Editorial

Disease Control and Active and Healthy Ageing: New Paradigms of Therapeutic Strategy

Worldwide, the percentage of people aged over 60 years is growing up quicker than any other age group, as a result of both longer life expectancy and declining birth rates as well as a success of the public health policies and the socioeconomic development. The World Health Organization (WHO) has been pointed out recently that: "*currently, one in every nine people in the world is 60 years of age or older. This is expected to increase to one in five people by 2050*". This success (the transition to a much older population) is a challenge for the modern society that shall maximize the health and the functional ability of older people as well as their social participation and safety to achieve an "*active ageing*". "Health" refers to physical, mental and social well being as expressed in the WHO definition of health: "*maintaining autonomy and independence for the older people is a key goal in the policy framework for active ageing*". "Active" refers to "*continuing participation in social, economic, cultural, spiritual and civic affairs, not just the ability to be physically active or to participate in the labour force*". In this issue Alzetta *et al.* (University of Genoa, Italy) reviews the grounds and patterns of the structuring of longevity and ageing in our society [1].

The older people, even in poor countries, die of non-communicable diseases (NCDs), such as heart disease, cancer or diabetes, rather than of infectious or parasitic diseases. On 2010, the UN General Assembly passed the resolution A/RES/64/265NCD recognizing "*the enormous human suffering, premature death and the seriously negative socioeconomic impact caused by the growing burden of NCD*" and called for "*global and national action at the highest level to address this development issue*". In this special issue Bousquet *et al*. (Inserm, France) review the complexity of NCDs intertwined with ageing, show an overview of the problem and propose practical examples of System Medicine (SM) applied to NCDs [2]. Moreover, Cesario *et al*. (IRCCS "San Raffaele Pisana", Italy) review the novel system approaches to NCDs, discuss the passage from System Biology (SM) to SM and present the scientific and clinical background of a SM platform [3].

In this issue different pathologies, clinical conditions and pharmacological approaches are reviewed considering the role of ageing. Mazzucco *et al.* (Catholic University, Italy) review breast cancer in various age-groups and the response to Trastuzumab, a monoclonal antibody that interferes with the HER2/neu receptor [4]. Piotrowicz *et al.* (Jagiellonian University, Poland) review the pharmacological management of hypertension [5], Matera *et al*. (Second University of Naples) propose new treatment for chronic obstructive pulmonary disease (COPD) [6], and Zanandrea *et al.* (University of Toulose, France) review the treatment of sarcopenia [7].

As the population ages, the burden of neurodegenerative disorders, including Alzheimer disease (AD), will increase creating an unsustainable healthcare challenge due to a lack of effective treatment. In this issue Hasnain and Vieweg (Memorial University of Newfoundland, Canada) overview the vascular risk factors in AD and vascular dementia [8].

AD is characterized by disturbance of various high pre- and cortical functions. Cholinergic projections innervate the prefrontal cortex and reduced cholinergic function is associated with cognitive deficits. Cholinergic neurons are specific neurons that synthesize and release acetylcholine (ACh). ACh acts at nicotinic receptors (nAChR) and muscarinic receptors (mAChR). U.S. Food and Drug Administration (FDA) and The European Medicines Agency (EMA) approved several prescription drugs to treat people who have been diagnosed with AD. The drugs include: Razadyne® (galantamine), Exelon® (rivastigmine), and Aricept® (donepezil). These drugs target acetylcholinesterase (defined acetylcholinesterase inhibitors: AChEI) and, in principle, elevate cholinergic signaling. Another drug is known as Namenda® (Memantine), an N-methyl D-aspartate (NMDA) antagonist. None of these medications stops the disease itself: they help to maintain thinking, memory, and speaking skills but don't influence the disease' progression. Unfortunately these drugs are effective only for some patients, and may help only for a limited period of time. In this issue different authors describe new pharmacological approaches to neurodegenerative diseases beyond AChEI. Russo *et al.* (IRCCS "San Raffaele Pisana", Italy) in this issue describe the neurobiology of the α7-nAChR, its role in cognition and in AD, and the clinical *status* of the most promising molecules for the treatment of cognitive dysfunction in AD [9].

MicroRNA (miRNA), single-stranded RNA molecules consisting of 21-23 nucleotides, are post-transcriptional regulators of gene expression. Impaired miRNA levels are considered causally involved in many diseases, including neurodegenerative and psychiatric disorders. In this issue Greenberg and Soreq (Hebrew University, Israel) outline the current "state of the art" regarding miRNA regulation in neuropathology and explore the possibilities of the development of miRNA as therapeutics for neurodegenerative diseases [10].

Many neurodegenerative diseases may be referred as misfolding diseases Cardinale *et al.* (IRCCS "San Raffaele Pisana", Italy) review the ability of intrabodies to recognize misfolding and discuss the use of intrabodies against neurodegenerative disorders [11].

Chronic pain is a widespread problem affecting elder people, in this issue Taylor *et al.* (NEMA Research, USA) review the association between pain and obesity [12] and Del Bufalo *et al.* (IRCCS "San Raffaele Pisana", Italy) review the background, findings, implications and problems in using compounds that act on α9α10-nAChR as potential target in the pathophysiology of chronic pain [13].

As well-known, ageing is a complex process resulting by the interaction between genetic, environmental/behavioral (such as smoking, diet, use of medication, occupational diseases), epigenetic (alterations in DNA methylation patterns, posttranslational modification of histones, and chromatin remodeling), and purely stochastic factors. The time-dependent accumulation of cellular damage is widely considered to be the general cause of ageing. Nine candidate hallmarks, that contribute to the ageing process and collectively determine the ageing phenotype, has been described recently. The conceptualizations of the hallmarks of ageing, as for the conceptualizations of the hallmarks of cancer, may offer an organizing principle to effort and rationalize the complexities of ageing (phenotypes and genotypes). In this issue Jylhava (University of Tampere, Finland) reviews the genetic component of human longevity and its phenotypic effectors and discuss several rejuvenation strategies [13]. Capuron *et al.* (University Victor Segalen, France) review the role of immune system and inflammation in ageing [14].

"Frailty" is considered "a practical, unifying notion in the care of elderly patients that directs attention away from organ-specific diagnoses towards a more holistic viewpoint of the patient and their predicament". Due to the increasing probability to develop chronic diseases with age, elderly are the main user group of drugs. Moreover, multiple co-occurring medical conditions enhance the complexity generating important therapeutic needs that in turn require drug optimal characterization (i.e. safety and efficacy) as well as appropriately prescription and use and compliance monitoring [discussed in references 2-6]. The term "geriatric drug therapy" explains well the whole value chain from the product development to utilization of the product by the patient itself. Interdisciplinary studies and integrated assessments are needed to deep understand the manifold sources of patient complexity and their interactions, and how provision of healthcare should be harmonized with complexity to optimize health [discussed in 2-3]. Better health promotion and disease prevention interventions will make a significant contribution to the sustainability of health and care systems.

'Omics' research (including genomics, epi-genomics, metagenomics, metabolomics and proteomics) allows the resolution of cell biological processes to "*an exceptional high definition*" that poses the challenge to determine "when" and "how" the "omics" information may be applied (public/private sectors) to develop personalized/stratified approach in health promotion, diseases prevention and diseases cure. Systems (bio, pharmacology) medicine approaches have the potential to tackle this complexity trough an integration of a variety of medical research and computational modeling. Passing from reductionism to a system-oriented perspective, medical research will take advantage of these high-throughput technologies unveiling their full potential [reviewed in 2-3].

An ageing population will have a strong upward impact on public spending for long term care. This is because frailty and disability rise sharply at older ages, especially amongst the very old (aged 80+) which will be the fastest growing segment of the population in the coming decades. According to the " Ageing Working Group (AWG) reference scenario" based on current policy settings, public spending on long-term care is projected to double, increasing from 1.2% of GDP (gross domestic product) in 2007 to 2.3% of GDP in 2060 in the EU as a whole. In the conclusions of this issue Cesario *et al.* (IRCCS "San Raffaele Pisana", Italy) in collaboration with Auffray (European Institute for Systems Biology and Systems Medicine, France) and Hood (Institute for System s Biology, USA) discuss the importance of an effective development of Predictive, Preventive, Personalized and Participatory (P4) SM that requires harmonization of experimental and computational methods for data, information and knowledge collection, storage and sharing and suggest a new organization of the health care system [15].

In the end the major key question is: will be the life expectancy increase associated with a parallel delay of functional limitations and disability or will be associated with more years but with poor health conditions? In the myth Tithonus, immortal but without eternal youth, lived forever *" But when loathsome old age pressed full upon him, and he could not move nor lift his limbs, this seemed to her in her heart the best counsel: she laid him in a room and put to the shining doors. There he babbles endlessly, and no more has strength at all, such as once he had in his supple limbs.*" [Homeric Hymn to Aphrodite (218-38)].

In this special issue a multidisciplinary team of international experts discusses all the determinants of ageing diseases in order to understand their etiologic significance, and to develop therapeutic strategies for intervention studies. We would like to thank the contributors to this special issue for their participation. We would also like to thank A. Van Rijn for critical revision and A. Del Bufalo and the IRCCS "San Raffaele Pisana" (Rome) that provided us all the editorial assistance in writing this special issue.

We believe that: "*Ita enim senectus honesta est, si se ipsa defendit, si ius suum retinet, si nemini emancipata est, si usque ad ultimum spiritum dominatur in suos*" [Catone, De Senectude XI, 38]. "For old age is honoured only on condition that it defends itself, maintains its rights, is subservient to no one, and to the last breathe rules over its own domain."

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