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(54) **GALECTIN-3 AND CARDIAC RESYNCHRONIZATION THERAPY**

GALECTIN-3 UND KARDIALE RESYNCHRONISATIONSTHERAPIE DAMIT

GALECTINE-3 ET THÉRAPIE DE RESYNCHRONISATION CARDIAQUE

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Description

BACKGROUND

[0001] Congestive heart failure, or heart failure, is a major cause of morbidity and mortality. Approximately 5 million people in the United States suffer from heart failure, with approximately 500,000 new cases diagnosed annually. In many cases, congestive heart failure patients also suffer an arrhythmia further reducing the heart's efficiency.

[0002] One treatment option for such patients involves implantation of a cardiac resynchronization therapy (CRT) device, also known as a biventricular pacing device. In a normal heartbeat, the two atrial chambers of the heart contract in unison, pumping blood into the two ventricular chambers. Less than a second later, the two ventricular chambers contract in unison, pumping the blood out of the heart and throughout the body. Some heart failure patients have an electrical delay between the ventricles, such that the two ventricular chambers no longer contract at the same time. The result is a substantial reduction in cardiac output. For example, in a normal heartbeat more than half of the blood in the left ventricle is pumped out with each heart beat. In other words, the "left ventricular ejection fraction" or "LVEF" is greater than 50%. In contrast, some heart failure patients whose heartbeats are uncoordinated have an LVEF less than one-third. In these patients, two-thirds of the blood remains "unpumped" with each heartbeat.

[0003] The goal of CRT therapy is to restore coordinated pumping of the ventricles. This is accomplished by a device with separate electrical leads stimulating the two ventricles to contract simultaneously with every heartbeat. CRT devices have improved quality of life and have decreased mortality in some patients with moderate or severe heart failure; an LVEF less than or equal to 35%; and an echocardiogram indicating a slow depolarization of the ventricles (a "QRS" complex greater than 120 ms). Still, about 30% of heart failure patients who receive CRT fail to respond to treatment (see, for example, Jeevanantham et al. (2009) Cardiol. J. 16(3)197-209). As one author warned in 2007, "better criteria for identification of the optimal CRT candidate are urgently warranted" (Stellbrink (2007) Eur. Heart J. 28:1541-1542). Further, even among heart failure patients who receive CRT intervention, the rate of adverse events such as unplanned hospitalizations for heart failure and death is high (*see*, for example, Cleland et al. (2005) "The effect of cardiac resynchronization on morbidity and mortality in heart failure." N. Engl. J. Med. 352(15):1539-49.

[0004] Van Kimmenade et al. (2006) Journal of the American College of Cardiology 48(6): 1217-1224 discloses the use of galectin-3 to predict prognosis in subjects with acute heart failure, but is silent with respect to the use of galectin-3 for predicting responsiveness to a therapeutic intervention.

[0005] Rocchiccioli et al. (2008) Hear Failure Reviews 15(4): 251-273 discloses that galectin-3 might be useful in combination with other biomarkers for identifying patients at high risk of heart failure, but is silent as to the use of galectin-3 to predict the responsiveness of these patient populations to CRT.

SUMMARY OF THE INVENTION

[0006] It has now been discovered that concentrations of the human protein galectin-3 in body fluids can be used to predict or monitor disease progression or therapeutic efficacy in patients treated with cardiac resynchronization therapy. A patient's galectin-3 blood concentration can be monitored after a CRT device is implanted to provide an ongoing indication of disease development or progression and/or of the continued propriety of the course of treatment. For example, the invention permits measurements of changes over time in galectin-3 concentration in a body fluid (*e.g.,* blood, serum, or plasma) of a heart failure patient and comparing the measured change in galectin-3 concentration to changes in galectin-3 concentration observed in other patients for whom cardiac resynchronization therapy was or was not beneficial.

[0007] Monitoring methods can include comparing a galectin-3 concentration in a patient to an earlier galectin-3 concentration in the same patient before or after implantation of a CRT device. The methods can also include comparing galectin-3 levels measured at several times following implantation of the CRT device to develop a history of galectin-3 concentrations. For example, disclosed are methods for assessing a patient by detecting the presence or absence of an increasing or decreasing galectin-3 concentration in a body fluid (*e.g.*, blood, serum, or plasma) of a heart failure patient in whom a CRT device has been implanted. The presence of an increasing galectin-3 concentration over time is indicative of a worsening congestive heart failure in the patient.

[0008] In one embodiment, the invention provides a method of predicting responsiveness to cardiac resynchronization therapy of a human who is a candidate for or has been treated with cardiac resynchronization therapy as defined in the claims.

[0009] The results of the assessment can be used to inform decisions involving treatment of the patient. For example, if the heart failure patient appears to be therapeutically unresponsive to cardiac resynchronization therapy, based on the patient's galectin-3 concentration or a change in the patient's galectin-3 concentration, other forms of treatment may be preferred, such as angioplasty or other surgery and/or administration of a diuretic, an inotrope, a beta-blocker, a natriuretic peptide, a statin, or a vasodilator.

[0010] It has also been discovered that concentrations of the human protein galectin-3 in body fluids can be informative in determining whether a presenting patient may benefit from cardiac resynchronization therapy. In this manner, CRT devices, with or without a defibrillator function, can be implanted in those heart failure patients who are more likely to benefit from the treatment. Thus, it is envisioned that patients who have experienced heart failure or who have been identified as at risk for heart failure will be tested to measure their circulating galectin-3 levels. The measured galectin-3 levels will permit the identification of two groups of patients: those who may benefit from cardiac resynchronization therapy, based on their galectin-3 concentration; and those who are unlikely (or less likely) to benefit. CRT devices would be implanted in those in the first group, whereas other courses of therapy would be selected for those in the second group.

[0011] Disclosed herein are methods which include measuring a galectin-3 concentration in a sample, such as a blood sample, a serum sample, or a plasma sample. The measured galectin-3 concentration is indicative of whether the patient is likely to respond favorably to cardiac resynchronization therapy. Favorable responses include, for example, an increased likelihood of survival over a period of time, or a reduced progression or development of heart failure, improved heart strength, increased LVEF, fewer unplanned hospitalizations for worsening heart failure, increase in peak oxygen consumption during exercise, decreased fatigue, reduced shortness of breath, or reduced sleep apnea.

[0012] Also described herein are methods which include measuring a galectin-3 concentration in a body fluid (*e.g.,* blood, serum, or plasma) of a heart failure patient who is a candidate for cardiac resynchronization therapy, prior to such treatment, and comparing the galectin-3 concentration to a galectin-3 concentration observed in other patients treated with CRT devices, with or without defibrillator functions, for whom cardiac resynchronization therapy has proven beneficial.

[0013] Also described herein are methods which include measuring a galectin-3 concentration in a body fluid of a patient who is a candidate for cardiac resynchronization therapy and comparing the measured galectin-3 concentration to a reference galectin-3 concentration. The reference galectin-3 concentration can be derived from observed concentrations of galectin-3 in other patients, and can be indicative of responsiveness or non-responsiveness to implantation of a CRT device. Cardiac resynchronization therapy can be restricted or refused if the measured galectin-3 concentration is different than a reference galectin-3 concentration.

[0014] Also described herein are methods which include implanting a CRT device, with or without pacemaker or defibrillator functions, in a patient having a determined galectin-3 blood concentration that is indicative of a favorable response to cardiac resynchronization therapy. In contrast to the methods of *selecting* a therapy, which involve the process of measuring a galectin-3 blood concentration, the *treatment* methods relate to the subsequent implantation of the CRT device. Thus, the treatment methods involve the implantation of a CRT device in a patient whose galectin-3 blood concentration has been determined to be indicative of a favorable response, regardless of how the galectin-3 determination was previously made, or by whom.

[0015] In a selected or treated patient, the blood concentration of galectin-3 may be determined to be above a minimum threshold, below a maximum threshold or within a target range defined by a minimum and a maximum threshold. The minimum threshold may be, for example, more than 10 ng/ml; between 10 and 15 ng/ml; between 15 and 20 ng/ml; between 20 and 25 ng/ml; between 25 and 30 ng/ml; or be more than 30 ng/ml. The maximum threshold may be, for example, below 70 ng/ml; below 60 ng/ml; below 40 ng/ml; between 30 and 40 ng/ml; between 25 and 30 ng/ml; between 20 and 25 ng/ml; or between 15 and 20 ng/ml.

[0016] The results of the assessment can be used to inform decisions involving treatment of the patient. For example, if a heart failure patient's galectin-3 concentration is dissimilar to those of other heart failure patients for whom cardiac resynchronization therapy has proven beneficial, implantation of a CRT device may not be indicated, and the patient may be offered a different medication or therapeutic option.

DETAILED DESCRIPTION OF THE INVENTION

[0017] Applicants have invented a method of predicting and/or monitoring a heart failure patient's physiological response to cardiac resynchronization therapy. In past clinical studies, between one quarter and one half of CRT device recipients were classified as "non-responders" because they failed to show significant benefit from the device (Hawkins et al. (2006) Eur. Heart J. 27:1270-1281). One study reported heart failure worsened in 40% of CRT device recipients after implantation, although a control group fared even more poorly (Cleland et al. (2005) New Engl. J. Med. 352:1539-49). Applicants have discovered that measuring the circulating galectin-3 levels in a patient can be used to identify those patients who are better candidates for cardiac resynchronization therapy. In this way, the therapy can be directed preferentially to those more likely to benefit from it, while other patients can be spared the risk and expense and directed to different courses of therapy. In addition, applicants have discovered that measuring galectin-3 upon and/or after a CRT device is implanted provides an ongoing indication of disease development or progression and/or of the continued propriety of the course of treatment.

[0018] The terms "heart failure," "HF," "congestive heart failure," or "CHF" as used herein, refer to the complex clinical syndrome that impairs the ability of the ventricle to fill with or eject blood. Any structural or functional cardiac disorder can cause HF, with the majority of HF patients having impaired left ventricular (LV) myocardial function. Symptoms of

HF include dyspnea (shortness of breath), fatigue, and fluid retention. The American Heart Association (AHA) has identified 4 stages in the progression or development of HF. Patients in stages A and B show clear risk factors but have not yet developed HF. Patients in stages C and D currently exhibit or in the past have exhibited symptoms of HF. For example, Stage A patients are those with risk factors such as coronary artery disease, hypertension or diabetes mellitus who do not show impaired left ventricular (LV) function. Stage B patients are asymptomatic, but have cardiac structural abnormalities or remodeling, such as impaired LV function, hypertrophy or geometric chamber distortion. Stage C patients have cardiac abnormalities and are symptomatic. Stage D patients have refractory HF in which they exhibit symptoms despite maximal medical treatment. They are typically recurrently hospitalized or unable to leave the hospital without specialized intervention.

[0019] Galectin-3 is a structurally unique member of a family of multifunctional β-galactoside-binding lectins (Gabius (2006) Crit. Rev. Immunol. 26:43-79). Expression of galectin-3 has been associated with the epithelium and inflammatory cells including macrophages, neutrophils and mast cells. Galectin-3 has been implicated in a variety of biological processes important in heart failure including myofibroblast proliferation, fibrogenesis, tissue repair, cardiac remodeling, and inflammation (Liu et al. (2009) Am. J. Physiol. Heart Circ. Physiol. 296(2):H404-12; Papaspyridonos et al. (2008) Arterioscler. Thromb. Vasc. Biol. 28(3):433-40; Henderson et al. (2006) Proc. Natl. Acad. Sci. USA 103:5060-5065; Sharma et al. (2004) Circulation 110:3121-3128; Sano et al. (2000) J. Immunol. 165(4):2156-64; Kuwabara et al. (1996) J. Immunol. 156(10):3939-44).

[0020] Applicants have developed methods permitting the use of circulating galectin-3 protein levels to predict efficacy of cardiac resynchronization therapy in heart failure patients. Knowledge of a patient's galectin-3 level is informative of patient outcome upon implantation of a CRT device. Furthermore, levels of circulating biomarkers such as galectin-3 levels after implantation are informative of patient outcome, and changes in galectin-3 levels may indicate a changing prognosis. Although higher concentrations of galectin-3 correlate with poor prognosis, such as death and hospitalization, patients with relatively high galectin-3 levels who receive CRT devices may benefit significantly, as measured by heart output, quality of life (as measured, for example, by the Minnesota Living With Heart Failure® Questionnaire, University of Minnesota), reduced progression or development of heart failure, decreased fatigue, reduced shortness of breath, or enhanced likelihood of survival.

Galectin-3 Detection

[0021] The present invention provides methods which comprise measuring a galectin-3 blood concentration in a sample from the human, thereby to determine the presence or absence of a galectin-3 blood concentration in the human predictive of responsiveness to cardiac resynchronization therapy. Many methods for detecting of a protein of interest, with or without quantitation, are well known and can be used in the practice of the present invention. Examples of such assays are described below and can include, for example, immunoassays, chromatographic methods, and mass spectroscopy. Such assays can be performed on any biological sample including, among others, blood, plasma, and serum. Accordingly, multiple assays can be used to detect galectin-3, and samples can be analyzed from one or more sources.

[0022] Markers can be detected or quantified in a sample with the help of one or more separation methods. For example, suitable separation methods may include a mass spectrometry method, such as electrospray ionization mass spectrometry (ESI-MS), ESI-MS/MS, ESI-MS/$(MS)^n$ (n is an integer greater than zero), matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF-MS), surface-enhanced laser desorption/ionization time-of-flight mass spectrometry (SELDI-TOF-MS), desorption/ionization on silicon (DIOS), secondary ion mass spectrometry (SIMS), quadrupole time-of-flight (Q-TOF), atmospheric pressure chemical ionization mass spectrometry (APCI-MS), APCI-MS/MS, APCI-$(MS)^n$, or atmospheric pressure photo ionization mass spectrometry (APPI-MS), APPI-MS/MS, and APPI-$(MS)^n$. Other mass spectrometry methods may include, inter alia, quadrupole, fourier transform mass spectrometry (FTMS) and ion trap. Spectrometric techniques that can also be used include resonance spectroscopy and optical spectroscopy.

[0023] Other suitable separation methods include chemical extraction partitioning, column chromatography, ion exchange chromatography, hydrophobic (reverse phase) liquid chromatography, isoelectric focusing, one-dimensional polyacrylamide gel electrophoresis (PAGE), two-dimensional polyacrylamide gel electrophoresis (2D-PAGE), or other chromatographic techniques, such as thin-layer, gas or liquid chromatography, or any combination thereof. In one embodiment, the biological sample to be assayed may be fractionated prior to application of the separation method.

[0024] Markers can may be detected or quantified by methods that do not require physical separation of the markers themselves. For example, nuclear magnetic resonance (NMR) spectroscopy may be used to resolve a profile of a marker from a complex mixture of molecules. An analogous use of NMR to classify tumors is disclosed in Hagberg (1998) NMR Biomed. 11:148-56, for example.

[0025] A marker in a sample also may be detected or quantified, for example, by combining the marker with a binding moiety capable of specifically binding the marker. The binding moiety may include, for example, a member of a ligand-receptor pair, *i.e.*, a pair of molecules capable of having a specific binding interaction. The binding moiety may also

include, for example, a member of a specific binding pair, such as antibody-antigen, enzyme-substrate, nucleic acid-nucleic acid, protein-nucleic acid, protein-protein, or other specific binding pairs known in the art. Binding proteins may be designed which have enhanced affinity for a target. Optionally, the binding moiety may be linked with a detectable label, such as an enzymatic, fluorescent, radioactive, phosphorescent or colored particle label. The labeled complex may be detected, *e.g.*, visually or with the aid of a spectrophotometer or other detector, or may be quantified.

[0026] Galectin-3 levels can be quantitated by performing an immunoassay. A galectin-3 immunoassay involves contacting a sample from a subject to be tested with an appropriate antibody under conditions such that immunospecific binding can occur if galectin-3 is present, and detecting or measuring the amount of any immunospecific binding by the antibody. Any suitable immunoassay can be used, including, without limitation, competitive and non-competitive assay systems using techniques such as Western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays and protein A immunoassays.

[0027] In a "sandwich" assay, two molecules ("binding moieties") such as monoclonal antibodies that specifically bind to non-overlapping sites (epitopes) on galectin-3 are used. Typically, one binding moiety is immobilized on a solid surface where it binds with and captures galectin-3. This first binding moiety is therefore also referred to as the capture binding moiety. A second binding moiety is detectably labeled, for example, with a fluorophore, enzyme, or colored particle, such that binding of the second binding moiety to the galectin-3-complex indicates that galectin-3 has been captured. The intensity of the signal is proportional to the concentration of galectin-3 in the sample. The second binding moiety is therefore also referred to as the detection binding moiety or label binding moiety. A binding moiety can be any type of molecule, as long as it specifically binds to a portion of the N-terminus of galectin-3. In a preferred embodiment, the binding moieties used are monoclonal anti-galectin-3 antibodies, i.e., monoclonals raised against or otherwise selected to bind to separate portions of galectin-3.

[0028] Such assay procedures can be referred to as two-site immunometric assay methods, "sandwich" methods or (when antibodies are the binders) "sandwich immunoassays." As is known in the art, the capture and detection antibodies can be contacted with the test sample simultaneously or sequentially. Sequential methods can be accomplished by incubating the capture antibody with the sample, and adding the labeled detection antibody at a predetermined time thereafter (sometimes referred to as the "forward" method). Alternatively, the labeled detection antibody can be incubated with the sample first and then the sample can be exposed to the capture antibody (sometimes referred to as the "reverse" method). After any necessary incubation(s), which may be of short duration, to complete the assay, the label is measured. Such assays may be implemented in many specific formats known to those of skill in the art, including through use of various high throughput clinical laboratory analyzers or with a point of care or home testing device.

[0029] In one embodiment, a lateral flow device may be used in the sandwich format wherein the presence of galectin-3 above a baseline sensitivity level in a biological sample will permit formation of a sandwich interaction upstream of or at the capture zone in the lateral flow assay. See, for example, U.S. Patent No. 6,485,982. The capture zone may contain capture binding moieties such as antibody molecules, suitable for capturing galectin-3, or immobilized avidin or the like for capture of a biotinylated complex. See, for example, U.S. Patent No. 6,319,676. The device may also incorporate a luminescent label suitable for capture in the capture zone, the concentration of galectin-3 being proportional to the intensity of the signal at the capture site. Suitable labels include fluorescent labels immobilized on polystyrene microspheres. Colored particles also may be used.

[0030] Other assay formats that may be used in the methods of the invention include, but are not limited to, flow-through devices. See, for example, U.S. Patent No. 4,632,901. In a flow-through assay, one binding moiety (for example, an antibody) is immobilized to a defined area on a membrane surface. This membrane is then overlaid on an absorbent layer that acts as a reservoir to pump sample volume through the device. Following immobilization, the remaining protein-binding sites on the membrane are blocked to minimize non-specific interactions. In operation, a biological sample is added to the membrane and filters through the matrix, allowing any analyte specific to the antibody in the sample to bind to the immobilized antibody. In a second step, a labeled secondary antibody may be added or released that reacts with captured marker to complete the sandwich. Alternatively, the secondary antibody can be mixed with the sample and added in a single step. If galectin-3 is present, a colored spot develops on the surface of the membrane.

[0031] The most common enzyme immunoassay is the "Enzyme-Linked Immunosorbent Assay (ELISA)." ELISA is a technique for detecting and measuring the concentration of an antigen using a labeled (*e.g.*, enzyme-linked) form of the antibody. There are different forms of ELISA, which are well known to those skilled in the art. Standard ELISA techniques are described in "Methods in Immunodiagnosis", 2nd Edition, Rose and Bigazzi, eds. John Wiley & Sons, 1980; Campbell et al., "Methods and Immunology", W. A. Benjamin, Inc., 1964; and Oellerich, M. (1984), J. Clin. Chem. Clin. Biochem. 22:895-904. A preferred enzyme-linked immunosorbent assay kit (ELISA) for detecting galectin-3 is commercially available (BG Medicine, Waltham, MA).

[0032] In a "sandwich ELISA," an antibody (*e.g.*, anti-galectin-3) is linked to a solid phase (*i.e.,* a microtiter plate) and exposed to a biological sample containing antigen (*e.g.,* galectin-3). The solid phase is then washed to remove unbound antigen. A labeled antibody (*e.g.*, enzyme linked) is then bound to the bound-antigen (if present) forming an antibody-

antigen-antibody sandwich. Examples of enzymes that can be linked to the antibody are alkaline phosphatase, horseradish peroxidase, luciferase, urease, and β-galactosidase. The enzyme linked antibody reacts with a substrate to generate a colored reaction product that can be measured. Any of the immunoassays described herein suitable for use with the kits and methods of the present invention can also use any binding moiety in the place of an antibody.

[0033] A detailed review of immunological assay design, theory and protocols can be found in numerous texts in the art, including Butt, W.R., Practical Immunology, ed. Marcel Dekker, New York (1984) and Harlow et al. Antibodies, A Laboratory Approach, ed. Cold Spring Harbor Laboratory (1988).

[0034] In general, immunoassay design considerations include preparation of antibodies (*e.g.*, monoclonal or polyclonal antibodies) having sufficiently high binding specificity for the target to form a complex that can be distinguished reliably from products of nonspecific interactions. As used herein, the term "antibody" is understood to mean binding proteins, for example, antibodies or other proteins comprising an immunoglobulin variable region-like binding domain, having the appropriate binding affinities and specificities for the target. The higher the antibody binding specificity, the lower the target concentration that can be detected. As used herein, the terms "specific binding" or "binding specifically" are understood to mean that the binding moiety, for example, a binding protein, has a binding affinity for the target of greater than about 10^5 M^{-1}, more preferably greater than about 10^7 M^{-1}.

[0035] Antibodies to an isolated target marker which are useful in assays for detecting heart failure in an individual may be generated using standard immunological procedures well known and described in the art. See, for example Practical Immunology, *supra.* Briefly, an isolated marker is used to raise antibodies in a xenogeneic host, such as a mouse, goat or other suitable mammal. The marker is combined with a suitable adjuvant capable of enhancing antibody production in the host, and is injected into the host, for example, by intraperitoneal administration. Any adjuvant suitable for stimulating the host's immune response may be used. A commonly used adjuvant is Freund's complete adjuvant (an emulsion comprising killed and dried microbial cells and available from, for example, Calbiochem Corp., San Diego, or Gibco, Grand Island, NY). Where multiple antigen injections are desired, the subsequent injections may comprise the antigen in combination with an incomplete adjuvant (*e.g.*, cell-free emulsion). Polyclonal antibodies may be isolated from the antibody-producing host by extracting serum containing antibodies to the protein of interest. Monoclonal antibodies may be produced by isolating host cells that produce the desired antibody, fusing these cells with myeloma cells using standard procedures known in the immunology art, and screening for hybrid cells (hybridomas) that react specifically with the target and have the desired binding affmity.

[0036] Exemplary epitopes from the N-terminus of galectin-3 include, but are not limited to, MADNFSLHDALS (SEQ ID NO:1); MADNFSLHDALSGS (SEQ ID NO:2); WGNQPAGAGG (SEQ ID NO:3); YPGAPGAYPGAPAPGV (SEQ ID NO:4); GNPNPQGWPGA (SEQ ID NO:5); YPSSGQPSATGA (SEQ ID NO:6); YPGQAPPGAYPGQAPPGA (SEQ ID NO:7); YPGAPAPGVYPGPPSGPGA (SEQ ID NO:8); and YPSSGQPSATGA (SEQ ID NO:9). Other galectin-3 epitopes, including non-linear epitopes, can also be used as targets for detection by an anti-galectin-3 antibody. Exemplary antibodies are discussed in U.S. 2010/014954, the entire contents of which are incorporated herein by reference.

[0037] Antibody binding domains also may be produced biosynthetically and the amino acid sequence of the binding domain manipulated to enhance binding affinity with a preferred epitope on the target. Specific antibody methodologies are well understood and described in the literature. A more detailed description of their preparation can be found, for example, in Practical Immunology, (*supra*).

[0038] In addition, genetically engineered biosynthetic antibody binding sites, also known in the art as BABS or sFv's, may be used to determine if a sample contains a marker. Methods for making and using BABS comprising (i) non-covalently associated or disulfide bonded synthetic V_H and V_L dimers, (ii) covalently linked V_H-V_L single chain binding sites, (iii) individual V_H or V_L domains, or (iv) single chain antibody binding sites are disclosed, for example, in U.S. Patent Nos.: 5,091,513; 5,132,405; 4,704,692; and 4,946,778. Furthermore, BABS having requisite specificity for the marker can be derived by phage antibody cloning from combinatorial gene libraries (see, for example, Clackson et al. Nature 352: 624-628 (1991)). Briefly, phages, each expressing on their coat surfaces BABS having immunoglobulin variable regions encoded by variable region gene sequences derived from mice pre-immunized with an isolated marker, or a fragment thereof, are screened for binding activity against the immobilized marker. Phages which bind to the immobilized marker are harvested and the gene encoding the BABS is sequenced. The resulting nucleic acid sequences encoding the BABS of interest then may be expressed in conventional expression systems to produce the BABS protein.

[0039] Multimarker analysis can be used to improve the accuracy of diagnosis and monitoring. For example, blood concentrations of galectin-3 (Gal-3) and brain natriuretic peptide (BNP) can be used to diagnose heart failure and to predict the long-term outcome of heart failure (van Kimmenade et al., J. Am. Coll. Cardiol., 48:1217-24 (2006); Sharma et al., Circulation, 110:3121-28 (2004); Lok et al., Eur. Heart J., 28:141, Abstract 1035 (2007)). BNP and its cleavage equivalent amino-terminal proBNP (NT-proBNP) are elevated in heart muscle and in blood during heart failure as a result of high filling pressures of heart chambers and the stretch of cardiac muscle fibers. Other secondary markers that could be used to diagnose heart failure may include non-polypeptidic cardiac markers such as sphingolipid, sphingosine, sphingosine-1-phosphate, dihydrosphingosine and sphingosylphosphorylcholine (see U.S. Pat. No. 6,534,322). When measuring the levels of the above markers, corrections for age and gender may be incorporated to improve the accuracy

of diagnosis.

Treatment methods

[0040] Patients whose galectin-3 levels identify them as candidates for cardiac resynchronization therapy can be treated by implantation of a CRT device.

[0041] Traditional pacemakers include one or two electrical leads placed in the right atrium, the right ventricle, or both, to pace their contractions. CRT devices include at least two leads: one in the right ventricle, and one in the coronary sinus against the wall of the left ventricle, to induce simultaneous contractions of the left and right ventricles. Often, a third, sensing lead is placed in the right atrium to provide data to time the ventricular contractions. Such CRT devices not only promote the coordinated contraction of the left and right ventricles, but also ensure their timing with respect to the contraction of the atria. The leads are connected to a battery-powered pulse generator implanted in the chest, beneath the skin. After the atrial contractions fill the ventricles with blood, the pulse generator sends small electrical signals to the ventricles, stimulating their coordinated contraction, expelling the blood from the heart and pumping it through the circulatory system.

[0042] CRT devices are available with or without an associated defibrillator function. Devices that include a defibrillator function are sometimes referred to as CRT-D devices. CRT-D devices are particularly useful in patients at risk of abnormal heart rhythms. For example, a rapid, irregular heartbeat can prevent the heart from completing a full contraction; very slow heartbeats can also be dangerous. If the heart develops an abnormal rhythm, a CRT-D device can shock the heart, disrupting the abnormal rhythm and giving the heart the opportunity to resume a more normal speed.

[0043] CRT devices are widely available from manufacturers such as St. Jude Medical (Atlas® II HF ICD, Atlas®+ HF ICD, Epic® HF ICD, Epic® II HF ICD, Promote® RF CRT-D), Boston Scientific (COGNIS®, Contak Renewal, LIVIAN™), Medtronic (Consulta™, Concerto®, Maximo® II, InSync® Maximo®), Sorin Group ERM (OVATIO™ and NewLiving™), and BIOTRONIK® (Stratos® LV and Stratos® LV-T).

[0044] Cardiac resynchronization therapy is optionally combined with one or more other treatments for heart failure. For example, a patient may also be treated with: a statin, such as rosuvastatin, atorvastatin, pravastatin, fluvastatin, lovastatin, pitavastatin, or simvastatin; a diuretic, such as furosemide, bumetanide, hydrochlorothiazide, spironolactone, eplerenone, triamterene, torsemide, or metolazone; an inotrope, such as dobutamine, milrinone, or digoxin; a beta-blocker, such as carvediol or metoprolol; and/or a natriuretic peptide, such as BNP.

[0045] Treatments can also include a vasodilator, such as: an angiotensin-converting enzyme (ACE) inhibitor (e.g. captopril, enalapril, lisinopril, benazepril, quinapril, fosinopril, or ramipril); an angiotensin II receptor blocker, such as candesartan, irbesartan, olmesartan, losartan, valsartan, telmisartan, or eprosartan; a nitrate, such as isosorbide mononitrate or isosorbide dinitrate; and/or hydralazine. Other forms of medical intervention such as angioplasty or other surgery can also be performed in appropriate cases.

[0046] The efficacy of therapy can be monitored over time by regular measurement of relevant biomarkers such as galectin-3. Galectin-3 levels and/or other biomarkers (such as BNP) can be measured in a CRT patient and can be compared to a previous galectin-3 concentration measured in the patient. An increase or decrease in galectin-3 concentration relative to one or more previous galectin-3 concentrations in the patient may be an indication that the patient is responding or not responding to cardiac resynchronization therapy. Marker levels can be monitored over time, such as in samples obtained from a patient at annual, semi-annual, bimonthly, monthly, triweekly, biweekly, weekly, daily, or at variable intervals.

EXAMPLE: Galectin-3 and Cardiac Resynchronization Therapy

METHODS

Study Population

[0047] A clinical trial enrolled patients with heart failure (HF) for at least 6 weeks (New York Heart Association functional class III or IV), with evidence of left ventricular systolic dysfunction and cardiac dyssynchrony (as indicated by QRS width greater than or equal to 150 ms or echocardiographic dyssynchrony if QRS was 120-149 msec). The design and primary results of the trial are reported in published literature [J. Cleland et al., "The effect of cardiac resynchronization on morbidity and mortality in heart failure." N Engl J Med. 2005 Apr 14;352(15):1539-49]. All patients received standard pharmacologic therapy including angiotensin converting enzyme inhibitors, beta blockers and diuretics. Patients were randomly assigned to treatment with optimized pharmacological therapy alone or combined with cardiac resynchronization therapy (CRT) in an open-label manner. Patients receiving CRT received an InSync® III CRT device (Medtronic Inc., Minneapolis, MN), in addition to their background pharmacological therapy. Atriobiventricular pacing was used, with atrial pacing to prevent rates slower than 60 beats per minute. Right ventricle and left ventricle were stimulated

simultaneously. Echocardiography was used to optimize atrio-ventricular delay using the mitral inflow signal. The shortest atrio-ventricular delay that did not shorten the atrial component of the inflow signal was considered optimal.

Blood sampling

[0048] Serum samples were drawn at baseline, at 3 and at 18 months. All samples were stored at -80°C.

Laboratory analysis

[0049] Determination of galectin-3 concentration in serum samples was assessed using ELISA kits (Galectin-3 assay; BG Medicine Inc., Waltham, MA, USA). The assay sensitivity (lowest concentration different from zero) was 0.96 ng/mL. Intra- and inter-assay variations were less than 8% and 10 % respectively.

Statistical analyses

[0050] All analyses were performed using SAS version 9 software (SAS Institute, Cary, NC, USA). Logistic regression was used to assess the association of analyte levels and outcomes. Only patients complete on all covariates of interest in a particular analysis were considered for inclusion in that analysis. The two-tailed significance level was set to 0.05, and probability values less than 0.05 were considered significant.

RESULTS

Galectin-3 concentration over time in patients

[0051] The mean and standard deviation of galectin-3 at baseline, which is defined as the time of enrollment in the study, and at 18 months after baseline are shown in Table 1 below, by intervention group. Note that not all patients had a serum sample available for galectin-3 measurement at each time point; Table 1 presents results for all patients with a galectin-3 measurement available.

Table 1. Serum galectin-3 concentrations (mean and standard deviation) at baseline and at 18 months after baseline, by intervention group. Numbers in parentheses indicate one standard deviation. The number of patients who had serum samples with galectin-3 measurement is also indicated in the Table for each time point and group.

	Patients who received CRT	Patients who did not receive CRT
Baseline	28.0 (14.8) ng/mL [N=124]	26.8 (8.8) ng/mL [N=122]
Month 18	26.4 (10.6) ng/mL [N=84]	26.8 (10.5) ng/mL [N=75]

[0052] It is observed from Table 1 that the mean serum galectin-3 concentration in patients who did not receive CRT is identical at baseline and 18 months after baseline, whereas the mean serum galectin-3 concentration in patients who did receive CRT decreased between baseline and 18 months.

Galectin-3 concentration over time in patients, and adverse outcome

[0053] The frequency of an adverse outcome, namely death or unplanned hospitalization for heart failure within 18 months after baseline, was investigated for the 10 patients who experienced the greatest reduction of serum galectin-3 between baseline and 3 months after baseline. It was observed that out of the 10 patients with the greatest reduction in galectin-3 levels between baseline and 3 months after baseline, 6 of these patients (60%) suffered the adverse outcome of death or hospitalization for heart failure within 18 months of baseline. In contrast, of the other patients with a serum galectin-3 value at baseline and at 3 months after baseline and available information on adverse outcome, 81% (128 patients out of 159 patients) suffered the adverse outcome of death or hospitalization for heart failure at 18 months.

Galectin-3 concentration at baseline in patients receiving CRT are associated with adverse outcome

[0054] It was observed that baseline galectin-3 serum concentration was significantly associated with the risk of a subsequent adverse outcome, namely death within 18 months or hospitalization within 18 months, in patients who received CRT. Table 2 below displays the results of a statistical logistic regression analysis to assess the association between baseline galectin-3 and subsequent adverse outcome. For details on the technique of logistic regression, see

e.g. David W. Hosmer and Stanley Lemeshow, Applied logistic regression (New York: Wiley, 2000). In the analysis, data from patients with a baseline galectin-3 levels greater than 30 ng/mL were placed into one group, and data from patients with baseline galectin-3 levels less than or equal to 30 ng/mL were placed into a separate group. In addition, the left ventricular end systolic volume (LVESV) for each patient was also considered in the statistical model as a covariate; as such, only the 98 patients who had measurements of both variables at baseline are able to be included in this analysis. Patients who received a CRT and who had a baseline galectin-3 level above 30 ng/mL had an approximately three times higher odds of death within 18 months or hospitalization within 18 months compared to patients who received a CRT and who had a baseline galectin-3 level less than or equal to 30 ng/mL.

[0055] Table 2.

Results of logistic regression analysis for the endpoint of death or hospitalization within 18 months, for patients who received CRT. Odds ratio for galectin-3 is relative to the group with baseline galectin-3 less than or equal to 30 ng/mL; odds ratio for LVESV is relative to the group with LVESV less than or equal to 200 mL.

Variable	Odds Ratio and 95% confidence interval (95% CI)	P-value
Baseline Galectin-3 > 30 ng/mL	3.31 (95% CI: 1.17-9.32)	0.024
Baseline LVESV > 200 mL	2.81 (95% CI: 0.99-7.93)	0.051

Galectin-3 concentrations at baseline are significantly associated with outcome among patients who received CRT but not among patients who did not receive CRT

[0056] It was observed that baseline galectin-3 serum concentration was significantly associated with the risk of a subsequent adverse outcome, namely death within 18 months or unplanned hospitalization within 18 months of baseline, in patients who received CRT, but not in patients who did not receive CRT. Table 3 below displays the results of a statistical logistic regression analysis to assess the association between baseline galectin-3 and subsequent adverse outcome. This analysis was performed separately for patients who received CRT, and for patients who did not receive CRT. For details on the technique of logistic regression, see e.g. David W. Hosmer and Stanley Lemeshow, Applied logistic regression (New York: Wiley, 2000). In the analyses, data from patients with a baseline galectin-3 levels greater than 30 ng/mL were placed into one group, and data from patients with baseline galectin-3 levels less than or equal to 30 ng/mL were placed into a separate group. In addition, the left ventricular end systolic volume (LVESV) for each patient was also considered in the statistical models as a covariate. Table 3 presents the results of these analyses. There were 98 evaluable patients who received CRT, of whom 22 (22.4% of 98) experienced an adverse outcome of death or hospitalization within 18 months. There were 96 evaluable patients who did not receive CRT, of whom 29 (30.2% of 96) experienced an adverse outcome of death or hospitalization within 18 months.

Table 3. Results of logistic regression analysis for the endpoint of death or hospitalization within 18 months, analyzed separately for patients who received CRT and for patients who did not receive CRT. Odds ratio for galectin-3 is relative to the group with baseline galectin-3 less than or equal to 30 ng/mL; odds ratio for LVESV is relative to the group with LVESV less than or equal to 200 mL.

	Patients who received CRT		Patients who did not receive CRT	
Variable	Odds Ratio and 95% confidence interval (95% CI)	P-value	Odds Ratio and 95% confidence interval (95% CI)	P-value
Baseline Galectin-3 > 30 ng/mL	3.31 (95% CI: 1.17-9.32)	0.024	2.92 (95% CI: 0.99-8.54)	0.051
Baseline LVESV > 200 mL	2.81 (95% CI: 0.99-7.93)	0.051	3.96 (95% CI: 1.38-11.38)	0.011

[0057] It was found that only among patients who received CRT was baseline galectin-3 statistically significantly associated with the adverse outcome of death or hospitalization within 18 months with the pre-specified statistical significance level. Baseline galectin-3 in the group of patients who did not receive CRT was not significantly associated with the same adverse outcome endpoint at the prescribed significance level of less than 0.05, and the 95% confidence interval in that group overlapped the null odds ratio value of 1, or unity.

CRT is associated with reduced event rates overall but with a larger reduction in patients with higher Galectin-3 concentrations

[0058] The number of patients in each of four categories who experienced an event of death or unplanned hospitalization for heart failure within 18 months of baseline is enumerated in Table 4 below. This table includes all patients from the study whose baseline blood sample had a galectin-3 baseline concentration value, and who were successfully followed for 18 months such that the endpoint of death or unplanned hospitalization for heart failure within 18 months of baseline could be ascertained.

[0059] **Table 4.** Numbers of patients, by CRT treatment and galectin-3 category. The number and percentage of events is indicated in each cell of the table. The event in this table is defined as death or unplanned hospitalization for heart failure within 18 months of baseline.

	Patients who received CRT	Patients who did not receive CRT
Baseline Galectin-3 > 30 ng/mL	Events: 10 No events: 20 Percentage experiencing event: 10/(10+20) = 33.3%	Events: 12 No events: 16 Percentage experiencing event: 42.9%
Baseline Galectin-3 ≤ 30 ng/mL	Events: 15 No events: 66 Percentage experiencing event: 18.5%	Events: 21 No events: 55 Percentage experiencing event: 27.6%

[0060] As may be observed from Table 4, patients who received CRT exhibited a decreased event frequency compared to patients who did not receive CRT. It is noted that in the low galectin-3 group, namely patients with baseline galectin-3 levels ≤ 30 ng/mL, the absolute reduction in event frequency was 9.1% (27.6% minus 18.5%). In the high galectin-3 group, namely patients with baseline galectin-3 levels > 30 ng/mL, the absolute reduction in event frequency was 9.6% (42.9% minus 33.3%). These data likely indicate that higher baseline galectin-3 values identify patients who exhibit a larger benefit from CRT, because the 9.6% reduction in the higher baseline galectin-3 group is greater than the 9.1 % reduction in the lower baseline galectin-3 group.

[0061] The foregoing embodiments are to be considered in all respects illustrative rather than limiting on the invention described herein.

SEQUENCE LISTING

[0062]

<110> BG Medicine, Inc. Muntendam, Pieter

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Claims

1. A method of predicting responsiveness to cardiac resynchronization therapy of a human who is a candidate for or has been treated with cardiac resynchronization therapy, the method comprising measuring a galectin-3 blood concentration in a sample from the human, thereby to determine the presence or absence of a galectin-3 blood concentration in the human predictive of responsiveness to cardiac resynchronization therapy.

2. The method of claim 1, wherein the human is a candidate for cardiac resynchronization therapy.

3. The method of claim 1, wherein the human has been treated with cardiac resynchronization therapy.

4. A method according to any one of claims 1-3, wherein the sample comprises blood, serum or plasma.

5. A method according to any one of claims 1-4, wherein responsiveness comprises improved survival, fewer unplanned hospitalizations for worsening heart failure, improved heart strength, decreased fatigue, reduced shortness of breath, or reduced sleep apnoea.

6. A method according to any one of claims 3-5, wherein the human has been implanted with a cardiac resynchronization device.

7. A method according to claim 6 wherein said cardiac resynchronization device comprises a defibrillator.

8. A method according to any one of claims 1-7, wherein the patient has a galectin-3 blood concentration determined to be within a target range.

9. A method according to any one of claims 1-8, wherein the patient has a galectin-3 blood concentration determined to be above a minimum threshold.

10. The method of claim 9, wherein the minimum threshold is: (a) more than 10 ng/ml; or (b) between 10 and 15 ng/ml; or (c) between 15 and 20 ng/ml; or (d) between 20 and 25 ng/ml.

11. The method of claim 9, wherein the minimum threshold is between 25 and 30 ng/ml

12. The method of claim 9, wherein the minimum threshold is more than 30 ng/ml.

13. A method according to any of claims 1-8, wherein the patient has a galectin-3 blood concentration determined to be below a maximum threshold, optionally wherein the maximum threshold is: (a) below 70 ng/ml; or (b) below 60 ng/ml; or (c) below 40 ng/ml; or (d) between 30 and 40 ng/ml; or (e) between 25 and 30 ng/ml; or (f) between 20 and 25 ng/ml; or (g) between 15 and 20 ng/ml.

14. A method according to any of claims 1-13, wherein the galectin-3 is detected using an antibody that binds to an epitope defined by GNPNPQGWPGA (SEQ ID NO:5).

15. A method according to any of claims 1-14, wherein the galectin-3 is detected using an antibody that binds to an epitope defined by YPGQAPPGAYPGQAPPGA (SEQ ID NO:7).

Patentansprüche

1. Verfahren zum Voraussagen des Ansprechens eines Menschen, der ein Kandidat für eine Herzsynchronisationstherapie ist oder damit behandelt wurde, auf die Herzsynchronisationstherapie, wobei das Verfahren ein Messen einer Galectin-3-Blutkonzentration in einer Probe des Menschen aufweist, um dadurch die An- oder Abwesenheit einer Galectin-3-Blutkonzentration in dem Menschen zu bestimmen, die voraussagend für das Ansprechen auf die Herzsynchronisationstherapie ist.

2. Verfahren nach Anspruch 1, wobei der Mensch ein Kandidat für die Herzresynchronisationstherapie ist.

3. Verfahren nach Anspruch 1, wobei der Mensch mit der Herzsynchronisationstherapie behandelt worden ist.

4. Verfahren nach einem der Ansprüche 1 bis 3, wobei die Probe Blut, Serum oder Plasma aufweist.

5. Verfahren nach einem der Ansprüche 1 bis 4, wobei das Ansprechen ein verbessertes Überleben, weniger ungeplante Krankenhausaufenthalte auf Grund einer Verschlechterung von Herzinsuffizienz, verbesserte Herzstärke, verringerte Erschöpfung, verringerte Kurzatmigkeit oder verringerte Schlafapnoe aufweist.

6. Verfahren nach einem der Ansprüche 3 bis 5, wobei dem Menschen eine Herzresynchronisationsvorrichtung implantiert wurde.

7. Verfahren nach Anspruch 6, wobei die Herzresynchronisationsvorrichtung einen Defibrillator aufweist.

8. Verfahren nach einem der Ansprüche 1 bis 7, wobei der Patient eine Galectin-3-Blutkonzentration aufweist, die innerhalb eines Zielbereichs liegt.

9. Verfahren nach einem der Ansprüche 1 bis 8, wobei der Patient eine Galectin-3-Blutkonzentration aufweist, die oberhalb eines minimalen Grenzwertes liegt.

10. Verfahren nach Anspruch 9, wobei der minimale Grenzwert beträgt: (a) mehr als 10 ng/ml; oder (b) zwischen 10 und 15 ng/ml; oder (c) zwischen 15 und 20 ng/ml; oder (d) zwischen 20 und 25 ng/ml.

11. Verfahren nach Anspruch 9, wobei der minimale Grenzwert zwischen 25 und 30 ng/ml liegt.

12. Verfahren nach Anspruch 9, wobei der minimale Grenzwert mehr als 30 ng/ml beträgt.

13. Verfahren nach einem der Ansprüche 1 bis 8, wobei der Patient eine Galectin-3-Blutkonzentration aufweist, die unterhalb eines maximalen Grenzwertes liegt, wobei optional der maximale Grenzwert beträgt: (a) unter 70 ng/ml; oder (b) unter 60 ng/ml; oder (c) unter 40 ng/ml; oder (d) zwischen 30 und 40 ng/ml; oder (e) zwischen 25 und 30 ng/ml; oder (f) zwischen 20 und 25 ng/ml; oder (g) zwischen 15 und 20 ng/ml.

14. Verfahren nach einem der Ansprüche 1 bis 13, wobei das Galectin-3 unter Verwendung eines Antikörpers detektiert wird, der an ein Epitop bindet, das durch GNPNPQGWPGA (SEQ ID NO:5) definiert ist.

15. Verfahren nach einem der Ansprüche 1 bis 14, wobei das Galectin-3 unter Verwendung eines Antikörpers detektiert wird, der an ein Epitop bindet, das durch YPGQAPPGAYPGQAPPGA (SEQ ID NO:7) definiert ist.

Revendications

1. Procédé de prédiction de la réponse à une thérapie de resynchronisation cardiaque d'un humain qui est un candidat pour ou a été traité par une thérapie de resynchronisation cardiaque, le procédé comprenant la mesure d'une concentration sanguine en galectine-3 dans un échantillon prélevé sur l'humain, pour ainsi déterminer la présence ou l'absence d'une concentration sanguine en galectine-3 chez l'humain permettant de prédire la réponse à la thérapie de resynchronisation cardiaque.

2. Procédé selon la revendication 1, dans lequel l'humain est un candidat pour une thérapie de resynchronisation cardiaque.

3. Procédé selon la revendication 1, dans lequel l'humain a été traité par une thérapie de resynchronisation cardiaque.

4. Procédé selon l'une quelconque des revendications 1 à 3, dans lequel l'échantillon comprend du sang, du sérum ou du plasma.

5. Procédé selon l'une quelconque des revendications 1 à 4, dans lequel la réponse comprend une meilleure chance de survie, moins d'hospitalisations non planifiées pour insuffisance cardiaque aggravée, une meilleure résistance cardiaque, une diminution de la fatigue, une réduction de l'essoufflement ou une réduction de l'apnée du sommeil.

6. Procédé selon l'une quelconque des revendications 3 à 5, dans lequel un dispositif de resynchronisation cardiaque a été implanté chez l'humain.

7. Procédé selon la revendication 6, dans lequel ledit dispositif de resynchronisation cardiaque comprend un défibrillateur.

8. Procédé selon l'une quelconque des revendications 1 à 7, dans lequel le patient présente une concentration sanguine en galectine-3 qui est déterminée pour être au sein d'une plage cible.

9. Procédé selon l'une quelconque des revendications 1 à 8, dans lequel le patient présente une concentration sanguine en galectine-3 qui est déterminée pour être au-dessus d'un seuil minimal.

10. Procédé selon la revendication 9, dans lequel le seuil minimal est : (a) de plus de 10 ng/ml ; ou (b) entre 10 ng/ml et 15 ng/ml ; ou (c) entre 15 ng/ml et 20 ng/ml ; ou (d) entre 20 ng/ml et 25 ng/ml.

11. Procédé selon la revendication 9, dans lequel le seuil minimal est entre 25 ng/ml et 30 ng/ml.

12. Procédé selon la revendication 9, dans lequel le seuil minimal est de plus de 30 ng/ml.

13. Procédé selon l'une quelconque des revendications 1 à 8, dans lequel le patient présente une concentration sanguine en galectine-3 qui est déterminée pour être inférieure à un seuil maximal, facultativement dans lequel le seuil maximal est : (a) inférieur à 70 ng/ml ; ou (b) inférieur à 60 ng/ml ; ou (c) inférieur à 40 ng/ml ; ou (d) entre 30 ng/ml et 40 ng/ml ; ou (e) entre 25 ng/ml et 30 ng/ml ; ou (f) entre 20 ng/ml et 25 ng/ml ; ou (g) entre 15 ng/ml et 20 ng/ml.

14. Procédé selon l'une quelconque des revendications 1 à 13, dans lequel la galectine-3 est détectée à l'aide d'un anticorps qui se lie à un épitope défini par GNPNPQGWPGA (SEQ ID NO : 5).

15. Procédé selon l'une quelconque des revendications 1 à 14, dans lequel la galectine-3 est détectée à l'aide d'un anticorps qui se lie à un épitope défini par YPGQAPPGAYPGQAPPGA (SEQ ID NO : 7).

REFERENCES CITED IN THE DESCRIPTION

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专利名称(译)	Galectin-3和心脏再同步治疗		
公开(公告)号	EP2470911A4	公开(公告)日	2013-08-14
申请号	EP2010815852	申请日	2010-08-25
[标]申请(专利权)人(译)	BG医药		
申请(专利权)人(译)	BG医药，INC.		
当前申请(专利权)人(译)	BG医药，INC.		
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外部链接	Espacenet		

摘要(译)

本发明涉及用于监测和预测心力衰竭患者对心脏再同步治疗的生理反应的材料和方法。更具体地，本发明涉及内源性蛋白质半乳糖凝集素-3及其在监测进行心脏再同步治疗的患者的疾病进展中的用途，以及作为对心脏再同步治疗的响应的预测因子。