RÉPUBLIQUE FRANÇAISE
Liberté
Égalité
Fraternité

INRAE

Nantes Université

UMR1280

Physiopathology of Nutritional Adaptations (PHAN)

Mission and objectives

The first 1000 days of life, including pregnancy, represent a critical period for the development of the fetus, newborn and child, significantly influencing their future health.

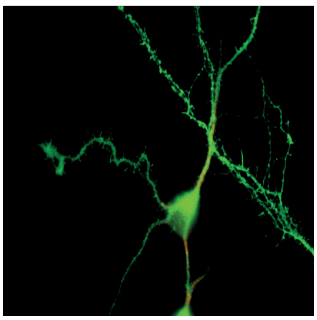
The goal of the PhAN lab is to determine how early events (fetal and neonatal period) such as malnutrition, exposure to xenobiotics (e.g., drugs, pesticides), and parental metabolic status increase the risk of cardio-metabolic diseases (e.g., diabetes, obesity, hypertension) and psychiatric disorders later in life. This programming underlies the memory of these perinatal events potentially carried by epigenetic marks, neurodevelopmental defects and abnormalities in the structuring of key metabolic organs. The Joint Research Unit 1280 PhAN investigates the programming of the microbiota-gut-brain axis and its role in the risk of chronic diseases in adulthood. Specifically (but not exclusively), the laboratory explores the effects of perinatal undernutrition using a translational approach which includes animal models and monitoring cohorts of children. The research also examines the role of placental flows and maternal milk in these processes.

Management

Head of the Lab: Hervé Blottière
Deputy-director: Gwenola Le Dréan

Team composition:

- 6 university and hospital professors
- 6 hospital practitioners
- 14 researchers and teacher-researchers
- 6 engineers
- 5 technicians and administrative staff
- 7 PhD students
- 3 post-doctoral fellows



Photos ©INRAE

Centre
Pays de la Loire

CHU - Hôtel-Dieu, HNB1 Place Alexis Ricordeau F - 44093 Nantes Cedex 1
Tél. : +33 (0)2 53 48 20 09
genevieve.fleury@inrae.fr
https://phan.angers-nantes.hub.inrae.fr

RÉPUBLIQUE FRANÇAISE
Liberté
Égalité
Fraternité

INRAE

hAN

Nantes Université

UMR1280

Specific features of PhAN lab

- Among the many laboratories exploring the concept of DOHaD (Developmental Origins of Disease and Health), the PhAN lab is unique in considering the young child not only as a future adult at risk for long-term chronic disease, but also as a subject/patient in his/her own right. This perspective emphasizes the importance of nutrition as a primary concern for clinicians caring for pregnant women or young children.
- PhAN is one of the few labs addressing the 'programming' of the microbiota-gut-brain axis.
- For the past 10 years, PhAN has been a pioneer in integrating multiple experimental and multi-omics approaches in the service of translational and clinical research within the DOHaD framework.
- Driven by the PhAN lab's initiatives, perinatal nutrition has become the 'flagship' theme of CRNH-Ouest (www.crnh-ouest.fr).
- Over the past 5 years, PhAN has been actively involved in organizing local research on gut microbiota.
- PhAN has significantly contributed to the region's, the University's, and the Nantes University Hostpital's growing interest and enthusiasm for nutrition and health, particularly focusing on a crucial life period for disease prevention.

RÉPUBLIQUE FRANÇAISE
Liberté
Égalité
Fraternité

INRAE

hAN

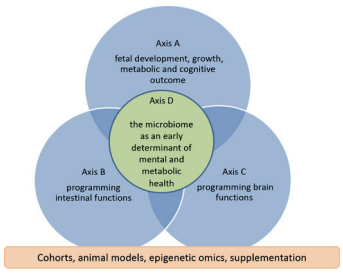
Nantes Université

UMR1280

Research

PhAN's research activities span both fundamental and translational science, bridging the gap from the newborn to the laboratory bench and vice versa. PhAN aims to Elucidate, Explain and Prevent the effects of nutritional and metabolic status from gestation to birth on development, major physiological functions and the risk of diseases later in life using preclinical models and human cohorts. We are identifying biomarkers of nutritional programming through comprehensive "omics" approaches and bioinformatics analyses (integration of multiple clinical and molecular datasets) to predict which individuals within at-risk populations will develop chronic pathologies. The studied mechanisms include epigenetics, cellular and molecular alterations to organs, early modulation of the microbiota and the immune system. Finally, strategies for preventing or correcting programming are implemented using nutritional approaches.

The unit's research themes are organized into 4 closely intertwined axis :



- Axis A: Demonstrating the impact of parental nutrition and metabolic status on nutrient transport/metabolism, epigenetic regulation of gene expression and its consequences for the child's growth, metabolic health and psycho-cognitive development.
- Axis B: Understanding the mechanisms by which the mother's nutritional and metabolic status influences intestinal functions (integrity of the barrier, endocrine and immune functions) and the risk of digestive pathologies (e.g., chronic inflammatory diseases, etc.) but also metabolic diseases (e.g., deregulation of food intake and energy homeostasis).
- Axis C: Investigating the mechanisms through which the maternal nutritional and metabolic status affects cognitive function and the acquisition of eating behaviors.
- Axis D: Demonstrating the role of the microbiota as an early determinant of mental and metabolic health.

Centre
Pays de la Loire

https://phan.angers-nantes.hub.inrae.fr

RÉPUBLIQUE FRANÇAISE
Liberté
Égalité
Fraternité

INRAE

hAN

Nantes Université

UMR1280

Collaborations

• Mexico Instituto Nacional de Salud Pública, Instituto Nacional de Nutrición, Hospital Infantil de Mexico; ANR Internat. Collaborative Project ;
• USA: Josef Neu, Univ of Florida, Gainesville, FL ; Guillaume de Lartigue, Monell Center and University of Pennsylvania (UPenn), Philadelphia, PA ; Theresa Powell, Univ of Colorado Anschutz Med Campus, Aurora, CO.
• Canada: Julie Robitaille (U Laval, Quebec);
• Europe : European Milk Bank Association (EMBA) F. Gribble & P. Reimann, MSC Institue, Cambridge, UK ; Ramon Reig Instituto de Neurociencias, CSIC-UMH (Aliquante, Spain)
• France: LABERCA (INRAE - Oniris, Nantes), BIA (INRAE, Nantes), CEISAM (CNRS, Nantes), NUMECAN (INRAE, Rennes), STLO (INRAE, Rennes), NUTRINEURO (INRAE, Bordeaux), CSGA (INRAE-CNRS, Dijon), TOXALIM (INRAE, Toulouse), CRESS (Inserm-Paris), TENS (Inserm Nantes), ITX (Inserm, Nantes), CHU (Lille, Tours), GABI, MGP et MICALIS (INRAE, Jouy-en-Josas), LBFA (Inserm, Grenoble), and Société In-Cell-Art ; Unité Biologie Fonctionnelle et Adaptative-BFA (CNRS UMR 8251), Université Paris Cité.

Teaching and doctoral training

• The unit is attached to the Graduate School – Future Health (Nantes Université).
• Teaching at a graduate level (Master-PhD program MICAS directed by Pr K. Ouguerram, PhAN and Dr K. Bach, TENS)
• Involvement of PhAN researchers in several Master 2 including SCMV Cellular and Molecular Life Sciences, University of Rennes; Master 2 ADNS Food - Law - Nutrition - Health, University of Brest, ALIMN Engineering School Agrocampus Ouest (Rennes), Sciences Agros, Master 2 SAME (STL / Master 2 ALIM IEL, Rennes);
• Students internship : Master 2, Master 1, BTS or DUT, TER, medical thesis.

RÉPUBLIQUE FRANÇAISE
Liberté
Égalité
Fraternité

INRAE

hAN

Nantes Université

UMR1280

Selection of results

- **Simultaneous exploration of nutrients and pollutants in breast milk and their impact on premature infant growth : An integrative cross-platform approach.**

There is very little information on the effects of exposure to persistent organic pollutants (POPs) present in human milk and likely to affect children's growth. We conducted a pilot study using an integrative analytical approach based on high-resolution mass spectrometry coupled with liquid and gas chromatography and combined with multi-variate statistical models to characterize breast milk in all its complexity (nutriome and exposome). This holistic approach has generated a list of biomarkers comprising 102 pollutants and nutrients measured by targeted analyses and 784 compounds detected by metabolomic/lipidomic approaches. This pilot study provides proof of concept of the value of an holistic approach combining metabolomic phenotyping and exposure profiles to generate information on the aetiology of exposure in a neonatal environmental health context.

DOI : 10.1016/j.envres.2019.109018
Contact : German.CanoSancho@inrae.fr

- **Prebiotics in infant formulas : what impact on adult eating behaviour?**

The first 1,000 days of life are currently recognized as essential to future health. Favourable or unfavourable nutritional conditions during this period can predispose to the development of healthy eating habits or, on the contrary, those that are harmful to adult health. Prebiotic oligosaccharides are commonly used in infant formulas to approximate as closely as possible the composition of breast milk. While the beneficial effects of these compounds in reducing appetite have been reported in adults, little information is available for children. A study of postnatal supplementation with prebiotics during the lactation period was carried out in rats. Our results show that this intake has no impact on feeding behaviour in adulthood, compared with unsupplemented rats. The marked changes in the composition of the intestinal microbiota and its interactions with the entero-endocrine cells in the intestinal mucosa that secrete appetite-regulating hormones, observed during the supplementation period, did not persist into adulthood. These results are therefore reassuring from the point of view of the safety of prebiotic-enriched infant formulas and their potential effects on adult eating behaviour.

DOI :10.3390/nu110919678
Contact : gwenola.ledrean@inrae.fr

RÉPUBLIQUE FRANÇAISE
Liberté
Égalité
Fraternité

INRAE

hAN

Nantes Université

UMR1280

• The role of bioactive compounds in breast milk in child growth

In children born prematurely, breastfeeding ensures better neuronal and psychomotor development, as well as protection against gastrointestinal and respiratory infections, despite slower postnatal growth compared with children receiving infant formulas. Children born prematurely and showing good early weight growth received breast milk that was richer in branched-chain amino acids and certain aromatic amino acids, compared with those whose weight growth was considered to be less than optimal. These amino acids play a fundamental role in insulin sensitivity and may therefore have an impact on development. Good early growth in children born prematurely is also associated with breast milk that is richer in an oligosaccharide, lacto-N-fucopentaose I, in choline and in a ketone, hydroxybutyrate. These three active compounds are known to play a role in the development of a child's body mass. These metabolic signatures of breast milk thus highlight the essential role in the child's growth of certain bioactive compounds in milk involved in the pathways for the use of energy substrates, protein synthesis, oxidative status and maturity of the gastrointestinal sphere.

DOI : doi: 10.3390/nu11030528
Contact : Marie-Cecile.Alexandre-Gouabau@inrae.fr

• Fenugreek and breast milk production

The World Health Organisation recommends exclusive breastfeeding of newborns for the first 6 months of life, due to the recognised health benefits for both mother and child. However, the number of women who breastfeed remains low in some developed countries, particularly France. In many cases, mothers stop breastfeeding because they feel they cannot give their child enough milk. To remedy this situation, plant extracts are sometimes added to mothers' diets to encourage milk production. Fenugreek, an herbaceous plant in the legume family, is probably the most widely consumed, although its effect on lactation remains poorly documented. The aim of the study was to test the effect of fenugreek in a rat model, in conditions where the mother has difficulty meeting the milk demand of her offspring, either by increasing the size of the litter (12 offspring per mother instead of the usual 8), or by maternal protein restriction (8g/100g instead of 20g/100g of the total diet). Fenugreek was added only during lactation: the rats were fed either a diet containing fenugreek (1g/kg/day) or a control diet. Fenugreek was added to the feed during the manufacturing process. In the litter size increase model, the results indicate that fenugreek promotes the flow of milk from the mother and therefore milk consumption by the pups (16% increase compared with a control without fenugreek). Furthermore, in this model, fenugreek promotes the flow of proteins, fatty acids and lactose, suggesting activation of the synthesis pathways for the 3 main macronutrients in milk. The mothers' daily food consumption, in relation to their body weight, did not differ with or without fenugreek. On the other hand, fenugreek had no effect on either the flow or the quality of the milk produced in the maternal protein restriction model, which was more deleterious for the mother's physiological state.

DOI : 10.3390/nu11112571
Contact : Clair.Boquien@inrae.fr

RÉPUBLIQUE FRANÇAISE
Liberté
Égalité
Fraternité

INRAE

hAN

Nantes Université

UMR1280

• Isite NEXT - SysMics Cluster: Toward Systems Medicine based on Genomics [NeXT Initiative]

Anticipating the emergence of systems medicine by co-developing 3 large-scale genomic screening approaches. The SysMics project has been selected as part of the Health of the Future - Innovative Biotherapies scientific priority of the NExT (Nantes Excellence Trajectory) Initiative's call for interdisciplinary research projects. SysMics is an integrated genomics research cluster accredited by the NExT I-SITE, based largely on the GenoBiRD infrastructure. Its aim is to unite the NExT community around a common objective: to anticipate the emergence of systems medicine by co-developing 3 large-scale genomic screening approaches: sequencing the genomes of patient populations, genomic profiling on single cells and metagenomics applied to the microbiota(s). SysMics' first mission is to build all the resources needed to implement or consolidate these 3 approaches on site. The second stage will be to combine these approaches in the context of pilot projects in immunology, haematology and pathophysiology of cardiovascular, metabolic, respiratory and neurodigestive diseases. These pilot projects will enable the construction of integrative individual profiles, which will be decisive for a better understanding of the cascades of events, from birth to adulthood, leading to a pathological state or an adverse event in the context of a chronic disease. As soon as possible, these translational research approaches will be adapted and transferred to molecular diagnostics and the clinic.

Contact : Patricia.Parnet@inrae.fr

• Distinct circuits of the gut-vagus nerve-brain axis, allowing positive reinforcement for fat and sugar, combine to encourage overeating

Food itself is a powerful natural regulator of our eating decisions. French and American researchers are shedding new light on the complex sensory circuits involved in motivational behavior towards fatty and sugary foods. Their work suggests that the joint consumption of fatty and salty foods, as a result of potentially additive distinct neural circuits, may encourage us to eat more, thereby hindering conscious efforts to follow a diet.

Contact : Vincent.Paille@inrae.fr