An infant enters the world with functionally mature, but naïve, mucosal and systemic immunity (1). In order to adapt to extrauterine life, the infant’s immune system must learn to differentiate between food and commensal microbial antigens and pathogens in order to avoid atopic diseases, while at the same time being competent to mount an immune response to an infectious challenge (1, 2). Human milk contains a multitude of immunomodulatory proteins, lipids, and oligosaccharides that provide innate immune protection, support the establishment of the microbiota, and stimulate adaptive immune development in early life (2–4). Over the past 30 y, infant formula composition has evolved to more closely mimic human milk composition (5). However, despite these attempts, differences in microbiome composition (6, 7), immune function (3), and atopic and infectious disease incidence (8, 9) persist between breast- and formula-fed infants.

For the past decade, the structural and functional complexity of the human-milk oligosaccharides (HMOs) has been an intense topic of research. These studies have shown that human milk contains a higher concentration (5–20 g/L) as well as a greater structural diversity and degree of fucosylation than the milk oligosaccharides in other species (10), particularly bovine milk (0.05 g/L) (11), from which many infant formulas are produced (12). The HMOs are multifunctional compounds that have been shown to affect infant immune and microbiome development (2, 4). Recent observational studies (12) and a systematic review (13) support associations between HMOs and reduced risk of immune-mediated diseases, including infection and food sensitization.

Pure forms of HMOs, synthesized chemically or by fermentation, have recently become available and are supplemented to a limited number of commercial infant formulas. However, other prebiotics have been added to infant formula for more than a decade and remain the predominant oligosaccharides that formula-fed infants are exposed to in the 4–6 mo of life before the introduction of complementary foods. A prebiotic is defined as “a substrate that is selectively utilized by host microorganisms conferring a health benefit” (14). Although the term prebiotic is often applied to any fermentable substrate, the only oligosaccharides that currently meet the definition of a prebiotic are HMOs, fructooligosaccharides (FOSs), inulin, and galactooligosaccharides (GOSs) (14). All of these, as well as polydextrose, have been supplemented to infant formula.

In recognition of the 90th anniversary of the Journal, revisiting one of the early studies on prebiotic supplementation and infant outcomes is warranted. A decade ago, Arslanoglu et al. (15) reported the findings of a prospective, randomized, double-blind, placebo-controlled intervention of prebiotic administration in the first 6 mo of life on allergic manifestations at 2 y of age. Healthy term infants with a parental history of atopy were fed either a prebiotic-supplemented [8 g short-chain (sc) GOS and long-chain (lc) FOS/L] or placebo-supplemented (8 g maltodextrin/L) hypoallergenic formula for 6 mo. They had previously reported that this prebiotic mixture significantly reduced the incidence of atopic dermatitis (AD) (16) and had a preventive effect against infections (17) in these infants during the intervention period. On the basis of the reduced incidence of AD in the first 6 mo of life, an early manifestation of the atopic march, they set out to test the hypothesis that a mixture of prebiotic oligosaccharides would mimic the immune modulatory function of HMOs, leading to a reduction in the cumulative incidence of allergic manifestations (primary endpoint) and the number of infectious episodes (secondary endpoint) at 2 y of age (15).

Of 152 participants in the original study, 134 infants (68 in the placebo and 66 in the intervention group) were available at follow-up. Researchers continued to be blinded to treatment at 2 y. During this period, infants in the scGOS+lcFOS group had significantly lower incidence of allergic manifestations. Cumulative incidences for AD (13.6% compared with 27.9%), recurrent wheezing (7.6% compared with 20.6%), and allergic urticaria (1.5% compared with 10.3%) were lower ($P < 0.05$) in the intervention group than in the placebo group. In addition, infants in the scGOS+lcFOS group had fewer episodes of physician-diagnosed overall and upper respiratory tract infections ($P < 0.01$) and fever episodes ($P < 0.00001$) and fewer antibiotic prescriptions ($P < 0.05$). This highly cited study (>470 citations to date) was the first, to our knowledge, to show that a dietary intervention with a mixture of scGOSs/lcFOSs exerted protective effects against both allergic manifestations and infections and that this dual protection lasted well beyond the intervention period.

On the basis of their findings, the authors suggested that modification of the intestinal microbiota could be a principal mechanism of action underlying the immune-modulating effect of the prebiotics. Indeed, the median bifidobacteria count at 6 mo of life was 10.3 CFUs/g stool in the scGOS+lcFOS...
group compared with 8.7 CFUs/g stool in the placebo group (P < 0.0001). Evidence from other studies shows that dysbiosis in the gut microbiota composition during the neonatal period and early infancy precedes the development of atopy (18). The dysbiosis has been related to a lower abundance of bifidobacteria and lactobacilli (19) or the higher abundance of Escherichia coli, which was associated with a higher risk of developing eczema, and Clostridium difficile, which was associated with a higher risk of developing eczema, recurrent wheeze, and allergic sensitization in the Child, Parents, and Health: Lifestyle and Genetic Constitution (KOALA) cohort (20). Recently, SCFAs, produced by microbial fermentation of prebiotics, have been highlighted as potential mediators of early-life immune development (21).

Despite the promising findings of the study by Arslanoglu et al. (15), coupled with subsequent work in the area, we are not in consensus in terms of the clinical benefit of routine supplementation of prebiotics to infant formula to prevent allergic manifestations. The most recent Cochrane review (22), which included the study of Arslanoglu et al. (15), concluded that due to the heterogeneity in the prebiotics tested and the reported outcomes, “further research is needed before routine use of prebiotics can be recommended for prevention of allergy in formula-fed infants. There is some evidence that a prebiotic supplement added to infant feeds may prevent eczema. It is unclear whether the use of prebiotic should be restricted to infants at high risk of allergy or may have an effect in low risk populations; or whether it may have an effect on other allergic diseases including asthma” (22). The American Academy of Pediatrics (23) cited the results of the study by Arslanoglu et al. (15) and concluded that “the addition of oligosaccharides as prebiotics to infant formulas is not unreasonable, but lacks evidence demonstrating clinical efficacy at this time” and “confirmatory studies, especially in children fed formula that is not partially hydrolyzed, are needed before any recommendations can be made” (23). Similarly, the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Committee on Nutrition similarly concluded that “available scientific data suggest that the administration of currently evaluated probiotic and/or prebiotic-supplemented formula to healthy infants does not raise safety concerns with regard to growth and adverse effects”; however, “there is a need in this field for well-designed and carefully conducted randomized controlled trials, with relevant inclusion/exclusion criteria and adequate sample sizes” (24). This was echoed in a recent article highlighting that the potential beneficial effects of maternal and infant prebiotic consumption for allergy prevention are promising, but more high-quality randomized controlled trials and detailed mechanistic studies are needed (21). In addition, more research on the biological effects of HMOS on infant immune development and infant outcomes is needed (21).

Acknowledgments
The sole author had responsibility for all parts of the manuscript.

References