

## **European Network on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome**

### **COST action CA15111**

#### **Minutes- Barcelona, 16-17 March 2017 Core Group meeting:**

**CA15111 MC Chair:** Modra Murovska

**Local Meeting Chair:** Jesus Castro

**Local Vice-Chair:** Julià Blanco

**Thursday, March 16, 2017**

#### **Core Groups Meeting**

Consecution of the current period of the project was discussed and existing gaps identified. WG tasks, objectives and networking tools for the second period of the project were presented by CM Chair Modra Murovska and discussed with the CG members. CG members had agreed with the following:

#### **1) WG tasks for the period from May 1, 2017 to May 30, 2018**

WG 1 Epidemiology: T2 Synchronisation; T3 Biobanks and protocols; T4 Ethical framework.

WG 2 Biomarkers: T4 Data synchronisation.

WG 3 Socio-economics: T2 Direct loss calculation; T3 Indirect burden.

WG 4 Clinical research/diagnostic criteria: T2 Optimal set; T3 Treatment efficacy.

WG 5 STMS, workshops, conferences: T1 Training schools «Summer school on-omics and bioinformatics in ME/CFS research»; T2 STMS Training panels «Novel methods in potential infection-associated biomarkers research for ME/CFS».

WG 6 Dissemination: T3 Website; T4 Research projects.

#### **2) Objectives**

Aim/Primary objective: Promote multidisciplinary strategies in ME/CFS research and foster a full chain of translational research

Secondary objective 1: Explore the potential of existing cohorts through workshop and seminar programmes as sources of potential cases of ME/CFS and the advancement of the epidemiological understanding of the disease. Exchange information facilitating the development of synchronised adequate local systems for the collection, storage, and cataloguing of biological samples for research purposes. Exchange information on local ethical issues and discuss on common ethic's framework.



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Secondary objective 2: Coordinate usage of innovative high-throughput technologies (genomic, transcriptomic, proteomic, and metabolomics strategies) for new biomarker recognition. Develop guidelines for usage of infection-associated biomarkers and immunological biomarkers in ME/CFS diagnostic.

Secondary objective 3: Facilitate the development of adequate local systems for case finding, data collection and storage via best practice exchange. Synchronise diagnostic criteria and develop common strategy protocol to identify and understand the biological disease pathways in a stratified way. Assess the efficacy/safety of available ME/CFS treatments in order to recommend optimal treatment approaches.

Secondary objective 4: Survey European countries existing data on economic loss due to ME/CFS. Develop approaches to calculate direct economic loss and indirect economic burden due to ME/CFS. Optimise models of prevention in health aspects.

Secondary objective 5: Increase capacity by organizing training panel “Novel methods in potential infection-associated biomarkers research for ME/CFS” and following training school on-omics and bioinformatics in ME/CFS research. Organize STSMs, accomplish them and monitor results.

Secondary objective 6: Manage research project preparation. Establish communication links with small/medium-sized enterprises (SMEs). Exchange on technology transfer capabilities.

Secondary objective 7: Maintain project webpage.

### **3) Networking Tools – 76 000 EUR**

|                 |   |                   |
|-----------------|---|-------------------|
| Meetings        | 2 | 30 400 EUR        |
| Training school | 1 | 23 660 EUR        |
| STSM            | 3 | 7500 EUR          |
| Dissemination   | 1 | 1500 EUR          |
| FSAC 15%        |   | 9913 EUR          |
| <b>TOTAL</b>    |   | <b>72 973 EUR</b> |

#### **I. Meetings**

##### **1. Title: MC/WG1 meeting on synchronisation**

Type: Management Committee Meeting, Working

Group No 1 Meeting

Dates: 07/09/2017 - 07/09/2017

Location: Belgrade (Serbia)



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Participants: 22

Reimbursed: 20

Travel costs: 14200 EUR

Support grant: 1000 EUR

2. Title: MC/WG 2 meeting on synchronisation

Type: Management Committee Meeting, Working Group No 2 Meeting

Dates: 08/02/2018 - 08/02/2018

Location: Sofia (Bulgaria)

Participants: 22

Reimbursed: 20

Travel costs: 14200 EUR

Support grant: 1000 EUR

**II. Training schools**

Title: Training school on *-omics* applications and bioinformatics in ME/CFS research

Dates: 17/07/2017 - 22/07/2017

Location: Pavia (Italy)

Lecturers: 4

Students: 12

Travel costs: 18660 EUR

Support grant: 5000 EUR

**III. Short term Scientific Missions**

Amount per STSM: 2500 EUR

Number of foreseen STSMs: 3 7500 EUR

**IV. Dissemination**

Webpage EUROMENE.EU maintenance: 1500 EUR



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## **V. Financial and Scientific Administration and Coordination (FSAC)**

MAX. 15% = 9459 EUR

## **VI. Budget reserve 3025 EUR:**

- invitation of high-class expert from non-EU country;
- publications.

## **SLIDESHOWS OF WORKING GROUP SESSIONS**

### **WG1 on Epidemiology slideshows presented by Dr Andrejs Ivanovs (LV):**

**Dr Fernando Estevez (ES):** He presented an overview of the al-Ándalus project which Prof Manuel Delgado (University of Granada, Spain) is PI. Since 2007 we are conducting an epidemiological cross-sectional study including a representative sample of women with fibromyalgia (n= 616) from southern Spain (i.e., Andalucía). In this study, fatigue was assessed by means of the Multidimensional Fatigue Inventory (MFI) questionnaire. Main findings of this project are: 1) physical fitness tests as a discriminative tool for the diagnosis and monitoring of fibromyalgia, 2) central and body fat, physical activity, and physical fitness are associated with the fatigue domains. The design of the al-Ándalus project includes also a potential candidate gene study, a follow-up study (with 2 and 5 years measures) and an exercise-based RCT study. Our aim is to determine potential factors that are associated with a better prognosis of the disease and the exercise–treatment effectiveness.

**WG2 Biomarker presentation** - First an update on the European biomarker landscape project was given and the map presented. Currently we have data from 13 countries, missing EUROMENE countries need to be completed within the next 4 weeks (task month 12). It was decided to include non-EUROMENE E.U. countries as well. Concepts for the 2<sup>nd</sup> task to be complete in year 4 were presented. Special interest groups were established for chronic persistent infections (chaired by Bhupesh Prusty), genetic markers (chaired by Enrica Capelli) and autoimmune markers (chaired by Carmen Scheibenbogen). It is planned to publish critical reviews on these topics including a list with open questions and recommendations for future development. It was discussed that metabolic marker should be another project and potential chairpersons were identified and will be contacted. Big data analysis and harmonization of data analysis will be topics for the forthcoming meetings.

**WG3 Socioeconomic presentation was done by Prof Derek –**



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**WG4 Clinical and Research Case Criteria was given by Dr Elin (NO)** -A brief summary of results from the survey among the EUROMENE on national guidelines, case definitions, clinical enablers as well as important topics to be ruled out on the current meeting were presented. A total of 12 countries have responded, and missing data from the remaining Euromene countries should be completed within the next two weeks. Thus the survey is almost completed and a preliminary report also is written. Topics and questions to be discussed at the current WG4 meeting were reported; such as case definitions and which criteria to choose as European standard, which questionnaires to apply and which symptom treatment and management strategies should be suggested. Decisions should be taken on these topics based on the survey, the Skype talk with Prof Jason later that day, and on suggestions and arguments from the various members of the WG4. Also it will be discussed to write a paper from the survey and the work in the WG4.

#### **Minutes of the WG4 activities - Clinical Research Enablers and Diagnostic Criteria**

There was a core meeting Thursday 16th march including a few WG 4 activities:

- A brief summary of results from the survey among the Euromene on national guidelines etc as well as important topics to be ruled out on the current meeting, was presented by the WG4 leader.
- Prof Leonard Jason (DePaul University, Chicago, USA) was invited for a Skype talk and to discuss about case definitions, assessments tools of symptoms in ME/CFS, etc.
- Jose Alegre (ES) (WG4 member) presented clinical features and patient-reported outcome measures used in the Spanish CFS/ME cohort from the CFS/ME Clinical Unit at the Vall d'Hebron Hospital in Barcelona.

**The following persons participated in a 2-hours meeting in WG4 at Friday 16<sup>th</sup>:** Angelika Krumina (Latvia), Jerome Authier as vice-leader (France), Magdalena Efraim (Rumania), Luis Nacul (UK), Ingrid B. Helland (Norway) and Elin Strand as leader (Norway). **Members not able to take part in the WG4 meeting:** Jose Alegre (Spain) and Patricia Grabowski (Germany).

#### **WG4 meeting on Friday**

Information from the EUROMENE leader Modra and agenda for the current WGs meeting was introduced by the leader. Materials from each country have been shared since Berlin meeting in Barcelona.



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There was no time to discuss this further in the current meeting, neither to present from the different countries as planned in Berlin. Luis Nacul had a short presentation from their group's last paper on "Differing case definitions point to the need for an accurate diagnosis of ME/CFS" published recently in *Fatigue: Biomedicine, Health, and Behavior*.

**WGs Report:** A complete report from the WG4 should be written within 15<sup>th</sup> April and all group members are responsible for this. Results from the survey should be attached to this report. It was suggested and discussed to write a paper either from the work of the WG4 or from all the WGs. No decisions were taken on this.

The following topics were discussed and some decisions were made on application of diagnostic criteria, exclusion process, assessments and standardized tests and questionnaires as well as symptom treatment and management.

#### **ME/CFS Case Definitions:**

- It was decided to suggest the 2003 Canadian Consensus Criteria (CCC) as standard in research for the EUROMENE member countries. Fukuda definition may also be applied for those who already apply them and do not want to change to CCC.
- It was decided to use an extended, standardized and validated symptom questionnaire also able to classify within different case definitions.
- An exclusionary examination (somatic and psychiatric/psychological) should also be carried out.

#### **Assessments tools/Questionnaires for symptoms:**

- The following questionnaires were decided to be used as common research instruments in diagnosing: DePaul Symptom Questionnaire (DQS), SF-36 and HADS.
- Additionally it may be necessary to assess other information for example health information, family health, or extended assessments on cardinal symptoms such as neurocognitive aspects or sleep. Jerome Authier (FR) will review literature on neurocognitive aspects and find out whether there exist any short screening instruments for cognitive aspects.



- We have to discuss further and look closer into the symptom assessments already applied in the different countries.

**Treatment/symptom relief:**

- Hardly any effect studies exist on the symptom treatment in CFS/ME, thus it is difficult to suggest any of medications. There is one study in the German group and a review from the Spanish group we should look into before any concrete suggestions are given. It was planned to present this in the WG4 but it was no time for it at this meeting.

**Management strategies:**

- As there are no medical cures for CFS/ME at this point, the patients need advice for coping of the symptoms and illness as well as learning self-management strategies for preventing worsening, maintaining or increasing their coping as well as their quality of life.
- Many of the countries apply CBT, GET, pacing and mind-body strategies that may be helpful for ME/CFS patients.

**Project for next year:**

- It was decided to translate the different national guidelines – from Spain, Italy and Norway - into English to make them available for the members in the group. The aim is to develop some sort of lowest common denominator of the already existing guidelines.

**WG5 Conferences, Seminars and Training Schools presented by Dr Shikova-Lekova (BG).**

1. Information and discussions concerning meetings during the second period of COST action CA15111
  - MC/WG1 meeting on synchronisation: Location - Belgrade (Serbia).  
Date – September 7, 2017; Duration – one day.
  - MC/WG 2 meeting on synchronization: Location - Sofia (Bulgaria).  
Date – February 8, 2018; Duration – one day.



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2. Information and discussions concerning the first training school planned in year 2:  
Main decisions:

- Title: Training school on *-omics* technology and bioinformatics in ME/CFS.
- Location: Pavia (Italy) at the UNIVERSITA DEGLI STUDI DI PAVIA.
- Local organizers - Enrica Capelli and Lorenzo Lorusso.
- Dates: July 17-22, 2017.
- Theoretical and practical sessions are foreseen
- Trainers: 4 (3 from Italy and 1 from Spain).
- Number of trainees to be accepted for reimbursement – 12
- Trainees will be supported by a grant of up to 1500 EUR for travel and subsistence (Request for the accommodation in a local University College is in progress).
- Eligibility criteria for trainees: From COST Action CA15111 countries; Early stage researchers (PhD students, PhD+5 years); Basic knowledge of molecular methods; Preference to scientists working in the field of ME/CFS, but others are not excluded.
- How to apply: Application form, CV, motivation letter.
- Deadline for applications: June 1, 2017.
- Enrica Capelli will prepare and distribute the training program and the information about trainers.

**WG6 on Dissemination and exploitation and patient involvement and digitalization** was presented by Dr Lorusso (IT) and Dr Anne M. Mengshoel (NO) which done a presentation on activities and realization of the final EUROMENE website.

The WG6 has developed a final form of the website and this was discussed during the Barcelona meeting with a general consensus regarding the structure and content of the webpage. Some members suggested deleting personal information on CV present in each WG presentation. Final suggestion and advice will be accepted by March 24<sup>th</sup>, 2017. The EUROMENE website will be of public domain in April 2017.

The future activities include:

- 1- Update or deliverables in the site of the each WG activities presented in Barcelona;
- 2- Update on different activities associated with Euromene Cost Action;
- 3- An involvement of the association of patients with a list of them in the website and a possible meeting;



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4- Survey existing in SMEs in drug and other ICT industries for developing a collaborative research.

**This is a summary concerning the WG7 on STSMs that Dr Els Tobback (BE) as coordinator presented** - A budget for 6 STSMs was provided for the first year, however, only 3 candidates applied for the STSMs. All 3 candidates come from Latvia (from the institute of and encouraged by Modra) and applied for a mission in Spain. Although especially early career investigators are encouraged to participate into STSM, no young researchers applied. Consequently, we lost the budget for 3 STSMs in the first year and loose budget for the second round as well. It is better to overuse than underuse the provided money. One of the reasons for not filling in the missions, may be the late announcement (cfr maternity leave of the primary STSM coordinator). Budget for 3 STSMs is provided for the second year (3x 2500€). As soon as the budget for the second round is approved, the STSM coordinator (Els Tobback) will make the announcement (by e-mail to all COST members + publication on EUROMENE website) and COST members as well should encourage their researchers (especially early career investigators) to participate into STSM in order to insure filling in the STSMs of the second year. STSM lasts for a minimum of 5 and a maximum of 90 days.

**Friday, March 17, 2017**

Modra (LV) summarized the Core Group Meeting held Thursday morning. The core group decided the location and budget of forthcoming meetings to be held in Belgrade, Serbia (Sep 7, 2017, for MC plus WP1) and probably in Sofia, Bulgaria (Feb 2018). Modra presented the scheduled Training course on – OMICS applications in ME/CFS research and the STMS and encourage COST members to actively participate. A small budget was left for other expenses (invitations, publications). Finally a document is circulated among participants in the meeting to indicate their main interest.

### **Workshop on Biomarkers**

Carmen Scheibenbogen (GE) described molecular mechanisms of autoimmunity: the role of susceptibility genes (mostly controlling immune function, such HLA) and the role of triggering factors in the autoimmune mosaic (infections, tissue damage, vaccines, and microbiome). Focus was mainly on molecular mimicry of EBV and potential targets of autoantibodies (in the case of ME/CFS some of them are directed against beta-2-adrenergic and M3- and M4-muscarinic receptors). Regarding immunomodulatory therapy, Rituximab and Cyclophosphamide are being employed to kill pathogenic B-



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cells. Another potential therapy is bortezomib (proteasome inhibitor) that has never been used in ME/CFS affected individuals. A second option is to remove or block auto-reactive antibodies by immunoabsorption or high dose of IgG, respectively. Interestingly, immunoabsorption leads to an improvement of fatigue in a significant number of ME/CFS patients treated at Berlin Charité Hospital.

Helma Freitag (GE) summarized the current knowledge on the classification of autoantibodies profile in ME/CFS reviewing the role of anti-nuclear, anti-gangliosides, anti-cardiolipin or anti-phosphatidylserine antibodies. She also showed that anti-M3 muscarinic antibodies block the binding of ligands “in vivo”.

Elisa Oltra (ES) described potential application of miRNAs (short regulatory and stable RNAs) in both diagnostic (as biomarkers) and clinical interventions (as replacement therapy). Emphasis is made on methodology procedures (sample choice, processing and high sensitive new technologies). Elisa introduced the concept of Extracellular Vesicles (EVs/exosomes) and the relevance of assessing EVs–encapsulated miRNA. Elisa is starting a pilot study (15 severe ME/CFS subjects and 15 HCs) from UK Cure-ME Biobank biosamples to assess differences in miRNAs profiling in PBMCs and EVs/exosomes in this cohort. The study results will be presented and discussed at the next 2018 Invest in ME meeting (BRMEC8 Research Colloquium and IIMEC13 Conference) in London, UK.

Discussion about this work focused on methodological aspects, especially on potential differences using PBMC, plasma or serum biosamples on the methods to isolation and characterization of EVs/exosomes population. Enrica Capelli summarized current knowledge on genetic biomarkers in ME/CFS, focusing in relative studies and reviewing single nucleotide polymorphisms (SNPs) associated with ME/CFS. GWAS analyses identified a missense mutation in CLEC4M (a pattern recognizing receptors) associated with ME/CFS that could be related with sensitivity or poor response to infectious agents. Enrica also focused on epigenetic report data currently av

