

10th

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Summary

Feeding the immune system 04

The link between nutrition and the immune system
How do fatty acids contribute to our immune system?
How do probiotics affect the immune function?
The impact of nutrition on immunity during lifetime
Principal clinical applications of Prof. Calder's research

Prof. Philip Calder 14

10th recipient of the Danone international Prize for Nutrition

The Danone International Prize for Nutrition 18

The Danone Institute International 22

Danone's commitment to Nutrition & Health

The Foundation for Medical Research 26



Feeding the immune system

Immune and inflammatory responses protect our body against infections. These bodily defences – 70% of the body's immune system is located in the gut – involve “an army” of components (antibodies, white cells, cytokines, ...) which require for their sustenance an appropriate diet that includes fatty acids whose derivatives (as prostaglandins, leukotrienes) can function as mediators.

Active immune responses can sometimes, however, be inappropriate and cause tissue damage and disease, for example inflammatory diseases such as allergies and Crohn's disease.

A good deal of research has been undertaken to understand how the immune system might be dampened when it functions inappropriately. Notable among this research has been the work of Prof. Philip Calder, who has made significant contributions to the understanding of the functional properties of fatty acids and the mechanisms involved. He has investigated their effects at various stages of the human life cycle, from the womb (influence on risk of atopic sensitisation and allergic manifestations, including asthma) to adulthood (Crohn's Disease) and old age (immunosenescence predisposes older adults to a higher risk of acute viral and bacterial infections and diminishes the efficacy of vaccines).

Prof. Calder's approach is rigorously translational. His recent work carrying forward the results of mechanistic and nutritional science to studies in humans has already given rise to nutritional recommendations on atherosclerosis prevention (reduction in the risk of heart attacks and strokes for example) and on the potential benefits of administering parenteral lipids to certain groups of intensive care patients.

Being healthy requires that one eat healthily. The proposition appears obvious, yet the specific mechanisms behind this truth have long remained very vague, not least with regard to fatty acids. The work carried out over the last 25 years, to which Prof. Philip Calder has made important contributions, has deepened the scientific community's understanding of the underlying mechanisms that explain the relationship between nutrition and immunity, the important first step in the formulation of nutritional advice for better feeding the immune system.

The link between nutrition and the immune system

What is the immune system?

The body's immune system is comprised of two types of defence mechanism:

- **Innate or non-specific responses:** this is the first line of defence against infection. It does not take into account the type of organism being combated. Several types of mechanisms are involved, including physical barriers such as the skin, and innate immunity cells such as macrophages and neutrophils which "eat" foreign material non-specifically.
- **Acquired or specific responses:** this response involves specialized white cells called lymphocytes which target specific pathogens. These include B lymphocytes, which produce specific antibodies when they encounter a pathogen, and T lymphocytes which are able to destroy foreign particles directly. Some T and B lymphocytes retain a memory of particular pathogens, enabling them to respond faster in future; vaccines are based on this property.

70% of the immune system is located in the gut. Indeed, since the intestinal lumen is in direct continuity with the outside environment and the intestinal lining presents such a large surface for exchange – a particularly convenient property for the absorption of nutrients but also one that offers considerable exposure to external pathogens – it is critically important that the gut host a well-functioning defence system.

The gut is home to more than 100 000 billion bacteria. These bacteria used to be termed "gut flora" and are nowadays often referred to as "gut microbiota". In the gastrointestinal tract they create a barrier against colonisation by pathogens. Disease and the use of antibiotics can disrupt this barrier, creating an environment that favours the growth of pathogenic organisms. A varied diet is a way of maintaining the gut's microbial richness and diversity, which are the key characteristics of its balance. Among other things, probiotics (live bacteria, that can be obtained from food) and prebiotics (specific carbohydrates that serve as nutrients for gut microbiota bacteria) can help restore the gut microbiota composition and thus have beneficial effects on human health.

"70% of the immune system is located in the gut."

"Interactions between the immune system and gut microbiota play a key role in maintaining the body's defences."



Why does the immune system need to be fed ?

First, the immune system makes high demands of energy. Nutrition supplies both the substrates necessary for energy generation and the micronutrients such as vitamins and minerals that enable to convert the substrates into energy.

Second, the immune system requires a large “army” comprised of a range of components: antibodies called immunoglobulins, white cells also called leukocytes, white-cell receptors, and lipid-derived mediators such as prostaglandins and leukotrienes (see below). Nutrition supplies these building blocks.

Finally, certain nutrients (vitamin A, zinc and omega-3 fatty acids, for example) play an important role in regulating the functioning of the immune system response.

Nutrients, then, have many channels of influence on the immune system, both direct and -for example, via microbiota which are affected by nutrition and which in turn impact on the immune system- indirect.

The role played by lipids in immunity and inflammation

So far as many people are concerned, lipids are just an energy provider and a means of storing extra energy in the adipose tissue. But lipids are a lot more than this. In the 1960s, the publication of two scientific papers about prostaglandins (oxygenated derivatives of very long lipids) in the journals *Biochemistry* and *Biophysica* drew the scientific community's attention to the fact that some lipids work as mediators in inflammation. Underlining the importance of this discovery, two of the authors (Sune Bergström and Bengt I. Samuelsson) received along with John Vane the Nobel Prize in 1982 for their work on prostaglandins.

Of course, prostaglandins are not the only derivatives of fatty acids that act as mediators. Step by step, research has identified other oxygenated derivatives of omega-3 (two in particular: eicosapentaenoic acid –EPA, and docosahexaenoic acid –DHA) and omega-6 (notably arachidonic acid –ARA), which can be converted into mediators with the action of the phospholipase, cyclooxygenase and lipoxygenase enzymes: EPA can be converted into prostaglandins, leukotrienes or resolvins; DHA can be converted into resolvins, protectins or maresines; arachidonic acid can be converted into leukotrienes, lipoxins, etc. All of them act on inflammation, some of them stimulating it, others quelling it.

Fatty acids, then, are not merely energetic or structural components; they also constitute reserves of lipidic mediator precursors.

Sometimes, immune and inflammatory responses are inappropriate

The purpose of immune and inflammatory responses is, of course, to protect the body from infections. However, active immune responses can sometimes be inappropriate, for example when triggered by normally benign structures or by host antigens. This can then cause tissue damage and “inflammatory diseases” such as allergy, asthma, Crohn's disease and rheumatoid arthritis.

“The immune system makes high demands of energy. Nutrition supplies both the substrates and the micronutrients necessary for energy generation.”

A lot of research has therefore been undertaken to find ways to "turn off" or "resolve" inflammation. Mediators derived from omega-3 have been shown to be very good at this: explained in a highly simplified schematic way, whereas mediators derived from the omega-6 ARA generally promote inflammatory reactions, omega-3 derived mediators have an anti-inflammatory effect; our bodies rely on these opposing effects to regulate its balance.

WHY ARE RESOLVINS SO-NAMED?

Immune and inflammation responses can sometimes be inappropriate, for instance the incorrect recognition of an immune trigger or an inability to turn-off what had been an appropriate response. The process of bringing inflammation to an end is termed resolution. Lipid mediators produced from omega-3 fatty acids EPA and DHA have been shown to play a central role in the resolution of inflammation. It is for this reason they are termed resolvins.

How do fatty acids contribute to our immune system? How do probiotics affect the immune function?

Prof. Calder has made major contributions to extending our understanding of the molecular and cellular mechanisms through which specific fatty acids act on the immune and inflammatory systems. And although fatty acids are at the centre of his work, he has also explored neighbouring areas, including the gut microbiota as it is highly connected to the immune system: 70% of the immune system is located in the gut.

Here we highlight just three of his major contributions under this heading, two of them dealing with fatty acids, the third with probiotics.

"Omega-3 fatty acids influence the expression of genes involved in the immune response."

Omega-3 influence leukocyte infiltration

During inflammation, appropriate or otherwise, white cells called leukocytes infiltrate the sites of infectious and inflammatory activity in order to combat them. This requires the prior adhesion of leukocytes to the walls of blood vessels (the endothelium.). In 1998, Prof. Calder published the first paper demonstrating that our diet influences this adhesion: the inclusion of omega-3 fatty acids (EPA and DHA) in the diet could reduce the ability of leukocytes to bind to endothelial cells; this is one pathway through which omega-3 fatty acids exert their anti-inflammatory effects.

Omega-3 inhibit some lymphocyte T-cell functions

Prof. Calder's research identifying both EPA and DHA as potent suppressors of some specific white cells called lymphocytes, T-cells in particular, was amongst the first to demonstrate that fatty acids could inhibit the production of certain molecules – interleukins - involved in the regulation



of the immune activity. Further work by Prof. Calder and his team suggested that omega-3 fatty acids changed the composition and the fluidity of T-cell membranes and that these changes, via early signalling events, were responsible for the inhibition of lymphocyte functions. These findings formed the basis for further discoveries over following years concerning the role of omega-3 fatty acids at the membrane level, especially in the formation of "rafts" involved in signal transduction of immune cell activation.

Probiotics effects on the immune function

Prof. Calder has recently been looking at how probiotics affect the immune function. Notably, in a recent randomised controlled trial, he administered probiotics (one of the two strains *Bifidobacterium animalis ssp. lactis* and *Lactobacillus paracasei ssp. Paracasei*) to more than 200 subjects who had just received their seasonal influenza vaccination. That specific context was an ideal opportunity to observe the ability of the immune system to respond to a "model infection" in which the dose of pathogens as well as the modality and the timing of exposure are standardised. The subjects who had received the probiotics displayed an improved immune reaction, producing a greater number of immune cells specifically directed to the influenza virus.

PUBLICATION OF A CONSENSUS PAPER ON THE DEFINITION OF PROBIOTICS

In 2014, Prof. Calder participated in an expert panel on probiotics convened by the International Scientific Association for Probiotics and Prebiotics (ISAPP). The panel reviewed the definition for probiotics proposed in 2001 by the FAO & WHO and adapted it thus: "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host". The Panel's consensus article was published in Nature Reviews in Gastroenterology and Hepatology.

The impact of nutrition on immunity during lifetime

As a long-existing species, humans have evolved mechanisms of innate immunity and immunological memory in order to combat recurrent infections. However, over the lifetime of an individual, these immune mechanisms change, first to adapt to the change from foetus to infant (the foetal environment requires that the immune system be tolerant to maternal antigens; emergence as an infant involves a sudden and enormous exposure to environmental antigens), then to steadily mature and expand during growth into adulthood, and in the case of women subtly changing in pregnancy, before finally decreasing in senescence. The impact of nutrition on immunity can vary at different stages of life. Prof. Calder's work has looked along the age-range, from the foetus through to childhood and adulthood, in healthy subjects just as in patients suffering from chronic diseases that have an inflammatory component.

"Interventions that modify the gut's microbiota can help maintain the immune system in older people, limiting immunosenescence."

Foetal development

Over the second half of the 20th century the consumption of some long-chain omega-6 fatty acids increased, coinciding with growing prevalence of atopy and its clinical manifestations. It has been suggested that a causal relationship exists between omega-6 fatty acids intake and allergic disease; biologically plausible underlying mechanisms have been suggested, involving lipid-derived mediators of the omega-6 fatty acid ARA. Moreover, there is evidence from some, but not all, association studies that a high intake of another omega-6 fatty acid (linoleic acid, LA) is linked with an increased risk of allergies and atopic sensitisation. Omega-3 fatty acids, on the other hand, have been shown to counteract the effects of omega-6 fatty acids on immune and inflammatory responses. It has therefore been proposed that they could protect against atopic sensitisation and against the clinical manifestations of atopy.

As for the effects of maternal consumption of omega-3 fatty acids during pregnancy, epidemiological studies have concluded that the children of those pregnancies tend to benefit from greater protection against allergies and atopic sensitisation. The provision of fish oil (rich in EPA and DHA omega-3 fatty acids) to pregnant women is associated with immunologic changes in cord blood, and such changes may persist. Studies also indicate that it may reduce sensitisation to common food allergens and reduce the prevalence and severity of atopic dermatitis in the first year of life, with a possible persistence until adolescence with a reduction in eczema, hay-fever and asthma.

Prof. Calder and his co-workers recently contributed to the development of the data in this area by setting up the *The Salmon in Pregnancy Study*, a randomised controlled trial where women with low habitual consumption of oily fish were given two portions of salmon each week during the second half of their pregnancy. The intervention resulted in a “cooling down” of some reactions in the immune system: a decrease in a molecule in charge of T-lymphocyte adhesion then migration into tissues and a decrease in the production of interleukins. But this did not result in differences in antibody immunoglobuline E (IgE) nor in the incidence or severity of atopic dermatitis in the neonates.

“The immune system and the gut mature together during early infancy.”

BREAKING NEWS!

*Prof. Calder has recently been looking at how early changes to the immune system have longer term consequences. He finds that **the offspring of mothers who consumed salmon - a source of omega-3 fatty acids - during their pregnancy appear to benefit from an improved immune function later on; the likelihood of suffering from asthma is diminished at 2.5 to 3 years old.** The working hypothesis is that this benefit is attributable to an early exposure to omega-3 fatty acids although some other nutrient in the salmon could be also involved.*



Infancy and childhood

Prof. Calder's work in the area of infancy and childhood has thus far focused on the effects of omega-3 fatty acids in later childhood (6-12 years), in countries where malnutrition can trigger immune dysfunctions and increase susceptibility to infections.

Iron is known to be important for immune function: iron deficiency impairs lymphocyte activation and proliferation, reduces bactericidal destruction by neutrophils and macrophages, and affects certain lymphocyte functions. Although iron supplements typically reduce infectious morbidity, iron can sometimes increase morbidity from infections as some pathogenic microorganisms, such as the one involved in malaria, also require iron for their development. So, iron can nourish the pathogen as well as the immune system.

In light of these inconsistencies, Prof. Calder set up a randomised controlled trial in South Africa to evaluate the effect on childhood illness of iron and omega-3 fatty acids supplements, given individually or combined to iron-deficient schoolchildren with a low DHA/EPA intake. When given alone, iron supplements were associated with increased childhood illness (mostly respiratory) but when iron was given in combination with DHA/EPA, this association was not present, suggesting an intriguing interaction between the two nutrients.

A study of Thai children by Prof. Calder and his team showed that omega-3 fatty acid supplements resulted in fewer episodes of illness (mainly respiratory) and a shorter duration, whereas the biomarkers of immunity response (plasmatic interleukins, interleukin receptors, etc.) were not modified by the intervention.

Prof. Calder's preliminary results open the door to further investigations of the effects of omega-3 fatty acids on the immune function, especially in malnourished children who could benefit from newly designed forms of supplements.

Adulthood

In his research on adults, Prof. Calder has focused on chronic diseases with an inflammatory component, such as Crohn's Disease. Compared with healthy subjects, the circulating mononuclear cells of patients with Crohn's disease display a modified production of inflammatory mediators including tumour necrosis factor α (TNF- α), prostaglandin E2 (PGE2) and interferon (IFN- γ). Prof. Calder conducted a randomised controlled trial in patients diagnosed with Crohn's disease to test the effects of omega-3 fatty acids from fish oil on these inflammatory biomarkers. The dietary supplement resulted in a lower production of PGE2 and IFN- γ by circulating monocytes or macrophages.

Old age

As age advances, the immune system undergoes profound remodelling and decline, with major impact on health and survival; this immune senescence predisposes older adults to a higher risk of acute viral and bacterial infections. In general, changes that occur in the T- and B-cell

“For children, adolescents and young adults it is important to maintain a good immune system in order to deal with infections and to try to ameliorate inflammatory conditions.”

compartments hamper the adequate immune response to new acute and latent viral infections and vaccinations (poor immune responses account for diminished efficacy of vaccines). Furthermore, aberrant immune responses in the aged can exacerbate inflammation, possibly contributing to other scourges of old age: cancer, cardiovascular disease, strokes, Alzheimer's disease and dementia.

Gut microbiota also changes with ageing, thereby compromising the homeostatic equilibrium between microbiota and host. Hence reduced bacterial diversity in the gut has been correlated with *Clostridium difficile*-associated diarrhoea, a major complication for the elderly in hospitals. So there could be also a gut microbiota immunosenescence.

Nutrition is once again involved as immune system deficiency is seen often in old people who are poorly nourished. By contrast, studies underline that better nourished older people shown less decline in immunity.

Principal clinical applications of Prof. Calder's research

A particular strength of Prof. Calder's contribution has been his *translational approach*, developing *clinically-relevant extensions of research in mechanistic and basic nutrition, thereby advancing the design of nutrition-based approaches to the prevention and treatment of disease*. Among his important work in this area, two aspects in particular should be highlighted: first, his landmark study which established that omega-3 fatty acids, by acting through anti-inflammatory mechanisms, stabilise advanced atherosclerotic plaques; the second, his demonstration that intravenous infusions of emulsions rich in omega-3 fatty acids reduce inflammation in patients with septicaemia.

Omega-3 fatty acids stabilise advanced atherosclerotic plaques

In 1999, the Gissi Prevenzione trial reported a significant reduction in cardiovascular mortality among survivors of myocardial infarction who had subsequently taken omega-3 fatty acids. *Prof. Calder reasoned that this finding might be explained by the anti-inflammatory effect of omega-3 fatty acids on the blood vessel wall stabilising atherosclerotic plaques, thereby reducing the likelihood of rupture*. To test this hypothesis, he conducted a randomised controlled trial of fish oil supplements among patients awaiting a procedure for the removal of advanced plaques from the carotid artery. It was found that plaques from patients who had received fish oil had a higher content of omega 3 EPA and DHA, a lower number of infiltrating macrophages, and a morphology indicative of increased stability. Prof. Calder conducted later studies that confirmed these results and further explored the underlying mechanisms. His findings suggest a *highly novel way of action by omega-3 fatty acids that results in fewer cardiovascular events and in reduced mortality*.

“Omega-3 fatty acids help stabilise the atherosclerotic plaques of patients suffering from advanced cardio-vascular diseases, thereby diminishing the likelihood of heart attacks and strokes.”



Intravenous infusion of omega-3 fatty acid emulsions reduces inflammation in patients suffering septicemia

In a small randomised controlled trial, patients in an intensive care unit suffering from septicemia were given intravenous infusions of fish oil in place of the usual vegetable oil. With 6 days of infusion, fish oil induced a marked anti-inflammatory effect and an improvement in lung function (gas exchange). The length of stay in hospital was reduced by over 50%. *These clinically meaningful findings have contributed to the development of new nutritional strategies to improve patient outcomes.*

These pieces of work demonstrate *Prof. Calder's great strength in translating findings "from the bench to the bedside"*. The European Society of Cardiology working group on atherosclerosis and vascular biology drew on his research for their *position paper on plaque stabilisation*, as did the *European Society for Clinical Nutrition and Metabolism* for their *guidelines on the use of parenteral lipids in intensive care*.

For over 25 years Philip Calder has carried out cutting edge research in the area of fatty acid metabolism and functionality with a focus on the immune, inflammatory and cardiometabolic systems. His work and its influence extend beyond fatty acids into other areas including amino acids, prebiotics and probiotics. A particular strength of his research has been its translational approach, linking mechanistic and basic nutrition science observations to studies in humans, including both healthy volunteers and patients, thereby influencing the development of nutritional guidelines and innovative treatments. The application of Philip Calder's work on omega-3 fatty acids in terms of public health and clinical treatment has therefore been wide-ranging.

"The anti-inflammatory effects of omega-3 fatty acids could have a really important clinical outcome."

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He has a PhD in Biochemistry from University of Auckland (New Zealand) and a DPhil in Biochemistry from University of Oxford (UK). He is a Registered Nutritionist and a Fellow of both the Royal Society of Biology and the Association for Nutrition. He spent four years as a Nuffield Medical Fellow in the Department of Biochemistry at the University of Oxford (1987-1991) followed by four years as a Lecturer in Biochemistry in that same department (1991-1995). In 1995 he took Lectureship at University of Southampton where he was subsequently appointed to a Readership in Human Nutrition in 1998 and then to a Personal Chair in Nutritional Immunology in 2002.

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2016 Danone International Prize for Nutrition recipient



For over 25 years he has conducted research in the area of nutritional immunology and has worked on fatty acids, antioxidants, amino acids, prebiotics and probiotics. Most of his research has been on the metabolism and functionality of fatty acids with an emphasis on the roles of omega-3 fatty acids in immunity, inflammation and cardiometabolic disease. He has received several awards for his work including the Nutrition Society's Sir David Cuthbertson Medal (1995), the Belgian Danone Institute Chair (2004), the Nutricia International Award (2007), the European Society for Clinical Nutrition and Metabolism (ESPEN) Cuthbertson Lecture (2008), the New Zealand Nutrition Society's Muriel Bell Award (2009), the Louisiana State University Chancellor's Award in Neuroscience and Medicine (2011), the Normann Medal from the German Society for Fat Science (2012), the Ralph Holman Lifetime Achievement Award from the American Oil Chemists' Society (2015), the British Association for Parenteral & Enteral Nutrition

(BAPEN) Pennington Lecture (2015) and the British Nutrition Foundation Prize (2015). He has served on many committees of professional societies including the Nutrition Society, BAPEN and ESPEN, he was a founding member of the Nutritional Immunology Group of the British Society for Immunology, and he was for three years President of the International Society for the Study of Fatty Acids and Lipids (ISSFAL; 2009-2012). He is currently Chair of the Scientific Committee of ESPEN and President-Elect of the Nutrition Society. Professor Calder has Chaired several expert groups of the European Branch of the International Life Sciences Institute, mainly in the area of biomarkers. He has been involved in organizing many scientific meetings including the 6th ISSFAL Congress in 2004, the 9th Fatty Acids and Cell Signaling Workshop in 2009, and the FASEB Summer Research Conference on Nutritional Immunology in 2015. Professor Calder was Editor-in-Chief of *the British Journal of Nutrition* from 2006 to 2013 and he is currently an Associate Editor of *Clinical*

Science, Journal of Nutrition, Clinical Nutrition, Lipids, Nutrition Research and Prostaglandins Leukotrienes and Essential Fatty Acids. He is a member of the several other Editorial Boards of journals in the nutrition, clinical science and lipidology fields and a Section Editor of *Current Opinion in Clinical Nutrition and Metabolic Care*.

Professor Calder has over 500 research publications (excluding abstracts), including over 250 peer-reviewed research papers and over 150 review articles in journals. His work has been cited over 20,000 times and he is listed by Thomson Reuters as a Highly Cited Researcher.



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Supporting nutritional science promoting public health

A story of success

The Danone International Prize for Nutrition (DIPN), which has now been awarded for the 10th time by the Danone Institute International in collaboration with the 'Fondation pour la Recherche Médicale' is one of the most distinguished honors in the field of nutritional science.

The DIPN which carries a donation of 120.000 € was established in 1997 and is being awarded every two years to reward internationally leading researchers who have achieved major advancements in dietary science, introduced new concepts and opened up novel fields with potential applications for human diet and health. This includes basic research on underlying biological mechanisms as well as disease prevention and management, dietary behaviour and public health issues.

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Professor Olivier Goulet
(Hôpital Necker Enfants-Malades, Paris)

President of the Danone Institute International

*“Selecting
Philip Calder
as the
10th laureate is in
full accordance
with the spirit
of the Prize.”*

The selection of the candidates follows an independent, international and consultative procedure, which is modelled after that used for the Nobel Prize thus guaranteeing transparency and objectivity. The Prize Committee is responsible for organizing and monitoring the selection process. For the 10th edition, the committee received 21 dossiers and selected 8 nominees.

INTERVIEW

“ Looking at the work of the ten awardees who have received the Danone International Prize for Nutrition so far it is fair to say that it mirrors the achievements of cutting edge research of the past two decades in the area of nutrition related science, covering a wide range, starting with basic research on nutrients such as proteins, iron or vitamin A, then followed by more conceptual approaches such as early programming – studied by David Barker – as well as translational aspects. We are witnessing a breathtaking increase of knowledge regarding the complex relationships between diet, biological mechanisms and health to which our two previous laureates Prof Gordon and Prof. Hotamisligil have contributed in particular.” says Prof. Goulet.

“This year’s awardee Philip Calder has been honored for his impressive work on the relations between nutrition and immune function and in particular on the role of omega-3 fatty acids as anti-inflammatory agents. Philipp Calder’s findings have resulted in far reaching applications relevant for public health such as clinical treatments in the field of nutritional immunology, prevention of allergy, protection against infection, maintenance of gut health and reduction of cardiovascular disease risk. Philip Calder’s research which also addresses the impact of nutrition at different stages of life provides great benefit for the general public as it leads to improved treatment outcomes. Selecting Philip Calder as the 10th laureate is in full accordance with the spirit of the Prize.” Prof. Goulet added.



Previous laureates

Examples of excellence



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Prof. David Barker
recipient of the DIPN in 2005.

The University of Southampton, where this year's awardee Prof. Philip Calder is teaching, has already established a "DIPN tradition" as one of the previous prize winners, the late **Prof. David Barker** who received the prize in 2005 also belonged to this academic institution. David Barker, who died in 2013, showed for the first time that people with a low birth weight are at greater risk of developing coronary heart disease, hypertension, stroke and diabetes.

He discovered that these wide-spread diseases are not always due to genes or an unhealthy lifestyle, but may also result from poor intrauterine and early postnatal health. His findings have led to a new understanding that chronic adult diseases are influenced by malnutrition in the womb, thus emphasizing the role of diet during development which can – to a certain extent – determine the body's structure and physiology. **His "fetal origins hypothesis" stimulated a wealth of still ongoing research exploring the complex interactions between nutrition and growth during intrauterine and early postnatal life, and their impact on the onset of adult disease.**



© Photo DR.

Prof. Jeffrey I. Gordon
recipient of the DIPN in 2011.

An outstanding example for pushing forward the frontier of nutritional science into new territory is the work of **Prof. Jeffrey I. Gordon** who was the DIPN awardee of 2011. As Director of the Center for Genome Sciences and Systems Biology at Washington University School of Medicine in St. Louis he has performed pioneering research by unveiling the complex interrelationships between different kinds of diets and the structures and functions of the microbial communities harboured by the human gut and intestinal and nutritional health.

Thanks to Prof. Gordon's findings, which are based on innovative methods in genomics combined with animal models and human studies, **new knowledge has been gained about the beneficial potential of the gut microbiota for diagnosing, preventing and treating diet-related conditions at different stages of life, thus outlining new strategies to enhance the health of children and adults alike.**

Immunometabolism a new research field



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Dr. Gökhan S. Hotamisligil
recipient of the DIPN in 2014.

*“Such
recognition
brought us new
opportunities
to expand our
research.”*

Landmark studies of similar significance have been performed by Dr. Gökhan S. Hotamisligil who received the DIPN in 2014. Gökhan S. Hotamisligil, who is Chair of Harvard University’s School of Public Health Department of Genetics and Complex Diseases opened up a new research field that is now known as immunometabolism. *“Having been recognized by this honor was a strong boost to our confidence in our programs and provided a tremendous motivation to our entire group. Receiving this highest recognition in the Nutrition field also stimulated interest in our efforts to merge molecular and cell biological approaches with nutritional underpinning to search for solutions for the greatest public health challenges of the century. We are most grateful for this distinction and the efforts of the Danone Institute International to promote basic research in the area of Nutrition. We still have the announcement on our wall to remind us that we need to work harder to deserve such an honor.”*, says Dr. Hotamisligil.

His findings have illuminated fundamental mechanisms underlying the susceptibility of modern humans to nutrition-related diseases. He has explored the multifarious connections between immunology, molecular pathways, inflammation and metabolic disorders. **He discovered several pathways and mechanisms that link obesity and diabetes, insulin and inflammation related processes as well as metabolic signals and immune responses.** Dr. Hotamisligil emphasises the impact the prize had on his further research: *“Internally, this prize gave us momentum in our efforts to exploit the molecular mechanisms underlying the biological effects of nutrients and how such knowledge can be translated for improving the quality of life for humans. This area now represents a major focus in our group and exciting leads are emerging from this effort. The prize also facilitated the recognition of this field in general and our efforts in it in the past three decades. Such recognition brought us new opportunities to expand our research and finally have the resources to think about long term and more risky projects and pursue translational avenues.”*



The Danone Institute International

Advancing Knowledge
on Nutrition

In the beginning, there was Danone, already inherently permeated by the values of nutrition and health.

In 1991, Danone decided to promote public health by developing and spreading knowledge about nutrition, diet and health, and set up its first Danone Institute.





© Photo DR.

Professor Olivier Goulet
(Hôpital Necker Enfants-Malades, Paris)

President of the Danone Institute International

“The Danone Institutes are non-profit organizations whose key missions are to contribute to the improvement of global public health by supporting research and education in the field of nutrition, and to compile and disseminate evidenced based knowledge about the many links between nutrition and health with a special focus on yogurt among other food categories. The Danone Institutes are partners in the fight against childhood obesity by promoting healthy eating practices.”

Olivier Goulet, *President Danone Institute International*

Twenty five years later, the Danone Institute International gathers a network of 16 Danone Institutes. The Danone Institutes are present in 19 countries and gather around 200 experts around the World (nutritionists, pediatricians, gastroenterologists, scientists, sociologists...). To date, more **than 900 research projects** have been supported; dozens of educational programs have been launched, and close to **one hundred symposia** organized.

Since 1997, The Danone Institute International (DII) has been awarding **the Danone International Prize for Nutrition** every two years to a research scientist or research team conducting noteworthy studies in human nutrition. Today, this prize is one of the Institute's key activities but also highlights Danone's long-standing commitment to nutrition and health.



In 2013, the YINI – **Yogurt in Nutrition, Initiative for a balanced diet** has been created in collaboration with the American Society for Nutrition and the International Osteoporosis Foundation. YINI mission is to advance scientific knowledge on the health effects of yogurt and to disseminate the findings broadly. This goes through revealing scientific data related to health effects of yogurt by organizing an annual Global Summit during the Experimental Biology Congress leading to publications in influential journals in biology and medicine, stimulating new research through a YINI Grant and sharing the information on a dedicated website (www.yogurtinnutrition.com) and social media (<https://twitter.com/YogurtNutrition>).



INTERVIEW

Emmanuel Faber, Danone CEO



Can a company like Danone have a role in impacting people's eating and drinking practices?

Thanks to our products, we are connected to millions of consumers worldwide. The opportunities we have to shape their approach to food and health as well as their lifestyles are endless.

Danone wants to start a slow revolution in the industry, challenging conventional thinking about food consumption and proactively influencing eating & drinking practices as part of the solution to address public health challenges.

Historically, food companies focused their product development on functional attributes [e.g. calories, proteins, hydration]. Through our 'alimentation' approach, we want to give more to our consumers. Beyond the physiological need, we want to provide nourishment in the broadest sense with eating and drinking as a pleasurable, cultural, social and emotional experience that brings people together. In this regard, Danone invests in research to understand eating and drinking practices in different communities and analyze behavioral drivers to promote healthy diets across the globe.

How does the Danone International Prize for Nutrition fit into Danone's policy?

With increasing obesity rates, an ageing population and severe malnutrition issues, maintaining a healthy population is a huge task. At Danone, we believe it is crucial to support academic research in the field of nutrition as it enables to unlock new approaches and efficient solutions to address these growing challenges. We have proudly been supporting the Danone Institutes for 25 years with the Danone International Prize for Nutrition as a key initiative helping us to meet our mission: "bringing health through food as many people as possible".

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by Philippe Lassale 2014

Nutrition and Health

a priority at the heart of the company's strategy

Danone was born from the conviction that food is health's most significant partner to build and to maintain well-being, at every moment in life. Nutrition and health are the cornerstones of its mission and business model.

Since its creation, Danone has always been directly linked with nutrition and health. Today, Danone relies on guiding principles:

A Healthy diet starts with healthy products

Beyond food composition, a healthy diet is about eating and drinking a variety of balanced nutrient-rich food and beverages with moderation. Danone focuses on a portfolio of products (waters, early life nutrition, medical nutrition and fresh dairy products) that are beneficial to health on a daily basis as they are nutrient dense and considered to be essential in the public nutrition policies and guidance.

Act locally to best impact

Healthy eating is part of every culture. Therefore Danone considers eating and drinking patterns to deliver the best impact to local communities. This is the reason why its nutrition model relies on understanding local nutrition issues and eating practices. Thus, the company has a country and community based approach to ensure that its products are relevant to local diets and preference, addressing local cultures and traditions. 53 countries are already covered by this approach.

Enjoyable experience is a key driver of healthier diet

To ensure the sustainability of healthy eating habits, beyond diversity, moderation and nutrient rich food, Danone believes that an enjoyable experience is key. This is why Danone maintains wherever possible consumer preference while offering a healthier option.

Research is the company best ally

Danone's Nutrition vision is supported by investment in research, with 6 research centers and teams in 55 branches, gathering 1,500 people around the world focusing on 4- fields of innovation:

- **Reliability:** committing to nutritional quality and managing natural resources sustainably,
- **Progress:** building bridges between science and nutrition to contribute to people's health,
- **Cultures:** linking food styles to local needs and create a unique consumer experience, meeting people's expectations, whatever their origin and culture,
- **Well-being:** promoting our products' categories to support daily health and well-being for all, through guiding and building points of reference.

Not alone, but with partners and stakeholders

Public Health implies all actors. Industry is only one part of the picture. Danone stands firmly by its belief that it is better to walk together than apart. Danone aligns with local authorities and engages with other stakeholders in a quest to bring better health through better food, to ensure the relevancy of its actions and to increase collective impact to public health challenges.

For this reason, Danone creates partnerships with consortiums, start-ups and many internationally renowned institutions in areas including probiotics, prebiotics, intestinal microbiota, nutrition, bone health, cardio-vascular health, immunology, neuroscience and more (e.g. Institut Pasteur, The Utrecht Institute for Pharmaceutical Sciences, the MIT, etc.).

The Danone Institutes and their projects actively and independently contribute to these commitments through their multiple research support and healthcare and educational programs.



The Foundation For Medical Research

supports French Medical Research
and the
Danone International Prize for Nutrition

Founded in 1997 as a Danone initiative, the Danone International Prize for Nutrition is supported by the Foundation for Medical Research (FRM), whose mission is to develop cutting-edge research, contributing to the health of all. Entirely independent, state-approved and certified by the Committee of the Charter for Trust Funds, the Foundation operates through the generosity of its donors.



Foundation objective:

To contribute to the development of pioneering and innovative French medical research, leading to medical advances for all.

HOW TO SUPPORT THE FOUNDATION FOR MEDICAL RESEARCH

- By check sent to:
"La Fondation pour la Recherche Médicale" (The Foundation for Medical Research)
54 rue de Varenne
75007 Paris, France
- By credit card on the FRM website: www.frm.org

Founded in 1947 by doctors and researchers, including Professor Jean Bernard, the Foundation for Medical Research is engaged in all areas of medical research: cancer, neurological diseases, infectious diseases, cardiovascular diseases, genetic and rare diseases... The Foundation's objective is to contribute to the development of pioneering and innovative French medical research, leading to medical advances.

Two Missions that Link the Researchers and the Donors

The primary mission of the Foundation is to develop public medical research by funding research projects

The second mission of the Foundation – scientific information – is to inform the general public on the research issues and results.

A Unique Position in France

The Foundation for Medical Research is the only non-profit organization to support all biomedical research domains. It provides a significant support to research projects engaging young researchers. All research areas combined, the Foundation contributes annually to the development of more than 750 research projects.

Three Major Research Programs

The Research Hopes program supports research in all disciplines. It constitutes the heart of the mission of the Foundation.

The Research Urgencies program is dedicated to the development of domains identified as priorities by the Foundation in terms of research and public health.

The Research Pioneers program aims to encourage interdisciplinary approaches to promote the emergence of therapeutic innovations.

Procedures to Ensure Proper use of Donations

Funds raised are awarded by different scientific committees composed of recognized french researchers:

- Scientific council composed of 32 members, representing all medical and scientific disciplines evaluates and selects research projects of the Research Hopes program.
- *Ad hoc* scientific committees, composed of experts from relevant research fields, are composed to evaluate and select research projects to benefit from the Urgency for Research and Pioneers of Research programs.

Evaluations and selections made by these committees are based on the scientific quality of the projects, and the excellence of the concerned researchers.

Full Transparency on the Use of Funds

The Foundation for Medical Research follows procedures and controls that ensure the quality of its management and enable its donors to be fully informed of the use of their gifts:

- Control by an auditor.
- Inform its donors and partners on financial accounts.
- Continuous monitoring of the Committee of the Charter for Trust Funds.
- Activity report available on its website: www.frm.org.
- A "traceability" of the use of donations: Any donor who directed his gift to a specific research area may, upon request, know exactly which research project was awarded by his gift.

10th

DANONE
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PRIZE FOR
NUTRITION

Feeding the immune system



www.danoneinstitute.org