

**PW 24:
Pharmacological
therapies –
Target identification/
clinical trials**

PW24-293	<u>MODIFICATION OF PROTEOTOXICITY ASSOCIATED TO NEUROMUSCULAR DISEASES: GENETIC ANALYSIS IN C. ELEGANS</u> PASCO M ¹ , CATOIRE H ¹ , TOURETTE C ¹ , PARKER A ¹ , NERI C ¹ (1) Inserm, Paris, FRANCE.
To contact the author:: neri@broca.inserm.fr.	<p>The goal of our study is to identify signalling pathways and networks that may modify proteotoxicity associated to neuromuscular diseases. The rationale of our study is that genetic/biological modifiers of proteotoxicity may constitute a useful source of disease targets and markers. We use a combination of genetic and pharmacological manipulations to test whether genes and compounds may modify the cytotoxicity produced by disease protein expression in transgenic nematodes. Results will be presented showing that disease protein expression produces cellular and behavioral defects in <i>C. elegans</i> transgenics and allows conserved modulators of proteotoxicity to be identified, some of them which may be manipulated by pharmacological means. Our data suggest that <i>C. elegans</i> genetics may be a useful translational research component and starting point to screen for neuromuscular disease targets by searching for in vivo modifiers of proteotoxicity.</p>

PW24-294	<p><u>INHIBITION OF PROTEASOME ACTIVITY PROMOTES THE CORRECT LOCALIZATION OF DISEASE-CAUSING ALPHA-SARCOGLYCAN MUTANTS IN A HETEROLOGOUS CELL SYSTEM EXPRESSING BETA-, GAMMA-, AND DELTA-SARCOGLYCAN</u></p> <p>SANDONÀ D¹, GASTALDELLO S¹, FRANZOSO S¹, FANIN M², ANGELINI C², VIDAL J³, BASSE N⁴, REBOUD-RAVAUX M⁴, BETTO R⁵</p> <p>(1) Department of Biomedical Sciences, University of Padova, Padova, ITALY. (2) Department of Neurological Sciences, University of Padova, Padova, ITALY. (3) Chimie et Photonique Moléculaires, CNRS - Université de Rennes 1, Rennes, FRANCE. (4) Equipe Enzymologie Moléculaire et Fonctionnelle, CNRS - Université Paris 6, Paris, FRANCE. (5) CNR Institute of Neuroscience, Padova, ITALY.</p>
To contact the author:: romeo.betto@bio.unipd.it	<p>Sarcoglycanopathies are progressive muscle wasting disorders caused by genetic defects of four proteins, α-, β-, γ-, and δ-sarcoglycan, elements of a key transmembrane complex of striated muscle. The proper assembly of the sarcoglycan complex represents a critical issue of sarcoglycanopathies, as several mutations severely perturb tetramer formation. Misfolded proteins are generally discarded through the cell's quality-control system that, however, could lead to the removal of functional polypeptides. To explore whether it is possible to rescue sarcoglycan mutants by preventing their degradation, we generated a heterologous cell system constitutively expressing three (α, β, and γ) of the four sarcoglycans. In these cells ($\alpha\beta\gamma$-HEK), the lack of δ-sarcoglycan prevented complex formation and cell surface localization, while the presence of δ-sarcoglycan allowed maturation and targeting of the tetramer. On the contrary, transfection of $\alpha\beta\gamma$-HEK cells with disease-causing δ-sarcoglycan mutants led to a dramatic reduction of mutated proteins, compared to wild type, and the absence of the complex from cell surface. This result closely reproduces the observations made in muscle patients. Proteasomal inhibition reduced the degradation of mutants and facilitated the assembly and targeting of the sarcoglycan complex to the plasma membrane. However, as expected for a critical process necessary for cell survival, the prolonged inhibition of proteasome severely compromised cell viability. Importantly, when the treatment included the inhibition of caspase activity, the cytotoxic effect of proteasome inhibitor was almost completely abolished. Finally, in a trial application of this approach to a skeletal muscle explant isolated from an LGMD-2D patient, incubation with the FDA-approved proteasome inhibitor Velcade (bortezomib) rescued the expression of mutant δ-sarcoglycan to the cell membrane. The present data provide important insights for the development of pharmacological therapies for sarcoglycanopathies. Funded by AFM (grant # 12988) and University of Padova.</p>

PW24-295	<p><u>SPECIFIC INHIBITION OF PROTEIN QUALITY CONTROL SYSTEM AS A THERAPEUTIC APPROACH FOR TREATMENT OF SARCOGLYCANOPATHIES.</u> SOHEILI T¹, GICQUEL E¹, BARRAULT L¹, BARTOLI M¹, RICHARD I¹ (1) Genethon/CNRS, Evry, FRANCE.</p>
To contact the author:: soheili@genethon.fr.	<p>Sarcoglycanopathies are recessive muscular disorders caused by defects in a group of transmembrane proteins, known as sarcoglycans, and part of the dystrophin-associated complex. Mutations in the α, β, γ and δ sarcoglycan genes lead to a similar phenotype and are referred as limb-girdle muscular dystrophies type 2D, 2E, 2C and 2F (LGMD2D, 2E, 2C and 2F) respectively. Dysfunction of one of the sarcoglycan destabilizes the whole sarcoglycan complex, leading to a partial or complete disappearance of the other sarcoglycans at the membrane. To date, no treatment exists for these diseases.</p> <p>The most frequently reported mutation in the α-sarcoglycan gene is the substitution of an arginine in position 77 by a cysteine (α-R77C). We demonstrated that this mutation encodes a misfolded protein that fails to be delivered to its proper sarcolemmal localization due to blockade in the endoplasmic reticulum (ER). The quality control system of the ER is an important monitoring mechanism in the protein maturation process, which ensures export of properly folded proteins from the ER. Incorrectly or incompletely folded proteins are retained in the ER for refolding or translocated in the cytosol for degradation by the ER associated proteasome (ERAD).</p> <p>We hypothesized that, by blocking the ER quality control system, we should be able to rescue the misfolded α-sarcoglycan protein at the cell membrane. Consistently, results of our experiments using an heterologous cellular model of sarcoglycan complex formation showed that the α-mannosidase I inhibitors prevent α-R77C degradation by proteasome/ERAD and restore correct localization of the protein. Furthermore, this membrane targeting allows the assembly of the sarcoglycan complex. Consequently, we were able to rescue other sarcoglycan mutations using the same approach. Overall, these results suggests a therapeutic approach for LGMD2 patients carrying mutations that impair sarcoglycan trafficking.</p>

PW24-296	<p>CHAPERONE MIMICS BASED STRATEGY TO TREAT NEUROMUSCULAR DISEASES SIMON S[†], ARRIGO AP¹ (1) CGMC-UMR5534-Université Claude Bernard Lyon1, Lyon, FRANCE.</p>
To contact the author:: arrigo@univ-lyon1.fr.	<p>Small stress proteins are characterized by a common alpha-crystallin domain. Among these proteins, Hsp27 and αB-Crystallin are oligomeric molecular chaperones that are highly expressed in pathological conditions such as those generated by neuromuscular diseases. These proteins share the ability to protect cells against the toxicity mediated by aberrantly folded proteins or oxidative-inflammation conditions. In addition, they have anti-apoptotic properties. The missense mutation R120G in human αB-Crystallin, which strongly decreases the chaperone activity of this protein, is associated <i>in vivo</i> with autosomal dominant myopathy, cardiomyopathy, and cataract (Vicart et al., 1998). In muscle cells, R120G mutant forms aggregates that contain desmin, the major chaperone substrate of αB-Crystallin. Consequently, the structural organization of muscle cells is disorganized. Overexpression of Hsp27 or Hsp22 (an other small stress protein) results in the formation of complex oligomeric structures containing R120 mutant. As a consequence, the toxicity induced by R120G mutant is reduced, probably because of the partial refolding and restoration of the activity of this mutant. This implies that it may be possible to restore the function of R120G mutant by chaperone mimics that interfere with the aggregative process of this deleterious protein. Recent approaches using peptides aptamers that specifically target this protein support this assumption.</p> <p>Since the expression of small stress proteins has implications in pathologies as diverse as neurodegeneration, myopathies, asthma, cataracts and cancers, approaches towards therapeutic strategies will be discussed.</p> <p><i>Arrigo, A. P., Simon, S., Gibert, B., Kretz-Remy, C., Nivon, M., Czekalla, A., Guillet, D., Moulin, M., Diaz-Latoud, C., and Vicart, P. (2007). Hsp27 (HspB1) and alphaB-crystallin (HspB5) as therapeutic targets. FEBS Lett.</i> <i>Vicart, P., Caron, A., Guicheney, P., Li, Z., Prevost, M. C., Faure, A., Chateau, D., Chapon, F., Tome, F., Dupret, J. M., et al. crystallin chaperone gene causes a desmin-related myopathy. Nat Genet 20, 92-95.</i></p>

PW24-297	<p><u>MYOSTATIN AND NOTCH SIGNALLING PATHWAYS: PARTNERS IN THE CONTROL OF POST-NATAL MYOGENESIS?</u> VERNUS B¹, CARNAC G², TASSISTRO V¹, KOECHLIN C¹, MORNET D², HUGON G², BONNIEU A¹ (1) Inra, UMR 866-Différenciation Cellulaire et Croissance, Montpellier, FRANCE. (2) Inserm, ERI 25-Muscle et Pathologies, Montpellier, FRANCE.</p>
To contact the author:: bonnieu@supagro.inra.fr	<p>Myostatin is an endogenous, negative regulator of muscle growth determining both muscle fiber number and size. Recently, inhibition of this pathway has emerged as a promising therapy for muscle wasting although more details of myostatin regulation and its mechanisms of actions need to be clarified. Despite the importance of myostatin signalling for proper myogenic differentiation, little is known about the interaction of the myostatin signalling pathway with other major signalling pathways involved in myogenesis. To begin to address this, we investigated the possibility of a signal integration between the myostatin and Notch signalling pathways, two negative regulators of myogenic differentiation. In a previous study using a potent inhibitor of presenilin-dependent cleavage of Notch, DAPT, we induced myotube hypertrophy in primary human myoblasts. Here we show that this myotube hypertrophy-induced by Notch inhibition was associated with downregulation of myostatin expression. Consistent with these data we further show that both pathways are integrated in the transcriptional regulation of Notch and myostatin responsive genes. These results suggest that targeting myostatin through manipulating Notch signalling could have important roles in regulation of muscle mass. We are now currently investigating the relevance of this interaction for adult myogenesis.</p>

PW24-298	<p><u>GPCR REPERTOIRE APPROACH TO IDENTIFY SPECIFIC PHARMACOLOGICAL TARGETS IN SKELETAL MUSCLE</u> MOORE-MORRIS T¹, VARRAULT A¹, LE DIGARCHER A¹, JOURNOT L¹, NARGEOT J¹, COUETTE B¹ (1) IGF, Montpellier, FRANCE.</p>
<p>To contact the author:: tom.moore-morris@igf.cnrs.fr.</p>	<p>Maintaining or even enhancing skeletal muscle mass is critical not only in inherited muscular disorders but also in the context of aging and in various disease states associated with muscle loss. The aim of any treatment for muscle wasting is to restore, maintain, or improve muscle size and strength. Many therapeutic trials have been undertaken to identify and validate new targets for treating muscular dystrophies. Compounds used include anabolic steroids, growth factors and interestingly agonists of G protein-coupled receptors (GPCRs) such as the beta(2)-Adrenergic receptor (AR). The later have been put forward as a promising new target for treating muscle wasting. However, their potential is limited because of the high doses of beta(2)-AR agonists required which have several deleterious effects such as cardiac hypertrophy.</p> <p>We have produced a repertoire of the GPCRs in mouse heart, revealing new cardiac receptors. Our data is validated by the identification of all the well known receptors and atypical or new receptors such as mGluR1 whose presence we evidenced at the protein and functional level. We have repeated this approach on proliferating and differentiating myoblasts and are currently also creating GPCR repertoires for normal and atrophied skeletal muscle. Our aim is to identify receptors actively involved in skeletal muscle atrophy that are weakly represented or absent in the heart.</p> <p>The work put forward in this proposal should enable the identification of new targets and molecules of interest for the treatments of skeletal muscle loss, owing to the GPCR repertoire approach. Indeed, GPCRs are well known for being highly accessible pharmacological targets.</p>

PW24-299	<p><u>CROSS TALK BETWEEN GLUCOCORTICOID AND WNT/BETA CATENIN SIGNALING PATHWAYS IN SCHWANN CELLS ON THE LEVEL OF MYELIN GENES</u></p> <p>MAKOUKJI J¹, TROUSSON A¹, FONTE C², GRENIER J¹, SCHUMACHER M², MASSAAD C²</p> <p>(1) CNRS UPR2228 University Paris Descartes, Paris, FRANCE. (2) Inserm UMR 788 Univeristy Paris-Sud, Le Kremlin-Bicetre, FRANCE.</p>
To contact the author:: charbel.massaad@univ-paris5.fr.	<p>Glucocorticoids play a major role in the nervous system and promote myelination. Their action is mediated by the glucocorticoid receptor (GR) that recruits coactivators(CBP or p300). We investigated the role of CBP and p300 in Schwann cells. We showed that neither CBP nor p300 enhanced GR transcriptional activation and unexpectedly, p300 acted as a corepressor. Functional and pull-down assays showed that beta catenin is the coactivator replacing CBP in the GR transcriptional complex, indicating that glucocorticoids may act by means of unusual partners in Schwann cells. Beta catenin is involved in Wnt signaling pathway which plays a role in development and diseases.</p> <p>We have then evaluated the physiological significance of our findings, by studying the regulation of myelin genes expression by glucocorticoids and Wnt/beta catenin. We showed that P0 and PMP22 genes (two major peripheral myelin genes) are stimulated by Wnt pathway, moreover, the combination of of glucocorticoids and Wnt signaling have a synergistic effect (i.e. 13-fold stimulation of P0 gene expression). We have then studied the mechanism of regulation of myelin genes by Wnt signaling by using either siRNA targeting beta catenin and LEF/TCF, or dominant-negative forms of the receptor frizzled and Disheveled. We found that Wnt/beta catenin pathway is essential for both basal and stimulated activities of myelin genes. Finally, we have studied the cross-talk between the GR and Wnt/beta catenin pathways and found that glucocorticoid enhances the expression of beta catenin, which is able to bind to GR and TCF. Our findings highlight the importance of Wnt/beta catenin and glucocorticoid in the expression of myelin genes, and opens a new strategy in the treatment of demyelinating disease such as Charcot-Marie-Tooth by modulating the action of Wnt/beta catenin and glucocorticoid pathways.</p>

PW24-300	<p><u>LONG-TERM BLINDED PLACEBO-CONTROLLED STUDY SHOWING PHENOTYPIC CORRECTION OF DYSTROPHIN DEFICIENCY IN THE MDX MOUSE BY SNT-MC17/IDEBENONE</u></p> <p>BUYSE G¹, VAN DER MIEREN G¹, ERB M², D'HOOGHE J¹, HERIJGERS P¹, VERBEKEN E¹, JARA A³, VAN DEN BERGH A¹, MERTENS L¹, COURDIER-FRUH I², BARZAGHI P², MEIER T²</p> <p>(1) University Hospitals K.U. Leuven, Leuven, BELGIUM. (2) Santhera Pharmaceuticals, Liestal, SWITZERLAND. (3) Biostatistical Center K.U. Leuven, Leuven, BELGIUM.</p>
To contact the author:: gunnar.buyse@uzleuven.be.	<p><u>Background</u> - Duchenne muscular dystrophy (DMD) is a severe and still incurable disease, with heart failure as a major cause of death. The identification of a disease-modifying therapy may require early-initiated and long-term administration, but such type of therapeutic trial is not evident in humans. We have performed such a trial of SNT-MC17/idebenone in the <i>mdx</i> mouse model of DMD, based on the drug's potential to improve mitochondrial respiratory chain function and reduce oxidative stress. The mouse model allowed presymptomatic initiation and veritable long-term administration of treatment, as well as the use of gold standard <i>in vivo</i> invasive pressure-volume measurements for assessing cardiac contractility.</p> <p><u>Methods & Results</u> - 200 mg/kg bodyweight of either SNT-MC17/idebenone or placebo was given from age 4 weeks until 10 months in <i>mdx</i> and wild-type mice. All evaluators were blinded to mouse type and treatment groups. Compared to wild-type mice, placebo-treated <i>mdx</i> mice showed cardiac hypertrophy, diastolic dysfunction, reduced contractile reserve with systolic failure and 58% mortality during low-dose dobutamine stress, cardiac inflammation and fibrosis, and reduced voluntary wheel running performance. Idebenone treatment significantly corrected cardiac diastolic dysfunction and significantly prevented mortality from cardiac pump failure induced by dobutamine stress testing, significantly reduced cardiac inflammation and fibrosis, and significantly improved voluntary running performance in <i>mdx</i> mice.</p> <p><u>Conclusions</u> - We have identified a novel potential therapeutic strategy for human DMD, as SNT-MC17/idebenone was cardioprotective and improved exercise performance in the dystrophin-deficient <i>mdx</i> mouse. These animal data encourage investigation of SNT-MC17/idebenone in human DMD. Our data also illustrate that the <i>mdx</i> mouse provides unique opportunities for long-term controlled prehuman therapeutic studies.</p>

PW24-301

**SNT-MC17/IDEBENONE IMPROVES CARDIAC AND RESPIRATORY FUNCTION
IN DUCHENNE MUSCULAR DYSTROPHY: RESULTS OF A 12 MONTH DOUBLE-
BLIND RANDOMIZED CONTROLLED TRIAL**

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<p>PW24-302</p>	<p><u>RATIONALE FOR THE USE OF BEZAFIBRATE IN THE TREATMENT OF VERY LONG CHAIN ACYLCOA DEHYDROGENASE DEFICIENCY.</u> GOBIN-LIMBALLE S², DJOUADI F¹, AUBEY F¹, OLPIN S³, ANDRESEN B.S⁴, FUKAO T⁵, WANDERS R.J⁶, KIM JJ⁷, BASTIN J¹ (1) CNRS UPR 9078, Université Paris Descartes, Paris, FRANCE. (2) Service de Genetique, Hôpital Necker, Paris, FRANCE. (3) Department of Clinical Chemistry, Sheffield Children's Hospital,, Sheffield, UNITED-KINGDOM. (4) Research Unit for Molecular Medicine, Aarhus University Hospital, Aarhus, DENMARK. (5) Department</p>
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	<p>Very-Long-Chain-AcylCoA (VLCAD) deficiency is one of the more common mitochondrial β-oxidation defect, without treatment to date, with three distinct phenotypes including neonatal-onset severe cardiomyopathy, liver failure in infancy, or adolescent-onset myopathy with exercise intolerance, myalgia and rhabdomyolysis. Because of the severity of symptoms, newborn screening of VLCAD deficiency is performed in several countries. Molecular studies have revealed >80 VLCAD gene missense mutations, with generally unpredictable effects on enzyme activity, and for which genotype/phenotype correlations are globally unclear. We sought to determine if, via activation of the PPAR (Peroxisome Proliferator Activated Receptors) signaling pathway, bezafibrate could be effective to stimulate residual metabolic capacities in this disorder. Palmitate oxidation tests were performed in a panel of patient fibroblasts from the three phenotypes, representing 36 genotypes and 45 missense mutations. About two thirds of the cell lines exhibited a marked increase in Fatty Acid Oxidation (FAO) in response to bezafibrate, whereas treatment was ineffective in the remaining cell lines. Similar increases in VLCAD mRNA were found in all cell lines, and the differences in FAO could then be ascribed to variable increases in VLCAD residual enzyme activity in response to the drug. Unresponsive genotypes were all found to correspond to severe clinical presentations whereas cells that responded to bezafibrate were from patients with the myopathic form of the disorder. Cross-analysis of genotypes allowed to characterize groups of individual severe or mild missense mutations accounting for the response to the drug.</p> <p>This pharmacogenetics study provides a new way for functional analysis of VLCAD-deficient genotypes, demonstrates the potential of bezafibrate in the correction of the more common myopathic form of the disorder, and provides a rationale for the selection of patients who might respond to bezafibrate in a future clinical trial, based on the association of <i>in vitro</i> tests and molecular data.</p>

PW24-303	<p><u>THE PSYCHOLOGICAL IMPACT OF PARTICIPATION IN A PLACEBO CONTROLLED TRIAL OF ENZYME REPLACEMENT THERAPY ON PATIENTS WITH LATE-ONSET POMPE DISEASE</u> HERSON A¹, GALLAIS B¹, MICHON CC¹, DOPPLER V¹, PAYAN C¹, HERSON S², EYMARD B¹, GARGIULO M¹, LAFORÉT P¹ (1) Institut of Myology, Pitié-Salpêtrière, Paris, FRANCE. (2) Internal Medicine service, Pitié-Salpêtrière, Paris, FRANCE.</p>
To contact the author:: ahers55@hotmail.com.	<p><u>Objective:</u> To prospectively evaluate the psychological impact of the participation in a clinical trial on patients with late-onset Pompe Disease.</p> <p><u>Method:</u> From the moment of the inclusion and until the end of the trail at 18 months: we assessed every 3 months the psychological status of 10 patients who have been included in a placebo-controlled study of enzyme replacement therapy.</p> <p><u>Assessment:</u> a) Open interviews were conducted by psychologists to qualitatively assess the impact of the clinical trial on the patient's personal, marital and socio-professional life. b) Mood and anxiety were assessed with Self-report scales: Beck Depression Inventory, Beck Hopelessness Scale (B.H.S) and State and Trait Anxiety Inventory of Spielberger (S.T.A.I. I and II). c) Impact of the clinical trial and coping were evaluated with Impact of Event Scale (I.E.S) and the IPC scale (Internal, Powerful others, Chance) of Levenson. d) Quality of life and social adjustment were assessed with Whoqol-26 and Social Adjustment Scale in self report (S.A.S S-R).</p> <p><u>Preliminary and partial results:</u> Throughout the trial mean scores of depression and anxiety-state improved. Quality of life and social adjustment were conserved. Patients privileged coping strategies focused on internal factor.</p> <p><u>Discussion:</u> According to the preliminary results, there is no negative impact of participation in clinical trial on psychological status, moreover some psychological dimensions improved. We can explain that by two features: a) The medical team offered an enough secure and supportive environment during the trial. b) Participation in a trial has an influence on patient's subjective position in front of their disease: it gives them a sense of having an active part in medical progress. For patients who are now under treatment (8 patients), the psychological assessment has to be continued in front of weight of treatment, involving a "medicalisation of their existence".</p>

PW24-304	<p><u>MONITORING OF CHANGES IN FRIEDREICH'S ATAXIA DURING A PERIOD OF 8 YEARS IN 49 PATIENTS IN REUNION ISLAND</u> MIGNARD C¹, CHARLIN C¹, MIGNARD D², ROELENS P² (1) Centre de Référence des maladies neuro musculaires, Saint Pierre(REUNION), FRANCE. (2) SCP Mignard-Roelens-Tabailloux, Saint Pierre(REUNION), FRANCE.</p>
To contact the author:: c.mignard@ch-sudreunion.fr.	<p>In Reunion Island, we followed fifty ataxic patients every six months during eight years, from November 1999 to July 2007, using the same protocol. <u>1 The work protocol:</u> Patients were included regardless of the stage of their disease. They were reviewed for a neurological examination, including a Kurtzke and an ataxia WFN scale, a biological and a cardiological assessment with ultrasound and holter monitor. A few patients were placed under ldebenone. They all received physiotherapy. <u>2 Patients:</u> All patients had a diagnosis confirmed by molecular biology. At the beginning of the study. 6 had a heart disease. 37 patients could still move, with or without support. 33 patients were treated for more than two years. <u>3 Results :</u> <u>Natural evolution</u> studied in 14 untreated patients: 5 aggravations, 9 stabilisations or improvements. <u>Under treatment</u>, studied in 33 patients: 23 aggravations, 10 stabilisations or improvements from a neurological standpoint: <i>a/ Stabilisations:</i> Among the patients most affected and throughout the study period, 11 patients have similar neurological signs at the end of the study, as those presented at the beginning of the study. <i>b/ Improvements:</i> 6 : often at a light stage of their illness. <i>c/ Aggravations:</i> 25 patients have worsened despite taking regular ldebénone. These exacerbations occur more often in patients with mild stage of the disease. From a cardiological standpoint: 6 patients had cardiomyopathy at the beginning of the study. At the end of the study, there are 9 patients. Out of the 6 patients already affected at the beginning of the study, two patients died, 4 have seen no worsening of their cardiac disease. Three people ended up with cardiac disease. <u>Conclusion</u> The evolution of the Friedreich's ataxia is spontaneously slow. The treatment stabilizes or improves a good number of cardiac disease and neurological, but many patients worsen regardless the stage of disease.</p>