# Bi410/510 Biology of Aging

Aging affects most living organisms and is the primary risk factor for common human diseases such as cancer, cardiovascular disorders, and neurodegeneration. Perhaps surprisingly, rates of aging are under genetic control and vary widely among different species. This course will use primary literature to examine the molecular and cellular mechanisms that regulate aging and to explore approaches that slow or reverse the aging process. This course will emphasize critical reading of the literature and critical thinking. Students will be required to complete regular homework assignments on the readings. During the course, students will develop original research proposals that address unanswered questions in the aging field by using the types of experimental approaches covered in the course.

**Learning objectives**: After completing this course students will be able to:

- explain the aging process at a molecular/cellular level, including how it is analyzed and quantified
- distinguish between alternative evolutionary explanations of aging
- interpret and evaluate experimental data from primary biological literature
- evaluate potential strategies for altering the aging process
- learn to write a compelling research proposal that identifies a scientific question, proposes a hypothetical answer to this question, and lays out a novel strategy to test this hypothesis.

**Course website**
All course materials will be available through Canvas.

**Office hours and email**
I will not hold regular office hours, but I welcome questions, comments, or requests to meet in person by email. Please email me (**herman@uoregon.edu**) from your **uoregon account** and include **BI410/510** in the header. I will generally respond to email messages within two days.

**Required readings**
The schedule of required readings is listed in the schedule below. All are available as pdf files posted on Canvas. You must complete the readings BEFORE the class indicated.

**Supplementary readings**
There is no textbook for this course. However, you may find it helpful periodically to consult two review articles available as pdf files on Canvas: "The hallmarks of aging" (2013) and "Signaling networks determining lifespan" (2016). The additional details they provide may be particularly useful when you are brainstorming ideas for your research proposals.

**Lecture notes**
The course format will be a combination of lectures, activities, and discussions. I will post my lecture notes on Canvas AFTER the lecture, but these notes are NOT a substitute for coming to class.

**Inclusiveness**
UO is working to create inclusive learning environments. Please notify me if there are aspects of instruction or design of this course that result in barriers to your participation. You may also wish to contact the Accessible Education Center (541-346-1155; usaec@uoregon.edu).

**Academic Integrity**
All students are expected to conform to the student conduct code (http://dos.uoregon.edu/conduct). You are encouraged to discuss ideas with each other, but all submitted written work must be your original work. Proper citation of sources is required.

**Grading criteria**
***Participation (10%):*** The course will be a richer experience for those who read the assigned material beforehand and attend and participate in class discussions. During each class period you will jot down one or two questions or comments you have about the class period or associated reading assignment and hand them in before leaving class.

***Homeworks (40%):*** There will be eleven homeworks. Homeworks 2-11 will include questions on the primary papers that will discussed in the upcoming class. You may discuss the homeworks with each other, but your answers must be your own work. These homeworks will be available on Canvas and, when completed, should be uploaded to Canvas by 11:45am on the days listed in the schedule below. Late homeworks will not be accepted. Only your top ten homework scores will count toward your grade - each is therefore worth 4%.

***Proposal exercises (24%):*** Each of you will write an original research proposal that uses approaches similar to those covered in the course in order to address an unanswered question in the field of aging. You will begin to work on your proposal in weeks 3 and 4 and will continue to develop it throughout the course. To help you along the way, there will be six "proposal exercises" - each worth 4% of your total grade. These will be due on Canvas by 11:45am on the days listed in the schedule below. Exercises submitted up to 24 hours after the deadline will be accepted but will receive no more than 50% of full credit.

***Completed proposal (26%):*** Detailed guidelines and criteria for assessment will be provided.

| Date | Topic | Required readings | DUE |
|---|---|---|---|
| **Week 1** | | | |
| M 4/2 | 1. Aging is a failure to maintain homeostasis | none | nothing |
| W 4/4 | 2. Evidence that aging is genetically controlled | 2a. Octopus and the puzzle of aging<br>2b. Is aging programmed? "Intro" & "Discussion"<br>2c. Evolution of aging: "Introduction" only | **Homework 1 due 11:45am** |
| **Week 2** | | | |
| M 4/9 | 3. Is aging inevitable? | 3. Hydra do not age (2015) | **Homework 2 due 11:45am** |
| W 4/11 | 4. Aging cells accumulate lifespan-limiting material | 4a. Using yeast to study aging: up through "The basic methodology and new variants"<br>4b. Asymmetric partitioning of "aging factors" between mother and daughter cells (2015) | **Homework 3 due 11:45am** |
| **Week 3** | | | |
| M 4/16 | 5. Long-lived yeast: dietary restriction, the mTOR pathway, and autophagy | 5a. Minireview accompanying paper 5b.<br>5b. Long-lived yeast mutants include those lacking TOR1 (2005) | **Homework 4 due 11:45am** |
| W 4/18 | 6. Increasing autophagy increases lifspan<br>Proposal writing overview | 6. Increasing autophagy in fly neurons prevents the accumulation of damaged proteins and extends lifespan (2008) | **Homework 5 due 11:45am** |
| **Week 4** | | | |
| M 4/23 | 7. Neurons are particularly sensitive to misfolded proteins | 7. Spermidine ameliorates age-induced memory impairment (in fly) in an autophagy-dependent manner (2013) | **Homework 6 due 11:45am** |
| W 4/25 | 8. Are free radicals responsible for aging?<br>Workshop: brainstorming specific aims | 8. The free radical theory of aging (review) | **Proposal ex1 due 11:45am** |
| **Week 5** | | | |
| M 4/30 | 9. The balance between replicative aging and cancer | 9a. Watson textbook p247-254<br>9b. Minireview accompanying paper 9c.<br>9c. Short telomeres limit tumors (2007) | **Homework 7 due 11:45am** |
| W 5/2 | 10. Telomerase can be harnessed to slow aging | 10. Increasing telomerase slows aging in cancer-resistant mice (2008) | **Homework 8 due 11:45am** |
| **Week 6** | | | |
| M 5/7 | 11. Senescent cells interfere with the function of healthy cells | 11. Senescent cells shorten healthy lifespan (2016) | **Homework 9 due 11:45am** |
| W 5/9 | 12. Systemic signals that control aging (part 1): IGF/Insulin/FOXO | 12. The first long-lived mutants (review) | **Proposal ex2 due 11:45am** |

| Date | Topic | Required readings | Homeworks and Quizzes |
|---|---|---|---|
| **Week 7** | | | |
| M 5/14 | 13. Systemic signals that control aging (part 2): young vs old blood | 13a. Minireview accompanying paper 13b.<br>13b. A protein in the blood of old mice that impairs cognitive function in young mice (2015) | **Homework 10 due 11:45am** |
| W 5/16 | 14. The search for anti-aging interventions for humans: dietary restriction | 14. Caloric restriction in rhesus monkeys (2017) | **Proposal ex3 due 11:45am** |
| **Week 8** | | | |
| M 5/21 | 15. Workshop: brainstorming experimental design/predicted outcomes | The hypotheses/specific aims of each member in your assigned group | **Proposal ex4 due 11:45am** |
| W 5/23 | 16. The search for anti-aging interventions for humans: drugs | 16a. Lifespan vs healthspan (minireview)<br>16b. The search for anti-aging interventions (review) | **Homework 11 due 11:45am** |
| **Week 9** | | | |
| M 5/28 | **Memorial Day** | **NO CLASS!** | |
| W 5/30 | 17. The search for anti-aging interventions for humans: regeneration | 17. Cell replacement to reverse brain aging (review) | **Proposal ex5 due 11:45am** |
| **Week 10** | | | |
| M 6/4 | 18. Workshop: refining your experimental design/predicted outcomes | The hypotheses/specific aims/experimental design of each member in your assigned group | **Proposal ex6 due 11:45am** |
| W 6/6 | 19. TBD based on student input | TBD based on student input | nothing |
| **Finals week** | | | |
| M 6/11 | | | **Proposals DUE by 9am** |

**Supplementary readings**

López-Otín C1, Blasco MA, Partridge L, Serrano M, Kroemer G. 2013. The hallmarks of aging. Cell 153:1194-1217.

Riera CE, Merkwirth C, De Magalhaes Filho CD, Dillin A. 2016. Signaling Networks Determining Life Span. Annu Rev Biochem 85:35-64.

**Required readings**

2a. https://www.nytimes.com/2016/12/02/opinion/sunday/octopuses-and-the-puzzle-of-aging.html

2b. Kowald A, Kirkwood TB. 2016. Can aging be programmed? A critical literature review. Aging Cell 15:986-998.

2c. Maklakov AA, Immler S. 2016. The Expensive Germline and the Evolution of Ageing. Curr Biol 26:R577-586.

3. Schaible R, Scheuerlein A, Dańko MJ, Gampe J, Martínez DE, Vaupel JW. 2015. Constant mortality and fertility over age in *Hydra*. Proc Natl Acad Sci U S A 112:15701-15706. .

4a. Longo VD, Shadel GS, Kaeberlein M, Kennedy B. 2012. Replicative and chronological aging in *Saccharomyces cerevisiae*. Cell Metab 16:18-31.

4b. Yang J, McCormick MA, Zheng J, Xie Z, Tsuchiya M, Tsuchiyama S, El-Samad H, Ouyang Q, Kaeberlein M, Kennedy BK, Li H. 2015. Systematic analysis of asymmetric partitioning of yeast proteome between mother and daughter cells reveals "aging factors" and mechanism of lifespan asymmetry. Proc Natl Acad Sci U S A 112:11977-11982.

5a. Rine J. 2005. Cell biology. Twists in the tale of the aging yeast. Science 310:1124-1125.

5b. Kaeberlein M, Powers RW 3rd, Steffen KK, Westman EA, Hu D, Dang N, Kerr EO, Kirkland KT, Fields S, Kennedy BK. 2005. Regulation of yeast replicative life span by TOR and Sch9 in response to nutrients. Science 310:1193-1196.

6. Simonsen A, Cumming RC, Brech A, Isakson P, Schubert DR, Finley KD. 2008. Promoting basal levels of autophagy in the nervous system enhances longevity and oxidant resistance in adult *Drosophila*. Autophagy 4:176-184.

7. Gupta VK, Scheunemann L, Eisenberg T, Mertel S, Bhukel A, Koemans TS, Kramer JM, Liu KS, Schroeder S, Stunnenberg HG, Sinner F, Magnes C, Pieber TR, Dipt S, Fiala A, Schenck A, Schwaerzel M, Madeo F, Sigrist SJ. 2013. Restoring polyamines protects from age-induced memory impairment in an autophagy-dependent manner. Nat Neurosci 16:1453-1460.

8. Hekimi S, Lapointe J, Wen Y. 2011. Taking a "good" look at free radicals in the aging process. Trends Cell Biol 21:569-576.

9a. Watson, Baker, Bell, Gann, Levine, Losick. Molecular Biology of the Gene, 6th edition, 2008. Pearson/Cold Spring Harbor Press. pp. 247-254.

9b. Sedivy JM. Telomeres limit cancer growth by inducing senescence: long-sought in vivo evidence obtained. 2007. Cancer Cell 11:389-391.

9c. Feldser DM, Greider CW. 2007. Short telomeres limit tumor progression in vivo by inducing senescence. Cancer Cell 11:461-469.

10. Tomás-Loba A, Flores I, Fernández-Marcos PJ, Cayuela ML, Maraver A, Tejera A, Borrás C, Matheu A, Klatt P, Flores JM, Viña J, Serrano M, Blasco MA. 2008. Telomerase reverse transcriptase delays aging in cancer-resistant mice. Cell 135:609-622.

11. Baker DJ, Childs BG, Durik M, Wijers ME, Sieben CJ, Zhong J, Saltness RA, Jeganathan KB, Verzosa GC, Pezeshki A, Khazaie K, Miller JD, van Deursen JM. 2016. Naturally occurring p16(Ink4a)-positive cells shorten healthy lifespan. Nature 530:184-189.

12. Kenyon C. 2011. The first long-lived mutants: discovery of the insulin/IGF-1 pathway for ageing. Philos Trans R Soc Lond B Biol Sci 366:9-16.

13a. Filiano AJ, Kipnis J. 2015. Breaking bad blood: β2-microglobulin as a pro-aging factor in blood. Nat Med 21:844-845.

13b. Smith LK, He Y, Park JS, Bieri G, Snethlage CE, Lin K, Gontier G, Wabl R, Plambeck KE, Udeochu J, Wheatley EG, Bouchard J, Eggel A, Narasimha R, Grant JL, Luo J, Wyss-Coray T, Villeda SA. 2015. β2-microglobulin is a systemic pro-aging factor that impairs cognitive function and neurogenesis. Nat Med 21:932-937.

14. Mattison JA, Colman RJ, Beasley TM, Allison DB, Kemnitz JW, Roth GS, Ingram DK, Weindruch R, de Cabo R, Anderson RM. 2017. Caloric restriction improves health and survival of rhesus monkeys. Nat Commun 8:14063.

16a. Hansen M, Kennedy BK. 2016. Does Longer Lifespan Mean Longer Healthspan? Trends Cell Biol 26:565-568.

16b. de Cabo R, Carmona-Gutierrez D, Bernier M, Hall MN, Madeo F. 2014. The search for antiaging interventions: from elixirs to fasting regimens. Cell 157:1515-1526.

17. Hébert JM, Vijg J. 2018. Cell Replacement to Reverse Brain Aging: Challenges, Pitfalls, and Opportunities. Trends Neurosci S0166-2236(18)30053-5.