Research Networking Programmes

Science Meeting – Scientific Report

Proposal Title: Opportunities for funding in the Horizon 2020 programme

Application Reference N°: 5363

1) Summary (up to one page)

The workshop began with a plenary presentation from Cordelia Denby on a range of potential opportunities for funding within the Horizon 2020 programme; the 3 pillars on which Horizon 2020 is based and the differences between Horizon 2020 and the preceding framework 7 programme.
Cordelia then elaborated further on the opportunities that are most relevant to the EuroCleftNet group i.e. specific calls for applications and also the bottom-up approach represented by the Marie Sklodowska Curie programme which has both a research and training element.
All delegates were given the opportunity to do a short 5-10 minute presentation on their areas of expertise and also suggestions of how these may feed into synergistic collaborative opportunities across the EuroCleftNet programme. The list of presenters was as follows:

1. Carine Carels
2. Jo Zhou
3. Elisabeth Mangold
4. Borut Peterlin
5. Ann Molloy
6. Michele Rubini
7. Ashraf Ayoub
8. Bill Shaw
9. Florence De Groot
10. Gareth Davies
11. Martin Persson
12. Youri Anastassov

2) Description of the scientific content of and discussions at the event (up to four pages)

Afternoon Workshops – consensus agreement on the area's most eligible for funding were PHC 2-2015: understanding diseases, systems, medicine and PHC11-2015: development of new diagnostic tools and technologies, in-vivo medical imaging technologies. These were agreed upon following plenary discussion of a range of other opportunities. These two calls were the subject of discussion in two workshops and after the feedback from these two workshops it was concluded that further development within the network through to the final calls in 2015 may create collaborative and synergistic opportunities for EuroCleftNet: but in the meantime it would be appropriate for the network to focus attention on the Marie Sklodowska Curie ETN (European Training Network) opportunities and the appendix below provides further commentary on the areas that EuroCleftNet could prepare a focused application on.
Short visits and exchanges – it was also noted that the programme of short visits and exchanges was being actively pursued by a number of EuroCleftNet partners and the focus

of attention was to build capacity between teams to improve future applications for horizon 2020 or MSc funding.

WORKSHOP 1: Discussion PHC2-2015: Systems Biomedicine

Participants: Jo Zhou, Carine Carels, Anne Molloy, Michele Rubini, Borut Peterlin, Sarah Jones, Kerstin Ludwig, Elisabeth Mangold, Ashraf Ayoub, Cordelia Denby, H2020 project

The group first distilled the important aspect of the Call (which is under health, ageing and disease):

- **new avenues for understanding the complexity of clinical phenotypes** in multifactorial diseases and/or their co-morbidities.

- **Development / optimisation and/or application of systems medicine approaches**, and **integration of biomedical and clinical data** to produce or refine disease models using **advanced statistical, computational and mathematical approaches**.

- **The predictive value** of such models should be validated in well-phenotyped patient cohorts, taking due account of gender, and their clinical potential thoroughly investigated.

Cordelia Denby also highlighted that we would need to ensure that all aspects of the "Impact" should be met:
1) Leverage of existing investments in Europe in the field of systems biomedicine
--> i.e., it would be required to bring someone on board who has been funded by the EU in FP7 or so in the field of systems biomedicine. A brief check in the internet on previous funding groups did not reveal a promising group at first glimpse.
2) New directions for better disease detection, prognosis and therapy development
--> We do not have a therapy for orofacial clefting, nor is therapy development a major aim of our group
3) Systems medicine tools and approaches tailored for medical research and/or the clinic, which represent an improvement over established practice.
--> improved counselling and diagnostics were considered to be one improvement, however, we are still far away from having these tools from a genetic / functional perspective ready yet.

Conclusion: the Call PCH2-2015 is more tailored for other phenotypes that have current (ineffective) treatments, not for birth defects such as orofacial clefting.

WORKSHOP 2: Discussion PHC-11- medical imaging innovations

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Present: Regine Steegers, Bill Shaw, Martin Persson, Yang Ju, Youri Anastasov, Gareth Davies, Peter Mossey

This workshop was to focus on innovations that offer a clear advantage over existing technology in the field. Two aspects were discussed in more detail.
1. Pre-natal ultrasound imaging
2. Post natal craniofacial 4d imaging (facial animation).
Pre natal ultrasound imaging can now be carried out as early as 6 weeks gestation and development of this technology enables diagnosis of craniofacial abnormalities at a much earlier stage i.e. 6-8 weeks and the technology would also enable quantitative measurements of size, areas and volume to be determined.
What are the advantages over existing technology?

1. Sensitivity and specificity of diagnosis differentiating syndromic from non-syndromic orofacial clefts
2. Diagnosis of isolated cleft palate which is not possible with existing technology

3. Other structural birth defects such as CHD, limb reduction, genitourinary and neural tube defects

The quantification and ability to estimate volumetric parameters means that crown size and volume in relation to maternal nutrition, folic acid supplements, maternal smoking etc. could all be accurately measured. Are there psychological advantages in early diagnosis?
It has been shown that psychological preparation of parents improves the acceptance and information on improvements in counselling and being able to supply more accurate information if the severity of the cleft and whether it is syndromic or not affects the information provided on prognosis.
It raises the ethical issue of whether earlier diagnosis would increase the likelihood of termination of pregnancy. There may be a rationale for delaying this dysmorphology ultrasound scan until 20 weeks if it were more acceptable to patients and families and having psychological intervention available but overall this package, if accompanied by provision of good counselling, could be life saving for conditions that may otherwise result in termination of pregnancy.
The second issue related to availability of this technology which if not affordable in the poorer countries could be seen to introduce inequalities.
Post natal craniofacial 4D imaging and facial animation. This would enable a better definition of the cleft phenotype and the 4D imaging would enable subjective or quantitative analysis of facial animation.

Marie Sklodowska Curie Action (MSCA) Workshop Report: Opportunities

In the workshops at the EuroCleftNet meeting in Amsterdam, the consensus was that our major research focus did not fit precisely the calls that we considered as possibilities in PHC "Health" / Horizon 2020. It was also agreed however that our teams are involved in some exciting and cutting edge research in the field and where we can rightfully claim to be world leading.
This was also reinforced by Cordelia Denby who was of the opinion that our network is well placed to apply for Marie-Sklodowska Curie funding and in dialogue at the end of the meeting there was enthusiasm for the submission of a MCSA application in April 2014.

With EUROCleftNet well placed for a MSCA application, and advice that a good proposal should involve around 8 partners with a balance between academic and non-academic we should consider a submission for April 2014. The framework of the project should be built on development of professional skills in an emerging and future facing field, as well as conducting the research.

There are a number of possible topics and we can prioritise:
1. Development of a gene chip that could be used for screening in families with an infant born with or a history of non-syndromic orofacial clefts.
2. Whole genome sequencing studies with large sample size and Europe as a leading partner
3. A collaborative project involving alveolar bone grafting in patients with CLP
4. An innovative medical imaging project that may extend from the early embryonic development ultrasound imaging; through to 4D post natal imaging

The overall vision is for a "Translational application of new technologies and scientific knowledge in clinical settings" to create pilot example of cleft-specific clinical genetics facilities. Implementing the latest technologies and the deepest knowledge on cleft etiology in clinical genetics setting.

The feasibility of these would be determined by the level of inter-centre synergy and collaboration to make the criteria for submitting applications with the appropriate number of collaborating partners and the appropriate blend of expertise. 2 opportunities elaborated on below:
1. Development of DNA micro array chip: this would be a novel and innovative project designed to develop a tool that could be used in genetic counselling for families

where and infant is born with an orofacial cleft. The development of this would require expertise in bioinformatics, teams with expertise and track record in GWAS, genes known to be involved in monogenic syndromes where clefts are part of the phenotype and genes identified through whole exome sequencing (rare variants).

2. Whole genome sequencing to discover rare mutations in large families, or to look for common susceptibility variants in large sets of parental trios, would also be seen as complimentary to this. Partner/s with expertise in genotype-phenotype correlation and / or gene-environment interaction could also be considered – provided they bring additional innovation and strength.

Any of these Marie Curie collaborations would benefit from non-academic partners such as the patient/parent group, the European Cleft Organisation (ECO) and the addition of a commercial or industrial/commercial partner e.g. Life and Brain Centre as well as Eurocat, Euromedicat and WHO would be beneficial. Being something that could possibly be used worldwide, in every clinical genetics setting, should be attractive to the EU-commission.

This report is to set the scene for dialogue / collaborative discussions with the above merely providing ideas for further actions / applications.

3) Assessment of the results and impact of the event on the future directions of the field (up to two pages)

During the afternoon workshops, the delegates were charged with the task of planning for the future of the Network in the light of research opportunities that may present in our field of interest, particularly in light of the H2020. Arising out of the Workshop discussions the following were prioritized:

Workshop 1 future directions:

Additional Discussion points in relation to:

- important: develop computational models. Herefore, strong mathematical / computational / statistical expertise is required. Jo Zhou knows computational biologist in Nijmegen, Christoph Lange from Bonn. Other statistical/computational/mathematical expertise is required.
- make sure that gender is not an issue (i.e., to include all gender /sexes in the project)
- Precise phenotyping (cleft lip / cleft palate) is crucial, but also 3D facial morphology depending on genotypes could be used for generating a statistical / computational model. The issue here is that the required sample size for such a genotype-phenotype project is not available yet.
- Suggestion: Sample collection (e.g., take 3D images of 3months old babies prior to surgery, then create genomics etc. data). It is strongly questioned that this is feasible in 4 years.
- another idea: what about analyzing parental genotypes as starting point, and correlate that with facial appearance etc. which might have been taken by optical measure methods. However, ethical issues apply (Xray in unaffected parents might be difficult to get ethical approval for)
- The main problem in SysBio: have large number of samples and data. Our group does not have either of those at the moment.

Workshop 2 future directions:

<u>Impact and future directions</u>

The ability to describe the morphology more precisely may lead to a more precise tailoring of a new surgical protocol to the particular type of cleft defect; although it was felt that there would be differing opinions on the most appropriate type of surgery and this subjectivity remains at the hands of surgeons. After cleft repair, use of 4d imaging would enable visualisation of facial animation and may also influence the type of operation that would

minimise residual deformity and in turn may improve appearance and reduce the tendency to bullying of individuals born with orofacial clefts.
Would allow further investigation of the genetic predisposition to scarring as individual variations are known to exist.
Limitations of such outcome measurements are the very long term measurement on ultimate facial morphology and function with cleft operations in the first year of life needing follow-up until adulthood to determine the ultimate outcome.
Additional components of this work package.
Would 4D imaging have any advantage in assessment of speech?
More information on the effects of facial appearance and function on psychology and bullying at individual or family level?
Could the much more precise quantification and statistical handling of 3d and 4d data be used in research that requires illustration of minor differences in outcome, and to do this objectively, for example, if a randomised trial were to be carried out on the effects of nasoalveolar moulding (NAM).
Would it be possible to determine criteria that would be able to differentiate between outcomes with different protocols and to determine/provide insight into what is surgical skill?

In conclusion, both the prenatal ultrasound and the post natal 4d imaging are innovative new technologies and could potent but there is no clear link between the prenatal and postnatal imaging technologies and limiting their application to the field of cleft lip and palate may be seen as a limitation to their more general utility and ultimately their value and overall impact.

Opportunity in PHC-26: Citizen engagement in Health: Future Direction

Rationale - European priority
Professor Regine Steegers presented information on a programme that is of interest to those working in the field of birth defects aetiology and prevention. In Europe, the problems met by our ageing population include a high prevalence of chronic age-related diseases. These disorders, which include obesity, continue to rise. In 2030, the incidence of adult-onset diabetes and of dementia is expected to nearly double (to 43 million and 14 million respectively), cardiovascular disease will increase by 35% (2030: 5 million deaths per year) and obesity by 40%.

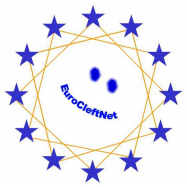
Poor nutrition and lifestyle significantly contribute to chronic age-related diseases, but not only in adulthood. Improvement in nutrition and lifestyle at the earliest stages in life is likely to have a major impact on prevention of age-related disease. Population based research has unequivocally, demonstrated that these poor behaviours in the preconceptional period, during pregnancy and in early childhood can contribute to the risk of cardiovascular and metabolic disease in both parents and children.

In Europe, more than 80% of the pregnant women and their partner have one or more poor nutrition and lifestyle behaviours. Our work has highlighted that those most vulnerable are socio-economically deprived. This has included studies amongst migrants, low educated inner city populations and pregnant adolescents whose pregnancies are at high risk of adverse outcome.

Proposed collaborative opportunity for EUROCleftNet
In Horizon 20/20 we will start with an inventory of available mHealth programs for nutrition and lifestyle coaching on the smartphone. One mHealth program will be chosen as prototype, which will be adapted according to the requirements in the participating EU countries. The EU digital preconception platform will be used as medium to reach the target groups of citizens and health professionals and to provide the innovative mHealth tools.

A number of delegates in the EUROCleftNet collaboration expressed interest in collaborating on this PHC-26 H2020 proposal.

Annex 4a: Programme of the meeting



"Opportunities for funding in the Horizon 2020 programme"

Friday 31st January 2014

PROGRAMME:

9.30 – 10.00 Registration

10.00 - 10.30 Overview of H2020 (Cordelia Denby)

10.30 - 11.30 Plenary presentations (6 presenters)

- Carine Carels
- Jo Zhou (incl. work with Mike Dixon)
- Elisabeth Mangold
- Borut Peterlin
- Anne Molloy
- Michele Rubini

11.30 – 11.50 Coffee / Tea

11.50 - 12.45 Plenary presentations (5 presenters)

- Gareth Davies
- Bill Shaw
- Florence de Groot
- Yang Ju / Ashraf Ayoub
- Martin Persson
- Youri Anastassov

All delegates will be given an opportunity to do a 5 min presentation / 5 min questions in a plenary to indicate which areas may result in collaborative grant applications.
12.45 – 13.00 Discussion / Planning of breakout groups on the basis of this discussion
13.00 - 14.00 LUNCH
14.00 – 14.40 Parallel workshops I
Select parallel breakout groups (40 minute discussions) where synergies can be explored further;
14.40 – 15.20 Workshop Feedback & identification of best opportunities
15.45 – 16.30: Action points:
1. Decisions on which projects to take forward - i.e. the ideas that may be fundable.
2. Network activities to support further development of grant application process e.g. Peer Review and short visits / exchanges

Annex 4b: Full list of speakers and participants

Youri Anastassov, Bulgaria; Gareth Davies, France; Peter Mossey, UK; Sarah Jones, UK; Cordelia Denby, UK; Bill Shaw, UK; Carine Carels, Netherlands; Martin Persson, UK; Eliasbeth Mangold, Germany; Kirsten Ludwig, Germany; Yang Ju, Glasgow; Ashraf Ayoub, Glasgow; Borut Peterlin, Slovenia; Anne Molloy, Ireland; Jo Zhou, Netherlands; Florence de Groot, France; Regine Steegers, Netherlands; Michele Rubini, Italy