ISOR | INAUGURAL SYMPOSIUM OF THE INTERNATIONAL SOCIETY FOR OMEGA-3 RESEARCH

# Omega-3 in Health Promotion & Disease Management

## ↳ FROM ANIMAL TO HUMAN

## Sunday, January 8, 2017

MASSACHUSETTS GENERAL HOSPITAL, BOSTON, MA • FREE REGISTRATION
ROOM 2204, MGH NAVY YARD, 149 13TH ST

# PROGRAM SCHEDULE
# SPEAKER BIOS & ABSTRACTS

NEW GENERATION • NOVEL CONCEPTS
INNOVATIVE TECH • GREATER IMPACT

## OMEGA-3 RESEARCH

## Morning Session — SUNDAY, JANUARY 8, 2017

Session Chair: Chih-Yu Chen

08:00-09:00 ***Registration & Welcome Reception (Breakfast Provided)***

09:00-09:30 **Opening Remarks: Current Challenges and Opportunities for Omega-3 Research**
JING X. KANG
Massachusetts General Hospital and Harvard Medical School (USA)

09:30-09:55 **Lipidomics & Discovery of Novel Bioactive Omega-3 Metabolites**
MAKOTO ARITA
RIKEN Center for Integrative Medical Sciences (Japan)

09:55-10:20 **Modulation of Gut Microbiota as a Novel Mechanism for Omega-3 Benefits**
KANAKARAJU KALIANNAN
Massachusetts General Hospital and Harvard Medical School (USA)

10:20-10:45 **New Insights into the Anti-inflammatory Effects of Omega-3**
KARSTEN H. WEYLANDT
Charité University Medicine (Germany)

*10:45-10:55 Coffee Break*

10:55-11:20 **Use of Transgenic Mouse Models to Elucidate the Anti-cancer Effects of Omega-3**
DAVID MA
University of Guelph (Canada)

11:20-11:45 **New Mechanisms Underlying the Preventive Effects of Omega-3 on GI Tumorigenesis**
KI BAIK HAHM
CHA University (South Korea)

11:45-12:10 **Omega-3 Intervention to Suppress Tumor Growth and Metastasis**
CHIH-YU CHEN
Massachusetts General Hospital and Harvard Medical School (USA)

12:10-12:35 **Modulation of Lipid Metabolism in Cancer Stem Cells by Omega-3**
MENG WANG
Massachusetts General Hospital and Harvard Medical School (USA)

*12:35-1:30 Lunch*

## Afternoon Session — SUNDAY, JANUARY 8, 2017

Session Chair: Kanakaraju (Raj) Kaliannan

1:30-1:55 **New Approaches to Uncovering Neuroprotective Effects of Omega-3**
HUANXING SU
University of Macau (Macau)

1:55-2:20 **Maternal Omega-3 Status Influence Offspring Gut Microbiota & Susceptibility to Obesity**
RUAIRI ROBERTSON
University College Cork (Ireland)

2:20-2:45 **Novel Effect of Omega-3 on HFD-Induced Dysfunction of Brown Fat**
LEI HAO
Texas Tech University (USA)

2:45-3:10 **Identification of a Novel Thermogenic Pathway Mediated by Omega-3 Metabolites**
LUIZ OSORIO S. LEIRIA
Joslin Diabetes Center (USA)

*3:10-3:20* *Coffee Break*

3:20-3:45 **Personalized Treatment of Depression with Omega-3**
KUAN-PIN SU
China Medical University (Taiwan)

3:45-4:10 **Treatment of Patients with Acute Myocardial Infarction with High Dose of Omega-3**
RAYMOND Y. KWONG
Brigham and Women's Hospital and Harvard Medical School (USA)

4:10-4:35 **Opposing Effects of Omega-6 and Omega-3 on Obesity Development in Women**
LU WANG
Brigham and Women's Hospital and Harvard Medical School (USA)

4:35-5:00 **Omega-3 Intake and Colorectal Cancer Incidence and Survival**
MINGYANG SONG
Massachusetts General Hospital and Harvard Medical School (USA)

5:00-5:20 **Omega-3-based Nutritional Intervention for Cancer Rehabilitation**
JING X. KANG
Massachusetts General Hospital and Harvard Medical School (USA)

5:20-6:00 **Closing Remarks: Discussion and Conclusion**

## Jing X. Kang, MD, PhD

Dr. Jing X. Kang is Director of the Laboratory for Lipid Medicine and Technology (LLMT) at *Massachusetts General Hospital/* Harvard Medical School and a Professor of Medicine at Harvard University. He is the Editor-in-Chief of the Journal of Nutrigenetics and Nutrigenomics (JNN), a founding board member and former Secretary of the International Society of Nutrigenetics and Nutrigenomics (ISNN), and a member of the World Council on Nutrition, Genetics, and Health. He is a "Changjiang Scholar" Chair Professor, appointed by the Ministry of Education of China, and an Honorary Professor of the PLA General Hospital (301 Hospital). He is also the author of one of China's best-selling books, "How to Eat Well for Good Health". He was named the 2016 Laureate of the Global Award for Omega-3 Research.

Dr. Kang is a leading scientist in the field of omega-3 research, particularly in studying the role of the omega-6/omega-3 fatty acid ratio in health and disease. His lab has made several pioneering discoveries, including the prevention and treatment of cardiac sudden death by omega-3 fatty acids and the creation of a biotechnology for producing essential omega-3 fatty acids in animals. His lab has generated several unique transgenic animal models for omega-3 research. His seminal work has advanced our understanding of the differential effects of omega-6 and omega-3 fatty acids on chronic diseases, including cancer, cardiovascular disease, neurodegenerative disease, obesity and diabetes. His studies were listed among "Top 100 Science Stories" by *Discover* magazine. He was named one of "The Best and Brightest 2007" by *Esquire* magazine. To date, he has published more than 180 scientific papers in high-impact scientific journals including *Nature, Science, and PNAS.* His publications have been cited for more than 12,000 times with a H-index of 58. Dr. Kang has been invited to speak at more than 120 national and international meetings.

Dr. Kang's current research ranges from nutrigenomics and cancer metabolism to translational applications, with a focus on metabolic interventions for cancer, diabetes, obesity, and aging-related diseases.

## Current Challenges and Opportunities for Omega-3 Research

Jing X. Kang, MD, PhD

*Laboratory for Lipid Medicine and Technology (LLMT),*
*Massachusetts General Hospital and Harvard Medical School*
BOSTON, MASSACHUSETTS, USA

Omega-3 polyunsaturated fatty acids as essential nutrients, dietary supplements, and pharmaceutical drugs have been widely investigated and used over the past few decades. The continued interest and ever-growing volume of research in the field point to omega-3 fatty acids as a key player in the management of chronic diseases. However, the main challenge of omega-3 research lies in its complexity and confounding factors. Variations, inconsistencies, and controversies on the study outcomes of omega-3 fatty acids remain to be clarified. Recent advances in analytical technologies (such as the "omics"), new animal models, and integrated experimental approaches have allowed us to more comprehensively and accurately elucidate the biological effects of omega-3 fatty acids and their mechanisms. Identification of biomarkers for efficacy evaluation will help the clinical application and implementation of omega-3-based strategies. An example of the contributions of the fat-1 transgenic mouse model in understanding the beneficial effects of omega-3 fatty acids and their utility in the management of chronic diseases will be presented. Novel concepts and innovative technologies with multidisciplinary collaborations are needed to develop pathway-targeted, biomarker-guided, and personalized omega-3-based interventions for health promotion and disease management.

## Omega-3-based Nutritional Intervention for Cancer Rehabilitation

Jing X. Kang, MD, PhD

The current treatment of cancer faces many challenges, including the low efficacy of chemotherapy and severe side effects, leading to a great burden for cancer patients. Many cancer patients do not receive sufficient rehabilitation support following conventional treatment, such as measures to prevent tumor metastasis or recurrence. Patients with late-stage cancer in particular are in need of safe and effective methods to reduce the side effects of chemotherapy or radiotherapy, improve quality of life, and prolong lifespan. In this context, we developed a comprehensive nutritional intervention system (including a combination of functional foods, dietary supplements, and efficacy evaluation) to target cancer cell metabolism and modulate the tumor microenvironment by correcting three major nutritional imbalances (omega-6 vs. omega-3 PUFA, oxidants vs. antioxidants, and refined carbohydrates vs. dietary fiber). Our pilot study showed that usage of the nutritional intervention system for two weeks was highly effective in improving quality of life, cancer-related biomarkers, and metabolic parameters (including chronic inflammation, gut dysbiosis, immune function, etc.). While further investigation is warranted, our findings demonstrate that this omega-3 based nutritional intervention is a promising approach for cancer rehabilitation.

## Makoto Arita, MD

[1]Team Leader, Laboratory for Metabolomics,

RIKEN Center for Integrative Medical Sciences, Yokohama, Japan

[2]Professor, Division of Physiological Chemistry and Metabolism,

Keio University School of Pharmacy, Tokyo, Japan

Dr. Makoto Arita graduated from Graduate School of Pharmaceutical Sciences, the University of Tokyo, and received a Ph.D. degree in 1997. After postdoctoral training at Brigham and Women's Hospital/Harvard Medical School, he became a junior faculty as an Instructor at Harvard Medical School in 2003. After returning to Japan in 2006, he became Associate Professor in the University of Tokyo. His research was focused on understanding omega-3 PUFA's anti-inflammatory properties using genetic models and LC-MS/MS-based lipidomics approaches. Since 2014, Dr. Arita heads the Laboratory for Metabolomics at RIKEN Integrative Medical Sciences (IMS) as a Team Leader. Also he became a Professor at Keio University School of Pharmacy in 2016. He has been awarded Young Scientists' Prize of Japan Ministry of Education, Culture, Sports, Science and Technology in 2009, for his contribution in elucidating structure and function of a series of endogenous lipid mediators that regulate inflammation and tissue homeostasis. Currently Dr. Arita's research is focused on development and application of non-target lipidomics platform to discover novel link between lipid metabolism and biological phenotypes.

# Lipidomics & Discovery of Novel Bioactive Omega-3 Metabolites

Makoto Arita, PhD

*Laboratory for Metabolomics, RIKEN Center for Integrative Medical Sciences*
*Division of Physiological Chemistry and Metabolism, Keio University School of Pharmacy*
YOKOHAMA, JAPAN

Omega-3 polyunsaturated fatty acids (PUFA), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are widely held to have beneficial effects in many inflammatory diseases. Also, elevation in tissue levels of omega-3 PUFAs in fatty acid *n-3* desaturase (*fat-1*) transgenic mice exhibits resistance to inflammatory disease models. To elucidate the molecular mechanisms underlying the beneficial effects of omega-3 PUFAs, we developed a comprehensive LC-MS/MS-based lipidomic system that can detect and quantify more than 500 of fatty acid metabolites simultaneously. Using a genetic model, namely *fat-1* transgenic mice, we examined the biological impact and lipid metabolome changes with enhanced omega-3/omega-6 fatty acid ratio at tissue and cellular levels. Also we demonstrated LC-MS/MS-based lipidomic analyses, and identified several unique omega-3 fatty acid metabolites with potent biological activities *in vivo*. These metabolites may underlie some of the beneficial actions of omega-3 PUFAs in controlling inflammation and related diseases.

*References*

1. Kunisawa J, Arita M, Hayasaka T, Harada T, Iwamoto R, Nagasawa R, Shikata S, Nagatake T, Suzuki H, Hashimoto E, Kurashima Y, Suzuki Y, Arai H, Setou M, Kiyono H. Dietary ω3 fatty acid exerts anti-allergic effect through the conversion to 17,18-epoxyeicostetraenoic acid in the gut. *Sci Rep* 5, 9750 (2015)
2. Endo J, Sano M, Isobe Y, Fukuda K, Kang JX, Arai H, Arita M. 18-HEPE, an n-3 fatty acid metabolite released by macrophages, prevents pressure overload-induced maladaptive cardiac remodeling. *J Exp Med* 211, 1673-1687 (2014)

## Kanakaraju Kaliannan, MD

Kanakaraju Kaliannan, MD, is a Senior Research Fellow currently working in the Laboratory for Lipid Medicine and Technology (LLMT) in Massachusetts General Hospital in the United States of America. Following completion of his MD at Thoothukudi Medical College (2008) in India, he completed his Postdoctoral Research Fellowship in the Laboratory of Gastrointestinal Epithelialogy at Massachusetts General Hospital located in Boston, Massachusetts, USA (2012). He then joined as a research fellow in the Laboratory for Lipid Medicine and Technology (LLMT) in Massachusetts General Hospital (2013). During his fellowship, Dr. Kaliannan discovered a novel pathway based strategy to prevent and treat high fat diet induced obesity and diabetes in mice, resulted in a first author publication in the PNAS journal and crucial to winning the grants and awards of $350,000. At LLMT, he discovered a new microbiota-based mechanism for the opposing effects of omega-6 and omega-3 fatty acids on chronic inflammation in the context of obesity and diabetes in mice, resulting in an outstanding publication in 'Scientific Reports'. Following this discovery, his group started a human clinical trial investigating this new mechanism collaborating with a medical group in Baltimore, USA and also in China. Dr. Kaliannan's work on the opposing effects of omega 6 and 3 fatty acids on microbiota further led him to find a novel omega-3 PUFA-based therapeutic strategy to prevent early life antibiotics-induced obesity in later life and this lead to an outstanding publication in a high impact journal. He also started many studies on transgenic mice to discover the beneficial effects of tissue omega-3 fatty acids on cancer drug-induced gut toxicity and chronic alcohol with high omega-6 fatty acids-rich diet-induced liver injury. He accomplished three first author and five co-authored publications in high impact journals and gave oral and poster presentations at international meetings such as the 2014 ISSFAL Congress, WCI 2015 and Digestive Disease Week (DDW) 2012. He received 'Posters of Distinction' and 'Posters of Merit' awards at international meetings and the MGPA Travel Award. He is also serving as a reviewer for journals such as Digestive Disease Science and Journal of Nutrition.

# Elevated tissue omega-6/omega-3 essential fatty acid ratio alters gut microbiota and metabolome with increased chronic disease risk in fat-2 transgenic mice

Kanakaraju Kaliannan, Xiang-Yong Li, and Jing X. Kang

*Laboratory for Lipid Medicine and Technology (LLMT),*
*Massachusetts General Hospital and Harvard Medical School*
BOSTON, MASSACHUSETTS, USA

The current Dietary Guidelines for Americans (2015-2020) recommend substituting polyunsaturated fatty acids (PUFA) for saturated fatty acids (SFA), but do not distinguish between omega-6 (n-6) and omega-3 (n-3) PUFA. Over the past few decades, however, the global trend of increased n-6 intake and decreased n-3 intake has coincided with the rising prevalence of chronic diseases, which suggests that excessive intake of n-6 PUFA with a low n-3 PUFA background may contribute to the development of chronic diseases. However, well-controlled models to prove this notion are still needed.

Chronic low-grade inflammation is known to be an underlying factor of many chronic diseases, and can be derived from gut dysbiosis and metabolic endotoxemia. In this study, we utilized multi-omics technologies with a transgenic fat-2, fat-1 and fat-12 mice model that endogenously produce n-6 PUFA, n-3 PUFA and both respectively to examine the effects of different levels of tissue n-6/n-3 ratio status on the gut microbiota, metabolic endotoxemia, chronic low-grade inflammation and chronic diseases.

We found that elevated tissue n-6/n-3 ratio adversely impacted the composition and functionality of fecal microbiota. Multivariate analysis showed that gut microbiota profiles were distinctly different between the high n-6 (fat-2) and low n-6 (WT) groups, including increased relative abundances of lipopolysaccharide (LPS)-producing bacteria (e.g. *E. coli*) and decreased LPS-suppressing bacteria (e.g. *Bifidobacterium*) in the fat-2 mice. In addition, analysis of microbial function and fecal and serum metabolites revealed significant increases in markers of LPS biosynthesis, gut permeability, bacterial invasion, obesity, type 2 diabetes, atherosclerosis, fatty liver, cancer, and metabolic syndrome. These changes were associated with increased metabolic endotoxemia, chronic low-grade inflammation, and the development of liver cancer in the fat-2 mice. All of these adverse effects were significantly reduced in fat-1 and fat-12 mice with lower n-6/n-3 ratio. Furthermore, correlation analysis indicated a positive relationship between the alterations in gut microbiota and metabolome and the markers of chronic inflammation.

Our findings indicate that elevated tissue n-6/n-3 PUFA ratio compromise the gut microbiota, leading to the development of chronic low-grade inflammation and thereby increasing the risk for chronic diseases. Given the imbalanced intake of n-6 and n-3 PUFA in the modern Western diet, it is critical that we recognize the consequences of excessive n-6 intake and the importance of balancing the n-6/n-3 PUFA ratio to control the modern disease epidemic.

## Karsten H Weylandt MD, PhD

Attending Physician in Gastroenterology and Hepatology at Virchow-Hospital, Charité University Medicine and head of the Lipid Clinic at the Experimental and Clinical Research Center (ECRC) of Charité and Max-Delbrück-Center for Molecular Medicine in Berlin, Germany. Research Fellow/Instructor in Medicine at Harvard Medical School and Massachusetts General Hospital from 2010-2011. Residency and Fellowship in Internal Medicine, Gastroenterology and Endocrinology, Charité University Hospital Berlin, Germany from 2002-2009. Received DPhil in Clinical Biochemistry from Oxford University in 2001 and attended Medical School in Heidelberg, Boston, King's College London and Berlin from 1993–1997.

# New Insights into the Anti-inflammatory Effects of Omega-3

Karsten H. Weylandt, MD, PhD

*Lipid Clinic, Experimental and Clinical Research Center (ECRC),*
*Charité University Medicine and Max-Delbrück-Center for Molecular Medicine*
BERLIN, GERMANY

Omega-3 fatty acids were shown to alleviate inflammation in murine colitis and hepatitis models, as well as in models of colon and liver cancer. Evidence in recent years implicates omega-3 derived lipid mediators in these protective effects. However, evidence of anti-inflammatory and anti-proliferative effects of omega-3 fatty acids in humans is less clear. Current and future work to close this gap of evidence and understanding will have to focus on fatty acid and lipidomics measurements of the omega-3/omega-6 lipidome in human studies.

## David W.L. Ma, PhD

Dr. Ma obtained his PhD in Medical Sciences in 2001 at the University of Alberta conducting research on the anticancer properties of ruminant fats in breast cancer. He then moved to Texas A&M University where he did postdoctoral research investigating the role of omega-3 fatty acids and folate in colon cancer. He returned to Canada where he joined the Department of Nutritional Sciences at the University of Toronto as an Assistant Professor in 2004. Then, in 2007 joined the faculty in the Department of Human Health and Nutritional Sciences at the University of Guelph where he is currently an Associate Professor and Director of the Health for Life Initiative. He is also the Vice President Research & President-Elect for the Canadian Nutrition Society playing an active role in many committees and conference planning.

Dr. Ma's research encompasses investigations to better understand the role of fats in human health and disease. Broadly, studies seek to enhance our understanding of the role of fats through the lifecycle and how various fats support health, prevent and treat chronic diseases. Specifically, to determine the fundamental nature by which fats including omega-3's, trans fats and CLA 1) affect cellular biology, 2) have utility as disease markers, and 3) how individual genetic differences involved in fat metabolism modify disease risk. Currently, studies are focused on 1) how omega-3 fatty acids may play a role in breast cancer prevention, 2) development of fatty acid reference ranges and 3) the role of genetic variation in genes involved in omega-3 and omega-6 fatty acid metabolism on health.

As the Director of the Health for Life Initiative, he is leading the Guelph Family Health Study (GFHS), a longitudinal cohort study of families with young children. The goal of the GFHS is to develop tools and new approaches to support healthy habits and behaviours that will have lasting benefits for the prevention of chronic disease. Responsibilities include leading a growing research team comprised of faculty, trainees and collaborators, stakeholder engagement, grant writing and fundraising.

The Canadian Nutrition Society is a leading nutrition organization advocating for evidence-based nutrition and practice. Membership is drawn from researchers and trainees from all major University nutrition programs across Canada, and professionals from industry and government. In his role as Vice-President Research he is involved in conference planning, partnership engagement, and communications.

# Use of Transgenic Mouse Models to Elucidate the Anti-cancer Effects of Omega-3

David W.L. Ma, PhD

*Department of Human Health and Nutritional Sciences, University of Guelph*
GUELPH, ONTARIO, CANADA

Breast cancer is one of the leading causes of death in women globally. However, cancer is largely preventable through diet and lifestyle. In particular, there has been much focus on the role of omega-3 fatty acids in breast cancer prevention. The study of single nutrients are challenging to study, especially to demonstrate cause-effect relationships. The Fat-1 mouse has enabled my laboratory to establish that omega-3 fatty acids have a profound effect on breast cancer outcomes. Using the Fat-1 mouse, we developed a hybrid model susceptible to developing mammary tumours and capable of de novo synthesis of omega-3 fatty acids. Using this novel model, we were able to show a direct link between lifelong exposure of omega-3 fatty acids and reduced mammary tumour size and multiplicity. These effects were mirrored in a parallel dietary arm of mice fed omega-3 fatty acids from fish oil. We have shown in subsequent work that the benefits of fish oil are also dose dependent. Recently, we have shown that the effects of eicosapentaenoic acid and docosahexaenoic acid found in fish oil are approximately 8-fold more potent than plant based, alpha-linolenic acid in reducing mammary tumour outcomes. This is relevant given that the majority of omega-3 fatty acids consumed in North America is from alpha-linolenic acid. On-going work focuses on understanding the individual role of omega-3 fatty acids using the delta 6 desaturase knock out mouse model and timing of exposure using a newly developed inducible Fat-1 mouse.

## Ki-Baik Hahm, MD, PhD

Dr. Ki Baik Hahm is currently Professor of Medicine at CHA University School of Medicine, Director of the CHA Cancer Prevention Research Center, and Director of the Research Division of CHA University Bundang Medical Center. He graduated from Yonsei University at 1983 and spent three years post-doc in NCI, MD from 1997. After serving as Assistant Professor of Medicine at Yonsei University from 1990 to 1994, he moved to Ajou University School of Medicine, where he was appointed as Professor of Medicine from 1994 to 2006. In 2012, he finally settled in CHA University with prestigious appointment as the leader of research driven hospital project, which will be funded by the government from 2013 for up to 10 years. He is performing translational research in the field of H. pylori infection, etio-pathogenesis and pathophysiology of peptic ulcer disease research, gastric carcinogenesis and their prevention, and inflammatory bowel disease. He has published more than 170 SCI publications and he is taking several research grants from the government. Since his background is gastroenterology, he has many concerns and contributions in the field of nutrigenomics, especially regarding Korean red ginseng and probiotics as well as stem cell application. He is currently appointed as President of the Korea Society of Cancer Prevention and Society of Free Radical Research.

# New Mechanisms Underlying the Preventive Effects of Omega-3 on GI Tumorigenesis

Young-Min Han[1], Jong-Min Park[1], Shin A Shin, Ji-Young Cha[2], Joo Young Cho[3], Sung Pyo Hong[3], Yong Jin Park[4], **Ki Baik Hahm**[1,3]

[1]*CHA Cancer Prevention Research Center, CHA Bio Complex, Seongnam, Korea*
[2]*Laboratory for Lipid Medicine and Technology, Massachusetts General Hospital and Harvard Medical School, Boston, USA*
[3]*Digestive Disease Center, CHA Bundang Medical Center, CHA University, Seongnam, Korea*
[4] *GI Medics Pharma, Seoul, Korea*

According to unmet medical needs in gastroenterology, the solutions for Helicobacter pylori-associated chronic gastritis and gastric cancer (how to prevent these troublesome clinical diseases? via eradication or other intervention?), prevention of non-steroidal anti-inflammatory drugs (NSAIDs) –induced gastrointestinal damages (urgent emergence of GI-safer drug in the era of super-aging societies), strategies against steady incidence of colon cancer world-widely (vigilant colonoscopic surveillance or faithful prevention with lifestyle modification, how about newer intervention through nutrient support?), and prevention of longstanding extensive involvement of inflammatory bowel disease as the concept of cancer prevention of colitic cancer, and lastly attenuation of non-alcoholic fatty liver disease beyond current lifestyle modification such as diet restriction, exercise, and more. In this symposium, we show our recent investigations how omega-3 polyunsaturated fatty acids can provide plausible solutions against these unmet medical needs in gastroenterology. In detail, I will ed one example shown at Scientific Reports, September issue, 2016, NSAIDs damage GI epithelial cell membranes by inducing several signals through lipid raft organization after membrane incorporation, whereas ω-3 PUFAs can relieve inflammation, reduce oxidative stress, and provide cytoprotection, consequent to lipid raft disorganization. Therefore, we hypothesized that ω-3 PUFAs can protect the GI from NSAID-induced damages by initiating the gatekeeper action of cell membranes, subsequent to anti-inflammatory and anti-oxidative actions. Administration of indomethacin (IND) leads to the formation of lipid rafts and activation of caveolin-1; however, no such observations were made upon co-administration of eicosapentaenoic acid (EPA) and IND. In addition, the EPA-induced lipid raft disorganization, caveolin-1 inactivation, and cellular cytotoxicity were inhibited when target cells were knocked-out using GPR120. EPA significantly attenuated IND-induced oxidative damage and apoptosis. IND administration induced significant ulceration, bleeding, and oedema in the stomach or small intestine of wild-type (WT) mice; whereas GI mucosal damages significantly decreased in *fat*-1 transgenic (TG) mice ($p < 0.001$), accompanied with significantly decreased cyclooxygenase-2 expression and apoptosis, decreased interleukin-1 and FAS concentrations, and increased HO-1 concentration. Among common sources of plant oils containing the ω-3 PUFAs ALA fatty acid include walnut which also showed that walnut-phenolic-extract had similar effects in IND-induced gastrointestinal damage via anti-oxidant and anti-inflammatory actions. Our study indicates that the gatekeeper function of ω-3 PUFAs improves GI safety when administered with NSAID (patent pending; omega-3-conjugated NSAID as GI safer NSAID).

## Chih-Yu Chen, PhD

Dr. Chih-Yu Chen graduated from National Taiwan University in 2005, received her MSc in Institute of Food Science and Technology from National Taiwan University in 2008, and completed her Ph.D. in the Department of Food Science of Purdue University in 2013, focusing on nutrition and adipogenesis. She undertook her postdoctoral training with Dr. Jing X. Kang at the Laboratory for Lipid Medicine and Technology of the Department of Medicine at Massachusetts General Hospital and Harvard Medical School. Dr. Chen is currently a research specialist at LLMT at MGH. Her current research interest is to study the effect of lipid metabolism on cancer as well as obesity development using diets rich in omega-3 fatty acids and lipid/lipid metabolites synthesis-controlled medicine.

# Omega-3 Intervention to Suppress Tumor Growth and Metastasis

Chih-Yu Chen and Jing X. Kang

*Laboratory for Lipid Medicine and Technology, Department of Medicine,*
*Massachusetts General Hospital and Harvard Medical School*
BOSTON, MASSACHUSETTS, USA

Lipid homeostasis is highly controlled in vertebrates and supports fundamental physiological structures as well as activities. Abnormal lipid metabolism is emerging as a metabolic biomarker associated with oncogenesis and tumor progression. This features in major cancer hallmarks and recently, becomes a potential target to treat human cancer and alleviate the side effects from anti-cancer drugs. The metabolic enzymes involved in lipid synthesis such as *de novo* lipogenesis, long chain fatty acids, and lipid metabolites including eicosanoids, have been exploited to develop a series of microenvironmental barriers that inhibit tumor transformation. Omega-6 and omega-3 polyunsaturated fatty acids (n-6 and n-3 PUFA) are the main components in phospholipids of the cell membrane and are essential fatty acids necessary for human health. However, an increased dietary n-6/n-3 ratio is associated with higher risks for some cancers and exhibits potential impacts on lipid metabolism in tumor microenvironment. Herein, we summarize our recent findings that elevating tissue n-3 PUFA can inhibit metastasis, using the *fat-1* transgenic mouse model (which can endogenously convert n-3 PUFA from n-6 PUFA) together with a dietary n-3 PUFA supplemented model. Our results showed that elevating n-3 PUFA blocks tumor growth and reveals differential effects on the tumor microenvironment compared to aspirin treatment. Additionally, elevating n-3 PUFA suppresses tumor re-growth and improves cachexia after chemotherapy withdrawal. Together, these results provide important knowledge for the importance of lipid metabolism in cancer biology and for the development of new approaches for the prevention and therapy of cancer.

**Meng Wang, PhD**

Instructor in Radiation Oncology

Massachusetts General Hospital

Boston, MA, USA

***Presentation: "Modulation of Lipid Metabolism in Cancer Stem Cells by Omega-3"***

## Huanxing Su, MD, PhD

Associate Professor of Biomedical Sciences at the Institute of Chinese Medical Sciences of the University of Macau. Dr. Su obtained his medical degree from Zhejiang University and PhD from the University of Hong Kong. His research mainly focuses on using *in vitro* models to elucidate molecular mechanisms of controlling neural differentiation of human embryonic stem cells (ESCs) and human induced pluripotent stem cells (iPSCs) and using nature products such as Omega-3 polyunsaturated fatty acids to treat neurological disorders. He has published more than 80 peer-reviewed research articles in well-reputed journals in the discipline.

# New Approaches to Uncovering Neuroprotective Effects of Omega-3

Huanxing Su, MD, PhD

*Institute of Chinese Medical Sciences, University of Macau*
TAIPA, MACAU

The central nervous system is highly enriched in Omega-3 series. Increasing evidence suggests that omega-3 polyunsaturated fatty acids (PUFAs) may confer benefits for a variety of neurological disorders. Using a mild traumatic brain injury model and a microinfarct model, we have demonstrated that endogenous omega-3 PUFAs significantly inhibited ROS expression and attenuated parenchymal cell death after compression injury during the early injury phase and protect mice against microinfarct via inhibiting apoptosis, mitigating tissue damage, and improving cognitive impairment. In addition, we have also demonstrated that omega-3 PUFAs could regulate the function of the brain clearance system and exert beneficial effects via activating the clearance function in the brain. These studies show that omega-3 PUFAs have a multitude of beneficial effects on brain function.

## Ruairi Robertson, PhD

Dr. Robertson is a postdoctoral research fellow within the APC Microbiome Institute in University College Cork, Ireland and Teagasc Moorepark Food Research Centre. Dr. Robertson has a B.Sc in Human Nutrition from University College Dublin and obtained his PhD from University College Cork in 2016. His PhD research examined the interaction between omega-3 fatty acids and the developing gut microbiota and implications for metabolic health. He spent one year as a Fulbright Scholar in the LLMT lab in MGH during which time he used the fat-1 model to examine the role of maternal omega-3 status in offspring microbiota development and obesity.

# Maternal Omega-3 Status Influence Offspring Gut Microbiota and Susceptibility to Obesity

Ruairi C. Robertson[1, 2, 3], Kanakaraju Kaliannan[3], Conall R. Strain[1, 2], R. Paul Ross[4], Catherine Stanton[1, 2], Jing X. Kang[3]

[1]*APC Microbiome Institute, University College Cork, Cork, Ireland*
[2]*Teagasc Moorepark Food Research Centre, Fermoy, Co. Cork, Ireland*
[3]*Laboratory for Lipid Medicine and Technology, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA*
[4]*School of Science Engineering and Food Science, University College Cork, Ireland*

*Background:* Dietary omega-3 polyunsaturated fatty acids (n-3 PUFA) have anti-obesigenic properties compared with n-6 PUFA. The pathogenesis of obesity however has its origins in the fetal and neonatal periods, therefore maternal PUFA status may influence offspring susceptibility to obesity. Furthermore, little is known about the role of the gut microbiota in the interaction between maternal n-3 PUFA status and offspring weight gain.

*Methods:* Wild type (WT) offspring of WT and transgenic *fat-1* mice, that endogenously produce n-3 PUFA, were placed on a high fat diet (HFD) to assess the role of maternal n-3 PUFA status on obesity susceptibility. Offspring were also fostered to mothers of the opposite genotype at birth to compare the role of prenatal and postnatal n-3 PUFA status. Weight gain, body composition, gut permeability, inflammatory markers and gut microbiota composition were all assessed following 3 months HFD feeding.

*Results:* Offspring born to a *fat-1* mother or fostered to *a fat*-1 mother during lactation gained significantly less weight than those of WT mothers (189-196% vs. 232%) suggesting that maternal n-3 PUFA *in utero* or during lactation reduce HFD-induced weight gain in offspring. Offspring n-3 PUFA dietary exposure during lactation, via milk, resulted in greater n-3 tissue accumulation than *in utero* n-3 exposure ($p<0.05$). Similarly, the effects on the gut microbiota were primarily driven by the mother's phenotype during lactation such that *fat-1* mothers reduced gut permeability ($p<0.05$), *Firmicutes*, *Clostridia*, *Lachnospiraceae* and increased *Akkermansia* and Bacteroidetes in offspring. The changes in microbiota composition induced by maternal n-3 PUFA status persisted throughout life after HFD-feeding and after differences in tissue PUFA status disappeared.

*Conclusions:* Elevated maternal n-3 PUFA status during pregnancy and/or lactation led to significantly reduced weight gain in offspring fed HFD following weaning. This is associated with comprehensive alterations to the offspring microbiota, which persist throughout life. Maternal n-3 PUFA supplementation poses potential as a therapeutic intervention to prevent obesity, gut microbiota dysbiosis and associated chronic disease.

## Lei Hao, MD, PhD

Dr. Hao currently is a research assistant professor in the Department of Nutritional Sciences at Texas Tech University. He graduated from Weifang Medical College with a bachelor degree in Clinical Medicine (M.D.) (2000) and MS degree in Pediatrics from Peking University (2003). Dr. Hao received his doctoral degree in Nutritional Sciences from the Pennsylvania State University (2013). Following receipt of his doctoral degree he completed his post-doctoral training at Massachusetts General Hospital and Harvard Medical School. Dr. Hao's research interests include understanding the mechanisms of obesity, non-alcoholic fatty liver diseases, and brown fat development. His area of expertise lies in the relationship between omega-3 fatty acids and obesity.

# Novel Effect of Omega-3 on HFD-Induced Dysfunction of Brown Fat

Lei Hao and Jing X. Kang

*Laboratory for Lipid Medicine and Technology, Massachusetts General Hospital/Harvard Medical School*
BOSTON, MASSACHUSETTS, USA

The role of omega-3 fatty acids in regulation of energy homeostasis remains poorly understood. In the current study, we aimed to investigate how endogenous omega-3 fatty acids regulate the morphology and function of brown fat in vivo and in vitro. Sixteen-week-old male wild type (WT) and transgenic fat-1 mice were fed a low fat diet (LFD) or a high fat diet (HFD) for 13 weeks. Metabolic tissues, including brown fat (BAT), inguinal white adipose tissue, and liver, were collected for biochemical and histological analysis. The mouse immortalized brown fat cell line was used for in vitro experiments. In the groups fed HFD, fat-1 mice had significantly lower body weight and total fat mass compared with WT mice. In addition, fat-1 mice had improved glucose tolerance compared with WT. We found that a high fat diet induced larger lipid droplet accumulation ("whitening") in brown fat of WT mice, whereas "whitening" in brown fat was significantly alleviated in fat-1 mice. Real time PCR showed that the thermogenic markers, such UCP-1, CPT -1, and CIDE-A, were expressed more in fat-1 mice compared with WT mice. Furthermore, fat-1 mice had significantly lower lipopolysaccharide levels (LPS) compared with WT mice. In a separate experiment, we found that fat-1 mice resisted UCP suppression by LPS. Lastly, we showed in vitro that LPS inhibits β3-adrenergic agonist, CL316243 inducing UCP-1 expression in mouse immortalized brown adipocytes. This study demonstrated that high fat diet led to obesity and "whitening" of BAT in WT mice; conversely, endogenous omega-3 polyunsaturated fatty acids in fat-1 mice preserved morphology and function of brown fat impaired by HFD. We revealed that the dysfunction of BAT may be attributed to increased LPS production due to high fat diet feeding, and that omega-3 fatty acids alleviate the dysfunction of BAT through inhibition of LPS production.

## Luiz Osorio S. Leiria, PhD

Dr. Luiz Leiria is a pharmacist with MS and PhD degrees in Pharmacology at the State University of Campinas (Sao Paulo-Brazil). He joined Dr Yu-Hua Tseng's lab at Joslin Diabetes Center/Harvard Medical School in July 2014. His main research interest is to determine the role of brown fat secreted molecules, mainly lipid metabolites, in the regulation of glucose homeostasis and liver lipogenesis as well as to understand the mechanisms underlying the improvements in glucose disposal, insulin sensitivity and triglycerides levels after cold-induced brown fat activation.

# Identification of a Novel Thermogenic Pathway Mediated by Omega-3 Metabolites

Luiz Osorio S. Leiria, PhD

*Section on Integrative Physiology and Metabolism, Joslin Diabetes Center and Harvard Medical School*
BOSTON, MASSACHUSETTS, USA

Brown adipose tissue (BAT) has a central role in protecting mammals against hypothermia through a process called adaptive thermogenesis. In addition to generate heat in response to cold, BAT has also an important endocrine role, as it is capable of releasing factors to improve insulin signaling and glucose homeostasis in distal organs. Recently, circulating lipid species have emerged as signaling molecules and novel metabolic regulators. Several lipids called "lipokines" with intracellular signaling properties promoting insulin sensitivity and glucose tolerance have been identified. Our main goal is to identify novel cold-released lipokines released with potential therapeutic application against diabetes and obesity. For this purpose we performed a series of lipidomics analysis in the serum from mice exposed to cold and humans treated with β3-adrenergic agonist. We identified the omega-3 metabolite 12-HEPE as a cold/adrenergic inducible lipokine, potentially released from BAT due to the increased 12-Lipoxygenase activity in this tissue in both mice and human species. 12-HEPE levels in the serum from human subjects positively correlates with BAT activity and negatively correlates with Body Mass Index (BMI), HOMA-IR, triglycerides and cholesterol. Our data supports the hypothesis that 12-HEPE is a cold-inducible omega-3 metabolite released from BAT to exert some of the beneficial metabolic effects caused by cold.

## Kuan-Pin Su, MD, PhD

Dr. Kuan-Pin Su is a Professor of Psychiatry and Neural & Cognitive Sciences of China Medical University (CMU), Taichung, Taiwan. After graduation from Kaohsiung Medical College in 1995 (MD), he received psychiatry residency training at Taipei City Psychiatric Centre. In 2008, he received his PhD and became an Honorary Faculty at the King's College London.

Prof Su's research has connected bedside to bench with novel interdisciplinary approaches by integrating clinical significance with the investigation of basic science. His significant contribution on the role of omega-3 polyunsaturated fatty acids (PUFAs) is opening the excitement and innovation of therapeutic strategies and has provided major insights into the biological mechanisms of depression. For example, he is one of the first to study the antidepressant effects of omega-3 PUFAs. The most relevant paper in this field has been cited for more than 579 times (Su et al., 2003) and the first meta-analyses (Lin and Su, 2007) has been cited for more than 486 times (GOOGLE SCHOLAR in Dec 2016). Prof Su also published the first study to demonstrate omega-3 PUFAs' antidepressant effects in pregnant women with major depression (Su et al., 2008; 231 citations). Recently, Prof Su has developed a specific model in the relationship between omega-3 PUFAs, inflammation and depression and extended researches to genetic and molecular approaches. For example, he discovered that certain genes regulating PUFA metabolism are associated with the risk of depression and somatic symptoms induced by interferon-α (Su et al., 2010), which is extended to an important clinical trial to show the prevention effects of omega-3 PUFAs in interferon-induced depression (Su et al., 2014). His recent in vitro papers have also revealed novel pathways linking to omega-3 PUFAs' anti-inflammatory effects (Lu et al., 2010) and inflammation-induced depression (Lu et al., 2013). According to the *h*-index (ELSVIER in May 2016), Professor Su is the 2nd-ranked principal investigator in the world and CMU is ranked at the top 6th among global research institutes in the research field of "omega-3 PUFAs in depression." (Details: https://sites.google.com/site/omega3su/home/).

Prof Su and his research team, the Mind-Body Interface Laboratory (MBI-Lab), have been involved in a series of clinical and basic research on major neuropsychiatric disorders and earned internationally renowned reputation. He has received prestigious research awards from professional societies, including Professor Robert Kerwin International Award from the British Association for Psychopharmacology (UK, 2008), the NARSAD Young Investigator Award (USA, 2008-2010), the International Society for the Study of Fatty Acids and Lipids (ISSFAL) New Investigator Award (2010 & 2012), the National Science Council Ta-You Wu Memorial Award (2011), GlaxoSmithKline Depression and Anxiety Award (2011), Thomson Reuters Research Front Awards (2011), USA Psychiatric Research Society Annual Meeting Travel Award (2012), Pacific Rim Psychiatrist College Young Psychiatrists Award (2012), Psychopharmacology Award from the British Association for Psychopharmacology (2013) and ISSFAL Early Career Award (2016). In the future, Prof Su and his colleagues at the MBI-Lab will keep looking for the novel remedy for depression and the understanding to interface for mind and body.

# Personalized medicine with omega-3 fatty acids for depression

Kuan-Pin Su, MD, PhD

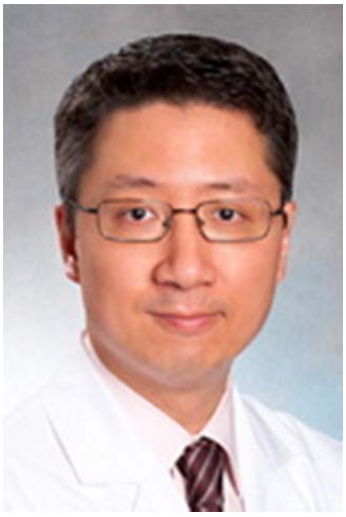
*Mind-Body Interface Laboratory (MBI-Lab), Taiwan China Medical University & Hospital*
TAICHUNG, TAIWAN

Depression is one of the leading causes of morbidity and mortality in medicine. Current available treatments clearly do not meet clinical needs, while clinicians and researchers are facing the huge challenge of developing effective depression treatments despite of the advance of neurosciences. As detailed in our Consensus Statements in the *Lancet Psychiatry* and *World Psychiatry*, nutritional medicine is a promising strategy for the crisis of under-effectiveness in depression treatment (1,2). Omega-3 polyunsaturated fatty acids (PUFAs), including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have a range of neurobiological activities in modulation of neurotransmitters, anti-inflammation, anti-oxidation and neuroplasticity, by which could contribute to the antidepressant effects (3-5). Evidence from epidemiological, pre-clinical, and clinical studies have revealed that omega-3 PUFAs play an important role in the treatment and prevention of certain subgroups of clinical depression (6-9). According to biological specificity and safety consideration, omega-3 PUFAs is a potential antidepressant treatment for pregnant women, children, adolescents, and inflammation-related depression. Omega-3 PUFAs are well tolerated and accepted by general populations for health promoting (10). Thus, more research on stratifying depression is needed to justify the clinical application of omega-3 PUFAs as one of the first-line antidepressant treatments in specific populations with depression.

*References*

1. Sarris J, et al. International Society for Nutritional Psychiatry Research consensus position statement: nutritional medicine in modern psychiatry. World Psychiatry 2015; 15: 370-1.
2. Sarris J, et al. Nutritional Medicine as Mainstream in Psychiatry. Lancet Psychiatry 2015; 2(3): 271-4.
3. Lu DY, Tsao YY, Leung YM, Su KP*. Docosahexaenoic acid suppresses neuroinflammatory responses and induces heme oxygenase-1 expression in BV-2 microglia: Implications of antidepressant effects for omega-3 fatty acids. Neuropsychopharmacology 2010; 35(11): 2238–2248.
4. Lu DY, Leung YM, Su KP*. Interferon-α induces nitric oxide synthase expression and heme oxygenase-1 down-regulation in microglia. International J Neuropsychopharma 2013; 16: 433-44.
5. Lin PY, Huang SY, Su KP*. A meta-analytic review of polyunsaturated fatty acid compositions in patients with depression. Biological Psychiatry 2010; 68(2):140-147.
6. Lin PY, Mischoulon D, Freeman MP, Matsuoka Y, Hibbeln J, Belmaker RH, Su KP*. Are omega-3 fatty acids anti-depressants or just mood-improving agents? The effect depends upon diagnosis, supplement preparation, and severity of depression. Molecular Psychiatry 2012; 17(12): 1161-3.
7. Chang JPC, Palani M, Chen CP, Su KP*. Polyunsaturated fatty acids in patients with cardiovascular diseases with and without depression. Brain, Behavior, and Immunity 2015; 44: 28-31.
8. Su KP, Lai HC, Yang HT, Su WP, Peng CY, Chang JPC, Huang CL, Chang HC, Pariante CM. Omega-3 fatty acids in the prevention of interferon-alpha-induced depression Results from a randomized, controlled trial. Biological Psychiatry 2014 Oct 1; 76(7): 559-66.
9. Song C, Shieh CH, Wu YS, Kalueff A, Gaikwad S, Su KP. The role of omega-3 fatty acids eicosapentaenoic and docosahexaenoic acids in the treatment of major depression and Alzheimer's disease: acting separately or synergistically? Progress in Lipid Research 2016; 62: 41-54.
10. Su KP*. Personalize medicine with omega-3 fatty acids for depression in pregnant women and children, and depression associated with inflammation. Journal of Clinical Psychiatry 2015; 76 (11): e1476-7.

## Raymond Y. Kwong, MD, MPH



Dr. Raymond Y. Kwong is the director of Cardiac Magnetic Resonance Imaging (MRI) at Brigham and Women's Hospital (BWH). A cardiovascular medicine specialist, he is also an associate professor of medicine at Harvard Medical School (HMS).

Dr. Kwong received his medical degree from University of Toronto Faculty of Medicine. He completed a residency in internal medicine at Vancouver General Hospital and a fellowship in cardiovascular disease at The George Washington University Hospital. He then completed a cardiac MRI fellowship program at the National Heart, Lung and Blood Institutes of Health. He received his MPH from the Harvard School of Public Health. Dr. Kwong is board certified in internal medicine and cardiovascular disease.

He has authored over 130 peer-reviewed publications. His clinical interests and research focus on cardiac imaging, specifically the use of cardiac MRI to assess ventricular remodeling after acute myocardial infarction. He has received multiple grants from the National Institutes of Health, American Heart Association, Canadian Institute of Health Research, and the Society for Cardiovascular Magnetic Resonance for his research.

***Presentation: "Treatment of Patients with Acute Myocardial Infarction with High Dose of Omega-3"***

## Lu Wang, MD

Dr. Wang received her medical degree from Beijing Medical University (currently Peking University Health Science Center) and Ph.D degree in Epidemiology from University of Minnesota School of Public Health. Dr. Wang joined the research team at Division of Preventive Medicine, Brigham and Women's Hospital of Harvard Medical School as a post-doctoral fellow in 2005 and later become a faculty member as Instructor in Medicine from 2007-2010 and now Assistant Professor of Medicine and Associate Epidemiologist since 2011.

Dr. Wang has extensive experience in conducting large-scale observational epidemiologic studies and randomized clinical trials. She investigated a wide range of traditional and novel risk factors, including dietary fatty acids and relevant biomarkers, for chronic diseases and has published more than 60 original research papers, review articles, and book chapters. Dr. Wang's research received grant support from various funding sources, including federal agencies, research organizations, and pharmaceutical companies. In many of these studies, Dr. Wang serves as the Principal Investigator and take a leading role in hypothesis development, study design and conduct, data collection, management, and analysis, and result interpretation and publication. Dr. Wang also serves as co-Investigator or Project Director in several on-going randomized trials. In these studies, Dr. Wang collaborates closely and extensively with other epidemiologists, statisticians, basic scientists, as well as clinical staff.

Beyond her role as a researcher, Dr. Wang also participates in various teaching activities within and outside the Harvard Medical School and Harvard School of Public Health, including teaching classes, mentoring students, and giving lectures to local and regional seminars and national and international conferences.

# Opposing Effects of Omega-6 and Omega-3 on Obesity Development in Women

Lu Wang, MD, PhD

*Division of Preventive Medicine, Brigham and Women's Hospital and Harvard Medical School*
BOSTON, MASSACHUSETTS, USA

Omega-6 (ω6) and omega-3 (ω3) fatty acid (FA) are two sub-types of polyunsaturated fatty acid (PUFA) in diet. In the past half-century, the total fat and saturated fat intake in industrial countries has substantially fallen, while the indiscriminate diet recommendations to substitute vegetable fats, which is high in ω6 FAs and low in ω3 FAs, for animal fats have led to a significant rise in intake of ω6 FAs. As a result, the ratio of ω6 to ω3 PUFA (ω6/ω3 ratio) in western diet has remarkably increased. This change in dietary PUFA composition, independent of the total caloric intake and total fat intake, may contribute to the obesity epidemic in many populations. ω3 and ω6 PUFAs compete for common metabolism pathways and incorporation to tissues. Experimental studies show that ω3 and ω6 FAs also play different roles in adipogenesis, lipid homeostasis, brain-gut-adipose axis signaling, and systemic inflammation, resulting in divergent effects on body fat growth. Evidence from human studies remains limited and inconclusive. Very few observational studies and clinical trials have examined the association between composition of PUFA, particularly ω6 FAs and ω6/ω3 ratio, with obesity-specific parameters. Our studies in prospective cohorts of middle-aged and older women showed that the dietary intake of ω6 FAs and ω6/ω3 ratio and the biomarkers were positively associated, while dietary intake of ω3 FAs and the biomarkers were inversely associated, with increased adiposity as measured by body weight, body mass index (BMI) and dual x-ray absorptiometry (DXA)-determined total and regional body fat. Although some research groups have recommended a reduction in ω6 FA intake to lower the ω6/ω3 ratio, a consensus on the optimal intake of ω3 and ω6 subtype PUFAs and ω6/ω3 ratio in diet is still lacking. Future studies are needed to further evaluate dietary FA composition and their biomarkers in association with objective and longitudinal measurements of body fat and elucidate whether a diet with balanced ω3 and ω6 FA component will have beneficial effects for the primary prevention of obesity and obesity-related chronic diseases.

## Mingyang Song, MD, PhD

After receiving my medical training from Shandong University, I studied cancer epidemiology at Peking University, and then obtained my doctoral degree in nutrition and epidemiology at Harvard T.H. Chan School of Public Health in 2015. Currently, I am an Instructor in Medicine in the Clinical and Translational Epidemiology Unit (CTEU) at Massachusetts General Hospital and Harvard Medical School. My research focuses on the role of diet, lifestyle factors and genetics in the development of colorectal neoplasia. In particular, I am interested in understanding how inflammation influences the course of colorectal cancer evolution and identifying nutritional factors that can be used to perturb this process for the purpose of cancer prevention and treatment. Much of my work is based on two large prospective cohort studies, the Nurses' Health Study and the Health Professionals Follow-up Study, using a variety of instruments, including dietary assessment, genetic testing, and biomarker measurement in plasma and tissue specimens. Recently, as growing evidence indicates a critical role of the gut microbes in human health and disease, particularly colorectal neoplasia, I am investigating how the gut microbiome interacts with host diet and genetics to affect energy balance, immune homeostasis, and cancer development.

## Omega-3 intake and colorectal cancer incidence and survival

Andrew T. Chan and Mingyang Song

*Clinical and Translational Epidemiology Unit (CTEU),*
*Massachusetts General Hospital and Harvard Medical School*
BOSTON, MASSACHUSETTS, USA

Leveraging epidemiologic data from two large prospective cohort studies with decades of follow-up, we assessed the relationship between marine omega-3 fatty acid intake and colorectal cancer (CRC) incidence and survival, with a focus on the variation by tumor molecular characteristics. Our findings indicate that high intake of marine omega-3 fatty acid is associated with lower risk of CRC subsets that are characterized by microsatellite instability (MSI) and high infiltration of FOXP3+ T-regulatory (Treg) cells. These findings suggest that omega-3 may protect against CRC development by ameliorating Treg-mediated immune suppression and unleashing antitumor immunity. In addition, we have linked high intake of omega-3 after diagnosis to favorable prognosis among CRC patients, providing novel human evidence for the beneficial effect of omega-3 across the continuum of colorectal carcinogenesis.