ILSI Europe activities related to ‘Human Microbiome & Health’

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A non-profit organization with private legal status and over 750 staff operating in several sites in the Trentino province.

It provides Research, Education, Technology Transfer and Advisory Service in the Agri-Food and Environmental sectors.
The GUT MICROBIOTA

• 1000 different species
• X10 number of human genes
• More metabolically diverse than liver
• Shaped by host genetics, age, drugs but especially diet (fiber, protein, fats and polyphenols)
Physiological Role of Gut Microbiota

- Pathogen inhibition (colonization resistance)
- Fiber fermentation (short chain fatty acids)
- Transformation of plant polyphenols into phenolic acids (PA)
- Enterohepatic circulation of bile acids (BA)
- Amino acid metabolism (e.g. TRP)
- Regulation of satiety (via incretins)
- Regulation of energy usage/storage
- Gut:brain axis (mood, depression, cognition)
- Immune function (immune education, tolerance, resolution of inflammation via SCFA, BA, PA)

Gut Microbiota Dysbiosis

- Colon cancer
- Inflammatory bowel disease (IBD)
- Irritable bowel syndrome (IBS)
- Celiac disease
- Food allergies
- Atopic eczema
- Obesity/metabolic syndrome/type 2 diabetes/heart disease
- Non-alcoholic fatty liver disease
- Poor sleep (sleep apnea)
- Osteoporosis
- Autoimmune & Rheumatic diseases
- Psychiatric disease (schizophrenia, depression, autism, Parkinson's, Alzheimer's disease)

“The gut microbiota a newly recognised organ within the human body”

O’Hara & Shanahan, 2006 EMBO Reports
Marcheisi et al 2016 Gut
“Who’s in charge here!”

Frequia and Kaleko (2016)
Genetric Engineering & Biotech News
Scientific Events by ILSI Europe related to Microbiome (Dec 2015 – Jan 2017)

ILSI Europe’s Workshop
The Gut Microbiome: Our Misunderstood Friend and Foe
Impact of the Gut Microbiome on Entero-hepatic Metabolism and Energy Availability
3-4 December 2015, Brussels, Belgium

ILSI Europe’s Session on ‘GUT BARRIER FUNCTION AND MICROBIAL METABOLISM’ at the International Scientific Conference for Probiotics and Prebiotics
21 June 2016, Budapest, Hungary

ILSI Europe’s Session on ‘HUMAN MICROBIOME AND HEALTH’ @ IUFoST 2016
24 August 2016, Dublin, Ireland

Join us for a Session on Human Microbiome and Health
Role of Human Microbiota for Health and Wellbeing
25 January 2016
St. Petersburg, Florida, USA
Meeting Room Majestic
14.00-17.30

Organised by ILSI Europe in collaboration with 8 ILSI Branches

One ILSI Exchange Platform ‘Human Microbiome & Health’
Meeting on 24 January 2017
Early Nutrition & Long-Term Health (formerly Metabolic Imprinting) Task Force

“Nutrition in early life and why it matters”

Current Activity
Early Bacterial Colonisation & Potential Implications Later in Life

Aim: Role of the microbiome and nutrition in programming health & disease during the earliest stages of life

Dr Bettina Schelkle
Early Nutrition and Long-Term Health Task Force

Objectives

• Evidence related to bacterial colonisation early in life (mammary gland and placental pathways)

• Nutritional mediation of metabolic, immunological & cognitive outcomes through the modulation of microbiota

Expected outcome

• Systematic reviews: evidence on breastmilk & placental transfer

• Guidelines: nutritional strategies for pregnant women & infants
Nutrition, Immunity and Inflammation Task Force

“Determining reliable markers for nutritional modulation of immune functions and inflammation.”

Dr Tobias Recker
Immune Competence Across Lifespan: Impact of nutrition on immune competence and its consequences later in life

New Activity

• **Sub-activity 1:** Impact of nutrition on key markers of immune competence early in life *(scenarios: acute gastrointestinal and respiratory infections & inflammatory conditions such as allergies)*

• **Sub-activity 2:** Review the impact of early life immune competence on immunity and health trajectory later in life

• **Workshop:** Draw associations between early life nutrition and immune competence later in life \(\rightarrow\) potential collaboration with Early Bacterial Colonisation & Potential Implications Later in Life and/or other branches

Experts will consider the actual impact of the human microbiota on the physiological development of the immune system and/or immune related markers
Prebiotics Task Force

Understand the Relationship between the Molecular Structure and the Physiological Effects of Prebiotic Compounds

Objectives

• The relationship between prebiotic structure and ability to modulate the gut microbiota;
• The **metabolic capacity of human gut microbiota**;
• To consider potential direct effects on the host.

➤ This project should be a first step in defining structure-function relations between prebiotics and beneficial effects for the host.
Fermentation of dietary and of manufactured carbohydrates

→ Identification of structural characteristics of compounds
→ Semi-systematic approach: Search string for each compound will be listed
→ At present: Collection of literature
→ Submission of manuscript: Q3/4 2017

### Carbohydrate compound

| Fructans (all types, although not all are the same) | Oligofructans/branched fructans |
| GOS (beta galactosides) | Alpha galactosides  |
| Lactose |
| Lactulose |
| Milk oligosaccharides: human/animals (limit bovine/goat) |
| Xylanes |
| Arabinanes |
| Pectins |
| Gluco-oligosaccharides (no starch) | Oligo dextranes |
| Glucanes (alpha) |
| Starch  |
| Resistant starch |
| Glucanes (beta)  |
| Cellulose |
| Other Hemi-Cellulose |
| Gums |
| Novel manufactured oligosaccharides |
| Enzymatic |
| Extraction |

Extraction → Identification of structural characteristics of compounds → Semi-systematic approach: Search string for each compound will be listed → At present: Collection of literature → Submission of manuscript: Q3/4 2017
Revealing the mechanistic role in human physiology and beneficial aspects of SCFA production in the gastrointestinal tract (GIT)

NEW activity:

Objectives

• **Systematic review** of the current evidence from in vitro, animal and human studies for the **biological significance of a saccharolytic fermentation pattern and SCFA production** with prebiotic consumption.

• **Description of possible underlying mechanisms** and postulate hypotheses by combining scientific evidence from various research areas.

• Identify gaps in evidence and propose research strategies **to achieve wider acceptance of SCFA production as health benefits**

Q3 2018 – **Workshop** (consensus meeting) with external experts
Probiotics Task Force

Probiotics – Interplay with Intestinal Barrier Function

Objectives
Examination of the intestinal barrier, its role in health and disease and the potential impact of probiotics on function.

Three manuscripts were developed
Homeostasis of the Gut Barrier and Potential Biomarkers; Wells et al. [accepted]
Human Intestinal Barrier Function in Health and Disease; König et al., 2016 [published]
Can probiotics modulate human disease by impacting intestinal barrier function? Bron et al., 2017 [published]

Dr Tobias Recker
Mechanisms of Probiotic Action

Objectives

• Investigate and evaluate current knowledge about the mechanisms of probiotic action
• Link health benefit, physiological function and probiotic mechanism
• Identify gaps in research and directions for future research

Potential upcoming activity
Prediction of individual responses to (probiotic) interventions
Functional Foods Task Force

“Developing tools (and materials) to facilitate the determination of the scientific substantiation of the benefits of foods in relation to maintenance and improvement of health and wellness.”

Current Activities

• Oral and Systemic Health Resilience
• Exploring the Role of the Major Gut Microbiota Clusters on Nutritional and Functional Benefits of Nutrients and Non-nutrients
Current Activity
Exploring the Role of the Major Gut Microbiota Clusters on Nutritional and Functional Benefits of Nutrients and Non-nutrients

Manuscript I – Systematic review

• Effects of IM on selected nutrients and non-nutrients (energy, carbohydrates, proteins, lipids, fibres & polyphenols);

• Major role in transformation of dietary substrates; Limited human data (excl. fibres & polyphenols); Results not always consistent across studies & methodological limitations/differences in IM analysis make comparisons difficult; Non-digestible component not well characterised;

• Need for controlled human studies + well-defined dietary substrates + omic-based technologies to characterise/ measure IM & function; Deeper knowledge of metabolic activities & interactions of the IM holds considerable promise in relation to host health.
Current Activity
Exploring the Role of the Major Gut Microbiota Clusters on Nutritional and Functional Benefits of Nutrients and Non-nutrients

Manuscript II – Rowland et al. Gut Microbiota Functions - Metabolism of Nutrients and Other Food Components

1. Review of the main gut microorganisms and microbial pathways associated with the metabolism of dietary carbohydrates, proteins, plant polyphenols, bile acids, and vitamins;

2. Review of the methodologies, existing and novel, that can be employed to explore metabolic pathways of gut microbiota. These include mathematical models, -omic techniques, isolated microorganisms, and enzyme assays.

Accepted
NAP on ‘Specific Guidelines for the Design and Conduct of Human Gut Microbiome Intervention Studies’

Aim of the New Activity
To propose a set of specific guidelines for the design and conduct of human microbiome interventions studies:

i) effects of GIM on metabolism & bioavailability of nutrients and non-nutrients,
ii) effects of diet on GIM composition & activity and
iii) effects of diet-induced changes of GIM on human health.

• NAP builds on the conclusions of the workshop in Dec 2015
• Kick-off meeting by end Q2 2017
“Omics” analysis

- High resolution “omics” data – apples are different to oranges
- Within the data, being red is highly correlated with being an apple
“Omics” analysis

• Doesn’t always make biological sense!
METABOLIC TRANSFORMATION OF APPLE POLYPHENOLS IN THE HUMAN BODY

Kajetan Trost, Maria M. Ulaszewska, Fulvio Mattivi
Fondazione Edmund Mach + INRAN Rome

• a cross-over blinded human acute feeding study Crispy Pink apple variety juice

• 12 healthy volunteers, 2 day “white” diet run

• one dose of 250 ml of non-reconstructed cloudy apple juice (control) in fasted state

• 250ml apple juice enriched with an apple extract (0.75 g) containing all four groups of apple polyphenols (treatment) in fasted state

• Two week “wash-out” between treatments

• Blood (0 to 5 hr & 24hr), urine (24 hr) & faeces

• Targeted and untargeted LC-MS based metabolomics & 454-pyrosequencing
Different apple derived metabolites show distinct nutri-kinetic profiles in blood and urine.

**DIHYDROCHALCHONE METABOLITES**
Phloretin glucuronide

**CHLOROGENIC ACID METABOLITES**
Feruloylquinic acid

**(EPI)CATECHIN METABOLITES**
(Epi)catechin-methyl sulfate

**CATECHOL METABOLITES**
Methylcatechol sulfate

**CINNAMIC ACIDS METABOLITES**
Ferulic acid sulfate

**VALEROLACTONE METABOLITES**
(Dihydroxyphenyl)-γ-valerolactone glucuronide

**VANILIC ACID METABOLITES**
Vanilic acid glucuronide sulfate

**PROPIONIC ACIDS METABOLITES**
Dihydroferulic acid sulfate

**HIPPURIC ACIDS METABOLITES**
Hippuric acid

*** p value <0.001; ** p value 0.01-0.001; * p value 0.05-0.01
Apple metabolites in 24 hr urine correlated with microbiota profile
Apple metabolites in plasma (5 hr) correlated with microbiota profile
Going beyond correlation analysis.
Efficiency of internal combustion engine.
Efficiency of internal microbiota engine.

Modern Western-style Diet microbiota

- Energy, Metabolites, Nutrients, Regulation of host immune and metabolic processes

Mouth

Faeces
Efficiency of internal microbiota engine.

- Energy, Metabolites, Nutrients, Regulation of host immune and metabolic processes
Nutri-kinetics of challenge foods before and after microbiota modulation – bariatric surgery

- High end metagenomics (strain level, Scholz, Donati, Segata)
- Targeted & Untargeted MS based metabolomics (Mattivi, Vrhovsek)
Nutri-kinetics of challenge foods before and after microbiota modulation – prebiotics

Post-prandial, microbiota metabolite flux
• Aims….. to establish circulating BA profiles as biomarkers of health, modulated by diet which reflect a change in metabolic health.

Bile salt hydrolases (lactobacilli, bifidobacteria)

Bile acid chelating/modifying, probiotics, prebiotics, polyphenols

• RoCAV cohort Varese, Italy (4000 CVD at risk population)

• Mechanistic study Reading, UK microbiota dietary modulation, BA profiles and BA signaling, Chronic (8 weeks) & acute postprandial BA response.

• Long-term (18 month), RCT, BGU, Israel. (n=300), targeting metabolic risk, cognitive function, microbiota and BA profiles in pre-diabetics.

• BA cell signalling (UCC)
“You are what you eat – so are your gut bugs!”

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- Fulvio Mattivi, University of Trento (C3A, CAFE)
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Traceability

Sensory Quality

Nutrition and Nutrigenomics

Metabolomics

Department of Food Quality and Nutrition
In the beginning………… there was man
More than the sum of our genes