

STW Partnership Program Plan

STW - DANONE-Research Centre for specialised Nutrition

Title: Specialised and disease specific nutrition through understanding of neuro-immune-gut interactions

March 2010

1. Introduction and industrial relevance

The Dutch technology foundation (STW) initiated the STW Partnership Programs to stimulate effective cooperations between academia and industries.

This particular program is an initiative in which Danone-Research Centre for specialised Nutrition proposes the program theme, and universities are invited to submit dedicated research proposals in a tender.

The research is carried out under the guidance of both university professors and industry staff, at university and industrial laboratories, and in a practical/hospital environment.

Danone-Research Centre for specialized Nutrition is focused on the development of science driven concepts aimed at the prevention and/or treatment of diseases that are nominated by the WHO as priority medicines.

Danone executes research and development of various nutritional products for Infant Nutrition/Baby Food and Medical Nutrition, and has been engaged in the equipment for the administration of these products. These specialized nutritional products are tailored towards the specific needs of vulnerable target groups and subject to distinct registration and/or legislation. The major focus areas of Danone-Research Centre for specialised Nutrition are linked to **immunology, neurology and metabolism**.

The Danone corporate R&D lab on baby and medical technology is currently located in Wageningen in the Netherlands. In 2012 the research facilities will be united into one organisation of approximately 500 employees, located at the university campus Utrecht. This will lead to close interactions with life-science faculties and academic hospitals both in Utrecht and other universities and academic hospitals in Amsterdam, Rotterdam, Nijmegen, Maastricht, Leiden, Wageningen, and Groningen.

This research plan has been developed in consult with -and through contributions from- national and international top research groups in the field. Prof. Dr. R. Witkamp, Wageningen University & Research Centre, Wageningen has assisted in the fine tuning of this program plan.

2. Focus, objectives and applications

Focus

Development and understanding of new concepts for specialized nutrition (medical food and infant nutrition): From ingredient to health benefit with a focus on neurology/endocrinology, immunology and related metabolic disorders, in particular on the interactions between these systems and the modulation of their activity by nutrition.

For instance, can neuro-immune interactions be influenced by dietary ingredients leading to prevention and/or treatment of immune and/or neuro related diseases such as allergy, neurodegeneration and chronic inflammation?

Objectives

The WHO states that the majority of priority medicines are in one way or another linked to immune and/or neurological related disorders. Major health outcomes/consequences are allergies, asthma, neurodegeneration, chronic inflammatory diseases and metabolic diseases including diabetes, cardiovascular disease and obesity.

Currently health scientists realize that the majority of these diseases are multi-factorial. For this reason systems biology, multi-targeted approaches, (epi)-genetic research are the appropriate tools to adequately tackle the research questions. Nutritional concepts are most probably the best option for such a multi factorial approach.

The goal of this Partnership Program is two fold:

1) to link very different expertises and know how i.e. immunology, neurology, endocrinology, physiology, metabolism, (epi-) genetics to each other in order to sustain and understand the process from ingredients to specialized nutrition products with a health benefit.

2) to understand the role of the gastro-intestinal tract in modulating neuro-immune interactions affecting metabolic disorders, diseases and health, with the aim to define and design the process from ingredients to specialized products with a health benefit.

Knowledge exchange, innovation and valorization leading to science driven and accepted products are key.

Applications

The results of the research will be applied in new multifactorial dietary concepts for the treatment and/or prevention of WHO-priority medicines as described above (allergy, chronic inflammation, neuro-degeneration, metabolic disorders).

Danone has understood that STW does not finance large scale clinical testing. Such a development phase will therefore be beyond the scope of the Partnership Program. Small scale proof of concept clinical testing will however be included to test the feasibility of new innovations.

3. Major Research Areas

The Partnership research program will focus on the combination of three major development/research areas and their interactions.

1. Direct and indirect role of the gastrointestinal tract in modulation of neuro-immune interactions

The gastro-intestinal tract is one of the most important immune organs having an extensive and close interaction with the nervous system. This gastro-intestinal nervous system, nominated to be the brain in the gut, is closely linked to the immune system and the central nervous system indicating its potential role in both gastro-intestinal as well as systemic diseases with an immune and/or neurological component such as allergy, asthma, IBD, IBS, autistic disease, stress, ADHD related disorders, Alzheimer, and even metabolic diseases such as obesity and diabetes. The close interaction between the nervous and immune system in the gastro-intestinal tract but also systemically is a major focus area of this partnership program. The central question here is:

Can neuro-immune interactions be influenced by dietary ingredients leading to prevention and/or treatment of immune and/or neuro related diseases such as allergy, neurodegeneration and chronic inflammation?

2. Role of neuro-immune interactions in metabolic disorders

Another relative new area is that more data are now suggesting that neuro-immune mechanisms play a crucial role in the onset and maintenance of metabolic disorders such as obesity. In obesity inflammatory components seem to play an essential role. Adipocytes can produce and synthesize pro-inflammatory cytokines and even hormones affecting both neuro-immune as well as metabolic processes leading to

e.g. metabolic syndrome, also called syndrome X. Within this focus area, research aimed at unraveling these “connecting” mechanisms translating into new concepts for the prevention and/or treatment of metabolic disorders, are key.

3. Long term effects of early nutritional programming for neuro-immune and endocrine function in later health and disease

Since immune and metabolic processes are so intensively linked to each other it is suggested that nutritional concepts early in life might predict the onset of immune, and or metabolic diseases later on in life. One concept that is suggested to play a role in this “imprinting” and/or “programming” phenomenon is activation and/or down regulation of particular/specific genes. For instance via methylation and alkylation of genes the expression and function of these genes can be influenced. If this results in switching on or off of processes that are crucial for immune and/or metabolic regulation this might have significant impact on immune and or metabolic related disorders later in life as well.

Danone has a longstanding experience with partnerships or partner-like programs and realizes that the construction as suggested by the STW-Partnership Program will increase the quality of our research portfolio significantly. On the other hand, synergy between academic centers and Danone-Research will help both academic and business driven research teams, leading to new products, and economic growth in the Netherlands. In this respect this approach is very different from contract research that is in general not focused at scientific collaboration and synergy between different expertise fields. Therefore, Danone Research looks forward to and foresees additional benefits in the open call for project proposals that will be issued to the Dutch research community.

Danone expects research projects proposals from the following universities: University Utrecht, UMCU, WKZ, Erasmus University Rotterdam, Free University Amsterdam, University of Amsterdam and AMC Amsterdam, University and Medical Centre Groningen, LUMC, University of Nijmegen, University of Wageningen, and University of Maastricht.

The scientific disciplines needed to execute the Danone Partnership program include:

- immunology
- food & nutrition technology
- neurology/endocrinology
- genetics/epigenetics
- gut biology
- physiology
- microbiology

4. Scientific challenges

The major scientific challenge is to bring/link different disciplines together in order to develop the best multifactorial therapy for immune-, neuro or metabolic- related diseases such as: chronic inflammation, allergies, asthma, stress, obesity and its link to various metabolic diseases such as type II diabetes and cardiovascular disease, cachexia, autism and neuro-degenerative diseases such as Alzheimer’s and Parkinson’s disease (see figure 1).

Finally epigenetic phenomena will be studied in order to analyze how early events may steer and impact health and disease effects later-on. Major research method challenge is to cover at least part of the translational research approach starting at the level of ingredients up to finally proof of concept pilot trials in man.

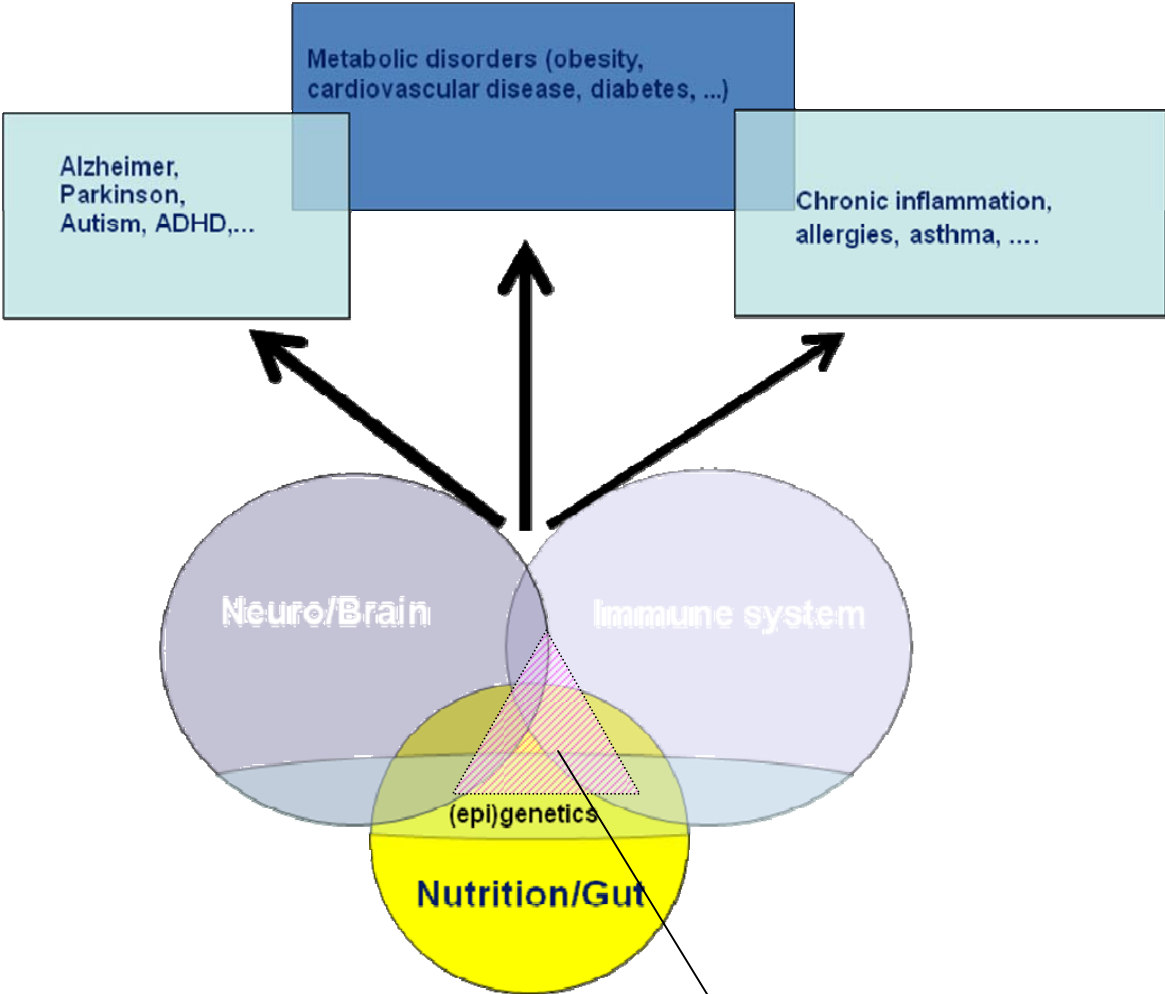


Figure 1. The research within this Partnership program and its scientific disciplines and possible application areas.

The focus should be oriented on at least two overlapping circles as depicted in this figure.

Project proposals should **only** be submitted when the research is conducted in the overlap area between at least two but preferably all three overlapping areas.

During early development each individual, including every organ by itself and in orchestra with each other, has the ability to grow into its full genetic potential that results in a well balanced and healthy phenotype with the ability to effectively deal with environmental challenges. The set points as determined by the environment within the womb and during the first years of life are determined by the genetic basis and by epigenetic processes that determine the functionality of cells in the body which ultimately result in a clear phenotype. Despite being primarily driven by environmental factors, also epigenetic characteristics have been shown to affect set points in subsequent generation(s) and thus that changes in specific epigenetic markers may require reprogramming to match the changing environment. The plasticity of the organism as set by these (epi)genetic processes determines the plasticity of the individual and its ability to come with challenges such as infections, but also the consequences of our western life style providing an obesogenic environment. In principle, a risk factor for a specific disease later in life can be an example of a perfect adaptation of the organism to early environmental challenges leaving the individual with an unbalanced metabolism to cope with challenges later on.

The tight interplay between the immune system, neuronal and hormonal signals and the effect of nutritional signals is the area of focus for this research program.

5. Fit of research proposals into the program

Proposals should be multidisciplinary and focus not only at disease risk and prevention but also on identifying ways to assess treatment effectiveness. One important aspect would be to address the underlying causes and mechanisms behind responders and non-responders to a specific treatment.

Part of this program are project proposals covering:

- The project proposals should address the interplay between nutrition, metabolism, immune function and neuronal regulation and address a substantial number of the following aspects (see the triangle in the middle in figure 1).
- Projects should be submitted from at least two different universities or research groups
- Projects should be multidisciplinary and should address at least two areas (circles) as depicted in figure 1. Overlapping three areas will have the highest priority.
- Projects should focus on application/valorisation into specialized nutrition, showing clear translational capacity towards disease management and/or (secondary) prevention
- Projects should focus on translational research and should follow the strict rules for animal ethics and clinical trial ethics although the clinical tests themselves will not be financed out of this program budget except small proof of concept trials

Not part of this program are project proposals covering

- Covering only one aspect i.e. nutrition, metabolism, immune function or neuronal regulation.
- Clinical trials (focussed on testing a new food) except small proof of concept trials focussed on mechanistic studies
- In vitro screening for new ingredients at a large scale (libraries)
- Development of new animal models
- Any research aiming at development of functional foods or general food products, for instance, dieting products, that do not meet the criteria for specialised nutrition (infant nutrition and medical food)
- Research aiming at convenience food and large scale consumer foods
- Technical product development aspects such as taste, shelf life, texture etc
- Only (computer) modelling
- DHA studies
- Research and development on the basis of existing patents that are not owned by the university applicants themselves

- Research topics on which there is a conflict of interest of one of the participants as a result of affiliations with Danone competitor industries

6. Unique character of the program

The uniqueness of the program is that Danone research for specialized Nutrition works closely together in one team comprising of a number of top university groups as well. The challenge as well as the opportunity is to build and manage one of the largest (internationally linked) Dutch scientific community within the Netherlands on specialized nutrition and its ability to prevent and/or treat diseases linked to WHO priority medicines (immunity, allergies, chronic inflammation, metabolic disorders, obesity, neuro-degeneration).

Since the majority of these diseases do have a multifactorial origin within this research network a unique combination is organized linking immunology, physiology, neurology, metabolism, and (epi-)genetics

The Dutch universities collectively will –through this partnership program- form a new and unique scientific community on the role of specialized nutrition in neuro-immune interactions leading to new concepts for disease management.

Currently there are no other programs running in the Netherlands on this specific program topic. For the purpose of maintaining competitive advantage, Danone sees this program as a spearhead to further sustain its commercial future.

The unique multidisciplinary approach generates a competitive advantage both for an industry and an academic perspective for the Dutch participants in this program

7. Duration and budget

The proposed duration of the program is 5 years, the budget is 3 M€ funded as 50% vs 50% by STW and Danone. The universities contributions are additional and implicitly on a pm base by making available infrastructure, use of equipment and professor + research staff guidance.

8. Program Committee

The program will be managed by a program committee (PC) consisting of four persons. Prof. dr. J. Garssen and dr. E. van der Beek by Danone Research- Centre for Specialised Nutrition and two members nominated by STW. The members of the PC have skills and expert knowledge appropriate to assess the proposals and have a high level and recognition of experience in the particular field. PC members may invite other advisory members to the PC meetings, although these will not have any voting rights. The PC is responsible for the overall directions and management of the program. PC meetings will be organized/planned twice a year unless PC decides differently based on needs. STW shall appoint a Secretary to the PC who shall not have voting rights but will assist regarding administration/organization. This secretary will not be funded from the project.

All members of the PC will sign a NDA to protect any ideas laid down in the university project proposals.

Danone utilisation PC expert candidates:

1. Prof.dr. J. Garssen, director immunology platform Danone Research- Centre for Specialised Nutrition.
2. Dr. E.M. van der Beek, director new health benefits Danone Research- Centre for Specialized Nutrition.

STW scientific PC expert candidates:

3. Prof. Philip Calder, Expert in Nutritional Immunology, University Southampton, School of Medicine, Division Developmental Origins of Health and Diseases, UK
4. Prof. Clare Mills, Expert in Food structure and Health (typically protein biochemistry), Institute of Food Research, IFR Norwich, UK