



EuroMyasthenia

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Dear Colleagues,

I hope you will find this new format of the newsletter attractive with more information for patients and summaries from the scientific literature on MG. We are very happy to announce that the EuroMyasthenia Booklet is now available in six different languages (page 6). Please do not hesitate to give us your feedback on the EuroMyasthenia Website.

Several new countries have been integrated in the EuroMyasthenia project and, today, our network, which spans 22 countries, includes 50 teams of which 12 are patients' associations.

It is time to prepare yourself for the EuroMyasthenia Meeting in Nicosia. On the first day (December 5), the EuroMyasthenia Partners will present their past year activities towards reaching the aims of the project in a private meeting; the program will soon be posted on the EuroMyasthenia Website. We shall endeavour to report on this meeting in the next newsletter. The second day (December 6) will be dedicated to information for patients and exchanges between neurologists, in a conference organized by the Cyprus MG Association in memory of Prof. John Newsom-Davis. You can find an invitation to this conference and its program on the EuroMyasthenia website. The third day (December 7) will be an opportunity for patients, scientists, and neurologists to mix during an excursion to the monastery of Kykkos organized by the Cyprus MG Patients' Association.

We hope that this meeting will culminate in the establishment of a European Federation of MG Patients' Associations that will be presented and abundantly discussed on both days; we expect about 8 representatives of MG associations from different European countries to attend both days and participate actively in the discussions. See you in Cyprus!

Sonia Berrih-Aknin, Coordinator

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Presentation of the EuroMyasthenia network partners

The Cyprus Myasthenia Gravis Association 2087 Nicosia, Cyprus (www.mgacy.org)

Members of the board. President: Rita Prodromou (ritapr@cytanet.com.cy), Vice President: Anna Zannetou, Secretary: Kyriacos Kaisiaris, Treasurer: Anna Siali, Members: Kyriacos Karatjias, Moesis Moisi, Maria Herakleous Lazarou, Androulla Charalambous and Eleni Andreou-Farmaka.

Brief history of the Association: The Myasthenia Gravis Association of Cyprus was founded in July 2005 in Nicosia and is headed by a committee of 9 members from all cities who work on a voluntary basis. The association has approximately 70 members so far. We do not have a permanent establishment therefore all activities are carried out from the homes of the committee members and meetings are held at the Cyprus Institute of Neurology and Genetics. The need for the formation of the Association was to deal with the increasing number of problems myasthenia gravis patients were facing.

Activities and goals: The primary aim of the Association is to ensure that all our members receive optimal medical treatment and hospitalization when necessary, as well as psychological and legal counseling. We strive to acquire the support of relevant government bodies and the community for our members and to be in close contact with all members of the society.

Other activities include the implementation of special programs to help patients have a better quality of life, to reintegrate patients to the society and the active workforce based on their abilities. We also help members by finding suitable career opportunities and by advising the public about the specific problems that myasthenic people have. We help members find job opportunities if they are unable to carry on with their normal career and are only able to work for a few hours each day. We further organize scientific seminars and lectures to educate patients, their immediate family members and friends about Myasthenia Gravis. We also organize social meetings for members with outings and different types of entertainment to become acquainted with each other and to exchange views.

Problems: Another goal of the Association is to solve the problem that currently there is no specialized ward or Neurology Department in any of the Government Hospitals, where patients with MG could receive specialized care and have access to intensive care when they are in a MG crisis. Physiotherapy is available only in Nicosia at the Cyprus Institute of Neurology and Genetics. Our aim is to make available this service to patients in all cities.

Funding: Financially the Association is supported by subscriptions and donations by members, friends and supporters and by organizing various fund raising events. All funds are used to achieve our aims.



From left: Anna Zannetou (1st), Eleni Andreou-Farmaka (3rd), Rita Prodromou (5th) and friends

Presentation of the Euromyasthenia network partners - continued

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Members of the group

Head of the lab: Sonia Berrih-Aknin (sonia.berrih-aknin@u-psud.fr),

Researchers: Nicole Kerlero de Rosbo, Rozen Le Panse

Research Assistants: Jacky Bismuth, Perrine Cuffi, Frédérique Truffault

Post-docs: Sylvain Bougoin, Mélinée Cuvelier, Nadine Dragin, Dani Nazzal

PhD student: Julia Weiss

Administrative Assistant: Valérie Leenhardt



Description of research work related to MG

Our research on Myasthenia Gravis focuses on the two organs implicated in the disease: the thymus (effector organ of the disease, where immune cells responsible for the generation of anti-AChR antibodies originate) and the muscle (target organ to which the anti-AChR antibodies are directed, causing damage leading to muscular fatigability). Our research projects aim to answer to the following questions:

From left: J. Bismuth, D. Nazzal, N. Dragin, N. Kerlero de Rosbo, F. Truffault, M. Cuvelier, S. Berrih-Aknin, P. Cuffi, V. Leenhardt, R. Le Panse, J. Weiss, S. Bougoin

◆ **Why are there changes in the thymus?** In most young female patients, the thymus is pathologically enlarged due to inflammation of the tissue and the formation of centers filled with immune cells. We take advantage of technological advances to uncover molecules and study cells that are involved in the formation of these centers, with the aim of preventing their formation. We are devising new animal MG models that are based on mice with specific mutation in these molecules to ascertain their role in MG. Because MG associated with thymic changes occurs mostly in young women, we are investigating the female prevalence in the young MG population. To do so, we analyze the susceptibility to MG in mice with defects in sexual hormone production (collaboration with Prof. Sara Fuchs, Israel) and we explore the effect of the hormones on the different components of the autoimmune response. In addition, we are taking into consideration the autoimmune nature of MG to investigate the possible defect in immune regulation of the autoimmune attack by immune cells, at the level of the thymus, but also in the blood. We have observed a defect in cells involved in this regulation and are characterizing this defect.

◆ **What happens in the muscle of MG patients?** We have demonstrated that there is a compensatory mechanism that takes place in MG muscle to remedy the damage induced by the anti-AChR antibodies, and recently we have demonstrated that anti-MuSK antibodies have a pathogenic effect on muscle cells. We are investigating what differs at the molecular level in muscle of patients with anti-AChR antibodies and those whose MG is mediated by other types of antibodies, always with the aim of identifying molecules that could be therapeutic targets.

Participations in networks, organisations, etc.

We coordinate two projects financed by the European Community: EUROMYASTHENIA, a Public Health project to improve information and communication in MG including scientific and medical teams as well as organizations of patients and MYASTAID, a research project that aims at developing new *in vitro* and *in vivo* models to increase knowledge and understanding of disease mechanisms in MG.

Relevant recent publications

Boneva, N., M. Frenkian-Cuvelier, J. Bidault, T. Brenner, and S. Berrih-Aknin. 2006. Major pathogenic effects of anti-MuSK antibodies in Myasthenia Gravis. *J. Neuroimmunol.* 177:119.

Le Panse, R., Cizeron-Clairac, G., Bismuth, J., and Berrih-Aknin, S. 2006. Microarrays reveal distinct gene signatures in the thymus of seropositive and seronegative myasthenia gravis patients and the role of CC chemokine ligand 21 in thymic hyperplasia. *J. Immunol.* 177:7868.

Meraouna, A., G. Cizeron-Clairac, R. L. Panse, J. Bismuth, F. Truffault, C. Tallaksen, and S. Berrih-Aknin. 2006 The chemokine CXCL13 is a key molecule in autoimmune myasthenia gravis. *Blood.* 108:432-440.

Gilboa-Geffen, A., Lacoste, P.P., Soreq, L., Cizeron-Clairac, G., Le Panse, R., Truffault, F., Shaked, I., Soreq, H., and Berrih-Aknin, S. 2007. The thymic theme of acetylcholinesterase splice variants in myasthenia gravis. *Blood* 109:4383.

Cizeron-Clairac G, Le Panse R., Frenkian-Cuvelier M., Meraouna A., Truffault F., Bismuth J., Mussot S., Kerlero de Rosbo N., and Berrih-Aknin S. 2008. Thymus and myasthenia gravis: what can we learn from DNA microarrays? *J. Neuroimmunol.* 201-202:57-63.

For clinicians and patients

Thymectomy techniques: the question is not just do or don't, but also how!

The thymus plays a central role in the pathogenesis of MG. Nevertheless, the role of thymectomy in the treatment of MG remains controversial. Despite the fact that there are not controlled prospective studies to support its role in the treatment of MG, clinical experience suggests that the more complete the thymectomy the better the results. In order to achieve complete remission in non-thymomatous MG, the goal of any surgical procedure should be the removal of all the thymic tissue. There are several surgical techniques employed for total thymectomy, but the selection of a technique continues to be an unresolved issue. Transsternal thymectomies are of two types, aggressive and standard; aggressive thymectomy is the most commonly performed procedure and usually removes all but a small amount of thymic tissue in the neck. The standard transsternal thymectomy is an incomplete resection and gives less good results. Transcervical thymectomies, extended and basic, which are routinely performed, are less extensive than initially considered. The combined transcervical and transsternal thymectomy appears to completely remove the thymus in the neck and mediastinum. In addition, there are several videoscopic-assisted thymectomies but their advantages are still under investigation. (Sonett J. R. and Jareski III A., Ann. N. Y. Acad. Sci. 1132: 315-328, 2008).

The latest technique is the telerobotic surgery, with the 3-arm da Vinci robotic system. At the Charite-University Clinic of Surgery in Berlin, 95 robotic-assisted thymectomies were performed in MG patients, and the results suggest that this is a promising technique that allows technical refinements during the operation and offers higher dexterity and a shorter learning curve. Nevertheless, additional clinical experience is required in order to further estimate the advantages and disadvantages of the robotic technology for this kind of surgery (Ruckert et al, Ann. N. Y. Acad. Sci. 1132:329-335, 2008).

In general, it is difficult to compare the various thymectomy techniques and to select the procedure of choice, due to the lack of controlled prospective trials. Well-designed studies, which are currently under way (Newsom-Davis et al, Ann. N. Y. Acad. Sci. 1132:344-347, 2008) could resolve the many conflicting statements about the selection of the thymectomy technique in the treatment of MG.



The 3-arm da Vinci robotic system

Symptoms in MuSK-antibody positive MG

Most patients with MG (~85%) have autoantibodies against acetylcholine receptor (AChR). However, there is a minor subgroup (about 5%) that have MuSK-antibody MG (MuSK MG) and their clinical findings usually do not fit the pattern typical for MG.

Sanders and Juel (J Neuroimmunol. 201-202:85-9, 2008) studied and presented five MuSK MG patients, each of whom presented with a diagnostic or therapeutic interest, characteristic of this condition. A number of questions was raised after the examination of these cases, with the most important being when should MuSK MG be suspected, in order not to be misdiagnosed. The authors suggest that, in general, MuSK MG should be suspected in patients without antibodies against AChR but with generalized MG. However, frequently, the clinical findings in MuSK MG are different from those in MG. In many cases, there is absence of clear symptomatic fatigability, cholinesterase inhibitors produce no improvement, and electro-diagnostic findings are normal in muscles usually tested for MG. Common symptoms in MuSK MG are facio-pharyngeal muscle weakness and tongue atrophy, which is rarely seen in non-MuSK MG. A less common manifestation of MuSK MG is neck and shoulder weakness. Furthermore, in rare cases, such as patients with purely ocular MG that do not have anti-AChR antibodies, it is possible to have MuSK MG. In a few cases of MuSK MG, axial muscle weakness is observed, as well as weakness of the upper esophagus, indicating that these muscles may be involved in MuSK MG.

In conclusion, many unanswered questions have been raised as far as this subset of MG is concerned, which could lead to further insight into the immunopathology and management of MuSK MG.

For clinicians and patients - continued

Quality-of-life instrument for MG: a useful tool for clinicians

Quality of life (QOL) instrument is a complex construct which gives information about the impact of disease and health-care involvements on daily living and disability. There are general QOL measures whose purpose is to assess the impact of a disease compared with other diseases by the use of a common metric system. In addition, there are disease-specific QOL which can be used to compare patients with the same disease. Dr Ted Burns and his collaborators presented an MG-QOL, a 15-item questionnaire (Muscle and Nerve. 38(2):957-63, 2008) based on a much longer 60-item MG-QOL. The MG-QOL15 is simple, user-friendly, quick and easy to interpret and help physicians to understand how MG affects the patients. The researchers recommend MG-QOL15 as a secondary measure for clinical trials and clinical evaluation of MG patients. The 15-item questionnaire is as follows:

	Not at all	A little bit	Somewhat	Quite a bit	Very much
	0	1	2	3	4
1) I am frustrated by my condition					
2) I have trouble using my eyes					
3) I have trouble eating					
4) I have limited my social activity because of my condition					
5) My condition limits my ability to enjoy hobbies and fun activities					
6) I have trouble meeting the needs of my family					
7) I have to make plans around my condition					
8) My occupational skills and job status have been negatively affected					
9) I have difficulty speaking					
10) I have trouble driving					
11) I am depressed about my condition					
12) I have trouble walking					
13) I have trouble getting around public places					
14) I feel overwhelmed by my condition					
15) I have trouble performing my personal grooming needs					

MG and elderly

For a long time, scientists considered that MG mainly affects young people and that it is less frequent among people over 50 years old. However, nowadays MG is diagnosed more often than previously, and the increase is mainly found in patients after the age of 50. MG in the elderly (or late-onset MG, LOMG) occurs age 50 and the peak for the LOMG is between the age of 70 and 80. Nevertheless, there is still evidence that MG may be considerably underdiagnosed in very old people. This is firstly because the symptoms like ptosis, diplopia, and weakness of the facial muscles are more difficult to detect in the elderly than in young people, and secondly because many neurologists still consider that MG is an uncommon disease for the elderly. LOMG varies from slight ocular to severe, generalized disorder. The disease activity tends to be lower and the prognosis good; however LOMG patients have a higher mortality than the EOMG patients and in general, full remission in elderly is rare. Additionally, coexisting disorders like cardiac disease or respiratory problems affect the severity of the disease. However, nowadays, neurologists see more old MG patients than before, and the modern diagnostic facilities contribute to the better diagnosis of MG (Aarli J. A., Ann. N. Y. Acad. Sci. 1132: 238-243, 2008).

EUROMYASTHENIA WEBSITE

Visit the [EuroMyasthenia Website \(www.euromyasthenia.org\)](http://www.euromyasthenia.org) to see its new postings and add your contributions

**Towards new treatments:
Some just established, some under clinical trials, some at experimental level yet**

Stem cell transplantation in MG: At Northwestern University (Illinois, United States) there is an ongoing study whose purpose is to evaluate the toxicity and feasibility of autologous stem cell transplantation in patients with refractory and severe MG. This phase I clinical trial (NCT 00424489) is currently recruiting participants and is expected to be completed by February 2012.

Combined thymectomy and prednisone: The University of Alabama at Birmingham in collaboration with the National Institute of Neurological Disorders and Stroke (NINDS) is conducting a randomized, multi-center, single-blind study in order to determine whether thymectomy combined with prednisone therapy is more effective in treating patients with non-thymomatous MG than prednisone alone. This clinical trial (NCT 00294658) is at present at phase III and its estimated completion date is November 2009.

Anti-complement mAb therapy: Another clinical trial (NCT 00727194) is conducted this time by Alexion Pharmaceuticals, which aims to determine if eculizumab, a humanized monoclonal antibody (mAb) directed against the complement protein C5, is safe and beneficial for the treatment of patients with generalized MG. This clinical trial is at phase II and is estimated to be completed on July 2010.

IVIg versus plasmapheresis: A randomized, controlled, multi-center clinical study of GB-0998 (Intravenous Immunoglobulin or IVIg) for the treatment of generalized MG is carried out from Benesis Corporation (Japan) to evaluate its effectiveness and safety compared to plasmapheresis. The clinical trial (NCT 00515450) is presently at phase III and is expected to be completed on May 2009.

All the above information was obtained from the ClinicalTrials.gov, a service of the U.S. National Institutes of Health.

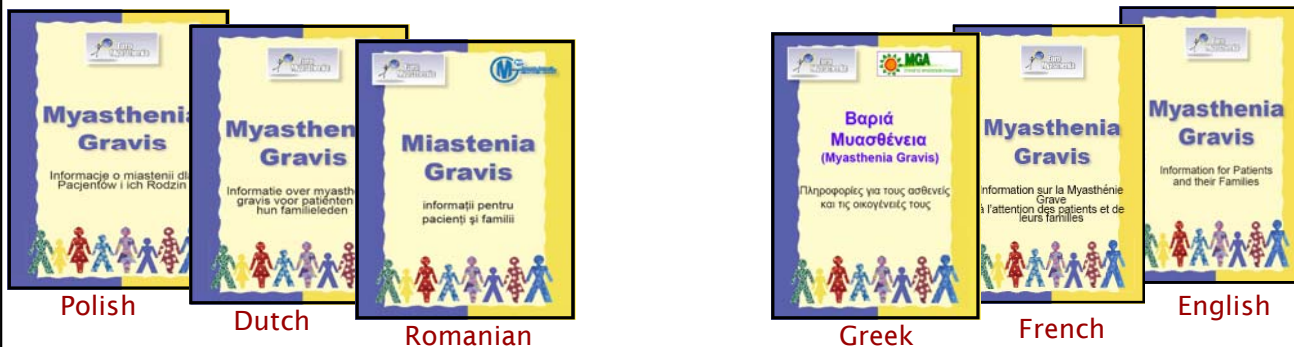
A promising therapeutic agent: Rituximab: The present treatments for MG include long-term therapy with immunosuppressive drugs, which usually eliminates the clinical symptoms. However, a small proportion of MG patients do not respond to conventional immunotherapy. A recent study (Illa et al, J Neuroimmunol. 201-202:90-4, 2008) indicated that, in six patients with severe MG who did not respond to first or second-line immunosuppressive drugs, Rituximab treatment resulted in obvious clinical improvement. Rituximab is a genetically engineered anti-CD20 monoclonal antibody that induces B-cell depletion and constitutes a novel promising therapeutic agent against MG (among other autoimmune diseases), especially for patients who are resistant to other established treatments.

MG treatment with Etanercept: Etanercept is a dimeric protein that binds to the cytokine TNF and renders it inactive. The exact role of TNF in the pathogenesis of MG is unknown; however there is evidence that TNF promotes MG mainly by acting together with other cytokines and affecting the immune response and by enhancing the production of anti-AChR antibodies. Hence, inactivation of TNF would be an effective strategy in the treatment of MG. Etanercept has been shown to be effective and safe in many rheumatological diseases and has also been shown to inhibit EAMG. Preliminary clinical studies in 11 MG patients suggested that Etanercept could be effective in some patients with chronic MG. However, further clinical trials are needed in order to better characterize the mechanism of action of Etanercept (Rowin J., Ann. N. Y. Acad. Sci. 1132: 300-304, 2008).

A combination therapy for experimental autoimmune MG: Pentoxifylline and steroids: Current management of MG includes mainly corticosteroids, which are a first-line therapy for moderate-to-severe MG. However, when steroids are administered for long periods and at high doses, they have frequently severe adverse effects. In a recent study, Prof. Sara Fuchs (collaborating partner of EuroMG) and her collaborators (Menon et al, J Neuroimmunol. 201-202:128-35, 2008) presented a new therapeutic approach in experimental autoimmune MG (EAMG) in rats that combines low doses of steroids together with low doses of a general phosphodiesterase inhibitor, Pentoxifylline (PTX). The same group had previously shown that PTX suppresses EAMG. They demonstrated that by using this combined therapy, the steroid doses could be reduced ten-fold compared to the optimal doses used in steroid treatment alone. Furthermore, the combined treatment resulted in a strong suppressive effect on EAMG and was more effective than the treatment with each of these drugs separately.

MG News and Events

The Euromyasthenia booklet now in many languages

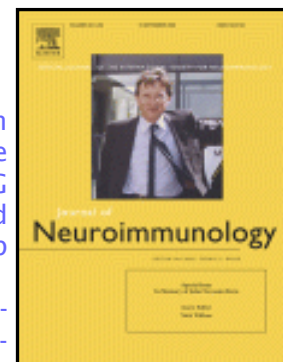


The booklet of our network “Information for myasthenia gravis for patients and their families” has been now translated in several languages (French, Greek, Romanian, Dutch and Polish); all these translations can be downloaded from our website, www.euromyasthenia.org. In this booklet patients can find useful information about the pathology, diagnosis and treatment of myasthenia gravis, as well as several answers to frequently asked questions and some useful contacts.

Journal of Neuroimmunology: special issue in memory of John Newsom-Davis

A recent issue of the Journal of Neuroimmunology, which was published on 15 September 2008 (volumes 201-202), is a special issue dedicated to the memory of the late John Newsom-Davis, an outstanding scientist and MG clinician. Many people who knew him, who had collaborated with him, had the opportunity to honor the memory of John Newsom-Davis and his superb achievements in science.

John Newsom-Davis was loved and respected by the scientific community as well as by innumerable MG patients and will be remembered by everyone as a generous and optimistic person.



MGFA Scientific Session

The Scientific Session of the MG Foundation of America (MGFA) was held on 20 September, one day before the annual meeting of the American Neurological Association (ANA), in Salt Lake City. According to Prof. Angela Vincent who attended the Scientific Session, the talks covered a variety of subjects, like the MG Composite score (Dr. Tend Burns) (see page 4), characteristics of childhood MG in Japan (Dr. Yoshiko Nomura), the efficacy of DNA vaccines for inducing tolerance to AChR in mouse models (Dr. Lucy Lou), experimental models for MuSK-MG and SNMG (Prof. Angela Vincent), methotrexate treatment for MG and an update in thymectomy trial (Dr. Gil Wolfe). The programme committee and meeting was chaired by Dr. Matt Meriggioli. The meeting also acknowledged the sad news of the death of a remarkable clinician researcher, Dr. David Grob, who was a very well known figure in MG over six decades. Nevertheless, Prof. Angela Vincent commented that the turnout of the meeting was a little disappointing, likely reflecting the venue of the ANA meeting, rather than lack of interest in MG research.

Euromyasthenia partners' news

Starting from this issue, we will make an effort to present short updates and news of novel activities of the EuroMyasthenia network partners (research, social etc.), which might be useful for specialists or non-specialists, to know.

MG news from the University of Bergen and Haukeland University Hospital, Norway

National Norwegian health registries (National Birth Registry, National Death Registry, National Cancer Registry, National Prescription Registry) are increasingly being used to study aspects of MG. For example recent studies by Prof. Nils Erik Gilhus and his MG research group in Bergen using material from these registries have indicated that MG has no or very little impact on the heart. Indeed, despite single case reports of MG-induced cardiomyopathy, their results suggest that this is not a general threat in MG.

Some recent publications about MG from Euromyasthenia Partners

- ◆ Elovaara I, Apostolski S, van Doorn P, Gilhus NE et al. EFNS guidelines for the use of intravenous immunoglobulin in treatment of neurological disease. *Eur J Neurol* 2008;9:893-908. **This is the report of an EFNS (European Federation of Neurological Societies) task force. As for MG, IVIG is recommended in the acute situation and when short-term effect is needed.**
- ◆ Helgeland G, Luckman SP, Romi FR, Jonassen AK, Gilhus NE. Myasthenia gravis sera have no effect on cardiomyocytes in vitro. *J Neuroimmunol* 2008;201-202C:74-79. **This paper reports that sera from MG patients have no cytotoxic effect on cardiac cell cultures in vitro, in contrast to what was previously found for the same sera on skeletal muscle cells.**
- ◆ MacLennan CA, Vincent A, Marx A, Willcox N, Gilhus NE, Newsom-Davis J, Beeson D. Preferential expression of AChR epsilon subunit in thymomas from patients with myasthenia gravis. *J Neuroimmunol* 2008;201-202C:28-32. **This paper shows that thymomas can express mRNA for all five AChR subunits, but most abundantly mRNA for the epsilon subunit.**
- ◆ Romi FR, Gilhus NE, Luckman SP. Serum matrix metalloproteinase-3 levels are elevated in myasthenia gravis. *J Neuroimmunol* 2008;195:96-99. **MMP-3 is capable of degrading proteins, including agrin which is important for neuromuscular signalling. 10-17% of MG patients have elevated MMP-3 levels, an observation which may be of pathogenic significance.**
- ◆ Skeie GO, Romi F. Paraneoplastic myasthenia gravis; immunological and clinical aspects. *Eur J Neurol* 2008;15:1029-33. **This is a review paper on clinical, immunological and therapeutical aspects of myasthenia gravis with thymoma.**
- ◆ Bitzopoulou K, Kostelidou K, Poulas K, Tzartos SJ. Mutant forms of the extracellular domain of the human acetylcholine receptor gamma-subunit with improved solubility and enhanced antigenicity. The importance of the Cys-loop. *Biochim Biophys Acta*. 2008;1784:1226-33. **This study presents mutant forms of the extracellular domain of the human acetylcholine receptor gamma-subunit with enhanced antigenicity, which can be used for the selective removal of anti-AChR antibodies from the blood of MG patients, a novel therapeutic approach, under development by this group.**
- ◆ Zisimopoulou P, Lagoumintzis G, Kostelidou K, Bitzopoulou K, Kordas G, Trakas N, Poulas K, Tzartos SJ. Towards antigen-specific apheresis of pathogenic autoantibodies as a further step in the treatment of myasthenia gravis by plasmapheresis. *J Neuroimmunol* 2008;201-202:95-103. **This review summarizes the up-to-date progress of the group on the use of recombinant extracellular domains of human muscle AChR subunits, immobilized on Sepharose beads, for the selective depletion of patients' blood from their anti-AChR autoantibodies (as an antigen-specific tentative therapy).**

Forthcoming meetings

- ◆ Society for Neuroscience 2008, 15-19 November, Washington, USA (<http://www.sfn.org>)
- ◆ Euromyasthenia Meeting 2008, 5-6 December, Cyprus (<http://www.euromyasthenia.org>)
- ◆ 5th International Meeting "Steroids and Nervous System" 2009, February 13-18, Torino, Italy (<http://www.dafml.unito.it/anatomy/panzica/neurosteroids/SNS09/HOME.html>)
- ◆ 5th Annual Update Symposium Series on Clinical Neurology and Neurophysiology 2009, Feb 16-17th 2009 Tel Aviv, Israel (<http://www.neurophysiology-symposium.com>)
- ◆ International Society for Autonomic Neuroscience (ISAN) 2009, 1-4 September, Sydney, Australia, (<http://www.isanweb.org>)