Better immunity in later life: a position paper

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Abstract Ageing is the greatest challenge that health-care systems will have to deal with this century. This is because a wide spectrum of pathological impairments emerge in the later part of the human life course which sharply increase mortality and reduce quality of life. Dysfunction of the immune system with advancing age is of crucial importance to the development of disability in later life and finally death. Understanding immune ageing, immunosenescence, has long been recognised as an essential prerequisite for the delivery of effective interventions which will improve late life health. Ten years ago, the ImAginE consortium undertook a broad ranging series of projects which added significantly to our understanding of how fundamental ageing mechanisms drove immune decline. In the decade which followed, abundant evidence has

accumulated from nonhuman model systems that ageing results from the progressive operation of a relatively few common processes which act across the major organ systems. These advances in fundamental understanding both allow better clarification of the potential cross-system dysregulation that occurs in ageing and open new avenues for intervention. Over the course of a 2-day workshop, the original ImAginE participants have considered these issues and present some suggestions for current priority areas in immunosenescence.

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The great triumphs of public health in the nineteenth and twentieth centuries were in public sanitation and in understanding the causes of infectious disease. Together, the application of these discoveries produced the ‘epidemiological transition’, a very marked reduction in mortality in the early part of the life course due to a sharp fall in deaths from acute infectious disease, followed by a rise in both mortality and morbidity resulting from chronic degenerative conditions as a result of larger numbers of individuals surviving into later life (Wilmoth 2000).

The latest (2011) census data for the UK shows that the proportion of the population aged 0–14 has dropped from 31 % in 1911 to 18 % a century later (Office for National Statistics 2011). Over the same period, the proportion of older people (aged 65+) more than trebled (from 5 to 16 %). These trends are set to continue, and it has been estimated that by 2050, between 40 and 50 %

of the population of the Western world and the Pacific Rim will be over the age of 60 (Lutz et al. 1997).

Ageing is associated with an increased susceptibility to a wide range of degenerative conditions, which range in seriousness from the trivial to the fatal. Health-care systems which developed to deal primarily with the illnesses of children and young adults (e.g. early life infectious disease or trauma) are now faced with the challenge of reorientating to address the disorders of later life. All of these illnesses cost money and reduce the quality of life of those who suffer from them. The challenge posed by the ageing population in the twenty first century is thus to avoid the nightmare combination of steep increases in health spending and an overall reduction in the quality of life for a growing proportion of the population.

The resource implications of dealing with the ageing population are considerably larger than the investments historically needed to improve early life health. The public health measures that were responsible for the demographic transition were cheap (Cutler and Miller 2005). In contrast, it has been estimated that ~40 % of the total budget of the British National Health Service is deployed combating the poor health consequences of ageing (Summerfield and Babb 2004). Within these overall costs, hospitalisation due to infection is much more common in the elderly than in younger individuals and is a major contributor to the development of disability in old people (Caljouw et al. 2013).

However, a study from the RAND Corporation on future medical advances which might benefit the elderly showed that the potential exists for new treatments which are fractions of the costs of those currently available (Goldman et al. 2005). Estimates of this type highlight the potential benefits of a better understanding of the fundamental biological basis of the ageing process and the necessity of exploiting the knowledge gained so far in the production of better late life interventions.

Why did ageing evolve and what are the implications for the immune system?

Whilst identifying ageing at the level of populations of organisms is relatively uncomplicated (the increase in age-specific mortality underlying the Gompertz relationship) (Hirsch and Peretz 1984), a definition of ageing which works well for individual members of the population has proved a little more contentious. Ageing

is often defined as a lesser capacity for maintaining homeostasis under conditions of physiological stress compared to younger counterparts (Comfort 1979). Thus, the increased likelihood of death of older humans under conditions of cold and the increased likelihood of death of older yeast cells and the conditions of UV irradiation share a common hallmark which defines these as ageing changes. Unfortunately, there are many reasons for failures of homeostasis and not all of them could be counted as ageing. Researchers wishing to use a more precise definition often cite that of Strehler (1977) who considered the defining features of ageing to be that it was universal, progressive, intrinsic and, above all, degenerative, but what is the evolutionary rationale for ageing when it clearly compromises organisational survival?

Medawar (1952) recognised that in wild populations, extrinsic mortality is the major component of total mortality. As a result, chronologically old animals are rare even if the organism in question does not show an ageing process. Under such conditions, early acting deleterious mutations are strongly selected against since they affect the ability of organisms to pass the genes to the next generation, but harmful mutations that occur later in the life course are not exposed to this selection pressure. ‘Ageing’ therefore develops and results from the accumulation of these late-acting deleterious mutations.

The antagonistic pleiotropy theory of ageing (Williams 1957) extended Medawar’s initial observations on the age dependence of reproduction by postulating the existence of pleiotropic genes, i.e. alleles that have different effects on the survival of organisms during the life course. Such genes exert favourable effects on early life fecundity (when the effect of natural selection is strong), but deleterious ones in later life when the effect of natural selection is weak. The predictions of antagonistic pleiotropy (e.g. that fertility and longevity are negatively correlated) have been confirmed in experiments using the fruit fly *Drosophila melanogaster*. Postponing reproduction increased life expectancy, and conversely, decreased fertility was observed in long-lived flies (Rose and Charlesworth 1981). Pleiotropic effects can occur both not only at the level of individual genes (e.g. p53 which plays a key role in the cellular anticancer mechanism at the cost of suppressing stem cell proliferation and survival) but also at the level of global processes such as immunity.

Antagonistic pleiotropy is not a concept which has been extensively applied to the ageing immune system. This is interesting in itself because the system is an exercise in tradeoffs. On the one hand, it must defend the organism against extrinsic threats (i.e. pathogens), but at the same time, it must face inward (suppressing malignancy and avoiding autoimmunity). In addition, in more complex organisms, the immune system must distinguish between beneficial and potentially pathogenic organisms in the microbiome.

It is known that extrinsic challenges to the immune system compromise evolutionary fitness in free-living old animals more than in young ones (Palacios et al. 2011), but in contrast, the intrinsic tradeoffs faced by later life organisms has been far less intensely studied. Antagonistic pleiotropy predicts that vigorous immune responses in early life would be selected for environments in which a significant component of extrinsic mortality was due to infectious disease incidence (e.g. in human populations before the epidemiological transition or in wild populations of animals today). Such selection would occur even if such an immune response was deleterious to older organisms.

Data exist which are consistent with such pleiotropic effects on the human innate immune system. The capacity to mount an inflammatory response is genetically determined in man, and a pro-inflammatory cytokine profile is associated with increased survival following meningococcal sepsis in the young whilst in contrast cytokine genotypes related to increased anti-inflammatory profiles can also be positively associated with longevity in protected populations (Westendorp et al. 1997, June 28). Studies from Ghana have compared populations in areas with recent (1973–1980) access to clean water to those still living in the immunologically challenging environment produced by drinking pathogen-containing water from rivers and wells. The researchers found a clear pleiotropic effect. Pro-inflammatory alleles of interleukin (IL)-10 protect carriers from excess mortality in adverse environments but produce somewhat increased age-specific mortality in more affluent areas (Boef et al. 2012; Kuningas et al. 2009).

The ImAginE participants also speculated that during the life course, inflammatory stimuli from microbial or other pathogen sources are likely to become increasingly compounded with endogenous stimuli. One plausible source of this endogenous ‘noise’ is the senescence-associated secretory phenotype. This is a spectrum of

proinflammatory cytokines secreted by ‘senescent’ cells which have permanently exited the cell cycle and which are known to accumulate to significant numbers with advancing age (compromising health status) (Tchkonia et al. 2013). Alongside with this, damage-associated molecular patterns (DAMPs) also become more frequent with advancing age. DAMPs are proteins which are usually sequestered in the cytosol but are released because of cell necrosis resulting from a range of age-related conditions (e.g. stroke and myocardial infarction). Interestingly, DAMPs include two preformed but poorly secreted members of the IL-1 family (e.g. IL-1 α) which are also made by senescent cells indicating potential overlap between senescence and sterile inflammation (Berda-Haddad et al. 2011; Burton et al. 2009).

Clearly, a highly pro-inflammatory cytokine profile early in life can have deleterious effects later in the life course. It could aggravate degenerative processes later in life in a pleiotropic fashion, ultimately contributing to a chronic inflammatory state. There are data consistent with this idea; most notably that a pro-inflammatory cytokine profile is a risk factor for cognitive decline (Wikby et al. 2005). Continued exposure to DAMPs and the steady increase in senescent cells also have the potential to produce dysregulation of inflammatory networks and a resulting state of chronic inflammation. The consortium members speculated that the low-grade chronic inflammation seen in ageing mammals (q.v.) is not only the result of chronic antigenic stress but also of a complex combination of genetically determined competency to produce a pro-inflammatory cytokine profile, senescent cells and DAMPs. These ideas are readily testable.

Immunosenescence: when it goes wrong, what goes wrong and what is ‘wrong’ anyway?

It has long been known that growing older is associated with an increased incidence of recognised disease entities (e.g. type II diabetes, arthrosis and cardiovascular disease) as well as increased susceptibility to infectious disease. This gives rise to a ‘chicken-and-egg’ etiological question as to whether ageing causes these diseases or whether these diseases constitute the ageing process.

It is also important to emphasise that the immune parameters measured in young humans today have the potential to be different from those of the 1950s which introduces the formal possibility that some of the

changes seen in cross-sectional human studies result from differential environmental exposure rather than biological ageing. This being said, the few longitudinal studies so far performed are consistent with the hypothesis that ageing changes over time in individuals are indeed occurring. However, these studies are mostly on exceptionally aged individuals, revealing large scale inter-individual heterogeneities in ageing trajectories even amongst these ‘successfully’ aged people.

To do justice to the physiology, it may be better simply to think of the mechanisms of immune decline as the group of immune-mediated effects which lead to decreasing life expectancy with increasing age (as some of the most thoughtful early gerontologists did with senescence as a whole) rather than attempting to classify them into ‘true’ changes and ‘underlying disease’ which is a largely artificial distinction. Individual ‘decline’ may also result from an adaptive process shaping the immune system to better deal with that particular organism’s specific past and current challenges (e.g. persistent pathogen infection).

An early attempt to identify ‘true’ age-related changes for immunogerontological studies was the development of the SENIEUR protocol (Ligthart et al. 1984). This protocol defines selection criteria and sets limits to disease and drug-induced changes in the immune system in an attempt to minimise the effect of underlying disease. Many changes in immune function previously attributed to ageing are less pronounced in optimally healthy elderly people selected by the SENIEUR protocol. Such individuals are rare (only ~5 % of Leiden’s inhabitants aged 85 years and older fulfilled the criteria for SENIEUR-ship), but they can be found. Thus, although the rationale for the development of SENIEUR may be philosophically questionable, the protocol itself has proven useful in demonstrating that the very elderly exhibit immune values very similar to modern young people. This is consistent with ‘successful’ immune ageing. Thus, from a practical research perspective, there is a pressing need to understand what accounts for this small fraction of exceptionally healthy people whatever the reason for their happy state. Is it their genetic background? Is it their lifestyle? Is it pathogen burden? Consortium members considered that all of these aspects contribute and need to be studied in a stratified manner comparing those who were aged successfully and those who have not.

Noting the limitations of previous studies, there appears to be an inverse relationship between immune

status, response to vaccination, health and longevity which are at least partly due to the immune system becoming less effective at the individual level with advancing age. Both humoral and cellular immune responses are different in elderly individuals, and this is believed to represent a change leading to an increased frequency and severity of infectious diseases and reduced protection from vaccination.

Innate (natural) immunity, the first line of defence that precedes antigen-specific humoral (B cell) and cellular (T cell) responses, plays a crucial role in preventing microbial invasion. Ageing significantly impairs the phenotype and the function of cells of the innate immune system (neutrophils, monocyte/macrophages, dendritic cells and NK cells), leading to their decreased activation, chemotaxis, phagocytosis and intracellular killing of pathogens (Solana et al. 2006). Ageing is also characterised by a dysregulation of inflammatory and anti-inflammatory networks, resulting in a low-grade chronic proinflammatory status (sometimes termed ‘inflammaging’), with persistent low-grade innate immune activation. Thus, age-related changes in innate immunity appear to reflect systemic remodelling (possibly as a consequence of immunological history) rather than simply decreased function.

Ageing affects the humoral immune response both quantitatively and qualitatively, as specificity and class of antibody produced are changed. The changes in the humoral immune response during ageing significantly contribute to the increased susceptibility of the elderly to infectious diseases and reduce the protective effects of vaccination. The decreased ability of aged individuals to produce high-affinity protective antibody responses against infectious agents results at least in part from their compromised B cell function. This may suffer from a lack of optimal T cell help in ageing, but intrinsic changes in B cells also occur and have a significant impact on antibody production. These changes include a decrease in activation-induced cytidine deaminase (AID), the enzyme responsible for class switch recombination, and in the transcription factor E47 that regulates its expression. AID also regulates somatic hypermutation, which is responsible for the production of high-affinity protective antibodies, whose production is impaired during ageing (Cancro et al. 2009).

Some of the most easily recognisable differences between young and old people’s immune parameters concern the T cell arm of adaptive immunity, particularly the CD8⁺ cells responsible amongst other things for

lysing virus-infected host cells. Because of developmentally determined thymic involution beginning at puberty, the source of naïve T cells in adults is greatly reduced. In general, the number and frequency of naïve T cells is lower in adults than in children and far lower in old adults. This is likely due to three factors: (i) thymic involution, resulting in a lower naïve T cell output; (ii) pathogen encounter by naïve cells (in early life), their differentiation to anti-pathogen effector cells and then the conversion of a small fraction of them to memory cells to maintain immune protection against the same pathogen throughout life; and (iii) homeostatic proliferation of the peripheral T cell pool. This results in one of the hallmarks of immune ageing: the reduction in naïve T cells and a concomitant increase in memory/effector T cells.

CMV: cause or consequence?

One of the main driving forces for this age-associated change in T cell phenotype is antigen exposure across the lifespan. This subsumes both periods of acute infection and chronic stimulation from persistent viral infections. In humans infection with the beta-herpesvirus HHV5 (cytomegalovirus, CMV) appears to be a major player in the latter context. Why this particular virus, and not other, even closely related herpes viruses have this effect is not known and is now beginning to be intensely investigated (Solana et al. 2012). CMV is only pathogenic under extreme circumstances (neonatal infection, iatrogenic immunosuppression and AIDS). However, unique amongst the herpes viruses and as far as we know unique amongst any immune challenges (even including alloreactivity), CMV infection results in the commitment of significant immune resources to immunosurveillance in order to maintain the virus in a latent state. This level of commitment increases with age until a significant portion of the CD8 T cells are devoted to CMV suppression with marked consequences for systemic and physiology. Thus, CMV is a driver of the accumulation of late-stage differentiated CD8⁺ T cells, which are distinguishing features of the ‘immune risk profile’ predicting mortality in longitudinal studies of the very elderly. They may be responsible for the emerging consensus that there are negative survival consequences of CMV infection even in earlier life (Pawelec et al. 2012) as also reflected in the impact of CMV infection on responsiveness to influenza vaccination

(McElhaney et al. 2012). We are slowly approaching a more mechanistic explanation of how these deleterious effects may be mediated and gaining an appreciation of inter-individual differences which may inform manipulations to improve clinical outcomes (Derhovanessian et al. 2013; Bartlett et al. 2012).

What can we do to improve vaccination?

Chronic exposure to viruses such as CMV can clearly either cause (or accelerate) immunosenescence or result in increased susceptibility to infections. In many developing countries, chronic infections (viral, bacterial and parasitological) are more frequent and persistent than in developed countries. For example, young Sub-Saharan African adults show significantly elevated serum IgG levels (~20 mg/mL) compared to young Europeans (~10 mg/mL). This elevated level of chronic immune stimulation (probably caused at least in part by the high prevalence of helminth and malaria infection, but obviously dependent on the locality and pathogen presence) is likely to place individuals living their entire lives under such conditions at a significantly increased risk of immune exhaustion and opportunistic infection.

The most effective method of preventing infectious diseases is vaccination. However, the effects of vaccination are markedly different in individuals of different ages (Goodwin et al. 2006; McElhaney 2010). For example, in the case of seasonal influenza vaccination, there is evidence that elderly individuals who have routinely received the vaccine can still contract the infection with secondary complications leading to physical debilitation, hospitalisation, exacerbation of underlying medical conditions and death.

Faced with this scenario, the ImAginE participants saw the need to obtain a better knowledge of the mechanisms for induction, development and maintenance of protective immunity in the elderly in response to vaccinations against emerging and re-emerging infectious diseases. Unsurprisingly, influenza, pneumococcus and herpes zoster were considered priority pathogens by the ImAginE participants, but new emerging pathogens such as dengue fever were also seen as important given the global health risks posed to older people.

Vaccines are still required which will provide optimal protection for the elderly. Although influenza vaccines currently provide some protection, they must be reformulated every year, and the time lag between the

spread of a pandemic virus and the availability of a vaccine is worryingly lengthy. Newly emerging infectious diseases, such as swine-origin H1N1 and avian H5N1 influenza, severe acute respiratory syndrome and dengue fever are a constant threat, and bacterial infections, such as the recurrent *Salmonella* outbreaks in the food industry, are costly to the society. However, vaccines in general were originally developed for young adults and pre-existing immunity in the target population is not considered. ImAginE participants noted that previous exposure to influenza strains is largely age dependent, which implies that the ideal influenza vaccine (strain composition and dosage) will differ between young and elderly populations. The importance of pre-existing immunity to influenza is best illustrated by the relatively low impact of the swine-origin influenza virus epidemic in middle age and elderly subjects (who were previously exposed to H1N1 influenza viruses) (Verma et al. 2012 May). Adjuvanted influenza (Hatz et al. 2012) or high-dose influenza vaccines show improved immunogenicity in elderly subjects and may confer better protection as compared to the ‘standard’ influenza vaccine (Cools et al. 2009). One difficulty in the development of more effective vaccines is the lack of predictors of efficacy although there are signs of progress in this area (Derhovanessian et al. 2013). These are needed because different individuals show different responses to vaccination, and not every vaccinated individual will mount a protective cellular or humoral immune response. There are emerging immunological indicators for determining who is likely to respond and who not at the level of the antigen-presenting cell (van Duin et al. 2007) and in terms of the measurement of pre-existing T cell reactivity to shared influenza antigens (Derhovanessian et al. 2013). Recent advances in molecular biology and proteomics have made possible genome-wide measurements of levels of transcripts and their splice variants, non-coding RNAs, metabolites, proteins, epigenetic changes and germline polymorphisms, thus opening new frontiers to vaccinology. High-throughput multi-omics data have been used to construct predictive models of interactions between the biological components of the pathogen-host system, obtain a global picture of the immune responses to vaccination in humans and identify early gene signatures that correlate with and predict later immune responses to vaccination. This approach has allowed the identification of predictors of vaccine responses (for influenza and yellow fever so far). However, it has not,

as yet, provided mechanistic insights on how a given vaccine elicits protective immunity. Therefore, a multi-biomarker characterisation of responders and non-responders is warranted. During the ImAginE meeting, a wide range of potential biomarkers were proposed. These included cellular biomarkers (e.g. B and T lymphocytes, monocyte/macrophages, dendritic cells and neutrophils), molecular biomarkers (e.g. cytokines and antibodies produced in vitro and transcription factors) and systemic biomarkers (e.g. CMV load, pro- and anti-inflammatory cytokine levels, hormones, micro-RNAs, mitDNA, microbial DNA and metabolites/nutrition). Future research in the biomarker area thus has the potential to first stratify the older population and then improve the percentage of older responders.

The immune system does more than you think

A decline in the function of the central nervous system is one of the most serious aspects of the ageing process but is not one in which the immune system has traditionally been considered to play a major role since the CNS is an immune-privileged site (Yeoman et al. 2012). However, fascinating links between these two systems are now emerging, and these in turn open new prospects for therapeutic advance. Data from the Schwartz group suggest that functional cell-mediated immunity is required for the maintenance of hippocampus-dependent spatial memory (Ron-Harel et al. 2008). Immune-deficient mice show an impaired spatial memory phenotype which can be rescued by immune reconstitution. Conversely, compromising the immune system of young mice also impairs their spatial memory. The same researchers have shown that memory loss in aged mice is attributable to age-related attenuation of the immune response, a phenotype which could be rescued by expansion of the existing T cell repertoire. These are exciting observations which suggest that the immune system plays a major but previously unsuspected role in the maintenance and repair of the normal CNS (Schwartz et al. 2009; Schwartz and Shechter 2010). Exploration of the crosstalk between the two systems in the context of immunosenescence has the potential to yield exciting results.

The phenotype of senescent cells clearly has the potential to contribute to the chronic inflammation which characterises later life, but the broader question of why senescent cells are proinflammatory was little

considered until a few years ago. Burton (2009) was amongst the first to propose that this inflammatory phenotype might play a functional role in both signalling and facilitating immune clearance. Almost simultaneously, Krizhanovsky and colleagues demonstrated that natural killer cells preferentially kill senescent-activated stellate cells in vitro and in vivo, facilitating the resolution of liver fibrosis (Krizhanovsky et al. 2008). Clearance has recently been shown to be primarily dependent on granule exocytosis by NK cells rather than death-receptor-mediated due to upregulation of a decoy death receptor by the senescent targets (Sagiv et al. 2012). However, since the phenotype of senescent cells is very variable across tissues, it may be premature to assume that this bias in pathway usage is a global phenomenon (Kipling et al. 2009).

The involvement of NK cells in senescent cell clearance is suggestive of a major new role for the immune system in the remodelling of multiple organ systems in later life. Interestingly, this has come to light at the same time that the longstanding view that only the adaptive immune system is able to build up immunological memory is being re-evaluated. Memory properties for NK cells monocytes and macrophages (in many ways exemplars of innate immunity) have recently been described (a phenomenon known as ‘trained immunity’) (Netea et al. 2011). It has become clear that the set point for production of inflammatory cytokines by the innate immune system can be modulated by either BCG vaccination or infection with *Candida albicans* (Kleinnijenhuis et al. 2012; Quintin et al. 2012). This change appears to be epigenetic and persists for up to a year. How this plays into immune senescence remains unclear, and thus, the time is probably right for the role of the immune system in ageing not to simply be ImAginEd but ‘Re-ImAginEd’.

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References

- Bartlett DB, Firth CM, Phillips AC, Moss P, Baylis D, Syddall H, Sayer AA, Cooper C, Lord JM (2012) The age-related increase in low-grade systemic inflammation (Inflammaging) is not driven by cytomegalovirus infection. *Aging Cell* 11(5): 912–915
- Berda-Haddad Y, Robert S, Salers P, Zekraoui L, Farnier C, Dinarello CA, Dignat-George F, Kaplanski G (2011) Sterile inflammation of endothelial cell-derived apoptotic bodies is mediated by interleukin-1 α . *Proc Natl Acad Sci U S A* 108(51):20684–20689
- Boef AG, May L, van Bodegom D, Kuningas M, Eriksson UK, Westendorp RG (2012) The influence of genetic variation on innate immune activation in an environment with high infectious pressure. *Genes Immun* 13:103–108
- Burton DG (2009) Cellular senescence, ageing and disease. *Age (Dordr)* 31(1):1–9
- Burton DG, Giles PJ, Sheerin AN, Smith SK, Lawton JJ, Ostler EL, Rhys-Williams W, Kipling D, Faragher RG (2009) Microarray analysis of senescent vascular smooth muscle cells: a link to atherosclerosis and vascular calcification. *Exp Gerontol* 44(10):659–665
- Caljouw MA, Kruijdenberg SJ, de Craen AJ, Cools HJ, den Elzen WP, Gussekloo J (2013) Clinically diagnosed infections predict disability in activities of daily living among the oldest-old in the general population: the Leiden 85-plus Study. *Age Ageing* 42(4):482–488
- Cancro MP, Hao Y, Scholz JL, Riley RL, Frasca D, Dunn-Walters DK, Blomberg BB (2009) B cells and aging: molecules and mechanisms. *Trends Immunol* 30(7):313–318
- Comfort A (1979) The biology of senescence. 3rd ed., Elsevier Science Publishing Co., Inc.
- Cools HJ, Gussekloo J, Remmerswaal JE, Remarque EJ, Kroes AC (2009) Benefits of increasing the dose of influenza vaccine in residents of long-term care facilities: a randomized placebo-controlled trial. *J Med Virol* 81(5):908–914
- Cutler D, Miller G (2005) The role of public health improvements in health advances: the twentieth-century United States. *Demography* 42:1–22
- Derhovannessian E, Theeten H, Hähnel K, Van Damme P, Cools N, Pawelec G (2013) Cytomegalovirus-associated accumulation of late-differentiated CD4 T-cells correlates with poor humoral response to influenza vaccination. *Vaccine* 31(4):685–690
- Goldman DP, Shang B, Bhattacharya J, Garber AM, Hurd M, Joyce GF, Lakdawalla DN, Panis C, Shekelle PG (2005) Consequences of health trends and medical innovation for the future elderly. *Health Affairs*. doi:10.1377/hlthaff.w5.r5
- Goodwin K, Viboud C, Simonsen L (2006) Antibody response to influenza vaccination in the elderly: a quantitative review. *Vaccine* 24:1159–1169
- Hatz C, Cramer JP, Vertruyen A, Schwarz TF, von Sonnenburg F, Borkowski A, Lattanzi M, Hilbert AK, Cioppa GD, Leroux-Roels G (2012) A randomised, single-blind, dose-range study to assess the immunogenicity and safety of a cell-culture-derived A/H1N1 influenza vaccine in adult and elderly populations. *Vaccine* 30(32):4820–4827
- Hirsch HR, Peretz B (1984) Survival and aging of a small laboratory population of a marine mollusc, *Aplysia californica*. *Mech Ageing Dev* 27(1):43–62
- Kipling D, Jones DL, Smith SK, Giles PJ, Jennert-Burston K, Ibrahim B, Sheerin AN, Evans AJ, Rhys-Williams W, Faragher RG (2009) A transcriptomic analysis of the EK1.Br strain of human fibroblastoid keratocytes: the effects of growth, quiescence and senescence. *Exp Eye Res* 88(2): 277–285

- Kleinnijenhuis J, Quintin J, Preijers F, Joosten LA, Ifrim DC, Saeed S, Jacobs C, van Loenhout J, de Jong D, Stunnenberg HG, Xavier RJ, van der Meer JW, van Crevel R, Netea MG (2012) Bacille Calmette-Guerin induces NOD2-dependent nonspecific protection from reinfection via epigenetic reprogramming of monocytes. *Proc Natl Acad Sci U S A* 109(43):17537–17542
- Krizhanovsky V, Yon M, Dickinson RA, Hearn S, Simon J, Miething C, Yee H, Zender L, Lowe SW (2008) Senescence of activated stellate cells limits liver fibrosis. *Cell* 134(4):657–667
- Kuningas M, May L, Tamm R, van Bodegom D, van den Biggelaar AH, Meij JJ, Frölich M, Ziem JB, Suchiman HE, Metspalu A, Slagboom PE, Westendorp RG (2009) Selection for genetic variation inducing pro-inflammatory responses under adverse environmental conditions in a Ghanaian population. *PLoS One* 4(11):e7795
- Ligthart GJ, Corberand JX, Fournier C, Galanaud P, Hijmans W, Kennes B, Müller-Hermelink HK, Steinmann GG (1984) Admission criteria for immunogerontological studies in man: the SENIEUR protocol. *Mech Ageing Dev* 28(1):47–55
- Lutz W, Sanderson W, Scherbov S (1997) Doubling of world population unlikely. *Nature* 387:803–805
- McElhaney JE (2010) Influenza vaccine responses in older adults. *Ageing Res Rev* 10:379–388
- McElhaney JE, Zhou X, Talbot HK, Soethout E, Bleackley RC, Granville DJ, Pawelec G (2012) The unmet need in the elderly: how immunosenescence, CMV infection, co-morbidities and frailty are a challenge for the development of more effective influenza vaccines. *Vaccine* 30(12):2060–2067
- Medawar PB (1952) An unsolved problem in biology. H. K. Lewis and Co., London
- Netea MG, Quintin J, van der Meer JW (2011) Trained immunity: a memory for innate host defense. *Cell Host Microbe* 9(5):355–361
- Office for National Statistics (2011) Census: population estimates for the United Kingdom, 27 March 2011. www.ons.gov.uk. Accessed 17 Dec 2012
- Palacios MG, Winkler DW, Klasing KC, Hasselquist D, Vleck CM (2011) [13] Pro-inflammatory cytokine profile consequences of immune system aging in nature: a study of immunosenescence costs in free-living tree swallows. *Ecology* 92(4):952–966
- Pawelec G, McElhaney JE, Aiello AE, Derhovanessian E (2012) The impact of CMV infection on survival in older humans. *Curr Opin Immunol* 24(4):507–511
- Quintin J, Saeed S, Martens JH, Giamarellos-Bourboulis EJ, Ifrim DC, Logie C, Jacobs L, Jansen T, Kullberg BJ, Wijmenga C, Joosten LA, Xavier RJ, van der Meer JW, Stunnenberg HG, Netea MG (2012) *Candida albicans* infection affords protection against reinfection via functional reprogramming of monocytes. *Cell Host Microbe* 12(2):223–232
- Ron-Harel et al (2008) Age-dependent spatial memory loss can be partially restored by immune activation. *Rejuvenation Res* 11(5):903–913
- Rose MR, Charlesworth B (1981) Genetics of life history in *Drosophila melanogaster*. II. Exploratory selection experiments. *Genetics* 97:187–196
- Sagiv A, Biran A, Yon M, Simon J, Lowe SW, Krizhanovsky V (2012) Granule exocytosis mediates immune surveillance of senescent cells. *Oncogene*. doi:10.1038/onc.2012.206
- Schwartz M, Shechter R (2010) Systemic inflammatory cells fight off neurodegenerative disease. *Nat Rev Neurol* 6(7):405–410
- Schwartz M, London A, Shechter R (2009) Boosting T-cell immunity as a therapeutic approach for neurodegenerative conditions: the role of innate immunity. *Neuroscience* 158(3):1133–1142
- Solana R, Pawelec G, Tarazona R (2006) Aging and innate immunity. *Immunity* 24(5):491–494
- Solana R, Tarazona R, Aiello AE, Akbar AN, Appay V, Beswick M, Bosch JA, Campos C, Cantisán S, Cicin-Sain L, Derhovanessian E, Ferrando-Martínez S, Frasca D, Fulöp T, Govind S, Grubeck-Loebenstien B, Hill A, Hurme M, Kem F, Larbi A, López-Botet M, Maier AB, McElhaney JE, Moss P, Naumova E, Nikolich-Zugich J, Pera A, Rector JL, Riddell N, Sanchez-Correa B, Sansoni P, Sauce D, van Lier R, Wang GC, Wills MR, Zieliński M, Pawelec G (2012) *Immun Ageing* 9(1):23. doi:10.1186/1742-4933-9-23
- Strehler B (1977) Time, cells and aging. 2nd ed., Academic Press, New York
- Summerfield C & Babb P Eds (2004) Social Trends 34 Published by London: TSO ISBN 0 11 621732 4
- Tchkonia T, Zhu Y, van Deursen J, Campisi J, Kirkland JL (2013) Cellular senescence and the senescent secretory phenotype: therapeutic opportunities. *J Clin Invest* 123(3):966–972
- van Duin D, Allore HG, Mohanty S, Ginter S, Newman FK, Belshe RB, Medzhitov R, Shaw AC (2007) Prevacine determination of the expression of costimulatory B7 molecules in activated monocytes predicts influenza vaccine responses in young and older adults. *J Infect Dis* 195(11):1590–1597
- Verma N, Dimitrova M, Carter DM, Crevar CJ, Ross TM, Golding H, Khurana S (2012) Influenza virus H1N1pdm09 infections in the young and old: evidence of greater antibody diversity and affinity for the hemagglutinin globular head domain (HA1 Domain) in the elderly than in young adults and children. *J Virol* 86(10):5515–5522
- Westendorp RG, Langermans JA, Huizinga TW, Verweij CL, Sturk A (1997) Genetic influence on cytokine production in meningococcal disease. *Lancet* 349(9069):1912–1913
- Wikby A, Ferguson F, Forsey R, Thompson J, Strindhall J, Löfgren S, Nilsson BO, Emerudh J, Pawelec G, Johansson B (2005) An immune risk phenotype, cognitive impairment, and survival in very late life: impact of allostatic load in Swedish octogenarian and nonagenarian humans. *J Gerontol A Biol Sci Med Sci* 60(5):556–565
- Williams GC (1957) Pleiotropy, natural selection, and the evolution of senescence. *Evolution* 11:398–411
- Wilmoth JR (2000) Demography of longevity: past, present, and future trends. *Exp Gerontol* 35:1111–1129
- Yeoman M, Scutt G, Faragher R (2012) Insights into CNS ageing from animal models of senescence. *Nat Rev Neurosci* 13(6):435–445