

Report of EUROcleftNet meeting in Glasgow

Friday 21st September 2012: Thistle Hotel, Glasgow



PRESENT: Regine Steegers (NL), Anne-Marie Kuijpers-Jagtman (NL), Peter Hammond (UK), Carine Carels (NL), Jo Zhou (NL), Michele Rubini (IT), Ashraf Ayoub (UK), Sarah Jones (UK), Peter Mossey (UK).

Research grant funding application: The primary objective of the meeting was the discussion of the submission of a research grant funding application through EU Framework 7: Marie Curie ITN (People's Programme). The detail of eligible projects, the best partnerships, mobility issues, funding issues in terms of financial benefits and matching of projects to the skills and needs of the partners involved; and in the context of the overall aims and objectives of EUROcleftNet.

1. Themes for EUROCRANET grant application

The two major themes that will underpin our future work in the field of orofacial clefts in Europe are **aetiology** (genetic and environmental) and primary **prevention** (via nutritional, environmental and behavioural means), with multi-disciplinary cutting edge technology and translational research being important underpinning themes. The Marie Curie ITN EUROCRANET collaboration aims to build on this world leading success, adopting a multi-disciplinary approach and to be fully inclusive across the EU, including the Eastern European States in collaboration with the World Health Organisation (WHO) and the European Cleft Organisation (ECO) whose aims include addressing the health inequalities across Europe.

The methods to be employed in this Network and the rationale for these is as follows:

(a) Genome wide association scan (GWAS) followed by gene sequencing

The discovery of additional genes involved in NS-OFC and the functional effects of identified mutations will require (a) GWAS plus fine mapping the putative regions and (b) evaluation of maternal and fetal genotypes along with gestational environmental exposures.

(b) Functional genomics and epistasis

Investigate the gene variants and haplotypes that lead to altered expression of genes involved in development and, consequently, to cleft lip and palate. This Network will focus on testing the potential functional consequences of these changes, and identify a panel of gene variants that could be screened for risk assessment in the clinical setting.

(c) Gene/environment interactions (GEI)

Epidemiology of OFC in the EU reveals that there are population sub-groups who have a particularly high or particularly low risk of clefts due to a combination of genetic susceptibility and exposure. Using the basic epidemiological principle in common diseases, a combination of common exposures and common genetic polymorphisms are an eligible line of enquiry. Consistency of association between different populations will provide evidence of causality.

(d) Epigenetics and potential for prevention

Epigenetics mechanisms underlie gene-environment (in particular nutrient) interactions on a biological level. Every gamete, embryo and placenta is subject to epigenetic (re)programming through which the genome interacts with environmental factors to eventually exert its phenotypic outcome.

2. Objectives of the Marie Curie ITN research programme

To achieve the stated aims of (a) optimum treatment and (b) prevention while building research capacity, the objectives of the EUROCRANET project are as follows:

1. Impart to the trainees state of the science knowledge and understanding in state of the art facilities.
2. Advance the fields of genetics / gene-environment interaction with epigenetics as an underlying mechanism, quality of care research and computational biology.
3. Provide educational networks to ensure Europe continues to be a world leader in cleft lip and palate research and is able to respond to future research challenges.
4. Have a clear translational remit with the research findings having potential impact on surgical and non-surgical treatment and ultimately prevention of OFC.

The ultimate goals of the activity would be to radically transform understanding of the OFC field, by extending and integrating research themes while at the same time building research capacity for the future. We believe the integrated research and training strategy will also serve as a model for other forms of rare but complex diseases associated with a substantial genetic component.

The EUROCRANET project will involve 3 Work Packages with 8 / 9 Research Projects:

WP1: Management and Supervision

This workpackage is concerned with setting up and ensuring good co-ordination of the educational programmes, optimising the educational benefits to the ESRs and ERs, engaging the visiting scientists and ensuring good industrial input to the training programmes.

WP2: Human population studies into aetiology of non-syndromic orofacial clefts

1. New gene discovery by GWAS, sequencing and use of GWAS data,
2. Bioinformatics, GGI and GEI studies functional studies
3. Nutritional and environmental exposure Mendelian Randomisation studies

4. Epigenetics and DNA methylation studies to identify genetic and environmental risk factors

WP3: Animal models: Functional genes, gene expression and GEI in OFC

5. Folic acid and cleft palate in wild type and *Tgf-β3* null mice

6. Generation of a gene expression atlas

7. Craniofacial shape analysis of mouse models of CL/P

8. Gene expression microarrays related to exposure in murine cleft palate

3. Involvement of Industry in Marie Curie ITN application

The following opportunities, raised at the Bonn meeting were discussed

Diagnostic:

3D imaging / facial morphology and quantification of facial dysmorphology; develop volumetric analysis. (e.g. 3DMd, Dimensional imaging)

Genetics / genomics / transgenics / micro-arrays aimed at gene discovery; (Polygene, Syngenta)

Diagnostic bio-markers and DNA / tissue collection (Skuldtech and DNDi – pharmacogenomics)

Characterisation of selected candidate genes: expression pattern during development e.g. through mouse, dog and zebrafish model (Polygene, DTID)

Preventive:

Environmental factors / GEI research in the quest for clues on exposures and modifiable risk factors such as folic acid, alcohol, smoking, medications and recreational drugs; with a view to personalised medicine applications. (e.g. Syngenta, Zambon)

Drug target identification: through the assembly of protein networks for complex diseases may stimulate research into discovery of drugable targets for these conditions; (e.g. Agilent, DTID)

Pharmaceutical firms interested in the development of nutritional e.g. multivitamin supplements used in conjunction with peri-conceptual care; (e.g. Zambon, Merck, DNDi – drugs for rare diseases model)

Management / clinical care / pre-conceptual care:

At Salzburg there was a call for RCTs and one RCT to study the efficacy of distraction osteogenesis v osteotomy for midface protrusion in adolescents with OFC. (3dMD, Dimensional Imaging)

The use of bone substitute to replace lost alveolar ridge, perhaps trialling use of osteoinductive calcium phosphate bone graft as a carrier for the BMP, for ABG or fistula repair without iliac crest bone. Trials could be conducted with or without stem cell technology; (Xpand, TERMIRA)

The possibility of closure of secondary palatal cleft by bone substitution as opposed to lateral releasing incisions (e.g. Hydrogel, TERMIRA) - and maybe scar free wound healing / tissue regeneration ?

Pre-conception counselling using SMS messaging (Voxiva, Slimmer Zwanger)

Other relevant EUROcleftNet issues discussed:

Website development: Progress the setting up of a website, directory of resources and EUROcleftNet biobank.

2013 EUROcleftNet conference: which is provisionally scheduled for Plovdiv on the 19th – 22nd June 2013. A draft programme for this meeting has already been prepared and the objective will be to have invitations sent to speakers shortly after the EUROcleftNet Steering Group meeting and also to finalise details of the meeting format, the detailed programme, allocate tasks for the preparations and estimate the overall cost of the conference.

EUROcleftNet Budget: Further discussions on budgetary issues and future planning for the network will also be on the agenda (see attached).

Professor Peter A Mossey (EUROcleftNet Convenor)

4th EUROcleftNet Steering Group meeting in Glasgow

Friday 21st September 2012: Thistle Hotel, Glasgow



DRAFT AGENDA:

1. Minute of previous meeting in Bonn on 4th July 2012 / matters arising
2. Update since Bonn meeting
3. Revisit strategy / mission statement
4. Preparation for MEPs meeting in Brussels
5. Website project update
6. Plovdiv meeting 19th – 22nd June 2013 – provisional programme
7. Marie Curie research grant application (see Appendices below)
8. Other grant funding opportunities
9. Industrial liaison – continuing the collaboration
10. Healing Foundation – the cleft collective
11. EUROcleftNet directory of resources and biobank
12. EUROcleftNet exchanges

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Finance report

| Glasgow costings | | |
|-------------------------|----------------|----------------|
| | GBP | EURO |
| Peter Mossey | 930.60 | |
| Peter Hammond | 219.75 | |
| Carine Carels | | 353.57 |
| Regine Steegers | 45.00 | 168.96 |
| Michele Rubini | | 573.21 |
| Sarah Jones | 9.95 | |
| Jo Zhou | 31.00 | 346.37 |
| SCALP | 426.10 | |
| venue | 96.00 | |
| meeting room | 276.25 | |
| Total | 2065.65 | 1442.11 |
| | | £1236.17 |
| | 3301.82 | 3851.87 |