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FRONTIERS
MEETINGS

Madrid 24 — 26 October 2022

Diet, Nutrition and Cancer Cell Metabolism

Organisers

Nabil Djouder
Spanish National Cancer Research Centre, CNIO, Madrid, Spain

Nikla Emambokus
Cell Metabolism, Cambridge, US

M. Carmen Fernández-Agüera
Cell Metabolism, Cambridge, US

Valter Longo
IFOM, Milan, Italy

Marcos Malumbres
Spanish National Cancer Research Centre, CNIO, Madrid, Spain

Speakers

Yasmine Belkaid
National Institute of Allergy and Infectious Diseases (NIH), Bethesda, US

Rafael de Cabo
National Institutes of Health (NIH), Bethesda, US

Sabrina Diano
Yale University School of Medicine, New Haven, US

Alejo Efeyan
Spanish National Cancer Research Centre, Madrid, Spain

Lluis Fajas
Center for Integrative Genomics (CIG), Lausanne, Switzerland

Mark A Febbraio
Monash Institute of Pharmaceutical Sciences, Monash University, Victoria, Australia

Marcus D. Goncalves
Weill Cornell Medicine, New York, US

Tak Mak
Princess Margaret Cancer Centre (UHN), Toronto, Canada

Nuria Malats
Spanish National Cancer Research Centre, CNIO, Madrid, Spain

Rubén Nogueiras
CiMUS, Santiago de Compostela University, Spain

Aurora Pérez Cornago
Oxford Population Health, University of Oxford, UK

Marina Pollán
National Center for Epidemiology (ISCIII), Madrid, Spain

Ana Ramírez de Molina
IMDEA Food Institute, Madrid, Spain

Romeo Ricci
IGBMC, Illkirch-Graffenstaden, France

M. Celeste Simon
Abramson Family Cancer Research Institute, University of Pennsylvania Perelman School of Medicine, US

Yu-Hua Tseng
Harvard Medical School, Joslin Diabetes Center, Boston, US

Matthew Vander Heiden
Koch Institute for Integrative Cancer Research, (MIT), Cambridge, US

Karen Vousden
The Francis Crick Institute in London, UK

EXCELENCIA SEVERO OCHOA 2012 - 2023

GOBIERNO DE ESPAÑA
MINISTERIO DE CIENCIA E INNOVACIÓN
Instituto de Salud Carlos III

cnio stop cancer

"la Caixa" Foundation

Madrid 24 — 26 October 2022

Diet, Nutrition and Cancer Cell Metabolism

Spanish National Cancer Research Centre (CNIO)
Madrid, Spain

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FRONTIERS
MEETINGS

Madrid 24 — 26 October 2022

Diet, Nutrition and Cancer Cell Metabolism

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FRONTIERS
MEETINGS

Madrid 24 — 26 October 2022

Diet, Nutrition and Cancer Cell Metabolism

Summary

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Madrid 24 — 26 October 2022

Diet, Nutrition and Cancer Cell Metabolism

Spanish National Cancer Research Centre (CNIO)
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cnio - CaixaResearch
FRONTIERS
MEETINGS

Madrid 24 — 26 October 2022

Diet, Nutrition and Cancer Cell Metabolism

Organisers and Speakers

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Madrid 24 — 26 October 2022

Diet, Nutrition and Cancer Cell Metabolism

Venue:

Spanish National Cancer Research Centre – CNIO Auditorium, Madrid.

Organisers:

Nabil Djouder
Spanish National Cancer Research Centre, CNIO, Madrid, Spain

Nikla Emambokus
Cell Metabolism, Cambridge, US

M. Carmen Fernández-Agüera
Cell Metabolism, Cambridge, US

Valter Longo
IFOM, Milan, Italy

Marcos Malumbres
Spanish National Cancer Research Centre, CNIO, Madrid, Spain

CNIO - CaixaResearch Frontiers Meeting

Speakers

Yasmine Belkaid
National Institute of Allergy and Infectious Diseases (NIH), Bethesda, US

Rafael de Cabo
National Institutes of Health (NIH), Bethesda, US

Sabrina Diano
Yale University School of Medicine, New Haven, US

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FRONTIERS
MEETINGS

Madrid 24 — 26 October 2022

Diet, Nutrition and Cancer Cell Metabolism

Programme

cnïo stop cancer

Monday October 24th, 2022

13:00 - 13:45 *Registration - welcome coffee for all participants (main hall)*

13:45 - 14:00 *Welcome address*

14:00 - 17:30 **S #1 - METABOLIC PATHWAYS AND CANCER**
Chaiperson: ***Marcos Malumbres***

14:00 - 14:30 *Influence of diet on tumor and systemic metabolism*
Matthew Vander Heiden,
Koch Institute for Integrative Cancer Research, MIT, Cambridge - US

14:30 - 14:45 *[short talk] - Short - chain fatty acid propionate as an attenuator of epithelial - to - mesenchymal transition in non - small cell lung carcinoma*
Paolo Ceppi,
University of Southern Denmark, Odense, Denmark

14:45 - 15:15 *Hypoxia, Metabolism, and the Tumor Microenvironment*
M. Celeste Simon,
Abramson Family Cancer Research Institute, University of Pennsylvania - US

15:15 - 16:00 *Coffee break (social room)*

Monday October 24th, 2022

16:00 - 16:30 *Oncogenic Isocitrate Dehydrogenase Mutations: Mechanisms, Models, and Clinical Opportunities*
Tak Mak,
Princess Margaret Cancer Centre (UHN), Toronto - Canada

16:30 - 16:45 *[short talk] - Targeting the translational machinery to overcome kinase inhibitor resistance of melanoma cells*
Adrian Alejandro Scholnik,
Hôpital Maisonneuve - Rosemont, Montréal, Canada

16:45 - 17:15 *A Role for Serine and One-Carbon Metabolism in Cancer*
Karen Vousden,
The Francis Crick Institute in London - UK

17:15 - 17:30 *[short talk] - The nutrient - Rag GTPase axis as a driver of cancer and inflammaging*
Alejo Efeyan,
Spanish National Cancer Research Centre (CNIO), Madrid - Spain

17:30 - 19:00 *Welcome Cocktail with all the participants (social room)*

Tuesday October 25th, 2022

09:00 - 13:15 S #2 - METABOLIC PATHWAYS AND DISEASE
Chaiperson: ***Lluis Fajas***

09:00 - 09:30 *Neddylation and glucose metabolism: from physiology to type 2 diabetes*
Rubén Nogueiras*,*
Center for Research in Molecular Medicine and Chronic Diseases,
Santiago de Compostela University - Spain

09:30 - 09:45 *[short talk] - Differential dietary regulation of proliferation of liver cells*
Manuel Alejandro Fernández Rojo,
IMDEA - Food Institute, Madrid, Spain

09:45 - 10:15 *Role of gp130 receptor activation in metabolic disease & cancer*
Mark Febbraio,
Monash Institute of Pharmaceutical Sciences, Monash University, Melbourne - Australia

10:15 - 10:30 *[short talk] - Analysis of fatty acid composition profile of tumoral and non - tumoral tissues from breast cancer patients*
Beatriz González Yebra,
Regional Hospital of High Specialty of Bajio, University of Guanajuato, Leon, Mexico

10:30 - 11:15 *Group picture & Coffee break (CNIO main door & social room)*

Tuesday October 25th, 2022

11:15 - 11:45 *CDK4 targets intracellular metabolism in cancer cells*
Lluis Fajas,
Center for Integrative Genomics (CIG), Lausanne - Switzerland

11:45 - 12:00 *[short talk] - A cell cycle kinase - phosphatase module restrains PI3K - Akt activity in an mTORC1 - dependent manner*
Begoña Hurtado,
Spanish National Cancer Research Centre (CNIO), Madrid - Spain

12:00 - 12:30 *Role of thermogenic adipose tissue in metabolic adaptation*
Yu - Hua Tseng,
Harvard Medical School, Joslin Diabetes Center, Boston - US

12:30 - 12:45 *[short talk] - Metabolic characterization of lysosome-rich enterocytes*
Gonzalo Herranz,
Severo Ochoa Molecular Biology Center, Madrid, Spain

12:45 - 13:15 *Endomembrane signalling in metabolism and inflammation*
Romeo Ricci,
Institute of Genetics and Molecular and Cellular Biology, Strasbourg - France

13:15 - 14:30 *Lunch (cafeteria)*

Tuesday October 25th, 2022

14:30 - 18:15 S #3 - NUTRITION, EPIDEMIOLOGY AND DISEASE
Chaiperson: ***Nuria Malats***

14:30 - 15:00 *Precision Nutrition and Cancer*
Ana Ramírez de Molina,
IMDEA Food Institute, Madrid - Spain

15:00 - 15:15 *[short talk] - Role of neutral amino acid transporter SLC38A2/SNAT2 in colorectal cancer progression*
Palanivel Kandasamy,
University of Bern, Switzerland

15:15 - 15:45 *Diet, WCRF/AICR Prevention Recommendations and Breast Cancer*
Marina Pollán,
National Center for Epidemiology (ISCIII), Madrid - Spain

15:45 - 16:30 Coffee break (social room)

16:30 - 17:00 *Redox state and hypothalamic regulation of metabolism*
Sabrina Diano,
Institute of Human Nutrition, Columbia University Irving Medical Center New York, US

17:00 - 17:15 *[short talk] - Targeting metabolic flexibility in hepatocellular carcinoma by nutrient restriction*
Jelena Krstic,
Medical University of Graz, Austria

17:15 - 17:45 *Integrating metabolic - dependent factors to understand pancreatic cancer aetiology*
Nuria Malats,
Spanish National Cancer Research Centre (CNIO), Madrid - Spain

17:45 - 18:15 *Diet, obesity and cancer risk*
Aurora Pérez Cornago,
Oxford Population Health, University of Oxford, UK

18:15 - 19:30 Poster session - Snack for all participants (social room)

Wednesday October 26th, 2022

09:00 - 12:45 S #4 - DIET, NUTRITION AND METABOLIC DISEASE
Chaiperson: ***Nabil Djouder***

09:00 - 09:30 *Fasting Mimicking Diet in Cancer Therapy*
Valter Longo,
The Firc Institute of Molecular Oncology, (IFOM), Milan - Italy

09:30 - 09:45 *[short talk] - Ovarian cancer treatment with a versatile glutamine antagonist JHU083 induces both anti - tumor T cell activation and cancer cell cycle arrest*
Yunta Chuang,
Johns Hopkins University, Baltimore, US

09:45 - 10:15 *Dietary and Therapeutic Targeting of Insulin Signaling in Endometrial Cancer*
Marcus DaSilva,
Weill Cornell Medicine, NY - US

10:15 - 10:30 *[short talk] - High cholesterol diet promotes the intravasation of breast tumor cells through an LDL - LDLR axis*
Ana Magalhães,
Institute of Molecular Medicine João Lobo Antunes, Lisboa, Portugal

10:30 - 11:15 *Coffee break (social room)*

Wednesday October 26th, 2022

11:15 - 11:45 *Caloric Restriction and Cancer Progression, From Calories to Fasting Times*
Rafael de Cabo,
National Institutes of Health (NIH), Baltimore - US

11:45 - 12:00 *[short talk] - Cyclic fasting - mimicking diet (FMD) plus bortezomib and rituximab as an effective treatment for Chronic Lymphocytic Leukemia (CLL)*
Olga Blazevits,
IFOM, Milan, Italy

12:30 - 12:45 *[short talk] - The bile acid/FXR axis in the spatial and temporal control of cirrhosis*
Paula Sánchez,
Spanish National Cancer Research Centre (CNIO), Madrid - Spain

13:00 - 15:00 *Lunch (cafeteria)*

15:00 - 15:30 *Farewell Lecture*
Microbiome control of host immunity
Yasmine Belkaid,
National Institute of A llergy and Infectious Diseases (NIH), Bethesda - US

15:30 - 16:00 *Prizes for best posters and best short talks – Concluding remarks - Farewell*

cnio - CaixaResearch
FRONTIERS
MEETINGS

Madrid 24 — 26 October 2022

Diet, Nutrition and Cancer Cell Metabolism

Monday Oct 24th 2022

Session #1
METABOLIC PATHWAYS AND CANCER

Chairperson: ***Marcos Malumbres***

cnio stop cancer

Influence of diet on tumor and systemic metabolism

Matthew Vander Heiden
Koch Institute for Integrative Cancer Research
Department of Biology - Massachusetts Institute of Technology, Cambridge, US

There is extensive evidence linking obesity and whole-body metabolism to cancer, and there is also a growing appreciation that dietary factors can impact tumor growth and the response to some therapies, but evidence is limited for which dietary choices are best for specific patients. Also unclear is how peripheral tissue wasting impacts tumor metabolism. We have found that diet composition can affect which nutrients are available to cancer cells in tumors. By comparing the effects of different diets on tumor nutrient availability, and those track with diet-induced changes in cancer phenotypes, we have uncovered novel mechanisms by which dietary nutrients can impact tumor growth. We are also uncovering the relationship between tumor growth in the pancreas, nutrient availability and tissue wasting. These data will be discussed along with how this information might be leveraged to impact care of patients with cancer.

Short-chain. Chain fatty acid propionate as an attenuator of epithelial-to- mesenchymal transition in non-small cell lung carcinoma

SHORT TALK

Vignesh Ramesh, **Paolo Ceppi**

Department of Biochemistry and Molecular Biology, University of Southern Denmark

Non-small cell lung cancer (NSCLC) represents an enormous health problem worldwide. The introduction of novel drugs has recently improved the scenario, but the patients' prognosis in many cases is still dismal because the drugs fail to prevent the metastatic spread. Epithelial to mesenchy mal transition (EMT) is a developmental cellular program that determines the aggressiveness of tumors by causing non only increased metastatization, but also promoting therapy resistance during tumor progression. Despite its importance in cancer, EMT properties have so far never been successfully attenuated by any drug available for cancer therapy. By large-scale transcriptomics and analysis of metabolic pathways in cancer, we found that EMT can be inhibited by metabolites belonging to the class of short chain fatty acids, like propionate. These are orally bio-available non-toxic small metabolites normally produced by our commensal gut microbiota, and therefore potentially very interesting for therapeutic use. Treatment of human lung cancer cell lines with sodium propionate (SP) 1) reinforced the epithelial identity of the cancer cells by increasing the expression of epithelial markers, 2) reduced their metastatic ability of cells injected in immune-deficient mice, and 3) significantly sensitized the cells towards cisplatin, backbone for cytotoxic chemotherapy in advanced-stage NSCLC patients. RNA-sequencing and validation/rescue experiments on SP-treated cells clearly indicated chromatin remodeling via histone acetylation as the mechanism behind EMT attenuation. Additional work to understand the role of lung microbiota on the EMT status of lung cancer cells is currently ongoing *in vitro* and in NSCLC tissue samples.
This class of dietary metabolites could be tested for chemoprevention of metastasis and for breaking EMT and chemotherapy resistance. Targeting EMT could have important potential implications in reducing the devastating effects of aggressive NSCLCs.

Hypoxia, Metabolism, and the Tumor Microenvironment

M. Celeste Simon

Scientific Director and Investigator, Abramson Family Cancer Research Institute
Associate Director-Shared Resources, Abramson Cancer Center
Arthur H. Rubenstein, MBBCh Professor, Department of Cell and Developmental Biology
University of Pennsylvania Perelman School of Medicine. Philadelphia, United States

Our laboratory investigates responses to changes in oxygen availability, as well as cancer cell adaptations to microenvironmental stresses that significantly contribute to advanced disease. Solid tumors frequently develop areas subjected to hypoxia and growth factor/nutrient deprivation, due to vascular insufficiency. I will discuss how this influences tumor progression.

Oncogenic Isocitrate Dehydrogenase Mutations: Mechanisms, Models, and Clinical Opportunities

Tak W Mak

Princess Margaret Cancer Centre (UHN), Universities of Hong Kong and Toronto
Toronto - Canada

Heterozygous mutations in catalytic arginine residues of isocitrate dehydrogenases 1 and 2 (IDH1 and IDH2) are common in glioma, acute myeloid leukemia, chondrosarcoma, cholangiocarcinoma, and angioimmunoblastic T-cell lymphoma. The mutant enzymes acquire a neomorphic activity that converts α-ketoglutarate (α-KG) to D-2-hydroxyglutarate (D2HG), a rare metabolite. In cells and tissues expressing mutant IDH, D2HG concentrations are highly elevated. D2HG may act as an "oncometabolite" by inhibiting a class of α-KG–dependent enzymes involved in epigenetic regulation, collagen synthesis, and cell signaling. Knock-in mouse models of IDH1 mutations have shed light on these mechanisms and will provide valuable animal models for further investigation.

SHORT TALK

Targeting the translational machinery to overcome kinase inhibitor resistance of melanoma cells

Schcolnik-Cabrera Alejandro[1,2],
Takdenti Meriem[1,2], Nouhi Zaynab[2], Topisirovic Ivan[3], Pelletier Jerry[3], Ronai Ze'ev[4], Hulea Laura[1,2]

1 Université de Montréal, Montréal, QC, Canada
2 Centre de recherche de l'Hôpital Maisonneuve-Rosemont, Montréal, QC, Canada
3 McGill University, Montréal, QC, Canada
4 Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA, USA

Unlike healthy cells, cancer cells harbor dysregulated signaling pathways converging to stimulate protein synthesis. Such signals remodel mRNA translation and metabolism to support neoplastic growth, and to develop therapy resistance.

Protein synthesis is one of the most energy-consuming cellular process, and oncogenic kinases (e.g. BRAF) play a central role in reprogramming translational and energy metabolism in neoplasia. Recent evidence has linked mTOR-4E-BPeIF4F-dependent translational regulation of metabolic genes to metabolic plasticity in oncogenic kinases-driven cancers (e.g. BRAFV600E melanoma), leading to partial resistance to metabolism-targeting therapies. Yet, how translational and metabolic programs are coordinated in cancer is poorly understood.

Drugs that interfere with translation initiation, such as eIF4A inhibitors (eIF4Ai) are effective against kinase inhibitor (KI)-resistant cancer cells. This suggests that inhibiting translation could be an alternative approach, by disrupting translational programs that support metabolic pathways fueling resistance to KIs, and limiting the capacity of cancer cells to surpass therapy.

We aim to test in BRAFV600E melanoma cells, resistant and sensitive to the BRAF inhibitor vemurafenib, the effects of eIF4Ai on translational programs supporting metabolic rewiring. We observed strong anti-proliferative effects of four different eIF4Ai on both vemurafenib-sensitive and -resistant cells, while reducing the expression of eIF4A-dependent proteins. Moreover, the eIF4Ai CR-1-31b induces apoptosis in a dose-dependent manner in both cell types, and ablates protein synthesis rate and mRNA translation levels. Finally, we observed significant alterations in the bioenergetic capacity, cellular metabolome and glutamine isotope incorporation following vemurafenib treatment in sensitive, but not vemurafenibresistant cells, while the addition of eIF4Ai alone was able to induce specific metabolic rewiring in both cell types.

A Role for Serine and One-Carbon Metabolism in Cancer

Karen Vousden
The Francis Crick Institute in London - UK

Many cancer cells depend on an exogenous supply of serine for optimal growth, and we have shown that limiting circulating serine levels by dietary intervention can reduce the growth and progression of some tumours. We are now exploring how modulation of one-carbon metabolism by the mitochondrial enzyme ALDH1L2 affects tumour cell migration and invasion. ALDH1L2 partitions one-carbon units to allow the production of formate, formyl-methionine and mitochondrial NADPH for antioxidant defence, and our studies show that each of these can impact the ability of cancer cells to migrate and metastasise. This work builds on our previous studies showing that loss of TIGAR – a protein with antioxidant activity – can retard or promote tumorigenesis in a mouse model of pancreas cancer. We have now found that loss of TIGAR in the cancer cells also impacts their interaction with the tumour microenvironment, driving a change in fibroblast and immune cell infiltration to support cancer cell dissemination.

Marc Hennequart, Eric Cheung and Karen Vousden
The Francis Crick Institute, London, UK

SHORT TALK

The nutrient – Rag GTPase axis as a driver of cancer and inflammaging

Alejo Efeyan

Group Leader, Metabolism and Cell Signaling Lab,
Spanish National Cancer Research Centre, CNIO, Madrid, Spain

The Rag GTPase signaling pathway activates the mechanistic target of rapamycin complex 1 (mTORC1) in response to cellular nutrient sufficiency. Recurrent mutations in components of the Rag GTPase pathway have been found exclusively in B cell lymphomas. We have engineered the RagC locus in mice with point, activating mutant variants found in human lymphoma to understand their impact on B-cell functions and lymphomagenesis. Cells from heterozygous RagC-mutant mice show a mild increase in mTORC1 activity, and heterozygous RagC-mutant mice exhibit aberrant B-cell activation and accelerated lymphomagenesis when bred to a lymphoma-prone strain. Conversely, genetic suppression of Rag GTPase signaling in mice, achieved by the expression of a hypomorphic RagC allele, compromises B-cell functions and delays lymphomagenesis.

Without a lymphoma-prone genetic background, full-body RagC-mutant mice show a 25% reduction in lifespan with a surprising reduction in spontaneous tumor development, but with multiple features of a premature aging phenotype. To our knowledge, this is the first genetic system with an increased nutrient signaling – mTORC1 axis in mice to understand cellular and molecular underpinnings that link this pathway to aging. The shortened lifespan of RagC-mutant mice occurs with prominent parenchymal senescence in peripheral organs, and extensive features of inflammaging. Acute control of myeloid inflammation in aged RagC-mutant mice reverts some of the premature aging features, and extended suppression of myeloid cells extends the longevity of mice with increased nutrient – Rag GTPase signaling.

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Diet, Nutrition and Cancer Cell Metabolism

Tuesday Oct 25th 2022

Session #2
METABOLIC PATHWAYS AND DISEASE

Chairperson: ***Lluis Fajas***

cnio stop cancer

Neddylation and glucose metabolism: from physiology to type 2 diabetes

Rubén Nogueiras
Center for Research in Molecular Medicine and Chronic Diseases, (CiMUS)
Santiago de Compostela University - Spain

Neddylation is an energy-dependent, post-translational mechanism that adds a ubiquitin-like protein, NEDD8, to a lysine residue of the substrate protein (predominantly on cullin proteins). This conjugation occurs in a three-step enzymatic process using NEDD8 activating enzyme E1 (NAE1) that initiates the NEDD8 transfer cascade, E2 conjugating enzymes and E3 ligases. Many of the known neddylation substrates are related with tumorigenesis, and preclinical results indicate that the inhibition of the NEDD8 conjugation might be an effective anti-cancer strategy.

Our laboratory has shown that neddylation in liver is modulated by nutrient availability. Inhibition of neddylation in mouse liver (either pharmacologically or genetically) reduces gluconeogenic capacity and the hyperglycemic actions of counterregulatory factors (glucagon, adrenaline and glucocorticoids). Further, people with obesity and type 2 diabetes (but not obesity and normoglycemia) display elevated hepatic neddylation levels that correlate positively with fasting glucose levels. Mechanistically, we determined that fasting or caloric restriction of mice leads to neddylation of phosphoenolpyruvate carboxykinase 1 (PCK1) at three lysine residues. Of note, we find that mutating the three PCK1 lysines that are neddylated reduces its gluconeogenic activity levels. Molecular dynamics simulations show that neddylation of PCK1 could reposition two loops surrounding the catalytic center into an open configuration, rendering the catalytic center more accessible. We propose that neddylation of PCK1 provides a finely-tuned mechanism of controlling glucose metabolism by linking whole nutrient availability to metabolic homeostasis.

Differential dietary regulation of proliferation of liver cells

SHORT TALK

Herrera LV[1], Moral-Sanz J[2], Garrido M[1], Martin R[5], Colmarejo G[5], Gonzalez D[4], Diaz E[4], Fajardo P[4], Monge Patricia[6], Garrido Alvaro[6,] Astudillo Alma M[6], Balsinde J[6,7], Cuenda A[4], Ikonomopoulou MP[2,3,8], **Manuel A. Fernandez-Rojo**[1,3]

Madrid Institute for Advanced Studies in Food, Madrid, 28049, Spain.
1 Hepatic Regenerative Medicine Laboratory,
2 Translational Venomics Laboratory,
5 Bioinformatic Unit, The University of Queensland, Brisbane, Australia
3 School of Medicine, Herston, QLD 4002
8 Institute for Molecular Bioscience, St Lucia, QLD 4047.
Consejo Superior de Investigaciones Científicas (CSIC),
4 Department of Immunology and Oncology, Centro Nacional de Biotecnología, Madrid, Spain
6 Instituto de Biología y Genética Molecular, Valladolid, Spain.
7 (CIBERDEM), Madrid, Spain.

Ketogenic Diet (KD)-feeding and the ketone body B-hydroxybutyrate have benn proposed as a nutritional intervention and metabolite with anti-tumour properties including in the liver. Indeed, KD has been proposed to reduce non-alcoholic fatty liver disease (NAFLD) and its progression to non-alcoholic steatohepatitis (NASH) that preclude the formation of liver hepatocarciomas (HCC). Now, our current investigations show that KD-feeding does not prevent the development of HCC induced by the pro-carcinogenic diethyl-nitrosamine (DEN). Mice treated with DEN under a KD-feeding 1 or 3 months prior to harvest the tumors (at 9 months of age), exhibited similar incidence, number and size of HCC than mice fed a chow diet. In contrast, we have found that KD is deleterious for overcoming the loss of liver mass after partial hepatectomy (aPHx) in healthy C57BL/6 mice and in mice exhibiting in diet-induced-NASH (MCD-NASH), and the majority of them died between the 24-48h aPHx. Accordingly, RNA-sequencing revealed that KD impairs the expression of DNA-replication machinery and the cytokine and growth factorsinduced pathways driving the proliferation of liver cells during regeneration. Hence, our data support a dual and differential role of KD-feeding during the malignant (HCC) and benign (regeneration) proliferation of liver cells.

Role of gp130 receptor activation in metabolic disease & cancer

Mark A. Febbraio

Cellular & Molecular Metabolism Laboratory, Drug Discovery Biology,
Monash Institute of Pharmaceutical Sciences,
Monash University, Parkville, Australia

The gp130 receptor (gp130R) cytokines interleukin-6 (IL-6) and ciliary neurotrophic factor (CNTF) can improve metabolic disease, but due to the known pro-inflammatory effects of IL-6 and the antigenic response to the clinically used form of CNTF (Axokine™), both proteins have limited therapeutic utility. Accordingly, we recently engineered a chimeric gp130R ligand, termed IC7Fc, where one gp130 binding site has been removed from IL-6 and replaced with the leukemia inhibitory factor receptor (LIFR) binding site from CNTF and then fused with the fragment crystallizable (Fc) domain of immunoglobulin G (IgG), that shows promise for treating metabolic disease[1]. Moreover, in multiple models of insulin resistance and T2D, IC7Fc either increases, or prevents the loss, of skeletal muscle mass via increased abundance and activity of the Yes-associated protein (YAP)[1]. In parallel studies, we recently demonstrated that activation of the gp130R in the intestinal epithelium activates YAP and, in doing so, prevents fructose feeding-induced gut barrier deterioration, systemic endotoxemia, non-alcoholic steatohepatitis (NASH) and NASH driven liver cancer[2]. The concept that spg130R ligands could, therefore, have therapeutic utility for the treatment of several age-related diseases will be discussed.

[1] Findeisen, M. *et al.* Treatment of type 2 diabetes with the designer cytokine IC7Fc. Nature 574, 63-68, (2019).

[2] Todoric, J. *et al.* Fructose stimulated de novo lipogenesis is promoted by inflammation. *Nat Metab* 2, 1034-1045, (2020).

Analysis of fatty acid composition profile of tumoral and non-tumoral tissues from breast cancer patients

SHORT TALK

Beatriz Gonzalez Yebra[1,2], Ana L. Gonzalez[3], Jorge. Molina Torres[4], Miguel Angel Guerrero Ramos[5], Enrique Ramirez Chavez[4], Noemí Gutierrez[1], Daniela Muñoz Lopez[1], Elia Lara Lona[1], Pablo Romero Morelos[6]

1 Universidad de Guanajuato, Depto. Medicina y Nutrición, Leon, Mexico.
2 Hospital Regional de Alta Especialidad del Bajio, Depto. Investigación, Leon, Mexico.
3 Universidad de Guanajuato, Depto. Ciencias Aplicadas al Trabajo, Leon, Mexico.
4 CINVESTAV, Depto. Biotecnología y Bioquímica, Irapuato, Mexico.
5 Hospital Regional de Alta Especialidad del Bajío, Depto. Oncología, León, Mexico.
6 Universidad Estatal del Valle de Ecatepec, Depto. Investigacion, Ecatepec, Mexico.

Breast cancer (BC) is the most diagnosed cancer in woman with 24.5% incidence and 15.5% mortality. Several factors including age, genetics, lifestyle, smoking, alcohol consumption, physical activity, and diet, influence the risk for this disease.

Evidence focusing on the role of diet in BC has emerged recently. Saturated and unsaturated fatty acids (FA) are associated with increased BC risk. The role of specific polyunsaturated fatty acids (PUFA) for protecting or promoting cancer effects have been studied. In western diets, the most common FA are n-6 PUFA, found in corn and safflower oils and could be precursors of development of mammary tumors. In contrast, n-3 PUFA may have anticancer effects. In the other hand, there are few studies investigating the FA composition in breast tissues, in this sense, our aim was to determine the FA profile differences in the tumoral and non-tumoral BC tissues. We analyzed FA composition by GC-MS from 50 mg of tumoral and non-tumoral tissue resected from the same patient (n=4 non-tumoral adjacent breast tissue and n=4 tumoral breast tissues). No significant differences were detected in a) total FA between non-tumoral and tumoral tissues (394.9±284 vs 228.9±136.6, p=0.33); b) saturated (48.23±50.7 vs 22.06±10.01, p=0.35); c) monounsaturated (69.08±81.82 vs 104.8±69.85, p=0.88); d) PUFA (3.553±1.978 vs 7.115±3.22, p=0.1), e) n-6 PUFA (49.36±56.16 vs 5.048±3.148, p=0.16), f) n-3 PUFA (136.2±106.9 vs 47.73±24.07, p=0.15) or g) n-6/n-3 PUFA ratio (0.2261±0.2379 vs 0.2025±0.2767, p=0.68). Interestingly, only n-6 PUFA, arachidonic acid (ARA) showed differences between non-tumoral and tumoral breast tissue (1.41±0.763 vs 3.74±1.19, p=0.02). The results suggest no different FA composition, neither in n-6/n-3 PUFA ratio between tumoral and non-tumoral adjacent breast tissue in patients. Increased AA levels in tumoral breast tissue may be related to mechanism of carcinogenesis at molecular level.

CDK4 targets intracellular metabolism in cancer cells

Lluis Fajas
Center for Integrative Genomics (CIG),
Lausanne – Switzerland

We focus this work to demonstrate the regulatory crosstalk between the cell cycle regulator CDK4 and metabolic pathways. We show that CDK4 is a significant sensor and effector of cellular metabolic homeostasis at the core of insulin and growth factor signaling. In cancer cells, CDK4 rewires metabolism towards biosynthetic processes, blocking energy expenditure. Consequently, CDK4 deletion or inhibition in breast cancer cells remodels the mitochondrial dynamics, and the calcium signaling pathways, resulting in unexpected resistance of CDK4-deficient cells to cell death.

SHORT TALK

A cell cycle kinase-phosphatase module restrains PI3K-Akt activity in an mTORC1-dependent manner

Belén Sanz-Castillo[1], **Begoña Hurtado**[1], Diana Vara-Ciruelos[1], Aicha El Bakkali[1], Dario Hermida[1], Beatriz Salvador-Barbero[1], Diego Martínez-Alonso[1], José González-Martínez[1], Clara Santiveri[2], Ramón Campos-Olivas[2], Pilar Ximénez-Embún[3], Javier Muñoz[3], Mónica Álvarez-Fernández[1,4]* and Marcos Malumbres[1],*

1 Cell Division and Cancer group, Spanish National Cancer Research Centre (CNIO), Madrid
2 Spectroscopy and Nuclear Magnetic Resonance Unit, Spanish National Cancer Research Centre (CNIO), Madrid
3 Proteomics Unit, Spanish National Cancer Research Centre (CNIO), Madrid
4 Present address: Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Instituto Universitario de Oncología del Principado de Asturias (IUOPA), Oviedo-Asturias

The AKT-mTOR pathway is a central regulator of cell growth and metabolism. Upon sustained mTOR activity, AKT activity is attenuated by a feedback loop that restrains upstream signaling. However, how cells control the signals that limit AKT activity is not fully understood. Here we show that MASTL/Greatwall, a cell-cycle kinase that supports mitosis by phosphorylating the PP2A/B55 inhibitors ENSA/ARPP19, inhibits PI3K-AKT activity by sustaining mTORC1- and S6K1-dependent phosphorylation of IRS1 and GRB10. Genetic depletion of MASTL results in an inefficient feedback loop and AKT hyperactivity. These defects are rescued by expression of phospho-mimetic ENSA/ARPP19 or inhibition of PP2A/B55 phosphatases. MASTL is directly phosphorylated by mTORC1, thereby limiting the PP2A/B55-dependent dephosphorylation of IRS1 and GRB10 downstream of mTORC1. Downregulation of MASTL results in increased glucose uptake *in vitro* and increased glucose tolerance in adult mice, suggesting the relevance of the MASTL-PP2A/B55 kinase-phosphatase module in controlling AKT and maintaining metabolic homeostasis.

Role of thermogenic adipose tissue in metabolic adaptation

Yu-Hua Tseng
Harvard Medical School, Joslin Diabetes Center,
Boston - US

Obesity and metabolic syndrome rapidly increase worldwide, leading to high morbidity and mortality in type 2 diabetes, cardiovascular disease, renal failure, and even some cancers. Increased adiposity is the main characteristic of obesity. In mammals, there are two functionally distinct types of fat: white adipose tissue (WAT), specialized for energy storage, and brown and related beige/brite adipose tissue (BAT, collectively called 'thermogenic adipose tissue') that dissipates energy for thermogenesis. Mounting evidence suggests that the presence and activation of BAT protect obesity-induced cardiometabolic disorders in humans. Thermogenic adipose tissue can rapidly respond to environmental changes, including diet or temperature, and such adaptation is essential to maintaining adipose function and metabolic health. Although BAT has been traditionally recognized for its energy-consuming function, it also exerts beneficial effects via the secretion of signaling molecules, such as lipids, proteins, microRNA, or other metabolites, to modulate systemic metabolism. Secreted factors may act as endocrine, paracrine, or autocrine agents to regulate physiological functions required for adaptive thermogenesis. Using targeted and untargeted liquid chromatography-tandem mass spectrometry, we discovered that cold exposure and beta3-adrenergic stimulation promote BAT to produce multiple bioactive lipids that can regulate nutrient metabolism, resolve inflammation and improve insulin sensitivity in obesity. In this talk, I will present our recent endeavors in understanding the mechanisms of action of BAT-derived bioactive lipid mediators in inter-organ crosstalk and their roles in energy homeostasis.

Metabolic characterization of lysosome-rich enterocytes

SHORT TALK

Gonzalo Herranz[1], Tamara González[1], Alejandra R. Manzano[1], Covadonga Díaz-Díaz[1], Marta Iborra-Pernichi[1], Patricia Boya[2], Nuria Martínez-Martín[1] and Fernando Martín-Belmonte[1]

1 Centro de Biología Molecular Severo Ochoa (CBMSO) CSIC-UAM,
2 Centro de Investigaciones Biológicas Margarita Salas - CSIC

Protein malnutrition is particularly harmful during early postnatal stages, resulting in stunted growth and reduced body weight, increased risk of infection and impaired brain development and function. Because during neonatal life proteins are not fully digested in the lumen of the gastrointestinal tract, protein absorption relies on intracellular digestion by specialized intestinal cells in the ileum called lysosome-rich enterocytes (LREs). In addition, the canalicular system of LREs allow the transport across the epithelial barrier, without loss of their biological activity, of maternal immunoglobulins, and antibodies, contributing to the development of innate and adaptive immune systems.

In mouse models, it has been reported that premature replacement of LREs results in growth retardation and elevated neonatal mortality. In the same way, suckling mice with deficient LREs endocytosis show signs reminiscent of kwashiorkor, a devastating infant human malnutrition syndrome.

We hypothesized that diet-microbiota-LREs network is crucial for the proper growth of the individual. The general aim of our project is the characterization of physiological properties of LREs during postnatal development by generating novel and comprehensive transgenic mouse models for testing LREs function.

Following RNA-seq analyses, we found that LREs display a different expression of genes involved in autophagy and mitophagy induction, as well as in lysosomal activity. Consequently, we have generated two mouse models: Atg16KO which eliminates autophagy, and TfamKO to stop mitochondria-lysosome interactions. Genetic analysis of neonatal Atg16KO mice revealed a downregulation of essential LREs genes, and an early metabolism switch to adultness. While Atg16KO enterocytes downregulate neonatal enzymes specialized in the processing of milk constituents, and upregulate adult enzymes required to process solid food; TfamKO neonatal mice show a noticeable weight loss and decrease in LREs gene expression resulting in them not surviving their postnatal stage. Understanding the physiology of both phenotypes, including their correlations with diet and microbiota, would ensure promising therapies for malnourished children.

Endomembrane signalling in metabolism and inflammation

Romeo Ricci

The Institute of Genetics and Molecular and Cellular Biology, IGBMC
Illkirch-Graffenstaden, France

Living organisms have developed intricate mechanisms to adapt to environmental stress. Our laboratory is interested in how stress sensing and signaling can be overwhelmed in a way it rather contributes to cellular dysfunction and disease focusing on endomembrane signaling events in the context of cellular metabolism and inflammation. In my talk, I will focus on our most recent findings providing evidence for endosomal stress to be a key event eliciting basic innate immune responses in macrophages.

Inflammasome complexes are pivotal in the innate immune response to pathogens and other danger signals. The NLRP3 inflammasome is activated in response to a broad variety of cellular stressors. Most of the stimuli act in a potassium efflux-dependent manner but a primary and converging sensing mechanism by the NLRP3 receptor initiating inflammasome assembly remains ill-defined.

Here we demonstrate that NLRP3 inflammasome activators primarily converge on disruption of ER-endosome membrane contact sites (EECS). This defect causes endosomal accumulation of PI4P and a consequent impairment of endosome-to-TGN trafficking (ETT), necessary steps for binding of NLRP3 to endosomes and subsequent inflammasome activation. Lowering endosomal PI4P levels prevents endosomal recruitment of NLRP3 and inhibits inflammasome activation. Disruption of EECS or ETT is sufficient to enhance endosomal PI4P levels, to recruit NLRP3 to endosomes and to potentiate NLRP3 inflammasome activation. Mice with defects in ETT in the myeloid compartment are more susceptible to LPS-induced sepsis in a NLRP3-dependent manner. Our study thus identifies a distinct cellular mechanism leading to endosomal NLRP3 recruitment and inflammasome activation.

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Madrid 24 — 26 October 2022

Diet, Nutrition and Cancer Cell Metabolism

Tuesday Oct 24th 2022

Session #3
NUTRITION, EPIDEMIOLOGY AND DISEASE

Chairperson: ***Nuria Malats***

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Precision Nutrition and Cancer

Ana Ramírez de Molina
IMDEA Food Institute,
Madrid - Spain

The World Health Organization estimates that around one third of cancer deaths are due to parameters related to diet and lifestyle and it has been estimated that more than 50% of cancers could be avoided, or their treatment significantly improved by applying science-based nutritional strategies. In this sense, emerging Precision Nutrition discipline refers to targeted application of nutritional and life-style factors that can exert an effective preventive and therapeutic action in the oncological patient, in which personalized recommendations are based on the molecular effect of the products, as well as the molecular and physiological characteristics of the patients. In this area, two different approaches will be presented, including a therapeutic nutritional product designed and formulated to inhibit tumor metabolism, as well as a mHealth platform for continuous patient monitoring. The results of this study support the benefit of including precision nutrition strategies within personalized management of cancer patients.

Role of neutral amino acid transporter SLC38A2/SNAT2 in colorectal cancer progression

SHORT TALK

Palanivel Kandasamy[1], Ashley Leon Fernandes[1], Inti Zlobec[2], Matthias A. Hediger[1]*.

1 Membrane Transport Discovery Lab, Department of Nephrology and Hypertension, Inselspital, and Department of Biomedical Research, University of Bern, Switzerland.
2 Institute of Pathology, Translational Research Unit (TRU), University of Bern, Murtenstrasse 31, Bern 3010, Switzerland

Many tumor cell types often rely on exogenous supply of amino acids and therefore tumor cells express increased levels of solute carrier (SLC)-amino acid transporters. Previous studies have shown that selected amino acid transporters (e.g. SLC7A5/LAT1 and SLC1A5/ASCT2) play a key role in human cancers including colorectal cancers (CRCs). SLC38A2 is another important neutral amino acid transporter, is upregulated in CRCs, and associated with poor survival. However, the role of its transport functions in CRC development and its mechanism of regulation are as yet poorly understood. Here, we investigated the role of SLC38A2/SNAT2 in CRC cell proliferation, mTOR signaling and metabolic reprogramming by specific gene deletion and pharmacological inhibition in different CRC cell lines. Our data show that pharmacological inhibition of SLC38A2-mediated amino acid transport and specific knockout of SLC38A2/SNAT2 reduces glutamine consumption, mTOR activation, mitochondrial membrane potential, ATP synthesis and CRC cell proliferation. In conclusion, SLC38A2 hold potential as direct drug target for cancer therapy to selectively slow down the growth of tumor cells without affecting the proliferation of healthy cells.

Diet, WCRF/AICR prevention recommendations and breast cancer

Marina Pollán
National Center for Epidemiology (ISCIII),
Madrid - Spain

Redox state and hypothalamic regulation of metabolism

Sabrina Diano
Institute of Human Nutrition, Columbia University Irving Medical Center
New York, US

Our research has been focusing on deciphering intracellular mechanisms that enable hypothalamic cells to sense and respond to changes in circulating nutrient and hormone levels in the control of food intake and energy and glucose metabolism. Our findings have unmasked changes in redox state as critical players in the regulation of neuronal functions. This presentation will highlight this cellular biological process in the hypothalamic regulation of energy and glucose homeostasis.

SHORT TALK

Targeting metabolic flexibility in hepatocellular carcinoma by nutrient restriction

Jelena Krstic[1], Zina Riahi[1], Helene Michenthaler[1], Elisabeth Moyschewitz[1], Corina Madreiter-Sokolowski[2], Andreas Prokesch[1]

1 Division of Cell Biology, Histology and Embryology, Gottfried Schatz Research Center, Medical University of Graz, Austria
2 Division of Molecular Biology and Biochemistry, Gottfried Schatz Research Center, Medical University of Graz, Austria

Hepatocellular carcinoma (HCC) is among the deadliest cancers worldwide. Due to a limited response to current therapies, there is an unmet need for additional treatment strategies. Cancer cells rely both on oxidative phosphorylation (OxPhos) and aerobic glycolysis for energy production, and can tune these metabolic pathways to support their proliferation and growth. Hence, inhibiting one of the two pathways can lead to the compensatory upregulation of the respective other pathway, leading to resistance to primary metabolic therapies. Therefore, we used a 'double-hit' approach in a xenograft HCC model: we inhibited OxPhos using sorafenib, a commonly used targeted therapy, and simultaneously reduced glucose availability by periodical fasting or a fasting mimicking diet. This combination therapy led to significant reduction in tumor growth. Next, we tested several OxPhos inhibitors in combination with nutrient restriction as a broad treatment strategy for HCC. Three HCC-derived cell lines were treated with six different OxPhos inhibitors in growth medium and in low glucose or glucose-free starvation media. Based on the initial viability screen, we selected two inhibitors, gboxin and atovaquone, for further analyses in HepG2 cells. The effect of atovaquone on cell viability was significantly enhanced already in low glucose medium, while gboxin was effective only in combination with glucose-free medium. Metabolic profiling demonstrated that HepG2 cells highly rely on OxPhos, which was significantly inhibited by both drugs. However, the cells were able to overcome this inhibition by increasing their glycolytic activity in the presence of glucose. Hence, glucose depletion was necessary to inhibit both pathways and completely block cell growth.
Together, our results shed light on the specifics of the synergism between glucose reduction and OxPhos inhibition in HCC and prompt further investigation of nutrient restriction as adjunct to OxPhos inhibitors for cancer therapy.

Integrating metabolic-dependent factors to understand pancreatic cancer aetiology

Nuria Malats
Spanish National Cancer Research Centre (CNIO),
Madrid - Spain

Pancreatic cancer (PC) aetiology is multifactorial with both genetic and non-genetic factors interacting over lifesplan. While diabetes and obesity are well-stablished risk factors for PC, their specific role in PC development is not yet understood. Recent evidences on the relationship between genomics, microbiome, metabolome, and diabetes and obesity may help in identifying the missing pieces of this complex puzzle.

Diet, obesity and cancer risk

Aurora Pérez Cornago
Oxford Population Health, University of Oxford, UK

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Diet, Nutrition and Cancer Cell Metabolism

Wednesday Oct 26th 2022

Session #4
DIET, NUTRITION AND METABOLIC DISEASE

Chairperson: ***Nabil Djouder***

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Fasting Mimicking Diet in Cancer Therapy

Valter Longo
The Firc Institute of Molecular Oncology, (IFOM),
Milan - Italy

Ovarian cancer treatment with a versatile glutamine antagonist JHU083 induces both anti-tumor T cell activation and cancer cell cycle arrest

SHORT TALK

Tianhe Li, **Yunta Chuang,** Hao-Lin Lin, Ellen Tully, Jayaprakash Mandal, Stephanie L Gaillard, Tian-Li Wang, Ie-Ming Shih

Departments of Pathology, Oncology, and Genecology/Obstetrics, The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, School of Medicine, Maryland, USA

Ovarian cancer is among the most malignant gynecologic diseases for the difficulty in early diagnosis and its drug resistance. Glutamine metabolism has been shown to play a critical role in tumor progression of ovarian cancer and cancer-specific inhibition of glutamine metabolism represents a viable cancer therapeutic strategy.

In this regard, a glutamine antagonist 6-Diazo-5-oxo-l-norleucine (DON) was modified to JHU083, which targets tumors upon activation by protease, an enzyme that is upregulated in ovarian cancers.

Treating the ID8 murine ovarian cancer syngeneic model with JHU083 (0.91 mg/kg) for 3 weeks, we observed significant anti-tumor effects with minimal toxicity. In the JHU083-treated mice, PD-L1 expression was significantly down-regulated in ascites tumors. Profiling of ascites tumor immune cell population by flow cytometry showed that JHU083 treatment enhanced recruitment of CD8 and CD4 positive T cells to the tumor environment, supporting potential efficacy of JHU083 in enhancing host immunity.

Although JHU083 demonstrated potent *in vivo* anti-tumor efficacy, the mechanism is still unclear. Therefore, we performed cell cycle analysis in resistant ovarian cancer cell lines SKOV3 and PEO4 and observed DON treatment induced S phase arrest and increased DNA double strand breaks. We analyzed global phospho proteome in DON-treated SKOV3 cells and found that low dose DON treatment elicits DNA damage repair response, activates cell cycle checkpoint, and inhibits ribonucleotide reductase, a critical pathway regulating DNA synthesis. Collectively, our findings indicate that prolonged S-phase arrest and nucleotide metabolism inhibition are dominant mechanisms of DON to induce cancer cell death.

In conclusion, our results demonstrate the efficacy of JHU083 in treating human ovarian cancer through host immune enhancement and potent anti-tumor cytotoxity, and provide mechanistic insights from glutamine inhibition to the observed therapeutic effect.

Dietary and Therapeutic Targeting of Insulin Signaling in Endometrial Cancer

Marcus DaSilva Gonçalves
Weill Cornell Medicine, NY - US

Endometrial cancer (EC) is the most common gynecologic malignancy in the developed world, and its incidence and mortality rate are increasing due, in part, to the obesity epidemic. Obesity increases the risk of death from endometrial cancer, and there are a variety of systemic changes that occur in the obese state that create a milieu that favors tumor initiation and progression. One of these factors, hyperinsulinemia, has been directly implicated in the pathogenesis of EC, and may underlie the strong association of obesity with tumor progression. Insulin stimulates PI3K to drive cell growth, proliferation, and anti-apoptotic pathways. Unfortunately, PI3K inhibitors have not been effective in clinical trials for EC. Using pre-clinical models, we identified hyperinsulinemia as an acute, systemic, drug-induced adaptation that limits the efficacy of these drugs. This adverse effect can be mitigated in animal models using dietary and pharmacologic approaches that target the endocrine system. In this presentation, I will present data from patient-derived tumor tissue, mouse xenograft models, and tissues from clinical intervention trials that support the clinical utility of this strategy.

High cholesterol diet promotes the intravasation of breast tumor cells through an LDL-LDLR axis

SHORT TALK

Ana Magalhães, Vanessa Cesário, Diogo Coutinho, Inês Matias, Germana Domingues, Catarina Pinheiro, Teresa Serafim, Sérgio Dias

Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa, Lisboa, Portugal

High systemic LDL levels correlate with increased tumor size and disease progression in both clinical and animal models. However, the mechanisms by which high LDL favors metastatic spread, are still undisclosed. Intravasation is an early event of the metastatic cascade that consists in cancer cells crossing blood vessel endothelial monolayers to reach the blood. The cellular and molecular mechanisms that regulate intravasation are still largely unknown, particularly how diet and systemic metabolic alterations affect it. Here we show that a short-term high cholesterol diet (HCD) that dramatically raises LDL without affecting BMI and triglyceride levels, promotes the intravasation of breast cancer cells through and LDL-LDL receptor (LDLR) axis. We used GFP-expressing 4T1, MDA-231 cells injected orthotopically in immunocompetent or immunosuppressed mice, respectively, and evaluated the presence of CTCs (GFP+ cells) by flow cytometry.We show that the feeding on high cholesterol accelerates the entry of tumor cells in circulation in a way that is independent of its effect on tumor size, increased number of blood vessels or blood vessel permeability. *In vitro*, we show that LDL directly affects tumor cell´s ability to interact, intercalate and transmigrate endothelial monolayers. Closer look suggested that this resembled vascular mimicry, which has been shown by others to contribute to intravasation through the action of Serpine2. We show that LDL induces the expression of Serpine2 and that this is partially reverted by blocking the interaction of LDL with the LDLR.

Finally, we show that blocking the LDLR *in vivo*, results in a partial reversion of both the HCD-induced increase in intravasation and lung metastasis. In summary, we propose that one of the mechanisms by which a HCD may lead to increased metastasis is due to the ability of high LDL levels to induce the tumor cell crossing –of endothelial monolayers during intravasation.

Caloric Restriction and Cancer progression, From Calories to Fasting Times

Rafael de Cabo

Chief of the Translational Gerontology Branch at the National Institute on Aging, National Institutes of Health, USA.

Cancer incidence increases with age and is a leading cause of death. Caloric restriction (CR) confers benefits on health and survival and delays cancer. However, due to CR's stringency, dietary alternatives offering the same cancer protection have become increasingly attractive. Short cycles of a plant-based diet designed to mimic fasting (FMD) are protective against tumorigenesis without the chronic restriction of calories. Yet, it is unclear whether the fasting time, level of dietary restriction, or nutrient composition is the primary driver behind cancer protection. Using a breast cancer model in mice, we compared the potency of daily CR to that of periodic caloric cycling on FMD or an isocaloric standard laboratory chow against primary tumor growth and metastatic burden.

Cyclic fasting-mimicking diet (FMD) plus bortezomib and rituximab as an effective treatment for Chronic Lymphocytic Leukemia (CLL)

SHORT TALK

Franca Raucci, Claudio Vernieri, Maira Di Tano, Giuseppe Fragale, Francesca Ligorio, Giulia Salvadori, **Olga Blaževitš,** Roberta Buono, Euplio Visco, Filippo de Braud, Valter Longo

IFOM, Milan,
Italy

Chronic lymphocytic leukemia (CLL) is the most common hematological malignancy in Western countries. Although several effective anti-CLL treatments have become available in the last two decades, long-term disease control is still an unmet clinical need in some patients with aggressive disease. Cyclic fastingmimicking diet (FMD) is an experimental nutritional intervention that has demonstrated potent antitumor activity in preclinical models of solid malignancies, and it has been recently shown to be safe, and metabolically/immunologically active in cancer patients. Here, based on promising outcomes of FMD cycles in two CLL patients, we investigated its effects in pre-clinical CLL models and show that cyclic fasting/FMD, have mild antitumor effects, which are mediated in part by the reduction of extracellular insulin and IGF-1 concentration. Among the potentially efficacious anti-CLL drugs, proteosome inhibitor bortezomib (BTZ) is the most effective in combination with fasting/FMD, which is explained by the strong activation of proteasome activity in startved CLL cells. Combining cyclic fasting/FMD and BTZ with the anti-CD20 monoclonal antibody rituximab (RTX), which is widely used in leukemia therapy, increases CLL cell death *in vitro* and delays CLL progression in intravenous and subcutaneous CLL mouse models, resulting in the prolongation of survival. Our findings point to FMD plus BTZ-RTX as a new, effective and non-toxic anti-CLL treatment to be tested in clinical trials.

SHORT TALK

The bile acid/FXR axis in the spatial and temporal control of cirrhosis

Paula Sanchez[1], Ajay Nair[2], Robert Schwabe[2] and Nabil Djouder[1]*

1 Molecular Oncology Programme, Growth Factors, Nutrients and Cancer Group, Centro Nacional Investigaciones Oncológicas (CNIO), Madrid, 28029, Spain
2 Institute of Human Nutrition, Columbia University, New York, NY 10032, USA.

*Correspondence: Nabil Djouder
Tel: 0034 91 7328000 (Ext.: 3830)
Fax: 0034 91 2246914
Email: ndjouder@cnio.es

Upon chronic damage and when hepatocyte turnover is affected, liver tissue engages complex regenerative mechanisms that involve expansion of cholangiocytes, leading to the formation of regenerative nodules and, the activation of the quiescent hepatic stellate cells (HSCs) that become myofibroblasts, which deposit extracellular matrix (ECM) components and promote fibrosis. If these two cellular processes occur continuously, liver cirrhosis develops, and then progresses to hepatocellular carcinoma (HCC), the most common and one of the most lethal liver cancers. Work from our lab demonstrated the causal relationship between bile acid (BA) flow perturbation and cirrhosis development. BAs secreted by hepatocytes accumulate in liver sinusoids of cirrhotic mice to activate HSCs via farnesoid X receptor (FXR). This supposes that BAs/FXR axis can act similarly on cholangiocytes and if so, why then cirrhosis is not an immediate process, and requires a long-term interval to develop, in most cases more than 10 years? This open question led us to speculate that regulatory mechanisms generated by BAs might control the activation of cholangiocytes and HSCs to limit cirrhosis over time and, consequently HCC development.

By omics, imaging techniques, *in vitro* studies combined with the generation of genetically engineered mouse model (GEMM), I demonstrate that BAs induce cholangiocyte expansion via FXR activation to limit HSC activation. Genetic deletion of FXR in mouse cholangiocytes relieves mechanical constraints that limit fibroblast activation, dramatically increasing fibrosis in a model of BA-induced liver injury. Moreover, cholangiocytes expand even further when their BA/FXR axis is abolished, indicating that fibroblasts also restrict cholangiocyte proliferation in a feedback mechanism.

Therefore BAs/FXR activation in cholangiocytes impose cell mechanical constraints to restrict cirrhosis development.

Microbiome control of host immunity

Yasmine Belkaid
National Institute of Allergy and Infectious Diseases (NIH),
Bethesda - US

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Nabil Djouder

Growth Factors, Nutrients and Cancer Group Leader
Spanish National Cancer Research Centre, CNIO, Madrid, Spain

Nabil Djouder, born in France, obtained his PhD in Molecular Pharmacology from the University of Strasbourg (France) and the University of Freiburg (Germany), where he worked in the laboratory of K. Aktories. He studied the molecular mechanisms underlying the activation of mast cells by cross-linking high affinity antigen receptors (Fcε-RI) and the involvement of small GTPases from the Rho family in this activation.

In 2001, he moved to Basel (Switzerland) as a postdoctoral research fellow and joined the laboratory of W. Krek at the Novartis Friedrich Miescher Institute. He has since worked in the field of growth control, cancer, and associated metabolic disorders. Most of his research focuses on the mTOR/S6K pathway and the integration of growth factors, nutrients, and energy homeostasis.

In 2003, he moved with W. Krek to the Institute of Cell Biology at the Eidgenössische Technische Hochschule (ETH) in Zurich. He became a member of the Competence Centre for Systems Physiology and Metabolic Diseases (CCSPMD).

In October 2009, Nabil Djouder joined the CNIO as a Junior Group Leader, establishing his group in the field of Growth factors, Metabolism and Cancer. In 2011, he was awarded with the prestigious Spanish award Ramon y Cajal. He was also very successful to secure several national and international funding, including 1 grant from WCR/AICR and 3 grants from EFSD.

In January 2018, Nabil Djouder was exceptionally promoted to Senior Group Leader at the CNIO, since then devoting efforts to understanding the molecular mechanisms linking environmental stresses to disease pathogenesis affecting the organs of the digestive system.

Nikla Emambokus

Editor-in-Chief, Med; Executive Editor Med, *Cell Metabolism*
Cambridge, US

Nikla Emambokus is the Editor-in-Chief of Med, *Cell Press's* flagship medical journal. Med's mission is to bring together academic translational researchers, clinicians, Biotech/Pharma scientists and policy experts to accelerate the bench-to-bedside transition. Nikla was previously the Editor-in-Chief of *Cell Metabolism*, where she diversified and expanded the scope of the journal, advancing it to first-in-class and improving the impact factor from 13.668 to 22.415. Nikla received her PhD/DPhil in Biochemistry and Molecular Medicine from the University of Oxford and did postdoctoral research on blood stem cells at the Weatherall Institute of Molecular Medicine and Boston Children's Hospital/Harvard Medical School.

Mari-Carmen Fernandez-Aguera

Scientific editor, *Cell Metabolism*
Cambridge, US

Mari-Carmen received her PhD at the University of Seville, Spain, where she studied the molecular mechanism of acute oxygen sensing in the Institute of Biomedicine of Seville (IBiS) with Dr. Lopez-Barneo. Then she moved to Boston to join Dr. Danial's lab at DFCI/Harvard as a postdoc. Her research focused on the effect of different nutrient utilization on neuronal excitability and, ultimately, on brain activity with the goal of developing new diet and drug-based therapies for pathologies such as epilepsy. Mari-Carmen joined *Cell Metabolism* in 2020 as a Scientific Editor.

Valter Longo

The Firc Institute of Molecular Oncology, (IFOM), Milan - Italy

Valter Longo is Senior Group Leader at IFOM, the Edna M. Jones Professor of Gerontology and Biological Sciences, and the Director of the Longevity Institute at the University of Southern California – Davis School of Gerontology, Los Angeles. Dr. Longo's studies focus on the fundamental mechanisms of aging in simple organisms, mice and humans. The Longo laboratory has identified several genetic pathways that regulate aging in simple organisms and reduce the incidence of multiple diseases in mice and humans. His laboratory also described both dietary and genetic interventions that protect cells and improve the treatment and prevention of cancer and other diseases in mammals. Dr. Longo's most recent studies are on interventions that can affect stem cell-based regeneration to promote longevity.

At the IFOM, the group directed by Longo studies the effects of extreme diets and drugs that mimic them on the prevention and treatment of cancer, with focus on the role of stem cells. Among the accolades received by Dr. Longo are the 2010 Nathan Shock Lecture Award from the National Institute on Aging (NIA/NIH) and the 2013 Vincent Cristofalo "Rising Star" Award in Aging Research from the American Federation for Aging Research (AFAR).

Dr. Longo was born and raised in Genoa, Italy and received his undergraduate degree from the University of North Texas, where he majored in biochemistry with a minor in jazz performance. He received his Ph.D. in Biochemistry from the University of California, Los Angeles (UCLA) in 1997 and his postdoctoral training in the Neurobiology of Aging and Alzheimer's Diseases at USC. He started his independent career in 2000 at the University of Southern California, School of Gerontology, one of the first and leading programs for aging research and education. In 2014, he joined the IFOM in Milan where he directs a laboratory focused on cancer and aging.
For more information:
https://www.ifom.eu/en/cancer-research/research-labs/research-lab-longo.php

Marcos Malumbres

Cell Division and Cancer Group Leader
Spanish National Cancer Research Centre, CNIO, Madrid, Spain

Marcos Malumbres studied Biology at the Universidad de Navarra and then moved to León for PhD studies on genes and molecular pathways required for amino acid biosynthesis in bacteria. He obtained the PhD in Molecular Biology at the Universidad de León in 1993 and moved to the New York University Medical Center (USA) for postdoctoral training. During this period, he focused on the effect of oncogenes in cell cycle control and cell proliferation. He returned to Spain in 1998 to join M. Barbacid's lab in the newly created Spanish National Cancer Research Centre (CNIO). In 2003 he obtained a Staff Scientist position at the Consejo Superior de Investigaciones Científicas (CSIC) and in June 2004 he was appointed senior group leader of the Cell Division and Cancer Group at CNIO.

Marcos Malumbres has authored more than 200 international articles including relevant contributions to understanding the *in vivo* function of key cell cycle regulators and their relevance in cancer therapy. His investigation in cell cycle proteins contributed to the approval of specific inhibitors that are currently the standard-of-care in metastatic breast cancer. His current research focuses on improving current cancer therapies and discovering new candidates for clinical use in the future.

Malumbres was elected member of the European Molecular Biology Organization (EMBO) in 2016 and received the Gold Medal of the Spanish Association against Cancer (AECC) in 2019 for his contributions to Science and commitment with Society and cancer patients. He is a visiting Professor of the Dana Farber Cancer Institute-Harvard University in Boston since 2019.

Yasmine Belkaid

National Institute of Allergy and Infectious Diseases (NIH),
Bethesda - US

Yasmine Belkaid is a Distinguished Investigator at the National Institute of Allergy and Infectious Diseases at the National Institute of Health (Bethesda). She obtained her Master at USTHB in Algeria and her Ph.D. from the Pasteur Institute in France. Following a postdoctoral fellowship at the National Institute of health (Bethesda) on immune regulation during infection, she started her research program at the Children's Hospital Research Foundation in Cincinnati. In 2005, she joined the National Institute of Allergy and Infectious Diseases (NIAID) and was appointed senior scientist in 2008. Her laboratory explores fundamental mechanisms that regulate tissue homeostasis and host immune responses and uncovered key roles for the microbiota and dietary factors in the control of immunity and protection to pathogens. Dr Belkaid also holds an appointment at the University of Pennsylvania and is the director of the trans NIH Center for Human immunology. She is the founder and Director of the NIAID Microbiome program. Dr Belkaid is a member of the National Academy of Sciences, the American Academy of Arts and Sciences, the National Academy of Medicine and recipient of numerous awards including the Lurie Prize in Biomedical Sciences, the AAI-Thermo Fisher Meritorious Career Award, the Emil von Behring Prize, and the Sanofi-Institut Pasteur Award.

Rafael de Cabo

Dr. Rafael de Cabo is Chief of the Translational Gerontology Branch at the National Institute on Aging, National Institutes of Health, USA.

Rafael de Cabo earned his Ph.D. in 2000 from the Department of Foods and Nutrition at Purdue University. He received a postdoctoral position in the Laboratory of Neurosciences at the National Institute on Aging in Baltimore, Maryland. In 2004, he was appointed as a tenure track investigator in the Laboratory of Experimental Gerontology. He is now a senior investigator and Chief of the Translational Gerontology Branch at NIA. His research has focused on the effects of nutritional interventions on basic mechanisms of aging and age-related diseases, the effects of caloric restriction on aging, and pharmacological interventions for healthy aging. Ultimately his research aims to identify interventions that will improve healthspan and lifespan with translational potential to benefit human aging.

Sabrina Diano

Institute of Human Nutrition, Columbia University Irving Medical Center
New York, US

My research has been focusing on role of the Central Nervous System in the regulation of food intake, energy and glucose homeostasis. I have a broad background in neuroendocrinology, with specific training and expertise in key areas related to this research project. As a postdoctoral fellow, I carried out research on the effect of several hormones, such as ghrelin, leptin and thyroid hormones on CNS circuits that regulate feeding, metabolism and reproduction, including the melanocortin system. As faculty and PI and co-investigator of several NIH-funded, I focused my research in the field of neurobiology of energy metabolism. In addition, I successfully administered the projects (e.g. staffing, research protections, budget), collaborated with other researchers, and produced several peer-reviewed publications from each project. As a result of these previous experiences, I am aware of the importance of frequent communication among project members and of constructing a realistic research plan, timeline, and budget. I have demonstrated record of productive research projects in an area of high relevance for humans, and my expertise and experience have prepared me to lead my projects.

Honors
2018 Recipient of the Helmholtz Diabetes Award by the Helmholtz Society (Germany)
2018 Journal of Clinical Investigation Lectureship Award, Deuel Conference on "Neural control of Nutrient Metabolism", San Diego (CA)
2015 Women in Metabolism 2015 series: The "Rosies" of *Cell Metabolism*. 10th year anniversary celebrations of *Cell Metabolism* with 14 inspiring and engaging stories from women scientists in the metabolism field. Diano S. *Cell Metab*. 2015 Dec 1;22(6):949-53. doi: 10.1016/j.cmet.2015.11.005. PMID: 26636490
2015 Novo Nordisk Foundation Laurate Award, (declined), Copenhagen, Denmark.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/pubmed/?term=diano+s

Alejo Efeyan

Group Leader, Metabolism and Cell Signaling Lab,
Spanish National Cancer Research Centre, CNIO, Madrid, Spain

After obtaining his BSc degree in Buenos Aires, Alejo Efeyan received his PhD from the Autonomous University of Madrid, for his studies on mechanisms of tumor suppression. His postdoctoral training was in the David M Sabatini Lab, studying the biology of mTOR and nutrient signaling. Since 2016, Alejo Efeyan is the head of the Metabolism and Cell Signalling lab at the CNIO, and his team studies the links between nutrients and metabolic homeostasis and the impact of deregulated nutrient and growth factor signaling in cancer and aging.

Lluis Fajas
Center for Integrative Genomics (CIG),
Lausanne, Switzerland

Lluis Fajas Coll was born in Barcelona. He studied Biology at the University of Barcelona. He next moved to the Ernst Boehringer Institute in Vienna, where he did his PhD studies. After two postdoctoral stages in France, at Pasteur Institute in Lille and at the IGMM in Montpellier, he was recruited as Inserm associated scientist at the IGBMC in Strasbourg. He was next appointed group leader with an Inserm Avenir grant in Montpellier. He was recruited in 2012 as professor and director of the department of physiology at the University of Lausanne. He is now group leader at the CIG.

Mark A Febbraio

Monash Institute of Pharmaceutical Sciences,
Monash University Australia
Victoria, Australia

Mark Febbraio is a National Health and Medical Research Council of Australia Investigator and the Head of the Cellular and Molecular Metabolism Laboratory within the Drug Discovery Program at Monash Institute of Pharmaceutical Sciences, Monash University Australia. Professor Febbraio is also the Founder of the recently incorporated company Celesta Therapeutics. His research is focussed on understanding mechanisms associated with exercise, obesity, type 2 diabetes and cancer and his aim is to develop novel drugs to treat lifestyle related diseases. He has authored over 280 peer reviewed papers in leading journals such as Nature, Cell, Nature Immunology, Cell Metabolism, and has over 45,000 career citations. Throughout his career, he has many prestigious awards including the A K McIntyre Prize for significant contributions to Australian Physiological Science (1999), the Kellion Award for the Australian Diabetes Society (2017), The Eureka Scientific Prize (2020), The GSK Award for Research Excellence (2020) and The Endocrinology Society UK International Medallist (2021).

Marcus DaSilva Gonçalves

Weill Cornell Medicine, NY - US

Marcus Goncalves is an endocrinologist and basic scientist at Weill Cornell Medical College in New York. He holds degrees in Biomedical Engineering from the Johns Hopkins University, and combined doctoral (M.D., Ph.D.) degrees from the University of Pennsylvania. His research focuses on the interactions between cancer and the metabolites and hormones that regulate systemic metabolism. As a practicing endocrinologist, he has developed therapeutic and dietary strategies to modulate systemic glucose and insulin levels in patients with cancer, and he is currently involved in several clinical studies to assess the effects of a very low carbohydrate (ketogenic) diet in this population. Dr. Goncalves has received grants from the National Cancer Institute, the AACR-The Mark Foundation for Cancer Research, and he is co-lead of a CRUK/NCI-sponsored Cancer Grand Challenge award. He regularly cares for patients with cancer experiencing endocrine complications such as hyperglycemia, cachexia, and other metabolic disease.
https://www.goncalveslab.com/

Tak Mak

Princess Margaret Cancer Centre (UHN)
Toronto, Canada

Tak W. Mak is internationally known for his work on the genetics and molecular biology of cancer and the immune system. He has been a major figure in the fields of immunology and molecular and cellular biology for almost 40 years, and is a world leader in basic and translational research into the genetics of immunity and cancer. In 1984, he led the group that cloned the gene encoding a chain of the human T cell receptor. This discovery laid the ground work for our understanding of much of T cell biology and heralded the CAR-T technologies now approved for the treatment of leukemias and lymphomas. Dr. Mak's lab was also a pioneer in the genetic modification of mouse strains ("knockout mice") to identify factors associated with susceptibility to immune disorders or various cancers. The Mak team used these mutant animals to elucidate the functions of numerous molecules involved in immune responses, programmed cell death, and tumorigenesis, including the important tumour suppressors p53 and PTEN, and the breast cancer-related genes BRCA1 and BRCA2. Notably, in 1995, his group used mutant mice to show that CTLA4 is a negative regulator of T cell activation, paving the way for the development of T cell checkpoint inhibitor regulators as immunotherapeutic agents. Dr. Mak's laboratory continues to develop novel approaches for designing and producing TCRs that are specific for antigens appearing on the surfaces of cancer cells. In a different vein of investigation, his team recently showed that the brain communicates with the immune system via T and B cells producing acetylcholine, a finding with implications for future treatments of cancer and autoimmune or neurodegenerative diseases. The Mak group continues to uncover immune cell subsets that can synthesize this prototypical neurotransmitter, and is delving into the novel functions of this molecule outside neurotransmission.

In addition to this academic success, Dr. Mak has made significant contributions on the biotech front, in particular co-founding Agios Pharmaceuticals and Treadwell Therapeutics. These companies specialize in delineating metabolic vulnerabilities in tumour cells that can be exploited as novel cancer therapies. Several first-in-class small-molecule compounds are now in clinical trials for the treatment of cancer and certain genetic disorders. This strategy has produced two IDH inhibitors that are now FDA-approved for the treatment of acute myeloblastic leukemias, as well as another first-in-class agent for the treatment of anemia. Two novel agents targeting the aneuploid cancer cells common in advanced solid tumours are now in phase II clinical trials.

Dr. Mak is a member of the Royal Society of Canada, Royal Society of London, National Academy of Sciences (USA), American Society of Arts and Sciences (USA), and American Association for Cancer Research (USA).

Nuria Malats

Genetic & Molecular Epidemiology Group Leader
Human Cancer Genetics Programme
Spanish National Cancer Research Centre – CNIO, Madrid, Spain

Núria Malats is currently the head of the Genetic and Molecular Epidemiology Group at the Spanish National Cancer Research Centre (CNIO), Madrid, Spain. Dr. Malats has a broad expertise in these fields of research by focusing mainly on pancreatic and bladder cancers. She coordinates several large national and international studies integrating different levels of information, including omics data, in both disease development and progression. The resources of these studies have contributed to further disentangling the complex aetiology of these cancers. Dr. Malats has over 300 publications and is external reviewer of national and international funding agencies and first rank scientific journals. Dr. Malats has been a board member of ESUR and of the EAU Research Foundation. She chaired the EUPancreas COST Action (BM1204) with >250 members; she was a board member of the International Pancreatic Cancer Case Control Consortium (PanC4), and she is the chair of the Research Work Stream of Pancreatic Cancer Europe (PCE) multistakeholder platform.

Rubén Nogueiras
Center for Research in Molecular Medicine and Chronic Diseases (CiMUS)
Santiago de Compostela University, Spain

Rubén Nogueiras completed his doctoral thesis in 2003 at the University of Santiago de Compostela and then carried out postdoctoral stays in Germany, Switzerland and the USA. In 2009 he obtained a Ramón y Cajal contract at the CIMUS of the University of Santiago de Compostela and began coordinating the Molecular Metabolism group. Since 2014 he is Associate Professor. His line of research is based on understanding the molecular mechanisms involved in the regulation of energy balance and that are related to obesity and its associated diseases such as non-alcoholic fatty liver disease and type 2 diabetes.

Aurora Pérez Cornago
Oxford Population Health, University of Oxford, UK

Aurora Pérez-Cornago is an Associate Professor in Nutritional and Cancer Epidemiology at the University of Oxford with a particular interest in understanding how diet and obesity impact cancer development and progression. She holds a Cancer Research UK Population Research Fellowship to investigate the association between obesity and aggressive prostate cancer, integrating information from large datasets based on biomarkers, imaging and genotyping. She has also established an international Consortium on Vegetarian diets and Cancer risk, funded by the World Cancer Research Fund, where she is pooling data from international prospective studies with large numbers of vegetarians and vegans to conduct individual participant data meta-analyses to look at the association of vegetarian and vegan diets with the risk of individual cancer sites. Moreover, she has developed new dietary resources and methodologies for users of the dietary questionnaire used in UK Biobank, which will facilitate research on diet and disease by researchers around the world.

Marina Pollán
National Center for Epidemiology (ISCIII),
Madrid - Spain

Marina Pollán is full Professor, coordinates the Area of Cancer and Environmental Epidemiology in the National Center for Epidemiology and is the Scientific Director of the Consortium for Biomedical Research in Public Health and Epidemiology (CIBERESP). As a cancer epidemiologist, she has focused on breast cancer and associated risk factors, particularly lifestyle and modifiable exposures. During the COVID-19 pandemic, she has been the scientific coordinator of the national population-based seroepidemiological study ENE-COVID. She currently coordinates the Predictive Medicine pillar of the IMPaCT call, whose objective is the creation of a large population cohort that serves as a research infrastructure for the country as a whole.

Ana Ramírez de Molina
IMDEA Food Institute, Madrid, Spain

Ana Ramírez de Molina has developed her career in nutrition, metabolism and health. She directs the Precision Nutrition and Cancer Research Program at IMDEA Food Institute, center specialized on precision nutrition as a main tool to promote public health. She has published more than 100 impact articles in the area, several book chapters, and 6 patents transferred to industry. She is promoter of two start-up companies with several products in the market, and coordinates IMDEA and UAM in the European Community EIT-Food, focused on leading a change to a new healthy and sustainable nutrition. She has obtained the Young Researchers MSD Award, the International John Kinney Award, and the distinction March 8th of the Community of Madrid as an outstanding woman in science.

Romeo Ricci

The Institute of Genetics and Molecular and Cellular Biology, IGBMC
Illkirch-Graffenstaden, France

Romeo Ricci studied human medicine at the University of Berne, Switzerland. After clinical training in surgical pathology at the University of Zurich, Switzerland, he joined the Research Institute of Molecular Pathology (IMP) in Vienna as a postdoctoral fellow in the research group of Prof. Erwin F. Wagner. He has subsequently worked at the Cardiovascular Research laboratory at the Institute of Physiology in Zurich, Switzerland. In the following time, he built up his own research laboratory at the Institute of Cell Biology at ETH Zurich receiving an Assistant Professorship in 2007. In 2010, he accepted a full professorship at University Hospital of Strasbourg having his research group at the IGBMC. Romeo Ricci's research uncovered novel molecular mechanisms that contribute to the understanding of inflammatory disorders, atherosclerosis and diabetes. For his research activity so far, he was awarded several distinguished research prizes. For example, he was selected as a new EMBO Young Investigator in 2009 and his laboratory received an ERC starting grant in 2012.

M. Celeste Simon

Scientific Director and Investigator, Abramson Family Cancer Research Institute
Associate Director-Shared Resources, Abramson Cancer Center
Arthur H. Rubenstein, MBBCh Professor, Department of Cell and Developmental Biology
University of Pennsylvania Perelman School of Medicine
Philadelphia, United States

M. Celeste Simon, Ph.D. is the Scientific Director of the Abramson Family Cancer Research Institute and an Associate Director of the Cancer Center at the Perelman School of Medicine at the University of Pennsylvania. Dr. Simon's research is focused on how cells sense and respond to changes in the availability of molecular oxygen and nutrients. She was an HHMI Investigator for twenty years and has been elected to the American Academy of Arts and Sciences, the National Academy of Medicine, and National Academy of Sciences. She was named a Fellow of the AACR Academy and a FASEB Lifetime Achievement Awardee.

Yu-Hua Tseng

Joslin Diabetes Center and Harvard Medical School, Boston, MA, USA

Yu-Hua Tseng is a Professor of Medicine at Harvard Medical School (HMS), a Senior Investigator at the Joslin Diabetes Center (JDC), and a Principal Faculty of the Harvard Stem Cell Institute. Dr. Tseng received her Ph.D. from the University of Wisconsin-Madison, and completed postdoctoral training at JDC, HMS. Dr. Tseng's laboratory is at the forefront of research focused on understanding the physiological role and therapeutic potential of energy-burning brown fat and its related beige fat, an area of great significance to both diabetes and medicine as a whole. Dr. Tseng was an Eleanor and Miles Shore Scholar in Medicine at HMS, and received the Armen Tashjian Award for Excellence in Endocrine Research and the J Denis McGarry Prize from Montreal Diabetes Center.

Matthew Vander Heiden

Koch Institute for Integrative Cancer Research
Department of Biology - Massachusetts Institute of Technology,
Cambridge, US

Matthew Vander Heiden is the Director of the Koch Institute for Integrative Cancer Research and a Professor in the Department of Biology at the Massachusetts Institute of Technology. He is also an Institute Member of the Broad Institute of Harvard and MIT, and an Instructor of Medicine at the Dana-Farber Cancer Institute and Harvard Medical School. Dr. Vander Heiden received his MD and PhD degree from the University of Chicago. He also completed clinical training in Internal Medicine and Medical Oncology at the Brigham and Women's Hospital / Dana-Farber Cancer Institute prior to completing a post-doctoral fellowship at Harvard Medical School. His laboratory studies how metabolism is regulated to meet the needs of cells in different physiological situations with a focus on understanding the role of metabolism in cancer.

Karen Vousden
The Francis Crick Institute in London, UK

Karen received her PhD from the University of London and following postdoctoral fellowships at the ICR and NCI, she returned to London to establish a research group at the Ludwig Institute. Returning to the US, she was Chief of the Regulation of Cell Growth Laboratory at the NCI before coming back to the UK to take on the role of Director of the CRUK Beatson Institute in Glasgow. In 2017, she moved her research group to the Francis Crick Institute in London and served as Chief Scientist for Cancer Research UK from 2016-2022.

Karen's research has made contributions to our understanding of how the tumour suppressor protein p53 is regulated and the functions of p53 that contribute to its ability to control cancer progression. During these studies, she revealed an unexpected ability of p53 to help cells adapt and survive under transient periods of nutrient starvation. This work led her to a more general investigation of cancer cell metabolism, focused on exploring the role of oxidative stress and serine metabolism in cancer development and metastatic progression.

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Diet, Nutrition and Cancer Cell Metabolism

Poster Session

cnio stop cancer

1

Metabolic Health profiling in Cancer: Precision Nutrition strategies for patients

Lara P. Fernández [1*], Silvia Cruz-Gil [1*], Gonzalo Colmenarejo [2], Cristina Aguirre-Portolés [1], Sonia Wagner-Reguero [1], Isabel Espinosa-Salinas [3], Enrique Casado [4], José Perea [5] and Ana Ramírez de Molina [1].
*Authors contributed equally

1 Molecular Oncology Group, IMDEA Food, CEI UAM + CSIC;
2 Biostatistics and Bioinformatics Unit, IMDEA Food, CEI UAM+CSIC;
3 GENYAL Platform on Nutrition and Health, IMDEA Food, CEI UAM + CSIC, Madrid, Spain;
4 Medical Oncology Department, Infanta Sofía University Hospital, San Sebastián de los Reyes, Madrid, Spain,
5 Molecular Medicine Unit-Department of Medicine. Biomedical Research Institute of Salamanca (IBSAL). Institute of Molecular and Cellular Biology of Cancer (IBMCC), University of Salamanca-SACYL-CSIC, Salamanca, Spain.

Metabolic health (MH), - a multifactorial condition that include parameters like obesity, dietary patterns, gene-diet interactions, and lipid metabolism- is as a relevant factor in cancer prevention and prognosis. In this sense, we should consider the effect of lifestyle factors (nutrition, physical activity), genetics (individual susceptibility), the consequent global metabolic state (healthy/unhealthy), in the development, progression, and response to treatment of patients with cancer.

We have proposed that MH together with a lipid genetic risk score predicts survival of small cell lung cancer (SCLC) patients. SCLC prognosis is the poorest of all types of lung cancer. Its clinical management remains heterogeneous and therefore, the capability to predict survival would be of great clinical value (Fernández et al., 2021). In line with these results, we have defined a highly specific biomarker of early-onset colorectal cancer that integrates the involvement of metabolic pathways, as well as intrinsic disparities due to gender (Fernández et al., Submitted). Importantly, rates of colorectal cancer (CRC) incidence in young patients are increasing nowadays, although little is known about the biological mechanisms implicated.

To investigate joint contributions of MH, nutrition, and outcome in CRC young patients, we are analyzing the role of individual MH in CRC growth, studying the impact of several parameters - the biochemical profile, the genetic susceptibility, and dietary patterns- in the growth of CRC spheroids exposed to different human plasmas. We have found that growth of CRC spheroids is significantly modulated in the presence of certain human plasmas that share a particular genetic and lipid profile as well as specific dietary patterns.

The MH profiling of cancer patients will serve as a guide for the design of precision nutrition products and strategies to improve treatment and tumor prognosis, as well as nutritional strategies to improve the quality of life of cancer patients.

Application of nutrigenetic tools: Improving the health outcomes of oncological patients

Cristina Mª Fernández*[1], Carolina Maestre*[1], [2], Lara P. Fernández[1*], Isabel Espinosa-Salinas[3], Gal·la Freixer[3], Enrique Casado[4] and Ana Ramírez de Molina[1].
*Authors contributed equally

1 Molecular Oncology Group, IMDEA Food Institute, CEI UAM + CSIC, Madrid, Spain;
2 Precision For Health, S.L.;
3 Nutritional Genomics and Health Unit, Research Institute on Food and Health Sciences IMDEA Food, UAM+CSIC, Madrid, Spain,
4 Medical Oncology Department, Infanta Sofía University Hospital, San Sebastián de los Reyes, Madrid, Spain.

Recent evidence from epidemiological and experimental studies supports the crucial role of metabolic health, dietary patterns, gene-diet interactions and lipid metabolism in cancer prevention and prognosis. Personalized nutritional interventions and medical decisions based on individual genetic predisposition are expected to significantly improve health outcomes in oncological patients. To achieve this goal, IMDEA Food and Precision 4 Health in collaboration with Infanta Sofia University Hospital are implementing two types of personalized nutrigenetic reports for both patients and oncologists, with the aim of improving the effectiveness of treatments and the quality of life of patients. Through this personalized reports, key information is exchanged with oncologists about patient's genetic predisposition related to clinical evolution and tumor prognosis, which help to medical decision-making and to optimize cancer treatment. Processes included in this report involved genetic susceptibility to the development of malnutrition and cachexia, and potential clinical prognosis based on lipid metabolism. On the other side, patients receive personalized nutritional and lifestyle recommendations based on their genetic predisposition aiming to improve their healthy patterns during the treatment, such as: gluten and lactose tolerance, physiological rhythms, and the response to toxic substances intake (tobacco, alcohol or caffeine). The development of these personalized nutrigenetic reports will constitute a step forward for the implementation of effective precision nutrition strategies in clinical oncology practice. Moreover, this genetic tool will impact on the way healthcare professionals tackle the issues related to disease management and treatment and the subsequent decision-making process.

3

URI loss-induced DNA damage response as a barrier against colorectal cancer

Irene Herranz-Montoya, Cristian Perna and Nabil Djouder

Growth factors, Nutrients and Cancer group, Molecular Oncology Programme, Centro Nacional de Investigaciones Oncologicas (CNIO), Madrid, Spain Department of Pathology, Hospital Universitario Ramón y Cajal, IRYCIS, Madrid 28034, Spain

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths worldwide. It is a multi-hit neoplasia that usually evolves from APC mutationinduced adenomatous polyps that become malignant by acquiring p53 loss. Yet the mechanisms of the mechanisms of the transitional mutations for the development of aggressive tumours remain to be elucidated. Here we show that the oncogenic protein URI (Unconventional Prefoldin RPB5-Interactor) is upregulated in human CRC tumors at both protein and mRNA levels, and its expression correlates with a further progression of the disease. Using genetically engineered modified mouse models, we demonstrate that reducing URI levels in the intestine prevents CRC progression in different models for intestinal cancer in a p53-dependent manner.

Mechanistically, URI downregulation impairs the Non-Homologous End Joining (NHEJ) mechanism for DNA damage repair, leading to upregulation of p53 protein levels, establishing a DNA damage response barrier for CRC progression. Our data reveal a "two" hit genetic model central for the transformation of polyps to malignant carcinomas where p53 downregulation is controlled by URI expression.

Cytokine-mediated crosstalk between cancer and host metabolism

Fedra Luciano-Mateo, Felipe Jiménez-Hernández, Miguel Hernández-Madrigal, Lidia Collado-Rodriguez, Ernest Nadal, Cristina Muñoz-Pinedo

Instituto de Investigación Biomédica de Bellvitge (IDIBELL)

Cachexia, glucose metabolism alterations, and hyperlipemia are some of the host metabolic changes associated with tumor development. Tumors can therefore interact with the host and promote host metabolic rewiring. We have investigated the possibility that the tumors drive metabolic changes, including high blood glucose, through the secretion of cytokines that can potentially be associated with metabolic stress in the tumor.

Previous data from our laboratory indicates that cancer cells subjected to metabolic stress, specifically glucose deprivation, show an increased secretion of several cytokines (such as LIF, IL6, and IL8) that can contribute to tumor homeostasis and the immune response. In this project, we explored the mechanisms responsible for tumor cytokine secretion and how these cytokines interact with host metabolic organs.

Using Lewis Lung Carcinoma (LLC) we developed a lung cancer mouse model which mimics the cancer metabolic alterations observed in humans. Tumor-bearing animals showed cachexia and insulin resistance compared to animals without tumors, together with an increase in cachexia-associated cytokines such as LIF or GDF15. The genetic deletion of LIF from tumor cells reduced tumor burden and endothelial angiogenesis. Moreover, using mice bearing tumors deficient in LIF we observed that the presence of LIF causes a reduction in food intake. LIF-producing tumors also showed a remarkable decrease in body weight compared to LIFdeficient tumors. Our data suggest that LIF secreted by the tumors could mediate crosstalk between cancer and host for their own benefit and that LIF is a potential target against tumor-induced cachexia.

5

Different effects of high fats diets on tumor metabolism depending on the type and timing of dietary intervention in an experimental breast cancer model

Maite Garcia-Guasch[1], Iola F Duarte[2], Mireia Medrano[1], Lourdes Navarro[1], Vanessa Rivero[1], Eduard Escrich[1], **Raquel Moral[1]**

[1] Department of Cell Biology, Physiology and Immunology, Faculty of Medicine, Universitat Autònoma de Barcelona, 08193 Bellaterra, Barcelona, Spain.
[2] Department of Chemistry, CICECO-Aveiro Institute of Materials, University of Aveiro, 3810-193 Aveiro, Portugal.

Breast cancer is the most frequent malignant tumor in women worldwide and nutritional factors play a key role in the etiology of this neoplasia. The aim of this work is to investigate the effect of two high-fat diets, high in corn oil (rich in n-6 PUFA) and high in extra virgin olive oil (EVOO, rich in MUFA and minor bioactive compounds) in the metabolism of experimental mammary tumors. Female Sprague-Dawley were fed a low-fat diet (LF), a high n-6 PUFA diet from weaning (HCO) or from induction (LF-HCO), or a high EVOO diet from weaning (HEVOO) or from induction (LF-HEVOO), and gavaged with DMBA at 53 days. Molecular analysis (protein and enzyme activity) of the main metabolic pathways have shown an effect of the high-EVOO diet on glucose (transport, glycolysis, PPP) and oxidative (TCA, UCP2) metabolism. Carcinogenesis effects and the changes in metabolism seemed to be interconnected to other signaling pathways such as proliferation and apoptosis, that were also differentially modulated by the high fat diets. Further analysis in tumor metabolome were performed by nuclear magnetic resonance (NMR). Polar hydrophilic metabolite profile did not show differences, while apolar hydrophobic metabolite profile revealed differences in lipid composition between groups, suggesting that tumor composition is influenced by nutrition and that reflects the most abundant lipid in diet. Thus, control and the high EVOO-fed groups had similar profile (with MUFA being the most abundant fatty acids in tumors), while the high corn oil diet groups were significant different (with PUFA being the most abundant fatty acids). Our study suggests that the high fat diets have different effects on metabolism depending on the type and time of dietary intervention, although metabolic changes, without the context of other pathways, may not reflect tumor malignancy. Moreover, these results point out the relevance that dietetic habits from childhood may have on the progression of the disease.

Encapsulation of bioactive compounds by high throughput Electrospraying assisted by pressurized gas of application Interest in personalized nutrition

Cristina Prieto[1*], Emma Talón[2], Zoran Evtoski[1], Jose M. Lagaron[1,*]

[1] Novel Materials and Nanotechnologies Laboratory, Institute of Agrochemistry and Food Technology (IATA), Spanish Council for the Scientific Research (CSIC), Paterna, Spain
[2] R&D Department, Bioinicia S.L., Paterna, Spain

One of the most promising approaches to preserve bioactive compounds is their encapsulation within protective matrices. A novel high-throughput roomtemperature technology, termed as electrospraying assisted by pressurized gas (EAPG), presents multiple advantages compared to conventional encapsulation techniques, such as reduced denaturation of bioactive compounds, high encapsulation efficiency, particle with a narrow size distribution, production of free-flowing powder, highly versatile in terms of the encapsulating materials and bioactive compounds. In addition, by means of this technology it is possible to achieve the production volumes required by commodity food applications. Up to this moment, outstanding results have been obtained in the protection and stabilization of omega-3 fatty acids, polyphenols and probiotics, among others, which could be potential ingredients of application interest in personalized nutrition.

The current presentation will introduce the technology and highlight some use cases for the stabilization, shelf-life extension and controlled release of different bioactive compounds.

7

Macrophage activation upon URI loss boosts liver regeneration

María del Mar Rigual[1], Yi Fengming[1], Karla Santos de Frutos[1] and Nabil Djouder[1]*

1 Molecular Oncology Programme, Growth Factors, Nutrients and Cancer Group, Centro Nacional Investigaciones Oncológicas (CNIO), Madrid, 28029, Spain
* Correspondence: Nabil Djouder
Tel: 0034 91 7328000 (Ext.: 3830)
Fax: 0034 91 2246914
Email:ndjouder@cnio.es

The liver is the largest organ of the mammalian body and has the remarkable ability to fully regenerate in order to maintain tissue homeostasis. Hepatocytes are the main cells that perform the liver's primary metabolic functions and are also considered to be the first cells involved in liver regeneration during homeostasis or after acute injury. Yet the cellular mechanisms involved in liver regeneration remain to be elucidated, and a deeper understanding of them will facilitate new alternative techniques to orthotropic liver transplantation for patients with end-stage chronic liver disease.

Using state-of-the art technologies and genetically engineered modified mouse models, here we show that the loss of the oncogenic protein URI (Unconventional prefoldin RPB5-Interactor), which is expressed in the hepatocytes located around the central vein, is crucial for liver regeneration after partial hepatectomy (PHx). Moreover, URI gain-of-function mouse model reduces the liver regenerative capacity after PHx. Mechanistically, URI downregulation recruits macrophages to restore liver regenerative capacity. Our data reveal that the inhibition of URI could be a therapeutic strategy to activate liver regeneration.

Potential therapeutic effect of obestatin in oral mucositis

Agnieszka Stempniewicz[1] , P. Ceranowicz[1], W. Macyk[2], J. Cieszkowski[1], B. Kusnierz-Cabala[3], K. Galazka[4], Z. Warzecha[1]

1 Department of Physiology, Faculty of Medicine, Jagiellonian University Medical College, Cracow, Poland;
2 Department of Inorganic Chemistry, Faculty of Chemistry, Jagiellonian University, Cracow, Poland;
3 Department of Diagnostics, Chair of Clinical Biochemistry, Faculty of Medicine, Jagiellonian University Medical College, Cracow, Poland;
4 Department of Pathomorphology, Faculty of Medicine, Jagiellonian University Medical College, Cracow, Poland

Objectives: Prevention and treatment of oral mucositis are still subject of research. Previous studies have shown that obestatin increases the healing of gastrointestinal mucosa.

Purpose of the research was to find if obestatin alleviates the severity of lingual ulcers in rats.

Methods: lingual ulcers were evoked by the use of acetic acid. Rats were given twice a day intraperitoneal injections of saline or obestatin(4, 8 or 16 nmol/kg/dose) for five days.

Observations were evaluated by testing lingual mucosa morphology, local mucosal blood flow and pro-inflammatory interleukin-1β level in the lingual mucosa. Results: In animals without induction of oral ulcers treatment with obestatin was without any effect. Obestatin administration in rats with lingual ulcers increased the healing rate of these ulcers. Obestatin given at the dose of 8 or 16 nmol/kg/dose caused the strongest and similar therapeutic effect. This result was associated by a significant increase in blood flow and cell proliferation in lingual mucosa, as well as by a significant decrease in IL-1β level. Conclusions: Obestatin increases the healing rate of lingual ulcers in animal model. It was accompanied by a significant increase in blood flow and cell proliferation in lingual mucosa, as well as decrease of IL-1β level. Obestatin is a promising factor and requires further research in the field of oral mucositis. Agnieszka Stempniewicz acknowledges the support of InterDokMed project no.

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Control of adipogenic differentiation and metabolic disease by CDC14 phosphatases

Diana Vara-Ciruelos, Ana Filipa B. Martins, María Salazar-Roa, Carolina Villarroya- Beltri and Marcos Malumbres

Cell Division and Cancer group, Spanish National Cancer Research Centre (CNIO), Madrid

Cyclin-dependent kinases (CDKs) are protein kinases that regulate progression through the different phases of the cell cycle. The CDC14 family are dual specificity phosphatases that counteract CDK activity by removing CDK-dependent phopshosites. In Saccharomyces cerevisiae, CDC14 is an essential regulator of CDK activity during mitotic exit. Recent results from our laboratory however suggest that CDC14 activity is dispensable for the cell division cycle in somatic mammalian cells. Vertebrate cells contain two CDC14 paralogs, CDC14A and CDC14B. We have generated Cdc14a and Cdc14b double knockout (DKO) mice. DKO mice displayed reduced weight and a striking paucity of adipose tissue concomitant with smaller adipocyte cells, suggesting that CDC14 could have an adipogenic-related function.

To clarify this, Cdc14 DKO adult male mice were challenged with high fat food diet (HFD) for 6 consecutive weeks. As expected, control animals showed a significant increase in their body weight, hepatic steatosis, adipocyte hypertrophy and white fat deposition into brown adipose tissue. But, in contrast, DKO mice displayed decreased incidence of these events, confirming a diet-related adipogenic function of CDC14 phosphatases. Adipogenic differentiation assays in mouse embryonic stem cells and primary fibroblasts demonstrated a reduction in differentiation in Cdc14b-, but not Cdc14a-, null cells, suggesting that specific role for CDC14B during adipogenesis. These results were confirmed in mice, being Cdc14b-null mice resistant to diet-induced obesity. Given obesity is an important risk factor for many western diseases, these results reveal the opportunity to develop CDC14 inhibitors as potential therapeutic targets. Further mechanistic investigation of the pathways regulated by CDC14 will provide important new insights, aiding the discovery of novel therapeutic approaches for metabolic-related diseases.

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Madrid 24 — 26 October 2022

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Previous CNIO Frontiers Meetings and CNIO Cancer Conferences

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2022

MOLECULAR, CELLULAR AND ORGANISMAL DRIVERS OF AGING
09/05/2022 – 10/05/2022
Organisers: Maria A. Blasco, Alejo Efeyan, Thomas Rando

2019

HETEROGENEITY AND EVOLUTION IN CANCER
23/09/2019 – 25/09/2019
Organisers: Fátima Al-Shahrour, Arnold Levine, Solip Park, Raúl Rabadán

ESTRUCTURAL AND MOLECULAR BIOLOGY OF THE DNA DAMAGE RESPONSE
20/05/2019 – 22/05/2019
Organisers: Oscar Llorca, Rafael Fernández Leiro, Laurence H. Pearl, Titia Sixma

2018

MOLECULAR, CELLULAR AND ORGANISMAL HALLMARKS OF AGING
07/05/2018 – 09/05/2018
Organisers: Maria A. Blasco, Alejo Efeyan, Kathleen Collins, Thomas Rando

FRONTIERS IN IMMUNOMODULATION AND CANCER THERAPY
09/07/2018 – 11/07/2018
Organisers: Victoria Aranda, Nabil Djouder, Joao Monteiro, Marisol Soengas, Laurence Zitvogel

2017

PRIMARY AND SECONDARY BRAIN TUMORS
19/02/2017 – 22/02/2017
Organisers: Massimo Squatrito, Manuel Valiente, Richard Gilbertson, Michael Weller

MOLECULAR CHAPERONES IN CANCER
02/05/2017 – 04/05/2017
Organisers: Nabil Djouder, Wilhelm Krek, Paul Workman, Xiaohong Helena Yang

2016

CANCEROMATICS III – TUMOR HETEROGENEITY
13/11/2016 – 16/11/2016
Organisers: Fátima Al-Shahrour, Núria Malats, Alfonso Valencia, Chris Sander

2015

METASTASIS INITIATION:
MECHANISTIC INSIGHTS AND THERAPEUTIC OPPORTUNITIES
28/09/2015 - 30/09/2015
Organisers: David Lyden, Yibin Kang, Gemma Alderton, Victoria Aranda, Li-kuo Su, Héctor Peinado

NEW TRENDS IN ANTICANCER DRUG DEVELOPMENT
22/03/2015 - 25/03/2015
Organisers: Manuel Hidalgo, Alberto Bardelli, Lillian Siu, Josep Tabernero

2013

CHROMOSOME INSTABILITY AND ANEUPLOIDY IN CANCER
27/05/2013 - 29/05/2013
Organisers: Robert Benezra, Ana Losada, Marcos Malumbres, René Medema

2012

ALLOSTERIC REGULATION OF CELL SIGNALLING
17/09/2012 - 19/09/2012
Organisers: Francesco Gervasio, Ermanno Gherardi, Daniel Lietha, Giulio Superti-Furga

2011

RECAPTURING PLURIPOTENCY:
LINKS BETWEEN CELLULAR REPROGRAMMING AND CANCER
07/11/2011 - 09/11/2011
Organisers: Maria A. Blasco, Konrad Hochedlinger, Manuel Serrano, Inder Verma

CANCEROMATICS II :
MULTILEVEL INTERPRETATION OF CANCER GENOME
28/03/2011 - 30/03/2011
Organisers: Søren Brunak, Stephen Chanock, Núria Malats, Chris Sander, Alfonso Valencia

BREAST CANCER
07/02/2011 - 09/02/2011
Organisers: Joaquín Arribas, José Baselga, Miguel Ángel Piris, Lajos Pusztai and Jorge Reis-Filho

2010

CANCER PHARMACOGENETICS: PERSONALIZING MEDICINE
22/11/2010 - 24/11/2010
Organisers: Javier Benítez, William E. Evans, Miguel Martín and Magnus Ingelman-Sundberg

MOLECULAR CANCER THERAPEUTICS
08/03/2010 - 10/03/2010
Organisers: Gail Eckhardt, Roy S. Herbst and Manuel Hidalgo

2009

THE ENERGY OF CANCER
02/11/2009 - 04/11/2009
Organisers: Toren Finkel, David M. Sabatini, Manuel Serrano and David A. Sinclair

CANCER-OM-ATICS II: MULTILEVEL INTERPRETATION OF CANCER GENOME
06/07/2009 - 08/07/2009
Organisers**:** Søren Brunak, Núria Malats, Chris Sander and Alfonso Valencia

STEM CELLS AND CANCER
23/02/2009 - 25/02/2009
Organisers: Elaine Fuchs, Maria A. Blasco, Eduard Batlle and Mirna Pérez-Moreno

2008

SIGNALLING UPSTREAM OF mTOR
03/11/2008 - 05/11/2008
Organisers: Dario R. Alessi, Tomi P. Mäkelä and Montserrat Sánchez-Céspedes

STRUCTURE AND MECHANISMS OF ESSENTIAL COMPLEXES FOR CELL SURVIVAL
23/06/2008 - 25/06/2008
Organisers: Niko Grigorieff, Eva Nogales and Jose María Valpuesta

DEVELOPMENT AND CANCER
04/02/2008 - 06/02/2008
Organisers: Konrad Basler, Ginés Morata, Eduardo Moreno and Miguel Torres

2007

LINKS BETWEEN CANCER, REPLICATION STRESS AND GENOMIC INTEGRITY
05/11/2007 - 07/11/2007
Organisers: Oskar Fernández-Capetillo, Jiri Lukas, Juan Méndez and André Nussenzweig

MYC AND THE TRANSCRIPTIONAL CONTROL OF PROLIFERATION AND ONCOGENESIS
11/06/2007 - 13/06/2007
Organisers: Robert N. Eisenman, Martin Eilers and Javier León

MOLECULAR MECHANISMS IN LYMPHOID NEOPLASM
19/02/2007 - 21/02/2007
Organisers: Elias Campo, Riccardo Dalla-Favera, Elaine S. Jaffe and Miguel Angel Piris

2006

TELOMERES AND TELOMERASE-CNIO / JOSEF STEINER CANCER CONFERENCE
13/11/2006 - 15/11/2006
Organisers: Maria A. Blasco and Jerry Shay

MEDICINAL CHEMISTRY IN ONCOLOGY
02/10/2006 - 04/10/2006
Organisers: Fernando Albericio, James R. Bischoff, Carlos García-Echeverria and Andrew Mortlock

INFLAMMATION AND CANCER
22/05/2006 - 24/05/2006
Organisers: Curtis Harris, Raymand Dubois, Jorge Moscat and Manuel Serrano

PTEN AND THE AKT ROUTE
08/05/2006 - 10/05/2006
Organisers: Ana Carrera, Pier Paolo Pandolfi and Peter Vogt

2005

CANCER AND AGING
07/11/2005 - 09/11/2005
Organisers: Maria A. Blasco, Kathy Collins, Jan Hoeijmakers and Manuel Serrano

MAP KINASES AND CANCER
30/05/2005 - 01/06/2005
Organisers: Philip Cohen, Roger Davis, Worcester, Chris Marshall and Ángel Nebreda

ANIMAL TUMOUR MODELS AND FUNCTIONAL GENOMICS
07/03/2005 - 09/03/2005
Organisers: Allan Balmain, Mariano Barbacid, Anton Berns and Tyler Jacks

2004

CADHERINS, CATENINS AND CANCER
29/11/2004 - 01/12/2004
Organisers: Amparo Cano, Hans Clevers, José Palacios and Franz Van Roy

STRUCTURAL BIOLOGY OF CANCER TARGETS
27/09/2004 - 29/09/2004
Organisers: Ernest Laue, Guillermo Montoya and Alfred Wittinghofer

2003

APOPTOSIS AND CANCER
01/12/2003 - 03/12/2003
Organisers: Gabriel Nuñez, Marisol Soengas and Scott Lowe

SMALL GTPases IN HUMAN CARCINOGENESIS
16/06/2003 - 18/06/2003
Organisers: Juan Carlos Lacal, Channing Der and Shuh Narumiya

TARGETED SEARCH FOR ANTICANCER DRUGS
17/03/2003 - 19/03/2003
Organisers: Amancio Carnero and David H. Beach

2002

MECHANISMS OF INVASION AND METASTASIS
18/11/2002 - 20/11/2002
Organisers: Maria A. Blasco and Jerry Shay

THE CELL CYCLE AND CANCER
30/09/2002 - 02/10/2002
Organisers: Marcos Malumbres, Charles Sherr and Jiri Bartek

CANCER EPIGENETICS : DNA METHYLATION AND CHROMATIN
29/05/2002 - 31/05/2002
Organisers: Manel Esteller and Stephen B. Baylin

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Spanish National Cancer Research Centre, CNIO, Madrid, Spain

Nikla Emambokus
Cell Metabolism, Cambridge, US

M. Carmen Fernández-Agüera
Cell Metabolism, Cambridge, US

Valter Longo
IFOM, Milan, Italy

Marcos Malumbres
Spanish National Cancer Research Centre, CNIO, Madrid, Spain

Speakers

Yasmine Belkaid
National Institute of Allergy and Infectious Diseases (NIH), Bethesda, US

Rafael de Cabo
National Institutes of Health (NIH), Bethesda, US

Sabrina Diano
Yale University School of Medicine, New Haven, US

Alejo Efeyan
Spanish National Cancer Research Centre, Madrid, Spain

Lluis Fajas
Center for Integrative Genomics (CIG), Lausanne, Switzerland

Mark A Febbraio
Monash Institute of Pharmaceutical Sciences, Monash University, Victoria, Australia

Marcus D. Goncalves
Weill Cornell Medicine, New York, US

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Princess Margaret Cancer Centre (UHN), Toronto, Canada

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Marina Pollán
National Center for Epidemiology (ISCIII), Madrid, Spain

Ana Ramírez de Molina
IMDEA Food Institute, Madrid, Spain

Romeo Ricci
IGBMC, Illkirch-Graffenstaden, France

M. Celeste Simon
Abramson Family Cancer Research Institute, University of Pennsylvania Perelman School of Medicine, US

Yu-Hua Tseng
Harvard Medical School, Joslin Diabetes Center, Boston, US

Matthew Vander Heiden
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*CNIO reserves the right to close registration and abstract submission when we reach full capacity.

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2023

GENOME ORGANIZATION AND STABILITY

22 - 23 May 2023

Organisers:

Felipe Cortés, Spanish National Cancer Research Centre, CNIO, Spain
Oscar Fernández-Capetillo, Spanish National Cancer Research Centre, CNIO, Spain
Ana Losada, Spanish National Cancer Research Centre, CNIO, Spain
Andre Nussenzweig, National Institutes of Health (NIH), US

METASTASIS

6 - 8 November 2023

Organisers:

Julio Aguirre-Ghiso, Icahn School of Medicine at Mount Sinai, US
Caroline Dive, Cancer Research UK Manchester Institute, UK
Eva González, Spanish National Cancer Research Centre, CNIO, Spain
Héctor Peinado, Spanish National Cancer Research Centre, CNIO, Spain
Manuel Valiente, Spanish National Cancer Research Centre, CNIO, Spain

Madrid 24 — 26 October 2022

Diet, Nutrition and Cancer Cell Metabolism

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Spanish National Cancer Research Centre
Melchor Fernández Almagro, 3
28029 Madrid, Spain
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