

## FARNESOID X RECEPTOR IN HUMAN MALIGNANCIES: AN OVERVIEW

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**Cancer represents a leading cause of death in developed and developing countries, accounting for 8.8 million deaths in 2015. These numbers are expected to continue rising with 13.1 million deaths estimated in 2030. Although the earlier diagnosis and increasing treatment options have improved the survival rates for the majority of cancers, many tumors exhibit therapeutic resistance and severe adverse effects remain major therapeutic hurdles. Thus, the main challenge of the cancer research area is the definition of additional treatment options tailored on the distinct tumor characteristics and the expression of appropriate targets. Nuclear receptors, controlling many biological features of cancers as proliferation, survival, apoptosis, and differentiation, possess a significant clinical relevance in disease management, representing a “druggable” class of molecules useful for potential therapeutic intervention. In the last years, among the nuclear receptors, the metabolic sensor Farnesoid X Receptor was recognized to play a role in carcinogenesis, acting either as an oncogene or as a tumor suppressor gene. Here, we will summarize the current knowledge on the FXR role in human cancers, highlighting its ligands as new potential anticancer tools.**

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## THE SIGNATURE OF LONGEVITY IN SICILY

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**Ageing is a natural and physiological condition that is the result of compromised stress response, homeostatic imbalance and increased risk of developing diseases. However, if aging with good health and functions (successful ageing) and aging with disease and disability (unsuccessful ageing) depends on a combination of “positive features”, including genetic, epigenetic and phenotypic characteristics in combination with favourable environment, economic status and social involvement. In our study, we summarize some key points for the identification of a longevity signature, with a particular focus on long-living Sicilian individuals and centenarians. Analysing three different Sicilian cohorts (young, people with no centenarian parents and long-living individuals (LLI) aged >90) we found APOE  $\epsilon 3/\epsilon 3$  in our LLIs and no presence of  $\epsilon 4$ . Regarding FOXO rs2802292 G-allele (G>T) we did not observe an association with longevity, probably because of the small sample of centenarians studied. Regarding haematological and anthropometric results, it is still difficult to point specific longevity features and so far, we cannot specify a single one. On the other hand, we believe that the synergy among genetics and environment might create successful interaction to achieve and obtain effective longevity.**

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## CLINICAL APPLICATIONS OF MICROENVIRONMENT-CONTROLLED IMMUNOSUPPRESSIVE PROPERTIES OF MESENCHYMAL STEM CELLS-DERIVED EXOSOMES: A REVIEW

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The discovery that mesenchymal stem cells (MSCs) modulate inflammation and promote tissue regeneration has revolutionized stem cells-based therapy. However, some observations have raised questions about the limitations of their clinical use. On the other hand, recent findings have demonstrated that exosomes released by MSCs contribute significantly to their therapeutic effect and may be used as an alternative MSCs-based therapy in regenerative medicine. In this review, we summarize the current knowledge about the immunosuppressive capacity of MSCs-derived exosomes and we discuss the critical role of the surrounding microenvironment in the modulation of their regenerative and therapeutic potential.

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## **DYSFUNCTIONAL EPICARDIAL ADIPOSE TISSUE (EAT) AND MALADAPTIVE HEART REMODELING IN PATIENTS WITH INCREASED VISCERAL ADIPOSITY: THE ST2/IL-33 CARDIO-FAT SIGNALING**

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**Recent clinical evidences suggested that the expansion of epicardial adipose tissue (EAT) and its transformation into a pro-inflammatory organ in visceral obesity are related to maladaptive heart remodeling and heart failure (HF). However, the sustained molecular mechanisms are poorly understood. The ST2/IL33 system has recently obtained great attention in the field of cardiovascular diseases due to its cardio-protective role in different stress conditions that can promote cardiomyocyte hypertrophy and deposition of extracellular proteins (fibrosis). Any imbalance in ST2/IL33 signaling may thus lead toward HF. Discussing how dysfunctional EAT may interfere with the protective role of ST2/IL33 pathway and its association with heart remodeling in visceral obesity are the aims of the present review.**

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## **GAMMA-GLUTAMYLTRANSFERASE (GGT) IN TUMOR PROGRESSION, DRUG RESISTANCE AND TARGETED THERAPIES**

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**The biological role of a protein seldom coincides with the function first described, i.e. the easiest to observe (the two aspects usually coexist). First observations usually settle down and address subsequent research during years to follow. However, it often happens, that from an out of frame data, indications later emerge that something else (possibly more interesting) may hide beneath the surface. An analysis free from preconceptions may therefore allow other aspects such as unexpected processes and novel functions of the protein under investigation, to emerge. This is well illustrated in the case of gamma-glutamyltransferase (GGT), whose pathophysiological significance we could specify and redefine in experimental studies carried out in our laboratories, first in Siena and then in Pisa.**

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*INVITED SPEAKER***CHEMOTHERAPY RESISTANCE-ASSOCIATED EPITHELIAL TO ENDOTHELIAL TRANSITION IN GASTRIC CANCER**

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**Gastric cancer (GC) is the fifth most common cancer worldwide and the third leading cause of cancer-related deaths. To date, gastrectomy and chemotherapy are the only therapeutic options, but drug resistance is the main cause for treatment failure. Vasculogenic mimicry (VM) is a new model of neovascularization in aggressive tumors and has been correlated with poor prognosis in GC patients. Our group has developed chemotherapy-resistant GC cells using the Caucasian adenocarcinoma cell line AGS and three drugs among the most used in clinic (5-fluorouracil, cisplatin and paclitaxel) henceforward denominated 5FUr, CISr, TAXr. Our study has highlighted phenotypical differences among chemo-sensitive and chemo-resistant cell lines such as acquisition of stem-like phenotype and increased capacity to form vessels.**

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## **SLC7A7/Y+LAT1, MUTATED IN LYSINURIC PROTEIN INTOLERANCE, HAS A SIGNIFICANT ROLE IN REGULATING THE INFLAMMATORY STATUS OF HUMAN MACROPHAGES**

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**Lysinuric protein intolerance (LPI) is a recessively inherited aminoaciduria caused by mutations of SLC7A7, the gene that encodes y+LAT1 light chain of system y+L for cationic amino acids (CAA; namely arginine, lysine, and ornithine) transport. Clinical signs of LPI are highly heterogeneous and only poorly understood: while hyperammonemia and protein intolerance can be explained by urea cycle slowdown due to the impairment of CAA absorption/reabsorption in intestinal and renal epithelial cells, little is known about the pathogenesis of the often fatal complications affecting lungs and immune system. Here, we explore the possibility that y+LAT1 protein directly exerts immunomodulatory functions and that LPI defects, besides affecting CAA transport, also activate inflammatory mononuclear phagocytes, ultimately leading to immunological complications.**

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## UPREGULATION OF CIRCULATING LEVELS OF RECEPTOR FOR ADVANCED GLYCATION END PRODUCTS (SRAGE) IN OBESE RATS MAY PROTECT AGAINST ECTOPIC FAT ACCUMULATION IN THE HEART

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**Receptor for advanced glycation end-products (receptor for AGEs, RAGE) is a cell-surface protein identified as a receptor for AGEs. RAGE activation mainly induces oxidative stress and inflammation. Indeed, in different organs, such as the adipose tissue and the liver, RAGE engagement has also been shown to promote lipid accumulation. Besides the cell-membrane form, RAGE exists as a soluble circulating molecule (sRAGE), a decoy receptor able to prevent the detrimental effects of AGEs at cellular level. As most of the obesity-related complications are due to the ectopic fat accumulation and no data are available about RAGE, sRAGE and heart steatosis, our aim was to explore any potential association of these molecules with heart steatosis in obesity.**

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## SRAGE: A PROGNOSTIC FACTOR FOR MORTALITY IN END-STAGE RENAL DISEASE PATIENTS ON DIALYSIS

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**End stage renal disease patients on dialysis (CKD-G5D) have a high mortality rate mainly due to cardiovascular diseases (CVD). In addition to traditional CVD risk factors, which are common in these patients, excessive oxidative stress, uremia and chronic inflammation may further increase the production of advanced glycation end-products (AGEs) which in turn promote CVD and CVD-related morbidity and mortality. Much attention has been paid recently to the soluble receptor for AGEs (sRAGE) as a marker of inflammation, oxidative stress, atherosclerosis and heart failure (HF) in CKD-G5D. However, its relationship with patient outcomes is still debated.**

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## UPAR FUNCTION IN MELANOMA DERIVED-EXOSOMES: PRO-ANGIOGENIC EFFECTS ON ECFCs

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**Tumor-derived exosomes are emerging mediators of tumorigenesis. Exosomes are small membrane vesicles (40-150nm) derived from the luminal membranes of multivesicular bodies, and are released via fusion with the cell membrane. Exosomes mediate local and systemic cell communication through the horizontal transfer of information (mRNAs, microRNAs and proteins). It is well recognized that uPAR, is one of the main systems involved in tumor invasion and metastasis. Several malignant tumors show a positive correlation between uPAR levels and a more aggressive phenotype together with a poor prognosis. We have showed that uPAR is strongly upregulated in A375 and in metastasis-prone A375M6 melanoma cells with respect to normal melanocytes. Here we explored the uPAR function in melanoma-derived exosomes and their pro-angiogenic capacity in ECFCs (Endothelial Colony Forming Cells).**

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## ST2 FIBRO-CITOKINE AND IL-33 ALARMIN PROTEIN ARE EXPRESSED IN OBESE FA/FA- ZUCKER RAT MODEL AND CORRELATED WITH PRO-FIBROTIC GENE PATHWAYS.

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**The function of ST2 fibro-mediator and IL-33 alarmin protein has been mainly investigated on immunological aspects, but recent data suggest that this pathway plays also an important role in cardiovascular system and adipose tissue inflammation. Whereas IL-33 has been demonstrated to exert anti-inflammatory and protective effects, circulating ST2 (sST2) has emerged as a prognostic biomarker in patients with myocardial infarction and heart failure. Furthermore, the IL-33/ST2 expression system is increased in severe obesity, although its role in the pathogenesis of detrimental cardiac remodeling associated with obesity is still not well defined. The aim of this study is to investigate the molecular pattern of IL-33/ST2 system and pro-fibrotic genes activation in experimental model of obese fa/fa- Zucker rat model.**

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## TARGETING CHRONIC MYELOID LEUKEMIA STEM CELLS WITH ERK5 PATHWAY INHIBITORS

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**Tyrosine kinase inhibitors (TKi) targeting BCR/ABL are very effective for the treatment of Chronic Myeloid Leukemia (CML). However, discontinuation and/or inefficacy on CML leukemia stem cells (LSC) may lead to relapse. To identify new druggable targets alternative to BCR/ABL, we investigated the role of the Extracellular signal-Regulated Kinase 5 (ERK5) pathway in CML LSC maintenance.**

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## CIRCULATING BIOMARKERS IN PROSTETIC JOINT INFECTION

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Post-operative prosthetic joint infection (PJI) is the most common cause of failure of total joint arthroplasty, but a gold standard for PJI diagnosis is still lacking. Among the scenario of infections diagnosis, an emerging molecule is Presepsin, the soluble fraction of CD14, recently described as a powerful diagnostic tool, to detect sepsis and to discriminate of sepsis severity. Among the scenario of infections diagnosis, an emerging molecule is Presepsin, the soluble fraction of CD14, recently described as a powerful diagnostic tool, able not only to detect sepsis but also to discriminate different grade of sepsis severity. Presepsin is a fraction of the soluble form of CD14, which is shedded from monocytes surface during inflammatory response and then released into blood. Therefore, Presepsin can be used a circulation marker of infection, but so far little is known about the mechanism of this sCD14 fraction shedding. A better understanding the mechanism of action of Presepsin in the inflammatory response and its correlation with other inflammatory mediators could improve the diagnostic potential and clinical application of Presepsin.

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## THE ROLE OF TUMOR-DERIVED EXOSOMES IN CANCER IMMUNE EVASION MEDIATED BY TOLL-LIKE RECEPTOR 4 ACTIVATION

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**Although, it is widely recognized that cancer cells actively utilize exosomes to promote tumor growth and metastasis, the biology of tumor-derived exosomes (TEX) is incompletely understood and much remains to be study in order to define the molecular and genetic mechanism by which exosomes operate in cancer. Increased expression and activity of toll-like receptor 4 (TLR4) in chronic infectious and inflammatory conditions is associated with cancer progression: its activation induces an inflammatory signaling that increases the tumorigenic potential of cancer cells promoting their immune evasion. The purpose of this study is to investigate the immunosuppressive properties of TEX released upon TLR4 activation.**

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## THE KERATINOCYTE DIFFERENTIATION INDUCED BY FGFR2B REQUIRES SEQUENTIAL INVOLVEMENT OF PKC $\delta$ AND PKC $\alpha$

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The fibroblast growth factor receptors (FGFRs) are receptor tyrosine kinases expressed, by tissue-specific alternative splicing, in epithelial IIIb or mesenchymal IIIc isoforms and controlling key physiological processes, such as cell proliferation, differentiation, survival and migration. We have previously demonstrated that the tumor suppressor epithelial isoform of the FGFR2 (FGFR2b) induces early differentiation of human keratinocytes. Since protein kinases C (PKCs) are known to regulate the differentiation program in several cellular contexts, including keratinocytes, aim of our present study was to clarify if FGFR2b could play a role also in the late steps of keratinocyte differentiation and to assess if this receptor-induced process would involve PKC isoforms.

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## A LARGE BIOMARKER INVESTIGATION IN YOUNG ASYMPTOMATIC PATIENTS WITH CEREBRAL SMALL VESSEL DISEASE IDENTIFIES ADMA AS A POSSIBLE KEY MOLECULE DRIVING ENDOTHELIAL DAMAGE

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**Cerebral small vessel disease (CSVD), detected as white matter hyperintensities (WMH) on brain MRI, could be a distinct pathological entity within cerebrovascular diseases. The increasing use of MRI has led to more incidental finding also in young people without classical vascular risk factor. The purpose of this work was to investigate different pathways implicated in endothelial dysfunction (inflammation, autoimmunity, coagulation, nitric oxide pathway) in a well selected, homogeneous population of patients with WMH, without significant vascular risk factors or neurological diseases.**

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## NUCLEO-CYTOPLASMIC SHUTTLING OF PROGESTERONE RECEPTOR AND CELL CYCLE PROGRESSION OF BREAST CANCER CELLS

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**Progesterone receptors (PRs) belong to the steroid receptor superfamily and regulate development, growth and transformation of breast tissues. Different mechanisms, such as ligand binding, post-transcriptional modifications, interaction with signalling effectors or scaffold proteins control the steroid receptor subcellular localization, thereby influencing their activity. Derangement of steroid receptor import/export process often causes receptor delocalization and proliferative diseases of target tissues, such as breast and prostate. However, while the mechanism of steroid receptor nuclear import is well documented, the mechanism of their nuclear export is still unclear.**

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## **FOXO3A RE-EXPRESSION OVERCOMES TAMOXIFEN RESISTANCE IN BREAST CANCER**

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**The poor outcome of patients resistant to endocrine treatments is a major clinical challenge in the management of estrogen receptor positive (ER+) breast cancers (BC) and demands additional studies. In this context, the role of FoxO3a transcription factor was investigated.**

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## ERK5 INHIBITION ELICITS CELLULAR SENESCENCE IN HUMAN MELANOMA CELLS

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Extracellular signal-Regulated Kinase 5 (ERK5) is a member of the Mitogen Activated Protein Kinase (MAPK) family. ERK5 is activated by MEK5 in response to numerous stimuli and is involved in several cellular processes including the proliferation of both normal and neoplastic cells. We previously demonstrated that ERK5 is required for the proliferation of melanoma cells, a neoplasia that, especially in the advanced stages, has a very poor prognosis. Human melanomas are frequently characterized by the loss or the reduced expression of markers of cellular senescence that results in tumor growth and progression. We evaluated the effects of the inhibition of the MEK5-ERK5 pathway on cellular senescence in melanoma cells.

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## GENOTYPIC ASPECTS OF LONGEVITY. DATA FROM DESIGN PROJECT

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## ANTHROPOMETRIC SIGNATURE OF LONGEVITY IN SICILY

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## CHK1 INHIBITION RESTORES INOTUZUMAB OZOGAMICIN CITOTOXICITY IN CD22-POSITIVE CELLS EXPRESSING MUTANT P53

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A. FIDILIO<sup>2</sup>, L. MANZELLA<sup>1</sup>, N. PARRINELLO<sup>3</sup>, F. STAGNO<sup>3</sup>, G. PALUMBO<sup>4</sup>, A. ROMANO<sup>3</sup>,  
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**Inotuzumab ozogamicin (IO) is an anti-CD22 calicheamicin immunoconjugate that has been recently approved for the treatment of relapsed or refractory B-Acute Lymphoblastic Leukemia (r/r B-ALL). We employed both immortalized and primary cells derived from CD22-positive lymphoproliferative disorders to investigate the signaling pathways contributing to IO sensitivity or resistance.**

## **EDF-1 CONTRIBUTES TO PPAR $\gamma$ TRANSCRIPTIONAL ACTIVATION IN ENDOTHELIAL CELLS TREATED WITH VEGF**

A. CAZZANIGA, L. LOCATELLI, V. ROMEO, R. SCRIMIERY, S. CASTIGLIONI and J. MAIER

*Dipartimento di scienze biomediche e cliniche L. Sacco, Università degli Studi di Milano*

**The endothelium is the gate-keeper of vascular health. Accordingly, endothelial dysfunction is a crucial event in macro-vascular and in small vessel diseases. Since the morbidity and mortality due to micro- and macro-vascular complications in patients with diabetes is very high, understanding the molecular bases of endothelial dysfunction in response to high glucose is a major issue.**

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## MESOPOROUS SILICA NANOPARTICLES AS A VEHICLE FOR HIGHLY SELECTIVE DELIVERY OF BORTEZOMIB TO FOLATE RECEPTOR EXPRESSING CANCER CELLS

M. PELLEGRINO<sup>1</sup>, A. NIGRO<sup>1</sup>, E. RICCI<sup>1</sup>, M. GRECO<sup>1</sup>, A. COMANDÈ<sup>1</sup>, I. PERROTTA<sup>2</sup>,  
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**The major limitation of traditional chemotherapeutic agents is their poor selectivity for cancer cells and their severe toxicity to normal cells. Therefore, localized drug delivery would, ideally, improve the therapeutic efficacy, minimizing side effects. The properties of mesoporous silica nanoparticles (MSNs) seem to cope with this aim. A MSN-based device, FOL-MSN-BTZ, bearing the antineoplastic drug bortezomib (BTZ), linked to MSNs by means of a pH-sensitive bond and the folic acid (FOL, a targeting function), was then developed and tested on folate receptor (FR+ cells) overexpressing cancer cells and on FR- normal cells, in order to investigate MSNs behaviour.**

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## **CXCL12 $\alpha$ IS A KEY FACTOR IN THE REGENERATION OF THE DAMAGED NEUROMUSCULAR JUNCTION BY ACTING ON THE CXCR4 RECEPTOR**

C. MONTECUCCO<sup>1</sup>, S. NEGRO<sup>1</sup>, F. LESSI<sup>2</sup>, E. DUREGOTTI<sup>1</sup>, P. ARETINI<sup>2</sup>, A. MEGIGHIAN<sup>1</sup>,  
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<sup>1</sup>*Department of Biomedical sciences, University of Padova;* <sup>2</sup>*Fondazione Pisana per la Scienza*

**The neuromuscular junction (NMJ) is one of the few human tissues capable of complete regeneration after major damages (1). We want to identify the cross-talk taking place among the different cell type of the NMJ: neuron, muscle, Schwann cells.**

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## HLA-B51 ALLELE CORRELATION WITH AUTOIMMUNE DISEASES OTHER THAN BEHÇET'S: A RETROSPECTIVE ANALYSIS

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**Behçet's Disease (BD) is a systemic vasculitis, prevalent in males, with a chronic and inflammatory course and with multi-organ involvement. Are affected young subjects (20-30 years). The etiology remains unknown but appears to be mediated by exogenous factors (bacterials or virals) that, through immunopathological mechanisms, start humoral or cellular responses. The main clinical manifestations are represented by: oral ulcers, genital ulcers, cutaneous, ocular, articular, vascular and neurological involvement. Frequent is the association (about 72%) with HLA-B51 histocompatibility antigen, which suggested that the disease is present, following external factors, in genetically predisposed patients. HLA (Human Leukocyte Antigen) is a highly polymorphic gene with different haplotypes that can agree the response of the human adaptive immune system or predispose individuals to a particular immune system disease. The diagnostic utility of HLA-B51, associated with Behçet's disease, has been clearly identified; however, its correlation with other autoimmune diseases has not yet been clarified. This study evaluate the presence of the HLA-B51 allele with other autoimmune diseases.**

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## UNRAVELING THE ROLE OF MAPK ERK5 IN HUMAN MELANOMA

S. GAGLIARDI<sup>1</sup>, A. TUBITA<sup>2</sup>, I. TUSA<sup>2</sup>, S. PANDOLFI<sup>1</sup>, X. DENG<sup>3</sup>, N. GRAY<sup>3</sup>, J. WANG<sup>3</sup>, E. ROVIDA<sup>2</sup> and B. STECCA<sup>1</sup>

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**Melanoma is the deadliest skin cancer, with a very poor prognosis in advanced stages. Available treatments for melanoma, including immunotherapy or inhibitors for BRAF-MEK1/2, have greatly improved the survival for this disease although they are not applicable to all patients and/or their long-term benefits are still unsatisfactory. As a member of Mitogen-Activated Protein kinase family, ERK5 could play a relevant role in melanoma regulating cell functions critical for tumor development, such as proliferation, invasion and angiogenesis.**

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## A NEW THERAPEUTIC STRATEGY IN MULTIPLE MYELOMA BASED ON SMALL MOLECULES DIRECTED TO NOTCH PATHWAY

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**Multiple myeloma (MM) is the second most common hematological malignancy. Although clinical advances, it is still incurable disease, sustained by a tight interaction of malignant plasma cells with the bone marrow (BM) microenvironment that promotes tumor growth, immunosuppression, drug resistance, neoangiogenesis and bone destruction. The oncogenic Notch signaling plays a crucial role in MM. In particular, aberrant Notch2 receptor activation and Jag1 and 2 ligands overexpression stimulate MM cells to establish pathological interactions with BM that trigger MM progression. Our previous data showed that these effects can be interfered by knocking down of Jag1 and 2 expression. Indirect approaches to inhibit Notch signaling are mainly based on inhibition of  $\gamma$ -Secretase that catalyzes Notch activation along with other several  $\gamma$ -Secretase substrates. Moreover, inhibition of all four Notch receptors is associated with a gut toxicity. This evidence prompted us to develop a therapeutic tool to selectively inhibit Notch2 signaling triggered by Jag1 and 2.**

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## ATYPICAL BCR-ABL BREAKPOINTS DISPLAY SELECTIVE RESPONSIVENESS TO TYROSINE KINASE INHIBITORS

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**The BCR-ABL oncoprotein is the culprit of CML as it transforms the hematopoietic stem cell by altering its survival and proliferation properties. The efficacy of Tyrosine Kinase Inhibitors (TKIs) of the canonical BCR-ABL variants e1a2 (p190), e13a2 or e14a2 (p210) has been well established. Alternative breakpoints involving different BCR and/or ABL exons have been previously described but yet to be characterized. We analyzed 50 CML patients, not presenting the canonical isoforms, finding three atypical BCR-ABL breakpoints in five subjects: one e12a2<sup>ins/del</sup>, three 13a3 and one e14a3 transcripts. These atypical isoforms (with the addition of two further deletion mutants lacking the BCR DC2 domain or the ABL SH3 domain) were investigated for their catalytic activity, transforming potential and TKI responsiveness.**

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## A NEW DOWEL IN ENDOTHELIAL ADAPTATION TO MICROGRAVITY: IMPACT ON MITOCHONDRIA

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**Blood vessels are lined by cells (ECs) that are crucial to maintain vascular and tissue homeostasis. Endothelial function is shaped by mechanical forces, i.e. shear stress and gravity (1G). Since life evolved under the influence of the earth's gravitational pull, it is not surprising that microgravity activates adaptive responses that impact also on the endothelium. Several studies have shown that real and simulated microgravity affect ECs behaviour in different aspects but very little is known about the metabolic adaptation of these cells. In particular, we focused our attention on the mitochondria, rod-shaped organelles that convert oxygen and nutrients into adenosine triphosphate (ATP).**

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## THE METABOLIC MICROENVIRONMENT IMPOSED BY GLUTAMINE SYNTHETASE-NEGATIVE MULTIPLE MYELOMA CELLS SHAPES THE BONE MARROW NICHE

M. CHIU, D. TOSCANI, M. BOLZONI, G. TAURINO, F. ACCARDI,  
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**Altered cancer metabolism satisfies high demand for nutrients but also has an impact on non-cancer cells of tumor microenvironment. In the bone marrow (BM) of multiple myeloma (MM) patients, glutamine (Gln) is lowered, while glutamate (Glu) and ammonium increase (Bolzoni, Chiu et al., Blood 2016; 128:667-679). Glutamine Synthetase (GS), which catalyzes Gln synthesis from Glu and ammonium, is lowered in most MM cells and down-regulated during osteoblastogenesis. Since bone lesions of MM patients are characterized by low osteoblast viability and function, we hypothesize that MM cells negatively affect osteoblastogenesis through the peculiar low-Gln, high-Glu bone marrow microenvironment.**

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**MEDITERRANEAN DIET AS PREVENTION STRATEGY OF AGE-RELATED DISEASE**L. CRISTALDI<sup>1</sup>, S. VASTO<sup>2</sup>, M. DI CARLO<sup>3</sup> and C. CARUSO<sup>2</sup>

<sup>1</sup>*Department of Pathobiology and Medical Biotechnology (DI.BI.MED), University of Palermo, Italy;* <sup>2</sup>*Department of Biological Chemical and Pharmaceuticals Sciences and Technologies, University of Palermo, Italy;* <sup>3</sup>*Institute of Biomedicine and Molecular Immunology “Alberto Monroy” (IBIM), CNR - Palermo, Italy*

Several evidence indicates a strong correlation between healthy lifestyle and age-related pathology, in particular neurodegenerative diseases, including Alzheimer’s disease (AD). This pathology is characterized by two histo-pathological hallmarks, the amyloid plaques, formed by A $\beta$  oligomers, and neurofibrillary tangles, due to hyperphosphorylation of tau protein. At molecular level, A $\beta$  induces mitochondrial and endoplasmatic reticulum dysfunctions, oxidative stress and apoptosis. The brain is susceptible to oxidative stress and several prevention strategy based on use of antioxidant molecules have been proposed. Traditional Mediterranean Diet (MD) includes high consumption of vegetables, fruits and herbs, food rich in antioxidant molecules, such as polyphenols. Some studies indicate that MD influences longevity as confirmed by studies on centenarian subjects. *In vitro* studied have demonstrated that Caffeic Acid (CA), one of the main polyphenol present in several foods that make up the MD, has high anti-inflammatory and antioxidant properties.

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## **CYTOPLASMIC CYCLIN D1 MEDIATES PROGESTERONE/PR-B INHIBITION OF HUMAN BREAST CANCER CELL INVASION**

F.I. MONTALTO<sup>1</sup>, C. CHIODO<sup>1</sup>, D. NAIMO<sup>1</sup>, M. SANTORO<sup>2</sup>, L. MAURO<sup>1</sup>, S. AQUILA<sup>1</sup>,  
F. DE AMICIS<sup>1</sup>, M. LANZINO<sup>1</sup> and S. ANDÒ<sup>1</sup>

*<sup>1</sup>Dpt. of Pharmacy, Health and Nutritional Sciences University of Calabria, Italy; <sup>2</sup>Health Center University of Calabria, Italy*

**Progesterone Receptor (PR) positivity is associated with a good prognosis and better response to breast cancer treatment. Conversely, cyclin D1 (CD1) is retained a marker of poor outcome since it has been associated with breast cancer metastasis in clinical studies.**

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## SIGNATURE OF LONGEVITY

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*<sup>1</sup>University of Palermo; <sup>2</sup>CNR*

**Ageing is a natural and physiological condition that is the results of compromised stress response, homeostatic imbalance and increased risk of developing diseases. However, if we age having a good health and functioning (successful aging) or with disease and disability (unsuccessful aging), it depends on a combination of “positive features”, including genetic, epigenetic and phenotypic characteristics in combination with favorable environment, economic status and social involvement. In our study, we summarize some key points for the identification of a longevity signature, with a particular focus on Sicilian long-lived individuals and centenarians.**

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## ADIPOCYTE-RELEASED FACTORS AFFECT VIABILITY, MIGRATION AND RESPONSE TO DOCETAXEL IN PROSTATE CANCER CELLS

A. LIOTTI<sup>1</sup>, E. LA CIVITA<sup>1</sup>, D. LIGUORO<sup>1</sup>, L. DE STEFANO<sup>2</sup>, A. PALMIERI<sup>2</sup>, V. MIRONE<sup>2</sup>, F. BEGUINOT<sup>1</sup>, P. FORMISANO<sup>1</sup> and D. TERRACCIANO<sup>1</sup>

<sup>1</sup>*Department of Translational Medical Sciences, Federico II University, Naples, Italy;* <sup>2</sup>*Department of Urology, Federico II University, Naples, Italy*

The prevalence of obesity is increasing at an alarming rate in developed countries throughout the world. Epidemiologic studies indicate that obesity is important risk factors for diabetes, cardiovascular disease and cancer. In particular, obesity is associated with a greater increase of aggressive prostate cancer (PCa) with increased local dissemination. Prostatic gland is surrounded by periprostatic adipose tissue (PPAT). PPAT is an active endocrine organ able to secrete molecules known as adipokines. The high prevalence of both obesity and PCa highlights the importance of understanding the biological features of this relationship. Recent studies uncovered that the secretion of mature adipocytes can affect the early stage of PCa progression by promoting the spread of cancer cells outside the prostate gland. It is clear that tumor-surrounding adipocytes might affect cancer phenotype, but the molecular mechanisms involved in this cross-talk are still unknown.

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## **ROLE OF ANDROGEN RECEPTOR IN BREAST CANCER-ASSOCIATED FIBROBLASTS: MAY ANDROGEN SHAPE BREAST TUMOR MICROENVIRONMENT?**

C. CHIODO<sup>1</sup>, C. MORELLI<sup>1</sup>, F. DE AMICIS<sup>1</sup>, C. GIORDANO<sup>2</sup>, D. SISCO<sup>1</sup>,  
S. ANDÒ<sup>1</sup> and M. LANZINO<sup>1</sup>

<sup>1</sup>*Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Rende, Italy;*  
<sup>2</sup>*Health Center, University of Calabria, Rende, Italy*

**Interaction between breast tumor epithelial and stromal cells is central for tumor growth and progression. Indeed, while providing a scaffold for the breast, the stroma also regulates epithelial cell function through physical and hormonal paracrine exchanges, providing a favorable environment for proliferation and metastasis. There is extensive knowledge of androgen receptor (AR) signaling in breast epithelial cancer cells, but less regarding AR-mediated action in breast tumor stroma. In the present report, we provide evidence of AR expression in breast cancer-associated fibroblasts (CAFs) isolated from breast cancer patients. We also examined the effect of CAFs exposure to androgens on: 1) secretory phenotype and 2) the migratory behavior of the estrogen-responsive breast cancer MCF-7, T47D and ZR-75 cells.**

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## INHIBITING FOCAL ADHESION KINASE (FAK) REDUCES THE GROWTH OF UVEAL MELANOMA GNAQ/GNA11-MUTATED CELLS BY TARGETING THE PI3K/AKT/MTOR PATHWAY

D.C. RIGIRACCIOLO<sup>1</sup>, X. FENG<sup>2</sup>, R. LAPPANO<sup>1</sup>, M. MAGGIOLINI<sup>1</sup> and J.S. GUTKIND<sup>2</sup>

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Uveal melanoma (UM) represents the most common intraocular malignancy in adults and approximately 50% of patients develops metastatic disease. The new genomic sequencing technologies on UM tumors allowed to identify mutations in the Gq alpha subunits GNAQ and GNA11. These mutations appear in a mutually exclusive manner and are consequently of prognostic importance (Van Raamsdonk et al., Nature 2009). FAK (focal adhesion kinase) is a cytoplasmatic tyrosine kinase localized at the sites of cell adhesion to the extracellular matrix. FAK is overexpressed in several tumors and mediates diverse signaling promoting cancer growth and metastasis. To date, it has been considered as a potential target for cancer therapeutics (Sulzmaier et al., Nat Rev Canc 2014).

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## **ESTROGENIC GPER SIGNALING PROMOTES FGF2/FGFR1 ACTIVATION BETWEEN BREAST CANCER-ASSOCIATED FIBROBLASTS (CAFS) AND TUMOR CELLS**

M.F. SANTOLLA, A. VIVACQUA and M. MAGGIOLINI

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**Many cancers acquire aberrant growth and invasion capacity through the dysregulation of fibroblast growth factors (FGFs)-mediated signaling (Carter EP, Trends Cell Biol. 2015). In particular, FGFs secreted by the tumor cells or stromal compartment activate the cognate receptors leading to cancer progression (Babina IS, Nat Rev Cancer. 2017). For instance, FGF2-FGFR1 autocrine and/or paracrine loop activation has been involved in the migration and invasion of cancer cells (Coleman SJ, EMBO Mol. Med. 2014). Remarkably, estrogens induced via the estrogen receptor (ER) the up-regulation and secretion of FGF2 in breast and lung cancer (Fillmore CM, PNAS. 2010, Siegfried JM, Oncotarget. 2017). Likewise, the G protein estrogen receptor (GPER) was also involved in the regulation of FGF2 by estrogens toward the activation of downstream signaling pathways in astroglial cells (Huang C, Neuroscience. 2016).**

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## GLUTAMINE METABOLISM AND ITS INHIBITION IN THE TARGETING OF STEM CELLS OF CHRONIC MYELOID LEUKAEMIA REFRACTORY TO STANDARD THERAPY

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We previously found that the adaptation of Chronic Myeloid Leukaemia (CML) cells to energy restrictions is paralleled by the suppression of BCR/Abl protein, the oncogenic driver of CML, notably in a subset of leukaemia stem cells (LSC). These LSC, while remaining genetically leukaemic, are independent of BCR/Abl signaling for maintenance in tissues (within the “stem cell niches”) and therefore refractory to tyrosine kinase inhibitors (TKi) used for CML therapy. We envisioned on these bases a “metabolic” stem cell niche model to explain the long-term persistence of LSC responsible for Minimal Residual Disease (MRD) of CML. In this model, glutamine plays an important role.

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## IDENTIFICATION OF NEW BIOMARKERS FOR CARDIAC DISORDERS EXPLOITING TISSUE-SPECIFIC METHYLATION PATTERN OF CIRCULATING FREE DNA: A PILOT STUDY

C. DI RESTA<sup>1</sup>, M.S. SPANÒ<sup>2</sup>, S. MERELLA<sup>3</sup>, M. FERRARI<sup>4</sup> and S. BENEDETTI<sup>3</sup>

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**Cardiomyopathies are a group of diseases leading to adverse outcome. Due to clinical heterogeneity and phenotypic overlapping, the identification of specific non-invasive diagnostic and prognostic markers can be useful and remains a challenge. Our aim is to exploit cardiac cfDNA as new cardiac biomarker based on the following assumptions: i) methylation patterns are unique and conserved in a specific tissue, hence their analysis could be used to identify the tissue of origin of circulating cell free DNA (cfDNA); ii) cfDNA levels of cardiac origin may be higher in the presence of cardiac disorder.**

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## NOTCH 1 PATHWAY AND EPCS IN BICUSPID AORTIC VALVE: IS THEIR INTERPLAY INVOLVED IN THE ASCENDING AORTIC ANEURYSM ONSET?

C.R. BALISTRERI<sup>1</sup>, F. CRAPANZANO<sup>1</sup>, A. ALLEGRA<sup>2</sup>, C. PISANO<sup>3</sup>, G. RUVOLO<sup>4</sup>, D. LIO<sup>1</sup>, L. SCHIRONE<sup>5</sup>,  
E. CAVARRETTA<sup>5</sup>, S. SCIARRETTA<sup>6</sup> and G. FRATI<sup>6</sup>

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**Bicuspid aortic valve (BAV) is frequently associated with development of ascending aortic aneurysm, even if the underlying mechanisms remain to be clarified. Here, we investigated if a deregulation of Notch1 signaling pathway and endothelial progenitor cells (EPCs) number is associated with BAV disease and an early ascending aortic aneurysm (AAA) onset.**

## **IGA NEPHROPATHY IN A 12-YEAR-OLD GIRL WITH PERSISTENT HAEMATURIA AND PROTEINURIA: A CASE REPORT**

R. MILANIC, G. STEL, L. SIGALOTTI, A.D. SPATOLA and F. CURCIO

*Institute of Clinical Pathology, ASUIUD, Udine, Italy*

**Immunoglobulin A nephropathy (IgAN) is an immune complex disease and a major cause of glomerulonephritis in pediatric patients. Clinical picture includes hematuria and proteinuria, and can progress into renal failure. Urinalysis, as well as renal biopsy, serve to confirm the diagnosis. We report a case of a 12-year-old girl with persistent haematuria and severe proteinuria, in whom subsequently an IgAN was diagnosed.**

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## INVOLVEMENT OF ANNEXIN A3 ISOFORMS IN MODULATION OF LIPID STORAGE INTO CLEAR CELL RENAL CELL CARCINOMA (CCRCC) CELLS

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**ccRCC cells show an adipocyte-like morphology due to neutral lipid accumulation. The molecular mechanism responsible for this phenotype has yet to be clarify. Notably, ccRCC cells show a gene expression signature consistent with adipogenesis and can undergo adipogenic transdifferentiation. The Ca<sup>2+</sup>-dependent phospholipid-binding praotein Annexin A3 (AnxA3) has been recently described as negative regulator of adipocyte differentiation. In RCC, we evidenced that AnxA3 is downregulated and shows a specific pattern of two isoforms of 36 and 33 kDa originated by an alternative splicing event. In the current study, we have investigated the role of AnxA3 isoforms in the modulation of lipid storage responsible of the adipocyte-like morphology of ccRCC cells.**

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**PKHHIGH/CD133+/CD24- RENAL STEM-LIKE CELLS ISOLATED FROM HUMAN NEPHROSPHERES CAN BE COMMITTED TO ENDOTHELIAL PHENOTYPE**

S. BOMBELLI<sup>1</sup>, M. BOLOGNESI<sup>1</sup>, A. BRUNO<sup>2</sup>, B. TORSELLO<sup>1</sup>, S. DE MARCO<sup>1</sup>, C. BIANCHI<sup>1</sup>, P. VIGANÒ<sup>1</sup>,  
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**Nephrosphere (NS) model permits to culture a heterogeneous population of renal stem-like cells (RSC) and progenitors. RSC are the quiescent (PKH<sup>high</sup>) cells with a CD133+/CD24- phenotype. We demonstrated that NS cells cultured on decellularized scaffolds repopulated proximal and distal tubular portions, the Bowman's capsule, and vascular portions differentiating into endothelial cells. We now aim to evaluate the capacity of endothelial commitment of RSC isolated from human NS.**

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**ROLE OF 1ALCTL AND 1BLCTL ARG ISOFORMS IN THE FIBROBLAST ACTIVATION**

B. TORSELLO, S. DE MARCO, S. BOMBELLI, V. CASSINA, E. CHISCI,  
C. BIANCHI and R. PEREGO

*School of Medicine and Surgery, University of Milano-Bicocca*

**The excessive scar tissue deposition of fibrotic process and the tumor stroma have in the activated fibroblasts (myofibroblasts) the main players. Myofibroblasts remodel the extra cellular matrix (ECM) by specialised cytoskeletal contractile features (stress fibres and focal adhesions) that reorganise the supportive tumour stroma. The non-receptor tyrosine kinase Arg binds directly to the cytoskeleton transducing extracellular signals into cytoskeletal rearrangements. ARG, through alternative splicing events, codes eight Arg isoforms that differently modulate stress fibers and motility. We analysed the role of 1ALCTL and 1BLCTL Arg isoforms in fibroblast activation using Arg KO murine embryonal fibroblast (MEF).**

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**JAGGED1/2 INHIBITION PROMOTES MULTIPLE MYELOMA CELL SENSITIVITY TO BORTEZOMIB *IN VITRO*, *EX VIVO* AND *IN VIVO* IN A NOVEL ZEBRAFISH MODEL**

M. COLOMBO<sup>1</sup>, M. MAZZOLA<sup>2</sup>, N. PLATONOVA<sup>1</sup>, S. GARAVELLI<sup>1</sup>, M.T. PALANO<sup>1</sup>,  
M. BARBIERI<sup>3</sup>, D. GIANNANDREA<sup>1</sup>, E. LAZZARI<sup>1</sup>, A. BASILE<sup>3</sup>, A. PISTOCCHI<sup>2</sup>,  
A. NERI<sup>3</sup> and R. CHIARAMONTE<sup>1</sup>

<sup>1</sup>*Department of Health Sciences, Università degli Studi di Milano;* <sup>2</sup>*Department of Medical Biotechnology and Translational Medicine, Università degli Studi di Milano;* <sup>3</sup>*Department of Oncology and Hemato-oncology, Università degli Studi di Milano*

**Multiple myeloma (MM) is the second most diffuse hematological malignancy and nowadays is still incurable, despite the development of innovative therapies. MM cells accumulate in the bone marrow (BM) and establish vicious interactions with the surrounding normal cells, inducing them to promote tumor progression and the development of drug resistance. In this process, a crucial role is played by the dysregulated Notch ligands Jagged1 and 2, whose overexpression boosts Notch both in MM cells and in the BM cells. Here, we investigated how Jagged1/2 inhibition affects MM cells resistance to the standard-of-care drug Bortezomib.**

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## THE MOLECULAR CROSS-TALK AMONG ARG/ABL2, TGF- $\beta$ 1 AND LOX IN CLEAR CELL RENAL CELL CARCINOMA PROGRESSION

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and R.A. PEREGO<sup>1</sup>

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**An involvement of TGF- $\beta$ 1 in promoting bone metastases affecting about 30% of clear cell Renal Cell Carcinoma (ccRCC) patients was described. The extracellular matrix enzyme Lysyl oxidase (Lox) through osteoclast activation and osteoblast inhibition induces pre-metastatic bone lesions in breast and colon cancer. We evidenced Lox overexpression in ccRCC and TGF- $\beta$ 1 production modulated by Arg tyrosine kinase in renal tubular cells. Arg modulates invasion and metastasis of breast and prostate cancer through cytoskeleton regulation. These data suggest that Arg, TGF- $\beta$ 1 and Lox might interact to promote tumor invasion and metastasis. Here we analyse the molecular and functional interactions among Arg, TGF- $\beta$ 1 and Lox in ccRCC and their effects on osteoclast and osteoblast pre-metastatic functions.**

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## **OBESITY, ADIPOKINES AND BREAST CANCER: UNRAVELING THE MOLECULAR LINKS**

S. CATALANO

*University of Calabria*

The prevalence of obesity has been increasing at an alarming rate in several developed and developing countries, reaching pandemic proportions over the last two decades. This growing incidence has deep clinical implications, since obesity is a key driver of serious health problems, such as type II diabetes, cardiovascular diseases, hypertension and cancer. Indeed, prospective epidemiological studies have shown that excessive adiposity strongly influences risk, prognosis and progression of multiple malignancies, including breast cancer. Several hypotheses have been proposed to unravel the direct link between obesity and breast cancer and these include hyperinsulinemia, estrogen signaling, inflammation and adipokine expression. Certainly, the revised concept of adipose tissues from an inert depot for body energy to endocrine and immunologically active organs placed particular emphasis on the potential role of adipokines in various biological processes and metabolic pathways. Acting through endocrine, paracrine and autocrine mechanisms, adipokines, that are not only produced by adipocytes but also by stromal cells, macrophages and cancer cells, impact the development and progression of obesity-related cancers. In this talk, I will present an overview of the clinical and experimental evidences highlighting the adipokines leptin and adiponectin, as the most important molecular mediators of obesity-breast cancer axis.

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## MMP-9 AS PROGNOSTIC MARKER IN MELANOMA PATIENTS WITH CIRCULATING-FREE DNA BRAF V600E MUTATION

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<sup>1</sup>*Department of Biomedical and Biotechnological Sciences, University of Catania, Catania, Italy;*  
<sup>2</sup>*Garibaldi Hospital - Clinical Pathology Unit - Catania, Italy;* <sup>3</sup>*Melanoma Research Unit, National  
Cancer Institute “G Pascale”, Naples, Italy*

Despite the revolution in the field of melanoma treatment with the introduction of novel therapies (immunotherapy and target therapy), there is still a percentage of melanoma patients that often experiences drug-resistance and therapeutic failure. The early recognition of therapeutic failure, by the identification of new biomarkers of therapeutic response, is the main challenge of medical oncology in order to personalize the therapeutic strategies and avoid the toxicity of ineffective treatments. The circulating-free DNA BRAF<sup>V600E</sup> mutation was proposed as a marker of therapeutic response. However, it cannot be revealed in all melanoma patients with this mutation, detected in tumour biopsy specimens. Therefore, there is a need to identify new prognostic biomarkers. Matrix Metalloproteinase-9 (MMP-9) could be one of them since its role in tumour invasiveness have been demonstrated.

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## FLAGELLAR MOTILITY REDUCTION IN *LISTERIA MONOCYTOGENES* AFTER TREATMENT WITH *CANNABIS SATIVA L.* ESSENTIAL OIL

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A major group of plant antimicrobial compounds is represented by essential oils (EOs), complex mixtures of volatile secondary metabolites belonging to different chemical families. *Cannabis sativa L.* has been grown for thousands of years for a multiplicity of purposes; in recent years, some genotypes containing low cannabinoid concentrations have been selected and used for research purposes. *Listeria monocytogenes* is a facultative intracellular food pathogen, mobile for the presence of several flagella. In humans, the treatment of listeriosis is hampered by the intracellular location of listeriae and the poor intracellular penetration of some antibiotics. Flagellum-based motility has been implicated in virulence since it is critical for initial surface attachment. The purpose of this study was to investigate the antibacterial and anti-virulence properties of an EO extracted from a legal *C. sativa L.* variety against a clinical isolate of *L. monocytogenes*.

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## **EPIMETHEX: AN *IN SILICO* PLATFORM TO EVALUATE THE CORRELATION BETWEEN GENE EXPRESSION AND GENE METHYLATION**

S. CANDIDO<sup>1</sup>, G. PARASILITI<sup>2</sup>, G. RUSSO<sup>2</sup>, F. PAPPALARDO<sup>2</sup> and M. LIBRA<sup>1</sup>

*<sup>1</sup>Department of Biomedical and Biotechnological Sciences, Section of General Pathology, University of Catania; <sup>2</sup>Department of Drug Sciences, University of Catania*

**Cancer transformation is a multistep process sustained by several molecular alterations including those of DNA methylation. The high-throughput technology allowed understanding the functional role of global methylation patterns in the regulation of genes involved in cancer development. In order to identify specific methylation patterns associated with gene expression, an R package algorithm able to perform integrated analysis of gene expression and methylation profiles datasets was developed.**

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## ROLE OF THE TRANSCRIPTION FACTOR YIN YANG 1 IN CANCER

S. VIVARELLI, S. CANDIDO, R. SALEMI, L. FALZONE and M. LIBRA

*Department of Biomedical and Biotechnological Sciences, Section of General Pathology,  
University of Catania*

**Yin Yang 1 (YY1) is transcription factor ubiquitously expressed, able to either activate or repress transcription through direct or indirect interaction with the chromatin. YY1 is thought to be involved in the modulation of a large number of mammalian genes. The ability of this DNA binding protein to promote or inhibit gene expression depends on its specific target sequence, chromatin structure as well as its specific protein interactors. YY1, found expressed at different levels in many cancer types, has been seen to have the effect of either stimulating or inhibiting cancer growth. The mechanism(s) responsible for such diverging effects needs to be further clarified.**

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## LOCAL ENDOTHELIAL ACTIVATION AND CONTRIBUTION TO ESTABLISHMENT OF LEISHMANIA SPP INFECTION

S. D'ALESSANDRO<sup>1</sup>, S. PARAPINI<sup>1</sup>, D. SCACCABAROZZI<sup>2</sup>, L. CAVICCHINI<sup>1</sup>, D. TARAMELLI<sup>2</sup> and N. BASILICO<sup>1</sup>

<sup>1</sup>*Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan;* <sup>2</sup>*Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan*

**Leishmaniasis comprises a group of neglected vector-borne diseases caused by intracellular protozoa of the genus *Leishmania*. The promastigotes are deposited into the human skin by the bite of phlebotomine sandflies and internalized by phagocytic cells where they develop into amastigotes, multiply and cause the cutaneous or visceral disease. Neutrophils, immediately recruited to the bite site, phagocytize *Leishmania* promastigotes, which elude the neutrophils killing mechanisms and infect macrophages. Although endothelial cells represent one of the first cells type encountered by *Leishmania* promastigotes, little is known on their role in the establishment of the infection. Here, the interaction between human endothelial cells and *Leishmania* promastigotes was studied.**

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## LUNG CANCER DIAGNOSIS BY USING A HYBRID GAS-LIQUID SENSOR ARRAY. PRELIMINARY DATA

M. BIZZARRI<sup>1</sup>, M. SANTONICO<sup>2</sup>, G. PENNAZZA<sup>2</sup>, R. VERNA<sup>1</sup> and A. D'AMICO<sup>3</sup>

*<sup>1</sup>Dept of Experimental Medicine, Sapienza University Rome; <sup>2</sup>Unit of Electronics for Sensor Systems, Department of Engineering, Campus Bio-Medico University of Rome, Italy; <sup>3</sup>Department of Electronic Engineering, University of Rome Tor Vergata, Italy*

**Sensors performances are highly improved when single sensor arrays are organized in multidimensional systems or networks for particular applications. This result is facilitated by the large improvements in the miniaturization process, power consumption reduction and data analysis techniques nowadays available. Multidimensional sensor systems are conceived to mimic the mechanisms of human senses. Among them, the so-called electronic nose and tongue are becoming more and more popular.**

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## FOLATE DEFICIENCY IN HEPATOCELLULAR CARCINOMA PATIENTS WITH PORTAL VEIN THROMBOSIS

G. MALAGUARNERA<sup>1</sup>, S. LATTERI<sup>2</sup>, V.E. CATANIA<sup>2</sup>, G. BERTINO<sup>3</sup>, M. PENNISI<sup>4</sup>,  
F. DRAGO<sup>1</sup> and M. MALAGUARNERA<sup>1</sup>

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*Medical, Surgical Sciences and Advanced Technologies “G.F. Ingrassia”, University of Catania;*  
<sup>4</sup>*Research Centre “The Great Senescence”, University of Catania, Catania, Italy*

**Portal vein thrombosis (PVT) is occurring frequently in advanced liver cirrhosis and in Hepatocellular carcinoma and often diagnosed in the course of a routine patient evaluation and surveillance for liver cancer. PVT may relate to metabolic alterations and thrombophilic conditions. The purpose of this study is to investigate the relationship between folate status and portal vein thrombosis.**

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## PARAMETERS OF EPITHELIAL-MESENCHYMAL TRANSITION AS PREDICTORS OF CANCER AGGRESSIVENESS

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**Cancer cell transition from a low-invasive phenotype into a more malignant one constitutes a critical event during tumor progression. The Epithelial-Mesenchymal Transition (EMT) occurring in solid cancers is at the core of such transformation. A recurrent metaphor for the complex developmental path of cell systems across different phenotypic states is given by the Waddington landscape in which cell phenotypes are depicted as stable attractors, while metastable or unstable states represent unstable attractors.**

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## THE COENZYME Q10 AS COUNTERMEASURE FOR RETINAL DAMAGE ONBOARD THE INTERNATIONAL SPACE STATION: THE CORM PROJECT

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Cells, tissues and organs of astronauts aboard the International Space Station (ISS) are exposed to the damaging effects of microgravity and cosmic radiation. Space Agencies are forced to find effective therapeutic countermeasures to safeguard astronauts' health. Since retina is one of the most vulnerable target, we undertook a project entitled The Coenzyme Q10 (CoQ10) as countermeasure for retinal damage onboard the International Space Station: the CORM project, funded by the Italian Space Agency (ASI) and launched in the summer 2017. We selected CoQ10 as promising candidate drug, having previously first demonstrated its direct antiapoptotic property due to its ability to inhibit mitochondrial depolarization.

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## CLINICAL IMPACT OF EARLY MOLECULAR RESPONSE IN CML PATIENTS TREATED WITH IMATINIB

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The approval of second-generation tyrosine kinase inhibitors (TKIs) for the first line treatment of Chronic Myeloid Leukemia (CML) has generated a need for early molecular parameters predictive of inadequate responses to the first-generation TKI imatinib mesylate (IM). Several groups have shown that BCR-ABL/ABLIS transcript levels <10% after 3 months (mos) or <1% after 6 mos of IM are strongly associated with superior clinical outcomes. We wanted to investigate which BCR-ABL threshold would be more reliable in predicting treatment outcome in patients (pts) with discordant molecular transcripts at the 3 and 6 mos time points, and also wished to evaluate if early molecular responses predicted the probability of achieving a sustained deep molecular response.

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## **ADIPOKINES AFFECT PCSK9 EXPRESSION: *IN VITRO* AND *IN VIVO* EVIDENCE**

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**Adipose tissue is an endocrine organ secreting active molecules, the adipokines, e.g., leptin and resistin). In a condition of dysfunctional visceral fat depots, adipokines are detrimental for cardiovascular system. Aim: To evaluate some of the molecular mechanisms linking the biology of adipokines and PCSK9.**

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**MICRORNA NETWORKS INVOLVED IN NEURAL STEM CELLS MAINTENANCE**

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**Neural Stem Cell (NSC) maintenance is of great interest since NSCs can be used to treat impaired cells and tissues or improve regenerative power of degenerating cells in neurodegenerative diseases or spinal cord injuries. Under maintenance conditions, NSCs require Hedgehog-Gli (Hh-Gli) signalling and express a number of stemness genes (e.g. Nanog, Oct4, Sox2) whose mechanisms of regulation have been investigated. However the interplay between other transcription factors and NSC maintenance is still being charted. Technological advances allow us to use next generation RNA sequencing (RNA-seq), a powerful method for quantifying steady-state mRNA expression levels and detecting alternative splicing events in transcriptomes.**

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## EFFECT OF OXYGEN LOADED NANODROPLETS ON HUMAN ENDOTHELIAL CELLS AND MACROPHAGES CULTURED IN NORMOXIC VERSUS HYPOXIC CONDITIONS

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**Chronic wounds are an emerging issue in Western countries, but their pathogenetic mechanisms have not been clarified, yet. Oxygen availability is crucial for tissue healing. Thus, hypoxia is detrimental in chronic wounds and new oxygen-based therapies should be investigated. Here, oxygen-loaded nanodroplets (OLND) with an oxygen-binding fluorocarbon (2H, 3H-decafluoropentane) in the inner core and dextran or chitosan in the outer shell are proposed as carriers of oxygen to the hypoxic milieu, to counteract the effects of hypoxia in wound healing.**

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## PHAGOCYTOSIS OF DIFFERENT STAGES OF PLASMODIUM FALCIPARUM GAMETOCYTES BY BONE MARROW MACROPHAGES

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**Gametocytes (GCT), the sexual stage of malaria parasites, develop in five stages (I-V). Stages I-IV are predominantly sequestered and differentiate in the extravascular compartment of the bone marrow, while stage V are released in the circulation from where they are taken up by a mosquito during a blood meal, causing malaria transmission. Few information are available about the role of the innate immunity against GCT. The aim of this work was to set up a model to study of the ability of *P. falciparum* (Pf) GCT to activate and be phagocytised by bone marrow macrophages.**

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## THE PATHOPHYSIOLOGY OF THE ENDOTHELIUM: MOVING FROM 2D TO 3D CULTURE AND BEYOND

L. LOCATELLI, A. CAZZANIGA, S. CASTIGLIONI, R. SCRIMIEMI and J.A.M. MAIER

*University of Milan, Department of Biomedical and Clinical Sciences L. Sacco*

Vascular endothelial cells (ECs) line the entire circulatory tree. In spite of their well known heterogeneity, ECs display a myriad of fundamental homeostatic functions such as keeping blood fluid, regulating blood flow, regulating macromolecule and fluid exchange with the tissues, preventing leukocyte and platelet activation, and participating in immune surveillance. Most of present knowledge has been achieved using 2D monolayer cell culture systems. However, they do not accurately recapitulate the structure and function of living tissues. To bridge the gap between classical 2D cell culture and *in vivo* models, 3D culture techniques have been generated.

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## TRPM7 AND MAGT1 AS NOVEL PLAYERS IN THE OSTEOGENIC DIFFERENTIATION OF HUMAN BMSC

V. ROMEO<sup>1</sup>, L. LOCATELLI<sup>1</sup>, A. CAZZANIGA<sup>1</sup>, R. SCRIMIERI<sup>1</sup>, S. ZECCHINI<sup>2</sup> and S. CASTIGLIONI<sup>1</sup>

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**Mesenchymal stem cell (MSCs) are crucial in bone repair and regeneration, since they differentiate into osteoblasts in response to specific stimuli from the microenvironment. It is known that magnesium is important for the osteogenic differentiation of MSCs. Since the kinase and cation channel TRPM7 and the magnesium transporter MagT1 regulate intracellular Mg homeostasis, we investigated the role of TRPM7 and MagT1 in the osteogenic differentiation of MSCs.**

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## AMORPHOUS SILICA NANOPARTICLES INTERFERE WITH LPS-DEPENDENT TRANSDUCTION OF INFLAMMATORY SIGNALS

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Besides the epithelial barriers, macrophages represent the first cells that interact with engineered nanomaterials (ENM) upon exposure. Many studies report that several ENM are able to trigger macrophage activation. However, possible interference of ENM with the effects of typical macrophage activators, such as PAMPs, has been much less investigated thus far. In this study, we have used two well characterized, food-grade nanoparticles of amorphous SiO<sub>2</sub> (ASNP), the precipitated NM200 and the pyrogenic NM203, to assess their effects on LPS-dependent activation of human macrophage-like cells.

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## **FOXO3 RESTORES THE NORMAL METABOLIC FUNCTIONS THAT ARE ALTERED IN TAMOXIFEN RESISTANT BREAST CANCER CELLS**

E. RICCI<sup>1</sup>, M. FIORILLO<sup>2</sup>, S. AQUILA<sup>1</sup>, A. NIGRO<sup>1</sup>, P. RIZZA<sup>1</sup>, M. PELLEGRINO<sup>1</sup>,  
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**The potential mechanisms underlying the evolution toward an anti-estrogen resistant phenotype have been attributed to various causes, including the alteration of normal metabolism. In this context, the involvement of FoxO3 was evaluated.**

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## RETINOIC ACID INDUCED DIFFERENTIATION MODIFIES HO-1 DEPENDENT NEUROBLASTOMA RESPONSE TO OXIDATIVE STRESS

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The ability to counteract oxidative stress (OS) plays a pivotal role in neuronal survival. The differentiation of neuroblastoma (NB) cells with retinoic acid (RA) generates a small amount of ROS involved in neurite elongation (Nitti, 2010). However, differentiated cells are more sensitive to the exposure to OS than undifferentiated ones (Piras, 2017). In the present study, we analyzed the behavior of two RA-differentiated NB cell lines, SH-SY5Y and SK-N-BE(2C) in response to OS. Furthermore, the regulation of HO-1 expression has been analyzed evaluating Nrf2 as the main activator and Bach1 as negative regulator.

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**ROLE OF FUSOBACTERIUM NUCLEATUM IN INTESTINAL TUMORIGENESIS**

P. PIGNATELLI<sup>1</sup>, P. RAIMONDI<sup>1</sup>, C. CELLINI<sup>2</sup>, A. CICHELLA<sup>2</sup>, R. GRANDE<sup>3</sup>, A. RICCI<sup>1</sup>,  
A. GENTILE<sup>1</sup>, R. COTELLESE<sup>1</sup>, A. PIATTELLI<sup>1</sup> and M.C. CURIA<sup>1</sup>

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**Colorectal cancer is one of the most common malignant tumors and an important associated-factor is intestinal microbiota. This may enhance the carcinogenicity by proliferation and differentiation of epithelial cells and by decreasing immune response to pathogenic organisms. The aim of the study is to analyze the link between the presence of Fusobacterium nucleatum (FN) in a series of matched oral brushing, colon adenomas/carcinomas and adjacent mucosa, and finally to elucidate the FN dissemination mechanism from oral cavity to colon. FN is detected in saliva, especially in smokers, with its quantities increased in patients with gingivitis and periodontitis, compared to the healthy controls.**

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## EFFECT OF RESVERATROL ON WNT/ $\beta$ -CATENIN SIGNALLING IN PANCREATIC CANCER CELL LINES

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**Pancreatic cancer is a very aggressive malignant disease due to lack of early diagnosis and chemotherapeutic resistance of the tumor cells. There is distinct evidence that food derived polyphenols possess chemopreventive effects in the development of several cancers including pancreatic carcinoma. Resveratrol, a phenolic compound found in grape skins and other fruits, is a nutraceutical with several therapeutic effects and known anticancer activity. The aim of the study is to analyze the expression of Wnt/  $\beta$ -catenin signaling pathway genes after treatment with resveratrol.**

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## EFFECT OF A NUTRACEUTICAL COMBINATION CONTAINING THE PROBIOTIC BIFIDOBACTERIUM LONGUM BB536 AND RED YEAST RICE EXTRACT ON CARDIOVASCULAR RISK BIOMARKERS - A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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D. DELL'ORTO<sup>1</sup>, M. DEL PUPPO<sup>4</sup>, M. BERLOTTI<sup>5</sup>, R. BOSISIO<sup>6</sup>, G. MOMBELLI<sup>6</sup>,  
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**In subjects with moderate hypercholesterolemia, probiotics incorporated into dairy products can reduce circulating total (TC) and LDL cholesterol (LDL-C). Probiotics with high biliary salt hydrolase activity, e.g. Bifidobacterium longum BB536, decrease TC and LDL-C by lowering intestinal cholesterol reabsorption and, combined with other nutraceuticals, may be useful to manage hypercholesterolemia in subjects with low cardiovascular (CV) risk. The objective of the study was to evaluate efficacy and safety of a nutraceutical combination containing Bifidobacterium longum BB536, red yeast rice (RYR) extract (10 mg/day monacolin K), niacin, coenzyme Q10 (Lactoflorene Colesterolo®). The end-points were changes of lipid CV risk markers (LDL-C, TC, non-HDL-cholesterol (HDL-C), triglycerides (TG), apolipoprotein B (ApoB), HDL-C, apolipoprotein AI (ApoAI), lipoprotein (a) [Lp(a)], proprotein convertase subtilisin/kexin type 9 (PCSK9) and of markers of cholesterol synthesis and absorption.**

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## THE ANTIBIOFILM EFFECT OF A MEDICAL DEVICE (MD) CONTAINING TIAB ON MICROORGANISMS ASSOCIATED WITH SURGICAL SITE INFECTIONS (SSIS)

V. PUCA<sup>1</sup>, T. TRAINI<sup>2</sup>, S. GUARNIERI<sup>3</sup>, R. GRANDE<sup>4</sup>, S. CARRADORI<sup>5</sup>, F. SISTO<sup>6</sup>,  
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**Surgical Site Infections (SSIs) are the most common nosocomial infections. Surgical sutures are optimal surfaces for bacterial adhesion and biofilm formation. The most commonly isolated microorganisms in SSIs are Staphylococcus aureus (Sa), coagulase-negative Staphylococcus spp., Enterococcus spp., Escherichia coli (Ec) and other Gram-negative bacilli. The aim of this study was to evaluate the antibiofilm activity of a Medical Device (MD) containing TIAB, which is titanium dioxide linked with monovalent silver ions.**

## ANALYSIS OF ESTROGEN–MEDIATED SIGNALING REVEALS A NOVEL EPIGENETIC TARGET FOR ENDOCRINE THERAPY-RESISTANT BREAST CANCER TREATMENT

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**Estrogen Receptor alpha (ER $\alpha$ ) is the master regulator of estrogen signaling in hormone-responsive breast cancer (BC) and it is the primary target of specific anticancer therapies. Nevertheless, the development of resistance to treatment represents the key problem in clinical management of patients affected by this disease. We reported that the epigenetic writer DOT1L (DOT1-Like Histone Lysine Methyltransferase) associates with ER $\alpha$  [1] as part of a multiprotein chromatin regulatory complex. We investigated here the role of this enzyme in estrogen signaling to the genome in luminal-like BC cells.**

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## EVALUATION OF DNA BASE EXCISION REPAIR AND ERBB SIGNALING IN EUTHYROID GOITERS

C. MOSCATELLO<sup>1</sup>, M.C. DI MARCANTONIO<sup>1</sup>, A. CICHELLA<sup>2</sup>, G. SPACCO<sup>3</sup>, G. MINCIONE<sup>3</sup>, A. MARCHETTI<sup>2</sup>, R. COTELLESE<sup>1</sup>, R. MURARO<sup>1</sup> and G.M. ACETO<sup>1</sup>

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**The onset of thyroid gland nodules (TN) is determined by loss of homeostasis regulation by interaction of endogenous/genetic and environmental factors. The nature of the oxidative processes that lead to physiologic synthesis of thyroid hormones together with environmental factors may be the root causes of thyroid nodular transformation due to an increase in DNA damages. A link between EGF and DNA damage repair signalling has been documented in cancer, but their cross-regulation is poorly understood in TN. In order to define the role of Base Excision Repair (BER) and ErbB signaling in TN, we analysed euthyroid goitres tissues that are not theoretically affect by any hormonal dysfunction.**

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## TRIGGERING OF TOLL-LIKE RECEPTORS IN THE ELDERLY. A PILOT STUDY RELEVANT FOR VACCINATION

C.M. GAMBINO<sup>1</sup>, G. ACCARDI<sup>1</sup>, A. AIELLO<sup>1</sup>, K. IOANNOU<sup>2</sup>, F. FARZANEH<sup>2</sup>, S. VASTO<sup>3</sup>,  
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**Immunosenescence impacts on the immune system of older people leading to an inefficient reaction to pathogens and reduced ability to develop a powerful immune response after vaccination. Recently, research in immunological ageing have suggested that stimulation of Toll-like receptors (TLRs) is a promising strategy to enhance vaccine efficacy in the elderly by activation of innate immune cells and production of inflammatory cytokines. In this scenario, great importance assume dendritic cells (DCs), the most potent antigen presenting cells, specialized for the uptake, processing, transport and presentation of antigens to T cells.**

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## ROLE OF KIR AND HLA INTERACTION IN HIV-INFECTED PATIENTS WITH LOW-LEVEL VIREMIA

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**The impact of host genetic variation on outcome of HIV infection in the absence of combination antiretroviral therapy (cART) has been well documented. Growing evidence reports relationship between specific killer-cells immunoglobulin-like receptor (KIR) polymorphisms and different HIV progression in the absence of treatment. The goal of the present study is to determine the association of KIR genes and their human leukocytes antigen (HLA) ligands with viral load and HIV progression in patients on cART.**

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## A CROSSTALK BETWEEN PROGESTERONE RECEPTOR B AND P53 ALTERS THE METABOLIC REPROGRAMMING IN BREAST CANCER CELL LINES

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**Progesterone-Receptor (PR) is good prognostic marker for breast cancer patients. The effects of Progesterone on its target tissues are mediated by the Progesterone Receptors (PR-A and PR-B). In breast tumors from patients with poor prognosis, a loss of PR-B occurs suggesting a protective role of PR-B in breast cancer. The molecular mechanisms of PR-B-protective effects are still to be defined. Recently, we reported in breast cancer cells a novel functional interplay between PR-B and PTEN in modulating autophagy, which is retained a way to reprogram cellular metabolism activating oncogenes and inactivating tumor suppressors. Among them, the p53 tumor suppressor gene has emerged as important mediator of energy metabolism. To deepen the PR-B anticancer role and given the relationship between autophagy and cellular metabolism, we investigated a role for OHPg/PR-B signaling through p53 in altering metabolic reprogramming of breast cancer cells.**

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## D-DIMER PLASMATIC LEVELS INCREASE IN HEPATOCELLULAR CARCINOMA WITH PORTAL VEIN THROMBOSIS

M. MALAGUARNERA<sup>1</sup>, S. LATTERI<sup>2</sup>, G. BERTINO<sup>3</sup>, R. MADEDDU<sup>4</sup>, M. PENNISI<sup>5</sup>, V.E. CATANIA<sup>2</sup>, G. CURRÒ<sup>6</sup>, A.M. BORZI<sup>5</sup>, F. DRAGO<sup>7</sup> and G. MALAGUARNERA<sup>7</sup>

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**Portal vein thrombosis (PVT) is one of the severe complications of Hepatocellular Carcinoma (HCC). PVT deteriorates the liver and its dysfunction increases the risk of bleeding, influencing the prognosis of patients with liver cirrhosis and HCC. The aim of our study was to investigate whether D-dimer testing could be a sensitive marker for the diagnosis and prognosis of HCC patients with PVT.**

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## **$\gamma$ -GLUTAMYLTRANSFERASE MODULATES L- $\gamma$ -GLUTAMYL-P-NITROANILIDE (GPNA) CYTOTOXICITY: THE POOR SPECIFICITY OF AN OLD INHIBITOR OF GLUTAMINE TRANSPORT**

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**Glutamine (Gln) plays a critical role in supporting cell growth and proliferation of different cancer cell types. Several studies have focused on the sodium-dependent Gln transporter ASCT2 as a potential therapeutic target and different approaches, including its inhibition or silencing, are commonly used. L- $\gamma$ -glutamyl-p-nitroanilide (GPNA) is a widely used ASCT2 inhibitor, even if several concerns about its specificity have recently emerged since GPNA has a limited selectivity for ASCT2, being able to inhibit many other transporters for amino acids.. Moreover, it is rarely considered that GPNA is also a well-known substrate of the enzyme gamma-glutamyltransferase (GGT). The aim of this study was thus to evaluate the effect of GPNA catabolism by GGT on its efficacy as an inhibitor of cell proliferation.**

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## XCT/CD44 MODULATION INDUCES THE SENSITIZATION OF NEUROBLASTOMA-STEM CELLS TO ETOPOSIDE

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The current anticancer therapies for human neuroblastoma (NB) include the use of etoposide, a drug that exerts its cytotoxic effect by inducing oxidative stress. Although the therapeutic approach with etoposide is initially efficacious, subsequently, it selects a chemoresistant cell population, which is able to adapt to the oxidative environment induced by the drug, increasing the levels of intracellular glutathione (GSH). The chemoresistance is also due to the presence of cancer stem cells (CSCs), which have a low proliferative rate and are less susceptible to therapies acting on highly proliferating cells. Moreover, CSCs expressing CD44, a PKC-alpha-modulated stemness marker, are able to influence GSH levels by stabilizing xCT, a transporter promoting the influx of cystine, essential for GSH synthesis. Based on this evidence, our aim was to investigate whether targeting CD44/xCT might be a useful strategy to increase neuroblastoma sensitivity to etoposide.

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**A 47-YEAR-OLD MAN WITH A 2-YEAR HISTORY OF MISDIAGNOSED DYSPHAGIA**

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**Here we present a clinical case of 2 year-misdiagnosed polymyositis (PM), where patient underwent unnecessary invasive procedure while he developed progressive muscular weakness. Erroneous diagnosis could have been correctly addressed by evaluation of serum Creatine kinase (CK), a cheap and easy to perform lab exam.**

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## HYPOMETHYLATING AGENT 5-AZA-2'-DEOXYCYTIDINE (DAC) AMELIORATES THE CLINICAL COURSE OF RHEUMATOID ARTHRITIS IN A MOUSE MODEL

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Increasing body of data suggest a key role for epigenetics in the etiopathogenesis/development of autoimmune disorders. Indeed, epigenetic dysregulations have already been described in rheumatoid arthritis (RA), lupus erythematosus (SLE), and multiple sclerosis (MS) patients. Decitabine (5-aza-2'-deoxycytidine, Dacogen, (DAC) is a hypomethylating agent used for the treatment of myelodysplastic syndrome. We have previously shown that DAC has both prophylactic and therapeutic disease-modifying properties in two mouse models of MS.

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## LIGAND ACTIVATED ESTROGEN RECEPTOR BETA DISRUPTS METABOLIC REPROGRAMMING IN HUMAN SEMINOMA TCAM-2 CELLS

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Testicular germ cell tumors (TGCTs) represent the most common invasive malignant tumors in young male. The most widely accepted model of TGCTs development proposes a tumorigenic event in utero followed by a dormancy period until puberty when TGCTs emerge, suggesting hormonal involvement and the estrogen-dependence of these tumors has been reported. Estrogens act through estrogen receptors and human testis mainly express ER $\beta$ . ER $\beta$  loss is associated with advanced tumor stage, however the molecular mechanisms of the ER $\beta$ -protective effects are not defined yet. Recently, we showed that estradiol (E2) induced death in human testicular seminoma cells TCAM2 by a crosstalk between E2/ER $\alpha$  and the tumor suppressor gene PTEN, inducing autophagy and necroptosis. Cell survival is closely coupled to the cellular metabolism and tumor metabolism is considered a cancer hallmark and a novel target for cancer therapy. To further elucidate the role of ER $\beta$  in human seminoma we studied its effect on glucose and lipid metabolism in TCAM2 cells.

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## HEME OXYGENASE 1 DOWN-REGULATION FAVORS NATURAL KILLER RECOGNITION OF PRIMARY MELANOMA CELLS TREATED WITH BRAFV600E INHIBITOR

A.L. FURFARO<sup>1</sup>, G. LOI<sup>1</sup>, I. COSSU<sup>2</sup>, S. OTTONELLO<sup>3</sup>, U.M. MARINARI<sup>1</sup>, L. MORETTA<sup>4</sup>, M.A. PRONZATO<sup>1</sup>, M.C. MINGARI<sup>5</sup>, G. PIETRA<sup>3</sup> and M. NITTI<sup>1</sup>

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**Cell redox balance is crucially maintained by heme oxygenase 1 (HO-1) activity through its metabolic products which exert antioxidant, anti-apoptotic and anti-inflammatory effects. HO-1 up-regulation has been correlated with the gain of resistance to therapy in different types of cancers and its involvement in cancer immune-escape has been hypothesized. In this work, we have investigated the involvement of HO-1 in BRAFV600E mutated melanoma cell resistance to Vemurafenib/PLX4032 (PLX) and in Natural Killer (NK)-dependent killing.**

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## EFFECT OF BIOCOMPATIBLE EXTRACTS OF *OLEA EUROPAEA L.* ON OVARIAN CANCER CELLS MODEL

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Ovarian cancer is characterized by a high mortality rate among gynaecological malignancies worldwide. Accumulating evidence indicates that impairments of DNA repair and energy metabolism are implicated in the initiation and progression of ovarian cancer (OC). However, the relationships among these aspects are not extensively studied in ovarian cancer physiopathology. The Extracts of *Olea europaea L.* may be used as a potential source of both antioxidant and anticancer effects, although the concentration of the phenolic fraction is several times higher in olive leaf than in olive oil and varies depending on the cultivar and climate. This study investigates the effect, on OC cell model, of phenolic bioactive compounds of *Olea europaea L.*: Verbascoside (VB) and Oleuropein (OL), the two major biocompatible extracts from olive leaf and extra-virgin olive oil.

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## CIRCADIAN CONTROL OF CANCER CELL PROLIFERATION AND RESPONSE TO ANTICANCER TREATMENTS

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Circadian clocks are intrinsic, coordinated systems that operates in all cells and enable organisms to anticipate environmental changes, thereby adapting their behaviour, physiology and metabolism to the appropriate time of day, thus contributing to maintain body homeostasis. Disruption of these rhythms has a profound influence to human health and has been linked to many diseases, from depression to metabolic disorders to cancer. Indeed, the circadian timing system controls rhythmic events in cell cycle, DNA repair and apoptosis in both normal tissue and cancer and drives daily rhythmic changes in drug metabolism. Consequently, the toxicity and anticancer activity of common anticancer drugs can be significantly modified by the time of administration in both experimental models and in cancer patients. The molecular mechanisms at the base of this event are still poorly understood and this is one of the factors that limit the establishment of a successful cancer chronotherapy in clinical practice. Our research is focused on identifying the molecular mechanisms linking circadian rhythm to cancer cell proliferation, explore the mechanisms responsible for the beneficial effects of circadian administration of anticancer drugs, and deciphering the direct effect of specific clock components on different cellular functions in response to anticancer treatment.

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## DETECTION AND QUANTIFICATION OF OUTER MEMBRANE VESICLES (OMVs) PRODUCED BY HELICOBACTER PYLORI IN THE PLANKTONIC AND BIOFILM PHENOTYPES

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**Helicobacter pylori (Hp) is a microorganism capable of adapting itself in both the human host and natural environment. Hp persistence and resistance may be associated to both its broad genetic variability as well as its capability of developing a biofilm. Outer Membrane Vesicles (OMVs) associated with extracellular DNA (eDNA) are a component of the Hp biofilm. OMVs are involved in several mechanisms such as pathogenesis, biofilm formation, cell-cell communication, bacterial-host interactions and nutrient supply. OMVs are able to spread and transport virulence factors into the host. The aim of this study was to detect and quantify the OMVs secreted from Hp ATCC 43629 and Hp NCTC 11637 in the biofilm (bOMVs) and planktonic (pOMVs) phenotypes as well as being able to detect the eDNA-OMVs association with the use of Flow Cytometry.**

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**DOXORUBICIN REMEDY OR HARM? CARDIOTOXICITY AND NOT ONLY**

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**Doxorubicin (Doxo) is a chemotherapeutic agent whose clinical use is hampered by the serious dose-dependent cardiotoxicity. The accumulation of Reactive Oxygen Species (ROS) is widely accepted as a key factor of cardiotoxic effects. Mitochondrial Connexin 43 (Cx43) conferred cardioprotection by reducing cytosolic and mitochondrial ROS production. Topic of this work was the identification of antioxidant enzymes and molecules involved in Doxo-induced damage, in absence and in presence of Radicicol (Rad), an inhibitor of Cx43 translocation to mitochondria. Due to increasing numbers of young cancer survivors and the raising concerns for their fertility state, elucidating the biological mechanisms of chemotherapy risk is highly relevant. Moreover, it is known that Doxo-induced ovarian toxicity is associated with apoptosis of mouse granulosa cells.**

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## CHARACTERIZATION OF HEPATITIS B VIRUS INTEGRATION LANDSCAPE IN PATIENTS WITH HEPATOCELLULAR CARCINOMA AND IN PLC/PRF/5 CELL LINES

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**HBV DNA integration into the host hepatocyte genome is an early event in HBV infection and it is found in about 85% of HCC. Most of the data on HBV integration in HCC have been generated by specific restriction enzymes and cloning methods that may favor preferential amplification and bias identification of unique integration sites. On the other hand, a limitation of the more recent next-generation sequencing (NGSs) approaches is the low coverage of HBV reads. Aims. To conduct a high-throughput viral integration detection analysis on tumor (T) and non-tumor (NT) liver tissues, and on PLC/PRF/5 cells, using NGS of enriched HBV integrants. To characterize the HBV DNA integration events and enumerate clones of expanded hepatocytes that bear identical integrations. To identify HBV junctures at the whole-transcriptome level and define the transcribed viral-human fusions.**

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**P27KIP1 IN PSORIASIS. A PRELIMINARY IMMUNOHISTOCHEMICAL STUDY**

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**Psoriasis, a chronic immune-inflammatory skin disease, is characterized by intense proliferation and abnormal differentiation of keratinocytes. It is a complex multifactorial disease and the exact pathogenesis remains to be elucidated. The cyclin dependent kinase inhibitor p27<sup>Kip1</sup> is known to play a key role in cell cycle regulation by controlling the G1 to S phase transition. It is a negative regulator of cell cycle progression, as well as an inducer of apoptosis. The aim of the present study was to investigate p27<sup>Kip1</sup> expression in skin samples from healthy subjects and psoriatic patients.**

## EVALUATION OF ENDOCRINE DISRUPTORS, TPHP AND DPHP, EFFECT ON DNA REPAIR DAMAGE PATHWAYS IN A NORMAL HUMAN THYROID CELL MODEL

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**Thyroid diseases affect about 20% of the Italian Population and thyroid cancer (TC) is the most common endocrine neoplasm. TC incidence showed an increase over the past few years, especially among women. The recent attention of researchers has turned to the possible role of environmental factors able to interfere as Endocrine Disrupting Chemicals (EDCs) may affect thyroid function. Some EDCs may play a role in the etiology of thyroid disorders and increase the risk of TC, based on interactions between metabolic homeostasis and DNA repair systems. Triphenyl phosphate (TPHP) is a commonly used flame retardant and plasticizer the exposure of them were been recently suggested to alter thyroid function. This study investigates the effect of TPhP and its metabolite, diphenyl phosphate (DPHP), on DNA repair and metabolism in a normal human thyroid cells model, Nthy-ori3-1.**

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## THE ONCOLYTIC ADENOVIRUS DL922-947: A POSSIBLE THERAPEUTIC STRATEGY AGAINST MALIGNANT PLEURAL MESOTHELIOMA

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**Malignant Pleural Mesothelioma (MPM) is a rare cancer type mainly caused by asbestos exposure. MPM has limited treatment options and a poor outcome. New therapeutic approaches are urgently needed. Promising anticancer therapeutics are Oncolytic viruses (OVs) that selectively replicate in and kill cancer cells, leading to the tumor lysis.**

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## ASPECTS OF MELANOMA CELLS ADAPTED TO A CHRONIC ACIDOSIS RELEVANT FOR THERAPY

S. PEPPICELLI, F. BIANCHINI, E. ANDREUCCI, J. RUZZOLINI and L. CALORINI

*Biomedical, Experimental and Clinical Sciences “Mario Serio”, University of Florence*

**The chaotic and incomplete vasculature of tumor stroma is frequently responsible for a transient and/or persistent state of hypoxia, and tumor cells adapt their metabolism to anaerobic glycolysis. Therefore, lactate and protons are produced in large excess and transported outside by redundant families of lactate and H<sup>+</sup> transporters in order to maintain an intracellular pH compatible with survival and/or proliferation. Therefore, the extracellular pH of tumors turns to acidic for a different period of time, conferring new adaptive aspects to cancer cells, characterizing the transient-exposed and chronically-exposed tumor cell subpopulations.**

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## MULTIPOTENCY OF EPICARDIAL ADIPOSE TISSUE-DERIVED MESENCHYMAL STEM CELLS IS IMPAIRED IN TYPE 2 DIABETES

S. CABARO<sup>1</sup>, G. PERRUOLO<sup>1</sup>, V. D'ESPOSITO<sup>2</sup>, V. PARISI<sup>1</sup>, M. LECCE<sup>1</sup>, I. CIMMINO<sup>1</sup>,  
A. CURCI<sup>1</sup>, F. ORIENTE<sup>1</sup>, D. LEOSCO<sup>1</sup>, F. BEGUINOT<sup>1</sup> and P. FORMISANO<sup>1</sup>

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<sup>2</sup>*URT GDD-IEOS, National Council of Research (CNR), Naples, Italy*

**Excess of visceral fat is a major culprit in the development of type 2 diabetes and related disorders. A growing body of evidence indicates that epicardial adipose tissue (EAT), the visceral fat of the heart, may play an active role in dysregulation of cardiac function. Indeed, EAT thickness positively correlates with the release of inflammatory molecules and with the severity of heart pathologies. In patients with diabetes, prolonged hyperglycemia damages several organs, including heart. Thus, potent pro-inflammatory activation of EAT suggests a direct involvement of cardiac visceral fat in inflammatory phenomena occurring in patients with cardiovascular diseases. This study aims at investigating whether different glucose concentrations may impact on EAT functions.**

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## ER $\alpha$ DRIVES LKB1 FUNCTIONAL ROLE IN ADIPONECTIN-TREATED BREAST CANCER CELLS

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M.L. PANNO and S. ANDÒ

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**Adipose microenvironment is involved in signaling pathways that influence breast cancer development and progression, through the secretion of different adipocytokines. Among these, adiponectin plays a pivotal role in the pathogenesis of breast cancer. An inverse correlation is reported between obesity and adiponectin, suggesting that low levels represent a risk factor for mammary cancer. In the recent years, our research group has identified ER $\alpha$  as an important regulator of adiponectin action in breast cancer, clarifying that the role of this adipocytokine seems to be dependent on cell phenotypes. LKB1 is an important target of adiponectin action, being involved in multiple cellular functions, such as cell metabolism, cell cycle arrest, apoptosis, motility and cell polarity. Here, we investigated the effect of adiponectin on expression and function of LKB1 in ER $\alpha$ -positive (MCF-7) and negative (MDA-MB-231) breast cancer cells.**

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## GLUCOSE MODIFIES THE CROSSTALK BETWEEN CANCER CELLS AND ADIPOSE-DERIVED MESENCHYMAL STEM CELLS CONTRIBUTING TO CANCER PROGRESSION

V. D'ESPOSITO<sup>1</sup>, T. MIGLIACCIO<sup>2</sup>, G. MOSCA<sup>2</sup>, M.R. AMBROSIO<sup>2</sup>, G. PERRUOLO<sup>2</sup>,  
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**Hyperglycaemia increases breast cancer (BC) incidence and progression. Glucose may exert its effects on both BC cells and tumour microenvironment. Here, we analysed whether glucose could interfere on the crosstalk between mammary adipose tissue derived- mesenchymal stem cells (MAT-MSCs) and oestrogen positive-MCF7 BC cells, thereby modifying MSC phenotype and affecting tumour progression.**

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**EFFICACY OF ABL001 - ALONE OR IN COMBINATION - ON CD34+ PROGENITORS ISOLATED FROM CML PATIENTS DISPLAYING HIGH OR LOW BCR-ABL TRANSCRIPTS AT DIAGNOSIS**

L. MANZELLA, C. ROMANO, E. TIRRÒ, M. MASSIMINO and P. VIGNERI

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**ABL001 (Asciminib) is a selective allosteric inhibitor of the BCR-ABL oncoprotein that binds to the myristoyl pocket of ABL favouring the formation of an inactive kinase conformation. We evaluated the sensitivity to ABL001 - alone or in combination with the tyrosine kinase inhibitors (TKIs) Imatinib (IM) and Nilotinib (NIL) - of CD34+ leukemic progenitors isolated from 30 patients displaying either high (n=15) or low (n=15) BCR-ABL/GUSIS levels at diagnosis.**

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## CELL-TARGETED RGD-SUNITINIB MOLECULAR CONJUGATES IMPAIR TUMOR GROWTH OF MELANOMA

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A. SARTORI<sup>2</sup>, L. BATTISTINI<sup>2</sup>, J. RUZZOLINI<sup>1</sup>, F. ZANARDI<sup>2</sup> and L. CALORINI<sup>1</sup>

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<sup>2</sup>*Department of Food and Drug, University of Parma*

Despite progress in the clinical management of advanced-stage melanoma with different treatment options available, mainly based on targeted therapy and immunotherapy, many concerns still exist dealing with the observed overall toxicity. Effective dosing regimens and the insurgence of resistance mechanisms lead to tumor relapse and progression to a metastatic disease with incredibly aggressive features. Given the involvement of multiple, yet strictly related biological targets and signaling cascades in the metastatic melanoma disease, the combination therapy has become the standard-of-care treatment, in both small molecule-based (e.g. vemurafenib+cobimetinib in BRAFV600E/K-mutant disease) and antibody-based therapies (e.g. ipilimumab+nivolumab), with the primary goal to improve clinical benefit while overcoming the insurgence of drug resistance and compensating mechanisms often observed using targeted monotherapy. In these cases, however, off-organ (and possible synergistic) toxicity remains a still unsolved issue. Thus, the creation of new molecular conjugates which combine the ability to target melanoma cells using recognition of specific surface-exposed receptors, enter melanoma cells via receptor-mediated endocytosis, and modulate key intracellular targets and signaling pathways, is an appealing approach toward enhanced drug efficacy at lowered drug dosage and increased safety window.

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## BRASSICA EXOSOME-MICRORNAS: NEW THERAPEUTIC APPROACH IN CANCER TREATMENT?

F.M. PEZZINO<sup>1</sup>, A. RUSSO<sup>1</sup>, L. LO CICERO<sup>1</sup>, D. CATALANO<sup>1</sup>, M. PULVIRENTI<sup>1</sup>,  
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Natural medicine has been practiced for centuries and, today, has receiving attentions in both pharmaceutical industry and academia. Although, many mechanisms of action of plant products remain unknown, new possible mechanisms are becoming evident: exosomes and their content, miRNA included, might regulate gene expression with potential therapeutic activities in human chronic diseases. Plant miRNAs are found in sera and tissues of mammals after plant ingestion, supporting an effective communication between the two kingdoms. In our lab, we have utilized exosomes isolated from *Brassica oleracea* sprouts to inhibit the growth of tumor cell lines, as assayed by *in vitro* wound scratch test and by 3D cultures. To better understand the molecular mechanisms, we performed an *in silico* study using the *Brassica* miRNA database to predict the human target transcripts. Among others, MIR414 exhibited a perfect base paring to Spindlin 1 (SPIN1), a human gene upregulated in melanoma cancer.

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## PHOSPHODIESTERASE 5 (PDE5) EXPRESSION AND FUNCTION IN BREAST CANCER STROMA: AN ATTRACTIVE OPPORTUNITY FOR TARGETED THERAPY

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**By catalyzing cGMP hydrolysis, phosphodiesterase (PDE) type 5 acts as a critical regulator of its concentration and effects in different (patho) physiologic processes, including cancers. We have previously shown that PDE5 overexpression greatly enhances the invasive potential of breast cancer cells and reduces survival in patients, highlighting the benefit of therapeutic targeting PDE5. To extend these observations, we propose to assess PDE5 function in tumor microenvironment, which has increasingly known as an active contributor to breast cancer growth and progression.**

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## A POSSIBLE ROLE OF A CMV-LIKE VIRUS IN HEAD AND NECK PARAGANGLIOMA PATHOGENESIS

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F. SCHIAVI<sup>5</sup>, S. SOLIMAN<sup>2</sup>, S. DE FABRITIIS<sup>1</sup>, V. TARANTINI<sup>1</sup>, S. VALENTINUZZI<sup>1</sup>,  
M. DI MARCO<sup>2</sup>, A. RAMASSONE<sup>2</sup>, R. FLORIO<sup>6</sup>, L. DE LELLIS<sup>6</sup>, A. SHEU<sup>2</sup>, M. SERLUCA<sup>2</sup>,  
A. CAMA<sup>6</sup>, S.C. PRASAD<sup>7</sup>, A. VERONESE<sup>2</sup>, R. VISIONE<sup>2</sup>, C. PATIES<sup>8</sup>,  
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**Paragangliomas (PGLs) are neurovascular autonomic nervous system tumors, still incurable when radical surgery is not possible. They are frequently associated with susceptibility mutations in genes encoding the mitochondrial SDH complex components. However, the etiology of PGLs remains unclear as the penetrance of SDHx mutations is incomplete (21% at age 50). Studying a large set of freshly-collected head and neck PGLs (HNPGs) by electron microscopy we found herpesvirus-like particles in all tumors. These were similar to particles attributed to cytomegalovirus (HCMV) reported in 1971 by Heine et al. in a retroperitoneal PGL.**

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**EFFECTS OF HDAC INHIBITORS ON GLIOBLASTOMA CELLS**

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**Glioblastoma Multiforme (GBM), a high-grade glioma (WHO grade IV), is the most aggressive form of brain cancer. Treatment options for GBM involving a combination of surgery, chemotherapy and radiation resulted in a poor survival outcome. Epigenetic mechanisms are increasingly implicated in GBM pathogenesis. Unlike genetic mutations, epigenetic changes are reversible and can be targeted by drugs. We evaluated whether different Histone Deacetylase Inhibitors (HDACis) are able to affect migration, invasion and vasculogenic mimicry in GBM cells.**

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## INTERPLAY BETWEEN CANNABINOIDS AND INFLAMMATORY CYTOKINES IN HUMAN BREAST CANCER

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**Breast cancer is a highly heterogeneous disease and one of the few tumour types molecularly characterized. While luminal and human epidermal growth factor receptor 2 positive (HER2+) tumours can be controlled by hormonal and anti-HER2 interventions, the triple-negative breast cancers (TNBC) are resistant to standard treatments. Since the tumour microenvironment is an important player in breast tumour progression, the stromal components could represent a source of new prognostic biomarkers and targets for potential therapeutic strategies mainly in tumors lacking molecular sites of intervention. We previously found that Met-F-AEA, agonist at cannabinoid receptor 1 (CB1) inhibited cell migration and epithelial-mesenchymal transition of the TNBC cell line MDA-MB-231, through modulation of MMP2 and Wnt/ $\beta$ -catenin signaling, respectively.**

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## EFFECT OF OXIDATIVE STRESS ON CANONICAL/NON-CANONICAL WNT PATHWAYS IN COLON CANCER CELL LINES

T. CATALANO<sup>1</sup>, C. MOSCATELLO<sup>2</sup>, M.C. DI MARCANTONIO<sup>2</sup>, R. CORSARO<sup>1</sup>,  
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**The importance of aberrant regulation of Wnt/ $\beta$ -Catenin signaling in the pathogenesis and colorectal cancer progression has long been recognised. Recent studies have shown that reactive oxygen species (ROS) production activates the Wnt/ $\beta$ -Catenin pathways, but the mechanisms involved remain unclear. Excess in ROS production is linked to chronic inflammation and promotes DNA damages and repair systems. We aim to evaluate the relationship among oxidative stress response and canonical/non-canonical Wnt pathways in colorectal cancer cell line models with different Wnt signaling behaviour.**

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## PHENFORMIN INHIBITS TUMOR GROWTH THROUGH A COMPLEX I-INDEPENDENT REDOX/COREPRESSOR MODULE

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**The antidiabetic drug phenformin displays potent anticancer activity in different tumors but its mechanism of action remains elusive. In this study we have investigated the mechanism of cancer growth inhibition of phenformin, using as a model SHH Medulloblastoma, a cerebellar brain tumor characterized by an inappropriate activation of the Sonic Hedgehog signaling.**

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## HEME OXYGENASE-1 AND BRAIN OXYSTEROLS METABOLISM ARE LINKED TO EGR-1 EXPRESSION IN AGED MICE CORTEX, BUT NOT IN HIPPOCAMPUS

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Age is the main risk factor for many pathologies, neurodegenerative disorders included. With the world population getting older, aging will represent the disease of the future leaving an increasing need to understand the molecular basis of this process in normal and pathological conditions. Egr-1 (early growth response 1) is a transcriptional factor rapidly induced by many stress stimuli and it is involved in cell survival, proliferation and differentiation, as well as in memory, cognition and synaptic plasticity. Another molecule with neuroprotective properties is HO-1 (heme oxygenase-1), which converts heme to iron, carbon monoxide and biliverdin and it was shown to regulate the metabolism of oxysterols (derivatives of cholesterol oxidation) which represent new markers of oxidative stress. The only evidence of a link between Egr-1 and HO-1 was described in mouse lung cells exposed to cigarettes smoke. The aim of this study was to investigate whether Egr-1 can be implicated in oxysterol metabolism during brain aging.

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## EFFECTS OF THE REPURPOSED DRUG CANDIDATE PARBENDAZOLE IN PANCREATIC CANCER CELLS

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**Pancreatic cancer (PC) is the fourth most common cause of cancer death. Classical chemotherapeutic drugs, used alone or in combination, have a limited advantage in term of 5-year survival, at the cost of a relevant toxicity. Thus, novel therapeutic options with minimal side effects are urgently needed for this lethal disease. In this regard, the use of several non-toxic repurposed drug candidates has been explored in preclinical models of several tumors. In the present study, we investigated the potential repurposing in PC of the FDA-approved anthelmintic drug parbendazole.**

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## STUDY OF THE TRANSCRIPTIONAL REGULATION OF THE ONCOSUPPRESSOR KCASH2

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**KCTD containing Cullin3 adaptor, suppressor of Hedgehog (KCASH2) belongs to the KCASH family of proteins, which are involved in the negative regulation of the Sonic Hedgehog (Hh) signaling pathway. All members of KCASH family have shown to be downregulated in Hh dependent Medulloblastoma (Mb), by either allelic loss or promoter methylation. Particularly, KCASH2 expression is reduced also in other tumors, not directly connected with Hh pathway modulation; moreover, chromosome 11q, where KCASH2 is localized, is lost in several sporadic tumors. In turn, correlation studies and data of laboratory show a role of KCASH2 in differentiation and cell cycle regulation, suggesting its fine regulation during development.**

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**ITCH/ $\alpha$ -ARRESTIN2-DEPENDENT NON-PROTEOLYTIC UBIQUITYLATION OF SUFU CONTROLS HEDGEHOG SIGNALLING AND MEDULLOBLASTOMA TUMORIGENESIS**

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R. ALFONSI, D. MAZZÀ<sup>1</sup>, M. SILER<sup>1</sup>, S. CONI<sup>1</sup>, A. PO<sup>1</sup>, M. PETRONI<sup>2</sup>, E. FERRETTI<sup>3</sup>,  
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**Suppressor of Fused (SuFu), a tumour suppressor mutated in medulloblastoma (MB), is a central player of Hh signalling, a crucial pathway for development and deregulated in tumours. Although the control of Gli transcription factors by SuFu is critical in Hh pathway, our understanding of the mechanism regulating this key event remains limited. To this end, the main objective of this study is to investigate the role of the ubiquitylation processes in the regulation of SuFu/Gli interaction.**

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## THE EFFECT OF THE HYPOXIC MICROENVIRONMENT ON GLIOBLASTOMA CELLS: BK CHANNELS BLOCKADE AS A NOVEL STRATEGY TO LIMIT DRUG RESISTANCE

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**Glioblastomas (GBMs) are brain tumors of glial origin characterized by a heavy hypoxic microenvironment, which correlates with tumor aggressiveness. GBM cells abundantly express large-conductance, calcium-activated potassium (BK) channels and, since hypoxia modulates their activity in GBM cells, the aim of the present work was to explore their role in the hypoxia-induced chemoresistance and to better understand the molecular mechanisms underlying the effect of the hypoxic microenvironment on BK channels-dependent drug resistance of GBM cells.**

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## SYNERGISTIC INHIBITION OF THE HEDGEHOG PATHWAY BY NEWLY DESIGNED SMO AND GLI ANTAGONISTS BEARING THE ISOFLAVONE SCAFFOLD

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**The Hedgehog (Hh) signalling pathway is evolutionarily conserved and its fine regulation is essential for proper development and tissues homeostasis. Aberrant activation of the Hh pathway is responsible for the onset of several malignancies, including medulloblastoma (MB), the most frequent pediatric brain tumor. Small molecules able to block the pathway at the upstream receptor Smoothed (Smo) or the downstream effector Gli1 have thus emerged recently as valuable anticancer agents. The aim of this proposal is to discover novel powerful Smo and Gli inhibitors targeting Hh signaling at both upstream and downstream level, and to investigate their pharmacological effects on MB.**

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## PD-L1 LEVEL IS UP-REGULATED IN NSCLC CELLS AFTER PEMETREXED TREATMENT

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**Immune checkpoint inhibitors, such as PD-1/PD-L1 targeting monoclonal antibodies, have shown efficacy in the treatment of non-small cell lung cancer (NSCLC) in the adjuvant, first- and subsequent-line settings, in monotherapy or combined to standard chemotherapy regimens in both adeno and squamous histologies. Recent results from KEYNOTE-189 trial indicates that the addition of pembrolizumab to pemetrexed and platinum-based drug results in longer OS and PFS than chemotherapy alone even in originally PD-L1 negative patients with lung adenocarcinoma (Gandhi L. et al. NEJM 2018). Nevertheless, the success of this therapy is limited and there is an urgent need for developing strategies to sensitize NSCLC to immune-checkpoint inhibitors. In this study, we evaluated whether chemotherapeutic agents may alter PD-L1 expression in order to guide optimal combination/sequencing with Immune checkpoint inhibitors in the clinic.**

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## DIAGNOSI DI LABORATORIO EMOMETRICA DI MIELODISPLASIA (MDS)

V. LATELLA, B. MODAFFERI and C. LAGANÀ

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**The aim of this study is to attention the important role that laboratory medicine plays today in the evaluation of hematological diseases. The utility of the collaboration between the laboratory staff and the clinicians has emerged as fundamental to diagnose complex diseases in a short time interval.**

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## DIAGNOSIS OF LYMPHOMA FROM COMPLETE BLOOD COUNT

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**The aim of the study is to attention the important role that laboratori medicine has in the evaluation of hematological diseases. The utility of the collaboration between the laboratory staff and the clinicians has emerged as fundamental to diagnose complex and specialistic diseases in a short time interval.**

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## GLYCINE/SARCOSINE RATIO AS NOVEL BIOMARKER FOR ALCOHOL-INDUCED LIVER FIBROSIS UNDER SUMOYLATION CONTROL

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Alcohol-induced liver fibrosis/disease (ALD) is characterized by excessive deposition of extracellular matrix (ECM) components in response to chronic abuse that could lead to cirrhosis and hepatocellular carcinoma development. Sarcosine is a derivative of the amino acid glycine, formed by the enzymes glycine N-methyl transferase (GNMT) or dimethylglycine dehydrogenase (DMGDH) and converted back into glycine via sarcosine dehydrogenase (SARDH). GNMT is silenced in human alcohol-induced cirrhosis. In addition, GNMT knockout mice develop oxidative stress, liver injury, fibrosis, and HCC. SUMOylation is a post-translational modification that requires an essential E2-conjugating enzyme 9 (UBC9) to covalently bind of small ubiquitin modifier (SUMO) and plays an important role in a wide range of cellular processes. We previously demonstrated that UBC9 level is induced in intragastric ethanol-infusion (EI) treated mouse liver. We performed SUMO-proteomics of alcohol-fed mouse liver and identified altered sumoylation of GNMT and SARDH. The goal of this work is to examine whether the dysregulated SUMOylation could regulate GNMT and SARDH enzymatic function in ethanol-induced liver fibrosis and elucidate the molecular mechanism(s).

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**LONGEVITY ASSOCIATED VARIANT OF BPIFB4 TUNES THE MACROPHAGES  
POLARIZATION AND MITIGATE MONOCYTE MEDIATED ACQUIRED IMMUNE RESPONSE:  
A POSSIBLE EXPLANATION OF HOW CENTENARIANS ESCAPE AGING DISEASES**

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Reaching exceptional longevity is a consequence of aging delay driven by genetic and epigenetic factors, which are either inherited or acquired. It has been postulated that aging is driven by imbalance between inflammatory and anti-inflammatory networks that results in the low grade chronic pro-inflammatory status causing most of the physiopathological changes triggered by aging. In this respect, the activation of monocyte-macrophages plays a major roles in finely tune the immune responses as they cover a continuum of functional states which oscillate from a patrolling protective effect toward an inflammatory ones. We previously identified a four-SNPs haplotype, the Longevity-associated variant (LAV) of bactericidal/permeabilityincreasing fold-containing-family-B-member-4 (BPIFB4) able to activate calcium, PKC- $\alpha$ , eNOS, rescuing endothelial dysfunction in aged mice and inducing revascularization through homing of progenitor cells. BPIFB4 abundance in serum of healthy centenarians as compared to non-healthy ones, the therapeutic potentials LAV-BPIFB4 in improving vascular homeostasis, at least in part mediated by Ly6Chigh monocytes, and BPIFB4 expression in bone marrow myeloid cells induced us to evaluate if LAV-BPIFB4 may improve immune regulation.

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