



# NEOMUNE research platform – work package synopses

## WP 1.4a: Donor human milk to preterm infants

**1. Related WPs, MG contact person:** Synergies with WP 1.4b, 1.6a, 1.7, 2.3, 2.4. MG contact: Per Sangild

**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**

**Aim:** To determine whether (supplemental) human donor milk has beneficial effects (in terms of reduction of infectious episodes and mortality) when compared to (supplemental) preterm formula during the first 10 days of life in very low birth weight (VLBW) infants.

**Sub-aims:** To determine if early use of donor milk results in a more diverse intestinal colonization, earlier attainment of full enteral feeding, reduced number of days on parenteral nutrition, similar growth rate, similar bone density and improved Bayley Scores of Infant Development III at 2 years, compared with infants fed preterm formula.

**4. Background and a central hypothesis:**

Feeding own mother's milk (OMM) to preterm neonates is thought to have important beneficial effects for VLBW infants when compared to formula feeding. Short-term effects seem to include a reduction in the incidence of sepsis and necrotizing enterocolitis (NEC). Neonatal sepsis, occurring in 20-60% of VLBW infants, is a major contributor to neonatal morbidity and mortality and compromised long term neurodevelopmental outcome. Unfortunately, it has proven to be very difficult to provide OMM within the first few hours and days of life as the onset of lactation is often delayed after preterm delivery.

*We hypothesize that a diet completely consisting of human milk (OMM and/or donor milk) during the first 10 days of life reduces the incidence of sepsis/NEC and/or mortality in VLBW infants.*

**5. Key analyses and methods:**

Blinded randomized controlled multicenter study, conducted in 5 Dutch hospitals. Infants with a birth weight <1500 grams will be included after obtaining informed consent. The intervention starts when the first enteral nutrition (MEF) is given according to the local protocol. If milk of the own mother is available this will always be used first in both groups. If milk of the own mother is not available, or the volume is not sufficient, infants in group A will receive donor milk and infants in group B will receive infant formula. The study intervention ends at day 10 of life and OMM or donor milk will not be fortified during these days, to avoid introduction of cow's milk protein before day 10 of life. Data on the primary and secondary endpoints will be collected until 60 d of age.

We consider a reduction in the combined incidence of serious infections and/or NEC and/or death from 40% in the control group to 25% in the donor milk group to be clinically relevant.



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### 6. Expected results:

Data will be collected on the incidence of the combined outcome of serious late-onset infections (sepsis/meningitis and NEC) and/or death occurring between age 72 hours and 60 days. Additionally, the composition of fecal microbiota (first stool and stool at days 10 and 30), time to full enteral feeding, days on parenteral nutrition, weekly growth rate (body weight, length and head circumference), bone density by ultra sound and Bayley Scores of Infant Development III at 2 years of age will be determined. We will determine differences in these outcomes between VLBW infants fed with a diet completely consisting of human milk and VLBW infants (partly) fed with formula during the first 10 days of life.

### 7. Estimated time frame

Task	2011				2012				2013				2014				2015				2016			
Planning, protocol	x	x	x	x																				
Sample collection					x	x	x	x	x	x	x	x	x	x	x	x								
Data analyses															x	x								
Analyses feces																	x	x						
Publication primary outcomes																					X			
Publication secondary outcomes																						X	X	
Finish follow-up period																								X

### 8. Estimated budget from NEOMUNE: 1.0 mio DKK

Also used to support participation and consulting in WPs 1.4b, WP 1.6a and WP 1.6b.

### 9. Estimated budget from elsewhere: 0.8 mio €

Mead Johnson Nutritionals.

### 10. Additional comments:

- There is important scientific synergy to a number of other NEOMUNE projects on feeding preterm infants or preterm pigs (see section 1). As such, there is a possibility to make use of shared analytical capacity and/or knowledge sharing in the areas of gut microbiota, immunity, metabolism and brain-related endpoints. Possible analyses of samples within the NEOMUNE network will be determined after completion of the intervention studies.
- The Amsterdam group has intensive experience on nutrition research in preterm infants and in using pigs as models for infants. The leader of the Amsterdam group is a central opinion leader for nutrition in preterm infants via ESPGHAN. Central role in leading WP 1.4b.
- The Amsterdam group is important in planning the NEOMUNE intervention studies on preterm infants in China and is already leading infant nutrition studies in China.
- The Amsterdam group may be important as a training site for researchers from elsewhere in NEOMUNE, including WP 1.7.



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## WP 1.4b: Database of feeding preterm infants

<p><b>1. Related WPs, MG contact person:</b> Synergies with WP 1.4-6, MG contacts: Per Sangild, Gorm Greisen</p>
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<p><b>3. Main aim and sub-aims:</b>  Aim: To know differences in nutrition practice and use of anti-/probiotics for preterm infants &lt;1500 g.  Sub-aims: 1) to relate different clinical practices to disease and growth patterns; 2) to relate different practices to biological and cultural factors (in connection with WP 1.7); 3) to obtain baseline information on feeding practices and –biotics uses to help design future diet intervention studies in these hospitals.</p>
<p><b>4. Background and central hypotheses:</b>  Feeding and gut colonization are believed to be two important factors for short and long term health of preterm infants. Feeding practices and use of anti- and probiotics for these patients vary widely around the world and the most beneficial regimen remains poorly understood. It is unknown to which extent the chosen feeding regimen is related to factors such as product availability, infant genetics and biology, clinical tradition or cultural elements. Our hypothesis is that 1) the time to achieve full enteral feeding (TFF, in this study set at 120 mL/kg/d) differs widely among hospitals, and variation in TFF is associated with type of diet and antibiotics use; 2) infants in units that achieve enteral feeding 120mL/kg/day earlier achieve higher body weight at the end of follow-up when corrected for GA and weight at birth; 3) differences in feeding practice is not significantly associated with differences in major neonatal morbidities.</p>
<p><b>5. Key analyses and methods:</b>  Collection of retrospective and prospective data from 14 hospitals worldwide into a web-based database. The participating hospitals will enter the data of eligible infants from the 1<sup>st</sup> Jan. 2011 to the 15<sup>th</sup> Sept. 2013 retrospectively, and from 16<sup>th</sup> Sept. 2013 to 15<sup>th</sup> Aug. 2014 prospectively. Formation of the web-based database is led by Marita de Waard and Johannes van Goudoever. Marita and Yanqi Li will lead the communication with hospitals, collection of data, and analyses of the data.</p>
<p><b>6. Expected results:</b>  The database collects data from preterm infants &lt;1500 g from the first day of birth to 37 weeks corrected gestational age or discharge, whichever comes first, in the 17 participating hospitals. The data include maternal</p>



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data, volume, composition and days of parental nutrition, volume, day, and type of enteral nutrition, weekly demographic data, clinical data (e.g. NEC) and use of anti- and/or probiotics. Each parameter will be compared among hospitals to investigate whether they differ. Correlations among parameters are done to identify relationships between nutritional and –biotics practices and clinical outcomes (e.g. TFF, postnatal growth rate, antibiotics use, NEC). The observational data provide indirect evidence for the optimal feeding regimen and provide a basis for identifying the most important variables that affect clinical practices in different parts of the world. As such, the data are also important for doing nutrition and –biotics intervention studies at each hospital site.

### 7. Estimated time frame (edit task and indicate time by “x”)

Task	2013				2014				2015				2016				2017			
Planning, database development	x	x	x	x																
Data entry			x	x	x	x	x	x												
Data analyses in each hospital							x	x	x	x	X									
Overall collective data analyses									x	x	x	x								
Publication(s), individual hospital*									x	x	x									
Collective overall publication(s)*															X	X				

\* Data are allowed to be analyzed in individual hospitals for their internal use or publishing on local or international journals. To retain the novelty of the overall collective data, comparison of data among different hospitals is not allowed until after the publication of the overall collective data.

### 8. Estimated budget from NEOMUNE:

0,4 mio DKK

**9. Estimated budget from elsewhere:** PhD/post doc salaries (3 yrs, 30%, Marita, Yanqi): 0.9 mio DKK  
Support from local hospital sites (man power to collect data, 16 x 5% salary): 0.5 mio DKK

### 10. Additional comments:

- The personnel who perform the data entry are provided by each participating hospitals or SYSU.
- The data base work is also instrumental in letting people come together and discuss the rationale for the clinical procedures taking place at different hospitals and in different countries.
- Regarding the authorship for future collective publications, we propose that we include everyone who contributes to the database work as the author. On the publication, the names of 1-3 junior authors (who contribute the most) are shown and the rest is shown as the Database group. An author list allowing 50 names with an alphabetical ordering is used to specify the Database group, and in this way every author can be indexed in pubmed.
- At each site a number of master’s students will assist PhD’s and Post docs in data collection.
- Base on this database work, we are discussing with SYSU about further collaborations to 1) follow-up the growth and brain development of infants recruited in this database from selected hospitals (e.g. FWCH) for up to two years; 2) investigate whether different feeding practices for preterm infants among different hospitals in east and west are related to cultural factors. These two side-projects are at very preliminary stage and depend on whether we can get extra budget. Zhu Yanna and her colleagues at SYSU aim for applying Chinese funds in 2014 in collaboration with NEOMUNE.