WP 1.6a: Minimal enteral colostrum for preterm infants

1. WP (related WPs, MG contact person): Synergies to WPs 1.4a,2.3. MG contacts: Per Sangild, Gorm Greisen

2. Key involved personnel, their institution and mail address (project leader + main study site underlined):
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3. Main aim and sub-aims:
a) To investigate the safety, tolerability and preliminary effects of bovine colostrum, used as the first enteral diet for preterm infants at 1000-1800 g body weight.
b) To assess the feasibility of study procedures, including recruitment rates, parental consent, adherence, sample collection, clinical routines, observing adverse effects.
c) To facilitate the determination of the primary endpoint and sample size for a future larger randomized, controlled trial with bovine colostrum administration.
d) To perform a randomized, controlled trial investigating bovine colostrum versus donor milk or formula.

4. Background and a central hypothesis:
Minimal enteral nutrition (MEN) is a term that reflects the small volumes of milk fed to preterm infants just after birth. It is assumed that MEN feedings promote gut maturation, provide extra nutrients and energy and allow more rapid advancement to full enteral feeding (EN, e.g 120-160 ml/kg/d), and thus cessation of parenteral nutrition (PN). It remains unclear what milk diet is best when mother's own milk is not available. Mother´s milk is superior to infant formula in promoting feeding tolerance, body growth, intestinal function, and NEC resistance in preterm infants. Feeding with human donor milk is also believed to be beneficial, relative to formula, but pasteurized milk obtained from mothers later in lactation may be less beneficial, relative to the first mother´s milk, the so-called 'colostrum'. Human milk needs to be fortified with extra nutrients to support growth of preterm infants. Colostrum from cows contains some documented beneficial properties and its maturational and NEC-protective effects are documented in a series of studies in newborn, preterm pigs.
We hypothesize that bovine colostrum, used as MEN for preterm infants, is safe and helps to provide nutrients and improve gut maturation in preterm infants, when enough mother's milk is not available.

5. Key analyses and methods
Phase a: Pilot study to test safety/tolerability of bovine colostrum, and feasibility of study procedures (n=20).
Phase b: Randomized controlled study, fully powered to detect differences in primary endpoints (n≈150)
Phase a will be run both at Copenhagen University Hospital and at Foshan Woman's and Children's Hospital.
Study site(s) for phase b is to be decided. Diet interventions for a maximum of 10 days. Control group: Donor milk (Copenhagen) or infant formula (Foshan) supplemented with mother´s own milk. Intervention group: Bovine colostrum supplemented with mother´s milk (Copenhagen) or infant formula (Foshan) as needed.

6. Expected results

We expect to document whether bovine colostrum can be used as a beneficial first enteral diet for preterm infants that have limited or no access to mother´s own milk. Results include clinical neonatal outcomes (time to full feeding, feeding intolerance, combined incidence of serious infections/NEC, days of hospitalization, anthropometry data, days to regain birth weight, days on PN, and stool characteristics) as well as paraclinical outcomes (plasma citrulline, intestinal permeability, fecal microbiota composition and fermentation.

7. Estimated time frame

Task	2013				2014				2015				2016				2017			
Exp. plans, ethical protocols phase a)	x	x	x																	
Phase a) execution, Copenhagen						x	X	X	X	X										
Phase a) execution, Foshan						x	X	X	X	X										
Laboratory analyses, Copenhagen							X	X	X	X										
Laboratory analyses, Foshan							X	x	x	X										
Publication from both phase a)										x	x	X								
Planning, phase b), ethical protocol									X	X										
Phase b) execution, Copenhagen												x	X	X	X					
Phase b) execution, Foshan												x	X	X	X					
Laboratory analyses, Copenhagen														X	X	X				
Laboratory analyses, Foshan														x	X	X				
Publication from phase b)																	x	X		

8. Estimated budget from NEOMUNE:

Phase a) 0.6 mio DKK (PhD, post doc salaries, Yanqi Li, Sandra Meinich)
Phase b) 1.0 mio DKK (PhD, post doc salaries, Yanqi Li, Sandra Meinich, other personnel?)

9. Estimated budget from elsewhere:

Phase a) 0.6 mio DKK (Zhu Yanna, Yanqi Li, PhD students, MSc students, hospital personnel). Co-financing.
Phase b) 1.0 mio DKK (Zhu Yanna, Yanqi Li, PhD students, MSc students, hospital personnel). Co-financing.

10. Additional comments:

- Ethical approval of the studies was applied for in both Denmark and China and is approved for phase a). The exact planning of phase b) will depend on the results from phase a). If results from phase a) are not promising, then phase b) will be cancelled.
- A large effort is involved in securing that the product, powered bovine colostrum, can meet current legislation for use as infant formula. The investigators work with Biofiber to secure this.
- Very close collaboration between Copenhagen University Hospital and Foshan Women's and Children's Hospital, China is required in this project.

WP 1.6b: Probiotics for preterm infants

1. Related WPs, MG contact person: Synergy with WP 1.3a, 1.4b, 1.5, 2.2, 3.2. MG contact: Gorm Greisen

2. Key involved personnel, their institution, mail address (project leader + main study site underlined):
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3. Main aim and sub-aims:
To perform a randomized clinical trial in newborn infants with probiotics in China and possibly other countries.

4. Background and a central hypothesis:
Probiotics have been shown to reduce the incidence of necrotizing enterocolitis (NEC) and overall mortality in infants with birth <1500 g and/or gestational age <32 weeks. This has been demonstrated in systematic meta-analysis covering more than 15 randomized trials and more than 2,500 infants. Several large trials are at present awaiting conclusions. While probiotic use in clinical routine is far from universal, its use is increasing, and a standard large-scale placebo-controlled trial runs the risk of becoming ethically difficult within such a trial's lifetime.
However, there are several problems and questions that remain unanswered before use of probiotics can be recommended as part of standard clinical care for preterm infants. In previous studies, many different probiotic strains, or combinations of strains, have been used in many different concentrations. In most trials, probiotics have not been given during the first days of life and there may or may not be an advantage in allowing spontaneous bacterial colonization take place prior to introduction of probiotics. Finally, the interactions between probiotic effects and the timing, dose and type of antibiotics given to preterm infants have not been investigated. Clearly, this WP cannot answer all these important questions. The choice of intervention in this WP shall, after careful evaluation of a) already ongoing international trials, b) current practice at NEOMUNE hospitals (WP 4.1b), and c) supporting evidence from NEOMUNE animal model studies (WP 2.2 and WP 3.2), be built on the following hypotheses:
1. The clinical effects of 10^9 and 10^{10} CFU per day do not differ.
2. Initiation of probiotics administration on day one, prior to the spontaneous colonization of the gut, improves the clinical outcome.
3. The clinical effects of probiotics are more pronounced following use of antibiotics for preterm infants.

5. Key analyses and methods:
Primary outcome to be determined. Blinded allocation. 2 x 2 factorial design (dose and time). Pragmatic design. External monitoring.

6. Expected results:
See 4. – hypothesis

7. Estimated time frame

Task	2013				2014				2015				2016				2017			
1. Exploring data base information				x	x	x	x	x												
2. Evaluation of pig model studies								x	x											
3. Evaluation of mouse model study								x	x											
4. Protocol formation									X	x										
5. Organization of clinical study											x	x								
(6. Clinical trial in preterm infants)												x	x	x	x	-	>			
(7. Analyses of results)																	x	x	X	x
8. Publication											x	x							X	x

8. Estimated budget from NEOMUNE:

Max. 2.0 mio DKK from NEOMUNE base funds for clinical studies in China (together with WP 1.4b/1.6a).
Possible industrial co-financing to be negotiated with potential partner(s)

9. Estimated budget from elsewhere:

3.0 mio DKK (university and hospital partners, internal staff and equipment).
Co-funding from other NEOMUNE projects (e.g. animal studies)

10. Additional comments:

- The WP depends significantly on the collaborative links among hospital partners formed as part of WP 1.4b. Considering the extensive NEOMUNE network in this area, results from WP 1.4b will help to gain ideal conditions for formulating a clinical trial that answers the most important question at the time of initiation.
- The WP is linked with animal model WPs to maximize basic knowledge transfer to this WP before the project plans are fixed (probiotics time, dose and interaction with antibiotics).
- The total scale and nature of proposed clinical trial depends heavily on sponsoring from industry partner(s). Possible partners still being negotiated.
- While the costs of the planning phase for this project (see above Gantt diagram) are mainly covered by funds from elsewhere in NEOMUNE, some funds may be allocated also from this project.