Biological research into aging: from cells to clinic

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The Research Centre on Aging is proud of the success of the first International Symposium on “The Challenge of Biological Research on Aging in the 21st century: from Cells to Clinic” organized by the Research Centre on Aging, with its partners the RQRV, the Université de Sherbrooke and the CSSS-IUGS. This symposium took place in Orford, Québec, Canada in November 2014. A large audience at the conference included students, professors, researchers and health care professionals who heard presentations on major challenges in aging research from local and internationally renowned scientists/clinicians.

More precisely, the symposium shed light on broad topics related to the biology of aging. The session topics included (1) systems biology of aging, (2) immunosenescence, infections and vaccines, (3) integrative biology and longitudinal studies, (4) cellular senescence and cancer, (5) genetics and epigenetics in aging, and (6) cell biology and engineering. Speakers transmitted their professional outlook on the current and future stakes in the field of aging, and discussed their latest projects with those in attendance. These topics fitted perfectly with the mission of the Research Center on Aging, which is to develop knowledge on

aging in order to promote the autonomy and development of seniors.

Nineteen papers, from the symposium, were submitted to this Special Issue and subjected to anonymous peer and revision before acceptance. In this Editorial, I summarize the main messages of each of these papers.

In the first paper, on systems biology, by Yashin et al. (Duke University, Durham, NC, USA) (Yashin et al. 2016) it is stressed that increasing proportions of elderly individuals in developed countries combined with the substantial increases in related medical expenditures make the improvement of their health a high priority today. If the process of individual aging is a major cause of age-related health deterioration, then postponing aging would be an efficient strategy for improving the health of the elderly. Implementing this strategy requires a better understanding of genetic and non-genetic connections between aging, health and longevity. The authors review the progress in research areas the development of which may contribute to a better understanding the dynamic connections among aging, health and longevity. These areas include studying the role of genetic factors in human aging and longevity, evaluating the effects of hidden heterogeneity of populations on estimates of morbidity and mortality risks, studying external and internal forces that shape the age patterns of human mortality, as well as forces responsible for secular trends in mortality decline, and development and implementing

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integrative mortality modeling using longitudinal data. The authors emphasize the need for, and demonstrated the possibility of, integration of knowledge accumulated in these areas within one conceptual framework that would allow for efficient analyses of available data about aging, health, and longevity from a systems biology perspective.

The paper by Ukraintseva et al. (also Duke University) (2016) on the role of genetic risk factors in human longevity, shows that many such risk factors for complex diseases may also act as pro-longevity variants, concluding that there is probably no such thing as unconditionally ‘bad’ or ‘good’ common genetic polymorphisms in this regard. They also stress the importance of considering the trade-off and conditional effects of genes in both aging research and personalized prevention. A complex systems biology approach to these factors is essential.

The final paper on this theme is from Mitteldorf (Department of EAPS, MIT, Philadelphia, USA) (2016) on epigenetic “clock” control of aging, stating that if we permit ourselves a shift of reference framework and regard aging as a programmed biological function like growth and development, then these observations fall into place and make sense. This perspective suggests that aging proceeds under control of a master clock, or several redundant clocks. If this is so, we may learn to reset the clocks with biochemical interventions and make an old body behave like a young body, including repair of many of the modes of damage that we are accustomed to regard as independent symptoms of the senescent phenotype, and for which we have assumed that the body has no remedy. We have seen that a few powerful transcription factors are capable of reprogramming the epigenetic state of chromatin, and this suggests a promising path for aging research. If only because the prize is potentially so large, this possibility is a worthy focus for intensive research in the near future.

Moving to the 2nd section, immunosenescence, Goldeck et al. (University of Tübingen, Tübingen, Germany) (2016) studied subjects from the Berlin BASE-II cohort, assessing hand-grip strength (strongly correlated with measures of muscle mass and possibly frailty, morbidity and mortality) for relationships with Cytomegalovirus (CMV) infection and immune parameters. Goldeck et al. tested the hypothesis that hand-grip strength would be associated with leukocyte telomere length, serum levels of

inflammatory and anti-inflammatory mediators (which may be influenced by CMV) and other immune parameters. They found that although IL-1 β levels tended to be negatively associated with grip strength, there was no association with IL-6 levels, leukocyte telomere length or CMV-seropositivity in men or women at any age. Hand-grip strength remains an important biomarker independent of CMV infection or shorter telomere lengths, and is poorly reflected in peripheral pro-inflammatory cytokine levels, all of which have been associated in some studies with frailty and mortality.

Weinberger et al. (Institute for Biomedical Aging Research, University Innsbruck, Innsbruck, Austria) (2016) consider the stimulatory effect of the TLR-4-mediated adjuvant glucopyranosyl lipid A in old age from the practical point of vaccine improvement. Various adjuvant candidates targeting toll-like receptors (TLRs) including the synthetic TLR4 agonist glucopyranosyl lipid A (GLA) are under development in order to improve immunogenicity of current and novel vaccines. Treatment with GLA efficiently increases the expression of co-stimulatory molecules on human monocyte-derived dendritic cells as well as on ex vivo dendritic cells. Production of pro-inflammatory cytokines (IL-6, TNF-alpha, IL-12) as well as of the anti-inflammatory cytokine IL-10 is induced in monocyte-derived dendritic cells. In PBMC cultures, dendritic cells and to an even greater extent monocytes produce TNF-alpha and IL-6 after stimulation with GLA. The stimulatory capacity of GLA is similar in young (<35 years) and older (>60 years) adults. Consequently, it is concluded that TLR4 agonists like GLA are particularly promising candidates as adjuvants of vaccines designed for elderly individuals.

Frasca et al. (University of Miami Miller School of Medicine, Miami, FL, USA) (Frasca and Blomberg 2016) summarize current knowledge on pathways contributing to inflammaging, such as single nucleotide polymorphisms in the promoter of pro-inflammatory cytokines leading to higher release of these cytokines and higher levels of systemic inflammation; chronic stimulation of cells of the immune system with infectious (e.g. CMV) or non-infectious (DNA or proteins modified by oxidation, acylation, glycosylation) agents leading to cell exhaustion; cellular senescence and acquisition of the senescence-associated secretory phenotype by immune cells; cellular products released into the extracellular space

(mitochondrial DNA) which can function as a damage-associated molecular pattern agent causing inflammation; microbial translocation from the gut which allows pro-inflammatory bacterial products to be released into the blood, thus contributing to chronic inflammation. All these down-regulate the function of cells of the immune system in both humans and mice.

The next paper on a complementary topic is by Fulop et al. (Université de Sherbrooke, Sherbrooke, Qc, Canada) (2016) on inflammaging, immune-paralysis and immune-adaptation. Aging is accompanied by many physiological changes including those in the immune system. These changes are designated “immunosenescence”, indicating that age induces a decrease in immune functions. However, for many years we know that some aspects are not decreasing but instead are increasing, such as the pro-inflammatory activity of innate immune cells, especially monocytes/macrophages. Recently, it became evident that these cells may possess a type of memory dubbed “trained memory” sustained by epigenetic changes occurring long after, even in the absence, of the initiating agent. In this review, the authors survey evidence that such changes may occur in aging and describe the relationship between inflammaging and immunosenescence as an adaptation/remodelling process leading on the one hand to increased inflammation and on the other to decreased immune responses (immune-paralysis) orchestrated by the innate immune system. These changes may collectively induce a state of alertness which assures an immune response even if ultimately resulting in age-related deleterious inflammatory disease.

The last paper on this topic is from Gonçalves et al. (University of Birmingham, Birmingham, UK) (2016) on the changes of the innate immune system which has profound consequences for the ability of the older adult to respond to the vast range of microbial pathogens. The latter include microbes of clinical significance such as *Streptococcus pneumoniae*, the major pathogen causing pneumonia in the elderly. Respiratory infections such as pneumonia are the 4th major cause of death worldwide and a major killer in the over 65 s. There are 93 different strains (serotypes) of *S pneumoniae* and immunity against this microbe is determined largely by the response of neutrophils and Th17 cells. Th17 responses are intact or slightly increased with aging but the bactericidal functions of neutrophils are severely compromised, with

migration, microbe uptake (phagocytosis) and killing mechanisms (ROS generation, degranulation and NET generation) all reduced in older adults. Improving neutrophil function in older adults thus represents a route to improving immunity to *S pneumoniae* and new drugs in development, such as PI3kinase inhibitors, have already been shown to improve age-related loss of neutrophil functions.

In the Integrative biology and longitudinal studies section, the first paper is by Cohen (Université de Sherbrooke, Sherbrooke, Qc, Canada) (2016) on complex systems dynamics in aging, presenting a summary of recent work on the need to incorporate complex systems dynamics in our understanding of the physiological underpinnings of aging. This work demonstrates that many aging-related physiological changes leave traces at the systems level, i.e. in the levels of many molecules conjointly, and can be detected robustly with very different combinations of biomarkers. Appropriate statistical integration of biological data thus promises improved understanding of the underlying changes, as well as more precise measurement of these changes.

The next paper by Berr et al. (Inserm U1061, Hôpital La Colombière, Montpellier, France) (2016) on the use of biobanks from population-based cohorts in aging research argues that optimization of biobanks is a “life-insurance” for biological research on human ageing. It requires close collaboration between biologists and epidemiologists, and optimization of sampling through two-phase designs (nested case control or case-cohort studies) to allow better efficiency. Their paper illustrates some methodological, practical, economical and ethical issues important for studying aging and chronic diseases in the frame of large human cohorts.

The final paper on this theme is from Mitnitski et al. (Dalhousie University, Halifax, NS, Canada) Mitnitski and Rockwood (2016) arguing that the rate of deficit accumulation does not change over the adult life span but that people age at different rates. These authors propose that rates of aging can be quantified by the speed at which individuals accumulate health deficits. Earlier estimates using cross-sectional analyses suggested that deficits accumulated exponentially, at an annual rate of increase of 3.5 %. Here, the authors estimate the rate of deficit accumulation using longitudinal data from the Canadian National Population Health Survey. They found that the longitudinal

average annual rate of deficit accumulation was 4.5 % (± 0.75 %). At the individual level, changes in deficit accumulation can be attributed to both changes in environmental stresses and changes in recovery time. In contrast, at the population level, changes in the number of deficits are proportional to the changes in recovery time. That deficit accumulation will, on average, double twice between ages 50 and 80 highlights the importance of health in middle-age on late life outcomes.

In the cellular senescence and cancer section, the first paper is from Gonzalez et al. (Université de Montréal, Montréal, Qc, Canada) (Gonzalez et al. 2016) on premature aging/senescence in cancer cells and whether this is good or bad. The efficacy of treatments to cure or control cancer can be enhanced via personalized management of therapeutic options that in turn requires improved knowledge and new tools to understand the biological responses involved. In reality, damaged cells have many options: they can repair the lesions (very often cancer therapy causes DNA lesions), they can die, or they can enter a state of permanent growth arrest termed senescence. Senescence is generally seen as a beneficial anti-cancer mechanism, but senescent cells sometime persist in tissues and actively alter their microenvironment via a senescence-associated proinflammatory secretome, which paradoxically negatively impacts tissue functions when such cells accumulate beyond a normal threshold during aging or following cancer therapy. It is currently proposed that senescence links aging and age-associated diseases with cancer development and cancer treatment, and understanding the biology of senescence should lead to the development of specific therapeutic interventions that target selected senescence-associated phenotypes to favor beneficial effects while negating detrimental ones.

The last paper on this topic is by Martelli et al. (Singapore Immunology Network (SIgN), A*STAR, Singapore) (2016) on immunosenescence in the mucosa. Immunosenescence, an age-related deterioration in immune functions, is considered a major contributory factor for the higher prevalence and severity of infectious diseases and the poor efficacy of vaccination in the elderly. Compared with systemic immunosenescence, alterations in the mucosal immune system with age are less well investigated. In this article, the authors provide an overview of age-associated changes occurring in systemic immunity

and discuss the similarities and the distinct features of mucosal immunosenescence. Indeed, mucosal surfaces constitute a discrete compartment of the immune system that is autonomous from the systemic branch in different respects: a unique process for initiating an immune response, different antigenic burden which it is exposed to, the presence of a different immunoglobulin isotype (IgA) and of diverse lymphocyte subpopulations. The mucosal immune response is altered in old animals and elderly humans mainly in terms of microbiota-host interactions, IgA secretion and macrophage function.

In the genetics and epigenetic section, Rea et al. (Queens University Belfast, Belfast, Northern Ireland, UK) (2016) explored the relationship between genes and lifestyle in a series of studies on nonagenarian siblings (in the EU-funded Genetics of Healthy Ageing project). Interesting, the beliefs, behaviors and life-style themes which emerged from the narrative insights of the GeHA nonagenarians themselves about factors which they considered contributed to their combination of ‘health-span’ and ‘age-span’, seemed to link with emerging understanding of epigenetic mechanisms and resonate with important public health messages about adopting a healthy life-course.

The next paper in this theme from Morrow et al. (Université Laval, Québec, Qc, Canada) (2016) considered whether the mitochondrial unfolding protein response (UPRMT) is a pro-longevity signaling pathway aimed at re-establishing mitochondrial homeostasis by triggering the expression of chaperones and proteases. *Drosophila* Hsp22 is one of the few small heat shock proteins to be localized inside the mitochondria and the review from Morrow et al. focuses on its links with the UPRMT and the aging process, in addition to highlighting its important role in mitochondrial proteostasis.

The last paper in this section is from Rose et al. (University of California, Irvine, CA, USA) (2016) arguing that the biotechnological task of controlling human aging will evidently be complex, given the failure of all simple strategies for accomplishing this to date. In view of this complexity, a multi-step approach will be necessary. One precedent for a multi-step biotechnological success is the burgeoning control of human infectious diseases from 1840 to 2000. Here the authors break down progress toward the control of infectious disease into four key steps, each

of which has analogs for the control of aging. Achievement of all four of these steps has allowed most people who live in Western countries to live largely free of the threat of imminent death due to infectious disease. Accomplishing the equivalent feat for aging over this coming century should lead to a similar outcome for aging-associated disease. Neither infection nor aging will ever be entirely abolished, but they can both be rendered minor causes of death and disability.

In the final section, reflecting the last topic of the Symposium, on cell biology and engineering, Brassard et al. (McGill University, Montréal, Qc, Canada) (2016) discuss Hutchinson-Guilford progeria syndrome as a model for vascular aging and provide a compelling argument for exploiting new model systems such as induced pluripotent stem cells to study vascular aging. This article emphasizes the important overlap between Hutchinson-Gilford progeria syndrome (HGPS) and vascular aging in terms of stem cell depletion and exhaustion, mechanotransduction and cardiovascular phenotype. This overlap provides a rationale for studying the vascular phenotype in HGPS to better understand vascular aging. Induced pluripotent stem cells derived from HGPS patients are proposed as a relevant model to perform challenging studies on aging, such as distinguishing cellular aging from other traditional cardiovascular disease risk factors. The induced pluripotent stem cell technology is a powerful new tool that could lead to significant advances in the field of biogerontology.

The next paper is by Nugent et al. (Université de Sherbrooke, Sherbrooke, Qc, Canada) (2016) on whether the cognitively-normal older person has a particular metabolic phenotype. The authors have investigated a broad range of metabolic and endocrine parameters including body fat composition that could form the basis for the concept of a ‘metabolic phenotype’ of the cognitively-normal older person. Their results show that healthy, cognitively normal older people have lower brain glucose uptake, almost exclusively in the frontal cortex, but also have widespread brain areas with lower grey matter volume and reduced cortical thickness. The metabolic phenotype of a cognitively-normal older person includes many parameters that are similar to those in healthy younger people but that percent total body fat and a measure of mild insulin resistance correlate directly with brain glucose uptake in the older group. Nugent et al. suggest that

regional brain glucose uptake in cognitively healthy older people could be age-normalized.

The final paper from Hirokawa et al. (Institute for Health and Life Sciences, Tokyo Medical and Dental University Open Laboratory, Tokyo, Japan) (2016) consider whether age-related decline of growth hormone, thymic involution and lifespan prolongation are related. A high level of growth hormone (GH) is necessary for the activation of thymic function to promote T cell differentiation in the early stages of life, and later administration of GH promotes the development of the immune system and rejuvenates immune function in elderly people. However, GH deficiency is favorable for longer lifespan, as hypopituitary dwarf mice such as Ames and Snell dwarf mice exhibit longer lifespans than control. The data indicate that GH is necessary for the development of thymus-dependent immunity, but GH deficiency is favorable for long lifespan and decreased occurrence of cancer and diabetes. This situation may represent a trade-off between the immune system and GH.

Final discussions at the end of the Symposium papers were in the form of a Round table moderated by G Pawelec (University of Tübingen). The physiological state of elderly people is variable and different in different individuals. Thus, we need to obtain a lot of variable data possibly by longitudinal studies from elderly people for a proper assessment of everyone's condition. In other words, we have to encourage clinicians and researchers in different fields to pay attention to aging and collaborate in biogerontological research, which in addition to unravelling the causes of aging will help to delay age-associated chronic diseases and result in longer healthspans. What we have to do is to ask investigators from different fields to incorporate the viewpoint of Biogerontology in their researches. This would result in a multidisciplinary systems biology approach facilitating progress towards better care of the elderly.

References

- Berr C, Gabelle A, Fievet N, Goldberg N, Zins M, Carrière I (2016) How to optimize the use of biobanks from population-based cohorts in aging research. *Biogerontology* 17(1). doi:[10.1007/s10522-015-9586-8](https://doi.org/10.1007/s10522-015-9586-8)
- Brassard JA, Fekete N, Garnier A, Hoesli CA (2016) Hutchinson-Gilford progeria syndrome as a model for vascular aging. *Biogerontology* 17(1). doi:[10.1007/s10522-015-9602-z](https://doi.org/10.1007/s10522-015-9602-z)

- Cohen AA (2016) Complex systems dynamics in aging: new evidence, continuing questions. *Biogerontology* 17(1). doi:[10.1007/s10522-015-9584-x](https://doi.org/10.1007/s10522-015-9584-x)
- Frasca D, Blomberg BB (2016) Inflammaging decreases adaptive and innate immune responses in mice and humans. *Biogerontology* 17(1). doi:[10.1007/s10522-015-9578-8](https://doi.org/10.1007/s10522-015-9578-8)
- Fulop T, Dupuis G, Baehl S, Le Page A, Bourgade K, Frost E, Witkowski JM, Pawelec G, Larbi A, Cunnane S (2016) From inflamm-aging to immune-paralysis—a slippery slope during aging for immune-adaptation. *Biogerontology* 17(1). doi:[10.1007/s10522-015-9615-7](https://doi.org/10.1007/s10522-015-9615-7)
- Goldeck D, Pawelec G, Norman K, Steinhagen-Thiessen E, Oettinger L, Haehnel K, Demuth I (2016) No strong correlations between serum cytokine levels, CMV serostatus and hand-grip strength in older subjects in the Berlin BASE-II cohort. *Biogerontology* 17(1). doi:[10.1007/s10522-015-9577-9](https://doi.org/10.1007/s10522-015-9577-9)
- Gonçalves MT, Mitchell TJ, Lord JM (2016) Immune ageing and susceptibility to *Streptococcus pneumoniae*. *Biogerontology* 17(1). doi:[10.1007/s10522-015-9614-8](https://doi.org/10.1007/s10522-015-9614-8)
- Gonzalez LC, Ghadaoui S, Martinez A, Rodier F (2016) Premature aging/senescence in cancer cells facing therapy: good or bad? *Biogerontology* 17(1). doi:[10.1007/s10522-015-9593-9](https://doi.org/10.1007/s10522-015-9593-9)
- Hirokawa K, Utsuyama M, Kikuchi Y (2016) Trade off situation between thymus and growth hormone: age-related decline of growth hormone is a cause of thymic involution but favorable for elongation of lifespan. *Biogerontology* 17(1). doi:[10.1007/s10522-015-9590-z](https://doi.org/10.1007/s10522-015-9590-z)
- Martelli S, Pender SLF, Larbi A (2016) Compartmentalization of immunosenescence: a deeper look at the mucosa. *Biogerontology* 17(1). doi:[10.1007/s10522-015-9628-2](https://doi.org/10.1007/s10522-015-9628-2)
- Mitnitski A, Rockwood K (2016) The rate of aging: the rate of deficit accumulation does not change over the adult life span. *Biogerontology* 17(1). doi:[10.1007/s10522-015-9583-y](https://doi.org/10.1007/s10522-015-9583-y)
- Mitteldorf J (2016) An epigenetic clock controls aging. *Biogerontology* 17(1). doi:[10.1007/s10522-015-9617-5](https://doi.org/10.1007/s10522-015-9617-5)
- Morrow G, Le Pécheur M, Tanguay RM (2016) *Drosophila melanogaster* mitochondrial Hsp22: a role in resistance to oxidative stress, aging and the mitochondrial unfolding protein response. *Biogerontology* 17(1). doi:[10.1007/s10522-015-9591-y](https://doi.org/10.1007/s10522-015-9591-y)
- Nugent S, Castellano CA, Bocti C, Dionne I, Fulop T, Cunnane SC (2016) Relationship of metabolic and endocrine parameters to brain glucose metabolism in older adults: do cognitively-normal older adults have a particular metabolic phenotype? *Biogerontology* 17(1). doi:[10.1007/s10522-015-9595-7](https://doi.org/10.1007/s10522-015-9595-7)
- Rea IM, Dellet M, Mills KI, The ACUME2 Project (2016) Living long and ageing well: is epigenomics the missing link between nature and nurture? *Biogerontology* 17(1). doi:[10.1007/s10522-015-9589-5](https://doi.org/10.1007/s10522-015-9589-5)
- Rose MR, Cabral LG, Kezos JN, Barter TT, Phillips MA, Smith BL, Burnham TC (2016) Four steps toward the control of aging: following the example of infectious disease. *Biogerontology* 17(1). doi:[10.1007/s10522-015-9588-6](https://doi.org/10.1007/s10522-015-9588-6)
- Ukrainitseva SV, Yashin A, Arbeev K, Kulminski A, Akushevich I, Wu D, Joshi D, Land KC, Stallard E (2016) Puzzling role of genetic risk factors in human longevity: “risk alleles” as pro-longevity variants. *Biogerontology* 17(1). doi:[10.1007/s10522-015-9600-1](https://doi.org/10.1007/s10522-015-9600-1)
- Weinberger B, Joos C, Reed SG, Coler R, Grubeck-Loebenstein B (2016) The stimulatory effect of the TLR4-mediated adjuvant glucopyranosyl lipid A is well preserved in old age. *Biogerontology* 17(1). doi:[10.1007/s10522-015-9576-x](https://doi.org/10.1007/s10522-015-9576-x)
- Yashin AI, Arbeev KG, Arbeeve LS, Wu D, Akushevich I, Kovtun M, Yashkin A, Kulminski A, Culminskaya I, Stallard E, Li M, Ukrainitseva SV (2016) How the effects of aging and stresses of life are integrated in mortality rates: insights for genetic studies of human health and longevity. *Biogerontology* 17(1). doi:[10.1007/s10522-015-9594-8](https://doi.org/10.1007/s10522-015-9594-8)