Fondazione Ri.MED

ISMETT Istituto di Ricovero e Cura a Carattere Scientifico

UPMC LIFE CHANGING MEDICINE

14th Ri.MED SCIENTIFIC SYMPOSIUM

INFLAMMATION AND AGING

Mechanisms, mediators and therapeutic interventions

19-20 MAY 2022

SALA DEI BARONI,
PALAZZO CHIARAMONTE STERI
PIAZZA MARINA 61 - PALERMO - ITALY

UNDER THE PATRONAGE OF

Università degli Studi di Palermo

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Dario A. A. Vignali, PhD
Scientific Director, Fondazione Ri.MED
The Frank Dixon Chair in Cancer Immunology,
Vice Chair and Professor of Immunology,
University of Pittsburgh School of Medicine,
and Co-Leader,
Cancer Immunology and Immunotherapy Program,
Co-Director, Tumor Microenvironment Center,
UPMC Hillman Cancer Center, Pittsburgh, USA

The Ri.MED Foundation, based in Palermo, promotes, supports and leads biomedical and biotechnological research projects, with an emphasis on the translation of innovative results into clinical practice. Our strategic partnerships with the University of Pittsburgh, UPMC and IRCCS-ISMETT promote cutting-edge research, generate proprietary intellectual property and joint patent applications, and facilitate the initiation of biotechnology start-ups. We strive to extend our network and scientific collaborations, and integrate complementary technologies though joint translational research projects.

Ri.MED is currently focused on a major building project and our new home - the Biomedical Research and Biotechnology Centre in Carini - which we hope will become a major basic and translational research hub for Italy and Southern Europe and a focal point for researchers from all over the world.

A major focus of the Ri.MED Foundation is also to train the next generation of Italian biomedical and physician-scientists, who will provide the human capital of our new Research Centre.

Activities focused to scientific dissemination and sharing of research results are part of the Foundation's core mission.

We are very proud to welcome you at the 14th Ri.MED scientific symposium, which focuses, every year in rotation, on one of our four core research areas: cancer (with an emphasis on immunotherapy), organ insufficiency (which includes organ transplantation and regenerative medicine), aging (with an emphasis on neurodegeneration and chronic inflammation), and infectious diseases. Although the COVID19 pandemic caused us to pause our symposia for a few years, we are delighted to restart our annual meetings with this symposium on Inflammation and Aging.

Welcome to Palermo!

Toren Finkel MD/PhD
Director, Aging Institute
University of Pittsburgh/UPMC

CHAIR of the Symposium

Welcome to the Ri.MED Symposium on Inflammation and Aging! After a two year delay due to COVID-19, it is indeed a great pleasure to welcome everyone. We are fortunate to have gathered leading experts from Italy, Europe and the USA to address the role that chronic inflammation plays in aging and age-related diseases. Over the next day and half, we will all hear a variety of presentations on the relationship between chronic immune activation in the elderly and the susceptibility to develop a host of age-related conditions. Together, we will explore the basic science mechanisms that underly the association between inflammation and aging, as well as more precise ways to assess and measure immune activation. The role of 'inflammaging' in specific disease conditions, from COPD to sepsis to Alzheimer's disease, will also be discussed. Finally, we will also hear how these emerging insights may allow for novel specific and targeted interventions to slow the aging process and thereby combat a host of age-related conditions.

It is our hope that those who gather here at the Palazzo Chiaramonte Steri, built in 1307, will listen, learn and engage in lively discussions. As one of the first international meetings dedicated solely to the intersection of aging and the immune system, we believe this will be an incredibly exciting two days!

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19 May
Thursday

2.00 PM SYMPOSIUM REGISTRATION

2.30 PM WELCOME AND INSTITUTIONAL GREETINGS
Paolo Aquilanti
Ri.MED President

Angelo Luca, MD
Ri.MED Vice President, IRCCS ISMETT Director

3.00 AM CHAIR INTRODUCTION
Toren Finkel, MD, PhD
Director, Aging Institute of UPMC, Pittsburgh, USA

3.15 PM KEYNOTE SPEECH:
Inflammaging as the most comprehensive conceptual framework for age-related diseases
Claudio Franceschi, MD, PhD
Professor of Immunology, University of Bologna, Italy

4.00 PM COFFEE BREAK

4.30 PM **Targeting inflammaging to enhance immunity in humans**
Arne Akbar, PhD
Professor of Immunology Experimental & Translational Medicine
Division of Medicine, University College London, UK

5.00 PM **Innate immune responses in age-related lung diseases**

Chiara Cipollina, PhD
Group Leader in Experimental Lung Research,
Fondazione Ri.MED,
Palermo, Italy

Alessandro Bertani, MD, PhD
Clinical Assistant Professor of Surgery, University of Pittsburgh
Chief, Division of Thoracic Surgery and Lung Transplantation, IRCCS ISMETT, Palermo, Italy

5.45 PM **New frontiers in Osteoarthritis as an inflammatory age-related disease**
Roberto Di Gesù, PhD
Principal Investigator in Musculoskeletal tissue engineering,
Fondazione Ri.MED, Palermo, Italy

6.15 PM CLOSING REMARKS
Dario A. A. Vignali, PhD
Ri.MED Scientific Director

20 May
Friday

8.30 AM SYMPOSIUM REGISTRATION

9.00 AM WELCOME AND INSTITUTIONAL GREETINGS
Alessandro Padova, PhD
Ri.MED Director General

9.15 AM CHAIR INTRODUCTION
Toren Finkel, MD, PhD
Director, Aging Institute of UPMC, Pittsburgh, USA

9.30 AM KEYNOTE SPEECH:
Chronic Inflammation in Older Adults: Clinically Relevant Pathways and Their Measurement
Jeremy David Walston, M.D.
Professor of Geriatric Medicine & Gerontology, Johns Hopkins Bayview Medical Center, Baltimore, USA

10.15 AM **Markers of inflammation and metabolic health in lifestyle interventions and multigenerational longevity**
Eline Slagboom, PhD
Professor of Molecular Epidemiology, Leiden University Medical Center, NL

10.45 AM COFFEE BREAK

11.15 AM **Painless NGF: a neuroprotective therapeutic candidate for Alzheimer's disease, targeting microglia**
Antonino Cattaneo, PhD
Professor of Physiology, Scuola Normale Superiore, Pisa, Italy
& EBRI Rita Levi-Montalcini, Rome, Italy

11.45 PM **Immune Ageing in Critical Illness**
Janet Lord, FMedSci
Professor of Cell Biology, Institute of Inflammation and Ageing, University of Birmingham, UK

12.15 PM **Multimorbidity and Inflammation in the older person**
Mario Barbagallo, MD, PhD
Professor of Internal Medicine and Geriatrics, University of Palermo, Italy

12.45 PM **Therapeutic approaches for age-related disease**
Toren Finkel, MD, PhD
Director, Aging Institute of UPMC, Pittsburgh, USA

1.15 PM SYMPOSIUM CLOSURE
Dario A. A. Vignali, PhD
Ri.MED Scientific Director

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19 May Thursday

Claudio Franceschi, MD, PhD
Professor of Immunology,
University of Bologna, Italy

At present: Editor-in-Chief of "Ageing Research Review" (IF 2021:10.895) and Professor Emeritus of Immunology University of Bologna, Italy. Authors of about 850 papers (82.407 citations, h-index: 135, Google Scholar, April 2022) - Keynote lecturer at Gordon Conferences, Keystone Symposia on Molecular Biology, Cold Spring Harbor Symposia, EMBO Courses, European and World Congresses on Aging. Major Research Achievements: I) discovery of important characteristics of immunosenescence in humans; II) proposal of the "inflammaging" theory of aging; III) pioneering studies on genetics, epigenetics, proteomics, metabolomics, metagenomics, glycomics of human aging and longevity (centenarians). Coordinator of European large collaborative projects: PROPAG-AGEING (Aging and Parkinson disease, 2015-2019; 6M€); ADAGE (Alzheimer disease; 2016-2019; 1.3M€); NU-AGE (Mediterranean Diet for the elderly, 2011-2016; 9M€); GEHA (GEnetics of Heathy Aging, 2004-2010; 7.2M€) and Partner/WP leader of several others EU projects. Awards: 2 laurea honoris causa (Universities of Cordoba, Argentina and Bordeaux, France) and 2 international prizes (Nencki Prize and Schober Price).

KEYNOTE SPEECH:

INFLAMMAGING AS THE MOST COMPREHENSIVE CONCEPTUAL FRAMEWORK FOR AGE-RELATED DISEASES

Human aging is characterized by a chronic, low-grade inflammation, a phenomenon that in 2000 I suggested to term "INFLAMMAGING1." Inflammaging is a highly significant risk factor for both morbidity and mortality in the elderly people, as most if not all age-related diseases (ARDs) and geriatric syndromes (GSs) share an inflammatory pathogenesis[2].

I will illustrate the last development of this inflammatory theory of aging ("GARBAGING") which suggests that the most important/causal inflammatory stimuli fueling inflammaging are to be identified in the lifelong, persistent exposure to endogenous [self and quasi-self (gut microbiota, GM)] "molecular garbage"[3].Such garbage is continuously/physiologically produced as a consequence of cell death (necroptosis; altered/misplaced molecules), metabolism[4] and GM function[5], but also continuously neutralized by the remodeling and adaptive capability of the body (degradation of inflammatory molecules/molecular fragments; production of anti-inflammatory molecules) which quickly and efficiently down-regulate inflammatory responses in young subjects[6] but fail to do so in older bodies. Self, non-self and quasi-self garbage/stimuli are sensed by and converge on a limited number of DAMAGE SENSORS (PRRs Pattern-Recognition Receptors, including TLRs cGAS-STING, NOD, DAI, RIG-I, AIM2, RAGE, AHR) which are highly "promiscuous", being characterized by a high degree of "DEGENERACY", and are activated to mount an innate inflammatory response. Accordingly, aging and INFLAMMAGING can be conceptualized as AN EVOLUTIONARY-UNPREDICTED BYPRODUCT OF THE DEGENERACY OF PRRs. Inflammaging is accelerated by persistent infections, lifestyle habits such as nutrient excess (overweight/obesity and metaflammation), low

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socio-economic status, emotional stressors and environmental pollutants[4].
The new perspective of GEROSCIENCE[7] suggests that aging is the most important risk factor for ARDs and GSs, and that aging and ARDs/GSs share the same basic molecular mechanisms, including inflammaging[2]. Accordingly, I will argue that:

- ARDs and GSs, including obesity and metabolic diseases can be conceptualized as manifestations of accelerated aging[8], and clinically different ARDs/GSs are the result of peculiar combinations of alterations regarding the same, limited set of basic mechanisms shared with the aging process. Whether an individual will follow a trajectory of accelerated or decelerated aging will depend on his/her genetic background interacting lifelong with environmental and lifestyle factors (nutrition, physical and mental activity)[4].
- According to this integrated view, aging and ARDs/GSs become part of A CONTINUUM[8] where precise boundaries do not exist, and the two extremes are represented by centenarians[9] and their offspring[10,11] who largely avoided or postponed most ARDs/GSs and are characterized by decelerated aging[11,] and patients who suffered one or more severe ARDs/GSs in their 60s, 70s, and 80s and show signs of accelerated aging, respectively.
- If ARDs and GSs are MANIFESTATIONS OF ACCELERATED AGING, it is urgent to identify markers capable of distinguishing between BIOLOGICAL AND CHRONOLOGICAL AGE in order to identify subjects at higher risk of developing ARDs and GSs. To this aim, I will propose the use of DNA methylation[12], N-glycans[13] profiling, GM composition[5] and circulating cell-free DNA[14] to complement the available disease-specific markers[4].

Within this scenario: 1. I will argue that human aging/inflammaging as well as human longevity, including their genetic[9,15-17] and metabolomics[18] basis, are highly context-dependent, dynamic processes/phenomena both historically and individually ("IMMUNOBIOGRAPHY"[19], "THYROID BIOGRAPHY"[20] liquid immune self"[21]), which necessitate a new integrated (nature/nurture) demographic[22], ecological and evolutionary perspective[9,15] to be fully appreciated and investigated;
I'll devote particular attention to: I) centenarians as calorie restricted-like persons[23] characterized by a peculiar/mild inflammaging[24]; II) GM-brain axis[5;] III) Mediterranean diet[25] and food timing[22], in turn related to the maintenance of circadian rhythms, including sleep; IV) inflammaging in between a digitalized/big data and a personalized, N-of-1 approach[26].

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Arne Akbar, PhD
Professor of Immunology
Experimental & Translational Medicine
Division of Medicine
University College London, UK

Akbar studies mechanisms that control the differentiation and senescence of human T lymphocytes. His research group consists of basic scientists and clinicians facilitating the translational aspects of his work. He was closely involved in the development of Basilizximab (Simulect), used for the prevention of acute solid organ graft rejection. He is currently the President of the British Society for Immunology (2018-2022).

1). Lanna A, et al (2017) A sestrin-dependent Erk-Jnk-p38 MAPK activation complex inhibits immunity during aging. Nat. Immunol. 18:354-363.
2). Vukmanovic-Stejic M et al (2018) Enhancement of cutaneous immunity during aging by blocking p38 mitogen-activated protein (MAP) kinase-induced inflammation. J. Allergy Clin Immunol 142: 844-856.3). 3). 3). 3). Pereira BI, et al (2020). Sestrins induce natural killer function in senescent-like CD8+ T cells. Nat. Immunol. 159(4):429-440. doi: 10.1111/imm.13173.

TARGETING INFLAMMAGING TO ENHANCE IMMUNITY IN HUMANS

Immunity declines with age that leads to re-activation of varicella zoster virus (VZV). In humans, age associated immune changes are usually measured in blood leukocytes however this may not reflect alterations in tissue-specific immunity. We used a VZV antigen challenge system in the skin to investigate changes in tissue specific mechanisms involved in the decreased response to this virus during ageing. We assessed cutaneous immunity by the extent of erythema and induration after intradermal VZV antigen injection. We also performed immune histology and transcriptomic analyses on skin biopsies taken from the site of challenge in young (<40 yrs) and old (>65 yrs) subjects. Old humans exhibited decreased erythema and induration, CD4+ and CD8+ T cell infiltration and attenuated global gene activation at the site of cutaneous VZV antigen challenge compared to young subjects. This was associated with elevated sterile inflammation in the skin in the same subjects, related to p38 MAPK-related pro-inflammatory cytokine production ($p < 0.0007$). We inhibited systemic inflammation in old subjects by pre-treatment with an oral small molecule p38 MAP kinase inhibitor (Losmapimod), which reduced both serum C reactive protein (CRP) and peripheral blood monocyte secretion of IL-6 and TNF-α.
In contrast, cutaneous responses to VZV antigen challenge was significantly increased in the same individuals ($p < 0.0006$). Therefore, excessive inflammation in the skin early after antigen challenge retards antigen-specific immunity. However this can be reversed by inhibition of inflammatory cytokine production that may be utilized to promote vaccine efficacy and the treatment of infections and malignancy during ageing. I will discuss some of the mechanisms involved in my talk.

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Chiara Cipollina, PhD
Group Leader in Experimental Lung Research, Fondazione Ri.MED, Palermo, Italy

Chiara Cipollina obtained her PhD in Industrial Biotechnology at the University of Milano-Bicocca in 2006. As Ri.MED Fellow at the University of Pittsburgh, she contributed to the discovery of novel mediators of inflammation resolution.
She has been working in Palermo since 2010. She studies chronic inflammation and lung disease, with a focus on cigarette smoke-associated diseases and innate immunity. Her work is unveiling a key role for inflammasome-independent activation of caspases, gasdermin cleavage and pro-inflammatory cell death in the pathogenesis of CS-associated lung diseases.

Alessandro Bertani, MD, PhD
Clinical Assistant Professor of Surgery, University of Pittsburgh
Chief, Division of Thoracic Surgery and Lung Transplantation, IRCCS ISMETT, Palermo, Italy

Dr. Bertani is the Chief of Thoracic Surgery and Lung Transplantation at IRCCS ISMETT since 2011 and a Clinical Assistant Professor of Surgery at the University of Pittsburgh. His clinical activity is focused on lung transplantation, thoracic oncology, and minimally invasive surgery.
Dr Bertani leads research projects on lung cancer, minimally invasive surgery, organ preservation and lung transplantation. He directs and participates to many surgical technical education initiatives in minimally invasive surgery. He directs the ISMETT large animal preclinical research facility in Palermo.

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INNATE IMMUNE RESPONSES IN AGE-RELATED LUNG DISEASES

Chiara Cipollina, PhD **Alessandro Bertani**, MD, PhD

Chronic obstructive pulmonary disease (COPD) is a heterogeneous chronic inflammatory lung disease that manifests clinically later in life. COPD can lead to end-stage respiratory failure and is the third leading cause of death worldwide according to WHO. There is no definitive treatment for COPD and in selected cases lung transplantation can be the only viable cure. COPD is characterized by an accelerated aging of the lung, with cigarette smoking being the greatest environmental risk factor. Cigarette smoking favors age-related alterations of innate immune responses contributing to a higher risk of infection and chronic inflammation. Alveolar macrophages (AM) are the most abundant cells in the alveolar space and are the first line of defense against inhaled particulate and pathogens. A better understanding of the molecular alterations induced by cigarette smoke (CS) in lung macrophages may unveil novel pathways involved in CS-associated lung diseases. It is known that exposure to CS impairs acute inflammatory response of macrophages to bacterial lipopolysaccharide (LPS) by inhibiting the NF-κB-dependent transcriptional responses.

We have recently reported inflammasome-independent activation of caspase-1, -4 and -8 and increased gasdermin D (GSDMD) cleavage both in CS-exposed human primary macrophages as well as in AM from smokers compared to non-smoker controls. Our data suggest that caspases play a key role in the pathogenesis of CS-associated chronic lung diseases. We are currently testing whether CS may relieve the anti-apoptotic breaks that normally operate under homeostatic conditions and enhance pro-inflammatory cell death in LPS-treated macrophages. The consequent release of damage-associated molecular patterns (DAMPs) could promote a chronic inflammatory state that escapes the resolution.

Overall, in the context of infection, CS may promote pro-inflammatory cell death of AM, thus impairing defense mechanisms and sustaining chronic inflammation. This may contribute to the pathogenesis of CS-associated lung disease therefore unveiling novel potential therapeutic approaches.

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Roberto Di Gesù, PhD
Principal Investigator in Musculoskeletal tissue engineering, Fondazione Ri.MED, Palermo, Italy

After my PhD, I was awarded a postdoctoral fellowship at the National Research Council (CNR) in Catania, during which I developed a device loaded with an anti-inflammatory drug to treat maculopathies as an alternative approach to intravitreal injections. This work received the attention from Merck KGaA, which offered me to be part of their research team at the New Biological Entities (NBEs) department in Rome, as an associate scientist. At Merck, I was called to coordinate a research team of immuno-oncology to contribute to the development of Avelumab, an anti-cancer monoclonal antibody working on the PD-1/PD-L1 interaction. During my second year at Merck, Avelumab received FDA approval and was commercialized in the US in partnership with Pfizer as BAVENCIO. Today, BAVENCIO is the first and only immunotherapy approved in the first-line maintenance setting for patients with locally advanced or metastatic urothelial carcinoma. After a period as researcher at the Alma Mater Studiorum University of Bologna, which is one of the top ranked University in Europe, I finally approached at the Ri.MED Foundation. Through Ri.MED and its partners worldwide, I was able to work as visiting researcher at the University of Pittsburgh and at the Children's Hospital of Philadelphia, two top research institutions in the US. I had the privilege to work under the supervision of Prof. Rocky Tuan, one of the most influential scientists in the field of biomaterials applied to tissue engineering and regeneration. Currently I am principal investigator at Ri.MED foundation, where I lead the musculo-skeletal tissue engineering laboratory.

NEW FRONTIERS IN OSTEOARTHRITIS AS AN INFLAMMATORY AGE-RELATED DISEASE

The etiology of Osteoarthritis (OA) is historically controversial as it has been linked to different factors deriving from pathological condition of genetic, biochemical, or metabolic origin. However, in the last decade the role of inflammatory process in the onset of Osteoarthritis has gained a growing interest among scientific community. Remarkably, a tight correlation between inflammation and ageing has been discovered, becoming the topic of a large number of studies.

In this context, we focused our research to investigate the correlation between Osteoarthritis and a frequent inflammatory condition affecting bowel known as Leaky Gut (LG). This latter, is an age-related disorder that causes a reduction of the permeability of the membrane in the gut-lumen, as well as a modification of the composition of the gut-resident microbiota (dysbiosis). Such modifications lead to a systemic multi-organ spread-out of pro-inflammatory molecules (e.g. Lipopolysaccharide - LPS) usually confined within the gut. Specifically, the migration into joints causes a local inflammatory response that leads to severe tissue degradation and end-stage damages (gut-to-joint axis). In this context, we used an innovative approach to develop an ex vivo OA model mimicking the gut-to-joint axis starting from healthy native porcine tissues. Additionally, we set-up an innovative platform able to apply cyclic mechanical stimulation regimens over viable tissue. Such set-up allows to thoroughly study the pro-regenerative effects of mechanical loads over cartilage at tissue and cellular level. Overall, our model represents an evolution of conventional in vitro models to test innovative pharmacological therapies on viable tissues. In addition, our mechanical-stimulation platform may open the way to the development of highly-effective regenerative rehabilitation protocols.

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Jeremy David Walston, M.D.
Professor of Geriatric Medicine & Gerontology, Johns Hopkins Bayview Medical Center, Baltimore, USA

Jeremy D. Walston, MD, is the Raymond and Anna Lublin Professor of Geriatric Medicine at Johns Hopkins University and the Principal Investigator of the Johns Hopkins Older Americans Independence Center (OAIC), which focuses on understanding the biology that drives physical frailty, its prevention, and its treatment. His laboratory and clinical translational research group focuses on inflammation, stress response systems, mitochondrial biology and energy metabolism, as well as on the development of novel diagnostic, preventive and treatment strategies that improve health and quality of life for older adults. Dr. Walston has authored more than 350 peer-reviewed publications, including publications in the New England Journal of Medicine, and the Proceedings of the National Academy of Science, and is the American Editor of the Oxford Textbook of Geriatric Medicine. He also maintains a clinical practice in Geriatric Medicine and leads a post-doctoral fellowship program focused on translational aging research.

KEYNOTE SPEECH:

CHRONIC INFLAMMATION IN OLDER ADULTS: CLINICALLY RELEVANT PATHWAYS AND THEIR MEASUREMENT

The chronic activation of the immune system is commonly observed in older adults, and is highly associated with multiple chronic disease states and Geriatric syndromes including physical frailty, sarcopenia and mild cognitive impairment. Chronic inflammation is multifactorial, and the individual inflammatory mediators that drive the development and propagation of disease states impact normal tissue homeostasis as well as stem cell vitality. This session will discuss age-related etiologies of chronic inflammation and specific inflammatory mediators and their measurement, including Tumor Necrosis Factor (TNF) alpha and its receptors. Inflammation-driven molecular pathways that most impact relevant chronic disease states such as the tryptophan degradation pathway, and its relationship to pathophysiological changes, will also be considered. Finally, discussion of potential treatment modalities, including several emerging from Geroscience research, will be described as will their impact on chronic disease states.

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20 May Friday

Eline Slagboom, PhD
Professor of Molecular Epidemiology, Leiden University Medical Center, NL
Max Planck Institute for Biology of Ageing (Cologne, Germany)

Professor P. Eline Slagboom, biologist by training, obtained her PhD at the Leiden University (NL) on genome instability and ageing. She was appointed in 2000 as professor of Molecular Epidemiology at the Leiden University Medical Center (LUMC). She is head of the section of Molecular Epidemiology within the Department of Biomedical Sciences, chair of the DUSRA – Dutch Society for Research on Ageing, PI of the Leiden Longevity Study (LLS) and Fellow at the Max Planck Institute for Biology of Ageing in Cologne. Her research focuses on biomarkers and mechanisms of metabolic health, biological age and longevity in a.o. the LLS and lifestyle intervention studies in older individuals (s.a. Growing Old Together study , GOTO) by genetic and multi-omics analyses. Slagboom was coordinator of IDEAL, a large scale FP7-EU project (Integrated research on DEvelopmental determinants of Aging and Longevity). She is PI of VOILA (Vitality Oriented Innovations for the Lifecourse of the Ageing Society), the largest public-private collaboration on ageing in The Netherlands and she leads national studies in BBMR-metabolomics (over 30 cohorts).

www.molepi.nl , www.nvvvo.nl.

OMICS BIOMARKERS INDICATING AT RISK ELDERLY AND THEIR RESPONSE TO LIFESTYLE INTERVENTIONS

When we study phenotypes of biological ageing, we often explore physiological parameters mortality, multimorbidity or longevity as endpoints. Biological age predictors have been generated in the past based on physiological read outs and clinical variables and the last 10 years many studies have added molecular data to this field. I will discuss especially the study of metabolomics as biomarkers indicating (multi)morbidity and mortality in population based studies. Scores generated from metabolomics data indicate vulnerability of patients in geriatric clinical studies and metabolomics data can be used as monitoring markers in lifestyle intervention studies in older individuals. Further exploration of the response of intervention studies is performed by transcriptome analysis of blood, fat and muscle. The impact of the inflammatory component in these biomarker profiles is discussed.

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20 May Friday

Antonino Cattaneo, PhD
Professor of Physiology, Scuola Normale Superiore, Pisa, Italy
& EBRI Rita Levi-Montalcini, Rome, Italy

After obtaining a degree in biophysics, Antonino Cattaneo worked as a PhD student at the Scuola Normale Superiore (Pisa) with Lamberto Maffei and as a postdoc and staff scientist with Nobel Laureate Rita Levi-Montalcini at the CNR Institute of Neurobiology in Rome. He later worked with Nobel Laureate Cesar Milstein at the MRC Laboratory of Molecular Biology (Cambridge, UK). From 1991 to 2008, he was Full Professor of Biophysics at the International School for Advanced Studies (SISSA) in Trieste (Italy), where he also served as Head of the Biophysics Department from 1991 to 1995 and the Deputy Director of SISSA from 1996 to 2001. Since 2008 he is Professor of Physiology at the Scuola Normale Superiore (Pisa), where he is also the Director of the Biology Lab BioSnS. Antonino Cattaneo is author of more than 200 publications in peer-reviewed international scientific journals and is recipient of several awards including Domenico Marotta Prize (Accademia Nazionale delle Scienze detta XL), the W. Jansenius Medal (Slovak Academy of Sciences) and the "G. Tartufari" International Prize for Biology (Accademia Nazionale dei Lincei). He is a member of EMBO (European Molecular Biology Organization) and member of the Accademia Nazionale delle Scienze detta XL, the Accademia Nazionale dei Lincei and the Academia Europaea. Since 2018 he is President of the European Brain Research Institute 'Rita Levi-Montalcini'.

A NEUROPROTECTIVE THERAPEUTIC CANDIDATE FOR ALZHEIMER'S DISEASE, TARGETING MICROGLIA

The neurotrophin Nerve Growth Factor holds a great potential as a neuroprotective treatment for Alzheimer's disease for its dual actions i) as a neurotrophic factor for cholinergic neurons and ii) for its recently discovered broad neuroprotective actions mediated by microglia. Thus, via its actions on microglia, NGF exerts a broad and effective neuroprotection also on neuronal populations that are not its direct target and deserves to be renamed a neurokine. However, the therapeutic applications of NGF have been limited by its well known pro-nociceptive activity. These pain-inducing properties of NGF have caused the interruption of clinical trials in man. To overcome this problem, we have designed and characterized human painless NGF (hNGFp), a mutant form of NGF inspired by a rare painlessness genetic disorder, Hereditary Sensory Autonomic Neuropathy type V (HSAN V). hNGFp has an equal neurotrophic potency as wild type human NGF (hNGF), but shows a much higher threshold for different forms of pain sensitization, providing a well-defined therapeutic window. In three AD mouse models, the intranasal administration of painless NGF (hNGFp) rescues the Alzheimer-like neurodegenerative phenotype, with a mechanism mediated by microglia, via an identified chemokine/cytokine signalling pathway. In 5xFAD mice, we showed that the broad biodistribution in the brain, obtained by nasally delivered hNGFp, is necessary to obtain the rescue of the neurodegeneration, while its local delivery directly to the basal forebrain cholinergic nuclei is ineffective. hNGFp is also strongly neuroprotective in several other lesion or degeneration models, including optic neuropathy models.
In this presentation I will review the potent neuroprotective properties of hNGFp that support its clinical testing in man and will describe the development status of this novel potent neuroprotective molecule.

Janet Lord, FMedSci
Professor of Cell Biology, Institute of Inflammation and Ageing, University of Birmingham, UK

Janet Lord is Professor of Immune Cell Biology and director of the MRC-Versus Arthritis Centre for Musculoskeletal Ageing Research. Her primary research focus is in the effect of ageing upon immune function and how this limits the ability of older adults to resolve inflammation and predisposes them to chronic inflammatory disease such as Rheumatoid arthritis. She also researches the link between chronic systemic inflammation and physical frailty, notably sarcopenia, in old age and chronic diseases including chronic liver disease and COPD. She has expertise in identifying primary drivers of disease and taking this through to interventions and clinical trials. One example is her work on compromised neutrophil function in old age which she established was due to overactive PI3kinase delta. This led to a trial inhibiting this pathway with simvastatin to correct this defect in a clinical trial which reduced pneumonia related deaths by 40%. In 2013 she was awarded the Lord Cohen of Birkenhead medal for her outstanding research in human ageing by the British Society for Research in to Ageing. She was elected a Fellow of the Academy of Medical Sciences in 2015.

IMMUNE AGEING IN CRITICAL ILLNESS

Sepsis is a leading cause of death in critically ill patients, with recent estimates from the US and Europe of 30-day mortality at 34.7% on average. It is a complex, multisystem disease resulting from a dysregulated and exuberant inflammatory immune response to infection that leads to immuneparesis and widespread inflammation mediated organ damage and multi-organ failure (MOF). Heightened inflammation and organ damage was also a feature of severe COVID-19 with many patients entering intensive care. Advanced age is a major risk factor for poor outcomes in critical illness including COVID-19 and our research has investigated whether immune ageing and overall biological ageing (determined by DNA methylation) are associated with sepsis and mortality in critically ill patients. This presentation will describe data from recent studies of critically ill patients with COVID-19 as well as non-COVID-19 illness and show that both immunesenescence and accelerated DNA methylation age are seen in critical illness and associated with disease severity and outcomes such as sepsis and death.

INFLAMMATION AND AGING

Mechanisms, mediators and therapeutic interventions

14th Ri.MED SCIENTIFIC SYMPOSIUM

19-20 MAY 2022

SALA DEI BARONI,
PALAZZO CHIARAMONTE STERI,
PIAZZA MARINA 61 - PALERMO - ITALY

20 May Friday

Mario Barbagallo, MD, PhD
Professor of Internal Medicine and Geriatrics, University of Palermo, Italy

Prof. Mario Barbagallo, MD, PhD, is Professor of Internal Medicine and Geriatrics; Director of the Department of Medicine and of the Internal Medicine and Geriatric Units, University Hospital of Palermo; Director Post-graduate program in Geriatrics; President of IAGG-ER (International association of Geriatrics-European Region) for the years 2019-2024.
Member of the Superior Council of the Italian Minister of Health. He is included in the list of the Top Italian Scientists (www.topitalianscientists.org). He worked in Parma and Rome where he obtained the PhD in 1989. From 1989 to 1992, worked at the Cornell University Medical Center, NY, NY, USA, and from 1993 to 1995 as a Fulbright Scholar and Visiting Professor at Wayne State University, Detroit, MI, USA.
He is an expert of problems related to the prevention and treatment of diseases associated with aging. Member of numerous national and international scientific societies and appreciated speaker in Italy and abroad. Author of about 500 publications in national and international scientific journals.

MULTIMORBIDITY AND INFLAMMATION IN THE OLDER PERSON

Increasing research has reported that low-grade inflammation could be considered as one of the most important factors for non-communicable chronic diseases in older people, from sarcopenia to dementia. However, previous research has reported the association between inflammation and single disease, whilst the prevalence of multimorbidity (i.e., the presence of two or more medical conditions) and inflammation is poorly investigated. On the contrary, it is widely known that multimorbidity is probably more important than single conditions in geriatric medicine since in older people disability and frailty often depend on a cascade of conditions.
It is known that multimorbidity is a robust predictor of disability in older people, but the mechanisms by which multimorbidity could increase the risk of disability and then mortality are still not entirely clear. Inflammation seems to be important as potential risk factor for multimorbidity, but also as mediator in the transition from multimorbidity to frailty and disability and other negative outcomes. In this regard, both bio-humoral and cellular response of immune system seem to be relevant. Higher levels of serum cytokines (such as IL-6, C reactive protein, TNFa) are associated not only with a higher risk of multimorbidity, but also of disability/frailty in older people already affected by multimorbidity. Moreover, the role of immune system cells (e.g., lymphocytes and neutrophils) is increasing in importance in a phenomenon commonly called immunosenescence that further contribute to multimorbidity and its consequences.
All these pathways are not only important from a research point of view, but also from a clinical one since they could represent possible targets for future pharmacological and non-pharmacological interventions.

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20 May Friday

Toren Finkel MD/PhD
Director, Aging Institute
University of Pittsburgh/UPMC

Toren Finkel received his undergraduate degree in Physics and his MD and PhD degree from Harvard Medical School. Following a residency in Internal Medicine at the Massachusetts General Hospital, he completed a fellowship in Cardiology at Johns Hopkins Medical School. In 1992, after completing his clinical training, he came to the NIH as an Investigator within the Intramural Research Program of the National Heart, Lung and Blood Institute (NHLBI). Over the next 25 years at the NIH, he held various positions including Chief of the Cardiology Branch and Chief of the Center for Molecular Medicine within the NHLBI. He is a member of the American Society for Clinical Investigation (ASCI) and the Association of American Physicians (AAP). He has also been inducted as a Fellow of the American Association for the Advancement of Science (AAAS) and is an elected member of the National Academy of Medicine. He serves on numerous editorial boards including currently serving on the Board of Reviewing Editors for Science. As of Sept 1st 2017, Dr. Finkel assumed the role of the Director of the Aging Institute, and the G. Nicholas Beckwith III and Dorothy B. Beckwith Endowed Chair of Translational Medicine at the University of Pittsburgh/UPMC.

THERAPEUTIC APPROACHES FOR AGE-RELATED DISEASE

I will discuss therapeutic approaches for treating aging. In particular, I will discuss the design of a clinical trial we intend to launch shortly that we are calling the RIGHT Trial. Along with my colleagues, Drs. Anne Neuman and Dan Forman, we will be attempting to understand the potential utility of lowering IL-6 levels in elderly patients with evidence of 'inflammaging'. In this trial, patients will be randomized to placebo or anti-IL-6 therapy using a targeted biological agent. A number of age-specific endpoint will be assessed including physical and cognitive function.
I will also discuss our internal development of novel small molecules that target specific hallmarks of aging and how we might use these agents for treating age-related diseases. This work, performed in collaboration with my Aging Institute colleagues Bill Chen and Yuan Liu, includes work targeting the transcription factor TFEB which plays a major role in autophagy and lysosomal function.

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