Summary

The fundamental aim of this conference was to add new dimensions to our understanding of how complex gene–environmental interactions influence immune programming and disease predisposition. This theme was selected based on the concerning global rise in many diseases associated with immune dysfunction, including allergic diseases and many autoimmune conditions. While these disorders have been most prevalent in industrialized countries, the same concerning trends are now being observed in many developing countries as they also undergo complex environmental change. All of these conditions arise as a result of inappropriate responses to otherwise innocuous environmental or self antigens. The very fact that these immune disorders are susceptible to environmental change highlights that environmental modification may also be useful for disease prevention, and this is the ultimate goal of research in this field. Thus, understanding candidate environmental factors that influence immune programming and how these interact with genetic predisposition, is fundamental for determining more effective strategies for preventing immune disease. As one of the leading candidates in the allergy epidemic, microbial exposure was of central interest to our discussions, particularly how early colonization interacts with antigen exposure and other immunomodulatory exposures to influence immune development.

The Gut as the Major Site of Host–Environmental Interactions

As the largest interface between the host and the environment, the gastrointestinal tract was the central focus in all of our discussions. While it is well recognized that the gut provides the largest exposure to colonizing bacteria, it is also the main route of exposure to environmental allergens (i.e. food allergens) and micronutrients with immunomodulatory properties, adding further dimensions to the age-old adage that ‘we are what we eat’. Thus, although the primary focus of the workshop was on ‘host–microbial interaction’, this
was considered in the context of other exposures (fig. 1) which are likely to interact to influence the development of oral tolerance, most notably patterns of antigen exposure and nutrition.

**The Importance of Developmental Programming**

The ultimate goal of research in this field is to achieve safe and effective environmental strategies to prevent or minimize the risk of immune dysregulation. It is now widely recognized that gene–environmental interactions have the greatest capacity to influence the development of health or disease (i.e. immune tolerance or immune dysregulation) during early development. The most effective prevention strategies are likely to be those that have effects during early critical periods of immune programming. For this reason discussions were heavily focused on events relating to (1) early colonization, (2) early antigen exposure, and (3) early immunomodulatory dietary exposures, and interactions between these critical factors during critical development periods. Concepts such as epigenetic programming in utero and subsequent epigenetic regulation were highlighted by a number of speakers as critical pathways through which environmental changes could alter expression of genes in patterns which lead to immune dysregulation.

While environmental effects are clearly greatest in early development it is also recognized that immune programming is ‘a life-long process’, as emphasized by Harald Renz in his presentation. This may explain the late emergence of disease in some individuals. Equally so, this implies that the ‘opportunities for reprogramming’ may not only be limited to the in utero and perinatal period.
Host–Microbial Interactions and the Hygiene Hypothesis

Our keynote presentations by Dennis Kasper and Bengt Björkstén provided an excellent introductory session and a sound basis for the rest of the workshop. Since microorganisms were discovered, they have largely been considered in terms of the threat that they pose to the human host. The ‘hygiene hypothesis’ is a major shift in emphasis from adverse host–microbial interactions to the essential, adaptive and symbiotic relationships that have evolved in the host gastrointestinal system. Dennis Kasper highlighted the essential role of bacteria in the development of mucosal homeostasis and illustrated how polysaccharide, an archetypal molecule of commensal bacteria, mediates development of the host immune system. This clearly demonstrated how products from commensal bacteria can mediate the critical balance between health and disease in the host.

Bengt Björkstén provided an excellent review of the hygiene hypothesis, highlighting the controversies and limitations of available data. He also suggested that this could be more accurately described as the ‘microbial deprivation hypothesis’. It was generally agreed that there is good evidence that early microbial exposure is critical for early immune development, but that further studies are needed to determine the role of altered microbial exposure in the pathogenesis of autoimmune and allergic disease (or the changing prevalence of these). There was also general consensus that these events are likely to be multifactorial and vary between individuals.

Normal Oral Tolerance and the ‘Extended Hygiene Hypothesis’

Since its origins in epidemiological studies, the immunological basis for of the hygiene hypothesis has become more developed. Per Brandtzaeg outlined the immunological effects of gut microbiota together with the role these have in mucosal immune development and the pathways that promote immune tolerance. His talk highlighted how postnatal development of mucosal immune homeostasis depends on appropriate microbial colonization. This is particularly important for gut barrier function, and the control of local inflammation, both of which appear critical to minimize local and systemic immune disease.

Microbial activation of innate pattern recognition receptors on a range of innate immune cells and regulatory immune cells is believed to play a central role in the maturation of these pathways, and the ability to suppress inappropriate effector T-cell responses. Both Per Brandtzaeg and Catherine Thornton highlighted how concepts of microbial effects on immune development had evolved, particularly with the expansion of the Th1/Th2 paradigm to include a more central role of regulatory T cells.

In the most current model there is considered to be a critical balance between T effector cells (which may be either Th1 or Th2 dominant) and
regulatory cells (fig. 2). It was proposed that following an inflammatory trigger it is important that this balance is restored to prevent persistent or excessive Th1 or Th2 inflammation. In the arising discussion it was hypothesized that, if there is persistent disruption of this balance, a ‘point of no return’ may be reached and unchecked inflammation may result in disease. This model is better able to explain how many and varied Th1 and Th2 diseases result from the same environmental pressures, and how these apparently divergent groups of conditions are increasing in parallel.

Ursula Wiedermann extended these discussions to explore how these innate immune pathways could be utilized to induce of mucosal tolerance with novel allergy vaccines. Specifically, she presented how genetically engineered allergen constructs and novel microbial (parasitic) derived adjuvant molecules could be developed as for novel allergy vaccines.

Collectively, these presentations and resulting discussions illustrated the precarious balance between tolerance and dysregulation, and provided some optimism that this might be modified for disease prevention or more definitive treatment.

An Emerging Role for Host–Microbial Interactions in Gastrointestinal Immune Disease

The workshop went on to explore the potential role of host–microbial interactions in a diverse range of gastrointestinal diseases which arise from mucosal immune dysregulation, including celiac disease (Nadine Cerf-Bensussan), inflammatory bowel disease (Balfour Sartor) and eosinophilic esophagitis (Ralf Heine) which has emerged most recently as a frequently undiagnosed association with the allergic phenotype. Although these conditions show contrasting pathology and etiology, the role of ‘altered gut barrier function’ and ‘suboptimal microenvironment’ at the time of first antigen encounter were recurring themes. The complexity of host–environmental
interactions, the role and timing of antigenic exposure and the role of micro-
biota were highlighted in the discussions.

Erika Isolauri also presented a novel hypothesis during this session, pro-
posing that aberrant compositional development of the gut microbiota may 
also be implicated in other inflammatory Western lifestyle disorders, namely 
obesity. Specifically, she proposed how deviations in gut microbiota compon-
tion could predispose to the excessive energy storage patterns that lead to 
obesity. This generated much discussion, and it was agreed that more studies 
are needed to investigate this interesting concept further.

The Role of Antigen Exposure in Immune Tolerance

Just as it is now recognized that microbial exposure can be beneficial 
under some circumstances, there has been more recent recognition that 
allergen exposure may not always have adverse effects. This is a fairly signifi-
cant change from previous approaches to allergy prevention, which focused 
heavily on early allergen avoidance to prevent sensitization. With the recent 
recognition that tolerance is an allergen-driven process and that allergens are 
not the cause of the allergy epidemic, there has been a reevaluation of many 
allergen avoidance strategies including delayed complimentary feeding and 
prolonged avoidance of potentially allergenic foods.

The potential use of allergen as ‘tolerogens’ in the prenatal (Harald Renz) 
and early postnatal period (Susan Prescott) was presented. Fabienne 
Rancé extended this concept to discuss the new approaches that are using 
food allergens to induce oral tolerance in food allergic children as part of ‘spe-
cific oral tolerance induction’ (SOTI) program. It was stressed that there is 
currently very little evidence to support the practice of allergen avoidance 
for the prevention of allergic disease. On the other hand, children with estab-
lished food allergies should continue to avoid the culprit foods as SOTI is still 
experimental. Sibylle Koletzko emphasized that elimination diets carry the 
risk of inducing insufficient supplies of critical nutrients with adverse effects 
on health and wellbeing, particularly with exclusion of multiple foods or those 
that provide a major part of dietary supply. This highlighted the need for care-
ful supervision and regular review in food allergic children.

The Role of Nutritional Factors in the Modern Epidemic of 
Immune Disease

The potential for many and various dietary immunomodulatory nutri-
tents to influence immune development and host–microbial interactions was 
a recurring theme in virtually all sessions. Immunomodulatory effects of 
specific micronutrients (including polyunsaturated fatty acids, antioxidant
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vitamins and other immunomodulatory factors), were reviewed by Susan Prescott. This presentation also served to highlight the complex interactions between diet, allergens and microbial exposures in the first months of life. Seppo Salminen and Mimi Tang explored the role of prebiotic and probiotic supplementation in young infants to promote colonization and oral tolerance. It was concluded that probiotics were showing promise in the prevention of eczema, but that the effects appeared to depend on the strain used. The effects in the treatment of established eczema and other forms of allergic disease are less convincing. More studies are needed to determine the role of prebiotics in allergic disease, although initial studies have shown some promise. This session concluded with discussion by Andrea Von Berg about the role of modified dietary allergens (hydrolyzed proteins) in promoting tolerance for allergy prevention. She presented the most recent data from the well-known GINI study which confirm a consistent long-term preventive effect of hydrolyzed infant formulas (pHF-W and eHF-C) on allergic manifestations in high risk children until the age of 6 years, particularly atopic eczema.

**Epilogue**

This conference has highlighted that, although the modern era is characterized by immune dysregulation, this susceptibility of the immune system to environmental changes also provides opportunities for prevention. As noted in figure 3, ‘modern diseases’ are primarily environmental, resulting from environmentally induced changes in gene expression. The high rates of diseases such as allergic disease indicate that susceptibility genes are almost universal in most populations, such that they can be induced readily with environmental change. Epigenetic regulation of gene expression is a
new research frontier providing new understanding of how the environment
can have heritable genomic effects and promote disease. A number of early
life exposures including dietary nutrients (as discussed by Susan Prescott)
and microbial exposure (Harald Renz) in utero have been recently shown to
have epigenetic effects on gene expression, and resulting effects on the clini-
cal phenotype. The remaining and most momentous research goals are still
to identify the key environmental factors (or combinations of these) and the
optimal window(s) of opportunity. This is sure to challenge the field for years
to come. We remain optimistic that this inherent plasticity in the immune sys-
tem will provide opportunities for early intervention (prevention) and subse-
quent reprogramming (more effective treatment) in the future.

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