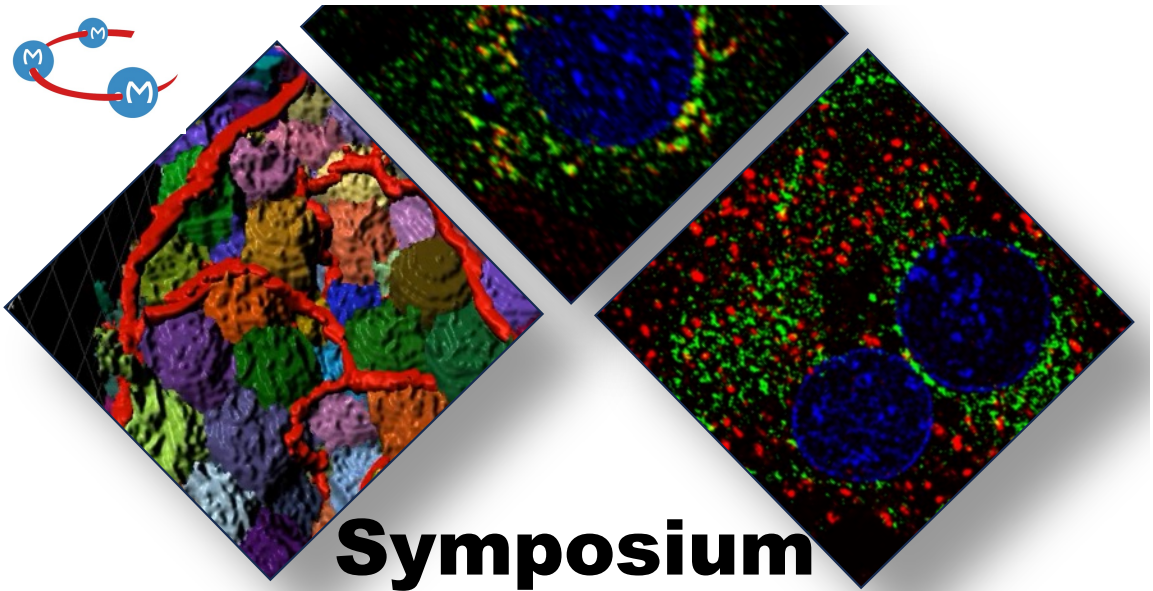

Symposium C3M Inflammation & Disease

November 7-8, 2024

Hopital Archet 2 Nice

OLIVIER DEMARIA
DOUGLAS R. GREEN
EICKE LATZ
DIDIER PAYEN DE LA GARANDERIE
VICTORIA SANZ-MORENO
LYNDA STUART

FREE REGISTRATION

Inflammation & Disease Symposium

November 7th-8th 2024, Hospital ARCHET 2 Amphitheater, Nice

Scientific Program

Thursday November 7th 2024

13h45-14h00 Welcome and Opening by **Dr. Sophie Tartare-Deckert (**Director of the Mediterranean Center for Molecular Medicine - C3M) and **Pr. Michel Carles** (distinguished Professor of Medicine).

Opening session

Chair : Dr. Véronique Angeli and Pr. Michel Carles

14h00-14h40 **Keynote Lecture : Pr Didier Payen de la Garanderie (emeritus prog at University of Paris, Cité, Sorbonne et CHU de Nice, France)**
Metabolic shift and immune response to sepsis

Session I : Inflammation, Infection and Chronic Diseases

Chairs : Dr. Orane Visvikis and Dr. Laurent Boyer

14h40-15h00 **Véronique Angeli** (C3M, team 9)
Functions of LYVE-1+ macrophage in health and disease

15h00-15h20 **Orane Visvikis** (C3M, team 6)
Evolutionary conserved regulation of TFEB stability by the E3 ubiquitin ligase WWP2 modulates response to stress *in vivo*

15h20-16h00 *Coffee break*

16h00-16h20 **Valérie Grandjean** (C3M, team 10)
Paternal Epigenetic Transgenerational Inheritance in metabolic disease development in mice

16h20-16h40 **Meri Tulic** (C3M, team 12)
Vitiligo auto-immune response upon oxidative stress-related mitochondrial DNA release opens up new therapeutic strategies

16h40-17h20 **Keynote Lecture : Pr. Lynda Stuart (Seattle, USA)**
TBC

17h20-19h30 *"Bellet Wine & Cheese"*

Friday November 8th 2024

Session II : Inflammation and Cancer

Chairs : Dr. Sandrine Marchetti and Dr. Carmelo Luci

9h00-9h40 **Keynote Lecture : Dr. Olivier Demaria (Marseille, France)**
Natural Killer cell engagers in oncology

9h40-10h00 **Thomas Strub** (C3M, team 1)
LKB1-SIK2 loss drives uveal melanoma proliferation and hypersensitivity to SLC8A1 and ROS inhibition

10h00-10h20 **Emeline Kerreneur** (C3M, team 2)
Targeting cathepsin B and non-apoptotic caspase-8 to inhibit pro-tumoral macrophage activity in cancer

10h20-11h00 *Coffee break*

11h00-11h20 **Jean-Ehrland Ricci** (C3M, team 3)
Unraveling the role of PINK1-dependent mitophagy in lung cancer progression and treatment

11h20-11h40 **Jean-François Peyron** (C3M, team 4)
Exploring New Therapeutic Strategies in Childhood T-cell Acute Lymphoblastic Leukemia: Fundamental and Translational Approaches

11h40-12h00 **Frédéric Bost** (C3M, team 5)
The polyamine/hypusination pathway regulates prostate cancer metabolism and aggressiveness

12h00-13h30 *Lunch*

Chairs : Dr. Béatrice Bailly-Maitre and Marcel Deckert

13h30-14h10 **Keynote Lecture : Pr. Victoria Sanz-Moreno (London, UK)**
Biomechanical hallmarks and vulnerabilities of metastatic cancer cells

14h10-14h30 **Marcel Deckert** (C3M, team 11)
Contribution of ExtraCellular Matrix signaling to tumor cell plasticity, invasion and drug resistance

14h30-14h50 **Pilar Dominguez** (C3M, team 14)
Superior efficacy of combinatorial epigenetic therapies in diffuse large B-cell lymphoma

14h50-15h30 *Coffee break*

Session III : Inflammation, Metabolism and Diseases

Chairs : Sophie Giorgetti-Peraldi and Dr. Laurent Yvan-Charvet

15h30-16h10 **Keynote Lecture : Pr. Eicke Latz (Bonn, Switzerland)**
TBC

16h10-16h30 **Mireille Cormont** (C3M, team 7)
Adipose tissue inflammation and obesity-associated insulin resistance involve endosomal recycling in T cells

16h30-16h50 **Philippe Gual** (C3M, team 8)
CD44 in myeloid cells: from marker to driver of chronic liver diseases

16h50-17h10 **Coraline Borowczyk** (C3M, team 13)
Artery wall remodelling by glutamine metabolism

Closing session

Chairs : Dr. Jean-Ehrland Ricci

17h10-17h50 **Keynote Lecture : Pr. Douglas R. Green (Memphis, USA)**
Perchance to Dream: Sleep and Neuroinflammation

17h50-18h00 Wrap up of the meeting by **Jean-François Tanti** (Deputy Scientific Director of C3M)

KEYNOTE LECTURE

Didier Payen de la Garanderie
emeritus prog at University of Paris, Cité, Sorbonne et CHU de Nice, France

Metabolic shift and immune response to sepsis

Biography:

Pr Didier Payen is a prominent figure in the field of intensive care medicine and anesthesia. He is best known for his significant contributions to research and clinical practice within critical care, focusing on areas such as sepsis, hemodynamic monitoring, and pain management.

He graduated from medical school in France and pursued further training in anesthesia and critical care. He has held prestigious positions, including the Director of the Intensive Care Unit at the University Hospital of Toulouse, where he has been instrumental in advancing protocols and practices in critical care. Throughout his career, Pr. Payen has been actively involved in numerous clinical trials and research projects, often emphasizing the importance of evidence-based medicine in improving patient outcomes. His work has led to significant advancements in understanding the pathophysiology of critical illness and the development of guidelines for the management of sepsis and acute respiratory distress syndrome (ARDS). In addition to his clinical roles, Pr. Payen has served on various editorial boards and has been an active member of international societies related to intensive care and anesthesia. His commitment to education is reflected in his teaching endeavors, mentoring many young physicians in the field. Pr. Payen's contributions continue to shape the landscape of critical care medicine globally.

Véronique Angeli
Université Côte d'Azur, INSERM, C3M, Nice, France
Team 9

Functions of LYVE-1$^+$ macrophage in health and disease

Few years ago, we identified a population of macrophages expressing LYVE-1 that resides in the arterial wall and regulates the arterial tone at steady state by controlling collagen production by smooth muscle cells. We have now extended this matrix regulatory function of LYVE-1$^+$ macrophages to other tissues including lung and skin uncovering their importance in maintaining tissue homeostasis through matrix regulation. Moreover, our recent findings on the function of these macrophages under pathological conditions demonstrate their protective effect against atherosclerosis and arterial ageing. Their potential implication in infectious diseases will be discussed. Altogether, these data indicate LYVE-1$^+$ macrophages as promising targets for designing new effective therapeutic strategies to combat inflammatory diseases.

Orane Visvikis
Université Côte d'Azur, INSERM, C3M, Nice, France
Team 6 - VIRINFLAM - Microbial virulence and inflammatory signaling in disease

Evolutionary conserved regulation of TFEB stability by the E3 ubiquitin ligase WWP2 modulates response to stress *in vivo*

TFEB is a key transcription factor that orchestrates the cellular response to stress, including challenges posed by infectious agents. Dysregulation of TFEB is associated with a range of human diseases, including inflammatory or metabolic disorders, cancer, and neurodegenerative diseases. Understanding the regulatory mechanisms of TFEB is crucial for comprehending TFEB-associated diseases. While TFEB phosphorylation has been extensively studied, less attention has been given to other post-translational regulations such as ubiquitination. In this study, we used Caenorhabditis elegans to screen for E3 ubiquitin ligases regulating the activity of TFEB's homolog, HLH-30, upon pathogenic infection. We identified WWP-1 as a regulator of HLH-30 stability, thereby controlling HLH30-dependent immune response and host defense. We found that HLH-30 interacts with WWP-1, supporting a model of WWP-1 directly regulating HLH-30. Furthermore, we found that WWP-1's human homolog WWP2 binds TFEB, directly induces TFEB ubiquitination and is required to maintain TFEB's stability. Overall, our work has identified an evolutionarily conserved regulation of TFEB by WWP2 and highlighted its role in modulating stress response. This finding unravels WWP2 as a potential therapeutic target to modulate TFEB levels and to restore cellular homeostasis.

Valérie Grandjean
Université Côte d'Azur, INSERM, C3M, Nice, France
Team 10 - CodEX - Control of gene expression

Paternal Epigenetic Transgenerational Inheritance in metabolic disease development in mice

Obesity is now a serious public health problem. Although this pathology is closely associated with poor lifestyle habits, several evidence show that our genes "remember" our parents' lifestyle habits. Thus, a diet-induced phenotype, such as obesity, can induce epigenetic modifications in the germline, that could be transmitted to offspring via a process called epigenetic inheritance. To determine the evolutionary potential of inherited-epigenetic changes, we maintained male mice on a Western diet for five successive generations and analyzed the phenotypes likely to be altered by this diet. Our analyses show that maintaining paternal Western-diet feeding for five consecutive generations in mice induces an enhancement in fat mass and related metabolic diseases over generations. Strikingly, chow-diet-fed progenies from these multigenerational Western-diet-fed males develop a 'healthy' overweight phenotype that persists for four subsequent generations, suggesting an accumulation of epigenetic modifications over generations. Sperm RNA-microinjection experiments into oocytes reveal that sperm RNA is sufficient for the establishment, but not for the long-term maintenance of metabolic pathologies epigenetic inheritance. Whether DNA methylation and chromatin structure alterations could be associated with this process is an open question. All together our results suggest that epigenetic inheritance could explain certain differences in individuals' susceptibility to developing metabolic diseases.

Meri Tulic
Université Côte d'Azur, INSERM, C3M, Nice, France
Team 12 - Study of molecular mechanisms involved in pigmentation and melanoma using translational approaches

Vitiligo auto-immune response upon oxidative stress-related mitochondrial DNA release opens up new therapeutic strategies

Background: Vitiligo is a complex autoimmune skin disease characterized by skin depigmentation. Despite the efficacy of JAK inhibitors, repigmentation is long and often incomplete. We have previously identified presence of mitochondrial DNA (mtDNA) in skin of vitiligo patients and we hypothesized whether mtDNA may be directly involved in vitiligo pathogenesis. **Methods:** MtDNA was sequenced from healthy and vitiligo melanocytes. Melanocyte mitochondrial immune and metabolic function, morphology, release of mtDNA and antioxidant activity was measured. To identify germline predictive biomarkers, we looked for changes in redox balance genes in matching PBMCs using whole-exome-sequencing (WES). **Results:** Vitiligo melanocytes have increased number of mtDNA variants compared to healthy melanocytes and can be classified as having low-(LV) or high-variant (HV) load. Vitiligo HV melanocytes have increased mitochondrial mass and function, ROS production but reduced catalase activity compared to LV or healthy melanocytes. Sensing of released mtDNA by the cGAS-STING pathway results in pro-inflammatory response promoting recruitment of cytotoxic CD8+ T cells. These events can be blocked with mitochondrial-specific SOD2, NRF2 activators and TBK1 inhibitor. **Conclusion:** We demonstrate two previously undescribed sub-groups of vitiligo patients based on mitochondrial variant load in their melanocytes. These findings have clinical implications as HV melanocytes are more likely to respond to treatments that specifically target mitochondria in their stressed melanocytes.

KEYNOTE LECTURE

Lynda Stuart
Executive Director, Institute for Protein Design

Biography:

Dr. Stuart earned her undergraduate degree from the University of Cambridge, her medical degree from the University of London, and a PhD in microbiological sciences and immunology from the University of Edinburgh. From 2003 to 2013, she was a faculty member at Massachusetts General Hospital and Harvard Medical School, and an affiliate of the Broad Institute of Harvard and MIT.

From 2013 to 2022, Dr. Stuart was the Deputy Director for Vaccines & Biologics at the Bill & Melinda Gates Foundation. She oversaw the preclinical development of vaccines—including mRNA vaccines—and antibody therapies targeting urgent global health issues. Following the Ebola outbreak, she contributed to conceptualizing "just-in-time" platform approaches for pandemic responses. Between 2020 and 2022, she led the foundation's COVID-19 discovery and translational vaccine response efforts, managing a significant portfolio of SARS-CoV-2 and pan-coronavirus vaccine candidates, including the IPD's computationally designed COVID-19 vaccine SKYCovione, and guided its development and approval. After leaving the Gates Foundation, she spent a year as Vice President of Infectious Disease at BioNTech, an mRNA company.

Since 2022, Dr Stuart has been serving as the Executive Director of the Institute for Protein Design (IPD) at the University of Washington School of Medicine. The IPD uses computational approaches to create proteins that address modern challenges in medicine, technology, and sustainability. In her role, Dr Stuart oversees translational research, institute operations, and collaborations with corporate and foundation partners.

Dr Stuart is an advocate for leveraging cutting-edge technologies to solve global health and societal challenges

KEYNOTE LECTURE

Olivier Demaria
Innate Pharma Research Laboratories, Innate Pharma, Marseille, France.

Natural Killer cell engagers in oncology

Harnessing innate immunity is emerging as a promising therapeutic approach to improving the efficacy of cancer treatment. We developed antibody-based natural killer (NK) cell engager therapeutics (ANKET®), which are single molecules designed to engage the NK cell-activating receptors NKp46 and CD16a, and targeting a specific tumor antigen to boost NK cell activity against cancer cells. These trispecific ANKET® molecules effectively stimulated NK cell antitumor functions and controlled tumor growth in mouse models of both solid and invasive tumors.
Building on this platform, we engineered a next-generation ANKET® by incorporating a binder for the interleukin-2 receptor (IL-2R), creating a tetraspecific engager. This advanced molecule adds new mechanisms of action by further enhancing NK cell activation and promoting their proliferation, increasing the number of NK cells capable of targeting and destroying tumor cells. Tetraspecific ANKET® significantly enhanced NK cell proliferation and demonstrated superior antitumor activity in preclinical models compared to the trispecific version and other benchmark molecules, including T-cell engagers. These molecules, thus, constitute a new technological platform for harnessing the functions of NK cells and inducing preclinical antitumor efficacy, supporting their development as next-generation cancer immunotherapies. A detailed description of our current understanding of the modes of action of these molecules will be presented.

Biography
Dr. Olivier Demaria holds a PhD in Immunology from Aix-Marseille University in Marseille, France. He pursued postdoctoral trainings at the Centre d'Immunologie de Marseille-Luminy (CIML), and the Centre Hospitalier Universitaire Vaudois (CHUV) in Lausanne, Switzerland. During this time, his research focused on the critical role of innate immunity in autoimmune diseases and cancer. In 2016, Dr. Demaria joined the biotech company Innate Pharma as a Science Leader, where he leads efforts to identify and develop promising new candidates for immunotherapy.

Thomas Strub
Université Côte d'Azur, INSERM, C3M, Nice, France
Team 1 - Biology and pathologies of melanocytes: From skin pigmentation to melanoma

LKB1-SIK2 loss drives uveal melanoma proliferation and hypersensitivity to SLC8A1 and ROS inhibition

Metastatic uveal melanomas are highly resistant to all existing treatments. To address this critical issue, we performed a kinome-wide CRISPR-Cas9 knockout screen, which revealed the LKB1-SIK2 module in restraining uveal melanoma tumorigenesis. Functionally, LKB1 loss enhances proliferation and survival through SIK2 inhibition and up-regulation of the sodium/calcium (Na+/Ca2+) exchanger SLC8A1. This signalling cascade promotes increased level of intracellular calcium and mitochondrial reactive oxygen species, two hallmarks of cancer. We further demonstrate that combination of an SLC8A1 inhibitor and a mitochondria-targeted antioxidant promotes enhanced cell death efficacy in LKB1- and SIK2-negative uveal melanoma cells. Our study also identified an LKB1-loss gene signature for the survival prognostic of patient with uveal melanoma that may be also predictive of response to the therapy combination. Our data thus identify not only metabolic vulnerabilities, but also new prognostic markers, thereby providing a therapeutic strategy for particular subtypes of metastatic uveal melanoma.

Emeline Kerreneur
Université Côte d'Azur, INSERM, C3M, Nice, France
Team 2 - INOVTEAM - Innovative therapies in myeloid leukemias

Targeting cathepsin B and non-apoptotic caspase-8 to inhibit pro-tumoral macrophage activity in cancer

Macrophages are essential white blood cells involved in immune responses, tissue repair, and inflammation. In the context of cancer, M2 macrophages, particularly tumor-associated macrophages (TAMs), contribute to tumor progression by promoting angiogenesis, inhibiting anti-tumor immunity, and supporting metastasis. High levels of TAMs correlate with poor prognosis in solid tumors. Our research highlights the critical role of CASP8 and CTSB in macrophage differentiation and polarization. We discovered a novel caspase activation mechanism where CTSB initiates CASP8 activation, leading to the differentiation of monocytes into M2 macrophages via non-canonical cleavage of CASP3 and CASP7. Targeting this pathway with inhibitors like Emricasan or CA-074 not only prevents M2 polarization but also reprograms macrophages to a pro-inflammatory state. This approach offers a potential strategy to enhance cancer immunotherapy by reprogramming immunosuppressive macrophages.

Jean-Ehrland Ricci
Université Côte d'Azur, INSERM, C3M, Nice, France
Team 3 - mCARE - metabolism, CAncers and immune REsponses.

Unraveling the role of PINK1-dependent mitophagy in lung cancer progression and treatment

Lung cancer remains one of the deadliest malignancies worldwide, with a 5-year survival rate that remains at a dismal 15% despite significant therapeutic advances. This stark reality underscores the urgent need for innovative strategies to improve patient outcomes. Autophagy, a cellular degradation process that plays a central role in inflammation, has been recognized for its dual role in cancer initiation and progression. However, the specific impact of ***mitophagy*** - the selective removal of damaged mitochondria - on tumor dynamics is less understood. Among the various pathways mediating mitophagy, the PINK1-dependent pathway is the most extensively characterized, yet its role in cancer remains largely unexplored.

In this presentation, we will explore the critical role of PINK1-dependent mitophagy in lung cancer, examining its influence on tumorigenesis and response to chemotherapy. Using state-of-the-art *in vitro* and *in vivo* models, including mitophagy reporter mice in lung cancer preclinical models, we have elucidated how PINK1-mediated mitochondrial quality control impacts cancer cell survival and therapeutic resistance. Our findings, further validated in human lung cancer samples, demonstrate that PINK1-dependent mitophagy is a critical determinant of cancer progression and treatment response. These findings not only deepen our understanding of cancer biology, but also highlight a potentially novel therapeutic target in the fight against lung cancer.

Jean-François Peyron
Université Côte d'Azur, INSERM, C3M, Nice, France
Team 4 - DysHéma - Fundamental to Translational Research on Dysregulated Hematopoiesis

Exploring New Therapeutic Strategies in Childhood T-cell Acute Lymphoblastic Leukemia: Fundamental and Translational Approaches

T-cell acute lymphoblastic leukemia (T-ALL) is a highly aggressive cancer that arises from the malignant transformation of T lymphocytes. In Europe, T-ALL accounts for 15% of childhood ALL, with 650-1,400 cases diagnosed annually, making it a significant subset of the most common pediatric cancer. Despite achieving high cure rates (80-90%) through intensive multi-agent chemotherapy and hematopoietic stem cell (HSC) transplantation, relapsed cases remain challenging, with only 30% of children achieving long-term survival.
In this presentation, we will discuss translational and fundamental approaches to identify novel therapeutic targets and active compounds in T-ALL:
1. We are characterizing novel anti-leukemic compounds that specifically target the 80S ribosome. These compounds were rationally designed using structural insights into the ribosome obtained through cryo-EM. The ribosome is key to sustain the high proliferative capacity of leukemic cells and represents a metabolic vulnerability, as it lies at the intersection of two critical oncogenic pathways: constitutive mTORC1 signaling and c-MYC amplification.
2. We are also exploring new therapeutic targets specific to relapsed T-ALL. By analyzing the transcriptome of matched diagnostic and relapsed T-ALL samples at single-cell resolution, we aim to identify genes implicated in drug resistance and relapse, potentially unveiling novel targets for therapeutic intervention.

Frédéric Bost,
Université Côte d'Azur, INSERM, C3M, Nice, France
Team 5 - CAMEEN - Cancer, Metabolism and Environment

The polyamine/hypusination pathway regulates prostate cancer metabolism and aggressiveness

Prostate cancer (PCa) cells undergo significant alterations in mitochondrial metabolism to meet their heightened energy demands to promote survival, proliferation, and aggressiveness. Hypusination, a unique post-translational modification of the eukaryotic translation initiation factor 5A (eIF5A) required for its activity and regulated by polyamines. We demonstrate that hypusination is upregulated in PCa patients and we took advantages of patient-derived tumoroids and PCa cells to study the role of hypusination in PCa. Using GC7 (a chemical inhibitor of dhps, the first enzyme of hypusination) and genetic tools (inducible shRNAdhps), we inhibited eIF5A hypusination resulting in decreased proliferation and aggressiveness. Furthermore, inhibition of hypusination significantly reduced tumor growth and metastasis in mice. Using metabolomic and fluxomic techniques, we demonstrated that targeting hypusination decreases mitochondrial metabolism. Additionally, employing proteomics, and ribosome profiling, we identified the mitochondrial proteins controlled by hypusination and implicated in mitochondrial translation. Our study highlights the dysregulation of the eIF5A hypusination pathway and its central role in driving metabolic reprogramming and cancer progression. By elucidating the molecular mechanisms underlying eIF5A-mediated metabolic alterations, we lay the groundwork for rational therapeutic interventions targeting metabolic vulnerabilities in PCa.

KEYNOTE LECTURE

Victoria Sanz-Moreno
Head of Cytoskeleton and Cancer Metastasis Team, The Institute of Cancer Research, Chester Beatty Laboratories, London

Biomechanical hallmarks and vulnerabilities of metastatic cancer cells+

Cell migration plays a pivotal role in various biological processes including cancer dissemination and successful metastasis, where the role of mechanical signals is increasingly acknowledged. My talk will focus on the intricate mechanisms through which disseminating cancer cells coordinate actomyosin dynamics together with organelle adaptations and pro-inflammatory signals in response to the extracellular matrix (ECM).

Biography:
Victoria Sanz-Moreno received a degree in chemistry and later in biochemistry (University of Oviedo, Spain) followed by a PhD in chemical sciences studying Ras-MAPK signalling (University of Cantabria). She then joined Professor Chris Marshall's lab at The Institute of Cancer Research in London as a Marie Curie Intra-European Postdoctoral Fellow. In 2008, she received the Applied Biosystems and EACR 40th Anniversary Research Award for her work on Rho GTPase signalling during cancer dissemination. In 2011, she started her independent group and received a CRUK Career Development Fellowship at King's College London to study transcriptional programs driving metastasis. In 2015, she was highly commended as CRUK Communications and Brand Ambassador. In 2017, she was awarded the BSCB Women in Cell Biology Early Career Award Medal and she received a CRUK Senior Fellowship to study the role of Rho kinase in cancer progression and therapy responses. In 2017-2018, she was featured by Journal of Cell Science as "Cell Scientist to Watch" and by Journal of Cell Biology for her work on Rho GTPases. In 2018, Victoria joined Barts Cancer Institute (Queen Mary University of London) as Professor of Cancer Cell Biology to study how cytoskeletal dynamics in metastatic cancer cells alter the tumour microenvironment. In 2021, she was elected to be part of "Ruta de las Cientificas"- an App celebrating the achievements of 9 women in STEM. In 2022 she received the Estela Medrano Memorial Award from the Society for Melanoma Research, the VP Award for Research Excellence from Queen Mary's Faculty of Medicine and Dentistry and the Research Impact Award at Barts Cancer Institute. In September 2023, Victoria's lab moved to the Breast Cancer Now Toby Robins Research Centre at The Institute of Cancer Research. Combining cell biology, OMICs, mouse models, patient material and digital pathology, Victoria's lab works on understanding how cytoskeletal dynamics in cancer cells control local invasion, dissemination, survival and outgrowth at the secondary site. Her lab is interested in deciphering how metastatic cancer cells interact with their microenvironment while evading anti-cancer therapies while the ultimate goal is to find anti-metastasis therapies.
She is passionate about science communication and promoting diversity in science.

Marcel Deckert
Université Côte d'Azur, INSERM, C3M, Nice, France
Team 11 - MicroCan - Microenvironment, Signaling and Cancer

Contribution of ExtraCellular Matrix signaling to tumor cell plasticity, invasion and drug resistance

Our laboratory is interested in understanding microenvironmental influences and signaling networks that drive tumor growth and dissemination. We have been particularly involved in studying the role of the tumor microenvironment in metastatic niche formation and response to therapy in melanoma, the most aggressive and lethal form of skin cancer. Our current work focuses on deciphering how the extracellular matrix (ECM), a key component of the microenvironment, influences the response of melanoma cells to therapy targeting the $BRAF^{V600}$ oncogenic pathway or checkpoint blockade immunotherapy, and tumor cell plasticity. I will first present an overview of our recent findings showing that MAPK-targeted therapy induces a fibrotic-like response associated melanoma cell mesenchymal dedifferentiation, ECM remodeling, and tumor stiffening, and how melanoma cell plasticity dictates the response to extracellular mechanical signals with the functional involvement of DDR1/2 collagen receptors.
I will also present data showing how we can therapeutically manipulate tumor-associated fibrosis and ECM-mediated signaling to overcome therapy resistance and delay tumor relapse.
Finally, I will present new data implicating the ubiquitin-proteasome system and deubiquitinating enzymes (DUBs) in melanoma mechanotransduction, invasion and therapeutic response. These results lay the groundwork for exploiting mechano-addiction as vulnerability for the dedifferentiated, aggressive melanoma cell state.

Pilar Dominguez
Université Côte d'Azur, INSERM, C3M, Nice, France
Team 14 - CEPIMMY - Cancer EPIgenetics and iMMunotherapY

Superior efficacy of combinatorial epigenetic therapies in diffuse large B-cell lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma in adults. The standard treatment is effective in 60% patients. However, 40% of DLBCL do not respond to the treatment or stop responding, which lead to an average 6-month survival. Epigenetic deregulation is a characteristic of DLBCL, with frequent mutations in epigenetic proteins. We demonstrated that lymphoma epigenetic patterning includes reduced histone acetylation -mediated by histone deacetylase 3 (HDAC3)- and increased DNA methylation, which correlate with aberrant repression of differentiation genes. Thus, we tested a therapy consisting of the hypomethylating agent 5-azacytidine (5-Aza) plus a specific HDAC3 inhibitor (HDAC3i). We observed a synergistic effect of the combinatorial therapy, with higher induction of apoptosis and reduced proliferation in combo-treated DLBCL cells compared to single treatments. Transcriptional analysis revealed that the combination induced upregulation of genes controlling differentiation into plasma cells (XBP1). We are analyzing H3K27ac and DNA methylation to identify the molecular mechanisms underpinning these transcriptional changes. The combinatorial therapy also had superior efficacy *in vivo* in DLBCL-derived xenografts, with a significant survival advantage in combo-treated mice compared to single agent treatment. Our results highlight the importance of targeting multiple layers of the epigenome to maximize the efficacy of epigenetic-based therapies.

KEYNOTE LECTURE

Eicke Latz
Scientific Director, Deutsches Rheuma Forschungszentrum Berlin (DRFZ)

Biography :
Prof. Dr. (med.) Eicke Latz studied medicine at the Georg-August University in Göttingen and the Freie Universität Berlin, following which, he worked as an intensive care physician at the Charité Universitätsmedizin. In 2001, he moved to the USA, working as a postdoctoral researcher at Boston University, then at UMass Chan Medical School, where he held his first professorship. In 2010, he returned to Germany and founded the Institute for Innate Immunity at the University Hospital Bonn. He became Scientific Director of the German Rheumatism Research Centre Berlin, a Leibniz Institute, and Professor of Experimental Rheumatology at the Charité Universitätsmedizin Berlin in 2023. His research interests concern how the innate immune system maintains health and under what circumstances it can promote disease. In particular, he investigates the molecular mechanisms that lead to activation or inhibition of the immune system and how these influence the inflammatory reactions in various diseases, such as rheumatic diseases, arteriosclerosis or Alzheimer's disease.

Prof. Dr. Latz is spokesperson of the Collaborative Research Centre "Metaflammation and Cellular Programming" (SFB 1454) and was previously co-spokesperson of the Cluster of Excellence "ImmunoSensation²", both at the University of Bonn. He has also co-founded several biotech companies, including IFM Therapeutics (2017), Dioscure Therapeutics (2020), a 'Stealth' biotech' (2020), and Odyssey Therapeutics (2021), which translate his discoveries into novel therapeutics and preventive approaches. He has been a highly cited scientist in immunology since 2014 having published more than 300 publications. Prof. Dr. Latz was elected as a member of the German National Academy of Sciences (Leopoldina) in 2016 and has received a number of prestigious awards, including the Gottfried Wilhelm Leibniz Prize in 2018.

Mireille Cormont
Université Côte d'Azur, INSERM, C3M, Nice, France
Team 7 - IROD - Insulin resistance in obesity and type 2 diabetes

Adipose tissue inflammation and obesity-associated insulin resistance involve endosomal recycling in T cells

In obesity, alterations in the functions of adipose immune cells are involved in the inflammation of adipose tissue leading to its pathological expansion, insulin resistance, and type 2 diabetes. Identification of novel mechanisms involved in such alterations may provide new strategies to combat obesity-associated complications. We found that the expression of the endosomal small GTPase Rab4b in T cells is decreased in adipose CD4 T lymphocytes from obese individuals. Rab4b silencing in T cells favors pro-inflammatory Th17 at the expense of Treg, leading to inflammation and pathological expansion of adipose tissue, and insulin resistance. At the molecular level, using a combination of immunofluorescence, electron microscopy, and biochemical approaches, we found Rab4b in close proximity to mitochondria and in purified mitochondria. We also observed contact sites between large endosomes and mitochondria and showed that Rab4b controls the proximity between endosomes and mitochondria. Strikingly, Rab4b knockdown increases the uptake of iron-loaded transferrin through its recycling receptor, but inhibits iron transfer into mitochondria, which is critical for T cell function. Our data identify Rab4b in T cells as a gatekeeper of mitochondrial function, regulating iron mitochondria by targeting the machinery required for endosomal-mitochondrial iron transfer to specialized contact sites.

Philippe Gual
Université Côte d'Azur, INSERM, C3M, Nice, France
Team 8 - LIVDISEASES - Chronic liver diseases associated with obesity and alcohol

CD44 in myeloid cells: from marker to driver of chronic liver diseases.

Metabolic dysfunction associated steatotic liver disease (MASLD) and Alcohol-related liver disease (ALD) are the leading causes of severe liver disease with limited pharmacological treatments for fibrotic steatohepatitis (MASH/ASH). CD44, a glycoprotein mainly expressed in immune cells, has been implicated in multiple inflammatory diseases but never or poorly studied in ALD and MASLD context, respectively. We therefore studied its contribution to MASH/ASH development focusing on myeloid cell regulation. In MASH patients, hepatic CD44 was strongly upregulated and correlated with hepatic CCL2 and macrophage marker CD68 expression. Correction of MASH was associated with a strong decrease in liver CD44+ cells. In ALD patients, its hepatic expression increased with ALD severity and correlated with liver TNFα and CD11B expression. In mouse model of MASH and ASH, CD44 systemic or myeloid cell deficiency strongly prevented liver injury and inflammation including liver infiltration and/or activity of myeloid cells. In macrophages, CD44 deficiency enhanced the anti-inflammatory polarization and strongly decreased the activation of macrophages by lipopolysaccharide, hepatocyte damage-associated molecular patterns and saturated fatty acids. In neutrophils, CD44-deficiency reduced PMA-induced inflammatory mediator expression and increased phagocytosis of live bacteria. Finally, targeting CD44 with an antibody partially corrects ASH and NASH, making it a potential therapeutic strategy.

Coraline Borowczyk
Université Côte d'Azur, INSERM, C3M, Nice, France
Team 13 - HEMAMETABO - HEMAtometabolism and METAinflammation

Artery wall remodelling by glutamine metabolism

Cardiovascular diseases (CVDs) are a leading cause of morbidity and mortality and have been linked with both genetic and lifestyle-related risk factors. Metabolic dysregulation, including perturbed glutamine-glutamate homeostasis, is common among patients, but the causal role and underlying mechanisms remain largely unknown. Here we asked how plasma glutamine-glutamate ratio (GGR) differed between people with and without CVD, and among CVD patients. Using the human MESA cohort, we found that the plasma GGR is an independent risk factor for carotid plaque progression. Using mouse models of atherosclerosis, we revealed the key role of glutaminase 2 (GLS2), the enzyme that mediates hepatic glutaminolysis. Mice deficient in *Gls2* developed accelerated atherosclerosis and susceptibility to catastrophic cardiac events, while atherogenic mice overexpressing this enzyme were partially protected from disease progression. High-throughput transcriptional profiling and high-resolution structural biology imaging of aortas from mice with *Gls2* deficiency showed perturbed extracellular matrix (ECM) composition and increased stiffness in elastic fibers. This results from an imbalance of cross-linked proteins regulated by glutamine- and glutamate-dependent ECM matrix modulating enzymes within atherosclerotic lesions and cellular remodelling of plaque composition. Thus, hepatic glutaminolysis functions as a potent regulator of glutamine homeostasis, which rewires the pathophysiological dimension of the arterial wall of aortas during atherosclerotic plaque progression

KEYNOTE LECTURE

Douglas R. Green
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Perchance to Dream: Sleep and Neuroinflammation

Abstract:
Our personal experience informs us that sleep is important for health. It has been known for decades that inflammation induces slow wave sleep, but whether this is important is an open question. We established a model wherein injection of a sub-lethal dose of lipopolysaccharide (LPS) sufficient to promote sleep is followed by mild sleep fragmentation (SF), resulting in catastrophic lethality in all animals. This lethal effect is not associated with a systemic cytokine "storm" but is accompanied by dramatic activation of microglia. Accordingly, ablation of the LPS receptor, TLR4 in microglia protects animals from the lethal effects of LPS plus SF. I will discuss the requisite role of the NLRP3 inflammasome and IL1-beta in this effect, and how it may manifest. Further, we have found that lethality is accompanied by hypotension, hypothermia, and gut permeability, all of which are prevented by sub-diaphragmatic vagotomy. Using a novel Dec2 mutant mouse, mimicking human Familial Natural Short Sleep, a rare inherited trait, we found that the lethal effects of LPS plus SF are dependent on the wild-type Dec2 allele. We propose a model wherein the neuronal effects of slow wave sleep impact a lethal microglial activation state via vagus nerve signaling to the periphery.

Biography:
Doug Green holds the Peter C. Doherty Endowed Chair in the Department of Immunology at St Jude Children's Research Hospital. Prior to this he was Head of the Division of Cellular Immunology at the La Jolla Institute of Immunology. Doug received his Bsc ('77) and PhD ('81) from Yale University and joined the faculty at the University of Alberta in 1985, La Jolla Institute in 1990, and St. Jude in 2005. His research focusses on active cell death and cell survival, extending from whole organisms to fundamental molecular events in cells. He has published over 600 papers, chapters, commentaries, and books, and is an ISI "highly cited" investigator. In 2017, he was awarded the Jurg Tschopp prize for research on cell death and the Wilbur Cross medal from Yale. He is a fellow of the U.S. National Academy of Sciences, a foreign fellow of the Royal Society of Canada, a Distinguished Fellow of the American Association of Immunologists, a Fellow of the American Association for the Advancement of Science, an honorary fellow of Trinity College, Dublin, an honorary Einstein Professor in China, and received an honorary Ph.D. from Univ. Tor Vergata in Rome. His most recent book is "Apoptosis and Other Cell Death Mechanisms: Means to an End," published in 2018 by Cold Spring Harbor Laboratory Press. His family, laboratory, and colleagues appear to continue to put up with him.