



EASTBIO DTP Research Training Strand 1
Basic Bioscience Underpinning Health (Ageing) Priority Area
2014 Course Outline

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Supervisors

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Structure:

Introductory meeting:

Friday 31 January 2014, University of Edinburgh.

All other sessions will take place at 10.00pm on Fridays, starting Friday 28 February 2014 unless otherwise advised. Specific dates for the online sessions will be confirmed shortly by the EASTBIO Administrator.

Weeks 2-7: Basic mechanisms implicated in control of lifespan/regulation of normal healthy ageing

Week 2: RONS/damage theories - Teresa Valencak

Week 3: Evolutionary theory of ageing – Dan Nussey

Week 4: Impact of the fetal environment upon adult health – Neil Vargesson

Week 5: Caloric restriction – Craig Walling

Week 6: General theories of ageing (Hayflick/telomeres, mTOR pathway & ageing)- Henning Wackerhage

Week 7: Inflammaging – Lynda Williams

Weeks 8 – 12: Organ specific ageing

Week 8: Nervous system

- Neuronal vulnerability – Tom Wishart & Cathy Abbott

Week 9: Memory and Ageing – James Ainge, Akira O'Connor

Week 10: Immunosenescence – Clare Blackburn, Rose Zamoyska

- Immune responses in the aged population
- Stem cell ageing

Week 11: Ageing and Alzheimer's disease – Frank Gunn-Moore

Week 12: Sarcopenia (muscle ageing) – Henning Wackerhage

Week 1: Introduction:

Faculty: Clare Blackburn, Dan Nussey, Henning Wackerhage

All BBUH students to attend. All PIs are invited

This meeting covered:

Intro from Clare and Dan on the general aims of this element of the training

Intro to Blackboard (if needed) from computer support or Maria if needed

Short intros from all attendees.

Lecture: *Aging, Demographics & Policy Options* - Henning Wackerhage

The Scottish and UK population is ageing as a result of a low birth rate and high life expectancy. As a consequence the working population decreases and the elderly population increases. Societies need to adapt to these demographic changes which requires unpopular choices. These include an increase of the pension age, a lowering of the pension or an increase of the younger, working population by making it easier to raise children or by immigration. Finally, as the health and care costs are high at old age, promoting health and independent living in the elderly is a key measure to which scientists can contribute.

Required reading:

Centre for policy on ageing: http://www.cpa.org.uk/cpa/policies_on_ageing.html
Vaupel J.W. (2010) *Nature* **25**:536-541.

Question for discussion:

1. You are the government minister responsible for solving the Scottish aging problem. What is your strategy and how do you plan to convince your fellow Scots?

Week 2: RONS/damage theories

Faculty: Teresa Valencak

Summary In the 1920s it was observed that organisms with high rates of metabolism age faster than those with slow metabolism. This 'rate of living' idea was the first real theory of ageing, but it had no mechanism. In the 1950s it was shown that oxidative metabolism produces oxygen free-radicals as an incidental by product and that molecules formed from these radicals (called Radical oxygen species) can damage macromolecules like proteins, lipids and DNA. Organisms have a wide array of protective mechanisms to defend against radical oxygen species but some ROS always evade these protective defences and hence damage accumulates contributing to ageing related dysfunction and ultimately death. Twenty years ago this was the dominant theory of ageing. However, evidence contrary to the main idea has gradually accumulated, such that the idea that ROS underpin ageing is now not widely held by gerontologists. This evidence includes the fact that knocking out many of the key protective enzymes, or providing animals with antioxidant supplements has only minimal impacts on lifespan.

Required reading:

Beckman, KB and Ames BN (1998) The free-radical theory of ageing matures. *Physiological reviews* 78: 548-571

Speakman JR, Selman C. (2011) The free-radical damage theory: Accumulating evidence against a simple link of oxidative stress to ageing and lifespan" *BioEssays* 33: 255-9.

Perez, VI, Bokov, A, Remmen, HV, Mele, J., Ran, Q, Ikeno, Y and Richardson A. (2009) Is the oxidative stress theory of ageing dead? *Biochem Biophys Acta* 1790: 1005-1014.

Suggested additional reading:

Harman, D (1956). "Aging: a theory based on free radical and radiation chemistry". *Journal of Gerontology* **11** (3): 298–300.

Miller ER 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LG, Guallar E. (2005). "Meta-analysis: High-dosage vitamin E supplementation may increase all-cause mortality". *Annals of Internal Medicine* **142** (1): 37–46

Jang YC, Remmen HV. The mitochondrial theory of aging: Insight from transgenic and knockout mouse models. *Experimental Gerontology*. 2009;44(4) 256-60.

Questions for discussion:

1. What is the evidence for and against the ROS/Damage theory
2. After reading the evidence where do you stand on this idea? Do you think it is well supported or not?

3. Do you think it is wise to take antioxidant supplements to ward off free-radical attack?

Week 3: Evolutionary theory of ageing

Faculty: Dan Nussey

Summary: Ageing is usually defined as a progressive decline in function with increasing age that results in increased risk of mortality and decreased reproduction. Given that such a process is clearly bad for an individual's Darwinian fitness (i.e. the total number of offspring it produces during its life), the existence of ageing initially posed something of a paradox to evolutionary biologists. The aim of this module is to introduce the major evolutionary theories of ageing that resolved the apparent evolutionary paradox of ageing, highlight the differences and similarities between them, and discuss their usefulness in providing a framework to understand the mechanisms underlying the ageing process.

Required reading:

Kirkwood, T. B. L. & Rose, M. R. (1991) *Philos. Trans. R. Soc. B*, **332**: 15-24

Kirkwood, T. B. L. & Austad, S. N. (2000) *Nature*, **408**: 233-238

Partridge, L. & Barton, N. H. (1993) *Nature*, **362**: 305-311

Suggested additional reading:

The original papers that defined laid down classic theory:

Medawar, P. B. (1946) *An Unsolved Problem of Biology*. Lewis, London.

Williams, G. C. (1957) *Evolution*, **11**: 398-411

Hamilton, W. D. (1966) *J. Theor. Biol.*, **12**: 12-45

Kirkwood, T. B. L. (1977) *Nature*, **270**: 301-304

An interesting review of empirical field studies:

Williams, P. D. *et al.* (2006) *Trends Ecol. Evol.*, **21**: 458-463

Questions for discussion:

1. What are the most important insights from evolutionary theory for our understanding of the ageing process and variation in it?
2. What are the main distinctions between mutation accumulation and antagonistic pleiotropy mechanisms of the evolution of ageing? Which is better empirically supported? Does it matter which mechanism is involved?
3. How is disposable soma theory different from antagonistic pleiotropy explanations for the evolution of ageing?
4. Is an understanding of evolutionary theory important for studies of the mechanisms of ageing?

Week 4: Impact of the fetal environment upon adult health

Faculty: Neil Vargesson

Summary:

The Barker Hypothesis first suggested a link between maternal diet and fetal environment and the onset of adult diseases, particularly obesity and heart disease. Today, how maternal nutrition can influence child and adult health is an area of intense interest.

Epigenetics and DNA Methylation during fetal life have been shown to have roles in influencing adult-onset diseases. The aim of this module is to introduce research on fetal nutrition and adult health, the current debates around it and the mechanisms by which fetal nutrition and environment can influence adult health (and lifespan).

Required reading:

Barker, 1995 BMJ. 1995 Jul 15;311(6998):171-4
Barker 1997. Nutrition. 13: 807-13

Suggested additional reading:

Nutrition in early pregnancy and adult onset disease

Godfrey et al., 2011. Diabetes 60: 1528-34
Horikoshi et al., 2013. Nature Genetics 45: 76-82
Barker 2000. Theriogenology 53: 555-74.

Parental behaviour and behavioural changes in subsequent generations

Dias and Ressler 2013, Nature Neuroscience doi: 10/1038/nn.3594

Metabolic imprinting

Dyer and Rosenfeld 2011, Semin Reprod Med 29: 266-76

Early nutrition and later health

Moor and Davies 2001, Asia Pac J Clin Nutr. 2001;10(2): 113-7.
Capra et al., 2013, It. J. Pediatr 39:7 doi: 10.1186/1824-7288-39-7
Roseboom et al. 2001. Twin Res. 4: 293-8.

Transgenerational inheritance

Greer et al., 2011 Transgenerational epigenetic inheritance of longevity in *C. elegans*. Nature, pp. 365-72
Lim and Brunet 2013 Bridging the transgenerational gap with epigenetic memory. Trends in Genetics, March 2013, Vol. 29, No. 3, pp. 176-86

Questions for discussion:

1. How can fetal nutrition and environment (epigenetics) cause early onset adult disease?
2. What are mechanisms that are thought to be involved?
3. What evidence supports the Barker Hypothesis?

Week 5: Caloric restriction

Faculty: Craig Walling

Summary: Caloric restriction, a reduction in the availability of food below *ad lib* amounts, has been shown to increase longevity and reduce rates of ageing in a range of organisms. In fact it is probably the most consistent environmental intervention to influence longevity and ageing and as such is of considerable interest in terms of the underlying mechanisms. However, the effect of caloric restriction is not universal and it has been suggested it may be a result of adaptation to a laboratory environment. In addition the role of calorie restriction versus restriction of particular macro- and micronutrients is debated. The aim of this module is to introduce research on calorie restriction, the current debates around it and the potential mechanisms by which calorie restriction may influence lifespan and ageing.

Required reading:

Nakagawa et al. 2012. *Aging Cell* 11:401
Fontana et al. 2010 *Science* 328:321
Mattison et al. 2012. *Nature* 489:318
Lee et al. 2008. *PNAS* 2498

Suggested additional reading:

Meta-analyses of effect of CR
Simons et al. 2013. *Aging Cell* 12: 410
Review of some mechanisms
Bjedov et al. 2011. *Biochemical Society Transactions*
Partridge and Gems 2002. *Nature Reviews Genetics*
General review of CR
Speakman & Mitchell. 2011. *Molecular Aspects of Medicine* 32: 159
Swindell. 2012. *Ageing Research Reviews* 11:254
Piper et al. 2011. *Cell metabolism* 14: 154
Predominant evolutionary explanation
Shanley and Kirkwood 2000. *Evolution* 54: 740
CR versus macronutrients
Simpson & Raubenheimer 2007. *The Journals of Gerontology Series A: Biological and Medical Sciences* 62:707

Questions for discussion:

5. Is the effect of caloric restriction on lifespan a lab artefact?
6. Is any effect due to calories or other micro- and macro-nutrients?
7. What is the evolutionary explanation for the effect of calorie restriction on lifespan? Is it well supported?
8. What are mechanisms that are thought to be involved?

Week 6: General theories of ageing

Faculty: Henning Wackerhage

Summary: Ageing of organisms is comparable to the ageing of cars where the metal rusts, the colour fades and the ball bearings become worn. Similarly, the ageing of organisms is not just driven by one process but several including the shortening of telomeres (Hayflick limit) and mTOR pathway activation which we cover in this module. After briefly introducing telomeres and the Hayflick limit we will discuss the example of a dystrophy mouse model with shortened, 'humanised' telomeres to show how this causes premature ageing on a disease background. Next we will discuss caloric restriction and pharmacological and genetic mTOR pathway deactivation as two interventions that extend lifespan by targeting the mTOR pathway.

Required reading:

Blackburn E. H. (2005) *Mol. Cancer Res.* **3**: 477-482

Harrison D.E. (2009) *Nature* **460**: 392-395

Sacco, A. (2010). *Cell* **143**: 1059-71

Suggested additional reading:

Lopes-Otin C. (2013) *Cell* **153**: 1194-1217

Questions for discussion:

1. What are telomeres and how are they related to the Hayflick limit?
2. What is the relation between telomeres, ageing and cancer?
3. Do you expect body builders, who drive their muscle growth via mTOR activation, to die young? Discuss arguments in favour and against this hypothesis.

Week 7: Inflammaging

Faculty: Lynda Williams

Summary

The hypothalamus regulates many basic functions in life such as growth, development and reproduction as well as being the hub of whole body homeostasis. In complex organisms ageing appears to be coordinated and systemic. However, the mechanisms that guide the systemic ageing process are largely unknown. Recently it has been shown that the hypothalamus is crucial in this process and that ageing in mice is related to hypothalamic inflammation. It appears that in ageing the innate immune response via IKK β /NF κ B pathway is activated in microglia which then inhibit the expression of GnRH in hypothalamic neurons. Central GnRH replacement in ageing mice partially reverses the effects of ageing on skin, muscle and bone. The innate immune response in the hypothalamus is also activated by a high-fat diet resulting in diet induced obesity.

Required reading:

Zhang G, Li J, Purkayastha S, Tang Y, Zhang H, Yin Y, Li B, Liu G, Cai D. **(2013)** Hypothalamic programming of systemic ageing involving IKK- β , NF- κ B and GnRH. *Nature*. 497(7448):211-6.

Suggested additional reading:

Thaler JP, et al. **(2012)** Obesity is associated with hypothalamic injury in rodents and humans. *J Clin Invest*. 122:153-62.

Williams, L.M. (2012) Hypothalamic dysfunction in obesity. *Proc Nutr Soc*. 71: 521-33.

Questions for discussion:

1. Do you think that the concept that ageing is governed by the hypothalamus is credible?
2. Hypothalamic inflammation, as a result of ageing, resembles that induced by a high-fat diet in rodents. Can obesity be considered as a kind of premature ageing?
3. Why does the hypothalamic response to a high-fat diet resemble that seen in ageing – what are the mechanisms linking these responses?
4. How do theories linking caloric restriction and longevity fit into these findings?

Week 8: Nervous system: Neuronal vulnerability

Faculty: Tom Wishart & Cathy Abbott

Required reading:

Differential vulnerability

DeKosky ST & Scheff SW. Synapse loss in frontal cortex biopsies in Alzheimer's disease: correlation with cognitive severity. *Ann Neurol.* 1990 May;27(5):457-64. PMID: 2360787

Synaptic vulnerability in neurodegenerative disease. Wishart TM, et al *J Neuropathol Exp Neurol.* 2006 Aug;65(8):733-9. PMID 1689307 (REVIEW)

Mechanisms underlying synaptic vulnerability and degeneration in neurodegenerative disease. Gillingwater TH and Wishart TM. *Neuropathol Appl Neurobiol.* 2013 Jun;39(4):320-34. PMID: 23289367 (REVIEW)

Mitochondria and neuronal stability

Schon EA and Przedborski S. Mitochondria: the next (neurode) generation. *Neuron.* 2011 Jun 23;70(6):1033-53. PMID: 21689593 (REVIEW)

Muirhead KE, et al. The consequences of mitochondrial amyloid beta-peptide in Alzheimer's disease. *Biochem J.* 2010 Feb 24;426(3):255-70. PMID: 20175748

Yao J, et al Inhibition of amyloid-beta (Aβ) peptide-binding alcohol dehydrogenase-Aβ interaction reduces Aβ accumulation and improves mitochondrial function in a mouse model of Alzheimer's disease. *J Neurosci.* 2011 Feb 9;31(6):2313-20 PMID: 21307267

Suggested additional reading:

Borger E, et al. Is amyloid binding alcohol dehydrogenase a drug target for treating Alzheimer's disease? *Curr Alzheimer Res.* 2013 Jan;10(1):21-9 PMID: 22742981.

Du H, et al. Cyclophilin D deficiency attenuates mitochondrial and neuronal perturbation and ameliorates learning and memory in Alzheimer's disease. *Nat Med.* 2008 Oct;14(10):1097-105. PMID: 18806802.

Wishart TM et al Differential proteomics analysis of synaptic proteins identifies potential cellular targets and protein mediators of synaptic neuroprotection conferred by the slow Wallerian degeneration (Wlds) gene. *Mol Cell Proteomics.* 2007 Aug;6(8):1318-30. PMID: 17470424.

Wishart TM, et al Combining comparative proteomics and molecular genetics uncovers regulators of synaptic and axonal stability and degeneration in vivo. *PLoS Genet.* 2012;8(8):e1002936. PMID: 22952455.

Avery MA, et al. WldS prevents axon degeneration through increased

mitochondrial flux and enhanced mitochondrial Ca²⁺ buffering.
Curr Biol. 2012 Apr 10;22(7):596-600. PMID: 22425157.

Questions for discussion

1. What do we mean by neuronal compartmentalisation?
2. What is neurodegeneration?
3. How would you define vulnerability? Why would synapses appear more vulnerable to neurodegenerative stimuli (ageing/injury/toxins) than other neuronal compartments or cells in the nervous system?
4. How can we examine what is happening in different neuronal subpopulations/subcellular compartments/organelles?
5. What implications does differential compartmental vulnerability have for therapeutic development?

Week 9: Ageing and Memory Function

Faculty: James Ainge & Akira O'Connor

Summary:

Ageing affects a wide range of cognitive processes. Last week you covered the mechanisms underlying neurodegeneration. This week we will examine functional consequences of neurodegeneration in normal ageing and in disease. Studying the specific cognitive processes that are impaired in diseases of the elderly is important for two reasons. Firstly, we need understand which neural systems and mechanisms that support the cognitive processes that decline to allow us to target potential therapeutic strategies to those systems. Secondly, we need to be able to assess animal models of disease using appropriate behavioural tests.

Required reading:

- BURKE, S. N., WALLACE, J. L., HARTZELL, A. L., NEMATOLLAHI, S., PLANGE, K. & BARNES, C. A. 2011. Age-associated deficits in pattern separation functions of the perirhinal cortex: a cross-species consensus. *Behavioral Neuroscience*, 125, 836-47.
- SWAINSON, R., HODGES, J. R., GALTON, C. J., SEMPLE, J., MICHAEL, A., DUNN, B. D., IDDON, J. L., ROBBINS, T. W. & SAHAKIAN, B. J. 2001. Early detection and differential diagnosis of Alzheimer's disease and depression with neuropsychological tasks. *Dementia and Geriatric Cognitive Disorders*, 12, 265-280.
- WILSON, I. A., IKONEN, S., GALLAGHER, M., EICHENBAUM, H. & TANILA, H. 2005. Age-associated alterations of hippocampal place cells are subregion specific. *Journal of Neuroscience*, 25, 6877-6886.

Questions for discussion:

1. How is memory affected in normal ageing?
2. What are the mechanisms and systems underlying these deficits?
3. What are the specific cognitive deficits seen in Alzheimer's disease?
4. How can we use this information to help the search for therapeutics for AD?

Week 10: Immunosenescence

Faculty: Clare Blackburn & Rose Zamoyska

Synopsis

Immunosenescence is the term given to the stereotypical decline in immune system function associated with normal ageing. As we age, we acquire impaired ability to respond to newly encountered antigenic challenge, such that older people are less likely to develop protective immunity after vaccination and are more susceptible to new infectious diseases, such as new strains of influenza.

There are a number of contributing factors to immunosenescence, including:

- *Changes in production of new naïve effector cells.* The thymus, the major site of T lymphocyte generation, required for generation of a functional, self-tolerant T cell repertoire, is one of the first organs to degenerate in normal healthy individuals, a process termed 'age-related thymic involution'. This leads to a marked decrease in production of new T lymphocytes from around age 40 in humans and is a major contributing factor in immunosenescence. The reduced output of naïve T cells after age-related thymus involution in humans severely impairs the ability to respond to newly encountered antigens. Furthermore, impaired thymic function, is implicated in increased susceptibility to autoimmunity and higher risk of cancer development with age.
- *Changes in peripheral responses.* As a consequence of thymic involution naïve T cells are not available to be recruited to fight either novel or persistent infections. In the case of persistent/latent infections continuous exposure to the antigen can result in exhaustion of existing T cell clones and a weakened capacity to resist infection. Understanding the basis of clonal exhaustion raises the possibility of reversing this condition and prolonging immune vitality. The reasons behind lymphocyte senescence and possible strategies for improving lymphocyte lifespan and function will be discussed.

Required reading:

Chinn, IK., Blackburn, CC., Manley NR., Sempowski, GD. (2012) Changes in primary lymphoid organs with aging. *Semin Immunol.* 2012 **24** 309-20 (review)

Goronzy and Weyand (2013). Understanding immunosenescence to improve responses to vaccines. *Nature Immunology* 14 428-35 (review)

Larbi, et al. (2008). [Immune receptor signaling, aging and autoimmunity.](#) *Advances in experimental medicine and biology*, 640, 312–24. (review)

Pawelec, G., et al. (2009). [Cytomegalovirus and human immunosenescence.](#) *Reviews in Medical Virology*, 19(1), 47–56. (review)

Suggested additional reading:

Goronzy, J. J., Li, G., Yang, Z., & Weyand, C. M. (2013). The janus head of T cell aging - autoimmunity and immunodeficiency. *Frontiers in immunology*, 4, 131.

Moro-García, M. A., Alonso-Arias, R., & López-Larrea, C. (2012). *Current genomics*, 13(8), 589–602.

Geiger, de Haan and Florian 2013. The ageing haematopoietic stem cell compartment. *Nature Reviews Immunology* 376-89.

Dowling and Hodgkin (2009) Why does the thymus involute?
A selection-based hypothesis *Trends Immunol.* 295-3000

Questions for discussion:

1. In view of clonal exhaustion should we be immunising the elderly with Influenza vaccines?
2. If we reverse T cell exhaustion will we improve anti-pathogen responses at the expense of more autoimmunity?

Week 11: Ageing and Alzheimer's disease

Faculty: Frank Gunn-Moore

Required reading:

- Muirhead KE, Borger E, Aitken L, Conway SJ, Gunn-Moore FJ. The consequences of mitochondrial amyloid beta-peptide in Alzheimer's disease. *Biochem J.* Feb 24 2010, 426(3):255-70.
- Yao J, Du H, Yan S, Fang F, Wang C, Lue LF, Guo L, Chen D, Stern DM, Gunn Moore FJ, Xi Chen J, Arancio O, Yan SS. Inhibition of amyloid-beta (Abeta) peptide-binding alcohol dehydrogenase-Abeta interaction reduces Abeta accumulation and improves mitochondrial function in a mouse model of Alzheimer's disease. *J Neurosci.* Feb 9 2011, 31(6):2313-20.
- Borger E, Aitken L, Du H, Zhang W, Gunn-Moore FJ, Yan SS. Is amyloid binding alcohol dehydrogenase a drug target for treating Alzheimer's disease? *Curr Alzheimer Res.* Jan. 2013, 10(1):21-9.

Questions for discussion:

1. What is the role of mitochondria in Alzheimer's disease?
2. How can Alzheimer's disease be treated?

Week 12: Sarcopenia (muscle ageing)

Faculty: Henning Wackerhage

Summary: Sarcopenia is the slow loss of muscle mass and function during normal ageing. Generally muscle mass and function varies greatly at all ages but especially after the age of ≈ 60 years. Three major causes are discussed in this module: First, motor neurones and muscle fibres are lost. A key cross-sectional study suggests that 50% of muscle fibres are lost from 20 to 80 years of age. Second, old skeletal muscle responds less to anabolic signals such as amino acids, hormones and insulin. This has been termed 'anabolic resistance'. Finally muscle regeneration is impaired in old muscle and there is an increased infiltration with connective tissue and fat. The mechanisms behind these causes are incompletely understood but include changed concentrations of signalling proteins and a drop of testosterone in males.

Required reading:

Lexell J. (1988) *J Neurol. Sci.* 84: 275-294

Cuthbertson D. (2005) *FASEB J.* 19: 422-424

Chakkalakal J.V. (2011) *Nature* 490: 355-360

Suggested additional reading:

Mitchell M., K. (2012) *Front Physiol.* 3: 260

Questions for discussion:

1. What are the key differences between sarcopenia and other forms of muscle atrophy such as immobilisation atrophy or cancer cachexia?
2. Based on your knowledge of the causes, how would you treat individuals with sarcopenia?
3. Why do old muscles often have an increased fat and connective tissue content?