein the neuregulin comprises of SEQ ID NO:1.

22. The use of claim 18, wherein the chronic heart failure is caused by ischaemic, congenital, rheumatic, idiopathic, viral or toxic factors.

23. The use of claim 18, wherein the medication can be used together with anti-heart failure drugs.

24. The use of claim 23, wherein the anti-heart failure drugs is one or more selected from a group consisting of: ACE inhibitors, β-blockers, ARBs, diuretics, and digitalis.

25. A method of treating chronic heart failure comprising administering neuregulin, wherein the administration of neuregulin improves the clinical indication of the patient.

26. The method of claim 25, wherein the clinical indication is prolonged survival.

27. The method of claim 25, wherein the clinical indication is reduced

re-hospitalization.

28. The method of claim 25, wherein the clinical indication is the expression level of biomarkers for diagnosis or prognosis of heart failure.

29. The method of claim 28, wherein the biomarker is NT-proBNP or BNP.

30. The method of claim 25, wherein the neuregulin is neuregulin-1.

31. The method of claim 25, wherein the neuregulin comprises of EGF-like domain of neuregulin-1.

32. The method of claim 25, wherein the neuregulin comprises of SEQ ID NO:1.

33. A pharmaceutically effective amount of neuregulin for treating a chronic heart failure patient whose plasma level of NT-proBNP is within a favorite treatment zone prior to neuregulin treatment.

34. The pharmaceutically effective amount of neuregulin of claim 33, wherein said favorite treatment zone is $\leq$ 4000 fmol/ml.

35. The pharmaceutically effective amount of neuregulin of claim 33, wherein said favorite treatment zone is between 1600 fmol/ml and 4000 fmol/ml.

36. The pharmaceutically effective amount of neuregulin of claim 33, wherein said favorite treatment zone is $\leq$ 1600 fmol/ml.

37. The pharmaceutically effective amount of neuregulin of claim 33, wherein the plasma level is measured by immunoassay.

38. The pharmaceutically effective amount of neuregulin of claim 33, wherein the neuregulin is neuregulin-1.

39. The pharmaceutically effective amount of neuregulin of claim 33, wherein the neuregulin protein comprises of EGF-like domain of neuregulin-1.

40. The pharmaceutically effective amount of neuregulin of claim 33, wherein the neuregulin comprises of SEQ ID NO:1.

41. A pharmaceutically effective amount of neuregulin for treating a chronic heart failure patient whose heart funtion is NYHA class II or III.

42. The pharmaceutically effective amount of neuregulin of claim 41, wherein the

neuregulin is neuregulin-1.

43. The pharmaceutically effective amount of neuregulin of claim 41, wherein the neuregulin protein comprises of EGF-like domain of neuregulin-1.

44. The pharmaceutically effective amount of neuregulin of claim 41, wherein the neuregulin comprises of SEQ ID NO:1.

45. A method of selecting a heart failure patient for treatment by neuregulin, comprises performing a companion diagnostic test before treatment and decide whether the result of the test is indicative for the treatment by neuregulin.

46. The method of claim 45, wherein the companion diagnostic test is measuring the plasma level of NT-proBNP in said patient.

47. The method of claim 46, wherein the result of the test is indicative for the treatment by neuregulin when the plasma level of NT-proBNP$\leq$ 4000 fmol/ml.

48. The method of claim 46, wherein the result of the test is indicative for the treatment by neuregulin when the plasma level of NT-proBNP is between 1600 fmol/ml and 4000 fmol/ml.

49. The method of claim 46, wherein the result of the test is indicative for the treatment by neuregulin when the plasma level of NT-proBNP is $\leq$ 1600 fmol/ml.

50. The method of claim 46, wherein the plasma level is measured by immunoassay.

51. The method of claim 45, wherein the companion diagnostic test is evaluating heart function by NYHA heart function classification.

52. The method of claim 46, wherein the result of the test is indicative for the treatment by neuregulin when the heart function is NYHA class II or III.

53. The method of claim 45, wherein the neuregulin is neuregulin-1.

54. The method of claim 45, wherein the neuregulin protein comprises of EGF-like domain of neuregulin-1.

55. The method of claim 45, wherein the neuregulin comprises of SEQ ID NO:1.

56. A diagnostic kit for selecting a heart failure patient for treatment by neuregulin, wherein diagnostic kit comprises immunoassay reagents to measure plasma level

of NT-proBNP in a heart failure patient, wherein a plasma level of ≤ 4000 fmol/ml is indicative of the patient being suitable for heart failure treatment by neuregulin.

57. The diagnostic kit of claim 56, wherein a plasma level of between 1600 fmol/ml and 4000 fmol/ml is indicative of the patient being suitable for heart failure treatment by neuregulin.

58. The diagnostic kit of claim 56, wherein a plasma level of ≤ 1600 fmol/ml is indicative of the patient being suitable for heart failure treatment by neuregulin.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2011/081699

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07K; A61K; A61P

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

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

VEN，CNKI，CNABS，CPRSABS, CNTXT, EPTXT, USTXT, WOTXT, JPTXT, ISI web of Knowledge，EMBASE, NCBI：neuregulin, chronic heart failure, NT-proBNP, NYHA class, sequence search on SEQ ID NO:1.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LIU Chao, Protective effects of Neuregulin-1β on Chronic contractibility cardiac failure and correlative mechanisms research. Chinese Master's Thesis Full-text database, Medicine and Health Sciences, June 2010.	11-24, 33-58
A	CN101877961 A(ZENS-N) 3 Nov.2010(03.11.2010) see the whole document.	11-24, 33-58
A	CN101636656 A(HOFF) 27 Jan.2010(27.01.2010) see the whole document.	11-24, 33-58

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&"document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 Jul. 2012(06.07.2012)	**12 Jul. 2012 (12.07.2012)**
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer WU,Li Telephone No. (86-10)62411046

Form PCT/ISA /210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2011/081699

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

1. ☒ Claims Nos.: 1-10, 25-32
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 1-10, 25-32 are directed to a method of treatment of human/animal body by therapy (Rules 39.1 (iv) PCT), thus are not searched.

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

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

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

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

Group I: claims 1-10, relate to a method for treating chronic heart failure comprising performing a companion diagnostic test before treatment.
Group II: claims 11-17, relate to use of neuregulin for the preparation of medications for treating chronic heart failure patients, wherein the patients have a plasma NT-proBNP level of ≤4000 fmol/ml before treatment.
Group III: claims 18-24, 41-44 relate to use of neuregulin for the preparation of medications for treating chronic heart failure patients, wherein the patients have a class II or class III heart functions as classified by NYHA functional classification.

(See extra sheet)

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on protest

☒ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2011/081699

CLASSIFICATION OF SUBJECT MATTER

C07K 14/475 (2006.01) i
A61K 38/18 (2006.01) i
A61P 9/04 (2006.01) i

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

Group IV: claims 25-32, relate to a method for treating chronic heart failure comprising administrating neuregulin;

Group V: claims 33-40, relate to a pharmaceutical effective amount of neuregulin for treating a chronic heart failure patient, whose plasma level of NT-proBNP is within a favorite treatment zone prior to neuregulin treatment;

Group VI: claims 45-58, relate to a method of selecting a heart failure patient for treatment by neuregulin and the diagnostic kit thereof.

The same or corresponding technical feature among the groups is the treatment of chronic heart failure with neuregulin peptide, which is indicated in prior art(see e.g. WO2010060265 A1, 3 June 2010, claims 3-8, paragraph [0032]). Therefore, the technical feature mentioned above can not be a special technical feature making contribution over the prior art, and the groups do not belong to a single general inventive concept and do not meet the requirements of unity of invention as defined in Rule 13.1 PCT.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2011/081699

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
CN101877961A	03.11.2010	JP2010539107A	16.12.2010
		US2009156488A1	18.06.2009
		WO2009033373A1	19.03.2009
		EP2200427A1	30.06.2010
CN101636656A	27.01.2010	WO2008089994A8	22.05.2009
		WO2008089994A1	31.07.2008
		US2010285491A1	11.11.2010
		JP2010517023A	20.05.2010
		CA2671298A1	31.07.2008
		EP2115477A1	11.11.2009