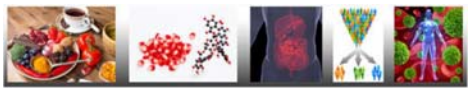
POSITIVe NEWSLETTER

EUROPEAN COOPERATION IN THE FIELD OF SCIENTIFIC AND TECHNICAL RESEARCH



ISSUE IV, DECEMBER 2016

WELCOME

We have got to the 4th edition of our POSITIVe newsletter, December 2016 !!!! Right in the mid-period of the Action. We would like to use this occasion to wish you all a joyful Christmas time and a wonderful New Year full of happiness. We also want to congratulate everybody for the huge amount of work carried out so far and the many contributions that have been done and have promoted the excellent progress of the Action.

As listed in our index, this issue summarizes the past recent conferences & activities of the Action, presents the STSMs carried out by the ECIs this year, as well as some of the latest publications. It also brings to your attention some coming meetings and the new training school. We can also read a new and interesting opinion of our Scientific Expert and Get to Know some more of our partners in the Action.

We hope you enjoy it!

IN THIS ISSUE:

NEWS

FOOD BIOACTIVES AND HEALTH CONFERENCE 13-15, September, 2016, Norwich, UK

The 1st Conference on Food Bioactives & Health (FB&H) was held at the John Innes Conference Centre, Norwich Research Park, Norwich (UK), from the 13th to the 15th of the past September (2016). The Conference was chaired by Dr Paul Kroon from the Institute of Food Research (IFR) and was designed to put together the latest evidence that supports the benefit of consuming food derived bioactive compounds as well as the challenges that still need to be solved and the opportunities for future research and development on functional foods.

The FB&H Conference also hosted the 2nd Scientific Workshop of the COST Action POSITIVe. The complete programme, gallery of pictures and the main presentations of the conference can all be seen at: http://www.fbhc2016.com/ .

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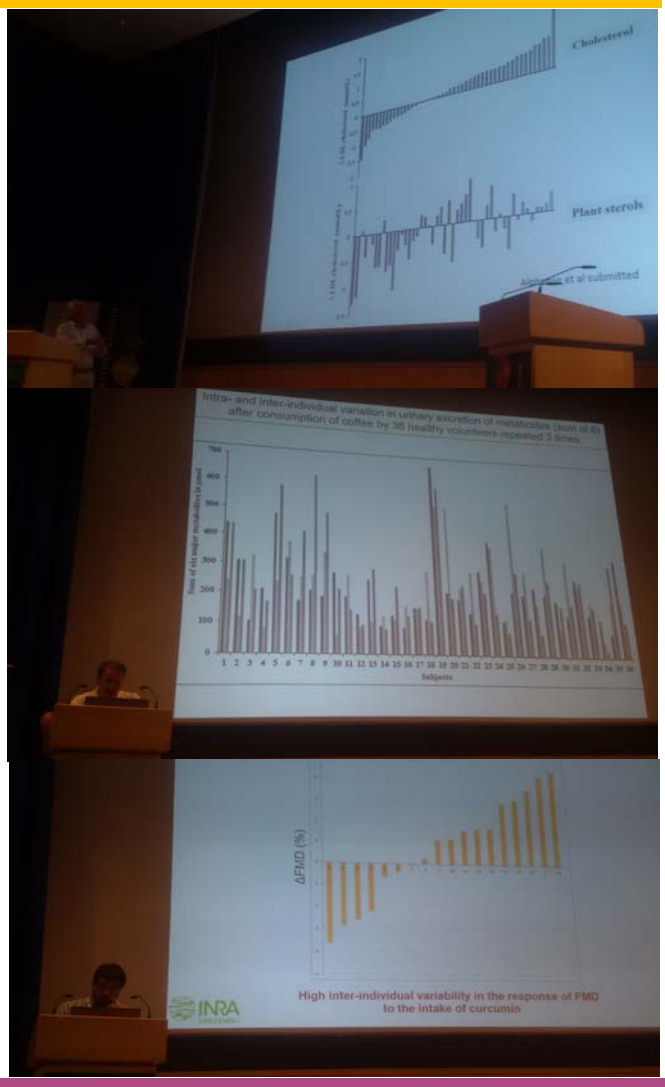
RESEARCH HIGHLIGHTS

Briefly, the talks presented at this FB&H conference dealt mostly with the effects of food bioactives on cardiometabolic health, brain function, cancer, gut health, etc, with a main focus on human intervention studies. The mechanisms of absorption, metabolism and their connection with the potential mechanisms of action were also covered by different presentations. Of special interest, there were also some presentations about the important interaction between colonic microbiota and the metabolism of food bioactives as well as about the human metabolic variability and differences in the responses from different groups of individuals.

2nd POSITIVe Scientific Workshop (Norwich, UK, 15 September 2016) "Inter-individual variation in response to food bioactives"

On Thursday the 15th of September the FB&H conference was entirely devoted to '*Inter-individual variation in response to food bioactives*', a session that constituted the 2nd Scientific Workshop of the POSITIVe COST Action. The detailed programme of this scientific session can be found at : https://www6.inra.fr/cost-positive/Events/2nd-Scientific-Workshop-Norwich-2016



The first talk of this workshop was offered by Dr Peter Jones, invited speaker from the University of Manitoba, who presented some of their latest results on inter-individual variation in response to lipid-lowering sterols and PUFAS with a focus on genetic factors, i.e. genes and SNPs, that have an impact on this response. Following his talk, several members of POSITIVe also presented their research dealing with inter-individual variation and factors affecting it. For example, Dr Anne Marie Minihane from the UEA in Norwich spoke about the role of the APOE genotypes in cardiovascular health in response to fish oil intake or, Dr Gary Williamson from the University of Leeds spoke about intra– and inter-individual variability in the metabolism of coffee phenolics. Several other partners also presented some of their latest results and some of the work carried out within POSITIVe in relation to inter-individual variability in metabolism and responses.

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4th COST Action POSITIVe Meeting, 15-16 September, 2016
Institute of Food Research, Norwich, UK

Work Group 1
Leader: Tom VAN DE WIELE
Co-leaders: Claudine MANACH & Rikard LANDBERG

As in previous occasions, the 4th WG1 meeting started off with several presentations by partners with an update of the progress carried out in their respective tasks. The leaders of different subgroups, Torsten Bohn (Carotenoids subgroup), Claudia Santos (Flavonols subgroup) and Rikard Landberg (Lignans subgroup), presented summaries of the reviews completed and the draft papers that are already submitted, ready or nearly finished. These articles review the current literature on carotenoid, flavonol and lignan metabolism and the factors affecting ADME for these compounds. Of particular interest, an important role of the microbiota in the lignan metabolism has been established. Additionally, future topics to deal with were also introduced by the subgroups leaders, such as the continuation of the initiated meta-analysis, the need to clarify the metabolic pathways for carotenoids or the progress of a study looking at factors affecting enterolactones concentration in plasma.

Maria Bronze (Metabolomic subgroup) informed about the *Multiplatform Coverage Test*. A list of 50 compounds will be used to prepare two test-solutions. The mixtures and the SOP to follow will be sent to all the participants that will analyze the samples in their own laboratories. There was a general discussion about the final goal of this Cooperative Test which is to establish a consensus multiplatform methodology to cover the analysis of all phytochemical metabolites in future metabolomics studies. An additional outcome of these studies will be the comparison between NMR and MS approaches.

Tom Van de Wiele (Microbiome subgroup) exposed the difficulties found in the drawing of the complete metabolic pathways for the different compounds due to a general lack of information. Then, a reductionist approach has been proposed to focus only on the crucial rate limiting steps of these pathways. A template will be distributed to help with this task.

After constructive discussions within the group, it was concluded that the next actions within each subgroup will be to collect information on crucial absorption and metabolic steps and to identify biotransformation enzymes and transport proteins. Comparison to pharmacogenomics studies was proposed as a help.

Finally a STSM in the microbial variant subgroup was proposed.

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Work Group 2
Leader: Ana RODRIGUEZ-MATEOS
Co-leaders: Eileen GIBNEY & Dragan MILENKOVIC

Meta-analysis subgroup

Eileen Gibney initiated the 4th WG2 meeting in Norwich by presenting a summary of the ongoing activities, the current outputs and the future initiatives. Regarding the meta-analysis of cardio-metabolic variables, some papers have now been accepted (a position paper, a review on inter-individual variability in biological responses to the consumption of food bioactives) or submitted for publication (systematic review meta-analysis protocol, an article on inter-individual variability in cardio-metabolic markers in response to the intake of flavonols).

Other meta-analysis looking at specific groups of compounds and cardio-metabolic variables are still ongoing. Emilie Combet and others discussed various common problems occurring during data extraction and the need for independent double check of the data and changes in the data-extraction templates. During the meeting, Paula Pinto and Antonio González-Sarrías presented an update of the articles prepared or in preparation on the effects of flavonols, anthocyanins and ellagitannins on cardiometabolic endpoints. Other participants also presented an update of the progress of their respective meta-analysis on different group of compounds. It was agreed not to start any other meta-analysis but to complete and publish the ones already initiated. Further, a Data Collaboration Agreement has been elaborated and circulated to everybody for comments. It was discussed how to approach the next stage of the analysis and how to access datasets. Datasets analysis was encouraged to be carried out through STSMs.

Cell & Molecular Targets subgroup

Dragan Milenkovic, leader of the *Cell & Molecular Targets* subgroup, also summarized the activities done so far. The three subgroups within this one: human, animal and *in vitro* studies have advanced in their work. In the animal group, all potential papers have been evaluated and those that complied with the criteria already selected. There will be a template prepared and circulated for data extraction. A similar point has been reached in the *in vitro* studies subgroup. In the human subgroup, an important number of papers have been identified and classified into an Excel file ready for the next step. A template for data extraction will also be prepared and circulated in the next months. There were several discussions on how to prepare this template and how to enhance the data extraction. Other issues such as the inter-species differential metabolic capacity, or how to tackle the analysis of the data including bioinformatics approaches were also commented.

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Work Group 3
Leader: Baujke DE ROOS
Co-leaders: Marina HEINONEN

The 2nd WG3 meeting took place in Norwich. There, Dr. Baujke De Roos had the opportunity to present to all the participants the main ideas and activities already initiated and those to be further developed by this group with regards to the preparation of strategies to disseminate the Action aims and results to different stakeholders and other end-user groups. A questionnaire which was already sent to different end-users has already provided a number of responses although many more are needed before it is possible to get a good overview of the opinions of these stakeholders and user groups. Hopefully, a lot more will be gathered and presented during the next meeting in Poland.

There were also some general discussions about other strategies such as the preparation of small videos and webinars describing successful interactions and projects between researchers and industrial partners. There were several offers by various partners to prepare some of these videos that should be ready for February. In addition, other strategies presented and discussed were:

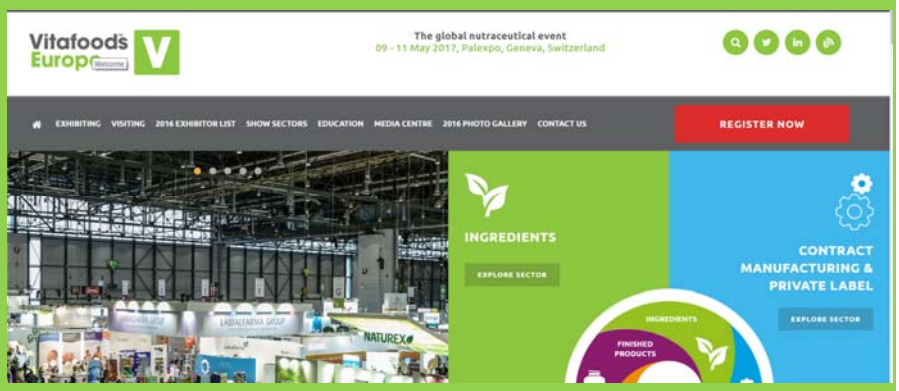
- the possibility of a COST scientist to present the scientific outcomes and deliverables of POSITIVe in a major meeting directed to stake-holders and end-users
- the preparation of a white paper to disseminate POSITIVe amongst the Agro-food industry, on-line forums, etc
- the development of an easy-to-use on-line tool to allow stakeholders find the information that relates foods-ingredients-bioactive compounds-proven beneficial effects-interindividual responses. This will be based on the results of all the meta-analysisi and activities that are being developed within the Action
- the writing of a final 'roadmap' will be undertaken later on in the Action.

OF INTEREST TO THE POSITIVe COMMUNITY

09 - 11 May 2017, Palexpo, Geneva, SWITZERLAND

VITAFOODS EUROPE

http://www.vitafoods.eu.com/



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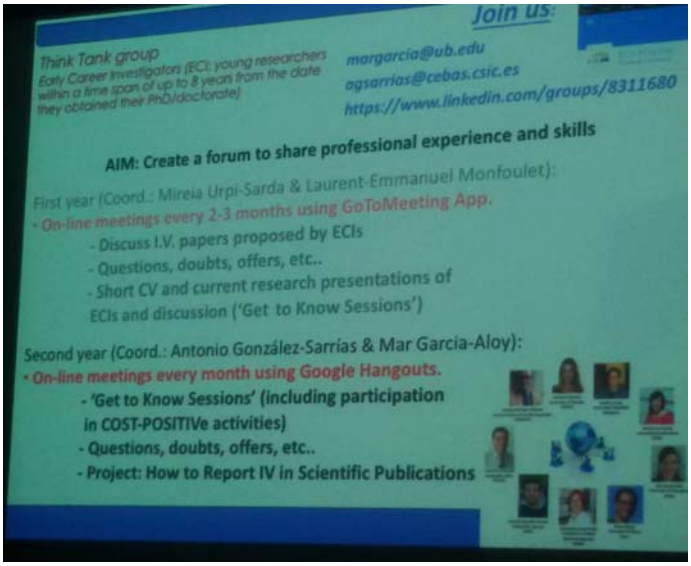
Think Thank Group

Although there was not an official Think-Tank-Group (TTG) meeting in Norwich, the current coordinators of the TTG, Dr. Mar García-Aloy and Dr. Antonio González-Sarrías, attended the meeting and had the opportunity to present a summary about the progress of the Early Careers Investigators (ECIs) contributions to the general objectives of POSITIVe.

They specifically referred to the development of one of their current and very interesting projects: the elaboration of a manual on '*How to Report Interindividual Variability in Publications*' where one of the main goals is to propose and gather general guidelines, suggestions, recommendations and a checklist to cover the requirements necessary to correctly report data concerning inter-individual variability in the most accurate way for future publications. Eventually, this information will be published as an opinion paper.



In addition to this, the activities of the TTG include monthly webinars where ECI members present a short introduction about the research that they are carrying out in their own institutions. These webinars allow for a nice and friendly interaction between the ECIs, while increasing their knowledge of the techniques and research areas of each participant. This information could be very useful to any ECI for future work and collaboration or should they be interested in applying for any specific STSM.

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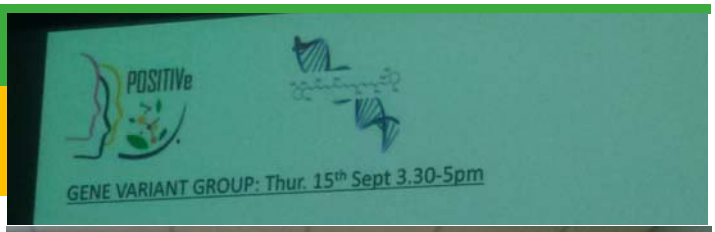
Gene Variant Group
Leader: Anne Marie MINIHANE



The gene variant group (GVG) led by Dr. Anne Marie Minihane had its first gathering *via* teleconference on the 8th of the past July. During this call Anne Marie presented an overview of the main issues that should be investigated and discussed within this subgroup of the Action. The GVG will focus on the impact of genetic variability of metabolic enzymes in the ADME of flavonoids. Genetic variation is also likely to have an effect on the specific targets of these compounds and biological responses triggered by their consumption. Nevertheless, the data in the literature about all this are still limited and need to be rechecked and expanded. There were a number of points and activities that were considered for further discussion in Norwich.

During the 1st meeting of the GVG in Norwich, Anne Marie Minihane initiated the session with a scientific overview of the relevance of genetic variance in the role of food bioactives intake on human health. After the short introduction, Anne Marie herself, Charles Demarchelier and Julie Dumont exposed to the audience their experiences with some of their respective human intervention trials investigating the impact of genotype, as well as with the different approaches and analyses applied.

These presentations were followed by a general discussion about what may be the best future strategies to follow and how to focus the work and research to do. It was suggested to concentrate on a few compounds and specific metabolic enzymes. The GVG and the WG2 will collaborate in the preparation of a review article on already known genetic variants of relevance for bioactive compounds and cardiometabolic end-points and will establish a database of candidate genes. These genes and variants will be selected from the reviews and analyses currently being developed in the WG2 Cellular & Molecular targets subgroup.

The GVG will also collaborate with other Action members in the preparation of the second Training School next September.

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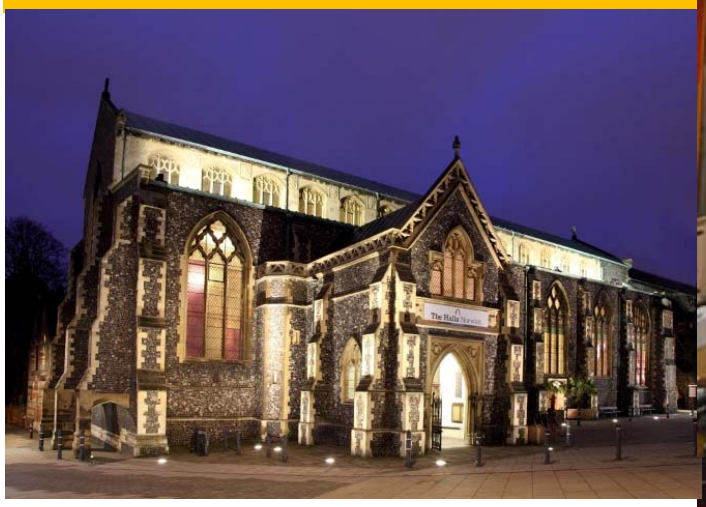
SOCIAL EVENTS



During the meeting in Norwich, a gala dinner was held at Saint Andrews Hall, a magnificent building located in the heart of Norwich.

On this occasion, the Hall offered to all the participants at the Food Bioactives & Health Conference as well as many of the POSITIVe partners that attended this conference a delightful meal that included, among other things, a tasty and 'healthy' super-brocculi soup. After the dinner, many brave participants volunteered to entertain the rest of the people with dancing. Great fun!!!!

SAVE THE DATE

21-22, February 2017

COST Action POSITIVe 5th Meeting

Organized by Prof. Mariusz Piskula, Dr. Wiesław Wiczkowski, & Iwona Kieda

Institute of Animal Reproduction & Food Research PAS

Olsztyn, Poland

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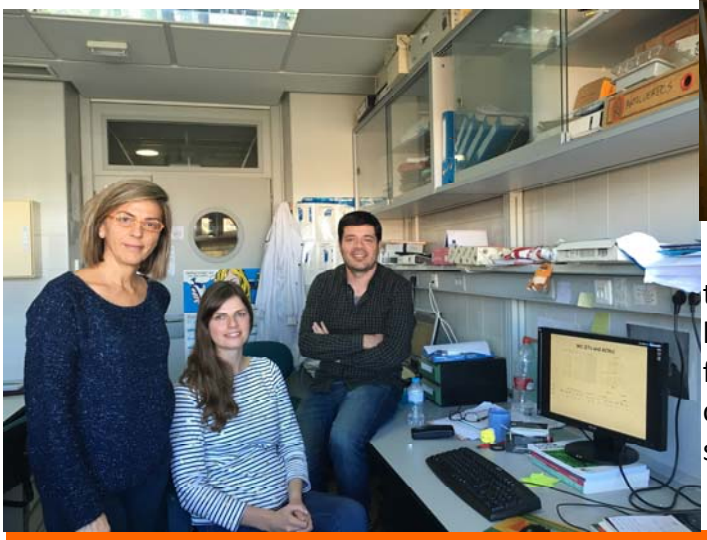
SHORT TERM SCIENTIFIC MISSIONS

KAREN CHAMBERS from the UK went to CEBAS-CSIC, Murcia, SPAIN

I took part in a STSM in November at CEBAS-CSIC, Spain with Dr. Mayte Garcia Conesa and Dr. Antonio Gonzalez. The STSM was undertaken in order to complete meta-analysis related to the working objectives planned within the COST Action. The meta-analysis included evaluating the effects of ellagitannins and anthocyanins on cardio-metabolic biomarkers and subsequently determining the effects of inter-individual variability.



I would recommend a STSM in order to foster collaboration and expand knowledge between groups. Although I could not speak Spanish, this was not a problem in the lab at least. Mayte took me on a night time tour of the city, which is very beautiful.

I also took a trip to nearby Cartagena to visit the Roman Theatre. By the end of the experience I had learnt a few essential phrases, like how to ask for wine (red of course), how to ask for tea with cold milk and most importantly how to say “can you speak English”.

STSM Topic:
Training in meta-analysis to assess the impact of ellagitannins and anthocyanins on cardiometabolic biomarkers

Three weeks of solid data entry were undertaken to complete all of the outcomes for cardio-metabolic markers (BMI, WC, FMD, HOMA, Hb1ac, SBP, DBP, Insulin, Glucose, TGs, LDL, HDL and total cholesterol). A further week was spent determining subgroups for the inter-individual variability and performing the meta-analysis. The data was segregated according to several outcomes such as gender, smoking, and disease status. The STSM was a great opportunity for me to learn how to use the Comprehensive Meta-analysis V3 software. I have been inspired to further develop my statistics knowledge, particularly related to Bias.

Muchas gracias Karen!!!!

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SHORT TERM SCIENTIFIC MISSIONS

NEVENA KARDUM from Serbia went to

My STSM was placed at the Institute of Food Research (IFR), in Norwich, UK. My stay commenced the 12th of June 2016, but the arrangements for this visit started some time earlier. My main problems were related to the all the difficulties I had to overcome in order to obtain the Visa to be able to enter the UK. Because of this, my STSM had to be postponed more than once. But now, looking back to all this trouble I can happily say, it was all worthy. Coming to Norwich and IFR was indeed one of my best decisions and all the problems paid off as soon as I arrived. It was nice to know that Norwich is a twin city with my hometown Novi Sad and this helped me and made me feel less homesick.

Working at IFR has enriched my professional as well as my personal life. During this visit, the main task I had to accomplish was the analyses of a number of urine samples that were obtained during a RCT in which the volunteers were supplemented with Aronia juice. The work gave me the opportunity to be trained in advanced LC-MS/MS techniques. What's more, I had the opportunity to learn new methods and work with some equipment that is not currently available at my Home Institute. I went to the UK with some general misconceptions about this country: the bad weather and the very reserved English people. But, luckily, I was completely wrong.

My working experience at IFR brought me closer to the British people as well as to the people and culture of Poland, Italy, Mauritius, and other countries. I was also very fortunate to have the kindest Land Lord and Land Lady that I could ever wish for.

They provided me with a very nice and warm home environment and plenty of beautiful food. Tony and Dawn also shared with me their everyday life and showed me British traditions and beautiful landscapes around. Last, but not least, I had the opportunity to visit some good friends in the UK and enjoy several weekends in Leeds, Reading, and London.

Overall, a wonderful experience! Cheers.

STSM Topic:

Bioavailability of Aronia juice polyphenols as determinant of inter-individual variation in their effects on platelet function

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SHORT TERM SCIENTIFIC MISSIONS

FRANCISCO MADRID-GAMBIN from Spain went to the Swedish University of Agric. Sciences, Uppsala, SWEDEN

STSM Topic:
Development of methodology for plasma samples in the study of metabolic phenotyping

The Short-Term Scientific Mission grant allowed me to gain expertise in the processing of small volume urine/plasma/serum samples and also in the robust data analysis of these samples using NMR-based metabolomics techniques. The STSM was placed at Department of Food Science at the BioCenter of the Swedish University of Agricultural Sciences, with Dr. Rikard Landberg and Dr. Carl Brunius, where we applied untargeted analysis to urine and plasma/serum samples for the discovery of new biomarkers of intake.

Furthermore, the work carried out during my stay contributed to optimize several steps in the NMR-metabolomics workflow exploiting resources of the FOODBALL-JPI project, and also allowed the collaboration with the Swedish NMR center at the University of Gothenburg which, all together, improved my analytical skills substantially. More specifically, I explored and optimized the development of peak alignment algorithms, the double cross-validation of data and a more focused version of the statistical total correlation spectroscopy (STOCSY).

Last, but not least, this opportunity allowed me to discover how nice was to work with Rikard and Carl and how wonderful is Uppsala, “fika” and the Scandinavian places….

Statistics is fun! as Dr. Carl Brunius often said.

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SHORT TERM SCIENTIFIC MISSIONS

CHANDRA CHIRUMAMILLA from Belgium went to INRA, Clermont-Ferrand, FRANCE

STSM Topic: Biological interpretation of kinome generated data by Metacore® pathway analysis

The POSITIVe Short-term Scientific Mission (STSM) grant taken under the guidance of Dr. Dragan Milenkovic in the Unit of Human Nutrition at INRA, Clermont-Ferrand provided me with a huge experience in the analyses and understanding of complex data generated by Kinomic analysis as well as translating the results into a more meaningful biological interpretation using Metacore® pathway analysis tool. In addition to the pathway analysis software, I also had access to the *in silico* tool Nexus meteor® (Lhasam limited) that allows for prediction of the biotransformation of plant derived compounds in *in vivo* conditions. This may be relevant to understand the fate of plant compounds when not many experimental metabolic data are available.

My stay at INRA was not just limited to learning new *in silico* techniques, but also enabled me to perform some *in vitro* experiments. Using novel peptide microarray technology, we explored the molecular mechanisms underlying the cardioprotective effects of some plant flavanol compounds like epicatechin in the context of protein kinase signalling. The knowledge accumulated during my STSM stay not only allowed me to learn, but also to put forward the results obtained during my STSM stay in the form of a recently submitted research article. Apart from the purely scientific and experimental work, I also enjoyed the intellectually stimulating talks and feedbacks received from Dr.Claudine Manach, Dr.Dragan Mienkovic and Dr.Christine Morand. They were really helpful.

Last but not the least, I want to mention our enthusiasm to walk to Puy de Dôme from Clermont Ferrand on foot (although, in truth, we were only able to walk from Panoramique des Dômes to Puy de Dôme) and also to explore the city of Clermond-Ferrand itself, in the company of our English-to-French translator Natalia and another STSM student, Andreia Bento da Silva.

These were for me outstanding examples of cultural exchange !!!

FIRST ANNOUNCEMENT

Week 18-22 September, 2017, Alexandropolis (GREECE)

6th POSITIVe WG meeting & 3rd Scientific Workshop

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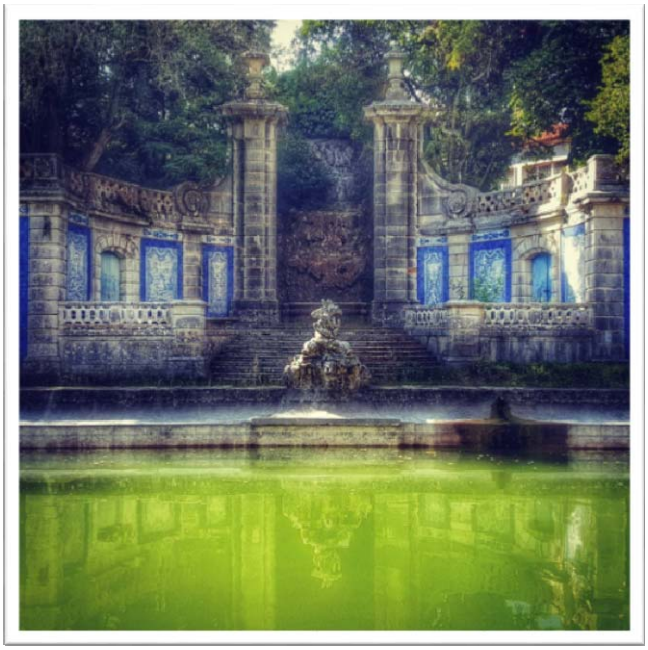
SHORT TERM SCIENTIFIC MISSIONS

VILLE KOISTINEN from Finland went to the University of Lisbon, PORTUGAL

I was sent for a short-term scientific mission to ITQB (Instituto de Tecnologia Química e Biológica) that belongs to the Universidade NOVA de Lisboa and is located in the city of Oeiras, about 15 kilometres from downtown Lisbon. My assignment was to prepare mixtures of phytochemical standards and carry out initial analyses on different Mass Spectrometry platforms in order to send the mixtures for further analysis in various analytical platforms across Europe. The idea was to create a small database of standards and their identification data along with information about their detection limit in each platform. Although the initial plan was to have at least some of this data ready by my arrival so that I could concentrate working on the data itself, the work was successful in forwarding the project and allowing me to get hands-on experience in working with various Mass Spectrometers.

Coming from the chilly Finnish October weather, +25 degrees in Portugal felt welcoming and like a small extension to the short summer I had in Finland. The stay was a very pleasant one with good food and inexpensive red wine, and my colleagues at the institute were awesome and helpful. I really felt like a special guest. I would especially like to thank Tiago who on my last day took me to see the historical city of Sintra and then drove me back to the airport with the heavy luggage full of wine.

I will certainly visit Portugal again, either for leisure or for more work !!!



FIRST ANNOUNCEMENT

2nd Training School

Nutrigenetics & Nutrigenomics, 2017

(more information about dates and programme will be available later)

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SCIENTIFIC EXPERT'S OPINION

Professor GARY WILLIAMSON
School of Food Science & Nutrition
University of Leeds, UK

Conducting a human intervention study is time consuming, costly and risky, especially if the trial lasts for months and requires large numbers of volunteers. Most of us involved in these trials have experienced some disappointing results at some point in our careers! A few years ago, we conducted a study over 3 months on 50 volunteers, taking many skin biopsies and using sophisticated measurements of skin health, but despite some promising results in a small study (1), numerous published animal studies and a plausible *in vitro* mechanism, the results showed no effect of a high dose of green tea supplements against UV damage (2). This could have been for several reasons, but one of the main limitations of studies on humans can be the variability in response between individuals. On closer analysis of the data, we could see that some volunteers exhibited a response, whereas others did not. Is this just experimental noise, or can we somehow separate the volunteers into subgroups and explain why they did or did not show an effect? The challenge here is to find a plausible mechanistic reason for allocating sub-groups, and not just separate the volunteers for our convenience. Sometimes we just need to accept that our beautiful theory really has been destroyed by ugly facts!

A personal view on the significance of inter-individual variability in studies on food bioactives

The variation between individuals can arise from numerous factors, such as gene polymorphisms, dietary history, gut microbiota composition and metabolic status. What is not known for bioactives is whether any inter-individual variability in response is correlated to an individual's bioavailability profile. In my experience, the extent of absorption of bioactives between subjects almost always varies by ~10-fold, however it is assessed. Logically we can then ask if the best absorbers of the active component exhibit the greatest biomarker response. One of the problems with food bioactives is that any biological response may be derived from several mechanisms from multiple active constituents.

It is also important to ask if a high responder or absorber is always high. We conducted a study where we assessed absorption and metabolism of phenolics from coffee, with a view to ranking 39 individuals in a continuum from high to low absorbers, thinking that we might then correlate this with health biomarkers. However, defining high and low absorbers was much more complex than we first envisaged. Chlorogenic acids from coffee give rise to numerous measurable metabolites and conjugates, as a result of metabolism by the small intestine, gut secretions, liver and gut microbiota. It was difficult to decide which metabolite (or sum of all?) to use to define a "good" absorber. Each participant was assessed by consuming the same amount of coffee in an identical procedure on 3 separate visits. We found that not only was there the expected inter-individual differences, but there was also a large intra-individual variation in the concentration of all metabolites excreted in the urine. This meant that we had to average the data from 3 visits in order to properly rank the participants. Most studies do not (or cannot) consider intra-

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SCIENTIFIC EXPERT'S OPINION

Sometimes with a robust effect, all or almost all of the individuals will respond. We can then consider how to exploit high and low responders. One of the earliest examples for bioactives was the suggestion that soy isoflavones would have a greater effect in those individuals who were able to make more equol (3). When we conducted an acute study examining the effect of a fruit paste on post-prandial blood glucose from bread, all 16 volunteers responded, and we were pleased to get an overall *p*-value of <0.001 for a human study (4)! However, even in this case, the response varied between individuals by ~2.5-fold. We are now designing further studies to see if these differences can help us to get mechanistic information *in vivo*.

So, how can we exploit inter-individual variation? Working on pre-characterised sub-groups with a particular response is one solution, for example on subjects with metabolic syndrome, well-defined polymorphisms, with an impaired response, or with at risk groups. Sometimes this is difficult if the active component is not known, if the effects are small or if the factors affecting the biomarker of interest are not well understood. We can also exploit data retrospectively if we can show that a particular effect is higher in certain types of individuals (bearing in mind the caveat above). If the study was not initially powered to show a significant effect in a sub-group, then this can be used to set the parameters for an appropriately powered second intervention study. One of the challenges for projects like POSITIVe is to work out additional ways to exploit data on individual variation, and in this way help to keep the costs of intervention studies manageable.

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RESEARCH DISSEMINATION

PUBLICATIONS

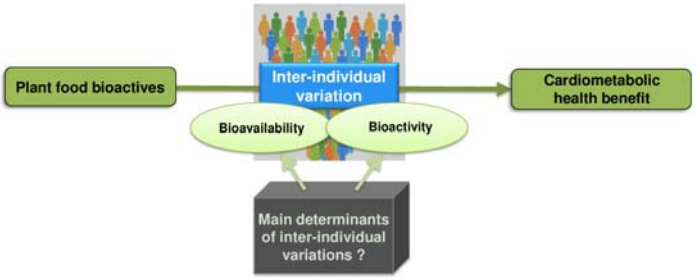
Mol. Nutr. Food Res. 2016, *00*, 1–16 DOI 10.1002/mnfr.201600557 1

REVIEW

Addressing the inter-individual variation in response to consumption of plant food bioactives: Towards a better understanding of their role in healthy aging and cardiometabolic risk reduction

Claudine Manach[1], Dragan Milenkovic[1]*, Tom Van de Wiele[2], Ana Rodriguez-Mateos[3], Baukje de Roos[4], Maria Teresa Garcia-Conesa[5], Rikard Landberg[6,7], Eileen R. Gibney[8], Marina Heinonen[9], Francisco Tomás-Barberán[5] and Christine Morand[1]*

Publication in *Molecular Nutrition and Food Research* of the first collaborative position paper addressing the objectives of POSITIVe. The paper examines the main factors likely to influence the individual responses to consumption of plant food bioactives, including those affecting bioavailability or bioactivity related to cardiometabolic health, and presents a range of perspectives for the future assessment and consideration of the human inter-individual variability.



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RESEARCH DISSEMINATION

PUBLICATIONS

AJCN. First published ahead of print November 23, 2016 as doi: 10.3945/ajcn.116.136051.

Narrative Review

The role of metabolism (and the microbiome) in defining the clinical efficacy of dietary flavonoids[1]

Aedín Cassidy and Anne-Marie Minihane*

Department of Nutrition and Preventive Medicine, Norwich Medical School, University of East Anglia, Norwich, United Kingdom

This recent review paper by Cassidy & Minihane (Am J Clin Nutr, 2016) is from POSITIVe partners: Dept of Nutrition & Preventive Medicine, Norwich Medical School, University of East Anglia (UK). It reviewed the current knowledge for the main subclasses of flavonoids, including anthocyanins, flavonols, flavan-3-ols, and flavanones, and concluded that current knowledge of the aetiology of the variability in flavonoid metabolism and how this affects health outcomes is limited. The key areas that were thought to require further research were:

⇒ To conduct adequately powered, longer term, clinical studies to determine the impact of age, sex, habitual diet, genotype, drug interactions, and the microbiome on flavonoid metabolism

⇒ To conduct trials to understand the bidirectional relationship between flavonoid metabolism and the microbiome; prospectively recruit participants to clinical trials on the basis of the extent of absorption and metabolism to establish dose-response relationships

⇒ To identify and validate a panel of robust biomarkers of flavonoid intake and subsequent metabolism that can be used to examine associations of bioavailable flavonoids with health outcomes in future prospective cohort studies

⇒ To further develop metabolomic data sets to assist in the development of biomarkers

⇒ To conduct hypothesis-driven research to investigate the impact of specific genotypes on flavonoid metabolism with a particular focus on variants in LPH, ß-glucosidases, phase I metabolism, and phase II metabolism, with prospective recruitment by genotype for associations established with the use of the retrospective genotype approaches

⇒ To conduct intervention studies to determine how food composition and flavonoid source affect bioavailability

⇒ To conduct trials in which metabolism and health outcomes are addressed simultaneously

Addressing these research gaps would provide the basis for the development of targeted dietary advice for subgroups who are likely to be most responsive and help us work toward the development of specific dietary guidelines for several dietary flavonoid subclasses.

AEDIN CASSIDY &
ANNE MARIE MINIHANE

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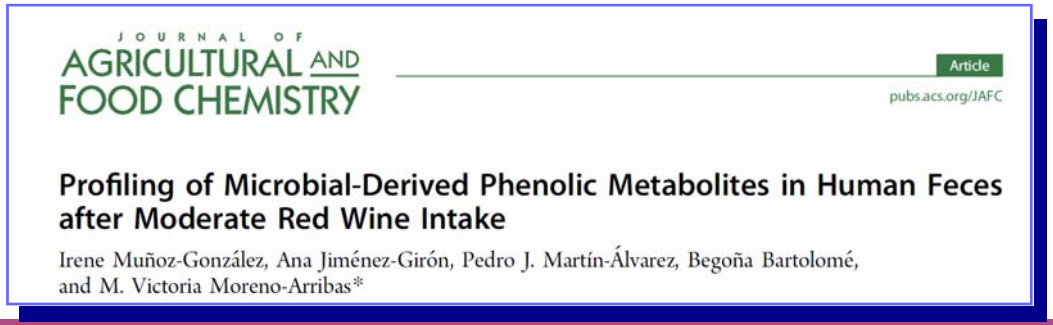
PUBLICATIONS

Interindividual variability in the interactions between wine polyphenols and gut microbiome

BEGOÑA BARTOLOMÉ & Mª VICTORIA MORENO-ARRIBAS

A current key issue regarding the health implications of polyphenols is their interaction with the microbiota, which has become a hot topic in order to improve nutritional strategies with potentially important health implications. Wine polyphenols comprising several classes of phenolic structures might be a good exponent of this potentiality. Recent scientific evidence suggests that wine polyphenols exert their effects through interactions with the gut microbiota, as they seem to modulate microbiota and, at the same time, are metabolized by intestinal bacteria into specific bioavailable metabolites. Microbial metabolites are better absorbed than their precursors and may be responsible for positive health activities in the digestive system (local effects) and, after being absorbed, in tissues and organs (systemic effects). Differences in gut microbiota composition and functionality among individuals can affect polyphenol activity and therefore their health effects. There is a great inter-individual variation in the profile and/or content of phenolic metabolites in physiological fluids (urine, plasma, faeces) after a controlled intake of phenolic-rich foods. Analysis of the fecal composition not only provides valuable information regarding microbial produced metabolites and unabsorbed dietary components, but also clarifies whether the functional stability of the gut ecosystem could undergo modifications after dietary interventions.

Within the general objective of deepening the effects of moderate wine consumption on gastrointestinal health, Muñoz-González *et al*. (*J.Agric Food Chem*. 2013., *61*, 9470-9479) evaluated changes in phenolic metabolites in human feces, after moderate and regular consumption of red wine in healthy volunteers. A controlled and randomized trial study involving 41 healthy volunteers (33 intervention and 8 control subjects) was performed in order to establish changes in the microbial-derived phenolic metabolite profile of feces after moderate consumption of red wine (250 mL/day, 4 weeks). Out of the 35 phenolic metabolites identified, 10 compounds (mainly benzoic and 4-hydroxyvaleric acids) showed statistically significant increases ($P < 0.05$) after the wine intake. Also, the total phenolic metabolites content was significantly ($P < 0.05$) higher in the samples after the wine intake (625 ± 380 µg/g feces) in comparison to the samples before (358 ± 270 µg/g feces). Most interestingly, and despite the great inter-individual variability observed, a tentative distribution of the individuals into 3 groups according to the levels of metabolites in the faeces: low, medium and high metabolizers (<500, 500-1000, and >1000 µg/g feces, respectively) by their capacity to metabolize wine polyphenols has been established. These results suggest different human phenotypes in relation to the ability to metabolize wine polyphenols, as it has been described for polyphenols found in other foods.


JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

Article

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Profiling of Microbial-Derived Phenolic Metabolites in Human Feces after Moderate Red Wine Intake

Irene Muñoz-González, Ana Jiménez-Girón, Pedro J. Martín-Álvarez, Begoña Bartolomé, and M. Victoria Moreno-Arribas*

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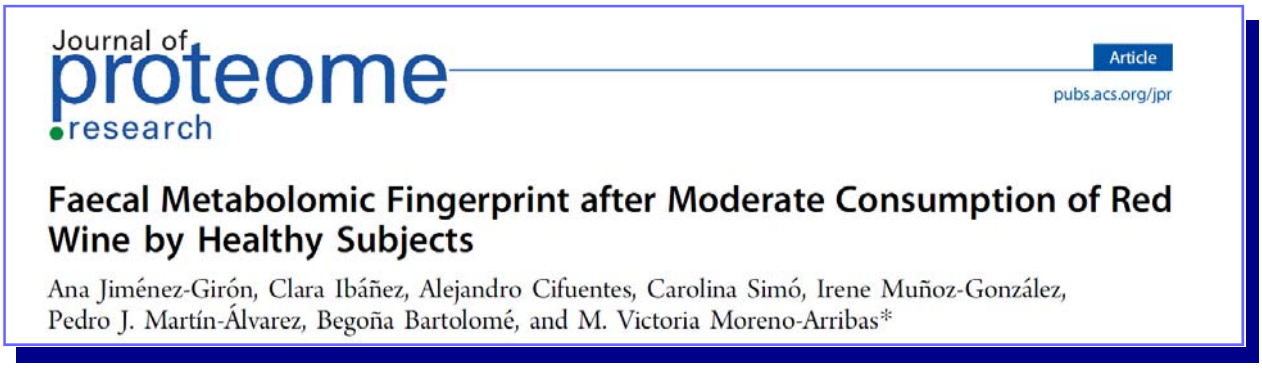
In an effort to improve our understanding on the biological effects that phenolic compounds (including red wine polyphenols) exert at the gut level, furthermore different omics studies were undertaken to characterize the metabolome (Jiménez-Girón *et al*., *J. Proteome Res.* 2015**,** *14* ,897-905) and the metagenome (Barroso *et al*., Mol. Nutr. Food Res., 2016, doi 10.1002/mnfr.201600620) of human faeces after moderate consumption of red wine by these healthy subjects for 4 weeks. A non-targeted metabolomic approach based on the use of UHPLC-TOF MS was developed to achieve the maximum metabolite information of 82 human faecal samples. After data processing and statistical analysis, 37 metabolites were related to wine intake from which 20 could be tentatively or completely identified, including: I) wine compounds, II) microbial -derived metabolites of wine polyphenols, and III) endogenous metabolites and/or others derived from other nutrient pathways. After wine consumption, faecal metabolome was fortified in flavan-3-ols metabolites. Also, of relevance was the down regulation of xanthine and bilirubin derived metabolites such as urubilinogen and stercobilin after moderate wine consumption. As far as we know, this is the first study of the faecal metabolome after wine intake. On the other hand, concerning the metagenomic study, the composition, diversity, and dynamics of fecal microbiota before and after 1 month of wine consumption were analyzed. The 16SrDNA sequencing allowed detection of 2324 phylotypes, of which only 30 were found over the 0.5% of mean relative frequency, representing 84.6% of the total taxonomical assignments. The samples clustered more strongly by individuals than by wine intake or metabotypes, however an increase in diversity associated to wine intake was observed.

Taking into account the aims of POSITIVe, further studies are now needed to investigate the large inter-individual variations on gut metabolism of wine polyphenols and, most importantly, getting stratification of individuals based on specific gut microbiota functional features to obtain positive polyphenol-mediated health effects.


Journal of proteome research

Article

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Faecal Metabolomic Fingerprint after Moderate Consumption of Red Wine by Healthy Subjects

Ana Jiménez-Girón, Clara Ibáñez, Alejandro Cifuentes, Carolina Simó, Irene Muñoz-González, Pedro J. Martín-Álvarez, Begoña Bartolomé, and M. Victoria Moreno-Arribas*


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RESEARCH ARTICLE

Phylogenetic profile of gut microbiota in healthy adults after moderate intake of red wine

Elvira Barroso[1], Irene Muñoz-González[1], Esther Jiménez[2,3], Begoña Bartolomé[1], M. Victoria Moreno-Arribas[1], Carmen Peláez[1], María del Carmen Martínez-Cuesta[1] and Teresa Requena[1]

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RESEARCH DISSEMINATION

Presenting POSITIVe to the Spanish public: THE WEEK OF SCIENCE at CSIC

The Department of Food Science & Technology at CEBAS (Murcia) and the Research Institute on Food Science CIAL (Madrid), both part of the Spanish National Research Institution CSIC, participated in the 2016 edition of 'The Science Week' the past November. The events took place in the city gardens of the 'Malecon' near the river in Murcia and, in the CIAL Institute at the University Autónoma, Campus of Cantoblanco in Madrid, respectively.

During the event, members from both Institutions presented the workshop entitled 'The role of Food in Health and the reasons behind the differences between individuals'. During the activities, the researchers talked to the consumers about general aspects of the investigation they carry out: Food & Health, Functional Foods and Nutraceuticals, Cardiometabolic Diseases and the issue of the Interindividual Variability and the POSITIVe project. In addition, and by means of a questionnaire, we asked the participants about their appreciation of a healthy diet and of our response to diet. We also offered the attendees the possibility of having some cardiometabolic variables (BMI, waist circumference, blood pressure) measured. It was very interesting to chat with many of them and to find out that an increasing number of people, both younger and older, are truly concerned about their metabolic health and are willing to learn more about how to promote health with the diet.

The week of the Science became, once again, an excellent scenario of communication and interaction between the scientific community and the general public.

There is a great opportunity within POSITIVe to prepare informative documents and workshops that will be of great benefit to the general public and their knowledge and practice of a healthy diet.

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GET TO KNOW YOUR POSITIVe PARTNER

SENIOR RESEARCHERS

CHRISTOS KONTOGIORGIS

Democritus University of Thrace, GREECE

What is the focus of your research?

Our Laboratory of Hygiene & Environmental Protection, Department of Medicine, University of Thrace, Greece, is focused on Epidemiological and Nutritional Studies. We run studies on the Greek Population regarding habits, attitudes and compliance with the Mediterranean diet. We also work on natural products used by the Greek population as a whole product or as an ingredient in other products and we evaluate their antioxidant and antimicrobial activity.

In what countries/organisations have you studied or worked?

I graduated in Pharmacy, at the Aristotle University of Thessaloniki, Greece. I continued with my PhD Studies at the same Faculty under the supervision of Professor Dimitra Hadjipavlou-Litina. From 2005 – 2013 I worked as a Postdoctoral Researcher in National and European Calls and as temporary Lecturer. From 6/2016 - 9/2016 I did some postdoctoral studies in Department of Pharmacy in the University of Maryland, U.S.A. on the use of natural products (coumarins) against Alzheimer's disease development under the supervision of Dr Luo Yuan. From 2/2010 – 9/2011, I was a postdoctoral researcher at the Imperial College and the King's College of London, UK.

What has been the greatest achievement in your career?

My collaboration with many different research groups of different scientific areas. I truly believe that a researcher should continuously adjust to new demands and to keep opened to new challenges and to as many options as possible.

Which is your favourite paper you have written/co-authored and why?

I am really proud of two of my articles, and not just because of the journals they were published in but mainly because of they meant to me the start of new research areas. The first one is the paper entitled: "Coumarin derivatives protection against ROS production in cellular models of Abeta toxicities. Free Radic Res. 2007 Oct;41 (10):1168-80". This was the first research project I was fully responsible for. I developed and completed the work following my own personal vision. I'm really thankful for this paper to Dr Luo Yuan who gave me the opportunity to carry out the project in his Department of Pharmacy, University of Maryland, U.S.A.. The second most important paper is: "Studies on the antiplatelet and antithrombotic profile of anti-inflammatory coumarin derivatives. J Enzyme Inhib Med Chem. 2015 Dec;30(6):925-33". The relevance of this paper in my career was that I was also entirely responsible for the project and for the organization and schedule of the work in collaboration with many different research groups.

Who is/was your most influential mentor/colleague and why?

Professor Dimitra Hadjipavlou-Litina is the most important mentor during my career. Not only because of her supervision during my PhD studies but also because of the way she treated me and showed me how to collaborate with other researchers and how to adapt my research background and skills to new projects and research areas.

What is your advice for young scientists?

The only advice that I can offer is that they should pursue their dreams and follow their own inspiration. There should be no fear for new ideas or new research areas. The way to progress in research is full of sacrifices, disappointments but also success and happiness. Whoever is really prepared to do this will be the one to be distinguished.

Where is your favourite place in the world and why?

My birth place, Thessaloniki in Greece, is my favourite place for various reasons. It combines unique characteristics like: long history, extremely beautiful Roman and Byzantine sights, a really nice seaside, great energy from the thousands of students and extremely delicious food!

What is your favourite music/book?

I like listening to Mozart and Verdi while I'm working in my office but when I'm in the lab I´d rather hear something more "energetic" like Greek pop music.
Regarding books, I enjoy reading historical books.

What is your favourite sport(s)?

I prefer to spend my spare time sailing and playing chess.

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GET TO KNOW YOUR POSITIVe PARTNER

EARLY STAGE RESEARCHERS

ANTONIA KALTSATOU

University of Thessaly, GREECE

What is the focus of your research?
My research belongs to the scientific discipline of clinical exercise physiology and environmental physiology. I investigate health aspects that can be improved by exercise training and study how the environment influences the human organism. My research focuses on chronic diseases where I design long-term and short-term exercise training programs and evaluate their effects on health indices under different environmental conditions.

In what countries/organisations have your studied or worked in?
I completed all my academic studies at the Aristotle University of Thessaloniki, Greece. Since then, I have worked in many European research programs and have collaborated with many different academic institutes all over the world. For the last four years I have been working at the University of Thessaly, Greece where I completed my post-doctoral research, and now I work at the FAME Lab laboratory as an independent researcher.

What has been the greatest achievement in your career?
Until now my greatest achievement is my PhD thesis. Reaching this goal was very stressful and when I defended it I felt really great.

Which is your favourite paper you have written/co-authored and why?
I have recently published a research paper in which the impact of inflammation and Autonomic Nervous System imbalance on cognitive impairment in chronic kidney disease patients during a hemodialysis therapy, were investigated. This paper is my favourite because it is unique and also entails the first research that has been conducted until now in this discipline. I believe that with the findings of this paper we can contribute to the better understanding of the pathophysiology and the treatment of the cognitive impairment that hemodialysis patients present.

Who is/ was your most influential mentor/colleague and why?

Until now my most inspiring and influential mentor has been Professor Evangelia Kouidi. She is a Professor of Sportmedicine at the Aristotle Univeristy of Thessaloniki, Greece and she was my PhD supervisor. I really admire her work because she was the first in collaboration with Professor Asterios Deligiannis who applied exercise training programs in patients with chronic diseases in Greece. Apart from her research background I admire her personality and her ethical character.

Where is your favourite place in the world and why?
I love Spain. I have visited many different places in Spain and each has a unique character. Also, the music and the food in Spain are perfect and they have perfect sweets. I really love churros.

What is your favourite music/book?
I like many different kinds of music depending on the occasion. For example, when I have to concentrate I like to listen to classical music. Generally, I like to collect the soundtracks of movies. My favourite group is Coldplay. Regarding my favourite book, I cannot decide. But my favourite authors are Mario Vargas Llosa and Leonardo Padura.

What is your favourite sport(s)?
I love swimming. I used to be an athlete in swimming when I was young. Unfortunately nowadays I do not have time for swimming. Nevertheless, I always try to find a few hours a week to train in the gym. Also, during the last 4 years I've developed an interest for hiking and I try to visit a different location every weekend.

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GET TO KNOW YOUR POSITIVe PARTNER

EARLY STAGE RESEARCHERS

SOFIA MOCO

Nestle Institute, Lausanne, SWITZERLAND

What is the focus of your research?
I work on the metabolism of bioactive small molecules. I am interested in the cellular functions and molecular interplay of bioactives as potential contributors to improved health. Looking into bioactive foods or mixtures, I am particularly focused on the concerted effects of bioactives on metabolic pathways in a systematic approach. Since my background revolves around analytical biochemistry, I mainly work with nuclear magnetic resonance (NMR) and mass spectrometry (MS) to study metabolites in biological samples.

In what countries/organisations have your studied or worked in?
I studied Chemical Engineering, with a specialisation in Biotechnology, at the Instituto Superior Técnico, part of the Technical University of Lisbon, Portugal. I obtained my PhD at the Laboratory of Biochemistry, Wageningen University in the Netherlands, in the areas of plant biochemistry and metabolomics, with a strong emphasis on big instrumentation (NMR and MS). Subsequently, I joined the Institute of Molecular Systems Biology at the ETH Zurich, in Switzerland. This was just before I joined research at Nestle.

What has been the greatest achievement in your career?
So far, it is my PhD thesis. When I started I had little-to-no knowledge on NMR or MS and even less on plant physiology. I managed to set up methods and strategies to perform analyses on small molecules and obtain one of the first Theses on Plant Metabolomics. These metabolomics strategies were then used by many students that joined the lab after me.

Which is your favourite paper you have written/co-authored and why?
I would have to choose my first article (A liquid chromatography-mass spectrometry-based metabolome database for tomato, Plant Physiology, 2006). I see that it has quite some citations, so I guess it is perceived as a useful piece of work.

Who is/was your most influential mentor/ colleague and why?
Jacques Vervoort, one of my PhD advisors. He was probably my most influential mentor. We had a lot of scientific discussions, and I learned a lot about biochemistry of small molecules and proteins. And he gave me a crucial piece of advice: 'You are in the driving seat' (perseverance is the key aspect in research).

Where is your favourite place in the world and why?
I have been recently to South Africa, and this place really caught my attention. If I turn to my roots in Portugal, there are a couple of narrow streets in the old city centre of Leiria, where I grew up, that are quite magic.

What is your favourite music/book?
Herbie Hancock is one of my favourites. The literature I enjoy the most is written by Portuguese authors, being Fernando Pessoa an absolute favourite.

What is your favourite sport(s)?
I like hiking in the Alps, running and swimming.

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CHAIR'S CORNER

POSITIVe has now reached mid-term which is a prefect moment for a quick assessment of all the work carried out so far and the achievements of the Action that have contributed to promote exchanges and interactions between partners and to progress in the scientific objectives of POSITIVe. Since its effective beginning (March 2015), POSITIVe has held four WG meetings & two scientific workshops, in satellite or as part of 2 large international conferences, Polyphenols & Health (Tours, France 2015) and Bioactive Compounds & Health (Norwich, UK 2016). The Action has also accomplished a very successful Training School on "Metabolomics and Nutrition Research".

At POSITIVe, a special attention is given to support and enhance the capacity building of the community of young scientists working in the area of plant food bioactives and health. This resulted in the creation of the Think-Tank Group constituted by early career investigators (ECIs). This group has proven to be very productive and is currently working in the development of a specific project of high interest for the main topic of the Action. In addition, POSITIVe has funded 13 short term scientific missions (STSMs) which have allowed young scientists within the POSITIVe community to work in different countries and labs of various other POSITIVe partners. The STSMs have resulted very fruitful as shown by the reports elaborated by the students and by the experiences they have shared with us through the newsletters.

Within the POSITIVE network, the dissemination work is also now well underway as illustrated by the submission and (or) preparation of the first collaborative reviews resulting from the WG activities and by the recent launching of a multiplatform metabolomics test across European laboratories.

The Chair and Co-chair of POSITIVe would like to use this occasion to thank all the members of the Action for all the good work done and their input in the preparation of the mid-term report for COST, which has put together all this work and has been the key for the approval of the budget for the next two years.

So, thanks a lot to everyone!

We hope that this POSITIVe dynamics within the network will continue for the next two years and will help in the preparation and launching of future fruitful collaborative research projects! We certainly need to introduce and highlight the relevance of the main topic of POSITIVe, interindividual variability in response to plant food bioactives, so that this is included in future calls of the H2020 European Programme. We all need to work together in this direction.

The Chair and Co-chair of POSITIVe also would to wish you all

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EUROPEAN COOPERATION IN THE FIELD OF SCIENTIFIC AND TECHNICAL RESEARCH

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