09.45----------

GATHERING, WELCOME & INTRO - Public

10.00----------

ASSESSING THE MOLECULAR EFFECTS OF PHYSICAL STIMULI - Public

Speaker: Wei Wang, Centre for Precision Health, Edith Cowan University, Western Australia

Title: Paracentral dogma: supporting the central dogma with sugar code

Abstract “Life requires more than nucleic acids and proteins; sweet sugar molecules could be another life code beyond the central dogma of molecular biology” .

Among the four equally important major building blocks of life: nucleic acids (DNA and RNA), proteins, lipids, carbohydrates (glycans) and lipids, the first two, DNA and RNA follow the well-established principle of the "central dogma” of transcription (DNA to RNA) and translation (RNA to protein). The latter two crucial components, glycans and lipids, however, are missing from biology’s central dogma. Regarding the communication between DNA, RNA, glycans and lipids and their roles in immunomodulation, there may be a yet-to-be discovered law: Does a paracentral dogma exist? This talk focuses on the roles of genetics and beyond in immunity, immune disorders, the equilibrium of pro- and anti- inflammation, and glycomedicine. Based on the WHO definition on health, an example of physical stimuli as a scientific-based potential therapy for suboptimal health intervention will be presented, which provides baseline information for WHO, OECD, EPMA, ISoGH for health policy making from the contexts of predictive, preventive, and personalized/precision health.

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10.20----------

Speaker: Carla Ferreri, Istituto per la Sintesi Organica e la Fotoreattività, CNR, Rome, Italy Lipinutragen, Italy

Title: Cell membranes, stimuli and anti-inflammatory potential

Abstract Membranes act as sensor and metabolic pacemaker of cells. They are not spectators but active participants of the stimuli effects, specifically for the inflammatory/anti-inflammatory balance. Strong scientific basis indicate membrane diagnosis therapies as crucial approach in the next-generation medical approaches.

10.40----------

Speaker: Simona Villalta, Dipartimento di Scienza Applicata e Tecnologia and PolitoBIOMed Lab, Politecnico di Torino, Italy.

Title: A 3D in vitro skin model for reproducible assessment of response to physical stimuli

Abstract The skin is the most external-facing organ of the human body and the first line of defence against injuries as well as the main site for therapeutic physical stimulation to induce healing responses. In particular, there exists promising physical stimulations for therapeutic application, but there are still problems concerning the design of preclinical experiments including a proper *in vitro* biological model and the selection of physical parameters for stimulation. In the talk, a 3D *in vitro* skin model will be described in combination with a proposed methodology for electrostimulation.

11.00----------

EXPLORING ELECTRO-MAGNETIC STIMULI - Public

Speaker Tiziana Guarnieri, Dept of Biological, Geological and Environmental Sciences, Alma Mater Studiorum Università di Bologna, Italy.

Title Optical Biosensors

Abstract For about 50 years, living cells or part of them have been employed as biorecognition elements (bioreceptors) in biosensors. Here, we describe whole cellular systems-based biosensors, endogen systems where the sensor and the transducer are cells or part. If we consider electromagnetic radiations, sensing elements can be either chromophores, which absorb selected wavelengths of UV/Visible radiations and reflect a certain colour (i.e., retinal of rods and cones), or photosensitizers, chemical entities which absorb and transfer energy to a reactant molecule that is not able to absorb energy directly. This is the case of FICZ (6-formylindolo-3-2-b-carbazole), a photoproduct of Tryptophan (Trp) in epidermal keratinocytes. It is an efficient UVA/Visible radiations photosensitizer and is the best endogen ligand of Aryl hydrocarbon Receptor (AhR), an evolutionarily conserved transcription factor. Due to its promiscuous ligand binding site, AhR is a biosensor for a long list of xenobiotics, among which 2,3,7,8 trichloro-dibenzo-p-dioxin (TCDD). It also binds a plethora of endogen metabolites, among which some Trp-derived photosensitizers, such as Kynurenine, Tryptamine and 6,12-di-formylindolo[3,2-b]carbazole (dFICZ). My research interest is focused on the role of AhR in inflammation as, depending on the ligand and the physiopathologic context, it can exert a pro- or anti-inflammatory effect. I am interested in defining its participation in inflammatory pathways and, in particular, in testing the possibility to turn its effect from pro- to anti-inflammatory, even through the use of activated chromophores and photosensitizers.

11.20----------

Speaker: Laura Calzà, Fabit, DIMEVET and CIRI-SDV, University of Bologna, Italy

Title: Very-low level laser therapy and photobiostimulation: defining efficacy and mechanism of anti- inflammatory action in in vitro and in vivo systems

Abstract: Extremely low power/energy laser stimulation (LLLT) and photobiostimulation (PBS) are examples of unexpected physical-biological interactions having potentially therapeutical

interest. In the past years, our laboratory investigated several aspects of the physical biological interaction, using *in vitro* and *in vivo* models.

By using a 670 nm laser, with extremely low peak power output (3mW/cm^2) and at an extremely low dose (0.45 mJ/cm^2) we demonstrated that laser irradiation stimulates nerve growth factor (NGF)-induced neurite elongation on a laminin-collagen coated substrate and protects PC-12 cells against oxidative stress, as evaluated through live-recording of mitochondria membrane potential (MMP) using JC1 vital dye and laser-confocal microscopy, in the absence (photo bleaching) and in the presence (oxidative stress) of H_2O_2 , and by means of the MTT cell viability assay. In fibroblasts, LLLT supplied at both at very low (0.21mW/cm^2) and low levels (500 mW/cm^2) modifies mitochondria network dynamics, as well as expression level of mRNA encoding for selective matrix proteins, e.g. collagen type-1 α1 and integrin α5, when dispensed in pulsed but not in continuous mode.

Using *in vivo* rat models of inflammatory and neuropathic pain, we reported that LLLT delivered at standardized bodily locations (also known as laser acupuncture) promotes the anti-edema and anti-hyperalgesia effects in acute inflammatory pain, e.g. CFA-induced inflammation and myofascial pain. We also indicated that spontaneous pain and thermal hyperalgesia are reduced in a neuropathic pain model, e.g. axotomy. On the contrary, no effects due to laser-acupuncture were observed on discomfort indices in a model of visceral pain, e.g. cystitis due to cyclophosphamide.

With regards to photobiostimulation (light-emitting diodes, LED), we identified defined wavelengths able to regulates mitochondria membrane potential and Redox balance in skin fibroblasts and endothelial cells (unpublished results). The selected LEDs were all 5mm in diameter and had emission angles ranging from 15° to 25°, and powers ranging from 2.4 to 45 mW, the investigated wave lengths were 440, 525, 645, 660, 780, 900 nm.

Overall, these data contribute to delineate the biological impact of LLL and photobiostimulation, also indicating that molecular pathways and cellular processes involved in inflammation are regulated by these physical stimuli.

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11.40----------

Speaker: Vitalii Zablotskii, Institute of Physics of the Czech Academy of Sciences, Prague, Czech Republic; International Magnetobiology Frontier Research Center (iMFRC), Science Island, China

Title: Anti-inflammatory Effects of Magnetic Fields

Abstract: The biological and therapeutic effects of low magnetic fields have been the subject of numerous studies for over a hundred years. However, investigations of the biological effects of moderate and high magnetic fields are still at an early stage. Several new anti-inflammatory effects of moderate and high magnetic fields (MFs) are discussed below. Effects of a high static MF on lung cancer bearing mice were examined in [1]. In mice treated 88h with a 9.4 T static magnetic field, tumor growth and DNA synthesis were significantly inhibited, G2 cell cycle was arrested, while the ROS and P53 levels were increased.

Surprisingly, the application of ultra-high static MF (up to 33T) causes the anti-depressive effect on mice, enhancing the levels of oxytocin and c-Fos in the mice brain [2]. Of note, this was the first attempt to apply such ultrahigh static magnetic fields to living organisms. A putative mechanism based on magnetic pressure has been proposed that may be responsible for the elevated levels of oxytocin, the happiness hormone [2]. Exposure (7 weeks, 24 h/day) to 15 mT static MF can reduce oxidative stress to improve wound healing and alleviate diabetic complications in mice [3]. It is important for clinical applications to treat a number of myopathies associated with the defective calcium regulation in muscle cells that exposure of skeletal muscle cells to a complex spatiotemporally modulated 70 mT magnetic field triggers a significant increase in cytosolic Ca^{2+} levels leading to actin polymerization [4]. The influence of spatially modulated high gradient MFs on cellular functions of human THP-1 leukemia cells was studied in [5]. Here, it was shown that a high-gradient moderate MF can: i) induce cell swelling, ii) increase prolonged ROS production, iii) inhibit cell proliferation, and iv) elicit apoptosis of THP-1 monocytic leukemia cells in the absence of chemical or biological agents. A high static MF can control the diffusion of biologically active molecules including oxygen, hemoglobin, and drugs, thereby affecting many physiological processes in organisms, e.g., wound healing [6].

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12.00----------

Speaker Simona Salati, IGEA SpA,, Italy

Title: Adenosine Receptors as a biological pathway for the anti-inflammatory and beneficial effects of low frequency low energy pulsed electromagnetic fields (PEMFs)

Abstract: The beneficial therapeutic effects of pulsed electromagnetic fields (PEMF) have been documented with increasing frequency over the last decades. PEMF stimulation therapies have been clinically successful in treating a variety of medical conditions, including healing of non-unions and halting the progression of osteoarthritis. One of the most prominent features of PEMF therapy is to protect the articular microenvironment from inflammation and degenerative processes. The molecular and cellular effects of PEMF exposure on pathways involved in the resolution of inflammation are a subject of intense investigations. In the last two decades, several evidence identify adenosine receptors as the target of PEMF action and as the mediators of the anti-inflammatory and protective effect of PEMF. Adenosine has been reported to be a potent immunomodulatory agent, with receptor activation on various cells curtailing excessive inflammatory responses. Of the four G-protein-coupled receptors, PEMF specifically influence A2A and A3 subtypes, enhancing the anti-inflammatory and protective functions of adenosine.

Preclinical studies showed that PEMF stimulation i) increases the anabolic activity of chondrocytes and cartilage explants, and (ii) antagonizes the catabolic effects of inflammation. In animal models of osteoarthrosis (OA), PEMFs stimulation was able to halt the progression of OA and to preserve the quality of the cartilage.

In joint pathologies, PEMFs have been successfully applied to control the inflammation, protect the mechanical and biological properties of the cartilage and to prevent chronic pain and functional disabilities. Extensive preclinical and clinical research demonstrates the effectiveness of PEMF stimulation in controlling inflammation and in preserving tissue homeostasis, thus suggesting PEMF stimulation as a non-invasive and safe physical therapy to accelerate tissue healing.

12.20----------

Discussion Part I: COST Action, Position Paper, Review – Private

13.00----------

BREAK

14.00----------

EXPLORING MECHANICAL STIMULI – Public

Speaker : Jean-François Moreau, ImmunoConcept - CNRS UMR5164 - Bordeaux University, France

Title : Inflammation.. Immunity.. Cell mobility and ExtraCellular Matrix..Where is the connection?

Abstract : Since its first uses by Celsus and then Virchow, the term ‘inflammation’ encompasses many different meanings and depending of the level at which it is considered, it can refer to cells, molecules, tissues, mechanisms or merely facts (rubor, calor, dolor, etc...). Its wide definition makes it an apparently attractive candidate for communication between people as it is easy to share, but conversely, because it is often used without enough precision about the level of complexity, it blurs the conclusions that could be drawn from studies.

Therefore, the need for a sharper and more universal semantic content of this term is still a relevant endeavor today.

Because inflammation in metazoans is deeply rooted in the immune system defined as an intricated array of cells and soluble molecules at the scale of the whole body, it has been widely used as a starting point to better understand it. Numerous reports dealing with the so-called inflammatory cells or cytokines as examples, are available. Still the big picture behind this flurry of information remains elusive. One reason for this could be that some important explanatory factor or factors that could allow for an integration of abundant, apparently heterogeneous data are ignored or neglected. One such factor could be physical and dealing with the extracellular matrix embedding cells.

The transition of life from unicellular to multicellular entails a complex evolution of the interrelationships existing between cells, including adherence, cell-cell communications, mechanotransduction and their mobility. Early in this evolution, the ExtraCellular Matrix (ECM) appeared. It plays many different roles in multicellularity including: space organization, soluble molecules storage, mechanical functions or a medium in which mobile cells can circulate in an ordered fashion. It is also found when primarily unicellular organisms such as bacteria or dictyostelium, become temporarily multicellular suggesting it could constitute the fundamental underpinnings of any type of multicellularity.

A cardinal and very specific property of the cells comprising the immune system in metazoans is their mobility. For example, hereditary mutations and loss of function of molecular components of the actin motor (Coronin-1 or DOCK8) necessary to do so, are enough to lead to deep immune deficiencies. More recently, it has been recognized that the vast majority (98%) of lymphocytes in metazoans are within the tissues constituting organs (T resident memory), their total number in the whole blood representing only a tiny fraction of them. There, they are highly motile cells poised to patrol relentlessly a large volume of these tissues making the basis for the local immunosurveillance able to hold away the consequences of many exterior borne modifying agents (e.g., infectious). Where do those cells can be mobile as obviously, other cells types constitutive of those tissues are immobile? By embedding and fixing in space cells of a given tissue, the mesh constituted by the ECM creates an intercellular space in which the mobile cells of the immune system could circulate, mediate their functions and be responsive to mechanical clues.

In this short talk, I would like to focus my attention on showing that the conditions of cell movements in tissue are key to understand inflammation besides and not solely what they do there locally.

Indeed, ECM chemical modifications have immediate bearings on the physical characteristics of the 3D microenvironment where immune cells operate. These physical alterations could be for example, a changed stiffness in the fibrillar nature of ECM or a modification in its mesh porosity leading to deep modifications in the behavior of immune cells locally and systemically. By physically constraining the cells movements and cell deformability, it could even lead to cell death and necrosis whose release of self-components in the vicinity fosters other potent inflammatory circuits constituting as many vicious amplification and self-perpetuating circles.

Recognition of the physical alterations of ECM could be not only beneficial for general knowledge purposes to reach a big picture on inflammation but also for triggering new therapeutical interventions where inflammation is at stake. It is foreseeable that cells immune and others, relying on specific physical characteristics of ECM could be controlled by inducing local modifications of it.

14.20----------

Speaker: Carla Stecco**,** Centre for Mechanics of Biological Materials, University of Padova, Italy

Title: Fascia and Mechanical stimuli

Abstract: Fasciae are a new target of treatment in the rehabilitation medicine. In the past 15 years, multiple articles have demonstrated that they are very well innerved (more than muscles, tendons and joints) and that they can play a role as pain generators. Besides, fasciae are organized in multiple layers of fibrous and loose connective tissues. The different layers have different mechanical proprieties and answer to different physical inputs. The loose connective tissue, being rich in hyaluronan and water, is very sensitive to temperature and pH, the fibrous tissue is more sensitive to mechanical inputs. Among the several physical treatment options, extracorporeal shock wave therapy (ESWT) is one of the most used, also if its biological effect into the fascial tissue is not clear.

To better understand the biological effect of the ESWT into the fascial tissue, primary fascial fibroblasts were collected from small samples of human fascia lata of the thigh of three volunteer patients (two men, one woman) during orthopaedic surgery, and put in culture. These cells were exposed to 100 impulses of 0.05 mJ/mm^2 with a frequency of 2.5 Hz, using 3D-printed support. This study demonstrated for the first time that ESWs can lead to in vitro production of hyaluronan-rich vesicles immediately after the treatment. At 1, 4, and 24h after treatment, Alcian blue and Toluidine blue staining; immunocytochemistry to detect hyaluronic acid binding protein (HABP), collagen I, and collagen III; and transmission electron microscopy demonstrated that these vesicles are rich in hyaluronan and collagen I and III. The diameter of these vesicles was assessed, highlighting a small size at 1h after ESW treatment, whereas at 4 and 24h, they had an increase in the size. Particularly evident was the release of hyaluronan-rich vesicles, collagen-I, and collagen-III starting at 1h, with an increase at 4h and maintenance by 24h. These in vitro data indicate that fascial cells respond to ESW treatment by regulating and remodelling the formation of extracellular matrix.

14.40----------

Speaker: Luigi Manni, Institute of Translational Pharmacology, CNR, Rome, Italy

Title: Modulation of Inflammatory Response by Sensory Stimulation

Abstract: Needle insertion at the body surface and their subsequent stimulation by manual rotation (manual acupuncture: MA) or by electrical impulses (electro-acupuncture: EA) activates a group of receptors in the skeletal muscles, which have both low- and high-threshold for mechanical stimulation, and elicits regular patterns of afferent activity in peripheral sensory nerves innervating the skin and deeper tissues [1]. Such receptors sense and convey information to the central nervous system about muscle contractions and activate physiological processes similar to those resulting from physical exercise.

Main target for the anti-inflammatory action of acupuncture is the inflammatory reflex, a complex, inflammation-limiting feedback loop, based on the cross talk between the immune and central nervous system, the activity of peripheral autonomic vagus and sympathetic nerves and the hypothalamus-pituitary-adrenal (HPA) axis [2]. The neuro-immune system, operating in the control of inflammation, works according to the classic homeostatic paradigm. Acupuncture, according to established experimental evidences [3], acts on both the neural afferent component,

modulating the sensing of the inflammatory state, and on efferent components, regulating the vagal, sympathetic and HPA activities, with an overall normalizing effect on the effector response and the immunomodulatory signal at the site of inflammation.

Here we will briefly summarize the neuro-functional basis of the acupuncture effects on inflammation and report some of our experimental data linking acupuncture to the modulation of neuromodulators, such as neurotransmitters, neurotrophins and neuropeptides, actively involved in the neuro-immune regulation of inflammatory processes.

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15.00----------

Speaker Christine Nardini

Title: Mechanical Stimuli and wound healing

Abstract: *Wound healing* (*WH*) is a complex phenomenon describing the ability of the organism to preserve homeostasis. WH describes both the very detailed molecular and cellular events occurring locally to a wound (Epithelial-Mesenchymal Transition TypeII) , as well as therapeutic macroscopic effects.

The connection between these two WH is, however, far from clear. Understanding WH and its eliciting/modulating factors, including physical stimuli, as a continuum between molecular (local) and clinical (systemic) events is of particular relevance for advancing in the management of chronic inflammation, a hallmark of non-communicable diseases (NCDs).

Towards this aim, I will discuss both our theoretical proposal to enlarge the definition of inflammation including wound healing and other relevant pathways (Greater Inflammatory Pathway [3]) and our results in the elicitation of wound healing by mechanical stimuli, with experimental data from different settings [4], [5] using as exemplar malady towards translation rheumatoid arthritis (RA).

References

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15.20----------

Speaker: Giancarlo Forte, St. Anne's University Hospital in Brno (FNUSA-ICRC), Czech Republic

Title: The molecular basis of pathological mechanosensing in the failing heart

Abstract: The onset and progression of aging-associated pathologies is paralleled by continuous local extracellular matrix (ECM) remodeling. This process serves as a compensatory strategy for tissues to cope with the altered conditions.

The modifications in the nanostructure and mechanics of cardiac ECM are driven by the activation of cardiac fibroblasts and impair cardiac cell function to progressively lead to organ failure. In turn, cardiomyocytes respond to the ensuing biomechanical stress by re-expressing fetal contractile proteins, by transcriptional and post-transcriptional processes, such as alternative splicing.

Our group demonstrated that the aberrant activation of mechanosensitive Yes Associated Protein (YAP) alters the assembly of focal adhesions in response to mechanical stress. Additionally, we contributed knowledge on YAP regulation during the acquisition of cardiac phenotype by adult and pluripotent stem cells, and found that its hyperactivation in patient-derived cardiac fibroblasts promotes ECM pathological remodeling, thus favoring the fibrotic process and fueling heart failure.

Lately our experimental data highlighted how the pathological remodeling of ECM in the failing heart directly affects the expression and function of RNA binding proteins in cardiomyocytes. This discovery demonstrated that mechanical stress can effectively rewire the alternative splicing of numerous genes involved in cardiomyocyte contractility, calcium handling and mechanosensing.

These studies allowed us to describe different layers of intracellular mechanosensing responsible for finely tuning the expression of splicing variants of important cardiac genes in response to pathological mechanical turmoil.

15.40----------

Speaker: Timothy J Koh, Department of Kinesiology & Nutrition, University of Illinois at Chicago, USA

Title: Low-intensity vibrations for improving tissue repair

Abstract: Mechanical signals have long been known to influence function of cells, tissues and organs and a number of different forms of mechanical stimulation have been used as therapy in various pathological conditions. Low-intensity vibrations (LIV) have been used in attempt to ameliorate bone loss, to improve muscle mass, to mitigate effects of obesity, to improve function in various neurological disorders and to improve wound healing. My laboratory has studied the impact of LIV on traumatic muscle injury and in diabetic skin wound healing in mice. Following

traumatic muscle injury, LIV applied either to the whole body or directly to the injured leg for 30 min/day increased cross-sectional area of damaged muscle fibers, and decreased damaged muscle area after 14 days of treatment. In addition, LIV increased fusion and diameter of cultured muscle cells. Following skin injury in diabetic mice, LIV increased angiogenesis and granulation tissue formation, and accelerated wound closure and re-epithelialization. LIV-enhanced wound healing was associated with increased levels of growth factors in wounds and reduced markers of inflammation. My laboratory along with others have also shown that LIV can improve blood flow through both the macro- and microcirculatory systems, which may contribute to improved healing of both muscle and skin. Our current and future work is focused on elucidating mechanisms of LIV-induced healing and on translating our preclinical mouse studies to human trials.

16.00----------

Discussion Part I: COST Action, Position Paper, Review – Private

16.40----------