WP 1.5: Probiotics, feeding and NEC in preterm infants

1. WP (related WPs, MG contact): WPs 1.4b, 1.6a, 1.7; 2.2, 3.1, 3.2. MG contact: Gorm Greisen

2. Key involved personnel, institutions, mail address (project leader + main study site underlined):
Elisabeth Lyore, Physician, Neonatology, Copenhagen University Hospital, elisabeth.lyore@regionh.dk (10%)
Gorm Greisen, Prof., Neonatology, Copenhagen University Hospital, greisen@rh.dk (10%)
Irina Lambæk, Physician, Neonatology, Copenhagen University Hospital, irinakirill@hotmail.com (10%)
Janet Berrington, Chief Physician., Newcastle Neonat Service Hosp, j.e.berrington@newcastle.ac.uk (5%)
Karen Krogfelt, Prof., Dept. Microbiology, Statens Serum Institut, kak@ssi.dk (5%)
Sandra Meinich Petersen, Phd stud., Copenhagen University Hospital, sandrameinich@gmail.com (60%)

3. Main aim and sub-aims:
1. To examine the periodicity of the NEC rate at Copenhagen University Hospital
2. To describe the epidemiology of NEC at the national level
3. To describe the association between gut microbiota and NEC
4. To examine the effect of routine use of probiotics
   a. on the rate of NEC
   b. on the fecal microbiota
5. To develop early diagnostic tools to discriminate simple feeding intolerance from early NEC.

4. Background and a central hypothesis:
NEC is one of the four major neonatal morbidities in preterm infants. NEC has high mortality and carries a high risk of long term consequences in the form of short bowel syndrome and neurological deficit. NEC is probably caused partly by too aggressive enteral feeding and bacterial overgrowth. Clinically, it is difficult to balance the risk of NEC with the nutritional needs of the small, preterm infant.
We hypothesize that:
a) The incidence and mortality of NEC is stable in absolute terms but decreasing when corrected for gestational age and weight at birth
b) The use of probiotics is associated with lower risk of NEC and probably with a 'better' gut microflora
c) A composite index of clinical and biochemical biomarkers is useful to discriminate simple feeding intolerance from early NEC

5. Key analyses and methods:
Collection of routinely recorded clinical data. Re-assessment of clinical X-rays. Access to local and national databases. Statistical analysis. DNA analysis of stool from cohorts of preterm infants from Copenhagen and Newcastle. Prospective study of preterm infants at high risk of NEC.

6. Expected results:
Confirmation or rejection of hypotheses (A-C)

7. Estimated time frame

Task	2013				2014				2015				2016				2017				2018			
1+2+4a. Data analysis				x	x																			
1+2+4a Publication						x	x																	
3+4b DNA analysis					x	x																		
3+4b Data analysis							x	x																
3+4b Publication									x	x														
5. Data collection					x	x	x	x	x	x	x	x												
5. Data analysis													x											
5. Publication														x	x									
Publication(s)							3			2					2+									

8. Estimated budget from NEOMUNE:

1.2 mio DKK (0.67 MD PhD + tuition + annum)

9. Estimated budget from elsewhere:

0.7 mio DKK (analytical costs 0.3, contribution from senior researchers 0.4). Additional funds will be required to perform all the indicated tasks and further support will be applied for (e.g. task 5).

10. Additional comments:

- This work package has synergies with ongoing projects at Copenhagen University Hospital and Statens Serum Institute, as well as collects new data from patients at Copenhagen University Hospital.
- The depth of the gut microbiota analyses (various levels of conventional and/or molecular techniques) will be decided upon depending on the quality of the samples collected in relation to the hypothesis and the funding available at the time of sample collection completion. Collaboration with other partners will be added as judged appropriate (BGI Shenzhen, Newcastle, Univ. Copenhagen).
- The data collected may influence the possible choice and the mode of probiotic interventions for preterm infants in WP 1.6b.
- The key institution is part of WP 1.4b (data base project) and part of this WP will relate to observations collected for the overall international data base (NEC, probiotics use, antibiotics).