

FUTURE HORIZON OF NUTRITION
Project Introduction to design the WORK PLAN STRUCTURE
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AIM : Prevention of human health is an integral part of thriving knowledge society that is closely intertwined with economic growth and sustainable contemporary development. Achieving good health for all means not just curing diseases, because is better preventing diseases.

- **Healthy Microbiome: Concept Frontiers in Nutrition and Diseases Prevention**
- The gut microbiome in human health and well-being represents a major transformational task in both nutritional research and diet-prevention strategy to decrease risks of metabolic and immunologic diseases . The optimized symbiosis between the host-genetics and the genetic diversity of the gut bacteria community provides a deep impact on food nutrients primary metabolic activities so that favoring a better symbiosis through enhancing biodiversity in microbiome is increasingly recognized as a major contributor to human health and disease.

→Logical Framework from idea generation , concept definition and planning ,all composed by getting a logical coherent replay to :the call KBBE.2013.2.2-02

→ **WP3: Human Gut Microbiome and Immune Deficiency.**

Goal : The WP3 will explore the nexus between nutrient metabolism and the immune system The Gut-Microbiome advanced knowledge is essential for an healthy development of the immune system. Alterations of the gut-microbiome may lead to dys-regulation that affects the both in the gut and in other organ's auto-immune

▪ **Purpose: introduction and backgrounds of WP3**

The innate and adaptive potential of human immune system, represents an area of scientific need, opportunity and challenge occurs at many levels, ranging from : a) the intestinal microbiome has the capacity to synthesize a variety of vitamins as K vitamin and some other of the group B involved in myriad aspects of microbial and host metabolism, including endocrine signaling to direct sensing of nutrients by immune cells; b) short chain fatty acids (SCFAs) provide one of the clearest examples of how nutrient processing by the microbiota and host diet combine to shape immune responses. SCFAs are end-products of microbial fermentation of macronutrients (called “ pre-biotics”) , most notably plant polysaccharides that cannot be digested by humans alone because human genomes do not encode the large repertoire of enzymes (‘dining utensils’) as they are provided by the microbiome. The luminal concentration of intestinal SCFAs can be modified by the amount of fiber in the diet: this in turn affects the composition of the gut- microbiome in addition to acting as an energy source for the host. Missing such pre-biotic fermentation can be seen as a mode of specific malnutrition leading to development of disease, as obesity and other co-morbidities and its relationship to the gut microbiome and the host immune responses .

Output :

- a) Restoring the healthy human host, a balance existing between members of the gut-microbiome, such that potential pathogenic and non-pathogenic organisms can be found in an harmonic symbiosis. The host’s immune system must properly calibrate the responses to pathogens and must differentiate indigenous and exogenous non-pathogenic organisms to

maintain the an healthy symbiosis and seems to do this through pattern recognition receptors, which mediate the detection of bacterial antigens and activate signaling cascades that regulate the immune response.

- b) *Develop research on Immuno-modulation products* as antimicrobial factors such as defensins, lysozyme and haemocidins can have a role in the restoration of microbial equilibrium. The host's immune system must properly help to calibrate the responses to pathogens and must differentiate indigenous and exogenous non-pathogenic organisms It seems to do this through pattern recognition receptors, which mediate the detection of bacterial antigens and activate signaling cascades that regulate the immune response.

See Figure in : <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3298082/figure/F1/>

Activities :

WP3 research in FUHONU project will explore how develop the possibility to get an higher potential for probing immune system healthy function as a preventative therapy. An expected results of WP3 research will fundamentally give a contribute to shift the paradigm of drug development for immunological diseases, exploiting as naturally appropriated diets, added with pre-biotics as well food-fortification and other functional foods evolutionarily designed, can give an impact to thwart auto-immune diseases or viceversa harness a best healthy relationship between gut-microbiome modulation and adaptive immune system.

Expected Results :

the WP3 in collaboration with other FUHONU WP's would improve and verify the interrelationships between our diets, malnutritional status, microbiomes and immune systems to prevent people from immune deficiency.

→ WP4 - HUMAN GUT MICROBIOME ,METABOLIC SYNDROME AND OBESITY

Goal :

- a) Developing more detailed knowledge of the human microbiome will yield next-generation of prevention strategies, diagnostics and therapeutics for metabolic syndrome and other human diseases as obesity and high cholesterol levels in blood stream
- b) Obesity and other comorbidities :
Obesity is not only a simple overweight because is associated with increased risk to metabolic syndrome, insulin resistance, type 2 diabetes mellitus, hypertension cardiovascular disease and cancer all those consequences find a relationship with an excess of body adiposity.
- c) Advancing knowledge about the role of Diets on gut microbiome modulation to overcome obesity.

Purpose : introduction and backgrounds of WP4

A number of studies have revealed that obesity has been associated with phylum-level changes in the composition of the intestinal microbiota. Increase in the relative abundance of *Firmicutes* (Gram positive) and reduction in the level of *Bacteroidetes* (Gram negative) has been observed in intestinal microbiota of obese mice and humans . However, a number of other recent studies have shown variable results with respect of microbiota compositional changes of the personalized microbiome of obese human individuals Thus, the relationships between the various bacterial groups and obesity still remain a matter of debate and is currently investigated in various European and International programs.

Infammation of Gut-barrier :Gut barrier alterations, described in animal models of obesity, probably favour inflammation. The inflammation has been related to alterations in the gut

microbiota composition . For instance it is known that obesity induced by high-fat diets and the associated metabolic disorders are characterized by a state of low-grade inflammation. Low grade inflammation is becoming accepted as key common feature among the different metabolic disorders associated with obesity (type 2 diabetes, insulin resistance, NASH, cardiovascular diseases, atherosclerosis, cancer). In turn, low grade inflammatory tone seems to constitute the link between the gut microbiota, gut barrier and innate immunity. The serotonergic system seems to be involved in these processes to a certain extent as well. Studies during the last decade have accumulated evidence that certain diets influence changes in both systems substantially. Currently there is strong support for the use of probiotics in the clinical prevention or treatment of metabolic syndrome. In fact studies on probiotics effects on microbiome variation have known anti-inflammatory properties. However, these are most investigated in *in vitro* models, or on inflammation in the gut itself.

Output:

- a) Developing a systemic anti-inflammatory properties as it will be necessary to new diets approach to assure a prevention strategy to modulate microbiome in order to develop a guide to decrease in the population metabolic syndrome and obesity in order to decrease the incidence of obesity, metabolic syndrome and type 2 diabetes is growing therefore
- b) The WP4 research of FUHONU project will also test the hypothesis that a new probiotic product can be effective in people with metabolic syndrome, or insulin resistance, in order to advance in the understanding how intestinal microbiota

Activities :

- a) For the goal and objectives the WP4 will collaborate to analyze the results of a epidemiologic trial that will be realized in WP6 to favor better nutritional conditions by the use of specific probiotic strains to assess if the fortified diets can have a positive effect on obesity , metabolic syndrome, insulin resistance, and/or cholesterol levels.
- b) Besides WP4 would examine the novel ways in which the study of the nutrigenomics of the host-microbiome interactions (gutome) , including the metabolic relationships between gut-microbiome end mitochondria .The above more complete vision of the interaction in human metabolism needs to be articulated in a manner that recognizes ways in which nutrigenomics science can effectively personalize the diets and inform population health prevention

Expected results :

In conclusion the expected results of WP4 will be to advance knowledge of the role of diet and gut microflora in chronic disease pathogenesis, the interaction of nutrition and host genome (nutrigenomics), which never been applied in a more complete manner searching for future horizon of nutrition derived by the possibilities of Human gut Microbiome modulation in chronic disease prevention.

See :E. Ryan :<http://www.intechopen.com/books/the-molecular-basis-of-plant-genetic-diversity/the-nutrigenome-and-gut-microbiome-chronic-disease-prevention-with-crop-phytochemical-diversity>

WP5 : Human Gut Microbiome ,brain development and behavior

Goal :

To advance in knowledge about the ability of gut microbiota to communicate with the brain and thus modulate behavior . This “ gut-brain axis “ is an emerging as an exciting concept in health and disease that need more analysis . In particular need to be focus how the Enteric Nervous System

interact with the host Central Brain to form essential relationships that govern the Gut-microbiota homeostasis. Such homeostasis seems to be a need to get a healthy human gut, based on a balance between the multiplicity of members of the gut-microbiome, such that potential pathogenic and non-pathogenic organisms can be found in an harmonic symbiosis.

Purpose : introduction and backgrounds of WP5

The regulation of the homeostasis of the Gut-Microbiome function, both in healthy and diseases states, are fundamentally co-organized through bidirectional signals between Central and Enteric (CNS-ENS) nervous systems. CNS-ENS interactions can influence the Gut-Microbiota changes in various pathways:

- 1) Indirectly via modifications of gastro intestinal motility and gut-barrier permeability
- 2) Directly via signaling molecules (neurotransmitters ,immune modulation molecules) released in the gut- barrier
- 3) Via afferent innervations of vagal nerve by transmitting pain, stress, ,emotions,... that interferes with CNS-ENS interactions.

Disturbances in bidirectional CNS-ENS multiple signalling interactions with Gut –Microbiome, can lead to downregulation of the homeostatic symbiosis by producing various toxin that are released by pathogens bacteria enhancing their competing opportunity to metabolize nutrients and by some biochemical arms to expel non-pathogenic bacteria from gut-barrier surfaces. Besides “Gut hormones activity” interfere to optimize the process of digestion and absorption of nutrients by the gut through their local effects on gastrointestinal motility and secretion altering the rate at which nutrients are delivered. Therefore the complex control made by neuro-endocrine (e.g. CNS-ENS-Hormones) interactions constitutes the focal point at which dietary intervention may promote efficient digestion and nutrient uptake of food.

Output:

- a) WP5 will develop a deeper study on Gutbrain Axis efficiency, ,starting from the importance of microbial symbioses based on the control of neuro-endocrine interactivities ; therefore the WP5 will focus the research on the effects of dys-biosis that may be involved in the pathology of acute gastrointestinal diseases states as well as in changing the humor and the normal behavior of the human host.
- b) In particular the WP5 would be oriented to develop a strategy focused to applied Nutrition towards dietary prevention of the metabolic syndrome and associated cognitive decline, emphasizing the gut-brain axis. The WP5 research includes studies in preferentially healthy subjects regarding effects of various food ingredients on metabolic risk markers and cognitive functions.

Expected results :

Bettering the Understanding about the "cross-talk" between gut-microbiome and peripheral markers of metabolism, besides will be evaluated the probable role of “taste receptors in the gut” not only to modulate appetite regulation but also with the over-all purpose to develop knowledge for design of "anti bowel-inflammation diets” with benefits also on cognitive decline associated with metabolic disorders. Hence the WP5 of FUHONU project expectation will be essentially to obtain as result an advanced contribution able to play a significant role in the elucidation of the intestinal Gut-microbiome with the two nervous systems interactions in order to underpin future disease prevention strategies, personalized health care regimens, and the development of novel therapeutic interventions in brain behavior. Hence the WP5 of FUHONU project expectation will be essentially to obtain as result an advanced contribution able to play a significant role in the elucidation of the intestinal Gut-microbiome with the two nervous systems interactions in order to underpin future disease prevention strategies, personalized health care regimens, and the development of novel therapeutic interventions in brain behavior.

→ WP6 – Effects of diet on Human Gut-Microbiome

Goal :

Diet factors are considered to be critical for human health promotion and prevention and play an important role in the prevention of life-style related diseases. One of the major challenges of WP6 in this context is to determine how multiple dietary factors associated with the change from gut-microbiome symbiosis to dysbiosis can be evaluated to avoid the risks of some of the causes of metabolic and immunologic diseases. Hence WP6 will research about those causes as well as will develop a method of detecting gut-microbiome modulation in the initial stage of such diseases in order to establish a diagnostic approach that can be used to advance in prevention studies of the impact of diet factors on the human health. . Finally , a new paradigm for health prevention will be promoted as an emerging health prevention knowledge which suggests that many diseases and ailments come from an imbalance with the gut-microbial ecology and food and lifestyle choices

Purpose : introduction and backgrounds of WP6

Dysbiosis provokes mucosal infection and immune sensitization causing bowel inflammation and cross-reactivity with bacterial antigens leads to secondary immune damage and cytokine cascades that disseminate inflammatory through different target of organs of our body and brain.

Intestinal dysbiosis altered permeability,(Leaky Gut) ,food intolerance , food allergy, Rheumatoid Arthritis, and detoxification to prevent and in some cases to reshape gut-microbiome from those diseases the WP6 would develop an epidemiological research focused on learn how gut-microbiome symbiosis play crucial roles in the human health and viceversa how dysbiosis may be influenced by dietary habits and changes between dietary components.

Output

- a) **WP6** , develop an epidemiological trial to examine the scientific basis to get an healthy modulation by for choosing and measuring appropriate “ biomarkers “found in blood, other body fluids, or tissues for enrich those results :
 - a1) Assessing new approaches for prevention of metabolic syndrome and brain impairments by analyzing and evaluating specific biomarkers as indicators of metabolic processes, the function of healthy biomarkers in diet and nutrition both on health and disease ,
 - a2) Identifying the role and the level of intake for preventing some specific nutrient deficiencies (as nutrients (vitamin A, vitamin B12, folate, iron, and zinc and other micronutrients) in gut microbiome health, favoring potential interactions amongst different different stages of the life span and under different physiological states, in particular for women , pregnancy, ageing and menstruation changes ,
 - a3) Supporting the development and evaluation of evidence-based epidemiological programs and policies to improve the knowledge in microbiome modulation through appropriated diets and nutrition as a way to prevent and improve health.
 - a4) Dietary prevention of dysbiosis *Guidelines will be the final result of WP6 that will represent an opportunity to make that document matter for a nutritional therapy and as a information and teaching moment by inserting microbiology and ecology into a diffused prevention on food and health.*

BOND Project : http://www.nichd.nih.gov/global_nutrition/programs/bond/pages/about.aspx

BIO NMD Project 2010-12 : <http://www.bio-nmd.eu/news/update-may-2010-full/>

<http://www.bio-nmd.eu/news/m18-full-version>