Journal of Gerontology & Geriatric Research

Demontis, J Gerontol Geriatr Res 2015, 4:3
DOI: 10.4172/2167-7182.1000216

Review Article Open Access

Comparative Analysis of Medieval and Modern Scientific Research on Ageing Reveals Many Conceptual Similarities

Luca Demontis*

School of Medieval Studies, Pontifical University Antonianum, via Merulana 124, 00185 Rome, Italy

Abstract

Ageing is the main risk factors for many degenerative diseases and thesearch for anti-ageing cures has been a quest for humanity since ancient times. It is wellknown that medieval elites were deeply interested in understanding the mechanisms ofageing and in developing anti-ageing interventions to extend healthy lifespan. However, it is little appreciated that many parallels exist between medieval science and currentbiomedical research on ageing: remarkably, similar aspects of human ageing weredeemed interesting and worthy of investigation by both medieval and modernresearchers. In this article, I examine the experiences of medieval Europe that havecontributed to the formation and historical persistence of long-lasting attitudes about theageing process. In particular, I highlight similarities between hypotheses formulated bymedieval scholars and current research themes and interventions that have beenexperimentally proven to combat ageing. Specifically, I report how prominent medievalscholars such as Roger Bacon understood that ageing is a process influenced by bothintrinsic (hereditary) and extrinsic (environmental) factors, and that hormesis, exercise,blood-derived factors, and dietary restriction can delay ageing. Thus, the experimentalevidence recently gathered on the molecular mechanisms of ageing provides answersfor long-outstanding questions that were already formulated by medieval scholars.

Keywords: Medieval science; Anti-ageing research; Theriaca; Hormesis; Dietary restriction; Exercise; Parabiosis; Roger bacon

Introduction

'Insel des Jupiter oder des Unsterblichen, wokein Mensch stirbt'(Island of Jupiter or the immortals, where no one dies)

The late-medieval Walsperger map (1448) depicts an island in the Atlantic Oceanwhere supposedly no ageing and death were experienced. Myths of immortality and extreme longevity, such as the "fountain of youth" (Figure 1), were common throughout ancient and medieval times and were usually associated with distant geographic locations, far to reach for most European inhabitants. These legends are a clear demonstration of the medieval credence that lifespan could be extended and that age related diseases could be avoided. These beliefs sparked investigations on the mechanisms of ageing and the search for interventions that could prevent frailty or even restore a youthful state [1-13]. Several medieval treatises of the 13th and 14th century demonstrate the profound interest for understanding and combating ageing, with the ultimate goal of the prolongatio vitae, i.e. extending lifespan. These include the De retardation accidentium senectutis (The slowing of accidents of old age), written by the lord of the castle of Goet [1]; De conservation ejuventut is et retardation sesenectute is (Preservation ofyouth and old age retardation) by Arnoldus de Villanova [14]; Deregiminesenum (The state of the elderly) by Al-Razi [3]; Essays on health by Maimonides [15]; Parvanaturalia (Short treatises on nature) and Deaetate (On age) by Albertus Magnus [16]; Gerontocomia scilicet desenumcuraatquevictu (Gerontocomia namely the care and diet for the elderly) by Gabriele Zerbi [17,18]; The cure of age and preservation of youth by Roger Bacon [19]; and De vita longa (On long life) by Marsilio Ficino [20]. These and other medieval treatises [21,22] in turn provided the basis for prominent renaissance works by Luigi Cornaro (1475-1566) and others [5,23]. Although medieval medical treatises on ageing were not experimentally grounded, there are several conceptual similarities between hypotheses that were formulated by medieval scholars to explain the causes of ageing and our current understanding of thisprocess. It is now known that both genetic pathways and environmental interventions influence ageing in humans and other organisms [24]. These recent findings are well in line with the hypothesis posited by the franciscan friar Roger Bacon (1214-1294), who proposed that ageing is influenced by inherent hereditary

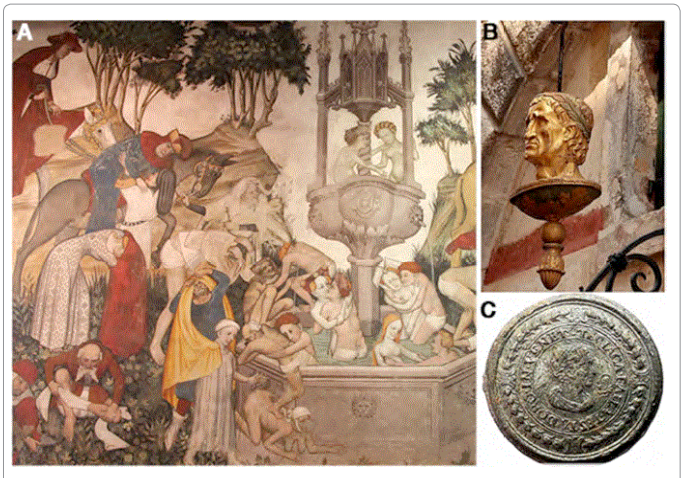

Figure 1: The search for interventions to extend lifespan in the Middle Ages. (A) *The fountain of youth* as painted by the Master of the Castel of Manta, near Saluzzo, Italy (1411-1416), represents the deep interest of medieval men in understanding the causes of ageing. The legend of the fountain of youth was a popular one in the Middle Ages and inspired many widespread tales and works of arts. (B) The golden head, symbol of the *Alla testa d'oro* pharmacy in Venice, renowned in all Europe for the production of theriaca, the first medical preparation thought to act as hormetic drug. (C) Theriaca box seal (17th century), with the emblems of Venice and *Alla testa d'oro* pharmacy. Theriaca was produced in several Italian cities since the Middle Ages till last century and sold throughout Europe.

***Corresponding author:** Luca Demontis, School of Medieval Studies, Pontifical University Antonianum, via Merulana 124, 00185 Rome, Italy, Tel: (902) 473-4995; E-mail: lucademontis@hotmail.com

Received April 20, 2015; **Accepted** May 27, 2015; **Published** May 29, 2015

Citation: Demontis L (2015) Comparative Analysis of Medieval and Modern Scientific Research on Ageing Reveals Many Conceptual Similarities. J Gerontol Geriat Res 4: 216. doi:10.4172/2167-7182.1000216

properties andextrinsic (environmental) factors [1]. Many medieval scholars, including Roger Bacon, postulated that delaying ageing can prevent the onset and/or limit the progression of age-associated diseases and that in turn the occurrence of diseases can accelerate or worsen ageing. For example, it was a common medieval belief that infections contribute to ageing; hence many physicians highlighted the importance of hygiene to decrease the risk of infections and to delay ageing. The strong connection between ageing and disease lead Zerbi to compile a list of the clinical aspects of 300 diseases commonly seen in old age [17] and to postulate that these diseases start to develop between 30 and 60 years of age and manifest themselves after 60 years of age. This clinical definition is well in line with the current understanding of the development of many age-related diseases such as frailty and sarcopenia (the progressive age-related loss of muscle mass and strength), which starts at around 30 years of age and leads to phenotypic defects that are typically prominent after 60 years of age [25]. In addition to Zerbi, other medieval scholars sub divided ageing into distinct progressive phases, with the lifespan being divided typically into 3, 4, 6 or 7 distinct periods each associated with progressive physical decay, as also represented in many medieval art works (Figure 2) [26,27]. The association between ageing and pathologies also sparked the first anatomical investigations of ageing via the dissection of the bodies of old people and centenarians by Leonardo da Vinci and others [28-30]. In addition to a link with disease, medieval scholars also noticed a connection between ageing and physiological processes. For example, Marsilio Ficino postulated a causal connection between reproduction and ageing [31], and recent scientific researches have indeed highlighted that exceptional longevity can be associated with decreased reproduction [32]. In addition to examining the ageing process in humans, medieval scholars have triedto understand the basic mechanisms governing ageing through the analysis of long-lived organisms. In the Parvanaturalia, Albertus Magnus discussed the observation that life span greatly varies among different animal species such as shellfish, crocodiles, and whales [16,22]. In the De regimen synonym, the medieval mesopotamia doctor Al-Razi hypothesized that anti-ageing 'substances' are born underwater and can be found in the viscera of long-lived animals [33]. The intuition that the extreme longevity of long-lived animal species may provide clueson the general mechanisms of ageing is underlying many current studies on the diversity of lifespan across species. These studies are helping identifying the genetic pathways and molecules ('substances') regulating ageing. For example, current researches have provided evidence that sea clams are among the longest-lived animals [34], and that tissue homogenates from these animals are extremely resistant to various types of proteostatic stress [35]. Although the molecular mechanisms responsible for this protection have not been defined, it will be interesting to see whether they are unique to these species or rather extremely efficient or enhanced versions of protein homeostatic systems found also in shorter-lived organisms. Furthermore, many plants and trees are known to have extremely long lifespan and are among the longest-living organisms [36]. Perhaps this explains why medieval physicians proposed fruit and botanical extracts as staples foranti-ageing treatments [37], a hypothesis that has been confirmed by the isolation of many anti-ageing compounds, such as resveratrol, from plants [38].

Figure 2: The representation of lifespan in the medieval period. The three ages of life, represented by the three kings in Gentile da Fabriano's Adoration of the magi (1423; Uffizi Gallery, Florence). From left to right: Melchior, Balthazar, and Gaspar respectively represent old age, middle age, and youth. The subdivision of lifespan into three ages echoes the current clinical understanding on the progression of many age-related diseases such as frailty and sarcopenia.

In addition to understanding the causes of ageing, medieval scholars proposed several interventions to reduce functional senescence and extend life span. A prominent medieval and ancient medical practice was based on the idea that exposure to low levels of poisons or stressors mounts an adaptive stress response that protects from subsequent exposures to harmful levels of poisons, and protects from ageing and diseases, a concept now known as "hormesis". For example, low levels of poisonous arsenic saltswere used to treat many diseases, such as cancer and malaria [39]. However, the most notable example of medieval "hormetic" anti-ageing intervention is the theriaca (also known as theriac or "treacle") whose name derives from the Greek therion, a word that indicates all poisonous animals. In medieval times, this was a complex mixture of many animal and vegetal ingredients. This expensive medicine was believed to be a cure for all diseases and ageing and an antidote against poisons [40]. The original recipe of theriaca dates back to 120 BC and MithridatesVI king of Pontus, who self-administered non-lethal doses of many poisons throughout this life with the goal of developing resistance to any future attempts to assassinate him with poisons. Subsequently, Andromacus the Old, physician to the roman emperor Nero, re-elaborated the recipe by including the use of viper's meat. As such, the theriaca magna (also known as Andromacus' theriaca) was considered a panacea bythe roman doctor Claudius Galen, and was produced during public ceremonies in many Italian cities throughout the Middle Ages and sold throughout Europe (Figure 1). Although Avicenna and others believed that the medical properties of theriaca arisefrom the combination of its ingredients, the viper's meat used for its preparation was by itself considered an elixir of long life by Roger Bacon [1,19]. Snake meat and skin were indeed used as medical preparations as such [40], in line with Hildegard von Bingen's idea that "something bad often dispels a bad thing".

Current biomedical research is now defining the genetic and molecular pathways responsible for sensing different types of environmental and cellular stressors and for mounting adaptive

protective responses. Indeed, hormetic responses have been shown to extend life span and delay ageing in many organisms in response to various types of stressors, such as heat, low levels of heavy metals and toxins, oxidative stress,mitochondrial dysfunction, and others [39,41-43]. For example, heat shock early in the life span induces the cytoplasmic unfolded protein response (UPR), which protects from subsequent challenges to protein folding later in life [41]. In addition to hormesis, several medieval physicians interested in anti-ageing interventions pointed to the importance of dietary restriction. Maimonides, Arnoldus de Villanova, Roger Bacon and other medieval scholars emphasize that dietary moderation is key to combat ageing [5], recalling the quotation Est modus in rebus (there is a mean in all things) of the ancient roman poet Horace, who valued moderation (mediocritas) in all things. Importantly, the concept of moderation and dietary restriction elaborated in ancient and medieval times will be echoed in Luigi Cornaro's Trattato de la vita sobria [23], which has inspired modern studies on dietary restriction. Recent investigations have indeed provided experimental evidence for a role of dietary restriction in delaying ageing and extending healthy lifespan in many organisms, including the nematode Caenorhabditis elegans, the fruit fly Drosophilamelanogaster, and higher organisms, such as mice, monkeys and even humans [44-46]. These studies therefore have provenvalid a long-standing hypothesis that traces back to the work of medieval scholars. In addition to anti-ageing remedies based on diet and hormesis, medieval scholars also thought of exercise as a means to delay ageing. Roger Bacon suggested in his seminal work on ageing. The cure of age and preservation of youth that exercise couldbe an effective intervention to delay ageing and age-related diseases [1,19]. Arnoldus de Villanova proposed that idleness should be avoided and indicated several exercise regimens suited for old age, including frequent walking, rhythmic bending and climbing towards higher places [37]. Other historical sources, including medieval Persian manuscripts, also highlight the importance of exercise in preventing ageing [47]. In line with thishypothesis, there is growing evidence that skeletal muscle contractile functions and exercise can preserve metabolic homeostasis, delay the progression of many age-related diseases, and perhaps even extend lifespan [25,48,49]. The mechanisms involved are presumably based on increased nutrient utilization by muscle (which should mimic a condition of limited nutrient availability, i.e. dietary Restriction, for other tissues) and secretion of muscle-derived signalling factors (myokines) into the blood, from where they can act systemically to regulate age-relatedprocesses in other tissues [50,51]. Another medical intervention that was proposed to delay ageing was based on therejuvenating action of blood-derived factors. The medieval scholar Marsilio Ficino (1433-1499) proposed in his De vita longa [17] that blood is the manifestation of the spiritusvitalis, i.e. a fountain of life that regulates ageing and life span [20]. On this basis, he postulated that transfusion or transmission ofblood can prolong lifespan, and that bloodletting should be limited or avoided. He alsoadvocated the drinking of blood from young donors as a therapy to cure or delay ageingin old people, believing that the blood can enter the circulation from the stomach (theplace where the blood was believed to be formed anew from the digested food [52] due to its affinity to the patient's blood [31]. Therefore, Marsilio Ficino considered the blood a vivifying substance that can be transferred from a donorto a patient and be used as anti-ageing therapy. Ficino's proposal recalls current research that has established important roles for circulating endocrine factors in the inter tissue regulation of systemic ageing and lifespan in many organisms [53,54]. For example, blood levels of GDF11 (growth differentiation factor 11) decline during ageing in mice and restoring normal GDF11levels in the blood delays the ageing of many tissues such as the brain, heart, and skeletal muscle [55-58]. Many ageing studies on the role of blood-derived signalling factors have employed a technique called parabiosis, whereby the blood circulation of one mouse ifconnected with the blood circulation of another mouse of the same or different age. Byusing this technique, scientists have observed rejuvenation of old mice when connectedto the circulation of young mice, an effect that was absent when the circulation of an oldmouse was connected to the circulation of another old mouse.

Current researches are defining the circulating signalling factors responsible for these effects, with GDF11 being one of the most important ones identified to date. In this article, I have highlighted key examples of remarkable conceptual continuityin anti-ageing research from medieval times to nowadays. Importantly, similar aspectsof human ageing were deemed interesting and worthy of investigation by medievalscholars and modern researchers. Moreover, hormesis, dietary restriction, and the roleof exercise and blood-derived factors were the theoretical principles underlying manymedieval anti-ageing interventions.For the first time in history, it is now possible to use simple model organisms, genetics, and molecular cell biology to unravel key mechanisms and pathwaysregulating ageing. The experimental evidence recently gathered indeed providesevidence for the validity of anti-ageing regimens based on hormesis, dietary restriction, exercise, and blood-derived factors. The remarkable parallels between medieval scienceand current anti-ageing research suggest a previously unanticipated persistence of ideas

about the causes of aging and potential therapies. On this basis, it is possible thathypotheses and theories on ageing that are deeply rooted in history have contributed tothe formation of contemporary attitudes about the ageing process which in turn haveinfluenced the trajectory of biomedical research in this field.

Refernces

1. Crisciani C, Paravicini BA (2003). Ruggero Bacone e l'alchimia di lunga vita. Riflessioni sui testi, in Alchimia e medicina nel Medioevo, Florence. Micrologus Library 9: 33-54.
2. Getz F (1998) Medicine in the English Middle Ages. Princeton University Press.
3. Gremk MD (1958) On aging and old age: basic problems and old aspects of gerontology and geriatrics. Monographiae biologicae.
4. Dunne M (2008) The causes of the length and brevity of life call for investigation: Aristotle's De longitudine et brevitate vitae in the 13th and 14th century commentaries. In "Vita longa. Vecchiaia e durata della vita nella tradizione medica e aristotelica anticae medievale. Atti del convegno internazionale. Metzler I. Ageing 92-15.
5. freeman Jt (1965) Medical Perspectives In Aging (12TH-19TH CENTURY). Gerontologist 5: Suppl: 1-24.
6. Minois G (1989) History of old age: from antiquity to the Renaissance. Chicago, IL: University of Chicago Press.
7. Paravicini Bagliani A (1991) Medicina e scienze della natura alla corte dei papi nel duecento. Società Internazionale per lo Studio del Medioevo Latino, Biblioteca di Medioevo Latino. Spoleto: Centro Italiano di Studi sull'Alto Medioevo.
8. Ritch A (2012) History of geriatric medicine: from Hippocrates to Marjory Warren. J R Coll Physicians Edinb 42: 368-374.
9. Shahar S (1997) Growing Old in the Middle Ages: "Winter Clothes us in Shadows and Pain". Translated from the Ebrew by Y. Lotan. Routledge, New York.
10. Sheehan MH (1990). Aging and the aged in medieval Europe. Toronto, Canada: Pontifical Institute of Medieval Studies.
11. Thorndike L (1923) A History of Magic and Experimental Science: the first thirteen centuries. Columbia University Press, books III, IV, and V.
12. Goodyear LJ (1996) Old Age in Late Medieval England. University of Pennsylvania Press, Philadelphia, PA.

13. Fortney K (1489) Gerontocomia, scilicet de senum cura, atque victu. Ad Innocentium VIII, Pont. Max. Prologus, Rome.
14. Villanova A (1544) De conservation juventutis et retardatione senectutis. Written for king James of Spain and translated by J. Drummond.
15. Maimonides (1958) The preservation of youth, translation of the original text "Essays on health" by Gordon HL, New York.
16. Weisheipl JA (1980). Albertus Magnus and the sciences: commemorative essays. Studies and Texts 49, Toronto.
17. Zerbi G (1489) Gerontocomia, scilicet de senum cura, atque victu. Ad Innocentium VIII, Pont. Max. Prologus, Rome.
18. Zeman FD (1944) The Gerontocomia of Gabriele Zerbi: a fifteenth-century manual of hygiene for the aged. Journal of the Mount Sinai Hospital 10: 710-716.
19. Bacon R (1683) The care of old age and preservation of youth. R. Browne, translator. T. Flesher, London.
20. Ficino M (2002) Three Books on Life, translated by Kaske CV and Clark JR, Tempe, AZ. The Renaissance Society of America.
21. Howell TH (1972) Avicenna and the care of the aged. Gerontologist 12: 424-426.
22. Lewry PO (1990) Study on aging in the arts faculty of the universities of Paris and Oxford, pp. 23-38, in Sheehan MH. Aging and the aged in medieval Europe. Toronto, Canada: Pontifical Institute of Medieval Studies.
23. Cornaro L (1558) Trattato della vita sobria. Gratioso Perchacino, Padua.
24. Kenyon CJ (2010) The genetics of ageing. Nature 464: 504-512.
25. Nair KS (2005) Aging muscle. Am J Clin Nutr 81: 953-963.
26. Covey HC (1989) Old age portrayed by the ages-of-life models from the Middle Ages to the 16th century. Gerontologist 29: 692-698.
27. Belt E (1952) Leonardo da Vinci's studies of the aging process. Geriatrics 7: 205-210.
28. Boon B (2009) Leonardo da Vinci on atherosclerosis and the function of the sinuses of Valsalva. Neth Heart J 17: 496-499.
29. Leibowitz JO (1980) Early accounts in geriatric pathology (Leonardo, Harvey, James Keill). Korot 7: CCLIII-CCLXIV.
30. Kodera S (2010) Lady vampires: Marsilio Ficino on blood, in Disreputable bodies: magic, medicine and gender in Renaissance natural philosophy. Essay and Studies 2, Publications of the Centre for Reformation and Renaissance Studies, Victoria University in the University of Toronto, Toronto.
31. Tabatabaie V, Atzmon G, Rajpathak SN, Freeman R, Barzilai N, et al. (2011) Exceptional longevity is associated with decreased reproduction. Aging (Albany NY) 3: 1202-1205.
32. Rosenthal JT (1996) Old Age in Late Medieval England. University of Pennsylvania Press, Philadelphia, PA.
33. Ungvari Z, Sosnowska D, Mason JB, Gruber H, Lee SW, et al. (2013) Resistance to genotoxic stresses in Arctica islandica, the longest living noncolonial animal: is extreme longevity associated with a multistress resistance phenotype? J Gerontol A Biol Sci Med Sci 68: 521-529.
34. Nussey DH, Froy H, Lemaitre JF, Gaillard JM, Austad SN (2013) Senescence in natural populations of animals: widespread evidence and its implications for bio-gerontology. Ageing Res Rev 12: 214-225.
35. Sussman R (2014) The oldest living things in the world. University of Chicago Press, Chicago.
36. Demaitre L (1990) Care of old age in medieval medicine, pp. 3-2, in Sheehan MH. Aging and the aged in medieval Europe. Toronto, Canada: Pontifical Institute of Medieval Studies.
37. Howitz KT, Sinclair DA (2008) Xenohormesis: sensing the chemical cues of other species. Cell 133: 387-391.
38. Miller WH Jr, Schipper HM, Lee JS, Singer J, Waxman S (2002) Mechanisms of action of arsenic trioxide. Cancer Res 62: 3893-3903.
39. Gems D, Partridge L (2008) Stress-response hormesis and aging: "that which does not kill us makes us stronger". Cell Metab 7: 200-203.
40. Yun J, Finkel T (2014) Mitohormesis. Cell Metab 19: 757-766.
41. Schmeisser S, Schmeisser K, Weimer S, Groth M, Priebe S, et al. (2013) Mitochondrial hormesis links low-dose arsenite exposure to lifespan extension. Aging Cell 12: 508-517.
42. Mirzaei H, Suarez JA, Longo VD (2014) Protein and amino acid restriction, aging and disease: from yeast to humans. Trends Endocrinol Metab 25: 558-566.
43. Tatar M, Post S, Yu K (2014) Nutrient control of Drosophila longevity. Trends Endocrinol Metab 25: 509-517.
44. Gkikas I, Petratou D, Tavernarakis N (2014) Longevity pathways and memory aging. Front Genet 5: 155.
45. Emami M, Sadeghpour O, Zarshenas MM (2013) Geriatric management in medieval Persian medicine. J Midlife Health 4: 210-215.
46. Metter EJ, Talbot LA, Schrager M, Conwit R (2002) Skeletal muscle strength as a predictor of all-cause mortality in healthy men. J Gerontol A Biol Sci Med Sci 57: B359-365.
47. Kaiser J (2014) Aging. 'Rejuvenation factor' in blood turns back the clock in old mice. Science 344: 570-571.
48. Pedersen BK, Febbraio MA (2012) Muscles, exercise and obesity: skeletal muscle as a secretory organ. Nat Rev Endocrinol 8: 457-465.
49. Demontis F, Piccirillo R, Goldberg AL, Perrimon N (2013) The influence of skeletal muscle on systemic aging and lifespan. Aging Cell 12: 943-949.
50. Ribatti D (2009) William Harvey and the discovery of the circulation of the blood. J Angiogenes Res 1: 3.
51. Dillin A, Gottschling DE, Nyström T (2014) The good and the bad of being connected: the integrons of aging. Curr Opin Cell Biol 26: 107-112.
52. Crisciani C, Recipi L, Rossi PB (2009) Micrologus Library.
53. Panowski SH, Dillin A (2009) Signals of youth: endocrine regulation of aging in Caenorhabditis elegans. Trends Endocrinol Metab 20: 259-264.
54. Bitto A, Kaeberlein M (2014) Rejuvenation: it's in our blood. Cell Metab 20: 2-4.
55. Loffredo FS, Steinhauser ML, Jay SM, Gannon J, Pancoast JR, et al. (2013) Growth differentiation factor 11 is a circulating factor that reverses age-related cardiac hypertrophy. Cell 153: 828-839.
56. Kaiser J (2014) Aging. 'Rejuvenation factor' in blood turns back the clock in old mice. Science 344: 570-571.
57. Sinha M, Jang YC, Oh J, Khong D, Wu EY, et al. (2014) Restoring systemic GDF11 levels reverses age-related dysfunction in mouse skeletal muscle. Science 344: 649-652.
58. Conboy MJ, Conboy IM, Rando TA (2013) Heterochronic parabiosis: historical perspective and methodological considerations for studies of aging and longevity. Aging Cell 12: 525-530.