

diagnosis is pivotal for enabling the correct treatment regimens, including those treatments which are approved and specific to the given pathology and opening for the possibility for testing combination treatment with therapies of Hsp70 supplementing and induction.

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A reduced level of Hsp70 has been demonstrated in brain tissue and liver tissue samples from a Niemann Pick disease Type C mouse model. However, a biomarker found in tissues such as brain tissue and liver tissue samples is not considered applicable in terms of diagnosing of NPC, let alone any other disease presenting with a reduced level of Hsp70. Hence, other means for identifying diseases presenting with a reduced level of Hsp70 are warranted.

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The present inventors have surprisingly found that specifically peripheral blood mononuclear cell (PBMC) samples from patients with Niemann Pick disease Type C contain substantially reduced or decreased levels of Heat Shock Protein 70 (Hsp70), as compared to healthy controls.

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A PBMC sample can be easily obtained from an individual by simply drawing a blood sample, and performing a few simple steps of separation and isolation of PBMCs. Hence, the new observation that the low Hsp70 levels observed in pathologically afflicted disease tissue, including brain and liver tissue, directly translate into low levels of Hsp70 protein in PBMC samples, provides a simple, easy and facile detection means of Hsp70 levels.

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In one aspect, the present disclosure refers to a method of detecting Hsp70 in a peripheral blood mononuclear cell (PBMC) sample, said method comprising the steps of

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- a) detecting Hsp70 in said PBMC sample obtained from an individual, and
- b) optionally quantifying or determining the level of Hsp70 in said PBMC sample.

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In another aspect, the present disclosure refers to a method for diagnosing a disease presenting with a reduced level of Hsp70 in an individual, said method comprising the steps of:

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- a) detecting Hsp70 in a PBMC sample obtained from an individual, and
- b) quantifying or determining the level of Hsp70 in said PBMC sample.

In another aspect, the present disclosure refers to a method for selecting a patient having a disease presenting with a reduced level of Hsp70, said method comprising the steps of

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- a) detecting Hsp70 in a PBMC sample obtained from an individual,
 - b) quantifying or determining the level of Hsp70 in said PBMC sample, and
 - c) classifying or determining whether or not the individual has reduced levels of Hsp70.

10 In yet another aspect, the present disclosure refers to a method for monitoring disease progression in an individual having a disease presenting with a reduced level of Hsp70, said method comprising the steps of

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- i. detecting Hsp70 in each of one or more PBMC samples obtained from said individual at two or more subsequent points in time,
 - ii. quantifying or determining the level of Hsp70 in each of said PBMC samples.

20 In yet another aspect, the present disclosure refers to a method for monitoring efficacy of a therapy for treatment of a disease presenting with a reduced level of Hsp70 in an individual having a disease presenting with a reduced level of Hsp70, said method comprising the steps of

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- a) detecting Hsp70 in each of said one or more PBMC samples obtained from said individual before, during and/or after a therapy has been applied, maintained, reduced or elevated,
 - b) quantifying or determining the level of Hsp70 in each of said one or more PBMC samples.

30 In yet another aspect, the present disclosure refers to a method for adjusting dosage of a small molecule hydroxylamine derivative capable of increasing the intracellular concentration (or levels) of Hsp70 in an individual by amplifying Hsp70 gene expression, the method comprising the steps of:

- a) detecting Hsp70 in said PBMC sample obtained from an individual,
- b) quantifying or determining a first level of Hsp70 in said PBMC sample,
- c) said small molecule hydroxylamine derivative is to be administered at a first dose,

- d) repeating steps a) – b) to identify a second level of Hsp70 in said PBMC sample,
 - e) comparing said first level to the second level of Hsp70, and
 - f) optionally adjusting the dosage of the small molecule hydroxylamine derivative based on said comparison.
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It is an example of the present disclosure to provide a method of detecting Hsp70 in a peripheral blood mononuclear cell (PBMC) sample, said method comprising the steps of

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- a) providing a PBMC sample, and
 - b) detecting Hsp70 in said PBMC sample, and
 - c) optionally quantifying or determining the level of Hsp70 in said PBMC sample.

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- In a further example of the present disclosure there is provided a method for diagnosing a disease presenting with a reduced level of Hsp70 in an individual, said method comprising the steps of:

- a) providing a PBMC sample from said individual,
- b) detecting Hsp70 in said PBMC sample,
- c) quantifying or determining the level of Hsp70 in said PBMC sample, and
- d) optionally, classifying or determining whether or not the individual has, or is likely to have, a disease presenting with a reduced level of Hsp70.

In a further example of the present disclosure there is provided a method for selecting a patient having a disease presenting with a reduced level of Hsp70, said method comprising the steps of

- a) providing a PBMC sample from said patient,
- b) detecting Hsp70 in said PBMC sample,
- c) quantifying or determining the level of Hsp70 in said PBMC sample, and
- d) classifying or determining whether or not the individual has reduced levels of Hsp70.

In a further example of the present disclosure there is provided a method for monitoring disease progression in an individual having a disease presenting with a reduced level of Hsp70, said method comprising the steps of

- i. providing one or more PBMC samples from said individual at two or more subsequent points in time,
- ii. detecting Hsp70 in each of said PBMC samples,
- iii. quantifying or determining the level of Hsp70 in each of said PBMC samples.

In a further example of the present disclosure there is provided a method for monitoring efficacy of a therapy for treatment of a disease presenting with a reduced level of Hsp70 in an individual having a disease presenting with a reduced level of Hsp70, said method comprising the steps of

- a) providing one or more PBMC samples from said individual before, during and/or after a therapy has been applied, maintained, reduced or elevated,
- b) detecting Hsp70 in each of said one or more PBMC samples,
- c) quantifying or determining the level of Hsp70 in each of said one or more PBMC samples.

In one example said disease presenting with a reduced level of Hsp70 is selected from the group consisting of a lysosomal storage disorder, a neurodegenerative disease, a neuromuscular disorder, muscular dystrophy and an inflammatory muscle disorder.

5 **Description of Drawings**

Figure 1. Quantification of the level of Hsp70 protein in PBMC samples isolated from individuals with Niemann Pick disease Type C (NPC) at a first and at a second clinical study visit, or from healthy individuals (controls). The level of Hsp70 was markedly reduced in PBMC samples obtained from NPC patients as compared with PBMC samples obtained from healthy controls, as determined by ELISA.

Figure 2. Comparison of the NPC-severity scale score (NPCCSS) with the Hsp70 level in PBMC samples obtained from individuals with Niemann Pick disease Type C. No correlation between Hsp70 level and NPCCSS was observed.

Figure 3. Comparison of the Hsp70 level in PBMC samples obtained from individuals with Niemann Pick disease Type C at a first and a second visit. The second clinical study visit was performed 6 to 14 months following the first clinical study visit. No change in Hsp70 level was observed over the time from clinical study visit 1 and 2.

Figure 4. HSP70 levels in NPC patients treated with arimoclomol incl. pretreatment.

Figure 5. HSP70 levels in NPC patients treated with arimoclomol.

30 **Detailed description**

The present invention is based on the finding of decreased levels of Hsp70 in peripheral blood mononuclear cells (PBMC) samples from patients with Niemann Pick disease Type C, a lysosomal storage disease presenting with reduced levels of Hsp70

Claims

1. A method of detecting Hsp70 in a peripheral blood mononuclear cell (PBMC) sample, said method comprising the steps of
 - 5 a) detecting Hsp70 in said PBMC sample obtained from an individual, and
 - b) optionally quantifying or determining the level of Hsp70 in said PBMC sample.
2. A method for diagnosing a disease presenting with a reduced level of Hsp70 in an individual, said method comprising the steps of:
 - 10 a) detecting Hsp70 in a PBMC sample obtained from an individual, and
 - b) quantifying or determining the level of Hsp70 in said PBMC sample.
3. The method according to claim 2 further comprising the step of
 - 15 i. classifying or determining whether or not the individual has, or is likely to have, a disease presenting with a reduced level of Hsp70.
4. A method for selecting a patient having a disease presenting with a reduced level of Hsp70, said method comprising the steps of
 - 20 a) detecting Hsp70 in a PBMC sample obtained from an individual,
 - b) quantifying or determining the level of Hsp70 in said PBMC sample, and
 - c) classifying or determining whether or not the individual has reduced levels of Hsp70.
- 25 5. The method according to any one of the preceding claims comprising detecting and optionally quantifying or determining Hsp70 selected from
 - i. HspA1A,
 - ii. HspA1B, or
 - 30 iii. HspA1A and HspA1B.
6. The method according to any one of the preceding claims, wherein said individual
 - 35 i) has, is suspected of having, is at risk of having or is likely to have, a disease presenting with a reduced level of Hsp70;
 - ii) has one or more family members diagnosed with a disease presenting with a reduced level of Hsp70; such as one or more of a sibling, a parent, a cousin, an

uncle and/or an aunt diagnosed with a disease presenting with a reduced level of Hsp70;

iii) has one or more family members with a genetic predisposition for a disease presenting with a reduced level of Hsp70; or

5 iv) has one or more symptoms associated with or indicative of a disease presenting with a reduced level of Hsp70.

7. The method according to any one of claims 4-6, wherein said step c) comprises determining the level of Hsp70 in the PBMC sample as compared to the levels in a
10 PBMC sample obtained from a healthy control.

8. The method according to any one of the preceding claims, wherein

i. a reduced or undetectable level of Hsp70 in the PBMC sample as compared to levels in a healthy control is indicative of the individual having,
15 likely to have or at risk of having a disease presenting with a reduced level of Hsp70; and/or

ii. a reduced or undetectable level of HspA1A in the PBMC sample as compared to levels in a healthy control is indicative of the individual having,
likely to have or at risk of having a disease presenting with a reduced level
20 of Hsp70; and/or

iii. a reduced or undetectable level of HspA1B in the PBMC sample as compared to levels in a healthy control is indicative of the individual having,
likely to have or at risk of having disease presenting with a reduced level of
Hsp70, and/or

25 iv. a level of Hsp70, HspA1A and/or HspA1B in the sample which is comparable to, equal to or higher than the level in a healthy control is indicative of the individual not having a disease presenting with a reduced level of Hsp70.

30 9. The method according to any one of the preceding claims, wherein the individual is likely to have a disease presenting with a reduced level of Hsp70 if

i. the level of Hsp70 in the PBMC sample is 1 to 1000 times lower than the level found in healthy controls, such as 1 to 2 times, 2 to 3 times, 3 to 4
times, 4 to 5 times, 5 to 6 times, 6 to 7 times, 7 to 8 times, 8 to 9 times, 9 to
35 10 times, 10 to 11 times, 11 to 12 times, 12 to 13 times, 13 to 14 times, 14 to 15 times, 15 to 16 times, 16 to 17 times, 17 to 18 times, 18 to 19 times,

- 19 to 20 times, 20 to 25 times, 25 to 30 times, 30 to 35 times, 35 to 40 times, 40 to 45 times, 45 to 50 times, 50 to 75 times, 75 to 100 times, 100 to 150 times, 150 to 200 times, 200 to 250 times, 250 to 300 times, 300 to 400 times, 400 to 500 times, 500 to 750 times, 750 to 1000 times lower than the level found in a healthy control, or undetectable, and/or
- 5 ii. the level of HspA1A and/or HspA1B in the PBMC sample is 1 to 1000 times lower than the level found in healthy controls, such as 1 to 2 times, 2 to 3 times, 3 to 4 times, 4 to 5 times, 5 to 6 times, 6 to 7 times, 7 to 8 times, 8 to 9 times, 9 to 10 times, 10 to 11 times, 11 to 12 times, 12 to 13 times, 13 to 14 times, 14 to 15 times, 15 to 16 times, 16 to 17 times, 17 to 18 times, 18 to 19 times, 19 to 20 times, 20 to 25 times, 25 to 30 times, 30 to 35 times, 35 to 40 times, 40 to 45 times, 45 to 50 times, 50 to 75 times, 75 to 100 times, 100 to 150 times, 150 to 200 times, 200 to 250 times, 250 to 300 times, 300 to 400 times, 400 to 500 times, 500 to 750 times, 750 to 1000 times lower than the level found in a healthy control, or undetectable.
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10. The method according to any one of claims 4-7, wherein said step c) of classifying or determining an individual as having, or likely to have, a disease presenting with a reduced level of Hsp70 comprises
- 20 i. determining if the amount of Hsp70 in said PBMC sample is below a predefined cut-off value, or undetectable; and/or
- ii. determining if the amount of HspA1A and/or HspA1B in said PBMC sample is below a predefined cut-off value, or undetectable.
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11. The method according to any one of the preceding claims, wherein the individual has or is likely to have a disease presenting with a reduced level of Hsp70 if the amount of Hsp70 in said PBMC sample is 7500 pg/mL or less, such as 7000 pg/mL or less, such as 6500 pg/mL or less, such as 6000 pg/mL or less, such as 5500 pg/mL or less, such as 5000 pg/mL or less, such as 4500 pg/mL or less, such as 4000 pg/mL or less, such as 3500 pg/mL or less, such as 3000 pg/mL or less, such as 2500 pg/mL or less, such as 2000 pg/mL or less, such as 1500 pg/mL or less, such as 1000 pg/mL PBMC or less.
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12. The method according to any one of claims 4-7, wherein the step of classifying or determining whether or not the patient has reduced levels of Hsp70 comprises a step of identifying a patient with reduced levels of Hsp70.
- 5 13. The method according to any one of claims 4-7 and 12, wherein the step of classifying or determining whether or not the patient has reduced levels of Hsp70 comprises determining the level of Hsp70 in the PBMC sample as compared to the levels in a PBMC sample obtained from a patient presenting with the same underlying disease but not having accompanying reduced levels of Hsp70.
- 10 14. The method according to any one of claims 4-7 and 12-13, wherein said step c) of classifying or determining whether or not the patient has reduced levels of Hsp70, comprises
 - i. determining if the amount of Hsp70 in said PBMC sample is below a predefined cut-off value, or undetectable; and/or
 - 15 ii. determining if the amount of HspA1A and/or HspA1B in said PBMC sample is below a predefined cut-off value, or undetectable.
- 20 15. The method according to any one of claims 4-7 and 12-14, wherein the patient is likely, or more likely, to respond to Hsp70 therapies including bioactive agents that increase the intracellular concentration and/or activity of heat shock proteins, including Hsp70, if the amount of Hsp70 is below said cut-off value.
- 25 16. The method according to any one of claims 4-7 and 12-15, wherein the patient presenting with a reduced level of Hsp70 is likely, or more likely, to respond to Hsp70 therapies if the amount of Hsp70 (such as HspA1A and/or HspA1B) in said PBMC sample is 7500 pg/mL or less, such as 7000 pg/mL or less, such as 6500 pg/mL or less, such as 6000 pg/mL or less, such as 5500 pg/mL or less, such as 5000 pg/mL or less, such as 4500 pg/mL or less, such as 4000 pg/mL or less, such as 3500 pg/mL or less, such as 3000 pg/mL or less, such as 2500 pg/mL or less, such as 2000 pg/mL or less, such as 1500 pg/mL or less, such as 1000 pg/mL PBMC or less.
- 30 17. The method according to any one of claims 4-7 and 12-16 further comprising a step of determining eligibility of said patient that a therapy is to be administered for treatment of said disease presenting with a reduced level of Hsp70 to the patient,
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such as Hsp70 therapies including bioactive agents that increase the intracellular concentration and/or activity of heat shock proteins, including Hsp70.

- 5 18. The method according to any one of the preceding claims further comprising the step that
- i. a therapy is to be administered for treatment of a disease presenting with a reduced level of Hsp70.

- 10 19. The method according to any one of the preceding claims, wherein the PBMC sample obtained from an individual comprises a step of
- i. separating whole blood obtained from an individual into its subcomponents to obtain a PBMC sample.

- 15 20. A method for monitoring disease progression in an individual having a disease presenting with a reduced level of Hsp70, said method comprising the steps of
- i. detecting Hsp70 in each of one or more PBMC samples obtained from said individual at two or more subsequent points in time,
 - ii. quantifying or determining the level of Hsp70 in each of said PBMC samples.

- 20 21. The method according to claim 20, wherein a first PBMC sample is taken at $t=0$ and one or more subsequent PBMC samples are taken at one or more later time points at $t>0$.

- 25 22. The method according to any one of claims 20-21, wherein one or more subsequent samples are taken at an interval of 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months and/or 12 months.

- 30 23. The method according to any one of claims 20-22, said method further comprising the step of determining whether the disease presenting with a reduced level of Hsp70 is in progression or in remission.

- 35 24. The method according to any one of claims 20-23, wherein

- a) a decrease in the level of Hsp70 over time is indicative of a progression of the disease; and/or
- b) an increase in the level of Hsp70 over time is indicative of a remission of the disease.

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25. A method for monitoring efficacy of a therapy for treatment of a disease presenting with a reduced level of Hsp70 in an individual having a disease presenting with a reduced level of Hsp70, said method comprising the steps of

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- a) detecting Hsp70 in each of said one or more PBMC samples obtained from said individual before, during and/or after a therapy has been applied, maintained, reduced or elevated,
- b) quantifying or determining the level of Hsp70 in each of said one or more PBMC samples.

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26. The method according to claim 25, wherein

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- i. one or more PBMC samples are obtained from an individual having a disease presenting with a reduced level of Hsp70 before a therapy has been applied, maintained, reduced or elevated;
- ii. one or more PBMC samples are obtained from an individual having a disease presenting with a reduced level of Hsp70 during a therapy; and/or
- iii. one or more PBMC samples are obtained from an individual having a disease presenting with a reduced level of Hsp70 after a therapy has been applied, maintained, reduced or elevated; and/or;
- iv. one or more PBMC samples are obtained from an individual having a disease presenting with a reduced level of Hsp70 before, during and/or after a therapy has been applied, maintained, reduced or elevated.

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27. The method according to any one of claims 25-26, said method further comprising the step of c) monitoring efficacy of a therapy for a disease presenting with a reduced level of Hsp70.

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28. The method according to any one of claims 25-27, wherein

- a) an increase in the level of Hsp70, after a therapy has been applied, maintained, reduced or elevated, is indicative of the therapy being efficacious; and/or

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- b) a decrease in the level of Hsp70, after a therapy has been applied, maintained, reduced or elevated, is indicative of the therapy being inefficacious.

- 5 29. The method according to any one of the preceding claims, wherein said detecting Hsp70 comprises detecting Hsp70 protein or RNA, such as Hsp70 protein.
30. The method according to any one of the preceding claims, wherein said Hsp70 is detected and quantified by means of enzyme-linked immunosorbent assay (ELISA).
- 10 31. The method according to any one of the preceding claims, wherein step b) quantifying or determining the level Hsp70 in a sample comprises one or more steps of
 - i. normalizing to a calibrated standard, and
 - 15 ii. quantification of Hsp70 in said PBMC sample.
32. The method according to any one of claims 25-31, wherein 'a therapy for treatment of a disease presenting with a reduced level of Hsp70' is a bioactive agent that increase the intracellular concentration and/or activity of heat shock proteins,

20 including Hsp70.
33. The method according to claim 32, wherein said bioactive agent that increase the intracellular concentration and/or activity of heat shock proteins, including Hsp70, is
 - 25 i) selected from Hsp70 protein, or a functional fragment or variant thereof, a heat shock protein inducer and a Hsp70 inducer or co-inducer;
 - ii) a small molecule hydroxylamine derivative capable of increasing the intracellular concentration (or levels) of Hsp70 by amplifying Hsp70 gene expression; or
 - iii) selected from the group consisting of arimoclomol, iroxanadine, bimoclomol, BGP-15, their stereoisomers and the acid addition salts thereof.
- 30 34. The method according to any one of the preceding claims, wherein said disease presenting with a reduced level of Hsp70 is a lysosomal storage disease, a neurodegenerative disease, a neuromuscular disorder, muscular dystrophy and an inflammatory muscle disorder.

35. The method according to any one of the preceding claims, wherein said disease presenting with a reduced level of Hsp70 is a lysosomal storage disease.
36. The method according to claim 35, wherein said lysosomal storage disease is selected from the group consisting of a lipid storage disorder including the sphingolipidoses; mucopolysaccharidoses; glycogen storage disorders; disorders of glycoprotein metabolism (glycoproteinosis); and mucolipidoses.
37. The method according to claim 36, wherein said lysosomal storage disease is a sphingolipidosis.
38. The method according to claim 35, wherein said lysosomal storage disease is selected from the group consisting of Niemann Pick disease (including types A, B and C), Farber disease, Krabbe disease, Fabry disease, Gaucher disease, Sialidosis (Mucolipidosis type I), sulfatidosis including Metachromatic leukodystrophy (late infantile, juvenile, and adult forms), saposin-deficiency, Multiple sulfatase deficiency (Austin disease), Gaucher disease (including type I, type II and type III), cerebrotendinous cholesterosis, Wolman's disease (Lysosomal acid lipase deficiency), cholesteryl ester storage disease, neuronal ceroid lipofuscinosis (NCL, including Batten disease (Spielmeyer-Vogt disease), Bielschowsky-Jansky disease, Kufs disease, Santavuori-Haltia disease), mucopolysaccharidosis (type I, type II, type III, type IV, type VI, type VII, type VIII and type IX), mucolipidosis (type II, type III and type IV), cardiac glycogenosis, Andersen disease, Cori disease (Forbes disease), Hers disease, McArdle disease, Pompe disease, Tauri disease (Tarui disease), von Gierke disease, type II Pompe disease, type IIb Danon disease, aspartylglucosaminuria, fucosidosis, annosidosis, alpha-mannosidosis, alpha-mannosidosis type I, alpha-mannosidosis type II, beta-mannosidosis, sialidosis type II (mucolipidosis I) and galactosialidosis.
39. The method according to claim 35, wherein said lysosomal storage disease is Niemann Pick disease, such as Niemann Pick disease Type C.
40. The method according to claim 34, wherein said neurodegenerative disease is selected from the group consisting of Parkinson's disease, Alzheimer's disease, Amyotrophic lateral sclerosis (ALS), Multiple Sclerosis, Huntington's disease, polyglutamine diseases and the spinocerebellar ataxias including Spinocerebellar

ataxia type 1, Spinocerebellar ataxia type 2, Spinocerebellar ataxia type 3 (aka Machado-Joseph's disease), Spinocerebellar ataxia type 6, Spinocerebellar ataxia type 7 and Spinocerebellar ataxia type 17), DRPLA (Dentatorubropallidoluysian atrophy) and SBMA (Spinobulbar muscular atrophy or Kennedy disease).

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41. The method according to claim 34, wherein said neuromuscular disorder is selected from the group consisting of Amyotrophic lateral sclerosis (ALS), Multiple Sclerosis, Parkinson's disease, Huntington's disease, Creutzfeldt–Jakob disease, Myasthenia gravis, Spinal Muscular Atrophy (SMA), Spinal muscular atrophy with respiratory distress type 1 (SMARD1; aka. Distal spinal muscular atrophy type 1 (DSMA1)), Congenital myasthenic syndrome (CMS), Congenital myopathy, Cramp fasciculation syndrome, Muscular dystrophies, Hereditary spastic paraplegia, Inclusion body myositis, Neuromyotonia (NMT, aka Isaacs syndrome, Isaacs-Merton syndrome), Mitochondrial myopathy, Lambert–Eaton myasthenic syndrome (LEMS), Myotonic dystrophy, Peripheral neuropathy, Spinal and bulbar muscular atrophy (SBMA, or Kennedy's disease), Stiff person syndrome and Guillain–Barré syndrome.

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42. The method according to claim 34, wherein said Muscular dystrophy is selected from the group consisting of Duchenne muscular dystrophy (DMD), Becker muscular dystrophy, Congenital muscular dystrophy, Distal muscular dystrophy, Emery–Dreifuss muscular dystrophy, Facioscapulohumeral muscular dystrophy, Limb-girdle muscular dystrophy, Myotonic muscular dystrophy and Oculopharyngeal muscular dystrophy.

43. The method according to any claim 34, wherein said inflammatory muscle disorder is selected from the group consisting of Inflammatory myopathy (inflammatory muscle disease or myositis), idiopathic Inflammatory myopathy, Polymyositis (PM), dermatomyositis (DM), Inclusion-body myositis (sIBM and hIBM), Polymyalgia rheumatica (or "muscle rheumatism") and Rhabdomyolysis.

44. A method for adjusting dosage of a small molecule hydroxylamine derivative capable of increasing the intracellular concentration (or levels) of Hsp70 in an individual by amplifying Hsp70 gene expression, the method comprising the steps of:

a) detecting Hsp70 in said PBMC sample obtained from an individual,

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- b) quantifying or determining a first level of Hsp70 in said PBMC sample,
 - c) said small molecule hydroxylamine derivative is to be administered at a first dose,
 - d) repeating steps a) – b) to identify a second level of Hsp70 in said PBMC sample,
 - e) comparing said first level to the second level of Hsp70, and
 - f) optionally adjusting the dosage of the small molecule hydroxylamine derivative based on said comparison.