EUROPEAN COOPERATION
IN SCIENCE AND TECHNOLOGY

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Draft minutes

Management Committee Meeting
COST Action no. BM1105
Action Title: GnRH Deficiency: Elucidation of the Neuroendocrine Control of Human Reproduction
Berlin, 05 March 2014

1. Welcome to participants: Chair Nelly Pitteloud provided opening comments regarding the Action

2. The MC approved the adoption of agenda

3. Report from the Action Chair: Nelly Pitteloud provided an update of the Action which at present includes >164 participants from 26 countries (38% of whom are female) (this includes students from the first Training School).

4. The location and date of next meeting is Paris (2015) and Milan (2016) as agreed upon by the MC at the MC meeting in Brussels in 2013.

5. Long term planning: the Chair reiterated the major goals of the action including networking of investigators and an anonymous patient registry to foster research.

6. Review of the 2013 - 2014 budget (period 1 Oct 2013 to 31 Jul 2014):

	Approved
Working Group Meetings (4500 € travel cost, 500 € organizational support)	5'000 €
Management committee meeting (50,000 € travel costs, 10'000 € organizational support)	60'000 €
Short-term scientific missions	18'000 €
Training school	30'000 €
Publications, dissemination, outreach, website	5'000 €
Total Science Expenditure	**118'000**
Administration and coordination	17'000
Total	**135'000**

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7. Website was launched (www.gnrhnetwork.eu) in March 2013. It currently includes the following sections:
    a. COST action: “About COST”, “Organization”, “Training”, “Meetings”, “Publications”
    b. Patients: “Learn about GnGH Deficiency/Kallmann Syndrome”, “Centres of Excellence”, “Join a Research Study”, and “Online Resources”
    c. Research: “Our Basic Scientists”, “Genetic Research Centres”, “Gene Curation”, “Patient Registry”

8. Scientific planning and follow-up of MoU objectives
    - Progress report of working groups:
        - **Working Group 1 (Clinical)**
            - One of the most important research tasks to be coordinated by the Action is the detailed characterization and recording of each patient’s phenotype, termed “phenotyping”, which will be performed in a comprehensive and systematic manner across participating physicians and patients. This characterization provides means to identify phenotype ontologies and establish consensus on phenotypic characteristics for database entry. *This has been completed*
            - Create and publish clinical guidelines for clinicians to access on the website on the evaluation and treatment of GnRH deficiency. *In progress: WG1 leader (L. Dunkel) together with the deputy Lead (R. Quinton) has written an extensive clinical practice guideline, which in press in the European Journal of Endocrinology. This article provides a resource to be uploaded on the website later on.*
            - Compile list of specialized referral centers and contacts for website and enhance outreach to other clinicians. *This has been completed.*
            - Enroll patients and appropriate control subjects, and document their phenotypes in a comprehensive and consistent manner. *This can be started only after the database is ready for patient data entry.*
            - Establish and curate a web-accessible database of the de-identified clinical and genetic information on the cohort. *This has been completed.*
            - Develop patient-oriented education/advocacy materials for the website. *This work will be started September 2014.*
            - Establish guidelines for genetic counseling once the genetic architecture of the disease has been sufficiently elucidated. *This work will be started September 2014.*
            - Correlate the patients’ phenotypes with the results of the genetic analyses (together with WG2members). *This work will be started at a later stage of this action.*
            - FSH protocol discussion: Several investigators expressed interest in developing an FSH Protocol. Pitteloud group to develop the protocol and disseminate for input.

        - **Working Group 2 (Genetics & Bioinformatics):**

- **Bioinformatics:** The recent decrease in the cost of next generation sequencing (NGS) has allowed several laboratories within this COST action to consider performing genome-wide studies, with the goal of discovering new genes involved in sexual development. NGS is excellent for unbiased gene identification, but the handling of large data volumes and the analysis of tens of millions of sequences is beyond the capabilities of the majority of researchers. This working group has provided expertise to COST researchers at several levels: (i) overviews of high-throughput methodology (e.g. NGS, GWAS, CNV arrays); (ii) discussion of analysis protocols; and (iii) experimental design to facilitate variant gene identification. The adoption of these new technologies will depend on how comfortable researchers feel about the paradigm shift to large data, genome-wide experiments. Uptake will improve through education in bioinformatics and its application. Good examples of this were the excellent talks at the 2014 Berlin meeting from Zoltán Kutalik, SIB/CHUV Lausanne ("Exome sequencing: When the low hanging fruits are gone"), and from Leo Dunkel, Queen Mary University of London, UK ("Genetic background of constitutional delayed of puberty"). In the meantime, researchers within the COST action will collaborate using a more traditional, PCR-based single gene approach to report variation (or not) within a gene of interest to the group.
- **Genetics:**
    - **Offer of DNA sequencing to COST participants.** First, the best sequencing strategy to perform molecular genetics in CHH patients was discussed. All attendees agreed that next generation sequencing (NGS) is the best strategy overall, with Sanger sequencing being still useful for very short genes and/or very specific phenotypes. As this situation is very rare for GnRH deficiency, Sanger sequencing should be used to verify NGS results. All participants agreed that the development of NGS in routine will take time specifically for CHH which is not a priority in molecular genetics lab with routine diagnostic. An overview of sequencing facilities in the COST was then done. The Cochin group (Catherine Dodé, Jean-Pierre Hardelin) from Paris is the only group which has developed NGS sequencing as a routine sequencing strategy, and they use a targeted approach (specific genes are analyzed). Two other groups from Paris, Bicetre and Robert Debré, are in the process of also developing NGS by targeted sequencing in routine practice. The Swiss group has also developed NGS for research (whole exome sequencing, WES). The groups in Italy, Germany, Greece, and Finland, have developed Sanger sequencing for all or specific known genes. Most of them also plan to develop NGS in the future. It was decided to send a questionnaire to all attendees to catalogue in detailed the information about the sequencing facilities of COST participants. This information will be uploaded on the web site to make it available to all COST members. It was decided that each group would report their own experience in NGS at the next COST meeting. The best method for NGS for clinical diagnosis in CHH will then be recommended.

- **How to interpret genetic results in CHH and which information must be provide to physicians.** Because GnRH deficiency is often an oligogenic disorder, James Acierno proposed that the group should write guidelines on mutation interpretation and reporting. He proposed to begin by writing guidelines for GnRHR, which would be expected to pose the least challenges. It was proposed that a scoring system could be developed to distinguish SNPs from true mutations. In the same context, functional studies were discussed. These are complementary to sequencing and are highly desirable for all mutations which have never been described before. However, research funds to perform such functional analyses may not be available to most participants, and may vary by country. The group, working with the other COST participants, will prepare a list of labs that can offer functional assays to test mutations in specific genes.
- **Collaborative projects.** The desirability of joint efforts to find a "COST" gene was reaffirmed. As a candidate gene approach, James Acierno proposed one gene. All participants agreed to screen at least 30 CHH patients each. Jim will send information and literature on the gene as well as primer sequences and tested PCR conditions to all COST participants, and everyone interested in participating in this collaborative project is welcome to screen their patients. Another gene could be discovered through a collaborative effort between groups using NGS for research. This could be achieved by pooling the exome data from multiple families, each one of which does have not yield a clear disease gene on its own. Groups having already familial cases and interesting candidate genes are invited to declare their interest to the WG leader (N. deRoux). The last point was about future directions. The large number of CHH cases, the detailed clinical phenotype and sequencing results should lead us to develop a project on population genetics in GnRH deficiency. Because CHH is often an oligogenic disorder, this approach could be informative for physicians and basic researchers. It would also be one way to classify the importance of each SNP in humans. Ken Ong who has an expertise on such difficult project gave some advices. We agreed that one main issue would be to define (and analyze genetically) a control population in Europe. This point needs further discussion, and finding funding will be critical as the participants' present funding resources will not be enough to develop such a costly project.

- **Working Group 3 (Basic Science):** During the last year, most of the activities of the WG-3 have been lead by the individual member groups, under the auspices and support of the WG, with the global aim of promoting collaboration and fostering join research projects within the groups of this WG and with other members of the COST Action. Similarly, international collaborations with external (associated) members of the Action, e.g. in New Zealand, and key reference laboratories in third countries (e.g. USA), have been promoted whenever possible and mainly at the individual group level. In addition, different core activities of the COST Action have been mainly driven by WG-3 members. This has also enlarged considerably during the last year, after proactive recruitment of new members, in order to include all possible expert groups working in this thematic area within Europe. The main lines of activity of this WG-3 can be briefly summarized as follows:
    - **Active promotion of mobility of researchers and networking activities within the Action**, mainly via short-term missions (STM). Many of the groups involved in exchange of researchers belong to WG-3 and have either sent or hosted a significant proportion of the actions of this key formative program within COST. Through this, several new collaborations have been fostered between members of the COST network. While publications resulting from these STMs will take some more time, this can already be regarded as a great success story of this COST action.
    - **Active participation in network formative activities**. As paradigmatic example, in close cooperation with WG-4 and his lead person, Prof. Prevot, members of WG-3, including its two chairs, have actively participated in the 2013 Prato School of Neuroendocrinology, jointly organized by the COST Action and the Monash University. A substantial component of the formative activities of this thematic workshop was lead by members of WG-3 or external associates, such as Prof. Allan Herbison (New Zealand). More recently, the co-chair of this WG-3 has been the local responsible for the organization of the COST Scientific Meeting in Berlin (March, 2014), which has gathered more than 110 researchers in different areas related with our Action, fostering active collaboration within COST and with international leaders in this area (invited to attend this scientific conference).
    - **Proactive recruitment of new group members for this working group has been conducted**, both by the head of the COST Action and the leaders of this WG. As a result, the number of members of WG-3, which was substantially smaller than WG-1 and WG-2, has increased significantly during the last year, thus allowing a better representation of the different research groups working in basic science in the thematic area of the Action, with various interests ranging from developmental biology of GnRH neurons to regulatory mechanisms of puberty or the metabolic control of fertility. This wider spectrum of research groups will be of help for fostering closer interactions with other (clinical, epidemiological, genetic) groups within the Action. As a next step, we are “constructing” an internet-based map of expertise within Europe, including basic science groups of WG-3, to further promote partnership and active collaboration with other COST groups.

- **Regular meetings with members of the working group 3 and/or leading persons of other working groups.** Because of budgetary limitations, and because of the limited number of initial members of this WG, such meetings have been associated to other meetings of either the management/steering board or educational activities. WG-3 meetings were held on the occasion of the management board meeting of COST in Berlin 2014, and in a less formal manner, at the Prato School of Neuroendocrinology (August, 2013). In addition, scientific discussions with leading members of other WGs took place in the context of the Lille meeting (September, 2013) of the COST steering board.
- **Active discussion of potential gene targets for clinical-to-basic science translation.** With the final aim of promoting an integral COST study involving all the different groups and WGs of the action, the heads of WG-3, together with other key groups, have participated in active discussion for selection of potential clinical (gene) targets for the conduction of basic science studies, covering the wide spectrum of expertise agglutinated around this WG. On-line discussions on this topic have been followed by personal meetings on the occasion of the Lille management board meeting and the recent COST Berlin meeting.
- **Promotion of international joint applications of research projects.** Departing from the assumption that COST funds do not permit coverage of running cost for research, WG-3 has launched the initiative of creating a working group aiming at the identification of potential topics for joint applications (by consortia formed by COST groups) to the upcoming 2014-2015 calls of H2020. Preliminary screening of funding opportunities has been conducted and this might be followed by one-day meeting in Brussels (if funds permit) for crystallization of partnerships and consortia.
- **Promotion of scientific collaborations with groups in other working groups.** While this has been conducted on an individual group basis, the members of the WG-3 have been especially proactive in setting collaborations with groups in WG-1 and WG-2, thus helping to consolidate the COST action as a whole. While, as said above, this has been made mostly on a group-to-group basis, we consider this also part of the WG-3 activities.

- **Working Group 4 (Training & Education):** The Working group reviewed that 6 STSMs were funded and that remaining funds may be used for a second call with the remaining funds. Discussions were held regarding the 3rd and final training school for the Action and it was suggested that this would take place at the end of June, beginning of July 2015 in Genoa Italy. Mohamad Maghnie would inquire about using the Hospital Villa there to host a Training School with the focus on translational research. This would provide avenues for both basic researchers and clinicians to participate and learn from experts in the field. This will be coordinated by Mohamad Maghnie, Vincent Prevot, Richard Quinton, and Andrew Dwyer.

9. STSM status: 6 have been funded (total = 12,100 €). See list of awardees below.

10. Dissemination planning
    - Website: see above
    - Training School: next meeting Genoa 2015

11. Requests for new members: no new members were put forth.

12. Non-COST applications to the Actions: review of Allan Herbison and Dave Grattan (New Zealand) and Iain Clarke (Australia) have been approved.

13. Summary of MC decisions
    - Adoption of agenda
    - Next Meeting: Paris (2015) and Milan (2016)

14. Closing

Short-term Scientific Mission Awardees 2014

Applicant: Valentina Andre, University of Milan, Milan Italy
Topic: Identification of new genes involved in GnRH neurons development using GFP-tagged GnRH tg zebrafish
Host: Prof. Yoav Gothilf, Tel Aviv University, Tel Aviv, Israel
Award: 3500€

Applicant: Andrew Dwyer, University of Lausanne, Lausanne, Switzerland
Topic: Examining coping and health promoting behavior in CHH patients
Host: Dr. Richard Quinton, University of Newcastle-Upon-Tyne, Newcastle-Upon-Tyne, UK
Award: 1200 €

Applicant: Erik Hrabovszky, Institute of Experimental Medicine, Hungarian Academy of Sciences ,Budapest, Hungary
Topic: Immunohistochemical detection of cGMP to reveal nitric oxide target cells
Host: Dr. Vincent Prevot, INSERM U837, Lille, France
Award: 1700€

Applicant: Johanna, Kansakoski, Helsinki University, Helsinki, Finland
Topic: Characterization of interactions between a novel KS candidate gene and the FGFR1 signaling network
Host: Prof. Nelly Pitteloud, University of Lausanne, Lausanne, Switzerland
Award: 1600€

Applicant: Carina Lund, Helsinki University, Helsinki, Finland
Topic: Isolation and characterization of mouse GnRH neurons
Host: Dr. Paolo Giacobini, INSERM U837, Lille, France
Award : 1600€

Applicant: Panos Ziros, University of Patras, Patras Greece
Topic: Exploration of the involvement of stress response pathways in GnRH deficiency.
Host: Prof. Nelly Pitteloud, University of Lausanne, Lausanne, Switzerland
Award: 2500€