## FOOD ALLERGY

# ADVERSE FOOD REACTIONS IN CHILDREN: FROM CLINICAL ASPECTS TO BASIC AND TRANSLATIONAL RESEARCH

*Roberto Berni Canani*

**Principal investigator**
Roberto Berni Canani

**Other components of the research group**
*Cristina Bruno / Laura Carucci / Serena Coppola*
*Tommaso Cozzolino / Giusy Della Gatta*
*Margherita di Costanzo / Carmen Di Scala*
*Ylenia Maddalena / Rita Nocerino*
*Lorella Paparo / Laura Pisapia Luana Voto*
*Anna Luzzetti / Linda Cosenza / Veronica Giglio*

**Background**

An adverse food reaction (AFR) is defined as any abnormal clinical response that occurs following ingestion of a food or food component. They are very common in the industrialized countries, where they affect up to 20% of the general population. According to the main pathophysiologic mechanism, AFRs are classified into two different groups: Food intolerance (non-immune mediated) and Food hypersensitivity (food allergy). Intolerance to carbohydrates is the most common type of non-immune-mediated AFR. The prevalence of these conditions seem to be increased during the last decades as a consequence of growing rate of carbohydrates consumption in the diet. Food allergy (FA) is an adverse health effect arising from a specific immune response that occurs reproducibly upon exposure to a given food. FA is one of the most common allergic disorders in the pediatric age, and it has been recognized as a global health problem. FA prevalence, persistence and severity have been on a rise in recent decades in industrialized world under the pressure of gene-environment interactions leading to immune-system dysfunction, mediated at least in part by epigenetic mechanisms. This changing scenario is leading to the increase in hospital admissions, medical visits, treatments, and in burden of care on families. All these factors contribute to a significant impact on people's morbidity, social costs and quality of life, with a psychological burden on patients and families. From all these

considerations it is clear that innovative strategies for the prevention and management of AFRs could have a huge impact for patients, families and the health care systems.

**Main achievements**

The research is mainly focused on the study of basic and clinical aspects of AFRs aiming to move disease biology from the laboratory to clinical practice. A bench to bedside approach is used to investigate new preventive and therapeutic strategies for AFRs. The main study aim is focused on the identification of best immune-nutritional strategies to promote immune tolerance and to modulate the expression of genes involved in the pathogenesis of AFRs including cellular and animal models, peripheral blood cells cultures, epigenetics biomarkers, gut microbiota structure and function, essential fatty acids metabolism, and clinical trials. The research team is composed by: 1. Clinical Unit, for the carrying out of clinical trials on large pediatric populations, bio-banking of biological samples, and availability of a team of biostatisticians for data analysis; 2. Nutrition Unit dedicated to the investigation of new dietary strategies and for the evaluation of the nutritional status with the state-of-the art of technologies (DEXA, calorimetry, BodPod); 3. Basic Science Unit with laboratories equipped with advanced technologies for metagenomics (last generation sequencers to perform 16s rRNA sequencing and shotgun) and metabolomics (HPLC, gas chromatography / mass spectrometry, MALDI-TOF) for the investigation of microbiota structure and function; cytoflorimeter and cell-sorter, microarray and pirosequencing for epigenetics analysis, animal models and cell lines. The three Units work with a high level of integration to provide a modern and multidisciplinary approach for the investigation of AFRs, the most recent and relevant achievements are summarized below:

- A new classification of congenital defects of digestion and transport of nutrients and electrolytes has been developed with the aim to help researchers and physicians in the modern approaches to food intolerances and other congenital diarrheal disorders.
- New integrated experimental tools for the investigation of AFRs have been developed.
- New therapeutic approaches for AFRs, based on probiotic and/or a post-biotic approach, have been developed.
- The role of gut microbiome as effective target for prevention and treatment of FA has been elucidated.
- The role and the mechanisms of action of several environmental factors involved in pathogenesis of FA have been defined (Figure 1).
- The role of L-PUFA metabolism in the pathogenesis of FA has been described.
- The epigenetic mechanisms regulating the disease course of FA have been identified.
- The potential of active dietotherapy in children with FA has been demonstrated. This active strategy is able to reduce disease duration and to prevent the occurrence of atopic march.

## Future perspectives

- The natural history of FA children: occurrence of other immune and non-immune conditions (Figure 2).
- The impact of nutritional counseling on nutritional status, body composition and quality of life in pediatric FA.
- Epigenetic biomarkers for the diagnosis and the follow up of FA.
- Butyric acid and butyric acid releasers for the prevention and treatment of FA.
- Solving the puzzle of non-IgE-mediated gastrointestinal food allergies (non-IgE-GI-FAs) in children: characterization of immune mechanisms, gut microbiota features, and new diagnostic tools
- The PREMEDI Study: the impact of Mediterranean Diet during pregnancy on pediatric allergy prevention.
- To explore direct effect of peptides from different dietary strategies on immune and non-immune tolerogenic mechanisms.
- Relationship between autism and AFRs.

## Publications


1. *Paparo L, Nocerino R, Bruno C, Di Scala C, Cosenza L, Bedogni G, Di Costanzo M, Mennini M, D'Argenio V, Salvatore F, Berni Canani R. Randomized controlled trial on the influence of dietary intervention on epigenetic mechanisms in children with cow's milk allergy: the EPICMA study. Scientific Reports. 2019; 26;9:2828.*
2. *Feehley T, Plunkett CH, Bao R, Hong SMC, Culleen E, Belda-Ferre P, Campbel E, Aitoro R, Nocerino R, Paparo L, Andrade J, Antonopoulos DA, Berni Canani R, Nagler CR. Healthy infants harbor intestinal bacteria that protect against food allergy. Nature Medicine. 2019; 25:448-453.*
3. *Berni Canani R, Paparo L, Nocerino R, Di Scala C, Della Gatta G, Maddalena Y, Buono A, Bruno C, Voto L, Ercolini D. Gut microbiota as target for innovative strategies against food allergy. Frontiers in Immunology. 2019; 10:191.*
4. *Berni Canani R, De Filippis F, Nocerino R, Paparo L, Di Scala C, Cosenza L, Della Gatta G, Calignano A, De Caro C, Laiola M, Gilbert JA, Ercolini D. Gut microbiota composition and butyrate production in children affected by non-IgE-mediated cow's milk allergy. Scientific Reports 2018; 8:12500.*
5. *D'Argenio V, Del Monaco V, Paparo L, De Palma FDE, Nocerino R, D'Alessio F, Visconte F, Discepolo V, Del Vecchio L, Salvatore F, Berni Canani R. Altered miR-193a-5p expression in children with cow's milk allergy. Allergy. 2018; 73(2):379-86.*
6. *Berni Canani R, Di Costanzo M, Bedogni G, Amoroso A, Cosenza L, Di Scala C, Granata V, Nocerino R. Extensively hydrolyzed casein formula containing Lactobacillus rhamnosus GG reduces the occurrence of other allergic manifestations in children with cow's milk allergy: 3-year randomized controlled trial. Journal of Allergy Clinical Immunology. 2017; 139:1906-1913.e4.*
7. *Paparo L, Nocerino R, Cosenza L, Aitoro R, D'Argenio V, Del Monaco V, Di Scala C, Amoroso A, Di Costanzo M, Salvatore F, Berni Canani R. Epigenetic features of FoxP3 in children with cow's milk allergy. Clinical Epigenetics. 2016; 12;8:86.*
8. *Berni Canani R, Castaldo G, Rosa B, Martìn M, Goulet O. Congenital diarrhoeal disorders: advances in this evolving web of inherited enteropathies. Nature Reviews Gastroenterology and Hepatology. 2015; 12(5):293-302.*

9. *Berni Canani R, Sangwan N, Stefka AT, Nocerino R, Paparo L, Aitoro R, Calignano A, Khan AA, Gilbert JA, Nagler CR. Lactobacillus rhamnosus GG-supplemented formula expands butyrate-producing bacterial strains in food allergic infants. ISME Journal. 2016; 10:742-50.*

10. *Berni Canani R, Nocerino R, Terrin G, Coruzzo A, Cosenza L, Leone L, Troncone R. Effect of Lactobacillus GG on tolerance acquisition in infants with cow's milk allergy: a randomized trial. Journal of Allergy Clinical Immunology. 2012; 129:580-2, 582.e1-5.*

## External collaborations

- *Zibauer M, Wellcome Trust-Medical Research Council Stem Cell Institute, University of Cambridge, Cambridge, UK*
- *Holhm H, Translational Gastroenterology Unit, University of Oxford, Oxford, England; Department of Pediatrics, University of Oxford, Oxford, England*
- *Walker A, Fasano A, Division of Nutrition, Harvard University Boston, Massachusetts General Hospital, USA*
- *Winter H, Bousvaros A, Lencer W, Katz A, Division of Pediatric Gastroenterology and Nutrition, Mass General Hospital for Children; Duggan C, Center for Advanced Intestinal Rehabilitation. Children's Hospital Boston, USA*
- *Guandalini S, Nagler C, University of Chicago, Illinois, USA, Section of Pediatric Gastroenterology Chicago Children's Hospital, USA*
- *Gilbert J, Argonne National Laboratory, Argonne, Illinois, USA*
- *Elias JE, Department of Chemical & Systems Biology Stanford University, Stanford California, USA*
- *Martin MG, Department of Pediatrics UCLA, Division of Pediatric Gastroenterology and Nutrition Los Angeles California, USA*
- *Cohen M, Division of Pediatric Gastroenterology and Nutrition, Children's Hospital University of Cincinnati, Ohio, USA*
- *di Lorenzo C, Division of Pediatric Gastroenterology and Nutrition, University of Columbus Ohio, USA*
- *Landberg R, Division Food and Nutrition Science Department of Biology and Biological Engineering, Chalmers University of Technology Gothenburg, Sweden*
- *Erian PH, Department of Pediatrics, University of Innsbruck, Austria*
- *Goulet O, Dupont C, Ruemmele R, Pediatric gastroenterology-hepatology-nutrition service, Necker-Enfants Malades Hospital, Paris, France*
- *Salminen S, Oresic M, Department of Pediatrics and Department of Medicine, University of Turku, Finland*
- *Eizirik DL, Libre, Center for Diabetes Research, University of Bruxelles (ULB), Belgium*
- *Sanz I, Spanish National Research Council (CSIC) at the Institute of Agrochemistry and Food Technology (IATA). Madrid, Spain*
- *Guest J, Catalyst Health Economics Consultants Ltd, Northwood,UK*
- *Terracciano L, Department of Pathological Anatomy, University of Basel, Switzerland*
- *Caprioli A, Bacteriology Laboratory, Food Microbiology Laboratory; Ruggeri FM, Virology Laboratory; Pozio E Laboratory of Parasitology, Istituto Superiore di Sanità, Rome, Italy*
- *Mosca F, Agostoni C, Zuccotti GV, Department of Clinical and Community Sciences, University of Milan, Italy*

- *Morelli L, Institute of MIcrobiology, Faculty of Agricultural, Food and Environmental Sciences Catholic University of the Sacred Heart, Piacenza, Italy*
- *Rescigno M, Humanitas University, Milan, Italy*
- *Bacchetta R, Regenerative Medicine, Stem Cells and Gene Therapy Division San Raffaele Hospital, Milan, Italy*
- *Maffeis C, Department of Odontostomatological and Maternal-Child Surgery, University of Verona, Italy*
- *Cucchiara S, Department of Pediatrics and Intantile Neuropsychiatry, Sapienza University of Rome, Italy*
- *Corsello G, Department of Pediatrics, University of Palermo, Italy*
- *Marseglia GL, Department of Pediatrics, University of Pavia, Italy*
- *Sforza S, Department of Food and Drug Sciences University of Parma, Italy*
- *Novembre E, Meyer Hospital - Allergology Unit, University of Florence, Italy*
- *Francavilla R, Interdisciplinary Department of Medicine, University of Bari Aldo Moro, Italy*
- *Putignani L, Microbiology, Fiocchi A, Allergology, Bambino Gesù Children's Hospital, Rome, Italy*
- *Miceli Sopo S, Department of General and Specialized Pediatrics, Catholic University of the Sacred Heart, Rome, Italy*

*Figure 1. Gut microbiota as a target of intervention against food allergy*
Several genetic, environmental and dietary factors could modulate the gut microbiota-immune system axis influencing the occurrence of FA. For instance, increased family size, exposure to pets and/or rural environment, healthy diet (full of fibers, fermented foods, antioxidants, omega-3), breastfeeding and use of probiotics are associated with protection to FA. Conversely, C-section, prenatal and early-life exposure to antibiotics/gastric acidity inhibitors/antiseptic agents, unhealthy diet (low fibers/high saturated fats and junk foods) may increase the risk for the development of FA. All these environmental factors act mainly on a modulation of gut microbiota composition and function which in turn could be responsible for the epigenetic regulation of genes involved in immune tolerance.

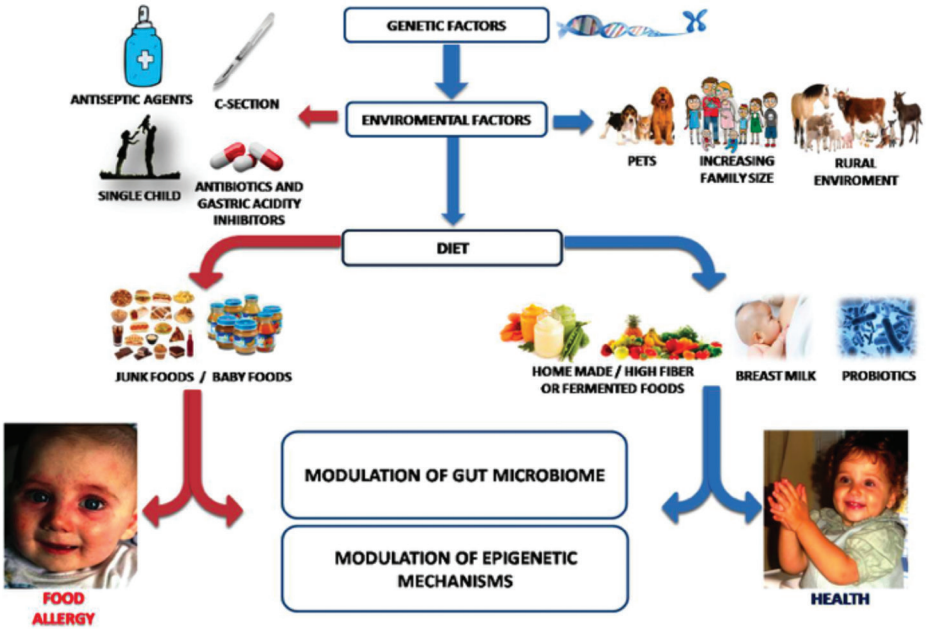

*Figure 2. The food allergy pyramid*

Children with FA could present an increased risk to develop later in the life other conditions such as allergic disorders (atopic march), inflammatory bowel diseases (IBD), functional gastrointestinal disorders (FGIDs), and neuropsychiatric disorders. Several genetic factors are implicated in the pathogenesis of these conditions, but recent evidence suggest the pivotal role of gut microbiota dysbiosis (induced by environmental factors). Emerging evidence support the hypothesis of dysbiosis as the first hit in the development of alterations in intestinal barrier and immune system function (responsible for the occurrence of FA and atopic march) and dysregulation of the brain-gut endocrine-immune system axis (responsible for the occurrence of FGIDs, IBD and neuropsychiatric disorders), at least in part through an activation of epigenetic mechanisms.